

Mainstreamed genetic testing in ovarian cancer:  
A case study of BRCA1/2 tumour testing

A thesis submitted for the degree of Doctor of Philosophy

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## **Declaration**

I, Belinda Rahman confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

## **Abstract**

### **Background**

With the advent of targeted therapies in ovarian cancer (OC), there is an impetus to identify patients with a BRCA1/2 mutation. Germline testing has already been integrated into the oncology setting using a mainstreamed model (MGT). Tumour testing is now available to detect the presence of somatic BRCA1/2 mutations.

### **Aim**

To explore the introduction of mainstreamed BRCA1/2 tumour testing (MTT) in OC, focusing on clinical outcomes and patient experience.

### **Methods**

A case study approach, using different research methods, was taken to gain an in depth understanding of the case (MTT) within its context.

### **Results**

A service evaluation of the current state of MGT at UCLH found that in the 122 patients who were tested over 12 months, germline BRCA1/2 mutation prevalence was 14.8%. Developing the MTT pathway was feasible but challenging; delays were related to retrieval and review of archived tumour tissue. First-line MTT was provided for fifty patients; one somatic and eight germline mutations were identified. More than half this sample (52.6%) required follow-up germline testing. A prospective study using validated measures found no change in distress or quality of life scores before, during and after MTT. Patients reported low decisional conflict scores and no decision regret over MTT. After results disclosure patients with a genetic alteration had significantly more testing-related distress. Qualitative interviews revealed MTT was a brief, transient experience in the context of facing OC. Genetic misconception was common, with patients incorrectly attributing a hereditary component to tumour testing. Primary motivations for testing were related to clarifying genetic risk information for family, rather than personal benefit for treatment options.

## **Conclusion**

A more streamlined process of providing MTT is needed. While MTT appears to have little psychosocial impact, poor understanding of the distinction between germline and somatic mutations indicates the need for improved communication and information provision in OC.

## Impact statement

Up to 15% of ovarian cancer cases will be caused by inherited germline BRCA1/2 mutations. An additional 5% of cases will have an acquired somatic BRCA1/2 mutation. With the development of novel treatments that specifically target BRCA-mutated ovarian cancer, it is becoming increasingly important to identify mutation status in patients with high grade serous disease.

This research has demonstrated both the feasibility and challenges of developing a mainstreamed pathway of delivering BRCA1/2 tumour and germline testing (MTGT) in the oncology setting. With the NHS preparing to deliver this model of testing in ovarian cancer across the UK, these findings are particularly timely and have the potential to inform the development of this service. Suggestions for implementation of an efficient MTGT pathway, including potential pitfalls to avoid, could be invaluable.

MTGT was also shown to have a small but significant impact on patient management. Eleven patients were found to carry a germline or somatic BRCA1/2 mutation from MTGT, six (54.5%) had subsequently been able to access targeted therapies. MTGT not only had a direct impact on treatment decisions, it also provides further evidence of the clinical utility of MTGT. In a disease which has historically shown poor survival, the hope of more treatment opportunities cannot be underestimated.

MTGT also has wider implications for prevention of ovarian cancer; once germline mutation carriers are identified from MTGT predictive testing can be offered to unaffected at-risk relatives where effective risk-reducing interventions exist if mutation status is confirmed. In the case of somatic BRCA1/2 mutations, relatives can be reassured there is no inherited component.

Studying the patient experience of MTGT has provided evidence that overall this approach is well tolerated and does not lead to poor psychosocial outcomes. Other ovarian cancer patients and their oncologists can proceed with testing in the knowledge that MTGT is manageable and does not lead to further burden in addition to cancer diagnosis and treatment.

The finding of genetic misconceptions in relation to germline and somatic mutations has important implications outside the context of MTGT and ovarian cancer. Tumour testing in other cancers is becoming more common. Being aware of areas in the

testing process which need better communication and further information provision has the potential to significantly improve patient understanding.

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## Abbreviations

BRCA1	Breast cancer gene 1
BRCA2	Breast cancer gene 2
BRCA+ve	BRCA1/2 mutation positive
BRCA-ve	BRCA1/2 mutation negative
gBRCA+ve	Germline BRCA1/2 mutation
sBRCA+ve	Somatic BRCA1/2 mutation
tBRCA+ve	BRCA1/2 mutation in tumour
DSB	Double strand breaks
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
EOC	Epithelial ovarian cancer
FCC	Familial cancer clinic
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
GC	Genetic counselling
GOSH	Great Ormond Street Hospital
GT	Genetic testing
GTN	UK Genetic Testing Network
GTEOC	Genetic Testing in Epithelial Ovarian Cancer
H&E	Haematoxylin and eosin
HADS	Hospital Anxiety and Depression Scale
HBOC	Hereditary breast and ovarian cancer

HNPC	Hereditary non-polyposis colorectal cancer
HR	Homologous recombination
HRA	Health Research Authority
HRD	Homologous recombination deficiency
HRQOL	Health related quality of life
IDS	Interval debulking surgery
IES	Impact of Events Scale
IHC	Immunohistochemistry
IQR	Interquartile range
ITH	Intratumoural heterogeneity
LGR	Large intragenic deletion/rearrangement
Mx	Mutation
MCG	Mainstreaming Cancer Genetics Programme
MGT	Mainstreamed genetic testing
MTGT	Mainstreamed tumour and/or germline testing
MLPA	Multiplex ligation-dependent probe amplification
MSI	Microsatellite instability
NGS	Next generation sequencing
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OC	Ovarian cancer
PARP	Poly(ADP-ribose) polymerase
RGCT	Rapid genetic counselling and testing

REC	Research Ethics Committee
SD	Standard deviation
TFGT	Treatment focused genetic testing
UCLH	University College London Hospitals
UK	United Kingdom
US	United States
VUS	Variant of unknown significance

## **Chapter 1 Introduction and background**

### **1.1 Ovarian cancer**

Ovarian cancer is the fifth most common cancer affecting women in the UK, but, despite a relatively rare age-standardised incidence of 17 cases per 100,000 females, it accounts for more deaths than all other gynaecological cancers combined [1]. As early stage symptoms are few and non-specific, such as bloating and/or abdominal pain, ovarian cancer is often only diagnosed at an advanced stage. Despite progress in surgical techniques and chemotherapeutic agents, five-year survival rates remain low at around 40% [2]. There is a recognised genetic component to ovarian cancer; germline mutations in the cancer susceptibility genes BRCA1 and BRCA2 confer risks of ovarian cancer up to 40% and 10% respectively [3].

Approximately 90% of ovarian tumours arise from the surface epithelium, and are known as epithelial ovarian cancer (EOC). These tumours can be distinguished by histology type; for example, between mucinous or non-mucinous (serous, endometrioid, clear cell and transitional cell) tumours which are believed to have distinct aetiologies [4]. As tumours with mucinous histologies are rarely observed in BRCA1/2 mutation carriers, genetic testing is targeted to women with high grade non-mucinous EOC, which accounts for up to 70% of all ovarian cancer cases.

### **1.2 Genetic testing and ovarian cancer**

Currently the most effective measure for preventing ovarian cancer is to identify women at increased genetic risk for the disease. Once women with BRCA1/2 mutations are identified, they can be offered prophylactic surgery to remove the ovaries and fallopian tubes, which has been shown to reduce the risk of cancer by up to 85% [5].

Not only is knowledge of genetic status of benefit for preventing ovarian cancer, BRCA1/2 mutation status is already being used to make specific treatment recommendations for women diagnosed with cancer. In particular, there is evidence that BRCA-associated ovarian cancers have a more favourable prognosis than sporadic ovarian cancers [6], that they respond differently to chemotherapeutic regimens and that they are responsive to novel agents that specifically target BRCA-associated tumours [7-10].

It is clear that there may be significant benefit to both the patient and her family for genetic testing to be made available. Historically women diagnosed with ovarian cancer were referred to a familial cancer clinic (FCC) for genetic counselling and consideration of BRCA1/2 genetic testing if they had a strong family history of breast and/or ovarian cancer or other high risk features such as Ashkenazi Jewish ancestry or early age of disease onset. Given these guidelines, BRCA1/2 genetic testing was only available to a minority of women with ovarian cancer.

The traditional approach of using family history as the major selection criterion for genetic testing has been challenged, as many as 44% of BRCA1/2 mutation carriers do not have a potentially significant family history [11]. Reasons for this include: small family size, few female relatives (or few living to an age to have developed cancer), patrilineal inheritance, lack of knowledge of family history, lower than predicted cancer penetrance and/or non-disclosure of relevant family cancer diagnoses. A large study on BRCA1/2 mutation frequency in women with ovarian cancer concluded that germline BRCA1/2 testing should be offered to all women diagnosed with non-mucinous EOC, irrespective of family history [12]. Therefore triaging for genetic testing using family history and/or age alone can no longer be recommended. Furthermore it may be beneficial if women are referred for genetic testing shortly after their diagnosis with primary or recurrent ovarian cancer to help guide their treatment options.

#### 1.2.1 BRCA1/2 germline vs tumour testing

The vast majority of genetic testing in ovarian cancer has involved germline testing for inherited mutations in BRCA1 or BRCA2 genes. This type of germline mutation is commonly detected through testing of blood or saliva samples.

In contrast, testing of tumour tissue can identify somatic mutations, mutations that are acquired and are non-heritable. Independent of any germline mutation, a tumour may have a somatic mutation not identifiable through germline testing. Studies have shown that testing ovarian tumour tissue enables identification of tumours with germline or somatic mutations and could identify up to 50% more patients with BRCA-mutated ovarian cancer compared to germline testing alone [13]. Thus tumour testing has the potential to expand the number of patients that may benefit from BRCA-targeted therapies.

Tumour testing is now available as a genomic test designed to detect the presence of a BRCA1/2 gene mutation in ovarian tumour tissue. Patients with an identified somatic

mutation can then be offered germline testing to confirm whether it is an inherited mutation (which provides important information to blood relatives) or an acquired mutation present only in the tumour.

### **1.3 Targeted treatments**

A new group of treatments targeting BRCA related cancers have been developed. Poly ADP-ribose polymerase (PARP) inhibitors are promising anti-cancer agents in ovarian cancer which act by blocking the DNA repair activity of PARP enzymes. In the absence of PARP activity cancer cells are sensitive to DNA-binding chemotherapeutic drugs and give in to cell death.

In December 2014 the first PARP-inhibitor, olaparib, was licensed for use in Europe specifically for women with platinum-sensitive relapsed ovarian cancer who carry BRCA1/2 germline or somatic mutations. Olaparib is associated with a statistically significant improvement in progression-free survival for BRCA-related ovarian cancer [14]. This approval represents the first targeted treatment for ovarian cancer. Other PARP-inhibitors are undergoing evaluation in early phase clinical trials, exploring different treatment schedules and platinum-sensitive vs platinum-refractory ovarian cancer.

As targeted treatments become increasingly available for BRCA-related ovarian cancer, providing genetic testing in the oncology setting offers the opportunity to determine BRCA1/2 mutation status for more patients . It also allows for testing to be offered along the cancer pathway; for example at ovarian cancer diagnosis, during treatment or after recurrence. Treatment decisions can then be made based on the results of testing. Women with recurrent ovarian cancer who are identified as BRCA1/2 mutation positive may be eligible to receive olaparib. 2 Mutation status can also indicate eligibility for participation in PARP-inhibitor clinical trials.

### **1.4 Mainstreamed genetic testing**

In 2013 changes to the UK National Institute for Health and Care Excellence (NICE) clinical guidance, specifically guideline CG164, recommended lowering the pre-test BRCA1 and BRCA2 carrier probability risk from 20% to 10% or more [15]. A diagnosis of high grade non-mucinous ovarian cancer would reach the 10% threshold, regardless of family history or age at diagnosis, making significantly more patients eligible for BRCA1/2 testing.

With advances in genetic testing technology it is becoming increasingly faster and more cost-effective to conduct large scale mutation testing, thereby making it available to more women. Coupled with the advent of targeted treatment, integrating genetics in mainstream medicine is a key strategy in response to the increasing demand for genetics services in conditions such as ovarian cancer where there is a substantial element of inherited disease.

As a result, systematic genetic testing for all women with high grade non-mucinous ovarian cancer is rapidly increasing. To adapt to the increasing number of patients who require BRCA1/2 genetic testing, streamlined approaches to providing testing and counselling have been developed. Mainstreamed genetic testing (MGT) is one such model, where BRCA1/2 testing is embedded within the oncology service; oncology health professionals directly provide genetic testing to their patients, with referral to clinical genetics service only as and when required.

MGT after ovarian cancer diagnosis thus has a number of purposes: BRCA1/2 mutation status can provide clinical information about risk of recurrence, response to treatment, prognosis and future cancer risks, it can guide treatment decisions including targeted therapy options and eligibility for clinical trials, and it can also inform family members of their own cancer risks.

#### 1.4.1 Mainstreamed BRCA1/2 tumour testing

Genetic testing of tumour tissue is already an important part of clinical care in diseases such as non-small cell lung cancer, where testing can help inform prognosis and is important for treatment decisions. Tumour testing of the EGFR gene and ALK gene has no hereditary implications and as a result rarely involves clinical genetics services. In contrast, BRCA1/2 tumour testing is just emerging as a part of ovarian cancer clinical care, and although its aim is to identify somatic mutations, it may still have implications for family members. If a mutation is identified on tumour testing, without follow-up germline testing it is unclear if the mutation is somatic or germline in nature.

With olaparib already licensed for use for patients with somatic BRCA1/2 mutations in the UK and increasing numbers of PARP-inhibitor trials available for eligible patients, there is added incentive to identify those with a somatic mutation. Like MGT, BRCA1/2 tumour testing can follow a mainstreamed model; both tumour and germline testing can largely be provided within the oncology setting with limited or no clinical genetics input unless requested.

If both germline and tumour BRCA1/2 testing will be available for ovarian cancer patients, there are some advantages to offering tumour testing as a first-line test compared to germline testing. It is likely to increase the number of patients eligible for new treatments and/or clinical trials targeting BRCA-mutated ovarian cancer by approximately 50%. It may reduce the number of patients facing the decision whether or not to undergo germline genetic testing to only those in which a somatic mutation is identified. This allows for the 'staggering' of genetic testing and testing results. In this way patients can consider somatic testing to guide their treatment decisions without learning of the inherited nature of their disease, thus removing the potential added distress of learning of cancer risk implications for family members.

### **1.5 MGT at UCLH**

Previously at UCLH, women diagnosed with ovarian cancer were referred to the North East (NE) Thames Regional Genetics Service, Great Ormond Street Hospital (GOSH) if they had features which suggested an inherited basis to their disease; for example, young age at diagnosis, Ashkenazi Jewish ancestry or strong family history of breast and/or ovarian cancer (HBOC). Given these criteria, only a small number of women were referred annually for genetic testing and counselling. There are reported barriers to referral and uptake of genetic counselling for both clinicians and patients [24-27], which could have further impacted the number of ovarian cancer patients who actually proceeded to testing.

MGT was implemented at UCLH in April 2015; BRCA1 and BRCA2 germline testing was offered to all high grade non-mucinous ovarian cancer patients who had not previously had BRCA1/2 germline or tumour testing. Genetic testing and testing results were provided by oncologists in the gynaecology oncology outpatient clinics. Patients who received BRCA1/2 mutation positive results or variant of unknown significance (VUS) were then referred to their local clinical genetics service for genetic counselling. Unaffected members of the wider family could be offered predictive genetic testing through the clinic as per standard procedure.

In July 2016 the NE Thames Regional Genetics Laboratories at GOSH introduced germline testing for three additional ovarian cancer susceptibility genes: BRIP1, RAD51C and RAD51D.



## **1.6 Psychosocial impact of MGT**

There is a wealth of data available on the psychosocial implications of BCRA genetic testing in unaffected individuals. It is encouraging that overall there are rarely adverse long-term impacts as a result of genetic testing [16]. However, there may be significant differences between genetic testing in an unaffected high risk cohort compared to a cancer patient sample. Ovarian cancer is already a disease associated with significant emotional burden. It is often diagnosed at an advanced stage and the risk of recurrent disease is relatively high, both of which can exacerbate patient distress. As a result, psychological distress is not uncommon. Studies have shown that between 20-33% of ovarian cancer patients have depression scores and 29%-38% have anxiety scores that warrant further clinical evaluation [17-19].

MGT is available for patients at any point along the cancer pathway from diagnosis, treatment, relapse, remission and recovery. Thus patients may already be managing complex information relating to their surgical and treatment decisions, coping with side effects from chemotherapy, facing a recurrence or be in remission. If MGT leads to an added or unmanageable psychological burden for ovarian cancer patients, offering BRCA1/2 testing in the oncology setting may not be in patients' best interests.

With improvements in long-term survival rates and treatment options, the importance of identifying and addressing psychosocial functioning during and after cancer treatment is increasingly recognised. Screening for distress is becoming a standard of care in the UK and worldwide. The NICE guidelines for supportive and palliative care require the assessment of patients' emotional as well as physical needs [20]. There is a need to evaluate the psychological outcomes of MGT to help inform the development of this clinical service and ensure the wellbeing of women with ovarian cancer.

Much of the psychosocial genetic testing research has been within cohorts of healthy women currently unaffected with cancer. It is important to describe the clinical experiences of ovarian cancer patients and the context in which MGT will take place as these may be factors that influence responses to psychological measures.

## **1.7 Genetic counselling and MGT**

Genetic counselling has been an important component of the genetic testing process. Working in a multi-disciplinary setting with clinical geneticists, clinical scientists and nurses, genetic counsellors are an essential part of the clinical genetics service

provision. Genetic counsellors are somewhat unique in their role as health professionals responsible for addressing and managing not only the clinical and informational needs of patients, but also their emotional and psychosocial needs. One definition of genetic counselling is:

*...the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following:*

- *Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence*
- *Education about inheritance, testing, management, prevention, resources and research*
- *Counselling to promote informed choices and adaptation to the risk or condition (p.79) [21].*

Over the last few decades, clinical genetic testing has moved from sequencing of single genes to next generation sequencing (NGS) of gene panels and whole genome sequencing. These continuing advances in genomic technology and the integration of genomics into mainstream medicine are leading to rapid changes in service delivery, with the UK Association of Genetic Nurses and Counsellors recently publishing a vision statement describing the role genetic counsellors now play. This includes:

- *Applying genomic information to overall future healthcare for an individual and family*
- *Providing practical and psychosocial support or those with, and at risk from, genetic disease*
- *Navigating the ethical challenges surrounding the disclosure and sharing of genetic information*
- *Interpreting and explaining complex, incidental or uncertain genomic information.*
- *Providing education for the wider healthcare workforce on the clinical application of genomics (p661) [22].*

Despite the evolution of genetics in medicine, the core competencies of genetic counselling remain largely the same, and can be adapted to different settings [23]. Furthermore what remains central to the role of genetic counsellors is the process of communication. When considering BRCA1/2 genetic testing this may include but is not limited to, implications and outcomes of testing, risks and limitations, risk-reducing interventions and other medical management, or facilitating the decision-making

process. In the model of MGT described in this thesis, the process of information provision and communication now falls to the patient's treating oncologist.

One of the key tenets of genetic counselling has been non-directiveness, described by Kessler as where the counsellor '...tries to persuade the counselees to think that they have the capacity and ability to make and carry out their own decisions' (p.11) [24]. Over the years the criticisms of non-directiveness include how and if it can be measured, and whether it can actually be achieved. An early empirical study by Michie et al which coded transcripts of genetic counselling consultations as well as rating scales completed by counsellors and counselees reported that all interactions had elements of directiveness [25]. In an editorial piece commenting on Michie's findings, Bernhardt foresaw a shift in practice where 'Genetic counselling and testing will increasingly... be provided by non-geneticists' (p.18), where the ethos of the patient-doctor relationship is unlikely to have a basis in non-directiveness [26]. Elwyn et al felt that an approach of shared decision-making and clinical recommendations better reflected both the realities and the nuances of genetic counselling [27]. This approach would also be more applicable to genetic testing encounters that take place outside of the clinical genetics context, which is becoming increasingly common with MGT.

Perhaps the most critical difference to a mainstreaming model of delivering genetic testing that is oncology-led, is the lack of genetic counselling. Non-genetic medical specialties can be provided with training programmes and educational resources in order to 'upskill' their genetics expertise; however, it may be more challenging to replicate the counselling expertise and psychosocial focus that genetic counsellors bring.

## **1.8 Justification for research**

Ultimately, providing germline testing and identifying a BRCA1/2 mutation in a woman with ovarian cancer not only provides important information regarding treatment and outcome, but is crucial for cancer prevention in relatives. There is also a potential psychological benefit to at-risk relatives; a recent study has shown that women at increased risk of ovarian cancer who did not know their genetic status significantly overestimated their own risk of cancer [28]. Relatives who are found not to carry the same mutation can be reassured that their risk of developing cancer is the same as that of the general population. For patients who have tumour testing and are found to have a confirmed somatic BRCA1/2 mutation, this alleviates concerns for relatives while potentially providing clinical benefits with access to targeted therapies.

Despite the benefits and increasing availability of MGT, the impact of moving testing from the specialised service of clinical genetics and genetic counselling to the oncology setting remains unknown. Although genetics in medicine is rapidly progressing towards a mainstreamed approach, it is important to identify if this is both feasible and acceptable to patients. In particular, little is known about ovarian cancer patients' interest or attitudes towards mainstreamed BRCA1/2 germline or tumour testing, their intentions to accept an offer of testing, the decision making process, or outcomes from testing. From a clinical perspective, the outcomes of BRCA1/2 tumour testing in this patient group and if or how the results are used for clinical management will also be of interest. Lastly it is also important to explore the logistics of introducing a new mode of genetic testing into the oncology setting, particularly when it involves different clinical departments and testing pathways.

### **1.9 Thesis chapter plan**

This thesis begins with a closer look at the clinical aspects of ovarian cancer and genetic testing in Chapter Two, before leading into Chapter Three and a review of previous research into the psychosocial aspects of ovarian cancer and genetic testing. Chapter Four covers the research methodology and outline of the studies undertaken. Chapter Five reports findings from a service evaluation of the first year of MGT at UCLH. Chapter Six details the implementation and clinical outcomes of mainstreamed BRCA1/2 tumour testing in ovarian cancer. In Chapter Seven, quantitative findings from the patient experience of mainstreamed BRCA1/2 tumour testing is described while Chapter Eight focuses on the qualitative findings. In my final chapter, Chapter Nine, I discuss my overall research findings and future directions in this field.

## **Chapter 2 Ovarian cancer and genetic testing – clinical perspectives**

### **2.1 Introduction**

This chapter expands on two key areas of this PhD thesis: (i) ovarian cancer and (ii) genetic testing in ovarian cancer, both of which are critical to the context in which this research was undertaken. The first section is an overview of ovarian cancer from diagnosis to treatment, to describe the clinical background of my patient group. The next two sections describe both germline and tumour testing in ovarian cancer. This chapter finishes with a summary of the new targeted treatments available for ovarian cancer.

### **2.2 Ovarian cancer**

#### **2.2.1 Incidence**

Ovarian cancer is still classified as a ‘rare’ cancer, although the incidence is rising [29]. England has an age standardised incidence of 17.5 ovarian cancer cases per 100,000 females [30]; recent data from the Office of National Statistics (ONS) reported 6430 cases were recorded in 2016 [31].

#### **2.2.2 Pathway to diagnosis**

##### **2.2.2.1 *Symptoms***

Although ovarian cancer has historically been referred to as a ‘silent killer’ due to the perception that women are only symptomatic with advanced disease [32], data from retrospective, prospective and case control studies refute this [33-35]. For example, a survey of more than 1700 ovarian cancer patients found that 95% reported symptoms prior to diagnosis, including 89% of women with early stage disease [36]. However, the symptoms of ovarian cancer are often described as ‘non-specific’ and can be mistaken for other or existing medical conditions such as irritable bowel syndrome (IBS) [37]. NICE guidance reports four symptoms that are suspicious of ovarian cancer, particularly in women over the age of 50 and/or if the symptoms are persistent:

- *'Abdominal distension (women often refer to this as 'bloating') feeling full (early satiety) and/or loss of appetite*
- *Pelvic or abdominal pain*
- *Increased urinary urgency and/or frequency' (p.10) [29].*

#### 2.2.2.2 *Presentation*

If ovarian cancer is suspected, the NICE guidance recommendations for primary care are sequential testing of biomarker CA125 followed by ultrasound if CA125 is above 35 IU/L [29]. Clinical findings that would require urgent referral for a two week wait appoint to specialist care include ascites and an abdominal or pelvic mass. Nearly one third of women with ovarian cancer will be diagnosed via acute presentation to emergency departments while an additional one third from other specialty departments [38].

#### 2.2.2.3 *Establishing a diagnosis*

Further testing in secondary care includes ultrasound and CA125 (if not already undertaken). CT scan of abdomen and pelvis may be indicated. A risk of malignancy score (RMI) calculated from CA125 level, menopausal status and ultrasound score; women with an RMI score above 250 or more are referred to a specialist multidisciplinary team (MDT) [29]. Other investigations such as laparoscopy, hysteroscopy or radiologically guided biopsy may be requested by MDT to establish diagnosis [39].

#### 2.2.3 Stage

Cancer Research UK data from 2014 reported on stage at diagnosis of ovarian cancer cases in England, with 31% of patients diagnosed with stage I disease, 5% stage II, 31% stage III and 18% stage IV; in 15% of patients stage was unknown [40].

Ovarian cancer is surgically staged following the International Federation of Obstetrics and Gynaecology (FIGO) system [41].

Table 2.1 FIGO ovarian cancer stages

<b>STAGE I: Tumour confined to the ovaries</b>	
IA	Tumour limited to one ovary, capsule intact, no tumour on surface, negative washings
IIB	Tumour involves both ovaries otherwise like 1A
IC Tumour limited to one or both ovaries	
IC1	Surgical spill
IC2	Capsule rupture before surgery or tumour on ovarian surface
IC3	Malignant cells in ascites or peritoneal washings
<b>STAGE II: Tumour involves one or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer</b>	
IIA	Extension and/or implant on uterus and/or Fallopian tubes
IIB	Extension to other pelvic intraperitoneal tissues
<b>STAGE III: Tumour involves one or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes</b>	
IIIA Positive retroperitoneal lymph nodes and/or microscopic metastasis beyond the pelvis	
Positive retroperitoneal lymph nodes only	
IIIA1	IIIA1(i) Metastasis $\leq$ 10 mm
	IIIA1(ii) Metastasis $>$ 10 mm
IIIA2	Microscopic, extrapelvic (above the brim) peritoneal involvement $\pm$ positive retroperitoneal lymph nodes
IIIB	Macroscopic, extrapelvic, peritoneal metastasis $\leq$ 2 cm $\pm$ positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.
IIIC	Macroscopic, extrapelvic, peritoneal metastasis $>$ 2 cm $\pm$ positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.
<b>STAGE IV: Distant metastasis excluding peritoneal metastasis</b>	
IVA	Pleural effusion with positive cytology
IVB	Hepatic and/or splenic parenchymal metastasis, metastasis to extra- abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

#### 2.2.4 Treatment and management

As up to 60% of women with ovarian cancer are diagnosed with advanced stage disease (stages III and IV) [1], this section will focus on the treatment and management aspects of these stages.

##### 2.2.4.1 *Surgery*

The NICE guidance for surgical treatment of ovarian cancer describe the objective as 'complete resection of all macroscopic disease' (p.19) [29]. Primary and interval debulking (after neo-adjuvant chemotherapy) involves bilateral salpingo-oophorectomy, total abdominal hysterectomy, omentectomy and lymphadenectomy [42]. Optimal cytoreduction is the resection of all macroscopic disease; increasingly this may involve ultra-radical surgical resections which can include stripping of the diaphragm, multiple bowel resections, cholecystectomy and/or splenectomy [42]. These procedures require specific expertise or undertaken in collaboration with other surgical specialties. Studies have shown that more aggressive surgical efforts aiming for complete cytoreduction lead to longer survival times [42-44] although it may also impact morbidity and quality of life.

If primary debulking is unlikely to result in optimal cytoreduction due to extensive disease, three cycles of neo-adjuvant chemotherapy followed by interval debulking has comparable survival outcomes [45].

##### 2.2.4.2 *Chemotherapy*

Taxane- and platinum-based combination chemotherapy, typically six cycles of adjuvant paclitaxel and carboplatin, are the standard first-line treatments for advanced ovarian cancer. CA125 biomarker and CT scans are used to monitor treatment response both during and after chemotherapy. Response rates for first-line chemotherapy are high, up to 70-80%, although the majority of women subsequently relapse [46].

Ovarian cancer patients who relapse receive several more lines of treatment. Patients who relapse within six months, up to 25%, are described as having 'platinum-resistant' disease. Within this patient group the aim of ongoing treatment is to maintain quality of life by preventing and controlling symptoms [46]. Patients with 'platinum-sensitive' disease continue to receive platinum-based therapies individually or in combination. Many patients will ultimately develop platinum resistance, limiting treatment options.



The goal of ongoing chemotherapy treatments, for example third- or even fourth-line chemotherapy, is largely to manage symptoms and prolong life and is not intended to be curative.

#### *2.2.4.3 Other treatments*

Bevacizumab (Avastin) is a biological therapy which acts by anti-angiogenesis, targeting vascular endothelial growth factor proteins thereby inhibiting tumour growth. It is often referred to as a 'maintenance' treatment and used in addition to first line chemotherapy until disease progression, unacceptable toxicity or for up to 18 cycles.

Bevacizumab has UK marketing authorisation, however it does not currently have NICE approval for use within the National Health Service (NHS) due to concerns about cost-effectiveness [47], although patients in England may access this therapy through the Cancer Drugs Fund.

#### 2.2.5 Histology

The histology of ovarian cancer is important in the context of genetic testing. Distinct histological types have different epidemiological and gene expression profiles and this may influence treatment regimens and prognosis. Ovarian cancer was previously thought to arise from the epithelial surface of the ovary, but recent evidence indicates that the distal end of the fallopian tube is involved in the development of serous carcinomas, whereas endometrioid and clear cell carcinomas develop from ectopic endometrium [48]. Invasive mucinous cancers are not ovarian in origin but metastases from other solid tumours [49].

High grade serous ovarian cancer is the most common subtype. Germline BRCA1/2 mutations are typically found in high grade serous disease, and patients with mucinous or low grade histology types are not routinely offered BRCA1/2 genetic testing unless there are other risk factors to consider such as family history or ethnicity.

### **2.3 Germline testing in ovarian cancer**

#### 2.3.1 BRCA1 and BRCA2 germline testing

Clinical genetic testing for BRCA1 and BRCA2 mutations has been available following the isolation of gene loci on chromosomes 17 and 13 respectively in 1994 and 1995 [50, 51]. The cancer susceptibility risks are well established for mutation carriers; the

average cumulative risk of developing ovarian cancer by age 70 for BRCA1 mutations is 39% (18-54%) and 11% (2.4-19%) for BRCA2 mutations [3].

The prevalence of germline BRCA1/2 mutations within an ovarian cancer cohort can vary by patient factors such as disease histology and ethnicity. BRCA1/2 mutations are less common in mucinous and non-high grade serous ovarian cancer, whereas Ashkenazi Jewish ancestry and founder mutations can inflate BRCA1/2 mutation prevalence. As a result, reported mutation rates range from 5.8 to 30.6% [12, 52-58]. One of the largest cohorts of population-based ovarian cancer patients (n=1001) reported a BRCA1/2 mutation frequency of 14.1% overall, and 17.1% in high grade serous cases [12]. The authors report that the majority of cases with endometrioid and clear cell histology with BRCA1/2 mutations were later reclassified as serous or unspecified adenocarcinoma.

BRCA1 and BRCA2 genes are known as tumour suppressor genes. BRCA1/2 proteins play an important role in maintaining chromosomal stability in response to DNA damage, specifically in the homologous recombination DNA repair process of double strand breaks (DSB) [59]. Germline and somatic BRCA1/2 mutations result in homologous recombination deficiency (HRD) and inability to repair DSB, leading to additional mutations accumulating, loss of genetic information, chromosomal instability and eventually cell death [60].

Data from The Cancer Gene Atlas (TCGA) reported that up to half of high grade serous ovarian cancers demonstrated HRD [61]. Other genes and their encoded proteins that are recognised to contribute to homologous recombination repair include ATM, CHEK2, BRIP1, RAD51C, RAD51D and PALB2 [10]; these are often referred to as HRD genes.

Genetic testing for HRD gene mutations are already being incorporated into clinical practice. At NE Thames Regional Genetics Service which provides BRCA1/2 testing for ovarian cancer patients at UCLH, a five gene panel including BRCA1, BRCA2, RAD51C, RAD51D and BRIP1 genes was introduced in July 2016. A recent position statement from the UK's national Cancer Genetics Group agreed to also include mismatch repair genes associated with Lynch syndrome (MLH1, MSH2, MSH6) in gene panels for ovarian cancer [62].

### 2.3.2 Genetic testing for ovarian cancer patients

Until MGT was introduced at UCLH, ovarian cancer patients were referred to the NE Thames Regional Genetics Service at GOSH by their oncologist if he/she suspected there may be an inherited basis to the diagnosis. Factors which may have triggered referral included family history of cancer, age at diagnosis, Ashkenazi Jewish ancestry, amongst others. Clinical genetics staff would then assess the patient for eligibility for BRCA1/2 testing based on the current testing criteria and offer testing if appropriate.

Identifying ovarian cancer patients who may be eligible for testing relied on oncologists recognising features which could indicate a hereditary basis to their patient's diagnosis, for example asking and recording a sufficient family history. Data from three UK gynaecological oncology centres showed that up to 12% of patients had no family history recorded [63]. Of 22 patients where a significant family history which met criteria for referral to clinical genetics was recorded, no action was taken for 68%.

Health professionals without specific genetics expertise or training may find it difficult to identify the clinical features, 'red flags', associated with inherited cancer predispositions. Low genetic testing referral rates for ovarian cancer patients have been identified across Europe, USA and Canada. A 2016 survey conducted of medical and gynaecological oncologists from Europe and USA found that 45-73% of their ovarian cancer patients had been tested for BRCA1/2 mutations, citing the absence of family history or other risk factors for not offering testing [64]. A review of BRCA1/2 genetic testing referral rates for ovarian cancer patients across America and Europe found rates varied between 7-100% [65].

Several factors have driven changes to guidelines for genetic testing in ovarian cancer. Firstly there is accumulating data on the high prevalence of germline BRCA1/2 mutations amongst patients [12, 53-58]. Secondly, one of the major selection criteria for genetic testing, family history, is now recognised to be a poor predictor of mutation status. Alsop et al reported 57% of mutation carriers had no family history [12]. Furthermore, a systematic review found in 78% of studies, a substantial proportion of ovarian cancer patients with a BRCA1/2 mutation had no significant family history of breast and/or ovarian cancer [66]. Thirdly, BRCA1/2 mutation status is of increased clinical significance thanks to new therapies that specifically target BRCA-mutated ovarian cancer.

Guidelines from Europe, in particular the European Society for Medical Oncology (ESMO) recommend patients with high grade ovarian tumours are tested for germline BRCA1/2 mutations [67]. After revisions to the NICE guidance were published in 2013 lowering the threshold at which BRCA1/2 testing could be offered, the UK Genetics Testing Network (GTN) developed consensus testing criteria to include germline BRCA1/2 testing for all women with high grade serous ovarian cancer [68].

As more centres adopt these recommendations and move to systematically offering genetic testing to women diagnosed with ovarian cancer, one approach to accommodate the growing number of patients who require BRCA1/2 testing is to streamline the testing process and embed testing within the oncology setting, otherwise known as 'mainstreamed genetic testing' (MGT).

### 2.3.3 Mainstreamed genetic testing (MGT)

Genetic testing when used in the clinical setting, is performed to '...determine the genetic cause of a disease, confirm a suspected diagnosis, predict future illness, detect when an individual might pass a genetic mutation to his or her children, and predict response to therapy' [69]. Genetic counselling is a clinical service typically delivered alongside genetic testing, to provide information and support to individuals with or at risk of genetic disease. The tenants of genetic counselling, non-directiveness and informed decision-making, ensure patients have sufficient and appropriate information to reach a decision, whilst being supported in their choice(s).

Until recently, genetic testing has been provided in a stepped approach of multiple appointments with clinical geneticists and/or genetic counsellors. The focus of testing was largely on identifying future cancer risks and the prevention strategies available for unaffected individuals at high risk and their family members. The introduction chapter of this thesis has touched on the changes that are influencing the traditional approach to BRCA1/2 genetic testing; family history is no longer advocated as the main selection criteria and there is increased recognition of the opportunity genetic testing can provide to guide treatment decisions in both breast [70] and ovarian cancer [66].

The model of MGT in ovarian cancer is a significant departure from how BRCA1/2 genetic testing has previously been provided. Instead of genetic counsellors and clinical geneticists, health professionals specifically trained in human genetics and communication skills, genetic testing is provided by oncologists. Testing takes place within the ovarian cancer patient's oncology appointment, and is discussed alongside

other treatment and medical decisions. If a patient consents to BRCA1/2 testing, she will receive her results from her oncologist. Where a BRCA1/2 mutation or VUS has been identified, the patient will then be referred to her local clinical genetics service for genetic counselling, which will also provide predictive testing for at-risk relatives.



Figure 2.1 Traditional model of genetic testing and counselling

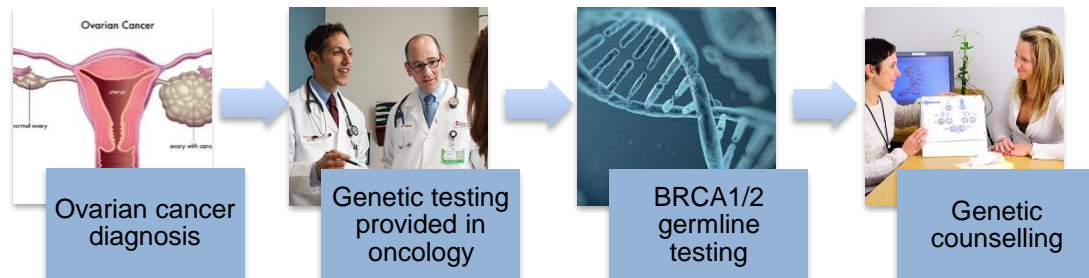


Figure 2.2 Mainstreamed genetic testing in ovarian cancer

Genetic counselling and testing is adapting to the growing demand for genetic testing services within oncology. Although MGT provides more ovarian cancer patients access to testing and streamlines the approach to testing by incorporating it within their current oncology care, it lacks the opportunity for genetic counselling prior to the testing decision. As testing may be offered shortly after diagnosis, during cancer treatment, in remission or on relapse, considering the implications of genetic testing along the cancer pathway is also important.

Meiser described the importance of measuring not only the clinical but psychosocial outcomes of genetic testing, 'Ethical practice requires that we are confident that information about genetic risk and test results can be provided without damaging psychological or behavioural consequences' (p.1061) [16]. Thus there is a wealth of literature on the psychosocial impact of genetic testing, particularly within hereditary cancer. However the change in context, service provider and lack of genetic counselling in the mainstreamed genetic testing approach is a significant change from the settings in which much of this research was conducted. With the introduction of MGT at UCLH, understanding the implications for patients is necessary to ensure the clinical benefits are balanced against any possible psychosocial impact.

#### 2.3.4 Mainstreamed BRCA1/2 testing in UK

When work for this PhD began in January 2015 there were three key programmes in the UK which had implemented and were exploring systematic genetic testing for ovarian cancer patients from a mainstreaming approach. These programmes and their published data are described below.

The Mainstreaming Cancer Genetics (MCG) in ovarian cancer programme was introduced at the Royal Marsden Hospital in 2013 offering systematic BRCA1/2 testing to women with non-mucinous ovarian cancer [71]. In this mainstreamed 'oncogenetic' pathway, BRCA1/2 germline testing was discussed and offered to eligible ovarian cancer patients by an approved cancer team member as well as being provided with an information sheet. Written consent was taken for patients who wished to have testing and if further counselling was required patients were referred to the clinical genetics service [72]. Published data on the first 16 months of the MCG programme reported of the 207 patients offered BRCA1/2 testing, all chose to proceed with testing. Thirty three patients were identified as carrying pathogenic BRCA1/2 mutations, leading to a prevalence of 15.9% [73]. Only 45% (n = 15) of these patients would have qualified for testing under previous guidelines. Genetic testing also had a significant impact on clinical management, with the results of BRCA1/2 testing deemed to be useful in treatment decisions in 64% of cases. George et al also tracked family management in the referral of unaffected at-risk family members to clinical genetics and the uptake of predictive testing. A patient experience survey found that all patients were pleased to have had testing with 98% glad testing was incorporated into their oncology care [73].

In East Anglia, the Genetic Testing for Epithelial Ovarian Cancer (GTEOC) study examined the feasibility and acceptability of BRCA1/2 germline testing [74]. Eligible patients had a diagnosis of high grade serous or endometrioid ovarian cancer in the prior 12 months. Using a 'genetics coordinated' delivery model, BRCA1/2 testing was initially offered and discussed by the treating oncology team, before the patient was referred to the study coordinator to provide more detailed information, take consent, organise testing as well as collect demographic and family history data. Between 2013 and 2015, 232 (87%) of eligible ovarian cancer patients consented to testing; 18 patients (7.8%) were identified as BRCA1/2 mutation carriers. Validated measures were used to explore the psychological impact of testing. Plaskocinska et al found overall genetic testing did not exacerbate distress already experienced as a result of receiving a diagnosis of cancer. Highest cognitive avoidance scores were reported for patients identified as carrying a BRCA1/2 mutation. The authors also reported that younger patients had significantly higher levels of intrusive thoughts and perceived stress post-testing. Similar to the MCG programme, patients' responses demonstrated good acceptability of genetic testing, with sufficient time and information to make their testing decision [74].

In Scotland, routine germline BRCA1/2 testing was introduced for non-mucinous ovarian cancer in 2012 following three different models of testing delivery [75]. In East Scotland (Edinburgh and Dundee), testing followed an oncology-led model, with pre-test counselling provided and written consent taken by the medical oncologist who then organised blood draw for testing. In Aberdeen a similar approach was used although all patients were then referred to the clinical genetics service for telephone genetic counselling. In the West of Scotland BRCA1/2 testing was managed in a genetics-led model, with all patients referred to the clinical genetics service. Data reported here focuses on testing results after changes were made to the selection criteria for testing to include all women with a diagnosis of non-mucinous ovarian cancer who were classified as either 'new criteria' on first-line treatment (n = 236) or 'prevalent population' patients who had not met previous testing criteria but were still under the care of the oncology department (n = 158). Across all sites rates of germline BRCA1/2 mutations were 13.1% in the new criteria patient group, and 12.7% in the prevalent population. Under previous testing guidelines, 48% (15/31) of BRCA1/2 mutation carriers in the new criteria and 45% (9/20) in the prevalent population would not have been eligible for testing. In total, 10 patients (2%) actively declined testing while 21 patients (13%) passively declined testing by failing to respond to contact from

clinical genetics. Patient and health professional satisfaction was not assessed in this study.

These three programmes of offering systematic genetic testing to ovarian cancer patients have shown that this is a feasible and successful method of delivering BRCA1/2 testing to more patients in the UK. In the MCG and GTEOC programmes, and mainstreaming models used in Edinburgh and Dundee, no formal pre-test genetic counselling was provided to patients. The lack of counselling appeared to have little impact on patients' experiences of genetic testing in terms of satisfaction and acceptability with both the MCG and GTEOC study reporting high satisfaction [73, 74].

The value of implementing universal BRCA1/2 testing for ovarian cancer patients is also reflected in the number of BRCA1/2 mutation carriers that would have been missed if previous testing guidelines and selection criteria were followed. Manchester scores were recorded for BRCA1/2 mutation carriers in Scotland and MCG programme; in both cases nearly half of patients had scores <15 and therefore would not have been eligible for testing [73, 75].

Across these three publications, there were low rates of patients declining genetic testing. It appears a completely oncology-led model of BRCA testing delivery may lead to higher rates of patient testing. For example, no patients declined the offer of testing in the MCG programme [73]. In the east of Scotland only three patients declined testing when offered by their oncologist, compared to west Scotland where seven patients actively declined testing offered by clinical geneticists and a further 21 who passively refused [75]. In the GTEOC study, where discussion of testing was initiated by the oncologist or specialist nurse and consenting and organising of blood draw was undertaken by the study team, from a sample of 281 eligible patients 87% consented to participate indicating there was a remaining 13% who declined study participation [74].

## **2.4 BRCA tumour testing in ovarian cancer**

The focus of this chapter so far has been on germline testing in ovarian cancer for inherited mutations in BRCA1 or BRCA2 genes. Germline mutations are commonly detected through genetic testing of blood or saliva samples and should involve discussion of implications for family members as first degree blood relatives are at 50% risk of carrying the same mutation. In contrast, genetic testing of tumour tissue can identify somatic mutations that are acquired and are non-heritable.



BRCA1/2 tumour testing involves NGS of BRCA1 and BRCA2 genes, typically from samples of tumour stored in formalin (formalin-fixed paraffin-embedded, FFPE) blocks which are used for histological examination and diagnosis [76]. Some patients may have multiple tumour blocks from extensive removal of tumour tissue during debulking surgery, while others only a single block, most commonly from an omental biopsy. A major technical challenge of BRCA1/2 tumour testing is ensuring there is both sufficient quantity and quality of DNA from stored tissue samples for genetic sequencing and analysis [77]. An additional challenge is DNA damage from the formalin fixation process which can lead to fragmentation of DNA and sequence artefacts [78]. Mutation artefacts can be false positives, and distinguishing true positive mutations from artefacts requires repeat analysis [76-78]. Despite these challenges, tumour testing for BRCA1/2 mutations by NGS is feasible and can be used to identify somatic mutations in ovarian cancer patients [79, 80]. In recent ESMO guidelines for ovarian cancer treatment recommendations, tumour testing for BRCA1/2 somatic mutations should be considered [67].

This has led to a growing body of literature on the prevalence of somatic BRCA1/2 mutations in ovarian cancer. As shown in the table below, from published data the reported rate of somatic mutations ranges from 3-9% [13, 61, 81-85]. Moschetta et al (2017) believe that the true rate of BRCA1/2 somatic mutations is likely to be between 5-7%; that is for every four or five ovarian cancer patients where a germline BRCA1/2 mutation is identified, one additional patient will have a somatic mutation [86].

Table 2.2 Published somatic mutation rates in ovarian cancer

<b>Study</b>	<b>Country</b>	<b>Cases</b>	<b>Ovarian cancer histology</b>	<b>Somatic BRCA1/2 mutations</b>
Hennessey et al. 2010 [13]	USA	235	Serous, non-serous, mixed, other	7%
The Cancer Genome Atlas Research Network 2011 [61]	International	316	High grade serous	3%
Pennington et al. 2014 [81]	USA	367	Serous, poorly differentiated not otherwise specified, clear cell, endometrioid, carcinosarcoma, other	6.8%
Yates et al. 2014 [82]	USA	88	High grade (histology not otherwise specified)	9%
Chao et al. 2016 [83]	Taiwan	99	Serous, endometrioid, clear cell	4.0%
Koczkowska et al. 2016 [84]	Poland	100	High and low grade serous	4.2%
Dougherty et al. 2017 [85]	UK, USA	209	High grade serous	9.6%

To classify mutations found on tumour testing as either somatic or germline in nature can only be achieved by germline testing. The majority of mutations found on BRCA1/2 tumour testing will be germline inherited mutations [13] which presents a challenge to how tumour testing is discussed with patients, what information is provided and how consent is taken [87].

#### 2.4.1 Mainstreamed tumour testing

At the time this work was undertaken, routine molecular testing of tumour tissue was primarily undertaken to identify somatic mutations that could inform and guide treatment (e.g. EGFR in non-small cell lung cancer) but which has no hereditary implications. One area where this is changing is colorectal cancer. Lynch syndrome, also known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC), is an inherited cancer syndrome associated with predisposition to not only colorectal cancer, but a range of other cancers including endometrial and ovarian [88]. Lynch syndrome accounts for 3% of all colorectal cases [89]. Previous tumour testing for Lynch syndrome in colorectal cancer patients was based on family history and other clinical

factors by using guidelines (e.g. Amsterdam II Criteria and Revised Bethesda) to identify those at high risk [90]. In 2017 NICE published guidance recommending immunohistochemistry (IHC) or microsatellite instability (MSI) testing at diagnosis for all patients with colorectal cancer, with the aim of identifying tumours with deficient DNA mismatch repair [91]. The results of MSI and/or IHC testing can then be used in turn to guide further testing for Lynch syndrome.

Although results from MSI and IHC tumour testing require confirmatory germline testing using a blood or normal tissue sample, nevertheless it presents the first systematic tumour testing in cancer patients that has the potential to identify a hereditary basis to the disease. NICE guidance reports, 'Healthcare professionals should ensure that people are informed of the possible implications of test results for both themselves and their relatives, and ensure that relevant support and information is available. Discussion of genetic testing should be done by a healthcare professional with appropriate training' (p. 5) [91].

This recommendation could also be extended to tumour testing in ovarian cancer. BRCA1/2 mutations identified on tumour testing may be germline and heritable in nature or may be somatic and non-inherited, and it is important that this is communicated clearly to patients.

#### 2.4.2 Mainstreamed BRCA1/2 tumour testing at UCLH

With the feasibility of BRCA1/2 tumour testing in ovarian cancer established, it is worth considering whether this could be implemented following an MGT model which is oncology-led. There is already a precedent of mainstreamed tumour testing in other cancers, for example testing for EGFR mutations to guide treatment decisions in non-small cell lung cancer [92]. MGT for BRCA1/2 germline testing has already been successfully implemented within the gynaecology oncology department (this is discussed further in Chapter 5); oncologists are familiar with discussing BRCA1/2 testing with patients, completing genetic test request forms and referring patients to their local clinical genetics service if required.

In terms of the process of tumour testing, there are existing links between UCLH gynaecological oncology and histopathology departments because of the importance of confirming histotype for ovarian cancer diagnosis. Patient tumour tissue is typically already available, either from debulking surgery or from a guided biopsy during the diagnostic pathway, and archived for up to seven years on site in the cellular pathology department. A genetic testing laboratory with validated methods of

BRCA1/2 tumour testing is also essential. At the time this research was undertaken, the NE Thames Regional Genetics Laboratories which provides BRCA1/2 MGT for UCLH patients did not offer this service.

An important consideration for mainstreamed BRCA1/2 tumour testing is the timing of germline and tumour testing. As BRCA1/2 mutation status can influence treatment decisions, testing at diagnosis could be beneficial for clinical management. Ngeow et al described the ideal timeframe for tumour testing as patients receiving pre-test genetic counselling prior to surgery, although this requires prompt consultation with health professionals, cancer genetics expertise as well as sufficient tumour tissue from a pre-surgical biopsy [93].

Using tumour testing as a first line genetic test for BRCA1/2 mutations has some potential benefits. This approach would provide genomic information upfront to guide treatment decisions; patients with an identified somatic mutation could then be offered germline testing to confirm whether it is an inherited mutation (which provides important information to blood relatives) or an acquired mutation present only in tumour [87]. Where there is no mutation identified in tumour, no further genetic testing is required. This approach could reduce the number of patients facing the decision whether or not to undergo germline genetic testing to only those in whom a mutation is identified on tumour testing. This would lead to focused germline testing, reducing the burden on clinical genetics services [80, 87]. Patients can consider tumour testing to guide their treatment decisions initially, without learning immediately of the inherited nature of their disease, thus removing the potential added distress of learning of the cancer risks for family members.

## **2.5 BRCA1/2 mutation status and targeted therapies**

### **2.5.1 Olaparib, the first PARP-inhibitor**

Understanding the role and function of HRD genes and proteins has shed light on chemotherapeutic response in ovarian cancer as well as potential for targeted treatments. Poly(ADP-ribose) polymerases (PARP)-inhibitors are the first class of new treatments that are targeted towards BRCA-mutated ovarian cancers.

As outlined earlier in this chapter, it is recognised that BRCA1 and BRCA2 are tumour suppressor genes which play an important role in the DNA repair process. PARPs are enzymes which are activated by DNA damage and facilitate DNA repair pathways. PARP inhibitors are believed to work by blocking PARP activity, thereby preventing

DNA repair and leading to synthetic lethality in BRCA-deficient tissues. Inhibiting PARP causes single strand DNA breaks to become DSBs. Due to HRD in BRCA-mutated tumours, the DSBs are unable to be repaired and the cell is directed to cell death [10].

Olaparib was the first PARP-inhibitor to be FDA approved in the treatment of platinum-sensitive relapsed ovarian cancer for patients with germline BRCA1/2 mutations who have completed at least three courses of platinum-based chemotherapy [94]. In December 2014 the European Medicines Agency (EMA) gave market authorisation to olaparib for use in BRCA-mutated recurrent platinum-sensitive high grade serous ovarian and fallopian tube cancer [95]. In January 2016 NICE guidance published recommendations for olaparib as a maintenance treatment after three or more courses of platinum-based chemotherapy in patients with high grade serous ovarian cancer carrying either germline or somatic BRCA1/2 mutations [96].

In February 2019 the EMA's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion supporting extension of olaparib authorisation for use as a maintenance treatment in high grade epithelial ovarian cancer for patients regardless of BRCA1/2 mutation status [97, 98]. As the request for extension awaits approval from the European Commission, this has yet to impact UK recommendations for the use of olaparib. However the potential to extend the use outside of a BRCA-mutated cohort has potentially significant implications for tumour testing in ovarian cancer; if mutation status is no longer an eligibility criteria to access this novel therapy, could this lead to less genetic testing in this patient population?

The most recent change to olaparib in the US has been FDA approval in December 2018 for olaparib to be used as a maintenance treatment for ovarian cancer patients with germline or somatic mutations earlier in the treatment pathway; it can now be accessed following first-line platinum-based chemotherapy rather than after third-line treatment [99].

Licensing of the first targeted therapy in ovarian cancer was an additional driver for genetic testing; there was clinical impetus to identify patients with germline or somatic BRCA1/2 mutations who could be eligible to receive olaparib maintenance treatment. This PhD began in January 2015, shortly after olaparib was approved for use in the USA and EU. In April 2015 pathways for germline testing were implemented and BRCA1/2 MGT introduced for ovarian cancer patients at UCLH. Recruitment of

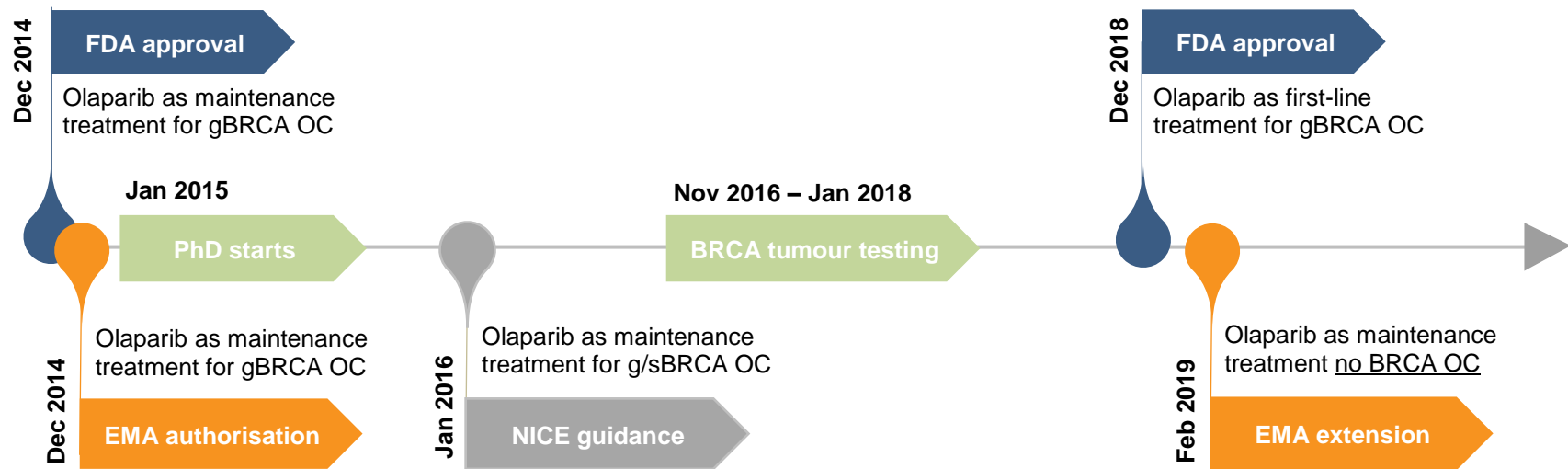
ovarian cancer patients for mainstreamed BRCA1/2 tumour testing ran from November 2016 until the last patient was recruited at the beginning of 2018.

### 2.5.2 The current state of PARP-inhibitors

A number of other PARP-inhibitors have been licensed for use both in the US and Europe. In July 2018 NICE guidance recommended niraparib via the Cancer Drug Fund and a managed access program only as further evidence on clinical and cost-effectiveness is needed [100]. Similar to olaparib, niraparib is also recommended for ovarian cancer patients with platinum-sensitive relapsed disease, either after two courses of chemotherapy if they carry a germline BRCA1/2 mutation or after three courses of chemotherapy for non-carriers.

In May 2018 rucaparib was granted conditional marketing authorisation by the EMA as a monotherapy for women with germline or somatic BRCA1/2 mutations who have had two lines of platinum-based chemotherapy but are unable to tolerate any additional chemotherapy [101]. In the UK rucaparib is currently under NICE appraisal [102] but may be accessed directly from Clovis under a compassionate access scheme [103].

Although olaparib was initially licensed for use only for ovarian cancer patients with BRCA1/2 mutations, clinical data is increasingly suggesting that PARP-inhibitors may also have clinical utility in other HRD-mutated cancers [104]. A recent systematic review reported significantly higher rates of progression free survival at six and 12 months in a cohort of patients with HRD-mutated ovarian cancer compared to non-HRD patients [105].



*gBRCA = germline BRCA mutation; sBRCA = somatic BRCA mutation, OC = ovarian cancer*

Figure 2.3 Timeline of key points in olaparib authorisation

## Chapter 3 Psychosocial aspects of MGT

### 3.1 Introduction

Since clinical genetic testing for HBOC became available for BRCA1/2 mutations in 1996, a large body of literature has developed on the psychological impact of BRCA1/2 genetic testing. Much of this research has focused on the experiences of 'high risk' individuals with a significant family history of cancer, but as yet unaffected by the disease. Overall, the literature shows that unaffected individuals show some psychological benefit from receiving mutation negative results (non-carriers), while those who are found to carry a BRCA1/2 mutation rarely show long-term adverse psychological effects [16]. Although these findings are encouraging, there are important differences between the approaches to genetic testing provided by the traditional genetic counselling model and that of MGT discussed previously in Chapter 2. There are also differences between tumour and germline testing which may impact psychosocial outcomes, particularly in a two-step approach where initial tumour testing arguably has less implications compared to the hereditary nature of identified mutations.

With more patients accessing tumour testing for somatic mutations, largely to inform treatment decisions or as part of clinical trial participation, there is a small body of literature exploring the patient experience. Qualitative interviews with advanced cancer patients (non-small cell lung, melanoma, colorectal, breast, ovarian, endometrial cancer) found that the majority understood testing was to guide treatment options, with half of participants describing tumour testing as DNA analysis for specific genetic mutations which could be targeted by novel drugs [106]. Motivations for testing were the personal benefit and hope offered via potential access to novel treatments based on genomic sequencing results [107]. Advantages of testing were personal benefits such as potential access to targeted therapies as well as informing cause of cancer [106, 108]. Some participants described advantages relevant only to germline testing such as motivation for behaviour change and improving earlier diagnosis. Participants felt disadvantages were associated with receiving mutation negative results which limited treatment options [107], as well as logistical challenges relating to biopsy and treatment delays [106]. Another study described disadvantages such as unwanted information, disclosure of incidental findings and potential psychological harm [108].



A quantitative survey of advanced cancer patients referred for genomic tumour testing for early phase clinical trials reported that 64% believed testing would significantly improve their cancer care [109]. Nearly half of participants felt they had sufficient understanding of testing to provide informed consent while a third wanted genetic counselling prior to testing.

Where incidental inherited genetic information was available, almost all participants expressed interest in receiving this in order to help family members. This was perceived to be an additional burden, while for others it was inconsequential in the context of their diagnosis and treatment [107]. In two studies a number of participants misinterpreted tumour testing as germline testing, describing concern about heritable risks to relatives, cancer prevention, as well as other concerns relating to insurance discrimination and psychological impact [106, 108].

In this emerging field of tumour testing in cancer, these papers provide some insight into patients' attitudes and experiences. However there is an important distinction between BRCA1/2 tumour testing and other somatic testing, as it has the potential to provide hereditary information.

As mainstreamed tumour testing in ovarian cancer is an emerging approach to BRCA1/2 genetic testing, to date there is no published literature exploring the psychosocial experiences of patients. As most mutations identified on BRCA1/2 tumour testing will be germline mutations [87], it is relevant to consider outcomes from MGT which is typically germline testing. Genetic testing in other contexts can also provide insight into the cancer patient's experience of genetic testing: rapid or treatment-focused genetic testing (TFGT) in the acute oncology setting where its purpose may be to guide treatment, and genetic testing for HBOC offered to individuals with a current or previous diagnosis of breast and/or ovarian cancer. Reviewing the literature on BRCA1/2 testing for women with cancer will inform our knowledge on the potential psychological impact of tumour and germline testing in both a patient and survivor cohort.

## **3.2 Psychological impact of MGT**

### **3.2.1 Methods**

#### **3.2.1.1 *Eligibility criteria***

### *Inclusion*

Studies were included if: (i) the focus of the study was on breast/ovarian cancer patients taking part in BRCA1/2 genetic testing, with or without genetic counselling; (ii) psychological outcome measures were used assessing the impact of genetic testing; and (iii) were published in a peer-reviewed journal in English. Studies which reported a mixed cohort of both unaffected and affected individuals were included only if results are reported separately for those affected with cancer. Articles published from the year 1996 onwards were included in the review as BRCA1/2 genetic testing for HBOC was introduced at this time. Both qualitative and quantitative studies were included for this review.

### *Exclusion*

This review excluded studies about uptake of genetic testing, prevalence of BRCA1/2 mutations amongst breast/ovarian cancer patients, multi-gene panel testing, pre-symptomatic genetic testing, genetic counselling interventions, books, lectures, reviews, single case reports, or conference abstracts.

#### *3.2.1.2 Psychological impact*

Psychological impact in genetic testing is a broad description encompassing the psychological effects and responses resulting from the experience of having genetic testing. Within the literature this includes anxiety, depression, cancer-specific distress, cancer worry and genetic testing-related distress. A range of validated psychometric quantitative questionnaires is typically used to measure psychological impact.

#### *3.2.2 Identification of studies*

A review of studies published between January 1996 and March 2016 was conducted. MEDLINE, EMBASE, PsycINFO and CINAHL databases were searched using the following key words individually and in combination: cancer [breast cancer, breast neoplasm, ovarian cancer, ovarian neoplasm, affected, cancer patient]; genetic testing [genetic testing, genetic counselling, diagnostic testing, mainstreamed genetic testing, mainstreaming, rapid genetic testing, treatment-focused genetic testing, symptomatic testing, mutation analysis, DNA analysis]; psychological outcomes [psychological impact, distress, anxiety, depression, worry, psychological stress].

### 3.2.3 Study selection

Titles and, where available, abstracts were reviewed against inclusion criteria. For those that appeared to meet inclusion criteria, one researcher (BR) reviewed full texts.

### 3.2.4 Data extraction

Data were extracted using EndNote X7 and Microsoft Excel 2011.

### 3.2.5 Data synthesis

Each of the studies included in this review was described by summarising the same features for each study (e.g. design, participants, outcome measures and findings). As the focus of this review was the psychological impact for individuals with a cancer diagnosis, and genetic testing approaches similar to that of MGT, studies were grouped by cancer history status (e.g. affected, affected vs non-affected, newly diagnosed). Within these groups studies were then organised by study design (retrospective vs prospective).

## **3.3 Results**

34 studies met the inclusion criteria and form this narrative literature review. Data extraction tables and flow diagram of the review can be found in the Appendix.

### 3.3.1 Design of included studies

Of the studies included in this review, 15 were retrospective in study design and the remaining 19 were prospective. Across the retrospective studies, time from genetic testing results disclosure to questionnaire completion ranged from 2-3 weeks post-results disclosure to up to 10 years. Most prospective studies reported on short-term outcomes post-testing, although long-term data up to three years after genetic testing was available.

### 3.3.2 Outcome measures of included studies

A range of validated and self-developed measures were used to record psychological outcomes of testing. Distress was measured using Hospital Anxiety and Depression Scale (HADS) [110-113], Impact of Events Scale (IES) [110, 112, 114, 115], State-Trait Anxiety Inventory (STAI) [114, 116, 117], Hopkins Symptom Check-list 25 [115], Irritability Depression and Anxiety Scale (IDA) [118], General Health Questionnaire (GHQ-28) [119], Centre for Epidemiological Studies Depression Scale (CES-D) [120].

Cancer specific-distress or worry was typically measured using IES [119, 121] or The Cancer Worry Scale (CWS) [122]. Genetic testing-related distress used the IES [123] or the Multidimensional Impact of Cancer Risk Assessment (MICRA) [124, 125]. Other measures related to genetic testing included the Decision Regret Scale (DRS) and Satisfaction with Decision Instrument (SWD) [126].

### 3.3.3 Psychological impact of genetic testing in women with a personal history of cancer (affected)

There is a small body of literature examining the psychological impact of the genetic testing experience specifically of women with a current and/or previous history of cancer. The data described here are reported separately for qualitative and quantitative research.

Six studies used qualitative methods to retrospectively explore the experiences of women with cancer undergoing genetic testing for hereditary cancer [111, 114, 127-129]. In one-on-one semi-structured interviews with women affected by breast and/or ovarian cancer, Hallowell et al reported that most women did not experience emotional difficulties during testing [127], and it was not an experience that increased anxiety [128]. Compared to their experiences of cancer diagnosis and treatment, genetic testing was inconsequential [128]. This was echoed by the findings of Kenen et al, where participants described the effects of cancer as worse than genetic testing [129].

Responses to genetic testing results varied; BRCA1/2 mutation carriers described both costs and benefits associated with their results [127]. Costs included anxiety for future cancer risks to self and relatives and/or responsibility of communicating results [114, 127-129] while benefits were described as relief from personal guilt attributed to developing cancer [129]. Although the majority were not surprised to learn their mutation positive status [111] or felt it was expected given their cancer history [114], a small proportion of women were distressed by their results [114], and felt as though they were reliving the trauma of their cancer diagnosis [111, 129]. Women receiving inconclusive results expressed positive responses such as relief [114] but also described disappointment, anger and disbelief [127].

Six studies quantitatively assessed the psychological impact of genetic testing in cohorts of affected women. Three retrospective studies observed no significant differences between BRCA1/2 mutation carriers and non-carriers on anxiety, depression or cancer-related distress [110, 114, 118], although carriers showed

significantly higher genetic testing-related distress compared to non-carriers [110]. Hughes Halbert et al reported that at one month post-results disclosure, women who received BRCA mutation positive results had significantly more perceived stress related to genetic testing compared to women with BRCA1/2 negative results [116].

Two prospective studies compared psychological outcomes pre- and post-genetic counselling and testing [112, 115]. In a large sample of breast cancer patients, no differences were observed between BRCA1/2 carrier status and distress, or between pre- and post-testing on anxiety and depression. There was a significant increase in cancer-related distress (intrusion) post-testing [112]. In contrast Wood et al demonstrated a significant decrease in anxiety from pre- to post-testing with no differences observed across carrier status [115].

#### 3.3.4 Psychological impact of genetic testing comparing women with and without personal history of cancer (affected vs unaffected)

A total of fifteen papers using a mixed sample of affected and unaffected individuals measuring the psychological impact of genetic testing met the inclusion criteria and are reviewed here [113, 117, 119-121, 123-125, 130-136]. As some studies report the impact of BRCA1/2 test results (e.g. mutation carriers vs non-carriers) and/or personal cancer history on psychological outcomes, results of these papers are organised by two categories: carrier status and affected status.

##### 3.3.4.1 *Mutation carrier status*

The impact of BRCA1/2 mutation carrier status on psychological outcomes for women with and without a personal history of cancer is mixed.

BRCA1/2 carrier status was not associated with changes in anxiety or depression from pre-testing, to one and 12 months post-test disclosure for either affected or unaffected women [113, 117]. Similarly, no differences were found on distress measures (cancer-related and general distress) between those receiving BRCA1/2 mutation positive and inconclusive results at six weeks, six months or 18 months after post-test disclosure [119, 121, 132]. In a sample of BRCA1/2 carriers, no differences were observed between affected and unaffected women at one and seven months post-testing on breast cancer-worry and distress [130]. Affected women with inconclusive results showed similar levels of worry and distress compared to affected women with BRCA1/2 mutation positive results [130].

Other studies report adverse effects related to receiving BRCA1/2 mutation-positive results in a mixed cohort of affected and unaffected women. Two weeks after receiving genetic testing results, BRCA1/2 mutation carriers had more test-related and general distress compared to non-carriers [123]. Post-results disclosure, BRCA1/2 mutation carriers were significantly more anxious than non-carriers across both affected and unaffected women [131]. This effect was seen long-term; five years post-results both affected and unaffected BRCA1/2 carriers had significant higher levels of genetic testing distress compared to individuals with inconclusive results [124].

In a retrospective study of carrier status and personal cancer history, affected women with a BRCA1/2 mutation positive result were at significantly higher risk for global psychological distress compared to non-carriers. Unaffected BRCA1/2 carriers also showed elevated distress levels [133].

A recent retrospective study examined long-term genetic testing outcomes across six groups approximately 12 months after receiving results: affected mutation carriers, affected VUS carriers, affected non-carriers, unaffected mutation carriers, unaffected VUS carriers and unaffected non-carriers. Using a specialised measure for the impact of genetic testing (MICRA), Lumish et al found that unaffected mutation carriers had the highest MICRA total and distress scores compared to any other groups [126]. This group also had significantly higher intrusion, avoidance and hyper-arousal scores as measured by the IES, compared to any other groups.

In another short-term retrospective study, women had received their results of BRCA1/2 genetic testing one month earlier [137]. Unaffected women had significantly higher anxiety and depression scores, but mutation status (i.e. carriers vs non-carriers) was not associated with distress or poor mood states.

#### 3.3.4.2 *Affected status*

A previous cancer diagnosis was associated with clinically significant levels of anxiety at 3 and 12 months post-test disclosure, regardless of BRCA1/2 testing result [113]. Affected women had significantly higher levels of cancer-related distress at baseline and after receiving results compared to unaffected women [119].

Personal cancer history influenced responses when receiving inconclusive results; affected women who received an inconclusive result had significantly higher levels of breast cancer worry and distress compared to unaffected women [130]. In a sample

of participants who all received BRCA1/2 mutation positive results, at one month post-disclosure affected women had significantly higher levels of cancer-related distress compared to unaffected women [117].

Time from diagnosis was shown to impact psychological outcomes; affected women who received a BRCA1/2 mutation positive result diagnosed within one year from genetic testing had significantly more anxiety and cancer-related distress compared to women diagnosed less recently [120].

Some findings reported poorer outcomes for unaffected women. No differences were observed at other time points (baseline and post-results). Unaffected BRCA1/2 mutation carriers showed greater test-related distress two weeks after results disclosure compared to affected carriers [123]. In a long-term follow-up study Hughes Halbert et al observed a non-significant association between genetic testing-related distress and personal cancer history, with unaffected women more likely to experience distress [125].

In three studies, personal cancer history did not play a role in psychological outcomes. No significant differences were observed between affected and unaffected women pre- and post-results disclosure on anxiety or depression at both six weeks, 6 and 18 months [119, 121, 132].

### 3.3.5 Psychological impact of genetic testing at diagnosis

There is a growing body of literature related to genetic testing at the time of breast or ovarian cancer diagnosis to inform treatment options. Seven papers were found examining the psychological outcomes of offering genetic counselling and testing to newly diagnosed cancer patients [122, 138-143]

A pilot study of breast cancer patients offered rapid genetic counselling and testing (RGCT) used a self-developed scale to measure psychological impact. Half the sample reported that RGCT caused additional distress, while 19% found it reduced distress and 27% felt it had no effect. BRCA1/2 mutation carriers had significantly higher cancer-related distress scores compared to non-carriers [138].

A larger prospective randomised-controlled trial of RGCT which compared cancer worries, cancer-related distress, anxiety and depression at pre-testing, six and 12 months post-testing, found no significant differences between women receiving RGCT and those receiving usual care [139]. Similarly no change in psychological distress (anxiety, depression and cancer-related distress) was observed across

breast cancer patients approached for genetic during adjuvant radiotherapy who accepted testing, those who declined testing or patients who were not approached, at timepoints from baseline up to 12 months [140]. In a long-term follow-up study, ten years after breast cancer patients had been approached for genetic testing and counselling while receiving radiotherapy, participants had low levels of distress [122]. No differences were found between patients offered testing, and a control group of patients not eligible for genetic testing [122].

Timing of genetic counselling and testing in newly diagnosed patients may influence psychological outcomes. Christie et al found women who received genetic counselling before their definitive treatment surgery showed a significant decrease in cancer-related distressed from pre- to post-counselling, while no change was seen for women who received genetic counselling after definitive surgery [141].

In a study of new breast and ovarian cancer patients who were offered BRCA1/2 testing, anxiety decreased significantly from the time of test offer to six months after receiving genetic testing results, while there was no change in depression scores within the same time frame [143]. There were no differences in distress scores between patients identified as mutation carriers, and non-carriers.

A qualitative study of TFGT for ovarian cancer described the experiences of receiving genetic test results shortly after diagnosis [142]. Women who learnt they were BRCA1/2 mutation carriers described feeling sad, attributing this to the implications their results had for family members, and relief for the increased treatment options now available and an explanation for their cancer development. Women who received inconclusive results expressed relief for their family members and were not disappointed at their ineligibility for BRCA-targeted treatments [142].

A prospective study of newly diagnosed breast cancer patients who underwent TFGT examined test related outcomes by family history status [144]. Overall, mutation carriers had both significantly more test-related distress and decision regret when compared to non-carriers across time and family history. Amongst mutation carriers, women with no family history had significantly higher test-related distress compared to women with a family history; no differences were observed amongst non-carriers. Similarly mutation carriers with no family history reported significantly more decision-related regret compared to women with a family history whilst no differences were observed in the non-carrier group.



In a recent study of systematic BRCA1/2 testing in ovarian cancer, women completed validated psychological measures twice, once anchoring to their diagnosis of cancer and a further time to their genetic testing experience [74]. Plakoscinska et al found women had significantly lower scores on the measures anchored to genetic testing when compared to their cancer experiences with the authors concluding that genetic testing did not exacerbate distress already experienced by receiving a diagnosis of cancer. Mutation status was shown to impact psychological functioning, with women who were BRCA1/2 mutation carriers reporting significantly higher cognitive avoidance scores.

### **3.4 Discussion**

Overall the large body of literature on the psychological impact of BRCA1/2 genetic testing in unaffected individuals indicates that non-carriers experience some improvement in psychological outcomes, while BRCA1/2 mutation carriers are largely unaffected [16]. However, the findings are inconsistent, with some studies demonstrating short-term adverse effects related to testing [145, 146]. Differences in findings may be attributed to differences in participant characteristics (e.g. number of affected relatives, awareness of family history, socio-demographic factors, perceptions of risk), genetic counselling practice across centres and countries, availability of risk management options for those identified as BRCA1/2 mutation carriers, and study methodology [16].

In this literature review of psychological outcomes post-BRCA1/2 genetic testing in women with a current or previous history of cancer, reported findings were similarly varied. Changes in anxiety and depression were not associated with BRCA1/2 mutation carrier status in affected women [110, 114]. However perceived stress and distress specific to genetic testing were increased in affected BRCA1/2 carriers compared to non-carriers [110, 112, 116].

Studies which included a mixed sample of both affected and unaffected women had similar findings; BRCA1/2 mutation carrier status had no impact on anxiety, depression or cancer-related distress [113, 117, 119, 121, 132]. However both short- and long-term increases in genetic testing-related and/or general distress were reported in affected and unaffected BRCA1/2 carriers [123, 124, 133]. Only one study reported differences in anxiety between carriers and non-carriers for a mixed sample, describing this as a 'natural' response' in most individuals [131].

It appears that overall genetic testing, and in particular receiving BRCA1/2 mutation positive results, has little psychological impact for women with and without a personal history of cancer. For both groups of women, adverse outcomes were mostly for genetic testing-related distress. Standard psychosocial measures may not be sensitive to the subtle and specific changes associated with the experience of genetic testing, such as responses to test results, fears for future health, responsibility of communicating results to relatives and worries for children. For most of the studies in this review, the IES was used to measure cancer-related worries as the traumatic event, rather than genetic testing. Using more specific measures such as the Multidimensional Impact of Cancer Risk Assessment (MICRA) could provide more informative data relating to the genetic testing experience.

Qualitative studies included in this review provide more insight into quantitative findings reported for affected women. Within the context of their cancer diagnosis and treatment, the experience and outcomes of genetic testing experience was comparatively insignificant [128, 129, 136]. Affected women who received BRCA1/2 mutation positive results described both positive and negative responses, with benefits such as relief from self-blame while acknowledging difficulties related to future risks for self and family and challenges related to disseminating results [114, 127-129]. A small number of women were distressed to learn their BRCA1/2 carrier status [114] describing this as exacerbating their previous cancer diagnosis [111, 129].

The role of personal cancer history on psychological outcomes in genetic testing is mixed; several studies report adverse psychological outcomes for anxiety and cancer-related distress in affected women post-testing [113, 117, 119], while others found anxiety or test-related distress was worse in unaffected women during testing, and at short- and long-term follow-up [123, 125, 134].

Although most affected women appear to cope well with genetic testing, there is some risk that genetic testing involves reliving the trauma related to their cancer diagnosis and/or treatment. Despite the acknowledgements of benefits related to genetic testing, it implies there is a risk of 'overburden'. Given their previous experiences with cancer diagnosis and treatment, it is not unexpected that for some affected women, genetic testing has a negative impact on psychological wellbeing. Studies have reported higher baseline scores for anxiety, depression and cancer-related distress in women with a personal history of cancer [119, 147, 148]. The findings relating to poorer outcomes in unaffected women may reflect the negligible impact genetic

testing has for affected women in the context of their prior cancer experiences. Affected women may be better prepared to receive cancer risk information and reflect on predisposed genetic risk.

The timing of genetic counselling and testing may be crucial; in a study comparing genetic counselling before or after definitive surgery for breast cancer treatment, women who received pre-test counselling before surgery had improvements in cancer-related distress. In contrast no change was observed for women who received counselling after their surgery [141]. Genetic counselling may have been perceived to be informative to the treatment decision. In the period prior to surgery counselling may have provided reassurance for concerns related to diagnosis, surgery and future cancer risks. Studies specifically evaluating the effects of genetic counselling have shown it to improve knowledge [149], perceived risk [150] and cancer-related concerns [151].

Genetic testing closer to diagnosis may have an adverse impact on psychological wellbeing. Affected BRCA1/2 carriers diagnosed less than one year prior to receiving genetic test results had worse outcomes for anxiety and cancer-related distress [120]. Within a year of diagnosis patients may still be adjusting to their diagnosis and undergoing treatment. Cancer treatment is already associated with negative psychological responses [152] that may be exacerbated by genetic testing.

These findings are particularly relevant given the growing interest in offering genetic testing to newly diagnosed cancer patients to inform and guide treatment decisions. With medicine increasingly taking a targeted approach, knowledge of BRCA1/2 mutation status at diagnosis can inform decisions related to contralateral risk-reducing mastectomy in breast cancer [70], and eligibility for targeted therapies such as PARP-inhibitors in ovarian cancer [66]. Although there are limited numbers of papers published in this area to date, it is encouraging that much of the literature reports no adverse outcomes from approach for genetic counselling and testing at diagnosis both in the short-term and long-term [122, 139, 140]. The potential for informing or expanding the treatment options available may ameliorate distress associated with genetic testing.

New approaches to genetic testing such as RGCT, TFGT and MGT are a significant departure from the traditional model of genetic testing which was typically offered post-treatment to inform unaffected relatives about their cancer risks. This review not only informs our understanding of the outcomes for women who undergo genetic

testing who have a recent and past history of cancer, but also identifies areas where further research is needed.

Many of the studies reviewed did not report on date from diagnosis in affected women. In some studies where this data was included, date from diagnosis was stratified to more or less than five or ten years making it difficult to draw conclusions on the influence of the cancer experience, in particular diagnosis and treatment, on genetic testing outcomes [124, 128]. For some studies, this data had a wide range from several months to decades post-diagnosis [110, 111, 129]. As discussed, timing may be an important influence on psychological outcomes during and after genetic testing [153]. Better reporting of diagnostic data, as well as current and/or past treatments, is needed for future research that includes individuals with a personal history of cancer.

There was also significant variation in sample sizes across studies, from 35 [115] to 464 [124]. Small study cohorts may only allow for the detection of large differences and can make generalisation difficult. However a number of studies with small cohorts did report significant differences between groups, even with low statistical power [110].

Several studies used a retrospective design. Without a baseline comparison of psychological state, this provides only a 'snapshot' of time and limits the ability to comment on the actual impact of genetic testing. Furthermore, there is some risk of recall bias or reconstruction of past events [154].

Despite these limitations, some of the reviewed studies had strengths which should be noted. A number of studies included comparative groups of affected women who were not referred or ineligible for genetic testing to control for effect of personal cancer history [122, 136, 139, 140]. Three quantitative studies incorporated a qualitative component [111, 114, 136]; qualitative data can be a rich addition to a study, helping to further explain or support quantitative findings.

#### 3.4.1 Implications for practice and research

In MGT for ovarian cancer, patients may have testing at any stage along the cancer pathway: diagnosis, treatment, relapse and remission. The oncology clinical team provides follow-up care for ovarian cancer patients and survivors up to several years post-diagnosis [39]. This review includes cohorts of affected women from diagnosis to up to ten years post-diagnosis. In general there is little psychological impact from genetic testing across these timeframes for women with a personal history of cancer.

However women with cancer diagnosed more recently who learn they are BRCA1/2 mutation carriers are at risk for psychological distress. The literature also demonstrates that there is a small sample of both affected and unaffected women who are at risk of psychological harm during or as a result of genetic testing.

Given the variation in the literature for reported ages, date from diagnosis and period between diagnosis, counselling and testing, it is difficult to make specific recommendations for women with breast or ovarian cancer who are faced with the decision to have MGT. Further research is needed to identify which factors (e.g. age, prior cancer diagnosis, family history) may be detrimental to psychological outcomes during testing.

High anxiety prior to testing has been reported as a predictor for poor outcomes in a number of studies. Psychological assessment before genetic counselling or the offer of testing is therefore essential to identify women who may be particularly affected by genetic testing and may find it difficult to cope with the process and/or outcomes. Vulnerable women could benefit from close monitoring during genetic testing and/or further psychological support. Integration of support services either via the oncology or psychology clinical team will ensure patients are referred promptly and appropriately if necessary.

Validated measures which are more sensitive to the specific experience of genetic testing should be used in future studies alongside the psychometric scales typically used in psycho-oncology research.

Studies that did not include receipt of genetic test results for participants, but involved the offer of genetic testing and/or genetic counselling were included in this review. For this PhD thesis, the genetic testing offer is in itself considered an important event. Genetic testing has not been part of the typical treatment pathway for ovarian cancer; cancer patients may be less aware of genetic testing, particularly if it is offered by their treating clinician or combined with other diagnostic tests [147]. Thus the offer of genetic testing may be unexpected and elicit a psychological response independently of test results.

#### 3.4.2 Implications for PhD design and methodology

This literature review has highlighted that date from diagnosis can impact psychological outcomes after learning their BRCA1/2 mutation carrier status, with women less than one year from cancer diagnosis experiencing greater distress than

those diagnosed less recently [120]. This PhD project is aiming to sample the experiences of women across the whole cancer pathway, as mainstreamed genetic testing is offered in this way within the clinical service. It is essential that data from diagnosis is collected for all participants. As newly diagnosed ovarian cancer patients may be particularly vulnerable, it is important that these patients are identified to the research team and can be closely monitored if they need further psychosocial support during their participation.

The need for further research into factors predictive of poor psychological outcome during genetic testing is highlighted in the previous section. For this study clinical and self-report data will be collected to identify if disease (e.g. symptom burden, stage at diagnosis, treatment, date from diagnosis), or socio-demographic (age, education, parity) factors impact on psychological responses.

High baseline levels of anxiety are a predictor of adverse psychological outcomes during genetic testing. The prospective quantitative study of this PhD research will include a baseline measure of distress prior to the offer of testing. This is a unique feature of this project; the vast majority of studies on the psychosocial impact of genetic testing have measured psychological functioning only after the offer of genetic testing. This also allows for the genetic testing offer to be measured as a separate event to the results of genetic testing. Comparisons can be made for psychological responses at baseline, after consenting to testing and after receipt of genetic testing results to inform our understanding of the impact of the entire genetic testing process.

Where possible, the psychological measures chosen for this project have been used in other psychosocial genetic testing research to allow comparison with previous research or have been developed specifically for the experience of genetic testing for hereditary cancer.

### **3.5 Summary**

There is a growing body of literature examining the psychological impact of genetic testing amongst individuals affected with cancer, and in more recent years the focus has moved to the newly diagnosed patient group to reflect the developments in targeted therapies. Overall it appears that genetic counselling and testing can be offered to newly diagnosed breast and ovarian cancer patients without leading to psychological distress.

## Chapter 4 Research methodology

### 4.1 Introduction

The provision of genetic testing for women with ovarian cancer has expanded rapidly. The most recent development to date has been the validation of BRCA1/2 genetic testing of ovarian cancer tumour tissue to identify somatic mutations [76, 79, 80]. In the UK there is currently limited access to BRCA1/2 tumour testing in ovarian cancer; at the time this research was undertaken could be accessed either as work-up for clinical trial eligibility, private payment or in collaboration with genetic testing companies (i.e. provision of free tumour tests). Such a collaboration led to an opportunity to explore the introduction of tumour testing for women with ovarian cancer at UCLH. Myriad Genetics provided fifty tumour tests (Tumour BRCAAnalysis CDx®) for use in this PhD research. This chapter describes the study design and research undertaken, as well as the methodological considerations which have underpinned this work.

#### 4.1.1 Research development

In 2014 I began developing my PhD project; initial plans were to explore MGT at UCLH and conduct a mixed methods study to examine ovarian cancer patients, relatives and health care professionals' attitudes and experiences of this new model of providing genetic testing. Reflecting the rapidly evolving field of clinical genetics and oncology, two large UK programmes looking at MGT and systematic genetic testing for ovarian cancer patients, including patient experience and outcomes, had begun in 2013.

In 2015 once enrolled on my PhD programme I developed a three-arm study design to examine psychological distress in ovarian cancer and the impact of MGT. A cross-sectional study would describe the levels of distress in patients with ovarian cancer from UCLH. This data would also provide a baseline measure of psychological state in this patient cohort. An observational prospective study would then explore the psychosocial impact of MGT. Lastly a qualitative study aimed to explore in depth the experiences of ovarian cancer patients who had undergone MGT.

By 2016 further developments in BRCA1/2 genetic testing and a collaborative approach from Myriad Genetics provided me with an opportunity to focus my research

on tumour testing in ovarian cancer. At the time, this new mode of genetic testing was not available within the NHS, although patients could access it privately. Seizing on this excellent opportunity to be involved in a new approach to genetic testing, the focus of my research shifted once more. I considered carefully what aspects of BRCA1/2 tumour testing would be of most interest and relevance, as well as contribute to our understanding of novel genetic testing methods.

With my background in psychosocial research in cancer genetics and having trained as a genetic counsellor, I chose to centre my research on the provision of BRCA1/2 tumour testing to patients, the patient experience of testing and the clinical outcomes. I felt one of the most important factors to be considered was the context in which tumour testing would be provided, following a 'mainstreamed' pathway (much like MGT) within an oncology setting. Wanting to reflect the context, process and outcomes in my research design and findings I sought a methodology which could encompass a multi-faceted approach.

#### **4.2 Making a case for a case study approach**

*The case study approach is particularly useful to employ when there is a need to obtain an in-depth appreciation of an issue, event or phenomenon of interest, in its natural real-life context. (p.1) [155]*

Case study research is an established approach with a long history across many disciplines, in particular social science domains. Although case study research has historically involved qualitative and ethnographic methods, increasingly the use of multiple methods of data collection and analysis is encouraged [156]. This flexible approach to case study design means the methodological nature is not compromised, while allowing for different methods to best elucidate the case under study.

In the literature case study is referred to both as a method in itself, or as an overarching approach to research [157]. This PhD work follows the definitions of Simons, where case study is seen as an overarching approach with '...research intent and methodological purpose', which in turn guides the various methods or 'techniques of research' which have been chosen to explore the current case or issues (p.3) [157].

A case study approach allows for an in depth examination or exploration of a particular phenomenon (the 'case') that requires an understanding of the contextual situation of the case. Yin describes factors where a case study approach would be relevant:



- Form of research questions is How, or Why
- Requires no control over behavioural events
- Focuses on contemporary 'real world' events [158].

Studying the introduction of mainstreamed BRCA1/2 tumour testing for ovarian cancer patients could have been undertaken as a series of quantitative surveys or qualitative interviews independently or as a mixed methods study, to explore patients' experiences of this new testing strategy. However there are other aspects of this new mode of genetic testing that are of interest and relevance. For example, what is the context in which this new mode of testing will be introduced? Why has genetic testing become such a key part of ovarian cancer care? What genetic testing is already being undertaken in the context of ovarian cancer care? How would BRCA1/2 tumour testing be delivered, i.e. what are the logistics, pathways and people required? How will the results of testing be used to inform patient care? Furthermore the contextual situation of tumour testing is significant – this model of mainstreaming may have an important impact on how testing is utilised by health professionals, and accepted and understood by patients.

A case study approach is multi-faceted, allowing for different research methods as well as the inclusion of other data sources to gain a better understanding of the case in its current context. For my PhD research, this approach enabled me to examine a number of elements related to introducing BRCA1/2 tumour testing in ovarian cancer. The emphasis on the 'contemporaneous' nature of a case study approach is particularly relevant to my research as the scientific, clinical, social and cultural landscape of genetic testing is ever evolving. As has been highlighted in earlier chapters, within the last five years there have been significant changes in the field of genetic testing for ovarian cancer starting with eligibility criteria for BRCA1/2 genetic testing expanding the number of patients who were able to access testing. Advances in targeted treatments in ovarian cancer have driven the need to identify more germline and somatic mutation carriers. There is also recognition that in order to keep pace with the growing number of patients where genetic testing is recommended, incorporating testing into mainstream medicine and within the cancer treatment and diagnostic pathway is essential.

Although I have presented my argument for taking this approach for my research, there are criticisms of case study research. The flexibility of case studies is appealing to researchers (including myself), however this can lead to poorly articulated and methodologically weak studies where it has been adopted as a convenient label [159].

Similarly the creativity of qualitative research still requires justification and adequate methodological description. Hyett et al emphasise the importance of including the research paradigm that has influenced study design, as well as clear methodological description, sufficient justification of why the case was selected and the context of the case [159].

Some of what I perceive to be the advantages of case study methodology have also been used as its weakness. The ability of this approach to take a focused examination of a case means that criticisms often lie in its inability to be generalisable, and therefore is considered to be a poor scientific method [159, 160]. There are two issues raised here, generalisability and research quality. Flyvbjerg argues that 'The goal is not to make the case study be all things to all people. The goal is to allow the study to be different things to different people' (p.239) [160].

The nature of case studies specifically and qualitative research more broadly, is that they differ markedly from hypothesis driven, experimental research and therefore their quality should not be measured by the same concepts [161]. Case studies, as with any other research methodology, can be conducted well if relevant steps to ensure rigour are undertaken. This is discussed further in this chapter.

### **4.3 Case study strategy**

My case study approach has been informed by the work from a number of leading case study researchers: Yin [158], Simons [157] and Stake [162] in particular. My academic and research background has followed a biomedical model of learning, rather than anthropological or ethnographic training. Thus I was drawn to case study approaches which felt comprehensible and achievable within my scope of experience and skills. Published articles by Baxter and Jack [156] and Crowe [155] have also been helpful. This chapter addresses the key components of this research including the case study design, plans for collecting, analysing and interpreting the data, and reporting the findings [155].

#### **4.3.1 Defining the case**

Miles and Huberman define a case as '...a phenomenon of some sort occurring in a bounded context' (p.25) [163]. A case can also be defined by the research question(s), existing literature and prior knowledge of the setting or context [155]. Simons takes a less prescriptive approach to defining the case, suggesting that the case can instead be identified as a 'specific statement of the research focus' (p.28) [157]. She also

believes that cases can be chosen because of an inherent interest in the case and more simply, 'a general intent to understand what is happening in the case' (p.29) [157]. As Baxter and Jack wrote, when defining the case it may be helpful to ask yourself as the researcher, what aspect will be under analysis – is it the individual or a programme? Or is the process the main research interest? Or perhaps the difference between organisations is where the research should focus [156].

A helpful starting place for defining my case was to firstly identify the 'phenomenon'; this was mainstreamed BRCA1/2 tumour testing, then consider the overall context of the phenomenon, i.e. genetic testing in ovarian cancer. Lastly, who the phenomenon involves, from patients and health professionals to histopathology staff. Some relevant research questions for this work focused on specific aspects of the phenomenon such as: How is BRCA1/2 tumour testing implemented for clinical use? How do patients experience BRCA1/2 tumour testing? What are the clinical outcomes of mainstreamed BRCA1/2 tumour testing?

Drawing these elements together, I defined the case under study as, 'The introduction of mainstreamed BRCA1/2 tumour testing: patient experiences and clinical outcomes'.

#### 4.3.2 Binding the case

Both Crowe and Simons use the boundaries of the case to help define it [155, 157], as it can clarify not only what or who is under study, but the timeframe of the case study and the type of data that is needed [155]. Therefore, establishing boundaries within a case study are imperative for not only managing the scope of the research but also for focusing and framing the research [164].

A case can be bound by: (a) by time and place; (b) time and activity [162]; and (c) by definition and context [155]. It is necessary to be both selective and specific in defining the parameters, including the participants, location, process and timeframe [164].

It was helpful that there were some clear boundaries to this case, the first of which was time. PhD projects, as with other research, are often constrained by time with a distinct period for research planning, data collection and analysis. The case timeframe was also dictated by its activity; there were a specific number of tumour tests available for patients (fifty tests) and the timeframe was dictated by the time required to recruit the necessary number of participants. These tests were also allocated solely for use at a specific place, in the UCLH gynaecological oncology outpatient clinic. Participants

were defined as ovarian cancer patients who would be eligible for BRCA1/2 tumour testing as specified by the testing criteria.

#### 4.3.3 Determining the type of case study

This component of case study research is sometimes referred to as selecting the case [155, 164], however Baxter and Jack refer to this aspect as considering what type of case study you plan to conduct [156]. The type or selection of case study may be determined by factors such as where the cases are located or what cases might lead to the most understanding about the phenomena [157]. However, it will also be guided by the overall study purpose [156].

Two key case study researchers use different terms to describe and define different types of case studies, although these terms are now use widely within the case study literature. In particular Yin identifies exploratory, explanatory or descriptive case studies [158], while Stake categorises case studies as intrinsic, instrumental or collective [162]. These case study types are shown in the table below.

Although there are differences to the study types, a case study can be both intrinsic and instrumental and categorising a case into one specific type can be challenging [165]. The selection of the case study type should also be guided by the overall study purpose – is the aim of this case study to describe, explore or compare a case?

Table 4.1 Examples of different case study types

<b>Case study type</b>	<b>Definition</b>
<i>Explanatory</i>	Employed to 'explain phenomena' Can explain causal relationships Useful for complex phenomena where survey or experimental methods would be inappropriate [166]
<i>Exploratory</i>	Useful for studying new phenomena or where outcomes are unknown Can be initial step for explanatory research and used to refine future research questions [167]
<i>Descriptive</i>	Describe a phenomena and real life context
<i>Intrinsic</i>	Not representative of other cases, unique [155] Researchers with genuine interest in the phenomena; intent is to better understand the phenomena [156] Case itself is of primary interest, research is driven by wanting to know more about uniqueness of the case. Often leads to thick description of the case. More focus on interpreting meaning rather than generalisation. Aims to reflect richness and complexity of the case [165]
<i>Instrumental</i>	Specific case chosen less important than selecting a case that allows investigation of an issue or phenomenon [155] Focus on specifics related to research question Attempts to identify patterns and themes Comparison with other cases [168]
<i>Collective</i>	Multiple case carefully selected Allows comparisons and/or replication to be made across cases [155] Explore differences within and between cases [156]

When reflecting on this case, it holds properties which were both intrinsic and exploratory. As I will discuss later in the chapter, my background in genetic counselling and psychosocial research in cancer genetics have meant my interests have long lain in the field of genetic testing, and have now focused on this specific context of BRCA1/2 tumour testing in ovarian cancer.

*'The real business of case study is particularisation, not generalisation. We take a particular case and come to know it well, not primarily as to how it is different from others but what it is, what it does' (p.7) [162].*

As Stake emphasises, a case study should aim to explore in detail the phenomenon and embrace its unique features, rather than making comparisons or drawing generalisations. Tumour testing is a new approach to BRCA1/2 genetic testing, and at the time this PhD was undertaken, not part of standard care for ovarian cancer patients. Given rapid changes in genetic testing technology, service delivery and for whom and how targeted treatments can be used, BRCA1/2 tumour testing may not be available or used in the same way, in this same context, again. Thus many features of this case are unique. This was an opportunity to explore in depth, not only how tumour testing can be implemented a mainstreamed model in clinical practice, but how it is used by oncologists and experienced by patients.

#### **4.4 Case study design**

There is no specific research design to follow for a case study. Rather, the design can be seen as a 'blueprint' for your research, which can be guided by what questions to study and determine methods of data collection and analysis [158]. Simons echoes this approach, as she writes 'In many types of case study the design is more emergent than preordinate. It provides a starting point' (p. 31) [157].

However, some structure or plan is needed to undertake any kind of research. There are some elements of case study research design which were considered, these are discussed below.

##### **4.4.1 Formulating research questions**

Simons recommends starting case study design with identifying or refining the research questions as they can provide a framework and/or focus for the case study [157]. These questions can be returned to throughout the course of the research which allows reflection on whether or how well they have been addressed.

Referring back to the case, 'The introduction of mainstreamed BRCA1/2 tumour testing: patient experiences and clinical outcomes', I developed research aligning to my specific research interests and previous experience. Having spent several years researching psychosocial aspects of genetic testing, focusing on patient experience was a priority for me. An oncology-led model of MGT is gaining ground in cancer centres across the UK although there is still a dearth of literature around patient experiences and outcomes. This was also an opportunity to contribute to the literature on this topic. A driver for both tumour and germline BRCA1/2 testing has been their potential to impact patient management and treatment decisions. Examining the

clinical outcomes is an important part of linking the outcomes from genetic testing to the clinical care of patients.

What is perhaps neglected in this case study is the experience of the oncologists who are involved in delivering germline and tumour testing. Although this is also an area of interest for me, I had already anticipated some of the logistical challenges associated with organising tumour testing and felt I may be limited with time. However this would be an important area of further research, particularly if an oncology-led model of MGT becomes part of clinical care more widely across the UK. In future, an ethnographic approach could be used to study how oncologists offer and discuss genetic testing, and the form, nature and content of these patient-facing encounters.

I also drew upon several key aspects of the case to specify my research questions. The first key aspect was determining the current state of BRCA1/2 genetic testing for ovarian cancer patients at UCLH by asking, 'How is BRCA1/2 germline testing in ovarian cancer currently used in the gynaecology oncology department?'. Referring to the people of the case, 'How do patients experience mainstreamed BRCA1/2 tumour testing?'. The last research question is descriptive, seeking to answer 'What are the clinical outcomes of BRCA1/2 tumour testing and how do they impact ovarian cancer care?'.

#### 4.4.2 Type of case study design

A key decision in determining the type of case study design is whether the research is best undertaken as a single or multiple case study. In a multiple or collective case study design, the researcher is able to examine the case *within* as well as *across* settings. Thus comparison is sought and a collective case study often looks for differences within a case.

Yin describes two types of single case study designs; a single 'holistic' case design where the case can be examined as a whole, or an 'embedded' design with subunits of analysis [158]. In an embedded single case study design, the subunits provide an opportunity for a more complex or extensive analysis and have the potential to enhance insights into the case. It is crucial that focus remains on the original case, as neglecting this will shift the aims and orientation of the intended research [158]. Other key authors in case study research and referenced in this chapter do not make a distinction between holistic and embedded study designs. However their use of multiple methods (discussed further below) and examining different aspects within a single case are not dissimilar.

Returning to the defined case, the overall context is genetic testing in ovarian cancer while the case is the introduction of mainstreamed BRCA1/2 tumour testing at UCLH. The embedded subunits will be used to explore the research questions around the use of genetic testing, patient experience and clinical outcomes.

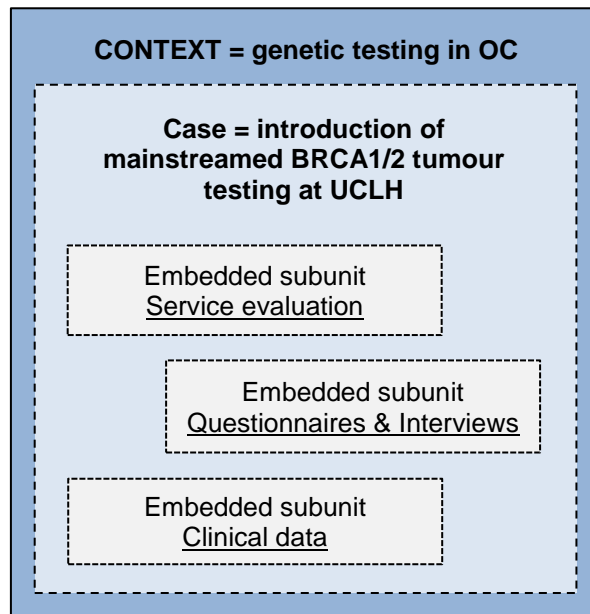


Figure 4.1 Embedded single case study

#### 4.4.3 Multiple methods and data sources

Using different or multiple methods to collect and analyse data is an approach that is encouraged in case study research. As noted by Baxter and Jack a case study approach '...facilitates exploration of a phenomenon within its context using a variety of data sources' (p.544) [156]. In particular, case studies which explore programmes, hierarchies or institutions would find using multiple methods helpful in order to develop a comprehensive understanding of the issue under study. Simons identifies three commonly used qualitative methods which '...facilitate in-depth analysis and understanding' as observations, interviews and document analysis (p.33) [157].

There is a distinction between a case study using multiple methods, sometimes referred to as a mixed methods case study, and mixed methods research. In a case study, although different or multiple methods are used, these methods are integrated and share the same research question [158]. Yin argues that in comparison, mixed methods research uses different methods in separate studies which are then



combined [158]. Some case studies already represent mixed-methods research to some degree. In an embedded single case study, different research methods may be used between analysis of the main case and embedded subunits.

Multiple data sources are typically found in case study research in comparison to other research methodologies such as experiments or surveys [158]. Use of multiple data sources from the same phenomenon is referred to as triangulation, and can be a method of increasing the validity of the research [155, 169]. What is key to using multiple methods and multiple data sources are that the findings are converged and considered together, with all data contributing to the researcher’s understanding of the phenomenon under study.

Ultimately the methods and data sources that are chosen should reflect the research aims and questions. In this case study the overall case was the introduction of mainstreamed BRCA1/2 tumour testing at UCLH. To explore the activity of the case, I organised BRCA1/2 tumour testing for all patients who consented to testing. This gave me first-hand experience of what introducing a new mode of genetic testing entailed, from developing a new testing pathway within the clinical service, to retrieving tumour blocks and reviewing them with the consultant pathologist, and finally packaging tumour blocks to send to the Myriad laboratories in Germany. This is discussed further in Chapter 6.

The embedded subunits address the research questions and are summarised in the table below. Each method and data source will be discussed briefly; a more detailed discussion of the methods, data collection and participants are provided in each chapter.

Table 4.2 Research methods

<b>Research question</b>	<b>Method to answer research question</b>
How is genetic testing currently used for ovarian cancer patients at UCLH?	Service evaluation of existing MGT service
How do patients experience mainstreamed BRCA1/2 TT*?	Quantitative surveys and qualitative interviews
What are the clinical outcomes of BRCA1/2 TT?	Provision of TT, reviewing TT results and medical records

\*TT = tumour testing

#### *4.4.3.1 Service evaluation*

A service evaluation aims to define or judge the current healthcare service of interest, with the purpose of using the outcomes from the evaluation to inform the service and local decision-making [170]. It differs from a clinical audit which is a systematic assessment of resource use as well as the impact of care on patient clinical outcomes and quality of life. A service evaluation can be seen as an in-depth study of the service of interest at a discrete point in time, which is key to a case study approach where the specific context is crucial for shaping our understanding of the case.

To begin my research, it was important to establish the context of my research and address the research question, 'How is genetic testing currently used for ovarian cancer patients at UCLH?'. To answer this I conducted a service evaluation to review the current state of BRCA1/2 genetic testing for ovarian cancer patients at UCLH. BRCA1/2 germline testing for ovarian cancer patients with high grade non-mucinous disease was implemented in 2015 at UCLH using a mainstreamed model of testing delivery. The service evaluation focused on the first year of MGT and sought to define who was being tested, the outcomes of testing and how the results of testing were used by oncologists. This is discussed further in Chapter 5.

#### *4.4.3.2 Questionnaires*

Questionnaires are popular research instruments and are often used in health care based research as a method to generate large amounts of data. Validated questionnaires have been rigorously tested for reliability and validity during the development process [171]. They also allow comparison with published data where the same questionnaire has been used. Although qualitative methods may be used more commonly in a case study approach, quantitative techniques can be of value; Baxter and Jack believe using quantitative survey data can facilitate a 'holistic understanding of the phenomenon being studied' (p.554) [156]. When used to supplement other data sources, questionnaires can provide empirical data for high-quality case studies [172].

To explore the research question relating to how patients experience mainstreamed BRCA1/2 tumour testing, I decided to use both quantitative and qualitative methods. The aim was to collect quantitative data from each participant who consented to BRCA1/2 tumour testing. Questionnaires were completed by patients at three timepoints along the tumour testing pathway from the offer of testing to receiving results. Validated measures across topics such as quality of life, attitudes and

knowledge towards genetic testing, decision-making and psychological distress were used. Choice of measures and results of questionnaires are discussed further in Chapter 7.

#### *4.4.3.3 Interviews*

Qualitative methods, in particular interviews, are ideal for new or poorly understood topics, and when we wish to describe and understand experiences, ideas, beliefs and values from the perspective of the local population [173]. Interviews are one of the most common methods in qualitative research and have been a key element of case study research. Interviews can document the interviewee's perspective on a topic, engage in dialogue with the interviewee, explore a topic in greater depth, and provide important insights into the phenomenon of interest [157].

There are acknowledged limitations with interview data, such as bias from both the researcher in the articulation of questions, and response bias from interviewees [158]. There may be inaccuracies in interviewee stories due to poor recall particularly if the interview is retrospective in nature.

In this research, interviews were a significant component of exploring how patients experience BRCA1/2 tumour testing. The interviews would overlap on some topics included in the questionnaires to develop a deeper understanding of the issues, as well as acting as a 'check' of the findings observed so far while allowing for new, emergent data.

A number of patients who underwent BRCA1/2 tumour testing were interviewed after receiving their results. Development of the interview schedule, participant details and findings are discussed further in Chapter 8.

#### *4.4.3.4 Clinical data*

To collect data on the outcomes of genetic testing, testing reports for all patients who had undergone BRCA1/2 tumour testing, and in some case germline testing, via MGT were reviewed. Relevant clinical data such as diagnosis, date of diagnosis, disease histology and treatment history, was collected from hospital medical notes. This is discussed further in Chapter 6.

## 4.5 Philosophical underpinnings

Reflecting on the philosophical paradigm which underpins research is an important part of developing a robust and rigorous study. In case study research, the way in which the case is approached and the research designed will be influenced by the philosophical position of the researcher. As Mills et al wrote, "To ensure a strong research design, researchers must choose a research paradigm that is congruent with their beliefs about the nature of reality' (p.2) [174].

Fossey et al believe that the philosophical paradigm is '...a system of ideas, or world view, used by a community of researchers to generate knowledge. It is a set of assumptions, research strategies and criteria for rigour that are shared, even taken for granted by that community" (p.718) [175].

This system of ideas includes four key components: ontology, epistemology, methodology and methods [176]. Simply put, ontology is the study of reality or the fundamental nature of existence where an ontological question might ask 'What is there?'. The role of ontology is to help researchers consider the certainty of nature and the existence of objects or subjects that we research. Epistemology is the study of knowledge, asking questions such as, 'What do you know?,' and, 'How do you know it?'. An epistemological standpoint influences how we discover knowledge about that reality. Methodology is the strategy behind which methods are chosen and why, and asks, 'How can we find out?'. Methodology will determine why, what, from where, when and how data is collected and analysed [176]. In turn the methods are the specific procedures to collect and analyse the data. The paradigms can use different methods to explore their research questions, using both or either quantitative or qualitative data.

Table 4.3 below outlines different research paradigms and their corresponding ontologies and epistemologies. This is by no means an exhaustive list, but a summary of the paradigms that are most commonly found within a case study methodology. Although there are clear distinctions in assumptions of reality, truth and knowledge, there are also shared features between paradigms, with overlapping ontologies and epistemologies. By reviewing the various paradigms and their underlying philosophies, one is able to draw upon more than one paradigm or be informed by various epistemologies; Crowe believes this flexibility is particularly useful when conducting health services research [155].

Table 4.3 Research paradigms, ontologies, epistemologies and methodologies

<b>Paradigm</b>	<b>Ontology</b>	<b>Epistemology</b>	<b>Methodology</b>
<u>Positivism</u> <ul style="list-style-type: none"> <li>• Explain relationships, identify cause and effect</li> <li>• Seeks verifiable evidence</li> <li>• Basis for prediction and generalisation</li> <li>• Deductive approach</li> <li>• Impartial and value neutral</li> <li>• Focus on facts</li> <li>• Does not allow subjective opinion of researcher</li> </ul>	<u>Realism</u> <ul style="list-style-type: none"> <li>• Objective</li> <li>• Objects exist independent of the knowledge of their existence</li> <li>• Reality exists independent of the researcher</li> <li>• Truths are absolute and do not change based on culture or history</li> </ul>	<u>Objectivism</u> <ul style="list-style-type: none"> <li>• Impartial</li> <li>• Discovering absolute knowledge about an objective reality</li> <li>• Researcher and phenomena are independent entities</li> <li>• Removes all contextual factors</li> <li>• Phenomena is independent of human subjectivity and/or influence</li> <li>• Knowledge is discovered through impartial observation</li> </ul>	<ul style="list-style-type: none"> <li>• Empirical studies, random samples, controlled variables and control groups</li> <li>• Large samples</li> </ul>
<u>Post-positivism</u> <ul style="list-style-type: none"> <li>• Seeks to understand causal relationships</li> <li>• Unlike positivism, participants' perspectives are sought</li> <li>• Knowledge is tentative and fallible</li> <li>• Knowledge can be shaped by contextual influences</li> <li>• Knowledge is not confined to what can be only be observed</li> </ul>	<u>Critical-realism</u> <ul style="list-style-type: none"> <li>• Contemporary uptake of realism</li> <li>• Reality is interpreted through social conditioning</li> <li>• Knowledge is achieved by observation and reasoning</li> </ul>	<u>Objectivism</u>	<ul style="list-style-type: none"> <li>• Experimentation, correlational studies</li> </ul>

<p><u>Interpretivism</u></p> <ul style="list-style-type: none"> <li>• Multiple forms of reality, meanings and understanding</li> <li>• Reality is interpretations by individuals</li> <li>• Knowledge is subjective and relative to circumstances</li> <li>• Context affects experiences and meaning</li> <li>• Role of researcher is critical – beliefs and feelings guide research and influence interpretation</li> <li>• Focus on recognising and narrating the meaning of human experiences and actions</li> </ul>	<p><u>Relativism</u></p> <ul style="list-style-type: none"> <li>• Reality cannot be separated from the subjective experience</li> <li>• Data and observations influenced by the observer</li> <li>• Multiple interpretations of experience lead to multiple realities</li> <li>• Aim is to understand the subjective experience of reality and multiple truths</li> <li>• Belief that reality is a finite subjective</li> </ul>	<p><u>Subjectivism</u></p> <ul style="list-style-type: none"> <li>• Knowledge filtered through lenses of ethnicity, social class, language</li> <li>• Value laden</li> <li>• Observations influenced by observer, and vice versa</li> <li>• Aims to understand and be more sensitive to ethical and moral issues</li> </ul>	<ul style="list-style-type: none"> <li>• Multiple methods to establish different views</li> <li>• Small samples researched in depth or over time</li> <li>• Qualitative</li> <li>• Case studies, phenomenology</li> </ul>
<p><u>Constructionism</u></p> <ul style="list-style-type: none"> <li>• Knowledge is constructed</li> <li>• Truth is relative and dependent on perspective</li> <li>• Close collaboration between researcher and participant – meaning is created</li> <li>• Participant stories inform researcher understanding</li> <li>• Researcher is separate but not truly objective from phenomena under observation</li> </ul>	<p><u>Critical realism</u></p>	<p><u>Subjectivism</u></p>	<ul style="list-style-type: none"> <li>• Qualitative</li> <li>• Interviews, document reviews, observations, case studies</li> </ul>

Embracing the flexibility extolled by Crowe, there is more than one paradigm which has underpinned this work. Overall, the interpretivist paradigm best fits with my philosophical beliefs; that knowledge is relative and subjective and there are multiple meanings and ways of knowing. With a relativist ontology I accept that there is no single reality. As Corbin and Strauss wrote, ‘...I realise there is no one ‘reality’ out there waiting to be discovered’ (p.10) [177]. Acknowledging and recognising my influence on the research I conduct and analyse is key to a subjective epistemology. Again, Corbin and Strauss articulate this, as they believe it is not possible to ‘...separate who I am as a person from the research and analysis that I do’ (p.11). There are also constructivist elements to my research, as I recognise that the collaboration between researcher and participant is where meaning is generated; research is a joint product of participants and the researcher. Furthermore reality can be socially constructed and dependent on the individual perspective. Meanings are generated within a particular social context, and it is likely that the same work undertaken by a different researcher will produce different knowledge and conclusions. By using quantitative methods in the form of questionnaires and validated measures, where the research is seen as confirmatory rather than exploratory, there are elements of a post-positivist paradigm. Although this data is considered collectively, I am aware of the individual and subjective way which the data was completed by participants and collected by myself.

#### **4.6 Analysis**

There are very different approaches to case study analysis which may be dependent on the aims and design of the research, but also on the researcher. Key authors in the case study field describe different analytic techniques, for example Yin describes five specific techniques: pattern matching, explanation building, time-series analysis, logic models, and cross-case synthesis [158], while Stake uses categorical aggregation and direct interpretation [162] and Crowe refers to the Framework approach [155]. Baxter and Jack emphasised the importance of reviewing various analysis types to determine which approach is not only appropriate for your research design, but that you feel most comfortable with using [156]. Regardless of the analysis chosen, clearly describing the analysis process and rationale is important for rigorous research.

My research data includes clinical data such as genetic testing reports and medical records, quantitative data from questionnaires, and qualitative data from interviews. Using multiple and diverse methods in this research presented a challenge to

developing a cohesive analysis plan. Applying one specific analytic technique to the whole data set felt incongruous, as many of these techniques did not offer the flexibility to include quantitative data. Furthermore some of the techniques aim to be explanatory, looking for causal effects in the data. In contrast, this research is explorative and descriptive, and though there are specific research questions articulated, they act to focus the research into a discrete and comprehensible component.

Thus what I found most helpful and methodologically sound, was to analyse my quantitative, qualitative and clinical data separately, whilst being clear about the analysis methods chosen and the procedures I followed (discussed further in each chapter). Simons' position is that analysis cannot be discussed without also discussing interpretation; '...interpretation is the key process for making sense of what has been learned' (p. 118) [157]. This echoes the interpretivist paradigm guiding my research, and it is with this approach in mind that I draw together the findings from each embedded subunit together in the final chapter of my thesis.

## **4.7 Ethical processes**

### **4.7.1 Formal ethics procedures**

A service evaluation does not require Research Ethics Committee (REC) or Health Research Authority (HRA) approval. To ensure I approached this aspect of my research rigorously I felt it was important that the aims, data collection plan and intended outcomes of the service evaluation were reviewed by a relevant governance body. The UCLH Applied Health Research in Cancer Governance Group reviewed and gave approval for the service evaluation to be conducted.

For the patient experience component of this research, ethical approval was granted by the Hampstead REC and HRA (REC reference: 16/LO/1226, IRAS: 199605). This included permissions to collect relevant clinical data from participants.

Both approval documents can be found in the Appendix.

### **4.7.2 Conducting research ethically**

Formal ethics procedures, as noted in the section above, help to ensure that the research is conducted in an ethical manner in terms of the study design, data collection, analyses and published outcomes of research. However, as Simon notes, 'It is not possible to govern ethical behaviour through forms and procedures' (p. 100)



[157]. Reflecting on the nature of ethics and what it means to conduct research ethically, Simons' definition resonated with me: '[Ethics] means establishing throughout the research process a relationship with participants that respects human dignity and integrity and in which people can trust' (p. 96). This is particularly fitting for case study research, which can often involve prolonged periods observing and interviewing participants.

Whilst my research did not involve formal observations, in the process of conducting the service evaluation, recruiting ovarian cancer patients, organising BRCA1/2 tumour testing and reviewing clinical data, I spent 12 months embedded within the UCLH gynaecological oncology team. Inevitably this time spent interacting with patients, participants, clinicians and other researchers raised some ethical and reflexive issues around expectations of my role, of establishing and maintaining trust and researcher-participant relationships. I discuss and reflect on these experiences in the relevant chapters.

#### **4.8 Rigour and research quality**

Although 'rigour' is often referred to in mainstream science and research following a positivist paradigm, it is not a term that is typically used within case study research; neither Simons [157], Stake [162] nor Yin [158] explicitly refer to rigour within their books. However the authors do discuss two key aspects of rigour, validity and reliability, as criteria for judging the quality of the research design. Yin believes that internal validity, the extent to which a study can rule out or make unlikely alternate explanations of the results, should not be used for descriptive or exploratory studies [158]. Simons adds that other forms of validity, such as construct validity and reliability, are not applicable to qualitative case study research [157].

These discrepancies highlight the struggle within the qualitative research domain about how to define and determine 'rigour'. Guba and Lincoln developed alternate criteria to measure rigour and judge the quality of research – striving towards an overarching goal of trustworthiness through credibility, transferability, dependability, and confirmability [as cited in 171]. More recently Morse evokes a return to the mainstream terminology of rigour, validity, reliability and generalisability [178]. In her paper she critiques the strategies currently used to achieve rigour, accepting some strategies with caveats, while actively suggesting to avoid others. Some strategies appropriate and relevant to use for achieving validity and reliability in qualitative research are suggested below, although Morse remains critical about most strategies:

- Prolonged engagement, persistent observation, and thick, rich description
- Interrater reliability, negative case analysis
- Peer review or debriefing
- Clarifying researcher bias
- Triangulation.

In the development of an 8 point quality assessment for qualitative research, Tracy lists four questions as a guide to achieving rigour [179]:

- Are there enough data to support significant claims?
- Did the researcher spend enough time to gather interesting and significant data?
- Is the context or sample appropriate given the goals of the study?
- Did the researcher use appropriate procedures in terms of field note style, interviewing practices, and analysis procedures?

Considering the suggestions provided by Morse and Tracy to achieving rigour, I found neither to be sufficiently comprehensive to encompass my research methods and this case study approach. Instead I found the guidance on rigour from Liamputtong and Ezzy to be informative, logical and inclusive. The authors believe that validity and reliability are important issues to be considered in research but need to be conceptualised differently for a qualitative framework [173]. They describe six criteria to ensure rigorous research which I chose to employ in my research, shown in the table below.

Table 4.4 Criteria for conducting rigorous research

<b>Criteria</b>	<b>Description</b>
<b>Theoretical rigour</b>	Sound theoretical/conceptual argument and appropriate choice of methods
<b>Methodological or procedural rigour</b>	Explicit account of research process and analysis
<b>Interpretative rigour</b>	Clear demonstration and justification of interpretation
<b>Triangulation</b>	Use of multiple methods and/or data sources
<b>Evaluative rigour – ethics and politics</b>	Addresses ethical procedures and ethical conduct
<b>Rigorous reflexivity</b>	Examines role of the researcher

Not all aspects of rigorous research are achieved during the design phase, in fact Morse believes that rigour should be achieved during the process of data collection and analysis [178]. However, these criteria provide an important basis from which to conduct rigorous research and therefore are helpful to consider at this point. In this thesis I have tried to address each of the six criteria. In this chapter have described the philosophical paradigm that guides this research to reflect theoretical rigour. To address methodological rigour, in the following chapters the research process and analysis are detailed for each embedded subunit. By using different methods, in this case a service evaluation, clinical data, qualitative interviews and quantitative questionnaires, this will hopefully lead to a comprehensive understanding of the case under study. Triangulation also becomes key in the final chapter as I draw together the different methods and data sources in the subunits to present a cohesive account of the case in its context. The ethical procedures have been described earlier in this chapter while I address ethical conduct later in Chapter 6.

#### **4.9 Reflexivity**

I have purposefully chosen to present my research in first person to reflect reflexivity. As an instrument of the research, writing in the first person acknowledges my role in the research and the impact this has on the participants, analysis process and dissemination of findings. Reflecting the interpretivist paradigm, Webb believes that writing in first person is acceptable when the researcher has played an important role in shaping the data or ideas presented [180].

Reflexive research requires an awareness of the researcher's contribution to the research process and how this influences and informs the research. As Rice and Ezzy wrote: 'Reflexive research acknowledges that the researcher is part and parcel of the setting, context and culture they are trying to understand and analyse. That is to say, the researcher is the instrument of the research.' (p. 41) [173].

Simon emphasises the importance of examining the 'self' in case study research, as 'You are the main instrument of data gathering; it is you who observes, interviews, interacts with people in the field' (p.81) [157]. Declaring values, preferences and world view is an acknowledgement of these influences on your actions, decisions and interpretations of the research.

I present some details about myself that may have had an impact on how I conducted and analysed the research. These characteristics may have influenced the way in which the participants responded and engaged with me in the research process. As

Webb states, participants ‘...make judgements about researchers’ backgrounds, motives, intentions, beliefs and preferences and respond as they judge appropriate’ (p. 749) [180].

In my professional background, I have been a researcher in psychosocial aspects of cancer genetics for nearly ten years. I am also a qualified genetic counsellor, having completed my Masters in 2009 from the University of Melbourne. These days I am much more likely to describe myself as a researcher, having gone straight from my Masters into a research role, than a genetic counsellor. However the influence of my training and experiences during this time means I remain at heart a genetic counsellor and this is the lens through which I view, interpret, communicate and conduct my research.

In the introduction chapter I touched on some of the key components of genetic counselling, such as non-directiveness, informed decision-making and communication skills. These components influenced not only my approach to undertaking my research, participant recruitment and engaging with patients, but also my expectations of what the genetic testing process and experience ‘should’ be. MGT is a significant departure from the traditional format of genetic counselling and testing which I’ve highlighted in the first two chapters of this thesis, where my experience and understanding of testing is drawn from. Throughout this thesis where relevant I acknowledge the influence of my preconceptions on my research conduct and interpretation of the data.

## **Chapter 5 Service evaluation of mainstreamed BRCA1/2 testing in ovarian cancer at UCLH**

### **5.1 Introduction**

Chapter 1 and 2 of this thesis have provided both an introduction to and a more detailed description of MGT. To summarise, there have been a number of factors contributing to a move towards providing BRCA1/2 genetic testing to more ovarian cancer patients, including:

- Recognition that family history is no longer the 'gold standard' for determining eligibility for genetic testing
- Prevalence of germline BRCA1/2 mutations in ovarian cancer patients is high
- Changes to national guidelines (NICE, Guideline CG164) recommending lowering the mutation detection threshold to 10%
- The first PARP-inhibitor, olaparib, licensed for use in the UK.

A mainstreamed model allows for a greater number of women with ovarian cancer to access BRCA1/2 germline testing, with the intention of identifying more patients who are able to access targeted therapies and unaffected relatives who may benefit from predictive testing and/or risk reducing interventions. This approach is becoming increasingly adopted by gynaecological oncology services in the UK; several centres across the UK have implemented systematic genetic testing for women with high grade non-mucinous or serous ovarian cancer, either via oncology or clinical genetics.

This chapter presents the first embedded subunit of research and data collection of this thesis and was a key component of the case study, describing the context into which BRCA1/2 tumour testing would be introduced. It provided an opportunity to not only develop an understanding of how the MGT works as a clinical service, but how genetic testing, both the service and the outcomes, are used by clinicians. It was also an opportunity to familiarise myself with the gynaecological oncology department which was to be a key part of my remaining PhD research.

### **5.2 MGT service at UCLH**

At University College London Hospital (UCLH), MGT was implemented as a clinical service in the gynaecological oncology department in April 2015, and is ongoing. At

the time of implementation, there was no core funding for systematic germline BRCA1/2 testing for ovarian cancer patients. I was involved in the development of a funding proposal to the UCLH Charity to provide BRCA1/2 germline testing to all UCLH ovarian cancer patients with a diagnosis of high grade non-mucinous disease. The UCLH Charity initially funded BRCA1/2 germline testing for 12 months which enabled the MGT service to begin.

UCLH adopted an oncology-led approach to MGT; information and consent for genetic testing as well as return of results was managed by the patient's oncologist during her standard outpatient appointments. Oncologists and other relevant staff such as clinical nurse specialists and registrars were provided with training on ordering, discussing and consenting for germline BRCA1/2 testing by the Royal Marsden Mainstreaming Cancer Genetics programme [181]. Oncologists requested germline testing using specialised test request forms, with blood samples for testing taken from the Macmillan Cancer Centre phlebotomy service and delivered to NE Thames Regional Genetics Laboratories, GOSH, where all BRCA1 and BRCA2 germline testing was undertaken. Eligibility for MGT was a diagnosis of high grade non-mucinous ovarian cancer, with no age or family history restrictions. Testing was offered both prospectively to newly diagnosed patients, and retrospectively to patients who may have been many months and even years from diagnosis but still under follow-up at UCLH. Women who were identified as carrying a BRCA1/2 mutation or VUS were referred to their local clinical genetics service, typically North East or North West Thames Regional Genetics Service, for genetic counselling.

### **5.3 Aims**

As the implementation of MGT was a new approach to providing BRCA1/2 germline testing to women with ovarian cancer at UCLH, a service evaluation was undertaken after 12 months. A service evaluation can define a current service, as well inform the development or improvement of a service.

The primary aim of this service evaluation was to describe the patient cohort at UCLH who had undergone MGT and to determine the prevalence of BRCA1/2 mutations. Secondary aims included evaluating: procedural outcomes such as timing of testing, and clinical outcomes such as changes to treatment and referral to clinical genetics.

Results from the evaluation were fed back to the gynaecological oncology department, as well as the hospital funding body.

## **5.4 Methods**

### *5.4.1.1 Governance approval*

The UCLH Applied Health Research in Cancer Governance Group granted approval for this service evaluation in January 2017. This document can be found in the Appendix.

### *5.4.1.2 Germline testing results*

The first step of this service evaluation was to determine which patients had been tested in the first 12 months of MGT.

There was no separate database for recording genetic testing activity for UCLH ovarian cancer patients who had testing via MGT. Instead, once testing was complete, genetic testing reports from NE Thames Regional Genetics Service were returned to the requesting oncologist at UCLH by post, and subsequently scanned into the patient's online clinical files in the Clinical Data Repository (CDR). Not all reports were clearly labelled as genetic testing reports which made identification challenging. Some oncologists would note the patient's BRCA1/2 mutation status in their clinic letter headers which were duplicated and then updated after each clinic, however this was also practiced inconsistently.

NE Thames Regional Genetics Service provided a list of all UCLH patients who had BRCA1/2 germline testing via MGT from February 2015 to April 2016. Using this as a reference, clinical files on CDR were reviewed for all patients who had been tested via MGT. Information on current age, date of diagnosis, diagnosis, pathology, genetic testing result and treatment was collected from CDR. The two local clinical genetics services were contacted to review referral patterns and family history data of patients who were identified as BRCA1/2 mutation positive or with a VUS.

## **5.5 Results**

### 5.5.1 Patient characteristics

122 women with ovarian cancer had BRCA1/2 germline testing via MGT between February 2015 and April 2016. Most patients (100/122, 82%) had high grade serous cancer, with stage III or IV disease (95/122, 78%). The median age at diagnosis was 62 years (range 28-88), with 68 (56%) aged younger than 60 years at diagnosis. Patient characteristics are presented in Table 5.1 below.

Table 5.1 Summary of patient characteristics

	<b>BRCA1/2 mutation (n=18)</b>	<b>BRCA1/2 VUS (n=9)</b>	<b>No mutation (n=95)</b>
<b>Age (years), median (range)</b>	58 (42-74)	66 (55-70)	62 (28-88)
<b>BRCA1 mx, n</b>	10	3	0
<b>BRCA2 mx, n</b>	8	6	0
<b>Pathology, n</b>			
Clear cell	0	0	5
Carcinosarcoma	1	0	4
Endometrioid	0	0	9
High grade serous	17	9	74
Mixed	0	0	2
Other	0	0	1
<b>Stage, n</b>			
I	0	1	14
II	1	1	9
III	10	4	45
IV	7	2	27
Not classified	0	1	0

### 5.5.2 BRCA1/2 mutation carriers

18 pathogenic mutations were identified via MGT: 10 BRCA1 and 8 BRCA2. Nine VUS were also identified. Known Ashkenazi Jewish/Polish founder mutations comprised 11% of pathogenic mutations (2/18).

The median age of BRCA1/2 mutation carriers was 57 years (range 42-74 years), compared to 66 and 62 years in the VUS and no mutation groups, respectively. There was no significant difference in age at diagnosis between women with a BRCA1/2 mutation and those without (Mann Whitney U test  $U=1125$ ,  $z=1.369$ ,  $p=.171$ ). BRCA1 mutation carriers were significantly younger at diagnosis than BRCA2 carriers ( $t(16)=2.84$ , 95% CI (18.4, 2.7),  $p=0.012$ ). Almost all BRCA1/2 mutation carriers (17/18, 94%) had high grade serous histology; one patient had a carcinosarcoma. Similarly, almost all were diagnosed with stage III or IV disease (17/18, 94%).



Overall, the prevalence of BRCA1/2 mutations in this cohort was 14.8% (18/122). A large cohort of epithelial ovarian cancer patients reported a similar prevalence rate of 14.1% [12]. Data from three UK sites offering systematic BRCA1/2 testing to ovarian cancer patients reported a prevalence of 7.8% in East Anglia [74], 15.9% in South West London [73] and 12.9% in Scotland [75] (shown in Table 5.2 below).

Table 5.2 Prevalence of BRCA1/2 mutations from systematic genetic testing in the UK

Site	UCLH	East Anglia	Royal Marsden	Scotland*
<b>Timeframe</b>	14 months	12 months	17 months	18 months
<b>Patient group</b>	High-grade non-mucinous EOC	High-grade serous or endometrioid EOC	Non-mucinous OC	Non-mucinous EOC
<b>Context</b>	Clinical service	Research	Research	Clinical service
<b>MGT strategy</b>	Testing offered and organised by treating oncologist; results disclosed by oncologist	Recruited by clinical team; testing offered and organised by research genetic counsellor; normal results disclosed by clinical team, mx+ve results referral to clinical genetics	Testing offered and organised by approved cancer team member, results sent by letter to patient from genetics team	East Scotland: Testing offered and organised by oncologist; in Aberdeen also telephone counselling from clinical genetics West Scotland: patients referred to clinical genetics
<b>Patients tested</b>	122	232	207	394
<b>BRCA1 mx</b>	10	12	17	25**
<b>BRCA2 mx</b>	8	6	16	27**
<b>VUS</b>	9	15	Not reported	30
<b>Overall BRCA mx prevalence</b>	14.8%	7.8%	15.9%	12.9%

\*Reporting data from the 'prevalent population' and 'new criteria' groups

\*\*One patient had mutations in both BRCA1 and BRCA2

### 5.5.3 Testing process and timing

All BRCA1/2 germline testing by NGS and multiplex ligation-dependent probe amplification (MLPA) was performed by NE Thames Regional Genetics Service Laboratories.

The median time from request receipt to results delivered was 26 working days (range 14-48 days). On average, 8 BRCA1/2 germline tests were performed each month. The number of tests and mutations identified per month is highlighted in the figure below.

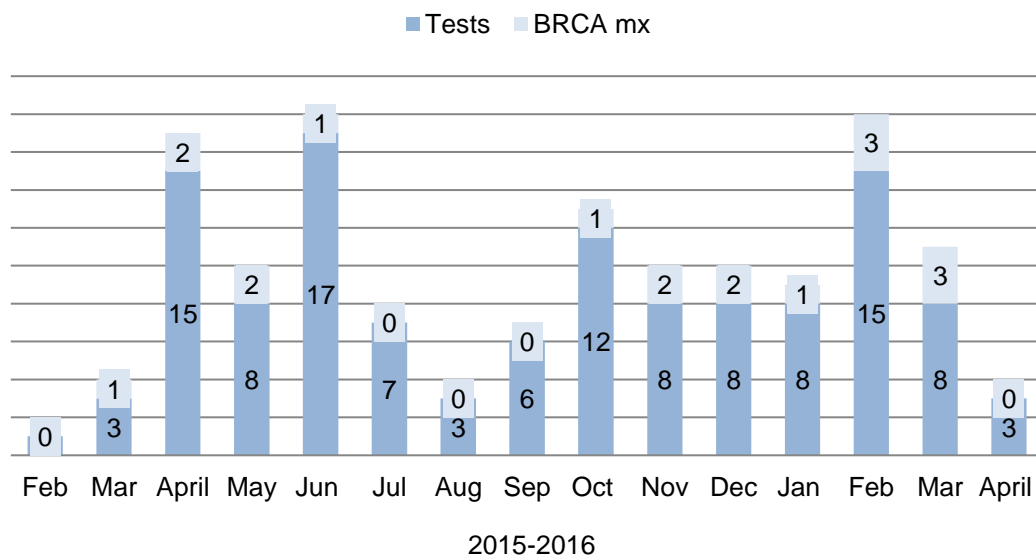


Figure 5.1 Mutation detection rate per month

As MGT was not restricted to newly diagnosed patients, less than half of patients had been diagnosed within the 12 months prior to testing (56/122, 46%). Within the newly diagnosed group, 19 patients were offered BRCA1/2 testing within one month of their diagnosis (35%).

Amongst BRCA1/2 mutation carriers, ten patients (56%) had been diagnosed within the last 12 months, six of whom were tested shortly after diagnosis (within one month). Eight patients had been diagnosed between 21 to 104 months prior to BRCA1/2 testing.

#### 5.5.4 Clinical genetics and family history

At the time of this evaluation, from 18 BRCA1/2 mutation carriers, four patients (22%) had not been referred to their local clinical genetics service for genetic counselling. Two of these patients were subsequently referred, 98 and 127 working days from date of MGT results. Of the remaining patients, most were referred promptly between 12 and 43 working days after their MGT results were reported. Only two patients (22%) who received a VUS result were referred to clinical genetics.

Due to referral delays to clinical genetics or because referred patients had yet to attend their genetic counselling appointment, family history data was only available for 13 BRCA1/2 mutation carriers. Using the Manchester scoring criteria, nine patients had some or a strong family history; four patients had no significant family history and would not have met previous guidelines for BRCA1/2 genetic testing (i.e. Manchester score <15) [182]; this is shown in Table 5.4 below. For predictive testing amongst family members of BRCA1/2 carriers, 15 family members had been referred to clinical genetics services with 11 undergoing testing.

Table 5.3 Family history and testing eligibility by Manchester score

<b>Family history</b>	<b>MGT result</b>	<b>Notes</b>	<b>Manchester score &gt;15</b>
Only patient affected	BRCA1	Small pedigree	No (13)
Only patient affected	BRCA2	Patient BC and OC	Yes
Only patient affected	BRCA2		No (10)
Only patient affected	BRCA1		No (13)
Sister cancer of unknown primary, daughter bowel cancer 33	BRCA1	Patient BC and OC	Yes
Daughter breast cancer 44	BRCA2		Yes
Mother cervical and pancreatic cancer 70s	BRCA2		No (14)
Maternal grandmother breast cancer 40s, paternal uncle prostate cancer 70s, paternal aunt breast cancer 31	BRCA1	AJ founder mutation	Yes
Mother ovarian cancer, maternal grandmother ovarian cancer	BRCA1		Yes
Daughter breast cancer 41, mother breast cancer 40s, brother colorectal cancer 60s	BRCA2		Yes
Mother ovarian cancer, sister cervical cancer 30s, maternal aunt ovarian/cervical cancer	BRCA1		Yes
Father lung cancer 60s, brother oesophageal cancer, sister breast cancer 70s, maternal cousin breast cancer 65	BRCA2		Yes
Sister cervical cancer 25, mother breast cancer 57, maternal half-sister cervical cancer 33, maternal aunt gastric cancer 33, maternal uncle colorectal cancer 53, maternal uncle bladder cancer 38, maternal first cousin breast cancer 42, paternal grandmother ovarian cancer 61	BRCA1		Yes

#### 5.5.5 Clinical management BRCA1/2 mutation carriers

Clinical outcomes were reviewed for the 18 patients identified as carrying pathogenic BRCA1/2 mutations. For 67% (11/18) there was no change to current treatment; four patients were undergoing first line chemotherapy, three patients had completed first line chemotherapy and were on maintenance treatment (bevacizumab), and four patients were undergoing or had completed second line chemotherapy treatment.

Six patients (33%) had been able to access PARP-inhibitors due to their mutation carrier status. Four patients were taking olaparib, one patient had accessed rucaparib via a Clovis Oncology compassionate use programme and one patient was participating in an olaparib clinical trial. When family history data was reviewed, data was available for five of these patients; three did not meet previous criteria for BRCA1/2 genetic testing.

One patient was deceased eight months after receiving MGT results without any change to her treatment plan.

#### 5.5.6 Germline vs tumour testing

Within this cohort of patients who had mainstreamed BRCA1/2 germline testing, two patients who had received germline negative results from MGT were later found to carry somatic BRCA1/2 mutations on tumour testing as part of clinical trial participation.

### **5.6 Discussion**

MGT at UCLH provided BRCA1/2 germline testing to 122 ovarian cancer patients, with 18 women identified as carrying a BRCA1 or BRCA2 mutation. This mutation prevalence of 14.8% is similar to international published data [12]. There is now data available on BRCA1/2 mutation prevalence in other UK ovarian cancer cohorts, as shown in Table 5.2. The variation in prevalence between the four UK sites may be due to a number of factors. The lower detection rate in East Anglia of 7.8% may be a result of prospective testing only newly diagnosed patients and a lack of ethnic variation; in particular no Ashkenazi/Polish founder mutations were identified [74]. The higher detection rate of 15.9% at the Royal Marsden may be due to a population enriched for younger patients, as an age cut-off of less than 65 years was used for the first 9/16 months of MGT [73]. The higher detection rates at UCLH, Scotland and the Royal Marsden may also be due to the retrospective nature of testing; some

patients offered MGT were several years from diagnosis, which could indicate selection based on treatment response and/or improved survival. Rust comments that in a truly unselected ovarian cancer population, BRCA1/2 mutation prevalence is likely to be slightly lower than rates currently reported in the literature [75]. There were also differences in how systematic BRCA1/2 testing was delivered across these four sites. East Anglia and the Royal Marsden initiated testing as research studies, while Scotland and UCLH implemented MGT as a clinical service directly. UCLH and the east of Scotland used an entirely oncology-led model where MGT is offered, organised and results disclosed by the patient's treating oncology.

Within MGT at UCLH, there was variation as to the point at which patients were offered BRCA1/2 testing, ranging from eight years after to around the time of diagnosis. Currently there is no consensus for the optimal time at which MGT should be offered to women with ovarian cancer for either patient outcomes or clinical decisions. One approach to MGT is to systematically offer BRCA1/2 testing to all newly diagnosed patients. However retrospective testing of all eligible patients at UCLH, one of whom had been diagnosed eight years previously, identified 44% of BRCA1/2 mutation carriers. Some oncology clinicians at UCLH chose to offer MGT early in the treatment pathway i.e. during first line chemotherapy. Research has indicated that women diagnosed with breast or ovarian cancer less than one year prior to receiving BRCA1/2 mutation positive genetic test results had poorer outcomes for anxiety and cancer-related distress [120]. However breast cancer patients approached for genetic testing and counselling at diagnosis had no adverse psychosocial outcomes in both the short- and long-term [122, 139].

At UCLH, MGT was not recorded systematically therefore it was impossible to determine which patients had been offered but declined genetic testing. Both the Marsden and Scottish testing programmes had very high rates of uptake, at 100% and 98% respectively [73, 75]. Uptake was slightly lower in East Anglia, however genetic testing was offered as part of a research study which may have discouraged some patients. Nevertheless, these rates are significantly higher than genetic testing uptake rates in unaffected individuals, where interest in testing is generally high but not necessarily reflected in testing uptake. For example, in families with a known BRCA1/2 mutation, interest in undergoing genetic testing was high although actual uptake of testing was low, despite the existence of options to manage or reduce cancer risks in individuals identified as carriers [183]. From 14 studies examining real breast cancer genetic testing decisions, the average uptake rate was 59%, with rates ranging from 25% to 96% across these studies [184]. However, given the experiences

at the Marsden and Scotland, it is likely that overall the uptake of MGT would also have been high at UCLH.

After learning their BRCA1/2 mutation status from MGT between six and 14 months earlier, six patients had been able to access a PARP-inhibitor either as part of NHS care, managed access programme or clinical trial. There was no change to current treatment for eleven patients. The lack of direct impact from MGT on clinical management may be attributed to the timing of testing. As olaparib is currently available only for relapsed ovarian cancer after three or more lines of treatment, patients who are still on first or second line chemotherapy would not be eligible to receive this treatment.

Knowledge of BRCA1/2 status can provide important cancer risk information for patients' relatives. Patients who are identified as carrying a BRCA1/2 mutation or VUS should be referred to their local clinical genetics service to discuss implications of their test results including communicating results with at-risk family members. First degree blood relatives are at 50% risk of carrying the same mutation. Predictive testing provides an opportunity to identify unaffected BRCA1/2 mutation carriers who can consider breast and ovarian cancer risk-reducing interventions. A lack of consistent referral to clinical genetics services was highlighted by this evaluation; 22% (4/18) of BRCA1/2 mutation carriers and 78% (7/9) who received VUS results were not referred. It is unclear how VUS results are used for ovarian cancer patient clinical management or how they are interpreted by oncologists. The inherent ambiguity of a VUS result and complex interpretation are also challenges for genetics and other areas of clinical medicine [185, 186]. However it is important for women with a VUS to be under the care of a clinical genetics service to discuss implications of such results for themselves and family members. Segregation analysis of the variant amongst cancer affected family members may be undertaken, and VUS results may also be reclassified as either deleterious or benign with ongoing review.

Within this cohort of patients who had MGT, two patients who received germline negative results were later identified to carry somatic BRCA1/2 mutations during clinical trial participation. Identifying somatic mutations in patients who are germline negative is important as these results may influence treatment decisions; these patients would be eligible for olaparib or other PARP-inhibitor clinical trials. It is estimated 5-7% of women with high grade serous ovarian cancer will carry a somatic BRCA1/2 mutation [86], which calls for greater access to tumour testing for patients.



BRCA1 and BRCA2 have been the high penetrance genes primarily associated with hereditary breast and ovarian cancer. Research continues to identify other genetic mutations which contribute to epithelial ovarian cancer. It is recognised that moderate susceptibility genes RAD51C, RAD51D and BRIP1 could be offered alongside BRCA1/2 for clinical genetic testing [187, 188]. NE Thames Regional Genetics Service is now able to simultaneously test multiple genes using a 'mini gene panel' for BRCA1, BRCA2, RAD51C, RAD51D and BRIP1. How these results will influence ovarian cancer patient management is an area for future inquiry.

## **5.7 Summary**

This service evaluation begins to inform our understanding of how BRCA1/2 genetic testing in ovarian cancer is being used by oncologists at UCLH, and what role it plays in expanding treatment options for patients. It appears MGT is a feasible process of providing BRCA1/2 germline testing to ovarian cancer patients although the lack of systematic recording of offers and acceptance of MGT makes it not possible to comment on uptake rates. Greater clarity of how oncologists review and use VUS results is needed, as is the improvement of referral pathways to clinical genetics for these patients. The impact of BRCA1/2 testing on clinical management may be delayed depending at which point in the treatment pathway the patient has had testing.

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## **Chapter 6 Implementation of mainstreamed BRCA1/2 tumour testing and clinical outcomes**

### **6.1 Introduction**

The service evaluation in Chapter 5 described the current state of BRCA1/2 germline testing at UCLH and the context in which BRCA1/2 tumour testing would be introduced. Compared to the retrospective nature of the service evaluation, the prospective approach of being involved in the provision of tumour testing is an opportunity to work with key individuals from patients and oncologists, to pathology and laboratory staff, and become immersed in the context itself.

PARP-inhibitors are known to be effective for patients with either germline or somatic BRCA1/2 mutations; in the UK olaparib is licensed for use in both cases. With 5-7% of ovarian cancer patients expected to carry a somatic mutation [86], there is impetus to identify more patients who may benefit from access to PARP-inhibitors. The first round robin trial of NGS-based BRCA1/2 tumour testing in ovarian cancer across Germany, Switzerland and Austria has demonstrated the feasibility of this approach [189], and BRCA tumour testing is increasingly being considered in the UK. There are no specific guidelines for BRCA1/2 tumour testing, although guidance statements have recently been published [76]. This research offers a unique opportunity to provide BRCA1/2 tumour testing within the clinical context using a mainstreamed model.

The aim of this chapter is to describe the clinical outcomes of mainstreamed BRCA1/2 tumour testing within our ovarian cancer patient cohort at UCLH. It also aims to understand the process of implementing a new testing pathway, including any pitfalls and challenges. The outcome of this work can be used in an academic sense to inform the case under study, as well as to inform future clinical practice for the development of an established tumour testing service.

### **6.2 Context**

As described earlier in Chapters 1 and 2, the gynaecological oncology department at UCLH has been providing systematic BRCA1/2 germline testing using a mainstreamed model to patients with high grade non-mucinous ovarian cancer since 2015. The previous chapter presented the findings from a service evaluation after the

first year of MGT which demonstrated that this was a feasible and effective way of identifying patients carrying a BRCA1 or BRCA2 germline mutation.

Myriad Genetics provided 50 BRCA1/2 tumour tests, the Myriad Tumor BRCAAnalysis CDx® test, for UCLH patients with high grade serous ovarian cancer for this research work. With BRCA1/2 germline testing already accepted and utilised by both oncologists and their patients, the gynaecological oncology clinical team was interested in this opportunity to provide BRCA1/2 tumour testing to their patients. Just like the MGT model, tumour testing would follow a mainstreamed approach and be incorporated into the patient's oncology outpatient appointments. I would be responsible for organising tumour testing and liaising between the necessary departments and Myriad laboratories. One of my academic supervisors, an oncology consultant within the department, was the named consultant for all tumour tests requested, and all results were returned to her via a secure email portal.

#### 6.2.1 Gynaecological oncology department at UCLH

I was embedded within the outpatient services provided by the gynaecological oncology department. UCLH is a large, tertiary teaching centre which provides specialist care across north-central London and West Essex. It is one of six hospitals which form the North London Gynaecological Cancer Network. Clinical trials are an important part of the clinical service provided which includes national and international clinical trials as well as a portfolio of translational research. A purpose built Clinical Research Facility (CRF) supports early phase clinical trials.

The outpatient oncology services are based in the Macmillan Cancer Centre, a purpose built centre '...designed with the needs of patients, and modern cancer care in mind, with lots of natural light, open spaces and a rooftop garden that everyone is welcome to use. To ensure that the building is truly patient-focused, patients were involved in both the design of the building and how the services operate within it' [190].

The outpatient clinic is situated on the first floor of the centre, with the oncology and surgical clinics running concurrently. There are typically four medical oncologists, two clinical oncologists, specialist registrars and a nurse practitioner for the gynaecological cancer patients. Pharmacy services are also embedded within the outpatient clinic, as is a clinical psychologist. As a tertiary cancer centre, some patients have been referred from their local, general hospitals for more specialist care; some patients travel from as far as Bath and Brighton. The portfolio of clinical trials

that the service offers also draws in patients from other hospitals and geographic sectors.

A typical clinic will have at least 100 gynaecological cancer patients scheduled for appointments, with the majority having a diagnosis of ovarian cancer. Chemotherapy services are provided in a dedicated chemotherapy suite on the second floor of the centre. A more detailed description of the outpatient clinic can be found in the Appendix.

### **6.3 Patient cohort**

An embedded subunit of this case study was to explore the patient experience of mainstreamed BRCA1/2 tumour testing; this is described further in Chapters 7 and 8. By participating in this study, patients were offered mainstreamed BRCA1/2 tumour testing.

The clinical eligibility criteria for patients were:

- Patients aged >18 years (no upper age limit)
- Patients diagnosed with high grade non-mucinous EOC and still under the clinical care of the Gynaecological Oncology Department at UCLH
- Patients who have had a previous primary cancer diagnosis and subsequent treatment

Exclusion criteria were:

- Patients who lack mental capacity to decide to take part in the study and to participate in it (upon clinical team's judgement in accordance with the Mental Capacity Act 2005 Code of Practice 2007)
- Patients who have already had genetic counselling and/or genetic testing
- Patients who are known BRCA1 or BRCA2 mutation carriers
- Patients who are too unwell, either due to their treatment or disease (based on clinician and/or researcher judgement)

Using this criteria, eligible patients were identified in the weekly pre-clinic meetings which I attended. In the outpatient clinic the patient's oncologist would briefly discuss the study with his/her patient during her appointment and then introduce the patient to me to discuss the study further and provide study documents. Further details regarding the recruitment process are provided in Chapter 7.

## **6.4 Tumour testing specifications**

Ovarian cancer tissue specimens are typically taken from a diagnostic biopsy (i.e. of the omentum or pleural fluid) or from debulking (primary or interval) surgery. Tumour tissue is then preserved as FFPE blocks with adjacent haematoxylin and eosin (H&E) stained sections. At UCLH, tumour blocks and H&E sections are stored and managed by the UCLH Cellular Pathology department.

Tumour testing for BRCA1/2 somatic mutations was performed by Myriad Genetic Laboratories. The Myriad Tumor BRCAAnalysis CDx® test uses NGS for DNA sequencing and large rearrangement analyses using MLPA of BRCA1 and BRCA2 genes. Technical specifications of the test can be found in the Appendix. For testing, DNA is isolated from FFPE tissue blocks of ovarian, fallopian tube or peritoneal serous carcinoma. Tissue blocks are required to contain a minimum of 5x5mm tumour and 20% tumour cellularity which is determined using the adjacent H&E stained section.

After discussion with one of my supervisors, who is a consultant clinical geneticist, a decision was made that a tumour test would be deemed 'incomplete' if the MLPA portion of the test failed. In these situations, to ensure large genomic deletions or rearrangements were not missed, patients were asked to undergo germline testing. Similarly, if tumour testing failed completely, as the tumour blocks best fitting the specified criteria had already been selected and sent for testing, the test would be reallocated to a different patient; germline testing would then be organised. If a mutation or VUS was reported, follow-up germline testing was organised.

## **6.5 Tumour testing pathway**

For this component of my PhD, I wanted to understand and experience what is involved in the development of a new genetic testing pathway in a mainstreamed context within the oncology setting. As I discovered, there are a number of integral components within the tumour testing pathway, which are described further below. Overall, the logistics of tumour testing are more complex than germline testing; obtaining a blood sample, though a more invasive process for the patient, and ensuring it is delivered safely to the relevant laboratory for testing, is a relatively straightforward process. I found the complexities of tumour testing were largely around the retrieval and reviewing of pathology material.

### 6.5.1 Tumour testing as a first line genetic test

The approach taken for the timing of mainstreamed BRCA1/2 tumour testing in this research was to provide it as a first line genetic test. Germline testing would then be offered if there was any indication for further testing, i.e. if a mutation or VUS was identified in tumour or if tumour testing failed. The rationale for this approach was two-fold. Firstly a key aspect of this case study was to examine the patient experience of tumour testing, thus it needed to be the primary mode of genetic testing. Secondly this approach could lead to ‘focused germline testing’ which has potential time and cost savings. As Capoluongo (2017) described, tumour testing can detect both somatic and germline mutations, therefore potentially only one genetic test is needed to identify all patients who may benefit from PARP-inhibitors [76]. However, given the importance of clarifying the hereditary nature of mutations identified from tumour testing for the benefit of future cancer risk surveillance and predictive testing for unaffected relatives, in this study any mutation or VUS identified on tumour testing would proceed with germline testing.



Figure 6.1 Components of tumour testing pathway

### 6.5.2 Patient consent

Consent to access and use tumour tissue for BRCA1/2 testing was taken by the patient’s oncologist or oncology registrar during her consultation by completing the Myriad Test Request Form (TRF). Patients were given a verbal description of the

tumour testing process, timeframe and potential outcomes, and were also provided with the Myriad information leaflet on tumour testing (please refer to the Appendix).

After each participant consented to testing, I would collect the completed Myriad TRF from the oncologist and begin the process of retrieving stored tumour specimens.

### 6.5.3 Retrieving and reviewing pathological material

At UCLH, all tumour specimens from diagnostic and surgical procedures are stored within the UCLH Cellular Pathology Department for up to seven years; after this time specimens are stored in a secure NHS archive site in Wales. To access necessary specimens for testing, I made Pathology Material Requests (PMRs) to the pathology archive clerks. Once the PMR was approved and processed, the archive clerk retrieved all pathology slides from the patient's diagnostic biopsy or debulking surgery as well as the accompanying pathology reports. I then collected the pathology slides and reports to review with the consultant gynaecological pathologist.

Selecting the appropriate tumour blocks required the consultant pathologist to review the available H&E slides for each patient and identify three slides of corresponding tumour tissue which best met the Myriad specifications described in Section 6.4. I then requested the corresponding tumour blocks from these slides, as well as new adjacent H&E slides to be cut by the Cellular Pathology department. Once the chosen tumour blocks and new slides were prepared, I would collect and package them using the Myriad test kits, including the pathology report and TRF, to be couriered to Germany for testing in the Myriad laboratories.

This process was repeated for all participants who consented to tumour testing.

As UCLH is a tertiary referral centre, some patients had undergone their initial biopsy and/or surgical procedures at other hospitals. PMRs were made to relevant cellular or histopathology departments with clear guidance on the specifications required for the tumour blocks.

Turnaround time from date of participants consenting to testing, to results reported by Myriad was estimated to take 8-12 weeks.

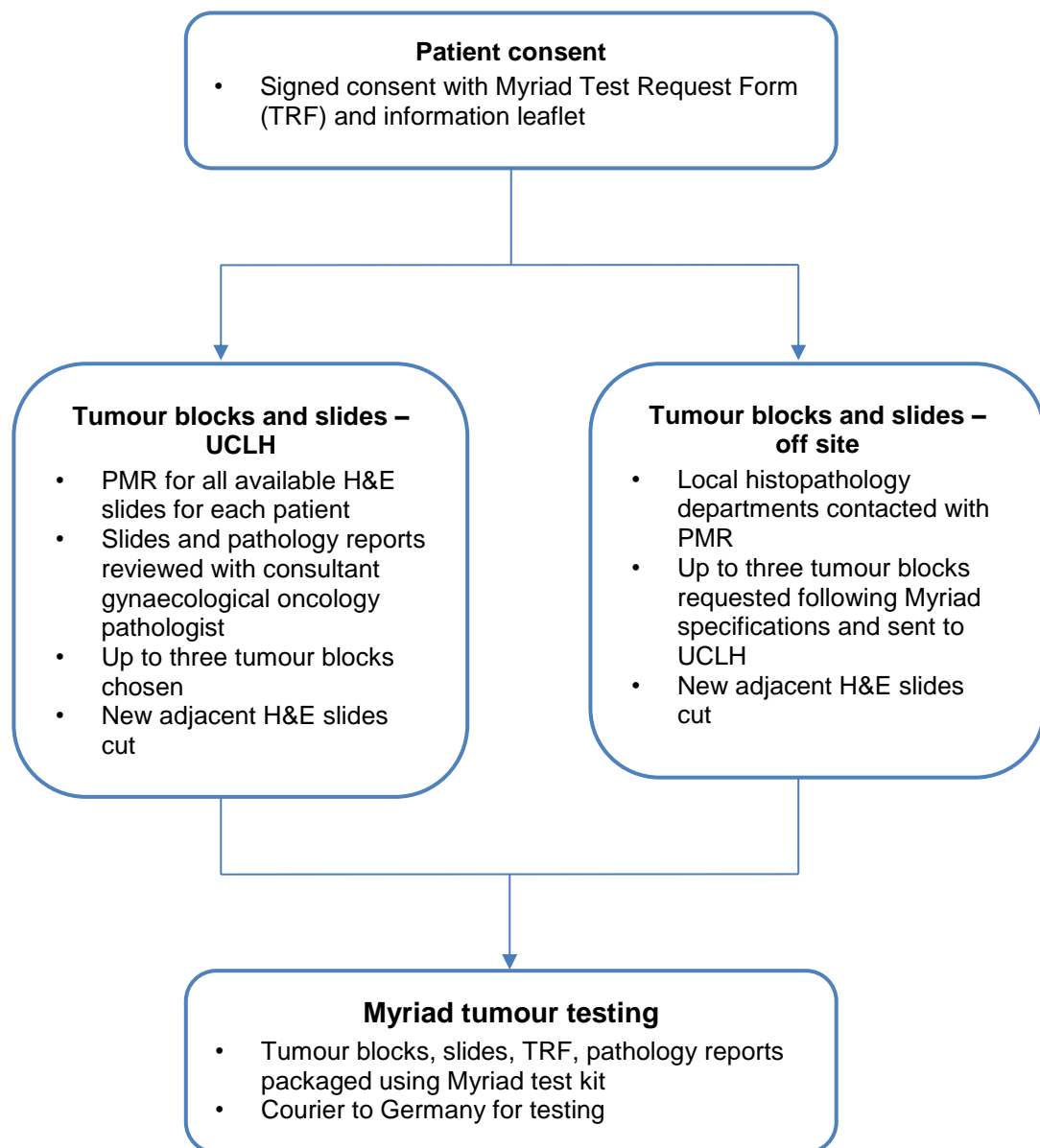


Figure 6.2 Tumour testing pathway



## **6.6 Results from mainstreamed BRCA1/2 tumour testing**

### **6.6.1 Turnaround time**

The mean time from consent for tumour testing to when results were reported by Myriad was 55 working days (approximately 11 weeks, range 24-82 days). The mean time taken from consent to when tumour blocks and sides were sent for testing was 42 days; once samples arrived at Myriad Laboratories testing and reporting was swift and results were usually provided in 10 working days. Although the majority of patients received their results within the estimated 8-12 week timeframe, some patients waited up to 82 working days for the results of testing.

### **6.6.2 Pathology material**

The tumour tissue used for testing for 20 patients were samples from primary debulking surgery, while 28 had samples from IDS after neo-adjuvant chemotherapy. For nine patients the only tumour samples available was a single diagnostic biopsy either from the omentum, fallopian tube or pleural fluid. In an additional four cases where patients only had a single tumour block from biopsy, the patient's oncology consultant chose not to proceed with tumour testing where only limited tumour tissue was available. These patients proceeded directly to germline testing via the usual MGT pathway. Outcomes for these patients are reported in Section 6.6.4.

### **6.6.3 Tumour testing outcomes**

In total 57 participants underwent first line BRCA1/2 tumour testing via MGT.

After tumour testing, Myriad reported no mutation or VUS results for 38 participants. For 26 of these participants, no further testing was required. However for three participants, their oncologist requested further germline testing via the usual MGT pathway because of relevant ethnicity or clinical indications as panel testing for an additional three genes (BRIP1, RAD51C and RAD51D) was available. One patient was subsequently found to carry a RAD51C germline mutation. In 12 cases (31.6%), the Myriad report noted that the MLPA component of testing had failed; follow-up germline testing was undertaken in 11 cases only as one participant's oncologist made the decision not to offer follow-up germline testing. On follow-up germline testing, no germline mutations or VUS were reported for nine patients, while two participants received a RAD51C VUS result.

For eight participants, Myriad reported BRCA1/2 mutations initially identified in tumour; five BRCA2 mutations and three BRCA1 mutations (including one BRCA1 Ashkenazi Jewish founder mutation). In seven cases, participants proceeded with follow-up germline testing, with all confirmed to be inherited, germline mutations. One participant did not proceed with germline testing – due to an error at recruitment, she previously had BRCA1/2 germline testing in 2016. As the previous germline testing reported no mutations, this participant was the only case where a BRCA1/2 somatic mutation was identified. These results are shown in Table 6.1 below.

For two participants, Myriad reported a VUS on tumour testing in BRCA1 and BRCA2, respectively. Targeted germline testing by NE Thames Regional Genetics Laboratories was undertaken; no evidence of the VUS was found in lymphocyte DNA for either participant suggesting that the VUS was not germline in origin.

One ‘inconclusive’ result was reported by Myriad; a large rearrangement of BRCA1 gene with an atypical pattern observed for BRCA1 exons 11(3’)-24 was deemed inconclusive. There was insufficient data to definitely determine the structure of the large rearrangement, its breakpoints and its location within the gene. The Myriad report specifically stated, ‘...this finding should not be used for clinical management’ and recommended follow-up germline testing. No mutation was identified on follow-up germline testing.

Tumour testing failed in six cases due to insufficient quantity or quality of DNA which likely reflected both issues with DNA extraction from FFPE samples and low tumour tissue yield. When the pathology material was reviewed retrospectively, tumour samples from five participants were taken from interval debulking which may indicate chemotherapeutic response and lack of viable tumour tissue for testing. For the other case where testing failed, the only tumour specimen available was a pleural fluid block which is likely to have had less tumour tissue compared to specimens from an omental biopsy or debulking surgery.

Two tumour tests were cancelled by Myriad Laboratories as the pathology report indicated samples were not high grade serous disease, but clear cell and endometrioid ovarian cancer, respectively.

One patient had two tumour blocks tested (counted as two separate tests) due to laboratory error.

The outcomes from tumour testing are shown in Figure 6.3.

Table 6.1 Germline and somatic BRCA1/2 mutations from tumour testing

Study ID	Age at dx (yrs)	Gene	Genetic alteration	Mutation/ VUS	Tumour	Germline
MGT042	63	BRCA1	c.1505_1509del (p.Leu502Serfs*2)	Mutation	Yes	Yes
MGT023	44	BRCA1	c.547+1G>T	Mutation	Yes	Yes
MGT059	53	BRCA1	c.5266dupC (p.Gln1756Profs*74)	Mutation	Yes	Yes
MGT029	61	BRCA2	c.5073dupA (p.Trp1692Metfs*3)	Mutation	Yes	Yes
MGT064	58	BRCA2	c.4859T>G (p.Leu1620*)	Mutation	Yes	Yes
MGT048	67	BRCA2	c.6535_6536insA (p.Val2179Aspfs*10)	Mutation	Yes	Yes
MGT068	64	BRCA2	c.8756del (p.Gly2919Valfs*8)	Mutation	Yes	Yes
MGT072	55	BRCA2	c.1562c>A (p.Ser521*)	Mutation	Yes	No
MGT017	77	BRCA1	c.5569del (p.Gln1857Argfs*65)	VUS	Yes	No
MGT027	65	BRCA2	c.7553T>G (p.Leu2518Arg)	VUS	Yes	No

#### *6.6.3.1 Additional tumour testing outcomes*

Two participants had repeat BRCA1/2 tumour testing by Foundation Medicine as part of a PARP-inhibitor clinical trial. For one participant Myriad tumour testing had initially failed due to insufficient DNA. For the second participant, Myriad had reported an inconclusive result of a large BRCA1 rearrangement (exons 11(3')-24). Both participants had follow-up germline testing within this PhD project and no mutations were identified. In both cases, Foundation Medicine reported BRCA1 somatic mutations.

#### *6.6.3.2 Summary of mainstreamed BRCA1/2 tumour testing outcomes*

In total 57 patients consented to first-line BRCA1/2 tumour testing. Thirty participants (52.6%) went on to have follow-up germline testing either because of clinical indications, mutation/VUS identified on tumour testing or process issues (MLPA failed, tumour test failed or test cancelled). Seven participants were found to carry a germline BRCA mutation for a prevalence of 12.3%, one participant with a germline RAD51C mutation (1.8%) while one participant was found to carry a somatic BRCA1/2 mutation (prevalence 1.8%). An additional two participants from this cohort were found to have a somatic BRCA1/2 mutation on repeat tumour testing, bringing the total somatic mutation prevalence to 5.3%.

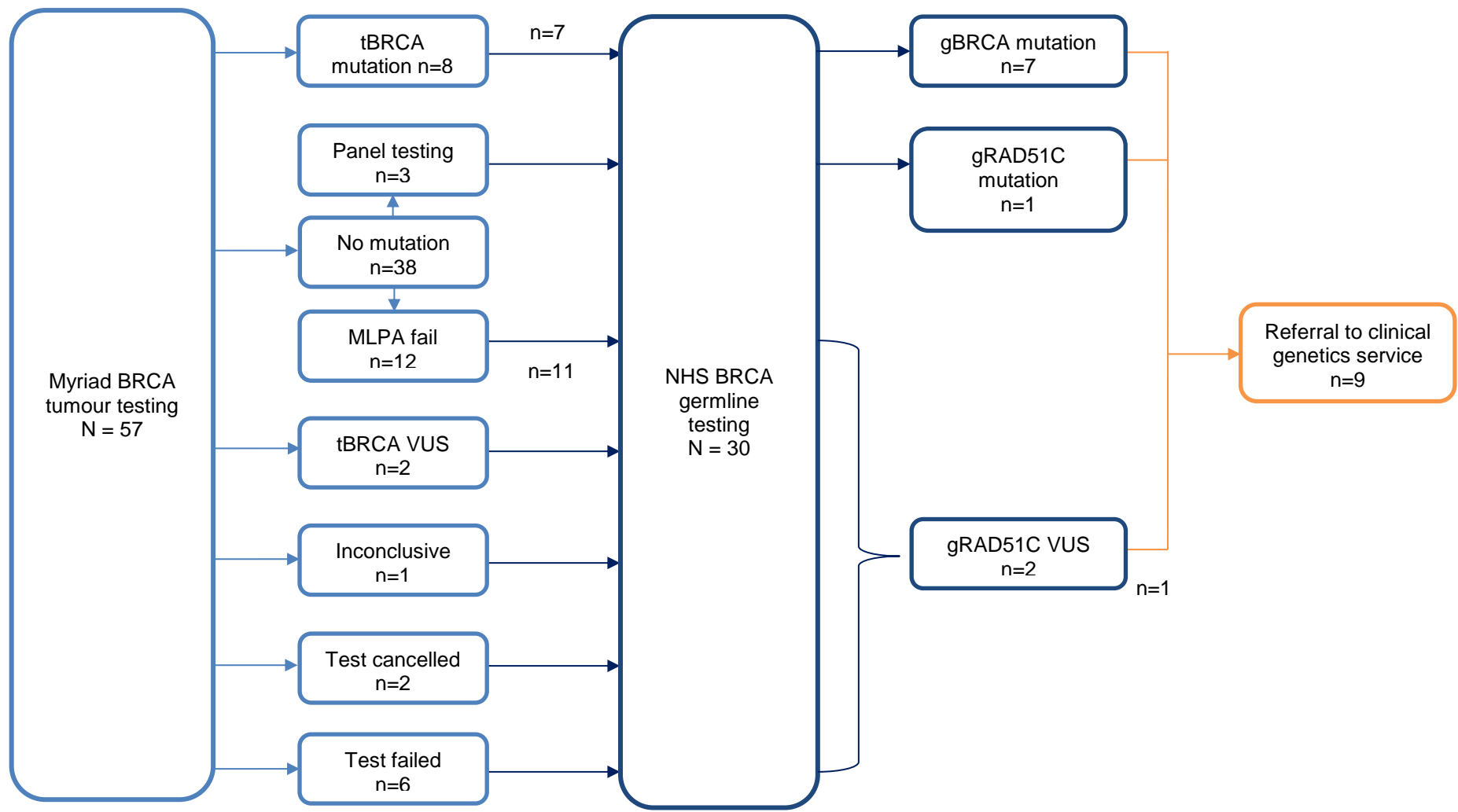


Figure 6.3 Outcomes for mainstreamed tumour testing

#### 6.6.4 First-line germline testing outcomes

As described earlier, four patients who had initially consented to tumour testing did not proceed with testing due to their oncologist's decision not to use the limited tumour samples available. These patients proceeded with first-line germline testing via the usual MGT pathway. One patient was found to carry a BRCA1 mutation.

#### 6.6.5 Clinical management for BRCA1/2 mutation carriers

Of the ten participants with a germline BRCA1/2 or RAD51C mutation or VUS, nine were referred to the local clinical genetics service. In the case of one participant with a RAD51C VUS, the oncologist decided not to make this referral as she felt it would be of little benefit to her patient.

In February 2019 I reviewed the medical records of all participants who had undergone tumour testing and been found to carry a mutation: seven patients who were found to carry a BRCA1/2 germline mutation, one patient with a germline RAD51C mutation and three patients with a BRCA1/2 somatic mutation. These outcomes are reported in the table below.

Eight participants had tumour testing early in their cancer pathway, either during or after completing their first line of chemotherapy. Six of the eleven participants (54.5%) had been able to access PARP-inhibitors treatment after receiving either their germline or somatic mutation positive results, with four participants subsequently enrolled on a clinical trial, one patient receiving niraparib via the managed access programme and one receiving rucaparib via the compassionate access program. The remaining five patients were not currently receiving any treatment.

Of the four participants who had first-line germline testing, the participant who was found to carry a BRCA1 mutation completed her third line chemotherapy shortly after receiving her results. Recently she was declared eligible for olaparib and commenced treatment in February 2019.

Table 6.2 Clinical outcomes for BRCA1/2 carriers

Patient ID	When tested in pathway	MGT result	MGT result received	Clinical outcomes
First-line tumour testing and second line germline testing				
<b>MGT013</b>	First line	gRAD51C mx	Nov 2017	Completed second line chemo Dec 2017. Rucaparib monotherapy (compassionate access) July 2018 ongoing
<b>MGT023</b>	First line	gBRCA1 mx	Aug 2017	PARP-i clinical trial Feb 2018. Progressive disease, stopped trial. Third line chemo Oct 2018 ongoing
<b>MGT029</b>	Second line	gBRCA2 mx	Sept 2017	PARP-i clinical trial May 2018 ongoing
<b>MGT042</b>	Second line	gBRCA1 mx	Nov 2017	Completed third line chemo Nov 2017. No further treatment, surveillance only
<b>MGT048</b>	First line	gBRCA2 mx	Nov 2017	No further treatment since first line chemo. Surveillance only
<b>MGT059</b>	First line	gBRCA1 mx	Mar 2018	Completed second line chemo Aug 2018. Niraparib Sept 2018 ongoing
<b>MGT064</b>	First line	gBRCA2 mx	Mar 2018	Completed second line chemo Aug 2018. No further treatment, surveillance only
<b>MGT068</b>	First line	gBRCA2 mx	June 2018	No further treatment since first line chemo, surveillance only
<b>MGT072</b>	Second line	sBRCA2 mx	June 2018	No further treatment since second line chemo, surveillance only
Repeat tumour testing				
<b>MGT007</b>	Second line	sBRCA1 mx	Unknown	PARP-i clinical trial May 2018. Progressive disease, stopped trial. Third line chemo Aug 2018 ongoing
<b>MGT056</b>	First line	sBRCA1 mx	Apr 2018	PARP-i clinical trial May 2018. Progressive disease, stopped trial. Third line chemo Sept 2018 ongoing
First-line germline testing				
<b>MGT032</b>	First line	gBRCA1 mx	Nov 2017	Completed third line chemotherapy Dec 2018. Olaparib Feb 2019 ongoing

*g(germline)BRCA, s(somatic)BRCA, PARP-i = PARP-inhibitors*

## **6.7 Discussion of mainstreamed BRCA1/2 tumour testing**

The most time consuming aspect of organising BRCA1/2 tumour testing was the logistics of accessing and selecting appropriate tumour blocks. As this testing was classified as research, clinical requests made to the UCLH Cellular Pathology department took priority, leading to delays in retrieval of the pathology material for this study. Staff shortages amongst archive clerks exacerbated delays, and in the end I was given permission to access and retrieve necessary pathology material myself. Given the pressures on the pathology department, classifying tumour testing as a clinical service may not have vastly improved turnaround times of retrieval of archived tumour material.

At the time of tumour testing implementation and set up, there was no appointed gynaecological pathologist consultant for this project. Pathology expertise is critical to the tumour testing pathway; pathology reports and H&E slides of ovarian cancer tumour tissue need to be reviewed to select tumour blocks with appropriate diagnosis (e.g. high grade serous disease), sufficient tissue and cellularity for tumour testing. Fortunately shortly after the initial set up, a newly appointed consultant gynaecological pathologist volunteered to provide her expertise to this project. In total the consultant pathologist reviewed 62 cases (57 ultimately proceeded to tumour testing), while one case was reviewed by another consultant pathologist while she was on leave. As the consultant pathologist had no allocated academic or research time, this was undertaken in addition to her clinical workload.

Despite some of the factors required for tumour testing already being in place or provided (e.g. cellular pathology department onsite, gynaecological pathology specialty, tumour testing kits) it was challenging to develop this pathway. A lack of staff and low prioritisation for research requests for pathology material led to significant delays in obtaining tumour blocks and adjacent slides. If this process could be streamlined by the provision of a dedicated archive clerk for BRCA1/2 tumour testing requests and access to more than one gynaecological pathologist consultant, this may reduce the time taken to retrieve and review tumour blocks for testing.

Depending on when tumour testing is undertaken, the turnaround time is important. If testing is provided shortly after diagnosis or during first line treatment, there is less pressure to provide results in order to inform eligibility for PARP-inhibitors as olaparib is licensed for use in the UK only after three or more courses of platinum-based chemotherapy [191]. However for post-relapse or second line treatment, the results



of tumour testing become more clinically urgent. Similar to Myriad, other validated centres in Europe that undertake diagnostic tumour testing in progressive, relapsed, high grade serous ovarian cancer have a turnaround time frame of 10 working days from date of tumour block(s) receipt [189] to ensure timely feedback of results to oncologists for treatment decisions. To provide tumour testing to a greater number of patients would require the development of an efficient timeline to source and review tumour blocks for testing. A guidance statement on BRCA1/2 tumour testing called for results to be available between 30-40 days from when testing is requested [76].

It was an important, and unexpected, outcome that two participants were later found to have BRCA1/2 somatic mutations which were not identified in the BRCA1/2 tumour testing undertaken in this PhD project. In one case tumour testing had failed; as noted earlier, in cases where tumour testing failed Myriad would allow the test to be reallocated. The strategy taken in this study was that the test would be reallocated to another participant, rather than retrieving and sending additional tumour blocks from the initial patient. In the other case Myriad had reported an 'inconclusive' result, whilst repeat testing by Foundation Medicine reported a BRCA1 mutation. It is likely there are differences between the mutation classifications between Myriad and Foundation Medicine, as Myriad retains its own databases and platforms for annotation and classification of variants which are not publicly accessible [192].

Classification systems and terminologies differ between reports and the complexities of creating a unified interpretation and reporting system are recognised [193]. Currently there is no single guidance for classifying, interpreting or reporting somatic mutations, with various databases and literature sources available [193, 194]. Efforts are being made to collaboratively develop expert consensus to collate current knowledge of genetic variants [11]. Variation around classification can have a significant impact in terms of clinical decision-making. As Spriggs and Longo comment, 'Different classifications may put the patient at risk for inappropriate treatment' (p.2568) [11]. In this case, Myriad issued an 'inconclusive' result for one participant and recommended that these results were not used for clinical management. As it stood, given the participant had no mutation or VUS identified on follow-up germline testing, she would not have had access to PARP-inhibitors. Repeat tumour testing by Foundation Medicine reported a BRCA1 somatic mutation and the patient was subsequently enrolled on a PARP-inhibitor clinical trial. Until there are both standardised and validated NHS-based laboratories as well as classification and reporting systems for BRCA1/2 tumour testing in the UK, there may be some variation

in reporting of somatic mutations which could have a significant impact on clinical decision-making.

Molecular genetic analysis in ovarian cancer of tumour tissue has assumed that the sample reflects the DNA expression profile of the entire tumour [195]. However cancer cells within a tumour can exhibit different gene expression patterns known as intratumoural heterogeneity (ITH) [196]. ITH has been shown to exist in epithelial ovarian cancer, which has implications for the reliability of tumour testing; Khalique et al suggested that in order to obtain a true representation of the genetic profile of ovarian cancer, multiple samples of tissue from the tumour would require analysis [195]. Due to a laboratory error, one participant did in fact have tumour testing using two distinct tumour tissues; testing was undertaken in both tumour tissue from IDS in 2012 and metastatic tissue from laparotomy and resection of a pararectal mass in 2018. No mutations were identified in either sample.

As reported earlier in this chapter, one somatic mutation was identified in the course of this research, and two additional patients were later found to carry somatic BRCA1/2 mutations after repeat tumour testing. The estimates of somatic mutations in ovarian cancer from the literature has been reported as 3% [61], 7% [13] up to 9% [82]. As described by Moschetta et al, we could expect to identify one somatic mutation for every 4-5 germline mutations [86]. The proportion of somatic mutations found in this cohort of participants (including the two somatic mutations later found on repeat testing) was similar, with a prevalence of 5.3% (3/57).

Patient management was reviewed for the participants identified as carrying either a germline or somatic mutation. In 58.3% of cases (7/12), participants had been able to access a PARP-inhibitor, either via a clinical trial, managed access or compassionate use program. Most participants had tumour testing early in their treatment pathway, either during or after completing first line chemotherapy. Therefore it is likely more of the participants in this group will go on to access PARP-inhibitors as they continue on their treatment pathway, either by meeting the criteria for olaparib or enrolling in a clinical trial. If authorisation for olaparib moves in line with US approval for use as a maintenance treatment after first line chemotherapy, more patients will have access to this treatment much earlier in their treatment pathway. There will be an impetus to offer tumour testing shortly after diagnosis in order to identify those eligible.

There has been some debate in the literature of MGT as to whether an age cut-off for testing should be implemented, in particular for germline testing [74]. In this study

there was no upper age limit in terms of participant eligibility, therefore there was no age limit for tumour testing. In this cohort there were two participants over the age of 70 where mutations were identified; one germline mutation carrier was 73 years at diagnosis, and one participant with a somatic mutation was 77 years. Anecdotally there was some variation in the maximum age at which the gynaecology oncologists were prepared to offer genetic testing, with some choosing not to test patients over the age of 70. Our knowledge of the clinical factors associated BRCA1/2 germline mutations includes younger disease onset, with increased ovarian cancer risks from age 40 for BRCA1 and age 50 for BRCA2 mutations [197]. Whether tumour testing should have similar age restrictions is as yet unclear. Currently it is unknown whether somatic mutations have a similar biological and/or clinical effect as germline mutations [86].

In the previous chapter, the service evaluation found that participants with a germline BRCA1/2 VUS result were under referred to clinical genetics for follow-up. The outcomes from this chapter suggest that this uncertainty amongst some oncologists about the value of clinical genetics management for VUS results has persisted. In the process of mainstreamed tumour testing, two participants were found to have a RAD51C VUS on follow-up germline testing. Only one participant was referred to clinical genetics. Despite a reminder for the other patient to be referred, the oncologist felt that this would be of little benefit given her clinical condition of a recent relapse and platinum-resistant disease (this encounter is discussed further in the clinical reflections section later in this chapter). The uncertainty related to interpreting and managing VUS results is not unusual in non-genetics medical specialties. A recent survey of breast cancer specialists in the UK found that the majority of the sample (71.0%) felt unprepared to interpret a genetics report [198]. Only 24.1% of clinical oncologists and 38.1% medical oncologists were confident in their perceived understanding of a BRCA1/2 VUS result. Furthermore clinical testing of RAD51C genes in ovarian cancer is still relatively new in the UK; this lack of familiarity may also contribute to poor understanding of these results, particularly in the case of a VUS. Informing oncologists of how these results are managed by clinical genetics and what information and support this service can provide to patients may help to encourage more consistent referral of patients with VUS results.

In this study, MLPA failed in 21.0% (12/57) of cases and participants went on to have germline testing to ensure any large intragenic deletions or rearrangements (LGRs) were not missed. LGRs are more difficult to detect in DNA from FFPE samples [76] and MLPA analysis can be unreliable in tumour testing because of the heterogeneous

nature of tumour samples containing both normal and tumour cells [199]. There are different approaches to detecting LGRs in tumour testing. In the context of research studies the use of a single platform to detect both point mutations and LGRs by an NGS strategy is increasingly common [77, 200]. Others are developing novel approaches such as single-molecule molecular inversion probe (smMIP)-based targeted sequencing to streamline workflows [201]. Taking these approaches into the clinical setting will require extensive validation [77].

The rate of tumour test failing completely was 10.5% (6/57) and attributed to insufficient quality or quantity of DNA. This is not an uncommon finding; data from the 100,000 Genome Project reported 30.9% of samples had insufficient quality DNA from FFPE samples [202]. The challenges of extracting DNA of sufficient quality from FFPE samples has been described extensively [76, 77, 199, 201]. Tumour samples which are fresh frozen (FF) offer superior DNA quality; however, as yet this is not a routine service and may not be available at all oncology centres [76].

The approach for this research was to offer tumour testing as a first line genetic test, with germline testing as a follow-up when necessary. In this study, more than half the sample (30/57, 52.6%) who had first line tumour testing went on to have second line germline testing either due to issues with testing (e.g. MLPA fail, test fail) or because a BRCA1/2 mutation or VUS was identified. Another issue with taking a first line tumour testing approach is that if a mutation is identified, it is unknown if it is somatic or germline in nature and second line germline testing is always recommended. Thus the process of genetic testing for these participants became somewhat drawn out; after the 8-12 weeks for tumour testing results, it was an additional 8 weeks before germline results were reported. Research is now looking at methods to predict the hereditary nature of a mutation identified on tumour testing using computational models [203].

An alternative approach is to offer tumour testing as a second line test after germline testing, restricted to patients where no germline mutation was found. In this scenario, approximately 85% of patients would continue on to have a second line tumour test. Again the majority of patients would require further testing and waiting for a second set of genetic testing results. A third approach would be to offer tumour testing and germline testing concurrently, rather than sequentially; this would allow for the sensitivity of tumour testing (i.e. correctly identifying the presence of a somatic mutation) to be established as well as being the most time efficient pathway. Consent

for both a blood sample and tumour tissue could be taken at diagnosis and both testing pathways initiated concurrently.

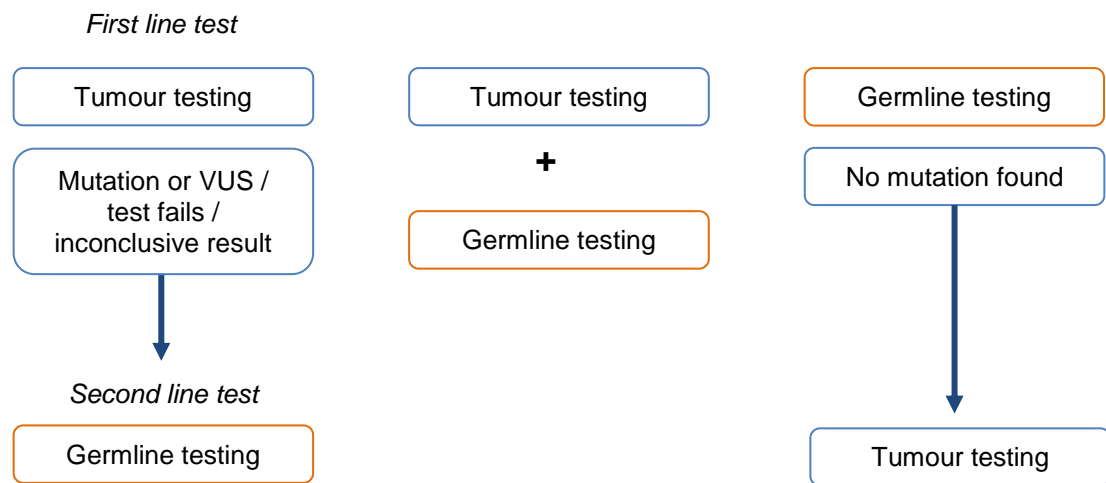


Figure 6.4 Models of tumour and germline testing timing

BRCA1/2 tumour testing in ovarian cancer is not currently NHS funded and is therefore not part of standard care. Cost as well as access to an accredited tumour testing laboratory may impact how testing is delivered, i.e. as a first line vs second line test vs simultaneous testing. Germline testing is currently cheaper costing approximately £307 compared to £564 for tumour testing, although the cost of tumour testing can exceed £2000 when undertaken privately.

Currently there is inequitable access to tumour testing for ovarian cancer patients in the UK with only a few centres providing testing as part of clinical care. Furthermore there remains disparity in access to germline testing across the country, with different testing protocols and guidelines in place [75]. Although more genetics and oncology centres are moving towards systematic BRCA1/2 testing for ovarian cancer patients, family history and age are still being used to determine eligibility for testing [73]. For genetic testing, whether germline or tumour, to reach as many ovarian cancer patients as possible, a systematic and unselected approach needs to be taken.

## **6.8 Clinic(al) experiences and reflections**

Prior to starting my PhD research, I had spent brief periods recruiting cancer patients for different psychosocial research projects from the outpatient oncology clinics in the UCLH Macmillan Cancer Centre. I had some other previous clinical, professional and personal experience working with individuals with cancer. However these interactions were typically short lived and transient.

Until I began patient recruitment, it was difficult to anticipate how much time would be needed to set up the tumour testing pathways and recruit 50 eligible patients. Ultimately I spent just over 12 months embedded within the gynaecological oncology department, spending 50 consecutive Tuesdays in the outpatient clinic. This was a significant amount of time, which enabled me to observe and experience the inner workings of the clinic. Importantly it also gave me many opportunities to interact with patients, those who became study participants as well as others, and offered insight into the ovarian cancer trajectory of treatment, response and relapse.

There is a body of literature around the potential benefits of qualitative research to participants, in particular in depth interviews which have been described as having a cathartic, validating and self-empowering effect on participants [204, 205]. It is increasingly acknowledged that qualitative research, particularly when studying sensitive topics or working with vulnerable groups, may have a less positive effect on the researcher(s) [206]. Challenges range from research concerns about boundaries, researcher-participant relationships, the research footprint and leaving the research field. However other challenges relate to the emotional toll research can take [207]. Furthermore, what remains undervalued is how the embedded nature of qualitative research and the long periods of fieldwork within the study setting and/or with participants has the potential to impact not only the researcher, but also their research [208]. Although my research did not include a formal ethnographic component, I was nevertheless embedded within the 'field' for a prolonged period of time. In this section of the chapter I reflect on some of the challenges I encountered during my time in the clinic and how these challenges shaped my research practice.

### **6.8.1 Emotions and empathy in research**

The cyclical nature of ovarian cancer where patients often respond well to treatment for several or many months initially, before progressing and requiring more treatment became very evident over the 12 months I spent in the outpatient clinic. During this time participants often shared with me their good news, that they were responding

well or finishing treatment, as well as their bad news, when disease returned or progressed. A small number of participants passed away during the course of my research. Whether they were my own study participants or other patients in the clinic, it was always upsetting to see patients who were very unwell, sitting and waiting in clinic, unable to hide their pain or discomfort. It was also distressing to see young patients, closer to my age, in clinic; although ovarian cancer is more commonly in post-menopausal women, it was a reminder that cancer does not discriminate in age. Compounding my distress was the feeling of helplessness – I had no clinical skills to offer these patients, nor any practical or logistical help; there was usually no available room to move a patient who was unwell or distressed. Even the water fountain was broken. Furthermore I felt anxious about overstepping the roles of the reception and nursing staff. The intensive nature of being in every clinic over a year meant that at times I was exposed to difficult situations, some of which have continued to stay with me.

These emotions are not uncommon in qualitative research, particularly around sensitive topics such as cancer. As Watts wrote, 'The subject of cancer can be emotive, evoking as it does a sense of one's mortality' (p.7) [207]. Responding emotionally to situations or experiences is part of human nature. Emotions also play a role in the research process [209]. Taking an interpretivist stance, I cannot be disembodied or objective to what I observe. Instead it is my role to find meaning from these experiences and use them reflexively for both myself and my research practice.

I found it very easy to build rapport with the patients I met and recruited for my research. Some of this ability harks back to my genetic counselling training; a key component of the genetic counselling consultation is building rapport with the counsellee. When conducting research on sensitive topics, establishing rapport is key to building trust between the researcher and participant. Using empathy has been described as one strategy to develop real connections with participants; Dickson-Smith et al believe 'The ability to be empathetic is one of the main skills needed to undertake qualitative research' (p.65) [209]. However being empathetic can take its own emotional toll, and I found establishing rapport involved managing not only my own but also participants' emotions. In contrast to the other people in the outpatient clinic, from the health professionals to the reception staff, I stood out as someone who had time to give. This meant I had time beyond discussing my research or going through study documents; I also had time to sit, talk and listen. With patients giving up so much of their time, sharing their stories and experiences with me, it was instinctive to respond in a similar manner. Often at the back of my mind was whether I had shared

too much of myself, and where the boundaries lay within the researcher-participant relationship. This is not uncommon in qualitative research where issues of self-disclosure are entwined with a reciprocal desire to give something back to participants [206, 209]. Because of my good rapport with participants, and interactions which lasted over many months, it was difficult not to develop an emotional attachment to some patients. Even now, after data collection has finished, there are patients whom I still think of. This has also been described as significant issue for other researchers [206], blurring the boundaries in the researcher-participant relationship.

Dickson-Smith et al describe the experiencing of emotions in research as 'emotional work', to encompass the face-to-face interactions with research participants which involves both dealing with one's own emotions as well as that of others [209]. The importance of acknowledging the emotional work involved in both clinical and qualitative research means it can not only be addressed in terms of research planning, but also in how it impacts data collection and interpretation. Furthermore it highlights the need for more professional support for researchers where existing self-care techniques and informal support networks may be insufficient. Wray et al write about their experiences embedded in a gynaecological cancer unit, describing the psychological burden they felt during their fieldwork [208]. The authors recommend professional counselling to be available via the research or academic institutions as well as regular supervision and debriefing.

I was fortunate to engage with formal support shortly after starting my research. After three months in the clinic, my primary supervisor recognised that I was struggling with some of the clinical aspects and emotional work of my research. She prepared regular clinical supervision sessions with the consultant clinical psychologist for the gynaecological oncology department, who was familiar not only with the health professionals and the patients, but had a good understanding of the nature of the clinic and how it operated. This provided me with a confidential, non-judgemental space in which to share my worries as well as practical suggestions about how to manage them.

### 6.8.2 Burden of responsibility

Unlike other case studies or qualitative research that largely draws from the research setting and participants, in my PhD I was providing a service, tumour testing, to selected patients who agreed to take part in this study. During the process of recruitment and completing the study documents, participants would often say, off-



hand, that they hoped the results would 'come back negative'. Inevitably, they would mention concern about risks to children and other family members.

Two patients were particularly anxious about genetic testing and the implications for their children. Both were already worried that 'the same thing could happen' to their daughters and found it distressing to consider that there could be an inherited component to their disease. For one patient, I even (somewhat directly) suggested that a genetic counselling appointment and having genetic testing within their local clinical genetics service may be the best route for them, to ensure they had sufficient time and support to consider their testing decision.

Despite having no control over their (or any) tumour testing outcomes, the expectations of both patients left me anxious. One of the patient's partner emailed me prior to their upcoming clinic appointment, to tell me it was her birthday that day and he hoped the genetic testing results would be the good news they wanted. I felt I had a responsibility to deliver to the patient the result they desperately sought. Another patient who had responded very well to a trial drug understood the potential clinical benefit of having a somatic mutation, telling me frequently she hoped testing would 'find a mutation'.

Hiller and Vears believe that to manage clinical expectations during patient-participant recruitment and data collection requires ways of communicating with patient-participants about the researcher such that any confusion between research with clinical care is reduced [210]. The challenge I faced was that this research was intertwined with clinical care; the results of tumour testing could potentially be used to determine treatment options.

These encounters also highlighted an additional issue I struggled with throughout my time in the clinic, which was being privy to clinical knowledge about patients (both my own study participants and others) despite not having a clinical role. It was difficult to avoid being exposed to clinical information particularly when attending the pre-clinic meetings where each patient and treatment plan is discussed; these meetings were a crucial part of identifying patients who would be eligible for my own research. But was this clinical information necessary for conducting my research? Given the logistical challenges of avoiding exposure to such information, I felt it was inevitable that I would learn about the treatment and clinical management of other patients, and focused more on how to treat this information ethically and sensitively. Regarding clinical information that related to patients who had consented and become study

participants, I felt that my access to this information was addressed by the signed consent forms which specifically included access to medical records. Furthermore it provided more insight into the diagnosis and treatment pathway that these women experience as ovarian cancer patients but from a different perspective, informing and shaping my understanding of the context in which genetic testing was taking place.

### 6.8.3 Blurred boundaries

As mentioned in Section 4.9, I have been a researcher for many years but my training as a genetic counsellor has had a significant influence not only on my research interests, but on my expectations and perceptions of how genetic testing should be discussed and provided.

A mainstreamed model of delivering genetic testing is a departure from the traditional model of genetic counselling and testing. Inevitably the way in which testing is delivered needs to adapt to its environment. In the case of the oncology setting, discussions around genetic testing need to be incorporated into the patient's usual clinic appointment with the likely outcome being that these conversations are much briefer than would typically occur in a genetic counselling context.

In some ways I found it difficult to accept that the conversations about genetic testing, and more specifically tumour testing, in the context of this research study, between oncologists and their patients would be different. I felt anxious about whether participants were receiving sufficient information from their oncology consultant or myself to make a sufficiently informed decision about whether to have tumour testing or not; I found myself having to suppress my desire to provide additional unsolicited information to participants.

When a clinician assumes the dual role of a researcher this can lead to role confusion [211], which may be external requiring clarification of what role you hold to others or internal confusion resulting from conflicting feelings between the two roles [212]. I do not perceive myself to be a clinician, and although the gynaecological oncology clinical team was already aware that I have a background in genetic counselling, in general there was no expectation that I was fulfilling this role. Nevertheless it had an impact on my experience and interactions with participants during my time in the clinic.

There were a number of occasions when a participant would ask what I termed a 'clinical query', a question relating to genetic testing or their treatment. It was straightforward to decline answering questions related to treatment as I have no

training nor expertise in this area, although I was happy to act as a sounding board. As I was responsible for organising tumour testing, I was confident it was my role to answer any questions relating to the process, outcomes and logistics. However when questions moved more into the realm of germline testing, and in particular, queries about implications for children or future cancer risks, I was unsure of where my boundaries lay. Furthermore, as a component of this research is also interested in what oncologists communicate about genetic testing (further discussed in Chapters 7 and 8), I was concerned about 'muddying the waters'. This is not an uncommon challenge in research. In a systematic review of the typology of the researcher-clinician role, feeling uncomfortable about answering a participant's clinical query typically arose if the researcher wanted to respond to the query, but was concerned about blurring their role or potentially impacting the data [210, 212].

Two participants received germline RAD51C VUS results after follow-up testing when the MLPA failed on their tumour tests. For both participants, I suggested to their oncologist that the patient should be referred to their local clinical genetics service to discuss the result further. In one case, the oncologist declined to do so as she felt it would be of little benefit to the participant who had progressive disease and was just starting on a new clinical trial. I struggled with what I felt was her paternalistic decision; on one hand genetic counselling could be beneficial clinically, perhaps not immediately but in the future, to the patient and her relatives. I also felt genetic counselling could potentially provide further clarity and psychosocial support to the patient around her VUS result. Nevertheless, in the end I chose to accept the oncologist's clinical decision, feeling that insisting or interfering further would overstep my boundaries as a researcher.

This scenario was the first 'ethically important moment' I encountered during my time in the clinic, what Guillemin and Gillam refer to as '...the difficult, often subtle, and usually unpredictable situations that arise in the practice of doing research' (p.262) [213]. The authors describe these moments as 'ethics in practice', making a distinction between the procedural ethics involved in regulatory ethical processes and the interactions between researchers and participants.

Guillemin and Hillers believe reflexivity plays an important role in managing the ethical tensions undertaken in research [210, 213], some of which I encountered during my clinical experience and have described above. Reflexivity can contribute not only to ensuring rigour and good research practice, but also a means to being aware of the ethically important moments and how to address ethical concerns when they arise.

Guillemin also discusses the importance of always being alert to ethical tensions [213]. The reflexive practice I took during my research was to be cognisant of the ethical moments, and take time to consider how and why these moments had arisen. In the case I described above, uncertainty of my role and where my responsibilities lay contributed to this particular ethical tension. I perceived the potential value of further genetic testing or counselling, but recognised that this was my motivation, acknowledging that the oncologist had a different priority. In the case of ethical moments with clinical implications, discussion with my academic supervisor, who is a consultant clinical geneticist, or during my clinical supervision sessions was a means to addressing these moments and developing strategies to respond.

My experience in the clinic was an invaluable part of my research. It was critical to developing my understanding of the context in which tumour testing was occurring, and in identifying my own strengths and limitations as a researcher. It also highlighted that my choices, beliefs and actions are still influenced by my genetic counselling background.

## **6.9 Summary**

BRCA1/2 tumour testing is becoming an increasingly important part of the clinical care for ovarian cancer patients. Mainstreamed tumour testing is feasible, however developing efficient pathology pathways and improved genetic testing platforms is essential to providing testing to more patients. Concurrent tumour and germline testing is likely to be the best approach to ensuring genetic testing results are delivered in a timely manner.

## **Chapter 7 Exploring the patient experience of BRCA1/2 tumour testing in ovarian cancer: a quantitative approach**

### **7.1 Introduction**

The service evaluation in Chapter 5 demonstrated that taking a mainstreamed approach to genetic testing is a feasible and effective model to identify women with ovarian cancer who carry germline BRCA1/2 mutations. In turn this has the potential to provide greater treatment options for patients as well as opportunities for predictive testing and/or risk reducing interventions in at-risk relatives.

Despite the benefits and increasing availability of MGT, the impact of moving testing from the specialised service of clinical genetics and genetic counselling to the oncology setting remains largely unknown. Currently little is known about how ovarian cancer patients experience MGT or the psychosocial impact of providing testing in this manner. In particular women's attitudes towards BRCA1/2 testing, their intentions to accept an offer of testing, the decision making process, or outcomes from MGT are poorly understood.

Although there is a wealth of literature on the psychosocial impact of genetic testing it largely relates to unaffected individuals at high risk of developing cancer, with a smaller body of research on the impact of testing in cancer patients. Furthermore much of this research is within the context of the traditional model of genetic counselling and testing for germline mutations.

There are subtle differences between the two genetic testing approaches. Independent of any germline mutation, a tumour may have an acquired somatic mutation not identifiable through germline testing. As outlined in Chapter 6, tumour testing involves a two-step procedure; if a mutation is identified in the tumour, germline testing can then be offered to determine if this is an inherited or somatic mutation.

At the time of writing, access to BRCA1/2 tumour testing for somatic mutations varies across the UK with some centres providing this as part of standard care, while at other centres tumour testing may only be available as part of clinical trial participation, other research studies or by private funding. Nevertheless there is a small but growing population of patients who are being offered both germline and tumour testing as part

of their ovarian cancer clinical care. As tumour testing can only provide non-hereditary genetic information initially, there may be less of the implications which have been typically associated with germline testing such.

However as the clinical outcomes in the previous chapter have demonstrated, first-line BRCA1/2 tumour testing is not always straightforward; more than half of participants required follow-up germline testing. One aspect of this work was also to consider if there are differences in the experiences and outcomes of patients who have first-line germline testing, and those who have first-line tumour testing. A cohort of patients who were offered germline testing, via MGT as per usual care at UCLH, would also be recruited.

This chapter took a quantitative approach to explore how ovarian cancer patients experience MGT, either via tumour or germline testing. This is now referred to as mainstreamed tumour and/or germline testing, or MTGT. The focus of this study is on three key areas of the patient experience, reflecting key stages of the MTGT pathway:

- Attitudes and knowledge of BRCA1/2 testing, prior to testing
- Decision making, when consenting to genetic testing
- Impact of BRCA1/2 testing, after receiving results.

## **7.2 Aims**

In order to address the key areas of the patient experience, the aims of this study were:

- To explore attitudes, intentions and knowledge about BRCA1/2 genetic testing
- To explore experiences of decision-making, including decisional conflict, motivations and uptake for MTGT
- To explore the impact of testing and receiving results.
- To explore differences in patient experiences and outcomes between tumour and germline testing.

## **7.3 Methods**

### **7.3.1 Study design**

This was a prospective observational study with three distinct parts. The study was designed to follow the MTGT testing pathway and to reflect the key areas of the patient experience and study aims described above.

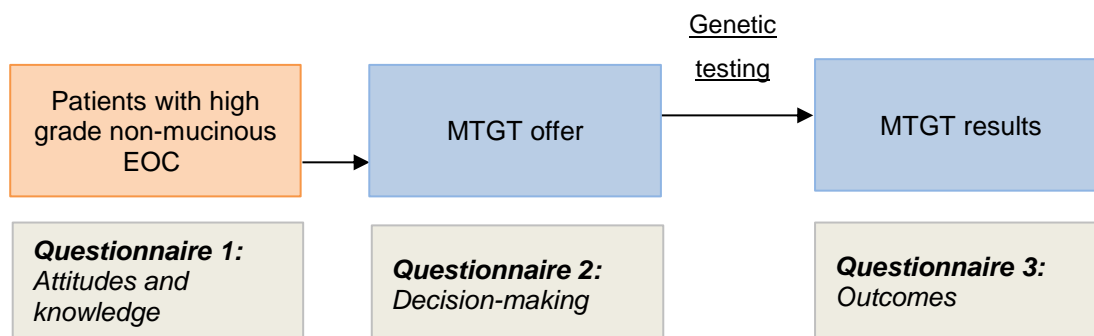


Figure 7.1 Overall study design and genetic testing pathway

### 7.3.1.1 Attitudes and knowledge of BRCA1/2 testing, prior to testing

In the first part of the study, eligible patients were invited to participate prior to the offer of MTGT. At this point, those who agreed to participate were asked complete Questionnaire 1, which explored attitudes to and knowledge of BRCA1/2 testing and their intention to take up the offer of MTGT.

### 7.3.1.2 Decision making, when consenting to genetic testing

After completing Questionnaire 1, at their next clinic appointment participants were offered MTGT (either first-line tumour or first-line germline testing) by their oncologist. Tumour testing would be organised by myself, germline testing via the usual clinical pathway. After consenting to testing participants were provided with Questionnaire 2 to complete, which explored the decision-making experiences of ovarian cancer patients offered MTGT. This included motivations for genetic testing, uptake or decline of MTGT offer and decisional conflict.

### 7.3.1.3 Impact of BRCA1/2 testing, after receiving results

Once reported, genetic testing results were disclosed to participants by their oncologist during their outpatient appointment. Participants were then provided with Questionnaire 3 which explored the outcomes of MTGT post-results receipt.

## 7.3.2 Participants

Approximately 350 ovarian cancer patients are seen annually in the Gynaecological Oncology Department at UCLH. Up to 75% of patients have clinical features which fit current guidelines recommending BRCA1/2 genetic testing, i.e. diagnosis of high-grade non-mucinous EOC [214].

From previous psycho-oncology research in genetic testing, typically 70% of patients approached agree to participate [215, 216]. As UCLH is a large tertiary hospital heavily involved in research and clinical trials, patients may be familiar with an invitation to participate in research. Similar participation rates were expected for this project.

As 50 tumour tests were available, this study aimed to recruit 50 participants who would be offered first-line BRCA1/2 tumour testing. An additional 50 patients who would be offered first-line BRCA1/2 germline testing would also be recruited in order to explore any differences between mode of testing and patient experience.

#### *7.3.2.1 Identifying participants*

Eligible ovarian cancer patients were identified during weekly pre-clinic meetings. I was present in these meetings to identify eligible patients who could be offered MTGT and invited to this study.

Patients from all stages of the cancer pathway were included, such as newly diagnosed patients, those on active treatment (e.g. pre- and post-surgery, chemotherapy, radiotherapy) or in remission. As disease relapse is common in ovarian cancer, patients on second or third line treatment were also included. If there was no relapse or recurrence, ovarian cancer patients were followed up for five years after primary treatment. As MTGT was offered both prospectively (i.e. at diagnosis) and retrospectively, some patients recruited could be many months or years from their initial diagnosis.

#### *7.3.2.2 Eligibility criteria*

The following criteria were used to identify eligible patients and those who would need to be excluded from participation.

##### *Inclusion criteria*

- Patients aged >18 years (no upper age limit)
- Patients diagnosed with high grade non-mucinous EOC and still under the clinical care of the Gynaecological Oncology Department at UCLH
- Patients who have had a previous primary cancer diagnosis and subsequent treatment
- Patients who are able to understand spoken and written English



### *Exclusion criteria*

- Patients who lack mental capacity to decide to take part in the study and to participate in it (upon clinical team's judgement in accordance with the Mental Capacity Act 2005 Code of Practice 2007)
- Patients who have already had genetic counselling and/or genetic testing
- Patients who are known BRCA1 or BRCA2 mutation carriers
- Patients who are too unwell, either due to their treatment or disease (based on clinician and/or researcher judgement)

### 7.3.3 Study timing

As outlined above, eligible patients who were invited to take part could be at any point along the cancer pathway. Some patients may be invited shortly after diagnosis, while other patients may be many months or years post-diagnosis. For patients on active treatment, outpatient clinic appointments were typically spaced between two to four weeks apart, depending on their treatment schedule. Patients on follow-up may be on six weeks, three or six months between appointments. Occasionally patients were on annual follow-up.

Wherever possible, this study attempted to fit within the participants clinical pathway in order to reflect the real-time process of genetic testing. Therefore no additional appointments were scheduled for study participants. Participants were met in the outpatient clinic, or during their chemotherapy treatment. Questionnaires were given in person at their clinic appointment or posted to the participant's home address. If there were many weeks or months between clinic appointments, participants were followed up by telephone.

### 7.3.4 Germline vs tumour testing

For this research, 50 tumour tests were provided by Myriad Genetics for eligible UCLH ovarian cancer patients. To ensure equality to access oncologists would randomly allocate patients to either germline or tumour testing. BRCA1/2 germline testing was already NHS funded and testing was provided by the NE Thames Regional Genetics Laboratories.

Random allocation would occur after participants had completed and returned the first study questionnaire, but prior to consenting to MTGT. Random allocation would follow that used by the department for other studies.

### 7.3.5 Recruitment and consent

#### 7.3.5.1 *Invitation*

Eligible participants were identified during the departmental pre-clinic team meeting prior to the week's gynaecology oncology outpatient clinic. The morning of the outpatient clinic, a coloured note was attached to the medical notes of each identified patient as a reminder for her oncologist. During her consultation, the patient's oncologist (registrar or consultant) briefly introduced the study to the patient. If the patient was interested in hearing more about the study, the oncologist then introduced the patient to me after her appointment. Patients who were not interested or declined to meet me at that point were not approached further, unless requested at a later date by either the patient themselves or their oncologist.

#### 7.3.5.2 *Consent process*

Once patients were introduced to me, we had a brief discussion about whether they wished to hear more about the study immediately, or whether they preferred to postpone this to a later date by telephone or face-to-face during another outpatient appointment or chemotherapy treatment. If patient preference was to discuss the study immediately, a quiet and private spot was found within the Macmillan Cancer Centre.

During the consent process, I first outlined the purpose of the study, what was involved, key timepoints and a description of tumour testing. I then went through the study information sheet and consent form with the patient, answering any questions she had regarding her participation or the study itself. At this point, unless patients declined outright, potential participants were given a minimum of 24 hours to make a decision regarding participation, at which time I contacted the patient to ask if she was willing to participate. At the follow-up phone call or face-to-face meeting, if patients expressed a desire participate and gave verbal consent, they were enrolled in the study and provided with the first study questionnaire (Questionnaire 1), information sheet and consent form, as well as a reply-paid envelope. Each participant was assigned a study ID which would be used throughout the duration of the study.

A number of patients wished to give consent immediately during the initial meeting; if I felt satisfied that the patient had read the information regarding the study and had sufficient understanding, the patient was enrolled immediately. The patient was

provided with the information sheet, consent form, Questionnaire 1 and reply-paid envelope.

#### 7.3.6 Data collection

As described above, once participants had been enrolled into the study they were provided with Questionnaire 1. When participants consented to MTGT, they were given Questionnaire 2 to complete. After MTGT results had been reported and disclosed to participants by their oncologist, they were provided with Questionnaire 3 to complete.

Participants were asked to return the completed questionnaire and consent form within a week, to ensure it could arrive and be processed prior to the next timepoint in the study timeline. Participants were given the option of completing each questionnaire at home and returning the questionnaire by post in the reply-paid envelope or bringing it to their next outpatient appointment, or completing the questionnaire in the presence of the researcher if they wished to.

##### 7.3.6.1 *Data completion*

To maximise the completion rate of participant questionnaires, if I had not received a completed questionnaire within 7 days after recruitment, the participant was followed up with a reminder telephone call. If a participant was returning to UCLH prior to her next gynaecology oncology outpatient appointment, I offered to collect the completed questionnaire in person.

The questionnaires used in this study were chosen not only for their clinical validity and frequent use within the research setting but also for their brevity in order to minimise participant burden and maximise completion rates. It was also emphasised during the consent process that the participants could contact the researcher by telephone if they had difficulty completing the questionnaire or needed to clarify any items and a number of participants did take up this offer.

#### 7.3.7 Questionnaires and measures

Participants completed three questionnaires over the course of this study. Each consisted of a number of core measures which were repeated within every questionnaire, as well as measures specific to the timing at that part of the testing pathway. Figure 7.2 shows the testing pathway questionnaires and measures. The questionnaires can be found in the Appendix.

#### 7.3.7.1 *Core measures*

As the average time from recruitment to receipt of MTGT results was estimated to be four months, within this time period there may be significant changes in a patient's clinical status or treatment. For example, some patients may have just started treatment for a new diagnosis or for relapsed disease, while for others treatment may be ongoing. Some patients may be recruited after having completed treatment and are on clinical follow-up only. As treatment, performance and/or disease status (i.e. remission or relapse) as well as symptoms can impact quality of life and psychological wellbeing, at each key part of the MTGT pathway it was important to measure psychological distress, quality of life and symptomatology.

**Demographic and disease data:** The questionnaires collected data on socio-demographic variables such as age, parity, education, employment etc. Clinical information was gathered from participants' medical records: date of diagnosis, FIGO stage and histological grade, type/date of surgery, tumour histology, past and current chemotherapy treatment. (See Appendix p.285)

**Hospital Anxiety and Depression Scale (HADS):** The 14-item HADS is a widely used measure of emotional distress and has two subscales measuring anxiety and depression [217]. (See Appendix p.286)

**Functional Assessment of Cancer Therapy (FACT-G):** This 27-item instrument is widely used to measure cancer-specific health-related quality of life (HRQOL). There are four subscales measuring wellbeing: physical, social/family, emotional and functional [218]. (See Appendix p.305)

**NCCN/FACT Ovarian Symptom Index-18 (NFOSI-18):** The NFOSI-18 is a validated measure used for ovarian cancer symptomatology developed as part of the Functional Assessment of Cancer Therapy (FACT) series of questionnaires which shows good content validity [219]. (See Appendix p.287)

#### 7.3.7.2 *Additional measures*

Measures differed in each part of the study to reflect the different key areas and study aims.

## **Questionnaire 1: Attitudes, Intention and Knowledge**

BRCA1/2 testing knowledge: This is an 11-item true-false measure of assessing knowledge of inheritance of breast-ovarian cancer susceptibility and genetic testing [220, 221]. (See Appendix p.289)

Attitudes to BRCA1/2 genetic testing: Attitudes were measured with 12 items about the risks and benefits of testing on a 5-point Likert scale which has been used previously in a large cohort of breast cancer patients [221]. Responses to the four benefit items and nine risk items were combined to create an overall score for benefits or risks of testing, with an internal consistency of 0.82 and 0.76, respectively. One risk item on cost of BRCA1/2 testing was excluded as this was not relevant for this study. (See Appendix p.288)

Genetic testing intention: Three items assessed participants' intentions to have genetic testing. Similar items have been used in other studies measuring genetic testing intentions [222]. (See Appendix p.290)

## **Questionnaire 2: Decision Making**

Motivations and expectations: This measure was adapted from the validated instrument Motivations And Concerns for GeNETic Testing (MACGNET) [223]. Some items were excluded or rephrased as they were not suitable for this population of cancer patients; other items developed from the literature and clinical experience were included. Motivational factors are assessed using a 5-point Likert Scale and include two open-ended questions. Expectations of outcomes for genetic testing results were also included. (See Appendix p.298)

Decisional Conflict Scale (DCS): This 16-item validated scale measured decisional conflict in relation to genetic testing choices, including uncertainty about alternatives, modifiable factors contributing to uncertainty and perceptions of effectiveness of decision-making. A DCS score <25 indicates no difficulties with decision-making. Internal consistency coefficients ranged from 0.78 to 0.92 [224]. (See Appendix p.300)

BRCA1/2 testing knowledge (as above).

Attitudes to BRCA1/2 genetic testing (as above).

### Questionnaire 3: Outcomes of MGT

Decision Regret Scale (DRS): This five-item scale was used to measure decision regret in relation patient's decision regarding genetic testing. The scale showed good internal consistency (Cronbach's = 0.81 to 0.92) [225]. (See Appendix p.310)

The Multidimensional Impact of Cancer Risk Assessment (MICRA): This 25-item questionnaire measured the specific impact of result disclosure after genetic testing with three subscales: Distress ( $\alpha = .86$ ), Uncertainty ( $\alpha = .77$ ) and Positive Experiences ( $\alpha = .75$ ) [226]. (See Appendix p.308)

Clinic evaluation: An in-house scale of items assessed the communication of genetic information by the clinicians, understanding of genetic information, satisfaction with offer, information and support. (See Appendix p.311)

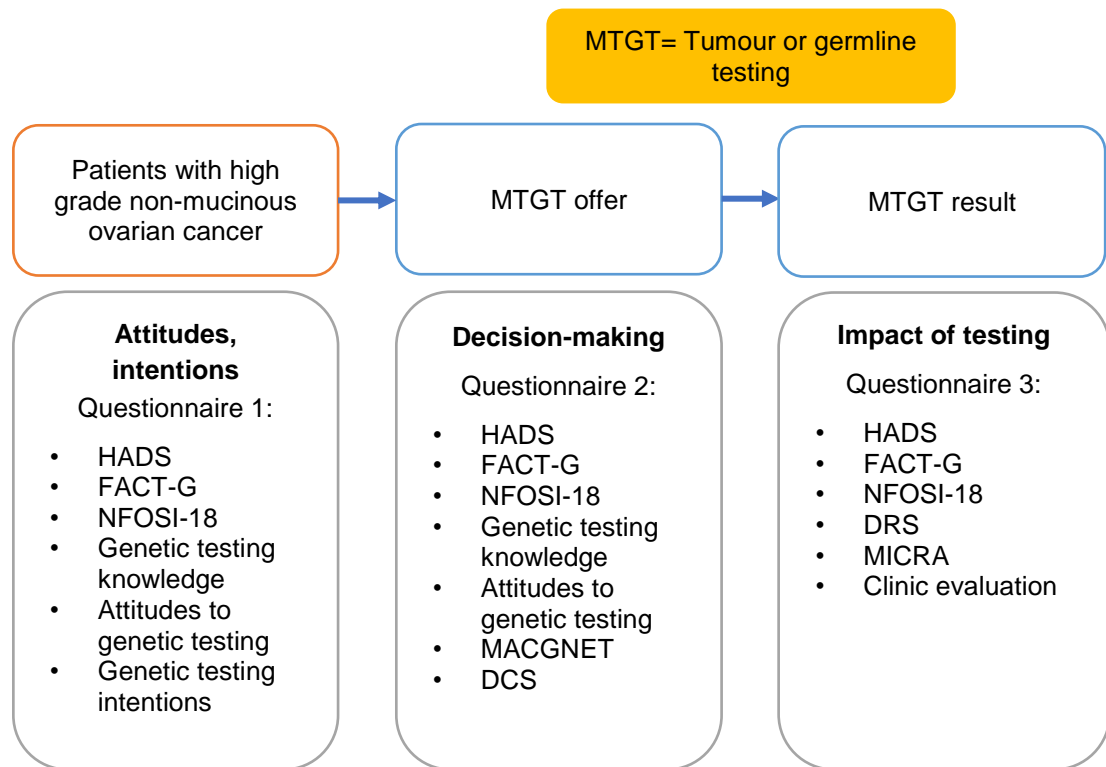


Figure 7.2 MTGT pathway timepoints and questionnaires

#### 7.3.7.3 Choice of measures

The HADS is a brief, validated measure which provides a useful overall screening tool of anxiety and depression. Since it was first published in 1983 it has been used extensively within the primary care and general population setting. It was also relevant

to this study because of its use in cancer patient samples [227]. It has been used extensively in genetic counselling and testing research [228], which may allow comparisons between our findings and the literature. However there are criticisms of the HADS, including a lack standardised cut-off points [229], issues relating to the measure's sensitivity and specificity [230] and whether a single-, two- or three-factor model structure is best [230, 231]. For example, although the HADS was developed to produce two separate scores to measure anxiety and depression, there has been a tendency to use the total score as a single measure of psychological distress in oncology studies [232]. As the aim of this study was not to identify the number of 'cases' but rather using the HADS as a descriptive tool for levels of patient distress, the HADS scores were considered as a whole, rather than the subscales anxiety and depression separately. Moreover, a meta-analysis of HADS data reported that it did not provide good separation between the two subscales [233].

The FACT-G was designed as a HRQOL assessment for cancer patients and is used in clinical trials and descriptive studies. Another widely used HRQOL measure is the European Organisation of Research and Treatment for Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) which has very similar psychometric properties and item numbers; choice between the two measures was guided by a decision tree [234].

The FOSI-18 has several benefits over other measures of symptomatology; it is brief and easy to complete, has global application and interpretation and has been validated within a sample of advanced ovarian cancer patients [219].

Motivations for genetic testing in unaffected individuals are well described, with learning cancer risks for self and/or family members and relief from uncertainty commonly cited [220, 235, 236]. Little is known about the motivations for women with a current ovarian cancer diagnosis to learn their genetic status. Previously motivation for testing was measured using statements based on clinical experience and the literature, and a validated scale was not available. Some adaptations to the MACGNET have been necessary because of the nature of the participant group, which renders some items inappropriate or obsolete; e.g., 'I want to know what my chances are of getting cancer'. Although this measure is quite lengthy and has not been used widely within the literature to date, it is a validated measure developed specifically for inherited cancer syndromes and genetic testing.

The two measures relating to decision making chosen for this study, DCS and DRS, have both been widely used as a measure for health care decisions, including genetic testing decisions. The DCS can discriminate between two groups, those who make and those who delay decisions. Both can be customised to specific health care decisions, in this case BRCA1/2 tumour or germline testing.

To date few studies have used measures that specifically explore the outcomes of genetic testing for hereditary cancer, rather adapting or anchoring other existing measures (for example the Impact of Events Scale, IES). The MICRA was developed to measure the specific impact of result disclosure after genetic testing. Strengths include its specificity, and its ability to differentiate between BRCA1/2 mutation carriers and non-carriers, and has been validated in a sample both with and without a cancer diagnosis. Variability in subscale scores reflects the range of response to testing and individual differences within individuals who have testing. The clinical significance of elevated MICRA scores remains to be evaluated.

In the genetic counselling context knowledge is a construct that has been used to measure the 'success' of the communication process, although more recently there has been a shift away from using this for assessing outcomes [228]. However in a research context it may still provide some useful insight into what patients already know and understand about genetic testing, and whether this changes over the course of testing. This is the intention for including a BRCA knowledge measure, to explore any changes during the mainstreamed genetic testing process. Other researchers have also adopted this approach either by adapting validated scales or developing their own scales without undertaking a formal validation process. The BRCA knowledge questions were chosen as they have been used previously in BRCA genetic testing research, were brief and easy to score, and covered key items relevant to this research [220, 221].

#### **7.4 Statistical analysis**

Statistical analyses were conducted using SPSS for Windows (Version 25.0; SPSS Inc., Chicago, IL). A minimum of two methods were used to determine the normality of data: Shapiro-Wilk's test ( $p > .05$  indicating normal distribution) and the visual inspection of a Normal Q-Q Plot and/or histogram.

Demographic and clinical factors were summarised with counts (percentages) for categorical variables. For continuous variables that were normally distributed, means



and standard deviations (SD) were reported; for skewed data, medians, ranges and interquartile ranges (IQR) were reported.

Three predefined sub-groups were identified a priori to investigate the effects of these variables on the outcome of interest for each questionnaire: participant age, time from diagnosis and treatment status. Due to the small sample size the sub-groups were divided into binary categories: participant age was categorised as 'younger, up to 70 years', and 'older, 70 years and over'; time from diagnosis '12 months or less' versus 'more than 12 months'; treatment status as 'active' (chemotherapy, immunotherapy or other cytotoxic treatment) or 'surveillance' only.

The independent sample *t*-test was used in the subgroup analyses to compare differences between two independent groups for normally distributed continuous data, and the non-parametric Mann-Whitney U test was used otherwise. A paired samples *t*-test was used to determine if there were differences in means between two related groups on the same continuous, dependent variable if the differences between pairs were approximately normally distributed. The non-parametric Friedman test was used to test for differences between groups on repeated measures otherwise ANOVA was used. The results of the hypothesis tests were regarded as significant at  $p < 0.05$ .

I undertook the statistical analyses of this data. Dr Aviva Petrie (Biostatistics Unit, Faculty of Medical Sciences, UCL) reviewed this chapter and provided feedback.

#### 7.4.1 Loss to follow-up between questionnaires

There was some loss to follow-up between Questionnaires 1 ( $n = 63$ ) and 2 ( $n = 53$ ), and then a significant loss to follow-up at Questionnaire 3 ( $n = 33$ ).

The dropout between Questionnaires 1 and 2 was due to participants not wishing to have genetic testing ( $n = 1$ ), withdrawing due to illness ( $n = 1$ ), genetic testing organised outside of the study ( $n = 3$ ), consultant decision not to continue with tumour testing ( $n = 1$ ), or non-completion/return of questionnaire ( $n = 4$ ). The further dropout between Questionnaires 2 and 3 was due to participants not proceeding with either tumour or germline testing ( $n = 3$ ), non-completion/return of questionnaire ( $n = 13$ ), or questionnaires not yet given to participant ( $n = 6$ ).

As significant loss to follow-up may introduce biased results as well as a loss of statistical precision, repeated measures analyses were only conducted using data from participants who had completed all three questionnaires ( $n = 29$ ).

#### 7.4.2 Missing data

Of the questionnaires that were completed and returned, overall there was a minimal amount of missing data. Missing data was typically missing not at random (MNAR), with participants tending to not respond to similar items. In some cases this was conditional; for example, the item was related to having children or a partner which depends on parity and relationship status. In other cases it perhaps reflected difficulty in responding to the item. For example, 13% of participants had missing data for the same MICRA item, 'Feeling happy about my test results'.

Participants with more than 5% of data missing within a measure were excluded from the analysis. For items with responses scored on a Likert scale (e.g. Attitudes to genetic testing scale), missing data was imputed as the mid-point value. Where data was missing on knowledge measures, this was taken as responding as 'Don't Know' and scored accordingly.

Missing data was felt to be as missing at random (MAR) if only one participant had missing data for that specific item within a measure, or if the item had been completed successfully by a participant in an earlier questionnaire. For MAR data, last observation carried forward (LOCF) was used.

### **7.5 Results**

#### 7.5.1 Adaptations to this research study

As described above in Section 7.3.1, initial plans for this research were to offer either mainstreamed BRCA1/2 germline or tumour testing (MTGT) to eligible ovarian cancer patients. Germline testing for all women with high grade non-mucinous ovarian cancer had already been implemented in this centre in April 2015, as described in the service evaluation of Chapter 5 earlier in this thesis. Germline testing remains the 'gold standard' approach to BRCA1/2 genetic testing within the UK and is the most common genetic testing service provided across clinical genetics and oncology centres.

The intention of including both testing modes was to draw out any differences in the experiences of patients offered germline testing to those offered tumour testing. Thus, the materials used in this research were designed to refer to 'mainstreamed genetic testing' or 'genetic testing' generically, rather than germline or tumour testing specifically, in order to capture both testing modes using one standardised set of study questionnaires.

As tumour testing was a finite resource of 50 tests, to ensure equality of access as well as limiting bias or inherent clinical differences between patients offered germline or tumour testing, the intention was to randomly allocate either mode of testing as patients were recruited into the study. However this approach of random allocation of testing mode was modified shortly after recruitment began, due to the slower than anticipated recruitment rate and the limited timeframe in which recruitment was planned (these issues are discussed further in this chapter). As a result, a decision was made to offer tumour testing to the first 50 patients recruited, as this would ensure all tumour tests would be allocated prior to the recruitment period ending. Once all tumour tests had been allocated, recruited participants would be offered germline testing as per standard practice within this centre.

Again, modifications became necessary during recruitment. More than the full recruitment timeframe of 12 months was required to recruit, provide and ensure 50 participants had tumour testing and received results. Difficulties recruiting patients having standard germline testing (described in the following section) and the limited timeframe remaining meant a decision was made to abandon this group and focus solely on the process, provision, clinical outcomes and patient experience of tumour testing.

These adaptations did not impact the study aims nor methods, and the structure of this study remained the same.

### 7.5.2 Recruitment

Participant recruitment commenced in November 2016. Recruitment was first completed in December 2017 when all 50 tumour tests had been allocated. However due to earlier tumour tests failing and subsequent reallocation of tests to other eligible patients, there still remained four tumour tests available. Recruitment recommenced in February 2018 and continued until the final tumour tests were allocated and participants received their results.

During recruitment in clinic, in total 73 patients gave verbal consent to participate and were enrolled in the study. These patients were provided with all the relevant study documents for the purpose of completing the first study questionnaire and accompanying consent form. Ten patients did not complete the initial consent form or other study documents and after further discussion, either actively withdrew or were withdrawn from the study for the following reasons:

- Issues with genetic testing: lack of interest in genetic testing, not wanting to know genetic testing results
- Psychosocial issues: feeling too overwhelmed to participate
- Clinical issues: becoming too unwell to participate
- Issues with research: not interested in taking part in a research project
- Failure to complete initial study documents despite repeated prompting from researcher
- Communication issues: two patients were offered and agreed to germline testing instead as their consultant was not aware they had consented to this PhD project.

A number of these patients proceeded with germline testing via the usual clinical route at a later date.

#### *7.5.2.1 Challenges to recruitment*

As described earlier in this chapter, eligible participants were identified during the weekly pre-clinic meeting attended by clinical and medical oncology consultants, registrars, clinical nurse specialists and the clinical trials team. The model of participant recruitment used in this study relied on oncologists initially presenting this study to their patient, and taking verbal consent from their patient for an introduction to me. Thus who could be approached and when, was to some degree guided by the oncologists; recruitment was a collaborative process.

The first challenge to recruitment was that there were fewer eligible patients than anticipated. As MGT for BRCA1/2 germline testing had already been implemented at UCLH in 2015, there was a large sample of ovarian cancer patients who had already undergone genetic testing and were therefore ineligible to participate. This limited the pool of patients who could be approached for this study to (a) newly diagnosed patients, and (b) a smaller pool of existing patients who had not been previously offered testing by their oncology consultant.

Ovarian cancer patients have intensive chemotherapy regimens and are closely monitored both during and post-treatment, and may spend many months or years in and out of treatment. As a result the medical and clinical oncology consultants were very well acquainted with their patients. This was both a benefit and, at times, a challenge to recruitment.

All the oncologists involved in this study demonstrated a protective nature over their patients. There was a reluctance for me to approach patients who would be receiving bad news during their clinic appointment that day (for example, disease progression or relapse), preferring to delay recruitment to another clinic visit. At times the oncologists were keen to avoid 'overloading' their patients with additional information or decisions, particularly for those who were newly diagnosed and beginning systemic treatment for the first time. Additionally, oncologists felt some patients had existing psychosocial issues which were not part of the study exclusion criteria, but meant they should not be approached for participation.

Although there was no maximum age criteria for participation, some oncologists felt less inclined to recruit patients over the age of 70. There is published data on genetic testing in ovarian cancer to indicate that the prevalence of BRCA1/2 germline mutations is lower in older patients [74]. However other research has identified mutations in patients older than 70 [73], including data from the service evaluation in this PhD (see Chapter 5) and the clinical outcomes from the previous chapter. As somatic mutations are driven by a different mechanism and do not reflect the age incidence related to germline mutations, arguably there should be no age restriction for tumour testing.

Medical gatekeeping is defined as a process where clinicians restrict access to research recruitment, either on an ad hoc or systematic basis, and has been recognised to take place within cancer clinical trials and research [237]. In particular, there has been an underrepresentation of elderly patients [238]. Despite the potential impact on recruitment, clinicians' concerns about the wellbeing of their patients are important and should not be devalued [237].

In this study, to some degree gatekeeping may have biased the sample to patients who were demonstrating better psychological and physical resilience than others. In some cases, repeated deferral of either introducing genetic testing or this study led to missing eligible patients, who in turn became ineligible because of poor health, or were offered germline testing outside of the study in the meantime. However, gatekeeping also ensured that the recruitment process was unlikely to have been an additional burden to patients and protected their wellbeing.

As recruitment rates and barriers to recruitment was not an aim of this research, there was no systematic procedure of recording the number of patients approached and the number who declined. However, the rate of recruitment (approximately 1.3 patients

per week) was significantly less than anticipated, particularly in reference to previous psychosocial research in genetic testing for women with breast or ovarian cancer [110, 139]. Another study which was recruiting both 'new' and 'old' ovarian cancer cases for biobanking of blood and tissues samples for genetic testing, found lower recruitment rates [239]. Barriers to recruitment were reported as patients being too unwell, lack of time because of medical appointments, wishing to focus on treatment as well as concerns about genetic research [239].

#### *7.5.2.2 First-line germline testing comparison group*

By the time this study was undertaken in 2017, germline BRCA1/2 testing in ovarian cancer had become standard of care; at UCLH it had been offered via MGT since 2015.

The challenges of recruiting participants for germline testing was two-fold. Firstly, because germline testing had been available for nearly two years for patients with high grade non-mucinous ovarian cancer, a large number had already undergone testing via MGT. As described on the previous page, this limited the pool of patients who would be eligible for this study.

Secondly germline testing had become routine, not only for the clinical team, but to some extent also for participants. Anecdotal evidence from my experience in the outpatient clinic as well as from the qualitative data in Chapter 8 showed that many patients knew genetic testing was available, and some had requested BRCA1/2 testing from their oncologist themselves.

At the time of recruitment, tumour testing was only available to patients if they were participants of this research. Thus taking part was potentially advantageous not only for participants but also for their oncologists, given that PARP-inhibitors are licensed for somatic mutations. In contrast, germline testing was and is readily available for patients outside of this study, thus there was little additional incentive to participating.

Once recruitment for first-line tumour testing was complete, recruitment then turned to participants who would be offered first-line germline testing. Over the course of several clinics, five eligible patients were approached and invited to take part in this research. Following the same process of recruitment described in above, after a conversation in person or by phone, the study documentation (information sheet, consent form, questionnaire) was provided. After one follow-up prompt, either in person or by phone, no consent forms or questionnaires were returned. As the

timeframe for recruitment had already expired, a decision was made not to pursue recruitment any further.

Low recruitment rates have also been an issue for other psychosocial research in MGT that was undertaken in the sample ovarian cancer cohort at UCLH. In an MSc project which I helped to supervise, as a follow-up to the service evaluation a brief questionnaire on experiences of MGT was developed. Of the 170 ovarian cancer patients who had MGT between February 2015 and June 2017 (as recorded by the NE Thames Regional Genetics Laboratories), 64 patients were excluded for the following reasons: 34 (53.1%) were deceased, 9 (14.0%) required an interpreter, 5 (7.8%) patients had no genetic testing report in their medical file, 2 (3.1%) patients had no medical file, 4 (6.3%) patients were too unwell and 10 (15.6%) at the oncologists' discretion. The remaining 106 eligible patients were invited to take part in the study by letter (signed by their treating oncologist) in which was enclosed a study information sheet and an 'opt-in' form. Using an opt-in approach, a study questionnaire and consent form was then posted to the patient along with a reply-paid envelope. Only thirty-three (31.1%) patients returned their opt-in form, with 29 questionnaires later returned by post leading to an overall response rate of 27.4%.

### 7.5.3 Sample characteristics

The sample characteristics were recorded from the first questionnaire which acted as a baseline questionnaire prior to testing (n=63); the characteristics are summarised in Table 7.1 below.

The mean age of participants was 63.8 years (range 36-86) at diagnosis, and 65.7 years (SD  $\pm$ 9.86) at study recruitment. The mean length of time between diagnosis and study participation was 22 months; this ranged from recruitment shortly after diagnosis (one month) to several years post-diagnosis (132 months).

Most participants (73.0%) described their ethnicity as White British, with a further 15.9% of any other White Background. At least 23.8% of participants had completed high school education at O level or GCSE equivalent. More than half of this sample (58.1%) were married or living with a partner, and the majority of participants (81%) had at least one child. Reflecting the mean age of participants, at least half of this sample had retired from employment (52.4%).

Table 7.1 Participant socio-demographic characteristics.

<b>Characteristic</b>	<b>Sample (n = 63)</b>
<b>Age, mean (SD)</b>	
Diagnosis	63.8 (9.96)
Recruitment	65.7 (9.86)
<b>Ethnicity, n (%)</b>	
White	57 (90.5)
Black	3 (4.8)
Mixed	2 (3.2)
Other	1 (1.6)
<b>Education, n (%)</b>	
Degree or higher degree	12 (19)
A-levels of higher	11 (17.5)
O level/GCSE equivalent	15 (23.8)
ONC/BTEC	4 (6.3)
Still studying	1 (1.6)
No formal qualifications	11 (17.5)
Other	9 (14.3)
<b>Living arrangements, n (%)</b>	
Own outright	33 (53.2)
Own mortgage	14 (22.6)
Rent from local authority	8 (12.9)
Rent privately	3 (4.8)
Other	4 (6.5)
<b>Marital status, n (%)</b>	
Single/never married	8 (12.9)
Married/living with partner	36 (58.1)
Separated/divorced	9 (14.5)
Widowed	9 (14.5)
<b>Employment, n (%)</b>	
Full-time	6 (9.5)
Part-time	7 (11.1)
Self-employed	2 (3.2)
Unemployed	4 (6.3)
Homemaker	4 (6.3)
Disabled/too ill to work	7 (11.1)
Retired	33 (52.4)



Participant clinical data was gathered from their online medical records, CDR. As can be seen in the table below, 76.2% of participants were diagnosed with stage III/IV disease, in keeping with expected stage distribution. As the initial study design was to recruit patients who would be having either tumour or germline testing, recruitment was initially open to all women with high-grade non-mucinous disease. After several months of recruitment when the focus shifted to only first-line tumour testing, Myriad Genetics also confirmed only tumours with high grade serous histology would be tested. Several participants with other histology types had already been recruited; tumour testing proceeded in some of these cases while some patients were instead referred for germline testing.

The majority of participants (74.6%) were on active systemic treatment (either chemotherapy, clinical trial or bevacizumab) at the time of recruitment. Most participants (69.8%) were undergoing, or had completed, first line treatment. One participant had not undergone any systemic treatment for her ovarian cancer.

Table 7.2 Disease stage at diagnosis

<b>Clinical characteristic</b>	<b>Sample (n = 63)</b>
<b>Disease stage, n (%)</b>	
Stage I	3 (4.8)
Stage II	7 (11.1)
Stage III	25 (39.7)
Stage IV	23 (36.5)
Unstaged	5 (7.9)
<b>Histology, n (%)</b>	
High grade serous	53 (84.1)
Carcinosarcoma	4 (6.3)
Clear cell	2 (3.2)
Endometrioid	3 (4.8)
Seromucinous	1 (1.6)
<b>Treatment line, n (%)</b>	
First line	44 (69.8)
Second line	16 (25.4)
Third line	2 (3.2)
No treatment	1 (1.6)
<b>Current treatment status, n (%)</b>	
Active	47 (74.6)
Surveillance	16 (25.4)

#### 7.5.4 Results from study questionnaires

As described earlier in this chapter, three questionnaires were completed by participants over the course of this study. For simplicity, the questionnaires will be abbreviated going forward, e.g. Questionnaire 1 (Q1) etc. A number of measures were repeated in each part of the study. Data for measures completed at each part of the study are presented together.

There was a drop-off in terms of questionnaire completion over the course of this study. Sixty-three participants returned completed Q1 questionnaires, then 54 completed questionnaires were received at Q2, and 33 at Q3. Only 29 participants completed all three questionnaires. Due to missing data on some of the measures, sample size (n) varied slightly. Of the 33 participants who completed and returned Q3, 23 (69.7%) had no mutation identified, seven (21.2%) had a germline BRCA1/2 mutation, one (3.0%) RAD51C mutation and two (6.1%) RAD51C VUS.

It is important to note here that there were no participants with a somatic mutation amongst the completed questionnaires. Of the three participants who had somatic mutations (described in Chapter 6), two only learnt of their somatic mutation status after repeat tumour testing which was undertaken outside of this research, and after they had completed their last study questionnaire. The third participant who had a somatic mutation identified during study participation did not return Q3 despite several reminders. Therefore the results include only participants who carried germline mutations.

#### 7.5.4.1 Distress

Distress was measured using the self-reported HADS, where higher scores reflect greater levels of distress. This was measured at Q1, Q2 and Q3.

Table 7.3 Descriptive statistics of HADS total scores at three timepoints

<b>HADS</b>	<b>Q1</b>	<b>Q2</b>	<b>Q3</b>
<b>n</b>	63	53	31
<b>Median</b>	10.5	8.0	8.0
<b>IQR</b>	6.8-14.3	4.0-14.0	4.0-13.8
<b>Possible range</b>	0-42	0-42	0-42
<b>Observed range</b>	1-39	0-24	0-25
<b>Score <math>\geq 19</math>, n (%)</b>	10 (15.9)	3 (5.7)	3 (9.7)

A Friedman test was run to determine if there were differences in HADS total scores across the three questionnaires. Median HADS total scores varied decreased from Q1 (Mdn = 10.5) to Q2 (Mdn = 8.0) and then remained the same for Q3 (Mdn = 8.0); the differences were not statistically significant ( $p = .071$ ).

The Mann-Whitney U test was used to determine differences in HADS scores for the following pre-defined sub-groups: age at study recruitment, time from diagnosis, and treatment status. The results are shown in the below.

The median HADS score was significantly higher in participants younger than 70 years of age than those 70 years or older at Q1 ( $p = .043$ ) and Q3 ( $p = .021$ ). There was no significant difference at Q2 ( $p = .510$ ). At Q1, the median HADS score was significantly higher for participants diagnosed within the preceding 12 months compared to those more than 12 months from diagnosis ( $p = .035$ ). There was no significant difference at Q2 ( $p = .854$ ) or Q3 ( $p = .918$ ). There were no statistically significant differences for treatment status at Q1 ( $p = .439$ ), Q2 ( $p = .067$ ) or Q3 ( $p = .313$ ).

Mutation status data was available at Q3. There was no significant difference in median HADS total scores between participants with no genetic alteration, and those with a pathogenic mutation or VUS ( $p = .749$ ).

Table 7.4 Distress scores across three study timepoints

HADS		Q1				Q2				Q3			
Sub-groups	n	Median (IQR)	<i>U</i>	p-value	n	Median (IQR)	<i>U</i>	p-value	n	Median (IQR)	<i>U</i>	p-value	
<b>Age</b>	<70 years	38	11.5 (8.0-18.0)	316.0	.043	33	9.0 (4.0-14.0)	309.5	.510	21	11.0 (7.5-16.5)	51.0	.021
	≥70 years	25	8.5 (6.0-11.8)			21	7.0 (4.0-12.5)			11	5.0 (4.0-7.0)		
<b>Time from diagnosis</b>	<12 months	28	11.0 (8.0-15.0)	620.5	.035	31	8.0 (5.0-12.0)	346.0	.854	16	7.5 (4.3-12.5)	115.0	.918
	≥12 months	35	9.0 (4.0-14.0)			23	8.0 (3.0-14.0)			16	8.5 (3.3-17.0)		
<b>Treatment status</b>	Active treatment	47	10.0 (6.0-14.0)	320.0	.439	41	8.0 (4.0-12.5)	204.5	.208	17	8.0 (5.0-16.5)	155.0	.313
	No treatment	16	11.5 (7.3-20.3)			13	9.0 (3.5-18.5)			15	7.0 (4.0-11.0)		
<b>Mutation status</b>	Mutation or VUS									10	8.0 (3.0-13.5)	103.0	.749
	No genetic alteration									22	8.0 (4.8-14.3)		

#### 7.5.4.2 Health-related quality of life (HRQOL)

HRQOL was measured using the NCCN FACT-G: Functional Assessment of Cancer Therapy - General (constitutes four core subscales; the FACT-G can be used with patients of any tumour type). It is one of the most widely used cancer-specific HRQOL questionnaires. The four subscales reflect physical, social, emotional and functional wellbeing, as well as a total HRQOL score. Higher scores represent better wellbeing and less symptom burden. HRQOL was measured at Q1, Q2 and Q3.

Descriptive statistics are presented in Table 7.5 below. Overall participants appeared to have good HRQOL, with high median scores across the four domains. A Friedman test was run to determine if there were differences in FACT-G total scores across the three questionnaires. FACT-G total scores varied between Q1 (Mdn = 86.5), Q2 (Mdn = 84.0) and Q3 (Mdn = 93.0), but the differences were not statistically significant ( $p = .615$ ).

The Mann-Whitney test was used to determine differences in FACT-G scores for the following pre-defined subgroups: age at study recruitment, time from diagnosis, and treatment status. These results are shown in Table 7.6 below. Median FACT-G scores were significantly higher in participants younger than 70 years of age than those 70 years or older at Q1 ( $p = .007$ ) and Q3 ( $p = .005$ ). There was no significant difference at Q2 ( $p = .475$ ). At Q1, the median FACT-G score was significantly higher for participants diagnosed within the preceding 12 months compared to those more than 12 months from diagnosis ( $p = .012$ ). There was no significant difference at Q2 ( $p = .535$ ) or Q3 ( $p = .717$ ). There were no statistically significant differences for treatment status at Q1 ( $p = .522$ ), Q2 ( $p = .420$ ) or Q3 ( $p = .208$ ).

Mutation status data was available at Q3. There was no significant difference in FACT-G median scores between participants with no genetic alteration, and those with a pathogenic mutation or VUS ( $p = .672$ ).

Table 7.5 Descriptive statistics for HRQOL scale FACT-G scores

FACT-G Scores	Q1 (n=63)			Q2 (n=52)			Q3 (n=33)		
	Median (IQR)	Possible range	Observed range	Median (IQR)	Possible range	Observed range	Median (IQR)	Possible range	Observed range
<b>Physical wellbeing</b>	24.0 (20.0-26.0)	0-28	0-28	24.0 (21.0-27.0)	0-28	9-28	25.5 (21.0-27.0)	0-28	0-28
<b>Social wellbeing</b>	25.0 (21.0-27.0)	0-28	12-28	25.0 (22.0-27.8)	0-28	12-28	26.0 (20.0-28.0)	0-28	13-28
<b>Emotional wellbeing</b>	19.0 (16.0-22.0)	0-24	3-24	19.5 (16.3-22.8)	0-24	8-24	20.0 (17.0-22.0)	0-24	6-24
<b>Functional wellbeing</b>	19.0 (13.0-25.0)	0-28	8-28	20.0 (14.3-24.0)	0-28	4-28	21.5 (17.0-22.0)	0-28	3-28
<b>FACT-G Total</b>	85.0 (73.0-96.0)	0-108	32-106	87.0 (73.5-98.3)	0-108	42-107	93.0 (72.3-100.0)	0-108	31-104

Table 7.6 HRQOL scale FACT-G scores across study timepoints by subgroups

FACT-G		Q1				Q2				Q3			
Sub-groups	n	Median (IQR)	U	p-value	n	Median (IQR)	U	p-value	n	Median (IQR)	U	p-value	
Age	<70 years	38	80.5 (66.3-90.0)	667.0	.007	32	85.5 (72.8-100.5)	358.0	.475	20	85.0 (65.3-95.0)	147.0	.005
	≥70 years	25	91.0 (83.0-99.0)			20	90.5 (73.5-95.0)			10	100.0 (93.0-103.0)		
Time from diagnosis	<12 months	28	90.5 (67.0-89.0)	309.0	.012	30	87.0 (76.5-99.3)	363.5	.535	15	92.0 (79.0-100.0)	106.0	.717
	≥12 months	35	80.0 (81.5-98.8)			22	87.0 (64.8-96.8)			15	94.0 (70.0-100.0)		
Treatment status	Active treatment	47	87.5 (73.0-94.0)	335.0	.522	40	87.0 (77.5-99.0)	261.5	.420	16	90.5 (65.3-97.3)	81.0	.208
	No treatment	16	83.0 (75.0-98.3)			11	86.0 (64.0-96.0)			14	95.5 (82.8-100.8)		
Mutation status	Mutation or VUS									21	91.0 (69.0-98.0)	71.0	.672
	No genetic alteration									9	95.0 (74.5-100.0)		

HRQOL was also measured more specifically for ovarian cancer. NCCN-FACT ovarian symptom index-18 (NFOSI-18) is an index of priority symptoms in advanced ovarian cancer. Higher scores represent better wellbeing and less symptom burden.

Table 7.7 Descriptive statistics for N-FOSI scores across timepoints

<b>NFOSI</b>	<b>Q1</b>	<b>Q2</b>	<b>Q3</b>
<b>n</b>	63	53	30
<b>Median</b>	54.0	59.0	58.5
<b>IQR</b>	48.0-62.0	51.0-65.5	51.0-64.0
<b>Possible range</b>	0-42	0-42	0-42
<b>Observed range</b>	11-72	27-72	17-69

Similar to FACT-G scores, overall participants had high median NFOSI total scores, indicating better HRQOL. A Friedman test was run to determine if there were differences in NFOSI total scores between Q1, Q2 and Q3. There was some variation in median NFOSI total scores (see Table X), but the differences were not statistically significant ( $p = .638$ ).

The Mann-Whitney test was used to determine differences in NFOSI scores for the pre-defined subgroups: age at study recruitment, time from diagnosis, and treatment status (Table 7.8). There was no association between age and NFOSI scores, with no significant difference in total scores between younger and older participants at Q1 ( $p = .093$ ), Q2 ( $p = .573$ ) or Q3 ( $p = .226$ ). At Q1, the median NFOSI total score was significantly higher for participants diagnosed within the preceding 12 months compared to those more than 12 months from diagnosis, reflecting more symptom burden ( $p = .035$ ). There was no significant difference at Q2 ( $p = .993$ ) or Q3 ( $p = .294$ ). There was no evidence that treatment status was associated with NFOSI scores at any timepoint (Q1,  $p = .424$ ; Q2,  $p = .924$ ; Q3,  $p = .085$ ).



Table 7.8 NFOSI scores across study timepoints by subgroups

NFOSI		Q1				Q2				Q3			
Sub-groups		n	Median (IQR)	<i>U</i>	p-value	n	Median (IQR)	<i>U</i>	p-value	n	Median (IQR)	<i>U</i>	p-value
<b>Age</b>	<70 years	38	54.0 (46.3-60.3)	594.0	.093	32	59.5 (51.3-66.8)	305.0	.573	20	55.0 (46.0-65.8)	115.5	.226
	≥70 years	25	58.0 (51.0-63.5)			21	58.0 (50.5-64.5)			10	59.5 (58.0-62.5)		
<b>Time from diagnosis</b>	<12 months	28	54.0 (46.0-58.0)	338.0	.035	30	60.0 (52.8-64.3)	345.0	.993	15	61.0 (51.0-66.0)	120.5	.294
	≥12 months	35	59.0 (53.0-64.8)			23	58.5 (47.0-67.0)			15	58.0 (46.0-62.0)		
<b>Treatment status</b>	Active treatment	47	54.0 (48.0-61.0)	325.5	.424	41	56.0 (52.0-64.3)	241.5	.924	16	54.0 (47.3-63.0)	70.5	.085
	No treatment	16	57.0 (46.8-61.0)			12	59.0 (46.3-67.8)			14	61.5 (57.3-66.0)		

### 7.5.4.3 Genetic testing

#### Testing knowledge

Knowledge of genetic testing scale was measured at Q1 and Q2. Following the analysis plan, testing knowledge was grouped by 'high' ( $\geq 6$  of 7 correct responses), 'sufficient' ( $\geq 4$  of 7) and 'poor' ( $< 4$  of 7) by cut-offs defined from Peter's 2005 paper [221].

Table 7.9 Knowledge cut-off scores

Testing knowledge	Q1	Q2
<b>n</b>	63	53
<b>Mean</b>	3.27	3.42
<b>SD</b>	1.70	1.78
<b>Possible range</b>	0-7	0-7
<b>Observed range</b>	0-7	0-7
Knowledge cut-offs	n (%)	n (%)
<b>High</b>	3 (4.8)	7 (13.2)
<b>Sufficient</b>	29 (46.0)	19 (35.8)
<b>Poor</b>	31 (49.2)	27 (50.8)

As can be seen in the table, at Q1 and Q2, approximately half of participants had poor testing knowledge, scoring less than half of the items correctly. At Q1 46.0% of participants showed sufficient testing knowledge, compared to a smaller proportion of participants (35.8%) at Q2. At both timepoints only a small number of participants had testing knowledge scores which were 'high'.

The testing knowledge item with the most correct responses was the same for both Q1 and Q2; item 'A woman who doesn't have an altered BRCA gene can still get cancer' having 81% ( $n = 51$ ) and 83.3% ( $n = 45$ ) of participants selecting 'True'. The item with the most incorrect responses was also the same at both timepoints. This item was for the prevalence of BRCA1/2 mutations in the population 'About 1 in 10 women have an altered BRCA gene'; 81.5% ( $n = 44$ ) and 92.1% ( $n = 58$ ) had an incorrect response, selecting 'True'.

A paired *t*-test was used to look at change in testing knowledge scores between Q1 and Q2. There was no evidence of any statistically significant differences in scores between the two timepoints ( $t(52) = -.651, p = .518$ ).

Due to the small sample size the seven education categories were collapsed to create three educational groups: basic (still studying, no formal qualifications, other), secondary (O levels, ONC, BTEC) and further education (A levels or higher, degree or higher). One-way ANOVA was used to determine if there was an association between educational level and testing knowledge scores, these results are reported in Table 7.10. There was no evidence of an association at Q1 ( $F(2, 60) = 1.927, p = .154$ ) or Q2 ( $F(2, 49) = 2.572, p = .087$ ).

Table 7.10 Knowledge by subgroups across study timepoints

Testing knowledge		Q1			Q2		
		n	Mean (SD)	p-value	n	Mean (SD)	p-value
Education level	Basic	21	3.14 (1.32)	.154	18	2.67 (1.33)	.087
	Secondary	19	2.79 (1.93)		13	3.62 (2.66)	
	Further	23	3.78 (1.73)		22	3.90 (1.90)	
Age	<70	38	3.50 (1.83)	.186	33	3.85 (1.68)	.021
	≥70	25	2.92 (1.44)		20	2.70 (1.75)	

An independent-samples *t*-test was used to determine differences in testing knowledge scores between younger and older participants. At Q1 there was no significance difference in scores ( $p = .186$ ), however at Q2, participants younger than 70 years of age had significantly higher testing knowledge scores compared to those who were older than 70 years ( $p = .021$ ).



Table 7.12 Attitudes to genetic testing scores across study timepoints by subgroups

Attitudes to genetic testing		Q1			Q2		
		n	Mean (95% CI)	p-value	n	Mean (95% CI)	p-value
<b>Age</b>	<70	38	31.92 (29.94, 33.91)	.350	33	33.76 (31.99, 35.53)	.922
	≥70	24	30.42 (27.78, 33.05)		20	33.90 (31.22, 36.59)	
<b>Time from diagnosis</b>	<12 months	35	31.31 (29.49, 33.14)	.973	31	33.42 (31.22, 36.59)	.530
	≥12 months	27	31.37 (28.55, 34.19)		23	34.35 (31.22, 36.59)	
<b>Treatment status</b>	Active treatment	47	32.11 (30.32, 33.89)	.078	41	34.20 (32.61, 35.78)	.412
	No treatment	15	28.93 (25.76, 32.10)		13	32.62(28.89, 36.34)	

## Motivations and concerns of genetic testing (MACGNET)

This scale of items reflecting motivations and concerns of genetic testing was measured at a single timepoint at Q2, after participants had consented to tumour or germline testing. Median scores, IQR and ranges for each subscale are reported in the table below.

Table 7.13 Descriptive statistics of MACGNET subscales

MACGNET Scores		Q2				
(n=54)		No. of items	Median	IQR	Possible range	Observed range
	Prevention and Medical Care (PMC)	8	32.0	30.0- 36.0	8-40	26-40
	Partner Influence (PI)	3	12.0	11.0-13.3	3-15	7-15
<b>Subscales</b>	Future Planning (FP)	4	10.0	9.0-12.0	4-20	3-15
	Ability to Cope (ATC)	5	13.0	11.0-14.0	5-25	8-25
	Medical Influence (MI)	3	12.0	10.0-13.0	3-15	7-15
	<b>Total MACGNET</b>	23	79.0	77.3-84.5	23-115	58-92

A Friedman test was run to determine if there were differences in the distributions of MACGNET subscale scores. Pairwise comparisons were performed with a Bonferroni correction for multiple comparisons after this. Overall, MACGNET scores were statistically significantly different between subscales ( $\chi^2 (2) = 113.159$ ,  $p < .0005$ ). Prevention and Medical Care subscale scores were significantly higher than other subscales, suggesting these items may have greater influence over motivations to have genetic testing.

Table 7.14 MACGNET scores by subgroups

MACGNET		Q2			
Sub-groups		n	Mean (CI)	Mean difference	p-value
<b>Age</b>	<70 years	31	79.42 (76.95-81.89)	-1.12	.612
	≥70 years	13	80.54 (76.70-84.37)		
<b>Time from diagnosis</b>	<12 months	16	81.25 (78.99-83.51)	-4.13	.044
	≥12 months	28	77.13 (73.32-80.93)		
<b>Treatment status</b>	Active treatment	33	80.45 (78.18-82.73)	-2.88	.248
	No treatment	11	77.64 (73.03-82.24)		

As the MACGNET total scores were normally distributed, an independent samples *t*-test was used to examine the predefined dichotomous variables of age, time from diagnosis and treatment status. These results are shown in Table X.

There were no significant differences in mean MACGNET scores for age ( $t(42) = .511, p = .612$ ) or treatment status ( $t(16.265) = 1.199, p = .248$ ). There was a significant difference in mean MACGNET scores for time from diagnosis, with participants diagnosed more recently reporting higher scores compared to those more than 12 months from diagnosis ( $t(42) = 2.079, p = .044$ ).

### Decisional conflict

The DCS measure was completed at Q2, after participants had given consent for their tumour samples to be retrieved and sent for genetic testing. Participants were asked to reflect on their decision to have genetic testing. A score of 0 indicates no decisional conflict, increasing to 100 which is very high decisional conflict. Table X shows results for DCS subscale and total scores.

Overall, participants appeared to have low levels of decision conflict, although there was a small number of participants ( $n = 3$ ) who had total DCS scores of greater than 50.

Table 7.15 Descriptive statistics for DCS subscales and total scores

DCS		Q2			
(n=54)		Median	IQR	Possible range	Observed range
	Informed	25.0	25.0-44.0	0-100	0-75
	Values	25.0	25.0-50.0	0-100	0-100
<b>Subscales</b>	Support	25.0	8.0-25.0	0-100	0-67
	Uncertainty	25.0	0.0-27.0	0-100	0-100
	Effective Decision	25.0	0.0-25.0	0-100	0-75
	<b>Total DCS</b>	25.0	18.3-33.0	0-100	0-81

Similar to other measures, the Mann-Whitney U test was used to look at associations between DCS scores and pre-defined subgroups of age, time from diagnosis and treatment status. These results are shown in Table 7.16. There was a statistically significant difference in DCS scores, with participants younger than 70 demonstrating lower scores (and therefore less decisional conflict) compared to participants more than 70 years of age ( $p = .027$ ). There was no significant difference in DCS scores in terms of time from diagnosis ( $p = .027$ ) or treatment status ( $p = .536$ ).

Table 7.16 DCS scores by subgroups

DCS		Q2			
Sub-groups		n	Median (IQR)	U	p-value
<b>Age</b>	<70 years	33	23.0 (13.5-27.0)	470.5	.027
	≥70 years	21	28.0 (24.0-41.0)		
<b>Time from diagnosis</b>	<12 months	23	25.0 (20.0-33.0)	424.5	.233
	≥12 months	31	25.0 (9.0-33.0)		
<b>Treatment status</b>	Active treatment	41	25.0 (17.5-30.5)	236.0	.536
	No treatment	13	25.0 (15.5-37.5)		



## Decision Regret

The DRS measure was completed at Q3, after participants had received their tumour and/or germline testing results. A score of 0 indicates no decision regret, increasing to 100 which is very high decision regret. The median DRS score was 0 (range 0-40, SD 11.76).

The Mann-Whitney U test was used to determine if there was an association with DRS scores and the following sub-groups: mutation status, age, time from diagnosis and treatment status. These results are shown in Table 7.17 below.

Mutation status was not associated with decision regret, with no significant difference in median DRS scores between participants with no genetic alteration, and those with a mutation or VUS ( $p = .749$ ). There was also no significant difference in median DRS total scores for age ( $p = .921$ ), time from diagnosis ( $p = .860$ ) or treatment status ( $p = .845$ ).

Table 7.17 Descriptive statistics of DRS scores

DRS	Q3				
	Median	IQR	Possible range	Observed range	
n=33	0.0	0.0-10.0	0-100	0-40	
Sub-groups		n	Median (IQR)	U	p-value
Mutation status	Mutation or VUS	10	0.0 (0.0-12.5)	91.0	.749
	No genetic alteration	23	0.0 (0.0-10.0)		
Age	<70 years	21	0.0 (0.0-10.0)	117.0	.921
	≥70 years	12	0.0 (0.0-18.8)		
Time from diagnosis	<12 months	16	0.0 (0.0-17.5)	124.0	.860
	≥12 months	17	0.0 (0.0-5.0)		
Treatment status	Active treatment	17	0.0 (0.0-15.0)	142.0	.845
	No treatment	16	0.0 (0.0-7.5)		

## Impact of genetic testing results

The MICRA scale was designed to explore the impact of receiving genetic testing results. At the time of writing, 33 participants had received their tumour and/or germline testing results and completed the final study questionnaire (Q3). Four cases were excluded from analysis because of missing data, including one germline mutation carrier. Of this remaining group of 29 participants, 20 (69.0%) were mutation negative, seven (24.1%) carried a germline (BRCA1/2 or RAD51C) mutation, while two participants (7.0%) had a germline RAD51C VUS. The remaining participants had received no mutation identified results. Descriptive statistics of the MICRA scale, including the three subscales, are shown in Table 7.18. Overall the median total MICRA score was low.

Table 7.18 Descriptive statistics for MICRA scores and subscales

MICRA (n=29)	Q3			
	Median	IQR	Possible range	Observed range
Distress	0.0	0.0-4.0	0-35	0-30
Uncertainty	4.5	1.5-8.8	0-35	0-19
Positive experiences	1.0	0.0-8.0	0-20	0-13
Total MICRA score	8.0	4.0-19.0	0-90	2-52

For participants with children, the majority (79.1%) sometimes or often wondered about the possibility of their child(ren) developing cancer. Nearly a third of participants (31.3%) felt that their genetic testing results often made it easier to cope with their cancer diagnosis, including two BRCA1/2 mutation carriers. More than half of participants (66.7%) sometimes or often worried about the risk of getting cancer again.

Again, the Mann-Whitney U test was used to determine if there were differences in MICRA scores in the following subgroups: mutation status, age and time from diagnosis. These are reported in the table below. MICRA scores appeared to be sensitive to germline mutation status, with participants who had received mutation positive or VUS results having statistically significantly higher MICRA scores on

average compared to those who were mutation negative ( $p < .001$ ). There were no significant differences in MICRA scores for age ( $p = .871$ ) or time from diagnosis ( $p = .813$ ).

Table 7.19 Subgroup analyses for MICRA

MICRA		Q3			
Sub-groups		n	Median (IQR)	U	p-value
<b>Mutation status</b>	Mutation or VUS	9	25.0 (10.0-42.0)	170.0	<.001
	No genetic alteration	20	5.0 (4.0-8.75)		
<b>Age</b>	<70 years	21	5.0 (3.8-19.3)	94.0	.871
	≥70 years	12	9.0 (4.0-20.0)		
<b>Time from diagnosis</b>	<12 months	23	8.5 (4.0-24.5)	99.5	.813
	≥12 months	31	5.0 (6.0-14.0)		

### Clinic evaluation

The final part of Q3 was a series of questions asking participants to evaluate their experience of MTGT and recall their testing results, as well as a free text response option.

Overall, participants agreed with having had sufficient time, information and support to make their decision about genetic testing. Similarly, almost all participants were satisfied with their experiences and planned to disclose results to family members. There was less agreement about the impact of testing results on treatment. Six of the nine participants (67%) who agreed that their genetic testing results had a significant impact on treatment, had received mutation positive results.

Table 7.20 Clinic evaluation items.

Clinic Evaluation	Strongly agree/agree	Neither agree nor disagree	Disagree/Strongly disagree
Item	n (%)		
Did you have enough time to make the decision about genetic testing?	30 (100.0)	0 (0.0)	0 (0.0)
Did you have enough information to make the decision about genetic testing?	30 (100.0)	0 (0.0)	0 (0.0)
Did you have enough support about your genetic testing decision?	29 (96.7)	1 (3.3)	0 (0.0)
My genetic testing result had a significant impact on my medical treatment	9 (30.0)	15 (50.0)	6 (20.0)
I am satisfied with my experience of genetic testing	29 (96.7)	1 (3.3)	0 (0.0)
I plan to share my genetic test results with my family members	30 (100.0)	0 (0.0)	0 (0.0)

Of the 33 participants who returned Q3, eight (24.2%) participants did not respond when asked to recall their genetic testing results; three of these participants were germline mutation carriers. Twenty-three participants (69.7%) correctly recalled their result, while one participant did not know her result (3%, result was mutation negative). One participant (3%) incorrectly recalled her result as 'Negative', as she carries a RAD51C germline VUS.

There were varying descriptions of genetic testing results. The majority of those with negative results recalled their result by simply stating 'Negative'. Other descriptions of negative results included: 'Do not have the BRCA gene', 'No mutant genes', and 'Not genetic'. Two participants made specific references to tumour testing: 'No pathogenic BRCA1 or BRCA2 mutation detected in tumour', and 'No genetic indication in tissue test'. Those who did report their mutation positive results either stated 'Positive' or reported their specific gene mutation i.e. 'Positive BRCA2 mutation, 'BRCA1 Positive'.

Twelve participants (36%) gave free text responses. Some comments were expressing gratitude for having had the opportunity to take part in this research project. One participant highlighted the benefits she perceived from taking part.

*I think there was a formulation in the first questionnaire 'Have you come to terms with your disease?'. I found this phrase helpful that I must come to terms with my illness. By now I feel I have accepted all that the illness causes to me. My participation in the research made me feel useful during my treatment. [MGT013, TT + GT, RAD51C+ve]*

Three participants described the relief from worry and anxiety after receiving negative results.

*I was happy to take part in this research. My concern was that there would be a genetic connection which might affect my granddaughters. I am delighted that this is not the case. [MGT020, TT, no mutation]*

*I am relieved my mostly female family will have the peace of mind knowing that the mutant BRCA gene is not a part of their make-up. [MGT057, TT, no mutation]*

*Even though I will continue to worry from time to time about the re-occurrence of cancer, having the genetic test reduced my anxiety about myself and my family. [MGT035, GT, no mutation]*

Two mutation carriers highlighted the impact their results may have on future treatment.

*...my understanding is that when cancer recurs I will be able to have PARP inhibitors before further chemo. [MGT048, TT + GT, BRCA1+ve]*

*Although I wouldn't say I was necessarily happy with the result, as I feel it may increase the likelihood of cancer returning, I do feel that following discussions with my consultant, that the results greatly increase my treatment and maintenance options, which can only be a good thing! [MGT059, TT + GT, BRCA1+ve]*

## 7.6 Discussion

### 7.6.1 Limitations

The limitation section of a research paper is typically found after the Discussion section. However there were three limitations of this study that I felt were important to keep in mind as the results are discussed further.

Firstly, as noted earlier in this chapter, unfortunately there were no participants with somatic mutations who completed the final study questionnaire (Q3). Therefore there was only data available for participants with germline mutations. Because of the small sample size, trying to make comparisons between mutation status and psychosocial outcomes using just three responses would have been prone to significant statistical bias. However, it is still disappointing that there is no quantitative data for this group.

Secondly, because this study initially set out to recruit patients who would be offered either BRCA1/2 germline or tumour testing via MTGT, the wording of the questionnaires relates to 'genetic testing' in general. Furthermore a small number of items are only relevant to germline testing. As shown in Chapter 6, more than half of this sample went on to have follow-up germline testing after tumour testing. Although this data provides interesting insights into the experiences of ovarian cancer patients who have undergone MTGT, it is difficult to draw any conclusions about specific experiences related to tumour testing. For clarity, in the rest of this discussion I will use MTGT to illustrate that tumour and/or germline testing was undertaken. I will refer to tumour testing specifically where appropriate.

Thirdly, this study only has a small sample size (particularly for Q3) and is likely to be underpowered which has implications for the statistical analysis. Limitations of small sample size include the increased possibility of false positive results by overestimating the size of an association. Similarly a lack of statistical significance may not reflect that there was no effect, but rather it failed to be detected (false negative result). Small sample sizes are also associated with lower levels of confidence and precision and a higher margin of error. Taken together, with such a small sample size the results are less conclusive and must be interpreted with caution.

### 7.6.2 Distress

The experience of an illness such as cancer triggers a range of emotional responses such as shock, worry and sadness [240]. These emotions can persist along the cancer pathway from diagnosis, treatment, recurrence and survivorship. A large body of research has shown that symptoms of anxiety and depression are common, and frequently reported amongst cancer patients. In some patients, levels of mental or emotional distress meet the strict diagnostic criteria for psychological disorders such as major depression, generalised anxiety disorder and adjustment disorder [241].

There is a significant emotional burden associated with ovarian cancer due to a number of factors: it is a disease often diagnosed at an advanced stage with poor prognosis, low survival rates and a high risk of recurrence. Treatment typically involves significant invasive surgery and multiple courses of chemotherapy. As a result, psychological distress is not uncommon.

Distress is defined by the National Comprehensive Cancer Network (NCCN) as a ‘...multifactorial unpleasant emotional experience of a psychological (ie, cognitive, behavioural, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis’ [242]. As the NCCN definition demonstrates, distress is term that encompasses a whole range of emotional states and symptoms.

Many of the psychological measures typically used within the psychosocial genetic testing literature are screening tools only and use cut-off points to indicate the likelihood of a clinical diagnosis. For this PhD, anxiety and depression does not refer to a clinically diagnosed disorder, but rather refers to the emotional symptoms that are experienced.

One of the main criticism of the HADS measure is the lack of clearly defined cut-offs. Zigmond and Sniath recommend HADS total scores of  $\geq 16$  as a threshold for identifying suspicious cases [217]. However this is based on a general population sample and a number of other studies where HADS has been used within a sample of cancer patients has recommended that the threshold should be lower, in order not to miss potential cases [243-245]. For example, Singer recommend a cut-off of  $\geq 6$  for HADS total scores for clinical purposes [243]. A more recent meta-analysis of HADS

for a sample of cancer patients reported thresholds of 10 or 11 on HADS total score were best as a screening cut-off with sensitivity of 0.80 and specificity of 0.74 [244].

Overall patients had mean total HADS scores of 11.46 at baseline, 8.76 after consenting to testing and 9.23 after receiving results; there was no statistically significant change in scores across the three timepoints. These results are comparable to what has been reported in the literature. For example, in a sample of 100 ovarian cancer patients, the mean HADS total score was reported as 8.6 (SD 5.9) [246].

When examining some of the predefined sub-group analyses, there were a number of statistically significant differences. For age, younger participants (<70 years) had significantly higher HADS total scores compared to those who were older at both Q1 and Q3, indicating they felt more distressed. There was no significant difference in HADS scores between younger and older participants at Q2. As highlighted at the beginning of this chapter, due to the small sample size all results should be interpreted with caution. Furthermore the age cut-off of 70 years to distinguish between 'older' and 'younger' participants is somewhat arbitrary, as there were too few participants falling into other categories (e.g. <60, or <50 years).

Despite these limitations, the impact of age on distress is not unexpected and is consistent with previous literature. Younger cancer patients experiencing higher levels of distress compared to older patients has been reported in breast, endometrial and colorectal cancer [247, 248]. A number of factors are thought to contribute to the lower levels of distress in older cancer patients. Older patients display greater resilience which helps to mediate distress [249], and have better coping strategies [247]. Being diagnosed with a serious illness may be less unexpected in older individuals, who typically demonstrate less death anxiety [250]. Younger patients are more likely to face disruptions to daily life such as employment, household responsibilities and caregiving [247]. The physical and psychological morbidity associated with cancer treatment may also have a greater impact on younger patients [251].

An additional statistically significant finding was in HADS scores at Q1 between participants diagnosed more recently (in the preceding 12 months) and participants who were more than 12 months post-diagnosis; those diagnosed more recently had higher HADS scores indicating more distress. This finding no longer reached significance at Q2 or Q3. Again due to the small sample size, these findings must be



interpreted with caution. However this finding is not unexpected given the initial trajectory of cancer diagnosis and treatment. More newly diagnosed patients may still be distressed from their recent diagnosis, starting and adjusting to a treatment regime, managing treatment side-effects, worrying about disease recurrence and feeling uncertain about prognosis and the future.

As each part of the diagnostic and treatment trajectory is navigated, patients may feel less uncertain and more reassured about their future treatment and disease outcomes. In a sample of breast cancer patients there was a significant reduction in distress between baseline and 12 months post-diagnosis [252, 253]. A similar reduction in distress was seen during the first year of diagnosis for patients with a gynaecological malignancy; there was a significant decrease in anxiety and depression and an improvement in overall mood states over time [254]. Comparing baseline measurements at diagnosis, Chan et al reported a reduction in anxiety at 6 months and 18 months post-treatment for gynaecological cancer patients, while depression remained stable [255].

Treatment status had no impact on levels of distress, with no statistically significant differences between patients on active treatment and those on surveillance. Although it was anticipated that patients on active treatment may have higher levels of distress due to the intense and cyclic treatment with potential side effects of nausea and fatigue, other research has reported no changes in HADS scores between pre-chemotherapy and end-of treatment [256]. A meta-analysis of psychological distress in ovarian cancer found that depression and anxiety varied along the treatment trajectory, with depression highest at pre-treatment before reducing during treatment and at end of treatment [257]. Anxiety, in contrast, was lowest at pre-treatment before rising and remaining stable during and after treatment. The authors speculate that this contrast may be due to the reduction in depression as patients adjust to their diagnosis, while increasing anxiety may be related initially to side-effects during treatment, and fear of cancer recurrence post-treatment.

Participants in this study who were on treatment were either receiving chemotherapy, maintenance therapy (bevacizumab) or combination chemotherapy/immunotherapy as part of clinical trial participation. Anecdotally, although many participants were dealing with fatigue, hair loss and other side-effects, overall they appeared to manage treatment well. The disruptions caused by treatment may have had more of an impact on overall quality of life, rather than affecting psychological functioning.

At Q3 participants had received their results of tumour and/or germline testing. To look at the effect of mutation status on distress this sample was divided into two subgroups: participants with no genetic alteration, and participants with a genetic alteration (pathogenic germline mutation and VUS were both included). There was no significant difference in HADS scores between the groups.

Studies which have also explored the psychological impact of BRCA1/2 mutation carrier status in breast and/or ovarian cancer patients have reported mixed findings. Two retrospective studies observed no significant differences between BRCA1/2 carriers and non-carriers on anxiety, depression or cancer-related distress [110, 114]. Similarly, two prospective studies compared psychological outcomes pre- and post-genetic counselling and testing in a large sample of breast cancer patients; no differences were observed between BRCA1/2 carrier status and distress, or between pre- and post-testing on anxiety and depression [112, 115]. A prospective study of patients newly diagnosed with breast and ovarian cancer found no differences in HADS anxiety or depression scores between mutation carriers and non-carriers [143]. In contrast, a retrospective study of carrier status and personal cancer history found patients with a BRCA1/2 mutation positive result were at significantly higher risk for global psychological distress compared to non-carriers [133]. Recent data from a program of systematic BRCA1/2 germline testing in East Anglia found that distress scores (as measured by the Depression Anxiety and Stress Scale, DASS-21) were significantly lower in response to genetic testing, compared to distress scores on the same measure in response to their cancer diagnosis [74]. Mutation status did appear to have some impact on distress, with patients who had received mutation positive results reporting significantly higher cognitive avoidance scores on the Impact of Event Scale (IES) compared to those who had received no mutation results.

### 7.6.3 HRQOL

HRQOL is a multi-dimensional concept encompassing domains relating to disease status which can include physical, social, emotional, sexual, functional and cognitive outcomes. One of the key aspects of HRQOL is that it is self-reported and reflects the patients' own perspectives, perceptions and experiences. HRQOL is becoming an increasingly important patient reported outcome measure for studies of new therapies, in particular clinical trials, where toxicities and side effects are balanced against clinical benefit and patient wellbeing. It is also used to inform clinical management and guide therapeutic decisions [258]; HRQOL has been shown to

correlate with disease status in ovarian cancer (e.g.) response, progression or survival [259] as well as overall and progression-free survival [260].

As the FACT-G is a commonly used measure of HRQOL, it is possible to compare scores from this sample to data from the published literature. Mean FACT-G total scores within this sample were 81.56, 85.71 and 84.21 across Q1-Q3. This was similar to ambulatory gynaecological cancer patients with regionally advanced disease (FACT-G total scores, M 82.88) [254] and normative data from both a general population sample of American adults (M 80.1) and a sample patients with mixed cancer diagnosis (M 79.3) [261].

Pearman et al demonstrated that FACT-G scores are sensitive to disease status; a large sample of cancer patients reported lower scores, reflecting poorer HRQOL, as performance status decreased, and as disease progressed from no evidence of disease to metastatic [261]. This is reflected in a sample of ovarian cancer patients with recurrent and progressive disease who reported much lower FACT-G scores (M 66.9) [262]. In this study cohort, it does appear that participants were not only managing both the physical and psychosocial elements of their diagnosis and treatment well, but may have good performance status and stable disease. As noted earlier in this chapter, there may be some selection bias from the recruitment process towards patients with better physical and psychological functioning.

There were statistically significant differences in HRQOL; at Q1 and Q3 younger participants reported poorer HRQOL compared to those who were older. A longitudinal study of ovarian cancer patients quality of life reported similar findings, with younger patients demonstrating poorer HRQOL [255]. The authors believe younger patients struggle more psychologically and socially with both the diagnosis and treatment of cancer [255]. This is not dissimilar with some of the factors related to younger age at cancer diagnosis and distress. In contrast, a study of Italian gynaecological cancer patients found older patients had lower HRQOL scores across all domains, indicating poorer quality of life [263].

At Q1 only, participants who were more recently diagnosed within the last 12 months reported significantly poorer HRQOL than those more than 12 months post-diagnosis. As this result was significant at only one timepoint, due to the limitations of the sample size it may reflect a false positive result. However it may also reflect a genuine finding and therefore is also discussed further here. Participants who are more recently diagnosed may still be adjusting to the shock of diagnosis, including psychosocial

adjustments, affecting emotional and social domains of HRQOL. The impact of initiating treatment such as surgery and/or chemotherapy as well as managing treatment side-effects may in turn affect physical and functional wellbeing. This was also reflected in NFOSI scores at Q1, where participants who were more recently diagnosed reported higher disease- and treatment-related symptom burden. Although neither of these findings were statistically significant at Q2 and Q3, they do suggest there is a challenging physical and psychosocial period post-diagnosis which ameliorates over time. Other studies have shown improvements in HRQOL in the year after diagnosis. A study of patients with both early stage and advanced gynaecological cancer found HRQOL improved at 12 months post-diagnosis compared to baseline, regardless of differences in treatment and prognosis [254]. Similarly a sample of gynaecological cancer patients showed HRQOL improvements six months post-treatment, suggesting patient HRQOL is impaired during, and for up to six months, after treatment is completed [255].

Receiving active treatment (chemotherapy or other systemic treatment) compared to surveillance was not related to HRQOL as measured by FACT-G or NFOSI-18 scores. Again this suggests that this sample of participants may be coping better with the physical, social and emotional aspects of treatment compared to other cancer patient cohorts. A literature review of some early QOL data in gynaecological cancer patients suggested that QOL can be affected by treatment [264]; QOL was lowest from the point of diagnosis until completion of treatment and when compared to treatment of other cancers, gynaecological patients had significantly worse QOL.

There was no association between mutation status and HRQOL, with no statistically significant difference in FACT-G scores. A study comparing BRCA1/2 mutation carriers with a personal history of cancer (survivors), unaffected carriers (previvors) and non-carriers (controls) found that survivors had low HRQOL for both emotional and physical issues [265] which may reflect their experiences of cancer diagnosis and treatment.

#### 7.6.4 Genetic testing

##### 7.6.4.1 *Knowledge*

Knowledge has been used as a measure of the 'success' of genetic counselling, where information has been imparted from the genetic counsellor to the counselee; a meta-analysis of genetic counselling outcomes has shown that knowledge of cancer genetics increases post-counselling [266].

Within the traditional genetic testing and counselling framework, individuals eligible for genetic testing would be provided with information regarding the disease, advantages and disadvantages of genetic testing, risks and limitations, possible outcomes and risk management options available. Patients would be supported in their decision, whether it be to have, or not have, genetic testing. Typically there is time available for patient's to reach their decision, for deliberation or consultation with other family members or health professionals for advice.

Information provision about genetic testing within a mainstreamed model of delivery, where testing is discussed alongside other medical issues within the patient's oncology consultation, is a significant departure from the traditional genetic counselling model. Decisions regarding testing may need to be made quickly, in order to inform treatment decisions or participation in clinical trials. However, in the absence of genetic counselling, sufficient information still needs to be provided by oncologists for patients to make an informed decision about whether or not to have testing. Currently there is a paucity of data exploring how oncologists discuss BRCA1/2 genetic testing with ovarian cancer patients and what information is imparted.

Measures have been used as a way to assess knowledge of key concepts associated with BRCA1/2 genetic testing within the context of research studies. In this study genetic testing knowledge was measured using items adapted from some of the first research on knowledge and attitudes to genetic testing by Lerman et al [220], and later work from Peters et al [221]. As raised at the start of this chapter, the study questionnaires were intended to serve both modes of testing (germline and tumour) although are more reflective of items related to germline testing.

In Lerman's original study, participants were affected and unaffected individuals with a family history of HBOC. The BRCA knowledge measure was completed at baseline prior to an education session. On average participants answered 55% of items correctly at baseline [220]. In this study, participants answered slightly fewer items correctly, with 47% and 49% at Q1 and Q2, respectively.

Another way to look at testing knowledge was to categorise participants as having high, sufficient and low knowledge with accompanying cut-off scores. Peters et al (2005) defined 'high knowledge' as responding correctly to at least six out of seven items. In a sample of breast cancer patients, a proportion of whom had already had germline BRCA1/2 testing or had considered testing, 46.2% of participants had high knowledge [221]. In the current study only 4.8% and 13.2% of participants at Q1 and

Q2 were categorised as having high knowledge. These differences may be due to socioeconomic variables; participants in Peters' research were aged 50 years or younger and 66% had been educated to college degree or higher, while in this sample of participants had a mean age of 65 years at recruitment and only 12% had completed tertiary education. In this study, educational level appeared to be unrelated to testing knowledge.

Although this did not reach significance at Q1, at Q2 younger participants had significantly higher knowledge scores compared to older participants. Other studies have also reported increasing genetic knowledge with younger age [267, 268]. This may be attributed to improved education in schools regarding genetic concepts and medical genetics as well as greater exposure to genetic concepts and terms through popular media. Perhaps the most pivotal recent event to bring breast and ovarian cancer genetics into the public spotlight is the 'Angelina effect'. Actor and filmmaker Angelina Jolie Pitt disclosed her BRCA1 mutation carrier status in 2013. From the media attention and public interest that followed, referral rates to familial cancer clinics not only increased significantly but were sustained [269].

In Peters' study women who had undergone BRCA1/2 testing had significantly higher knowledge than those who were untested [221]. The authors reported the largest differences on items related to: ovarian cancer risks, paternal transmission, and BRCA1/2 mutation prevalence [221]. This suggests these are specific knowledge items that may only be gained from a genetic counselling context, while other information relating to genetic testing may be part of existing knowledge or more easily attained from other sources such as popular media.

When participants were first recruited to this study, they received a verbal explanation of tumour testing from their oncologist. If necessary I supplemented this information to explain the process of tumour testing and how it differs to the standard genetic (germline) testing typically available, and the potential outcomes of testing. When participants consented to testing they received written information in the form of the Myriad 'Patient guide to tumour BRCA testing' (please refer to the Appendix).

In this study there was no change in knowledge scores between when participants were recruited to the study (Q1), and after consenting to testing and receiving the Myriad tumour testing information booklet (Q2). This suggests that the information booklet did little to add to participants' testing knowledge. Participants may also not have sought further information from other sources such as the internet. However it

is important to consider the limitations of this knowledge measure, and whether it can be considered an accurate measure of information provision and understanding. For example, in order for the questionnaire to be used across participants who had either germline or tumour testing, none of the items were specific to tumour testing.

#### *7.6.4.2 Attitudes to genetic testing*

Attitudes to genetic testing have typically been measured by comparing positive (advantages, benefits) and negative outcomes (limitations, risks, disadvantages), with positive attitudes reflecting greater endorsement of potential testing benefits over risks.

Positive attitudes to genetic testing have been anticipated to lead to increased intention and uptake of testing, however a number of studies have shown that testing attitudes do not necessarily correlate with uptake of testing. From 14 studies examining real breast cancer genetic testing decisions, the average uptake rate was 59%, with a wide range from 25% to 96% across these studies [184]. Interest for testing for HNPCC has been shown to be high (up to 80%) in both general population and at-risk patient groups [270, 271]. However actual uptake rates are significantly lower, approximately 43% [272].

The measure of attitudes to genetic testing used in this study was developed by Peters et al [221] and has been used in other research exploring testing attitudes in both cancer patients and the general population. As described above for use in this PhD study the wording in this measure was modified to reflect the MTGT context specifically, i.e. referring to 'oncologist', rather than 'doctor'.

Peters et al found the uptake of genetic testing in a sample of breast cancer patients was significantly associated with positive attitudes towards testing, with patients consistently endorsing the benefits of testing over potential risks [221]. A qualitative study exploring TFGT in a sample of ovarian cancer patients reported that the potential advantages of testing outweighed any disadvantages [142]. In contrast, this study found no statistically significant differences between risk and benefit item scores; participants did not endorse the benefits over the risks of testing, and vice versa, either before (Q1) or after (Q2) consenting to testing. This 'ambivalence' towards genetic testing may reflect poor genetics knowledge and/or a lack of understanding of the potential advantages and/or disadvantages of genetic testing. For example, a Finnish study found that individuals with lower levels of knowledge

had more difficulty in forming definitive responses to various genetic testing attitude statements [273].

#### *7.6.4.3 Motivations for testing*

Motivations for genetic testing have been explored since clinical testing became available in the 1990s for HBOC. This early data tended to study at-risk but unaffected individuals or members of the general population, with some studies presenting genetic testing as a hypothetical option only. Overall, in the literature motivations for testing have largely been related to contributing to research, concern about future health, and generating information for children and relatives [114, 274-277]. Less is known about the motivations for genetic testing in cancer patients, particularly in a 'real' decision context.

In this sample of ovarian cancer patients who had just consented to BRCA1/2 tumour (or germline) testing, items related to the 'Prevention and Medical Care' subscale were endorsed more than other subscales. The items in this subscale referred to personal medical decisions such as providing information for treatment decisions, monitoring for signs of cancer, getting appropriate medical care, with one item referring to clarifying cancer risks for children.

Given the context in which testing is taking place, it is not surprising that perhaps the focus of genetic testing has shifted to the potential personal implications it may provide to cancer patients. In a qualitative study of women with advanced ovarian cancer, their main motivation for genetic testing was to increase treatment options [142]. In a small study of breast cancer patients offered rapid genetic testing and counselling shortly after diagnosis, the three most cited reasons for having testing were all related to medical decisions about their cancer [138]. Amongst Dutch counselees who had been offered and undergone genetic testing for HBOC, a small subgroup of individuals who had 'fast tracked' genetic counselling and testing in order to inform treatment decisions were most motivated by interest in their own cancer risk, followed by risks for family [278]. This subgroup of counselees were also significantly more interested in using genetic testing to identify the cause of their cancer, compared to the rest of the sample.

As other genetic testing for somatic mutations in cancer does not provide inherited genetic information, motivations were associated with treatment and personal benefit rather than thoughts of unaffected relatives. In a qualitative study of advanced cancer patients examining their expectations of genomic sequencing of tumour tissue,



participants were motivated by the potential personal benefit offered by testing, in particular by a sense of hope that this testing was offering something novel [107]. In a survey of advanced cancer patients, 70% reported that the most important reason for choosing to have genomic sequencing of tumour tissues was to guide treatment decisions [109].

#### 7.6.4.4 *Decision making*

##### **Decisional conflict**

The decision to have MGT is not dissimilar from that of BRCA1/2 germline testing – individuals need to be provided with information regarding the test, possible outcomes, risks, advantages and disadvantages. However the context in which the decision is made for MGT is significantly different; the oncology setting potentially limits time available for decisions and the expertise of the health professional making the offer of genetic testing [279]. Currently there is little empirical data on the decision-making experiences of women with ovarian cancer offered MGT. A recent study of unselected genetic testing in ovarian cancer patients included three questions about decision-making [74]:

- I had access to enough information to make a decision about testing
- It was difficult to decide whether to have the genetic test
- I had enough time to think about whether to have the genetic test

Participants had high mean scores indicating sufficient information and time to make a genetic testing decision. Interestingly, scores for perceived ease of decision-making showed the widest variation (SD 1.80) suggesting that some patients may have struggled with the decision whether or not to have testing.

Decisional conflict is a psychological construct to reflect the level of ease (or difficulty) in making a specific decision. It refers to a state of uncertainty about choosing a course of action, particularly when the options may involve risk, loss or regret [280, 281]. Decisional conflict arises when the decision is difficult, and if the decision outcomes entail significant disadvantages as well as advantages [281]. High decisional conflict has been shown to impact decision regret [225] and manifest as delayed decision-making [282]. Factors that influence decisional conflict include feeling uninformed, unclear about values, feeling unsupported or pressured to make a decision [282]. In a validation study of the DCS for HBOC genetic testing, probands who had already undergone genetic testing had significantly lower DCS scores

compared to their untested relatives [280]. This suggests that decisional conflict may have a detrimental impact on testing uptake. It may also reflect the ability of genetic counselling to mediate decisional conflict by the provision of information, clarification of values and psychosocial support.

In this study, decisional conflict was measured in at the point at which participants consented to MTGT (Q2). Overall decisional conflict was low, with a median total score of 25.0, suggesting little difficulty with decision-making. Decisional conflict scores were also low (<25.0) across all subscales. However a small number of individuals (n = 3) did have total scores  $\geq$  50.0, indicating moderate to high levels of decisional conflict.

A small number of studies have looked at decisional conflict for genetic testing in contexts outside of the traditional face-to-face model of genetic counselling. In a sample of breast cancer patients, participants were provided with the option of choosing face-to-face genetic counselling and testing, or 'direct' genetic testing where educational resources and a testing kit were provided directly. Individuals who chose face-to-face testing and counselling had significantly higher decisional conflict scores, indicating uncertainty about the decision to have genetic testing and reflecting the desire to have additional information or support [283]. This provides support to still have an option for face-to-face genetic counselling, rather than only a mainstreamed model of delivering testing. However there is also evidence to suggest that clear, written information may be as effective as genetic counselling. A study of TFGT in newly diagnosed breast cancer patients compared face-to-face genetic counselling and testing to receiving written information only. After controlling for baseline levels, Quinn et al found no statistically significant differences in decisional conflict scores between the two groups [284].

In a sample of breast cancer patients, genetic testing decisional conflict was compared between patients who had already had definitive surgery (ADS) and those prior to surgery (BDS) [141]. There were no statistically significant differences in DCS totals scores before and after genetic counselling, and across both groups. Overall, DCS total and subscale scores were low and comparable to scores in this study cohort. On the Informed subscale, ADS patients had significantly higher scores (median 50.0) prior to genetic counselling indicating less clarity on the advantages and disadvantages of testing, although this decreased post-counselling (median 25.0).

## Decision regret

Decision regret is defined as a negative emotion associated with thinking about a past choice [225]. It is distinct from disappointment, and typically involves comparison to other choices that could have been made or outcomes that may have been different [285, 286]. Post-decision regret is not uncommon in cancer patients and has typically been related to treatment decisions. For example, in localised prostate cancer decision regret was associated with treatment side effects such as sexual or bowel dysfunction [286, 287]. Decision regret has also been associated with the way in which the decision has been made. Patients reported more decision regret if they had been less involved in their treatment decisions than they wished [288] or perceived to have made an uninformed treatment decision [286].

In this study the median total DRS score was 0.0, indicating overall participants experienced little regret over their decision to have genetic testing. However a small number of participants (n=4) had total DRS scores  $\geq 25$  suggesting that some decision regret was experienced. Decision regret was not associated with mutation status nor with any of the predetermined subgroups (age, time from diagnosis, treatment status).

As MGT is still a relatively new way of delivering BRCA1/2 testing there is little literature around testing decisions, in particular decision regret. Quinn et al also measured decision regret related to TFGT 12 months post-testing. The authors reported no statistically significant differences in DRS scores between breast cancer patients who had face-to-face genetic testing and counselling and those who had received written educational materials only [284]. In this study it appeared that changing the context and mode in which genetic testing was delivered did not influence decision regret.

In Brehaut's development and validation of the DRS, the authors found that increased regret was related to poorer health outcomes as a result of the decision [225]. Depending on the timing of testing in the ovarian cancer treatment pathway, genetic testing may not immediately impact health outcomes, although the results of testing may influence treatment decisions which could affect health status in the future. As decision regret was measured shortly after participants received their testing results, there would have been no change to treatment prior to completing Q3. Interestingly, issues about decision regret emerged in the qualitative interviews which were conducted several months after Q3. Brehaut comments that the DRS is useful at a specific point in time, suggesting that decision regret may evolve over time [225].

Currently it is unclear how long it takes for decision regret to be established [286] and this timeframe may be specific to the particular disease or treatment context.

Although data is still emerging it appears that in cohorts of cancer patients who are facing the decision of BRCA1/2 genetic testing, in general decisional conflict and decision regret for testing is low.

#### *7.6.4.5 Impact of receiving genetic testing results*

Chapter 3 in this thesis examined the psychological impact of genetic testing. In much of the literature this has largely been measured using psychometric assessment tools which may not be sensitive to the specific issues related to genetic testing [226]. The MICRA is a validated measure which was designed to measure the specific impact of receiving genetic testing results [226]. Increased MICRA scores indicate adverse psychological responses to genetic testing results. Currently there are no accepted 'cut-offs' for this scale to define high genetic testing distress [110]; responses are typically provided on a continuum (i.e. 'higher' or 'lower' scores).

In this cohort of participants, overall MICRA total and subscale scores were low. When looking more specifically at MICRA scores and mutation status, the measure was able to distinguish between participants who had received a mutation or VUS results and those with no genetic alteration; participants with a genetic alteration had significantly higher MICRA scores indicating more testing-related concerns compared to participants with no genetic alteration. Earlier in the chapter psychological distress, as measured by the HADS, was not associated with mutation status, which further suggests MICRA's ability to differentiate specific testing related concerns.

A study of ovarian cancer patients who had been referred for and undergone genetic counselling and testing were categorised into four groups: (1) mutation carriers, (2) patients with breast and ovarian cancer, (3) patients with a family history of breast and ovarian cancer and (4) patients with no family history [110]. Significantly higher mean scores on the MICRA were reported by mutation carriers, compared to the remaining three non-carrier groups. No significant differences were observed between groups on other generic distress measures (HADS and IES), again reflecting the ability of the MICRA to reflect specific testing concerns.

The MICRA has also been used to demonstrate that testing-related concerns can persist. In a long-term follow up study of individuals who had undergone BRCA1/2 genetic testing, women with a personal history of breast and/or ovarian cancer who

were BRCA1/2 mutation carriers reported significantly more genetic testing related distress, compared to women who had received uninformative results [124]. As mutation status was not related to cancer-specific distress as measured by the IES, the authors suggested that genetic testing specific distress and global psychological dysfunction is unrelated. In another long-term follow-up study, one year after receiving BRCA1/2 genetic testing results, across both affected and unaffected participants, those who had received mutation positive results reported increased testing related distress [125].

It appears that the MICRA is a useful tool to identify individuals with genetic testing-related distress. Given the long-term nature of the study published by Graves et al where participants were approximately five years post-testing [124], this does suggest the importance of longer term follow-up of patients and provision of psychosocial support specific to being a mutation carrier.

#### 7.6.5 Clinic evaluation

This was the final part of the last questionnaire (Q3) and was designed to explore participants' perceptions of their MTGT experience. It was encouraging to see that there was almost unanimous agreement with having had sufficient time, information and support to make the decision about MTGT. From a genetic counselling perspective, it was also reassuring to see there was intention to disseminate results from MTGT to relatives which is particularly important in the case of individuals identified as mutation carriers for predictive testing of unaffected at-risk individuals.

It was not unexpected that only a small proportion of participants felt that their MTGT results had impacted their ovarian cancer treatment. As discussed previously in Chapter 6, there may be no immediate change to treatment following BRCA1/2 germline or tumour testing because of the timing of testing in relation to their treatment pathway and eligibility for PARP-inhibitors (e.g. after three line of platinum-based chemotherapy).

Up to 24% of participants did not respond to the recall of genetic testing results question; three non-respondents were mutation carriers. It is possible some participants could not recall their result and therefore did not provide a response. However as participants were specifically provided with a prompt to the recall question ('If unsure, please write 'don't know)'), this is unlikely. For reasons of confidentiality, some participants may not have wanted to disclose their testing results. All

participants were also aware that I had knowledge of their testing results, and may therefore have felt that it was unnecessary to disclose them again.

Of the participants who provided responses to the recall of genetic test results question (25 of 33, 67%), two participants (2 of 25, 8%) incorrectly recalled their results. One participant could not recall her result, giving a 'Don't know' response (result was no mutation identified). One participant incorrectly recalled her result as 'Negative', however her actual result was a germline RAD51C VUS.<sup>1</sup>

Incorrect recall of results may suggest poor or lack of communication between oncologists and their patients. As we will see in the next chapter, disclosure of MTGT results could be improved. Regardless, incorrect recall of genetic testing results is not uncommon amongst individuals who have had BRCA1/2 testing. Previous research looking at mode of result delivery found that even after face-to-face genetic counselling, 2.9% of patients were unable to accurately recall their results [289]. The majority of those with incorrect result recall had received a germline VUS result.

BRCA1/2 VUS results are complex to understand and interpret, and these results can be confusing to both patients and clinicians. A retrospective study of 24 patients who had previously received germline BRCA1/2 VUS results after genetic counselling and testing compared recall and interpretation [290]. When reporting factual recall seven participants (29%) incorrectly recalled their VUS result as a pathogenic mutation. Despite correctly recalling their result, a much larger proportion of participants (79%) subjectively interpreted their VUS as a pathogenic mutation. It is important to note that the mean time between genetic test result disclosure and study participation was 3.0 years, a much longer period of time between testing disclosure and recall compared to this study.

## **7.7 (More) Limitations**

As mentioned earlier in the study, initial study plans were to compare experiences of patients offered mainstreamed BRCA1/2 germline or tumour testing and the language used in the study documents (including questionnaires) was designed to refer to 'genetic testing' generically. However after recruitment began, I had to adapt to the clinical context and chose to focus this research purely on the tumour testing experience. It is difficult to comment on whether the language which referred to 'genetic testing' acted as a primer to participants to reflect more on concepts related

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<sup>1</sup> This result was later clarified with the patient by her oncologist, and the patient was referred to her local clinical genetics service for genetic counselling.

to germline testing rather than tumour testing. Furthermore given the number of participants in this sample who had second-line germline testing, it may not be possible to distinguish tumour testing from germline testing experiences. What these results contribute to is our growing understanding of the patient experience of mainstreaming in general.

In this study there is likely to be a selection bias towards patients who were more physically and psychologically robust, partly driven by the recruitment strategy where oncologists were consulted initially as to which patients were suitable to approach for recruitment. There is an additional selection bias towards patients who were interested in genetic testing as participants also self-selected for this research.

The Testing Knowledge measure used in this study includes items that mostly relate to germline rather than tumour testing. Therefore it does not reflect what information participants were actually provided with and is a poor measure of their knowledge. With hindsight a simple self-developed measure with tumour testing knowledge items would have provided much more insight.

The small sample size of this study has been discussed earlier in relation to interpretation of results and also limits the generalisability of results.

## **7.8 Summary**

This chapter presented quantitative data on the participant experience of MTGT. Participants in this study reported psychological distress scores that were similar to other samples of cancer patients; these scores remained stable over the MTGT pathway. Participants reported good HRQOL which remained unchanged over the course of the study and reflected their general demeanour and appearance during the study. It was interesting to note that participants had somewhat ambivalent attitudes to genetic testing, despite taking part in this study. Reflecting the context in which testing was provided, participants were primarily motivated by the perceived medical care and prevention aspects of testing. At the point of consenting to testing, participants' scores did reflect some conflict about their decision. Encouragingly, there was no decision regret post-testing. There was no difference in distress or HRQOL scores by mutation status. Using a specific measure of impact of genetic testing showed that participants with a genetic alteration (mutation or VUS) had significantly more testing-related concerns compared to those without a genetic alteration.

## **Chapter 8 Exploring the patient experience of mainstreamed BRCA1/2 tumour testing in ovarian cancer: a qualitative approach**

### **8.1 Introduction**

This chapter moves away from the quantitative component of this study, which has used standardised measures and considered the patient group as a whole, to a qualitative perspective where the focus is on individual experiences. This component of this PhD study is an essential part of developing an understanding of how women with ovarian cancer experience MGT, in particular mainstreamed BRCA1/2 tumour testing.

There is a small body of qualitative research on patient's perspectives, experiences and impact of RGCT or TFGT in breast and ovarian cancer [142, 291-293]. Although there are shared features within these testing approaches and MGT, e.g. testing shortly after diagnosis and/or testing to guide treatment decisions, what is important to distinguish is the manner in which genetic testing and/or counselling is provided. Whilst different to the traditional model of genetic counselling and testing, TFGT may still involve information provision or consultation with a genetic counsellor or clinical geneticist. Similarly, while the testing may be undertaken within the specialty oncology centre or hospital, it may be organised by the clinical genetics service rather than the patients' oncology team. MGT as it is defined in this study, from test offer to result delivery is provided by the oncology health professionals who are already involved in the patients' care. BRCA1/2 tumour testing adds an additional layer of complexity to MGT, involving use of patient tumour tissue and potentially a two-step testing process.

Genetic testing of tumour tissue has been an integral component of the Genomic England 100,000 Genome Project. There are a number of factors that indicate BRCA1/2 tumour testing could soon become part of standard clinical care for women with high grade serous ovarian cancer, including: (i) decreasing costs of testing, in the UK BRCA1/2 tumour testing costs are approximately £500-600, (ii) improved methods of DNA extraction from historic FFPE samples, (iii) a move to using fresh frozen tissue samples, providing better DNA quality for testing, and (iv) efforts to develop infrastructure to support testing between oncology, cellular pathology and molecular genetics.



If BRCA1/2 tumour testing will be provided within an MGT model that is oncology-led, qualitative research is an essential part of informing the development of these new clinical pathways and the health professionals involved.

## **8.2 Aims**

The purpose of this qualitative component was to explore the patient experience of MTGT, both mainstreamed BRCA1/2 tumour and germline testing. This research aimed to expand our understanding of how women with ovarian cancer experience the process of MGT, in particular tumour testing, focusing on their understanding, expectations and experiences of making the decision to have MTGT, as well as the impact of receiving MTGT results.

## **8.3 Methods**

### **8.3.1 Participants and selection**

In qualitative research, the sample should reflect the social world, culture or phenomena of interest [173]. Targeted, or purposive, sampling is used to recruit participants who represent certain aspects of the culture or phenomena. In this case, purposive sampling was used to ensure there was diversity in participants' testing modes and testing outcomes, including:

- Tumour testing no mutation identified, no further testing
- Tumour testing MLPA fail, germline testing
- Tumour testing mutation identified, germline testing confirms mutation
- Tumour testing mutation identified, germline testing no mutation
- Germline testing only.

Participants were selected from the main cohort of ovarian cancer patients who had consented to take part in this PhD research on mainstreamed BRCA1/2 tumour testing (participants from the previous chapter). Patients who had completed MTGT and received their results were eligible to take part in a one-on-one interview with myself. Participants were invited consecutively as they returned to the gynaecology oncology outpatient clinics for their scheduled appointments.

### **8.3.2 Development of the interview schedule**

The interview schedule was developed and pilot-tested with two participants from the previous study prior to being submitted for REC and HRA review. The wording of the

interview schedule was designed to be adapted to each participant depending on the mode and outcome of MTGT. The interview schedule was informed from both this PhD research and clinical experience to date recruiting and providing mainstreamed BRCA1/2 tumour testing (and at times, germline testing) to ovarian cancer patients, my previous research and clinical experience in psycho-oncology of genetic testing, as well as the published literature.

To understand the participants' experiences in context, it was important to include in the interview schedule questions about ovarian cancer diagnosis and treatment. This has been a significant, life altering event for participants and inevitably their perceptions and experiences of genetic testing will be shaped by their diagnosis. The interview scheduled explored specific areas of the genetic testing process that I had anticipated would provide insight and meaning into the patient experience. The interview aimed to cover several topics I felt would be particularly relevant, first looking at context in their experiences of diagnosis and treatment of ovarian cancer, perceptions and expectations of genetic testing, decision making process and outcomes from genetic testing.

The interview schedule can be found in the Appendix.

### 8.3.3 Recruitment

All the participants invited for an interview were already enrolled in the MTGT study described in the previous chapter. In order to get a breadth of genetic testing experiences and outcomes, I firstly identified eligible participants based on their mode of genetic testing and testing results as outlined above. By this time, many of the participants had already been part of my research for at least three months. As I was familiar with all the participants and vice versa, it felt appropriate to take a more direct approach to recruitment. As each participant returned to the outpatient clinic, I approached her directly and asked if she would be interested in completing an interview as the final part of the study. Each participant was provided with an information sheet and given at least 24 hours to reach a decision whether or not they wished to take part in an interview. After this time, I followed up each invited participant by telephone. If she agreed to an interview, we decided on a date and time for the interview based on her preference.

## **8.4 Data collection**

Participants completed a one-on-one interview that typically lasted between 30 and 60 minutes. Most commonly interviews were conducted by telephone while the participant was at home. Five interviews took place within the Macmillan Cancer Centre's chemotherapy suite during the participant's treatment.

At the start of each interview, it was made clear to participants that they did not have to answer any questions that they did not wish to, and were free to stop the interview at any time. Participants were reminded that the interview would be recorded with their permission and transcribed verbatim, with the digital recording then being deleted.

All information was treated anonymously. Transcribed interviews removed references made to named places or people.

### **8.4.1 Transcription**

Transcription was undertaken by Devon Transcription, a professional transcribing service approved by UCL and one which we have previously used for other health research projects around ovarian cancer and genetic testing.

Interviews were transcribed verbatim and returned securely in an anonymised Word document format, which were then exported in to NVivo (QSR International, Cambridge, MA), a qualitative data management software for coding and analysis. All transcripts were kept in password protected computer hard drives and in a password-protected back-up drive (The UCL Data Safe Haven).

## **8.5 Analysis**

### **8.5.1 Co-coding**

Two transcripts (10%) were be coded independently by my primary supervisor who has both experience in qualitative research and genetic testing. Any differences were discussed until agreement was reached.

### **8.5.2 Thematic analysis**

The analysis method chosen for this data was thematic analysis, and was specifically guided by Braun and Clarke's 2006 publication [294]. In general, thematic analysis is a method which identifies, analyses and reports patterns or themes within the data

[48]. Similar approaches to thematic analysis include interpretative phenomenological analysis (IPA) and grounded theory, as both methods involve looking for patterns in the data. However both methods are theoretically bounded; IPA follows a phenomenological epistemology exploring in great detail the lived experience of the phenomena of interest, while grounded theory aims to generate a theory from the phenomena 'grounded' in the data [294]. In contrast, Braun and Clarke argue that thematic analysis can be used within different theoretical frameworks. This was also an analysis approach that I had used previously and therefore was familiar with.

### 8.5.3 Analysis choices

Braun and Clarke highlight key analytic choices that should be made explicitly clear, preferably prior to any data is analysed. I felt the first four analysis choices described below were related, with one analysis choice influencing another. As I will elaborate further below, the study's epistemology impacts whether themes are constructed on a semantic or latent level, if a rich description of the data set is produced rather than a more detailed account of a specific aspect, which is turn bound by the inductive vs deductive analytic approach taken.

#### *8.5.3.1 Research paradigm, ontology and epistemology*

In Chapter 4, I outlined different research paradigms and put forth the one I feel best reflects my own philosophical and research orientation. An interpretivist paradigm is informed by a relativist ontology and subjectivist epistemology, accepting that reality is interpretations by individuals. Each participant's experience of MTGT is unique, reflecting their own subjective interpretation of events. Thus there will be multiple interpretations of the experience of testing, leading to multiple realities. Context is critical to an interpretivist paradigm, influencing experiences and meaning. What were previous separate disciplines, genetics and oncology, have become intertwined through mainstreaming. How these participants experience MTGT is in turn influenced by their experiences as a cancer patient. Finally, my own beliefs and outlook not only guide the research, but also how the research is interpreted. Throughout this chapter I acknowledge when my own biases and perceptions come in to play, and reflect on how this influences my interpretation of the data.

### *8.5.3.2 A rich description of the data set, or a detailed account of one particular aspect*

The main aim of this work was to explore how women with ovarian cancer experience mainstreamed BRCA1/2 tumour testing, which covers a breadth of topics from cancer diagnosis and treatment to the impact of receiving genetic testing results. To meet these aims I aimed to produce a rich description of the data set, reporting only the key themes, which inevitably loses some complexity, but is a useful method for investigating an area of research where little is known. Subsequent analyses of the same data set or a similar participant group could focus on more detailed accounts of a particular aspect, e.g. testing consent, which may lead to greater depth and more nuanced account of the patient experience.

### *8.5.3.3 7.5.3.3 Semantic vs latent themes*

Another analytical choice is the 'level' at which themes are identified. Braun and Clarke refer to two options: (i) semantic level, where themes are identified within the '...explicit or surface meanings of the data' (p.84) and, (ii) latent level, which examines underlying ideas, patterns, and assumptions [294].

Although semantic themes may appear to require a more superficial form of analysis when compared to latent themes, it should still involve interpretation where the researcher explores the significance of the patterns in the data, and considers their implications in the context of previous literature. This is the approach I took when identifying themes; I looked to not only describe, but also to understand and explain the patterns in the data. Reflecting the interpretivist research paradigm, it was important to draw on my own knowledge and experience of genetic testing and consider how this informed my interpretation of the data. In the Discussion section I continue looking for meaning and implications in the data whilst referring back to other published data in this area.

### *8.5.3.4 Inductive vs theoretical thematic analysis*

An inductive analysis approach has no predetermined theory or framework, instead letting the data drive the identification of themes, in a way that is sometimes described as 'bottom up'. Inductive analysis is seen to be particularly useful when little is known about the area under research, as it allows the themes to be driven by the data itself. Braun and Clarke describe inductive analysis as being 'data-driven' (p.83).

A deductive or theoretical approach, in comparison, follows a pre-existing framework driven by a particular theoretical focus. This is useful when there are specific research questions of interest, as it often leads to a detailed analysis of a specific aspect of the data, rather than description of the data overall [294].

As little is known about the patient experience of mainstreamed BRCA1/2 tumour testing, an inductive approach gave more flexibility and allowed the themes to be a direct reflection of the data. Therefore in my analysis I coded freely rather than coding for a specific research question. However it is impossible to conduct any analysis without some theoretical or epistemological influence. In this case an interpretivist paradigm emphasises the role of the researcher; my existing knowledge and own experiences of genetic testing and counselling led me to search for certain elements in the data.

#### *8.5.3.5 When is a theme, a theme (Part 1)?*

The key component of thematic analysis is in its very name. A theme is defined as an idea that recurs in or pervades a piece of work. However, how the researcher decides on what data constitutes a theme is more nuanced. For example, a theme may be based on prevalence, that is how often the idea or concept is articulated by the interviewees. Alternatively, rather than the frequency in which a theme recurs within the dataset, a theme may also be related to how meaningful the idea or concept is to the phenomena of interest. Ultimately it is the researcher's judgement to determine what a theme is, although consistency of judging 'themeness' is key within the analysis. Although Braun and Clarke advised that the decision on what constitutes a theme should be made prior to analysis, I took a more flexible approach and chose to first begin my analysis and then be guided by the data.

#### 8.5.4 Analysis process

Braun and Clarke (2006) detail a step by-step guide to the six phases of their analysis process, which is also summarised in a table and reproduced below [294]. Their analysis process is recursive, allowing you to return to various phases during the analysis, rather than a rigid mode of analysis which is only linear in fashion.

The authors highlight that it is important to reflect on when to delve into relevant literature, noting '...a more inductive approach would be enhanced by not engaging with literature in the early stages of analysis' (p.86) [294]. At the beginning of my analysis process I decided not to formally explore the literature until Phase 5, when I

had developed and reviewed my themes. This was to allow me to take a more inductive analytic approach, but also given my previous research experience in this area I was already familiar with the psychosocial literature around genetic testing.

Importantly Braun and Clarke emphasise that this is their guideline to analysis, and these are not fixed rules that must be followed in order to carry out a successful thematic analysis. This allowed me to follow the six phases of their analysis process while maintaining my own analytic style as well as drawing on my previous qualitative analysis experience to inform my overall analysis process; this is detailed in the last column of the table.

Table 8.1 Description of thematic analysis process

Phase	Description of Braun & Clarke's process	Description of my process
1 Familiarising yourself with your data	Transcribing data (if necessary), reading and re-reading the data, noting down initial ideas	Data was transcribed by a third party. I read each transcript several times while making brief notes on each interview guide areas (e.g. ovarian cancer diagnosis and treatment, attitudes to genetic testing, impact of results etc).
2 Generating initial codes	Coding interesting features of the data in a systematic fashion across the entire data set, collating data relevant to each code	Each transcript was coded systematically. Following Braun and Clarke's advice to 'code for as many potential theme/patterns as possible', coding generated more than 800 codes across 18 transcripts. I continued to make notes and record ideas for the results and discussion sections while coding.
3 Searching for themes	Collating codes into potential themes, gathering all data relevant to each potential theme	Codes were then reviewed, collapsing similar and/or repeating codes together to build rough themes. Initial ideas and notes were fleshed out and developed further as themes were built. I began to select extract examples, or 'quotes', that were particularly striking. During this phase two distinct streams of themes emerged between those related to ovarian cancer, and themes related to genetic testing.

4	Reviewing themes	Checking if the themes work in relation to the coded extracts (Level 1) and the entire data set (Level 2), generating a thematic 'map' of the analysis	Checking and reviewing the themes generated key themes and their related and relevant sub-themes.
5	Defining and naming themes	Ongoing analysis to refine the specifics of each theme, and the overall story the analysis tells, generating clear definitions and names for each theme	Continuing refinement of each theme and subtheme. Developing an illustrated thematic map helped to visualise the two streams of data.
6	Producing the report	The final opportunity for analysis. Selection of vivid, compelling extract examples, final analysis of selected extracts, relating back of the analysis to the research question and literature, producing a scholarly report of the analysis.	Relating the data to the literature and drawing together a cohesive account of the research question. In this last analysis phase, only the quotes which best represented the theme were included.

In the table below is an extract from a participant interview showing my coding process.

Table 8.2 Example of data extract and codes

Data extract	Codes
<p><i>I was okay about it, that the girls stood as much chance as anyone else then. They will be aware now because I have had it, so your grandmother's got it, but I was okay with it not being genetic because then at least they would be more comfortable. So yes, I didn't feel one way or the other about it. It was like making a decision between having to move quickly to tell medics that my family had this wonky gene, or to go oh, okay, we don't have to panic yet then because my family doesn't have the wonky gene.</i></p> <p>[MGT057, TT, no mutation]</p>	<ul style="list-style-type: none"> <li>• Relatives' risks same as general population</li> <li>• Female relatives aware about ovarian cancer</li> <li>• MGT result better for female relatives</li> <li>• Neutral feelings about MGT results</li> <li>• If gene mutation would need to tell HPs quickly</li> <li>• Wonky gene = gene mutation</li> <li>• MGT result no need to panic</li> </ul>



#### 8.5.4.1 When is a theme, a theme (Part 2)?

I used the early phases of analysis, particularly coding and creating initial themes, to help shape and define what I would consider a theme. During the initial phases of data analysis, I was starting to see patterns in the data where codes were overlapping or clustering. I was also noticing two distinct but related streams of data – codes that related to ovarian cancer the disease, and codes relating to genetic testing. Codes were also naturally clustering around the interview topics of ovarian cancer diagnosis, experience of genetic testing and genetic testing outcomes. As I continued to collate my codes and search for themes, I defined a theme by both prevalence, how often the theme was occurring and recurring within the data set, and whether I felt that the theme represented an important finding.

Once I was clear on what I would consider to be a theme, I continued on with phases 3 and 4 of analysis where themes were further sought and reviewed. There were two key overarching themes around the experience of MTGT: (i) the specifics of MTGT, and (ii) the cognitive and emotional experiences. Relevant themes were reviewed again and denoted as sub-themes, which were then organised under their related key theme.

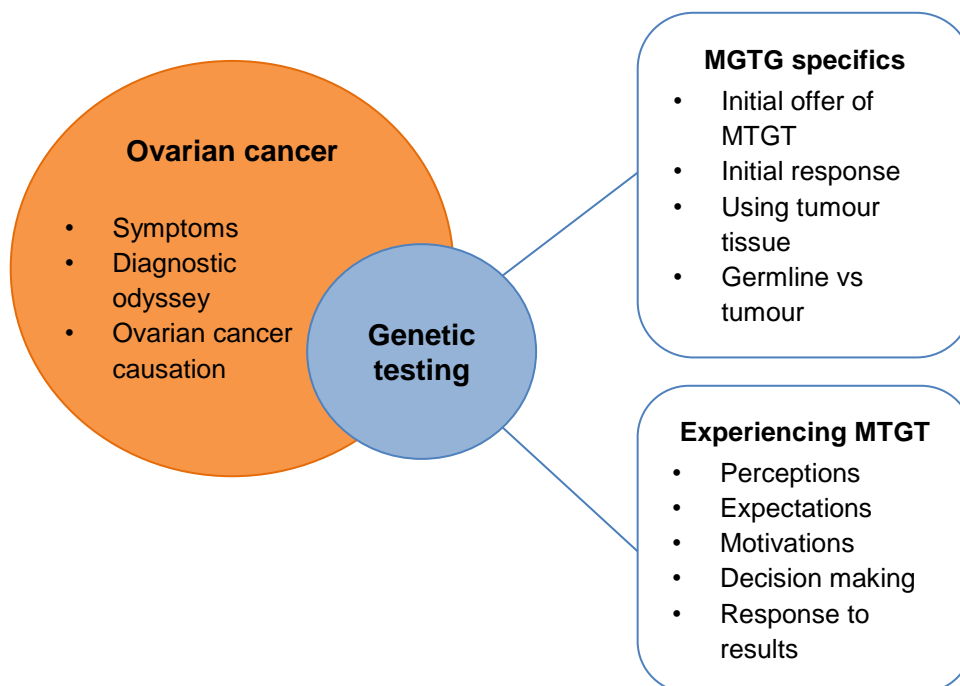


Figure 8.1 Thematic map

As the thematic map illustrates, the ovarian cancer stream is depicted as a larger circle to reflect the greater influence the disease has had on the participants' experiences, compared to genetic testing which is conceptualised as a smaller circle. These two streams, although distinct, are shown to overlap. This is to represent that to some extent these two events are intertwined; these participants were offered genetic testing as part of their clinical care for ovarian cancer.

#### 8.5.4.2 *Data saturation*

Unlike quantitative research, there is no mathematical formula in qualitative research to determine a sufficient sample size of participants. Data saturation has been typically used to justify sample size, which refers to the point at which the emergence of new themes becomes rare and older themes repeat themselves [295]. There is no agreed method of how data saturation is established, and there is often little explanation or justification of how it was achieved. As Morse writes 'Saturation is the most frequently touted guarantee of qualitative rigor offered by authors to reviewers and readers, yet it is the one we know least about' (p.587) [296].

Hennink et al have tried to address the poor definition of saturation, and develop parameters based on rigorous research to guide sample sizes for reaching saturation [297]. They begin by clarifying data saturation and making a distinction between code and meaning saturation. Code saturation refers to the point at which no additional issues are identified, and meaning saturation when the issues are fully understood. They undertook a study to determine what sample size would lead to code and meaning saturation. They found that most of the codes were developed in the initial interviews, and the number of new codes rapidly declined with successive interviews. The authors concluded that while it only took nine interviews to reach code saturation, between 16 to 24 interviews were needed to develop an in-depth understanding of the issues.

Hennink et al use a rigorous and detailed process of determining when code and meaning is reached. Rather than follow this exact approach, I used their findings to guide both my sample size and to conclude when I reached data saturation. With this in mind I aimed to recruit up to 20 participants for an interview. Following Braun and Clarke's analysis guide, I coded the transcribed interviews extensively. Unlike the findings of Hennink et al, I found that for each interview I was still generating a small but significant number of new codes. This was likely due to the breadth of interview topics coupled with the personal and individual experiences of cancer diagnosis and

genetic testing outcomes. As codes were collated to create themes, it became clear that for the purposes of this study many codes, by their prevalence and relevance to the research question, would not reach thematic level.

As themes were generated, I used the iterative nature of my analysis to return to the codes and themes checking if any additional codes were arising, and if there were new or different meanings emerging for the themes. After 18 interviews I felt that for the themes presented in this thesis, I had reached both code and meaning saturation.

As you will see below, there is some data included in the Results section that did not reach either code or meaning saturation, likely because these were both unique experiences of their specific MTGT outcomes. However I decided to include this data as it provides useful and informative insight into the patient experience, and will contribute to our overall understanding of MTGT implementation.

## **8.6 Reflections on issues raised during interviews**

Depending on the topic area, qualitative in-depth interviews may cover sensitive topics. Participants may not have previously had the opportunity to voice their thoughts and feelings of their experiences. As a result, it is not uncommon for interviewees to become emotionally distressed during the course of the interview. This is a risk of qualitative research that is often outlined in the study protocol and made clear in both the research ethics process and when consenting participants.

Participants spoke at length about their experiences of and journey to their diagnosis of advanced ovarian cancer. Despite some diagnoses having been many years ago, their recollections were clear and detailed; this was a memory that was still raw for many. Several interviewees became tearful when recalling the repeated delays and missed opportunities of their health care professionals. Whilst there was acknowledgement that a more rapid diagnosis was unlikely to have altered their prognosis, there was clearly frustration, anger and distress at what they perceived to be failures by the medical community.

It can be particularly difficult to manage an interview where the participant becomes distressed when the interview is not in person, but conducted by telephone. There are no visual cues in body language to show empathy, or physical actions for example reaching out to touch their hand or arm, or a simple but practical gesture of providing tissues. I found that I drew on my genetic counselling training where distress is not ignored, but addressed. I did not respond immediately with words trying to comfort or

reassure the participant, instead I gave them time to be tearful or upset. Where appropriate I would acknowledge their distress, for example a simple statement 'That must have been very upsetting. I'm here to listen'. When there was a quiet moment to gently ask if they would like to pause or stop the interview, participants invariably wanted to continue.

Although I was embedded in the gynaecological oncology clinic for more than a year and had known some of these participants for many months, I was not familiar with the specifics of each participants' journey to diagnosis. It was important, as a researcher, to hear these stories. It was a reminder that genetic testing is taking place within the context of ovarian cancer and any experiences of MTGT will be shaped by this.

As discussed earlier in Chapter 6, there are times when the boundaries as a researcher became blurred. As you will read further on in this chapter, on some occasions participants directly asked me to explain or expand on their genetic testing results and the implications of those results. It was difficult having been trained as a genetic counsellor and therefore having the knowledge to answer their questions, to rebuff their queries. If the question was straightforward and the answer simple, then I felt it was appropriate to provide an answer, particularly for participants who would not have been referred to their local clinical genetics service (i.e. participants who had received no mutation results). In some cases the queries were more complex. For example Janet, who received a RAD51C VUS result, was particularly anxious and confused about what her result meant. During the interview I debated whether or not to explain in general what a germline VUS result meant in attempt to bring her some clarity. However I felt that my explanation was unlikely to bring her much reassurance. Janet's sister had died from ovarian cancer several years earlier and her unexpected and uncertain result was only compounding her concern about a possible hereditary link. At the end of the interview Janet told me she was still waiting to be contacted by her local clinical genetics service. Although I felt it may be beyond my researcher role, I felt a genetic counselling appointment would bring relief and hopefully reduce ambiguity about her results. I contacted her oncologist to confirm that the referral had been made, and then provided Janet with a copy of the genetic testing report and referral, and the phone number of the relevant genetics service.

I found myself navigating uncharted territory during the interviews with one participant [MGT059]. Her tumour testing results had identified a BRCA1/2 mutation and subsequent germline testing had also confirmed this. I assumed prior to the interview

that she had received her germline results as this report had been scanned into her medical records and a referral to her local clinical genetics service had been made. However during the interview she made reference to still waiting for the results of 'the blood test' which would be discussed in her upcoming genetic counselling appointment. Her narrative about tumour testing indicated that she believed she carried an inherited mutation, despite not yet having received her germline results. I was unsure of how to proceed; should I clarify that her tumour testing results were not actually indicative of the nature of the mutation until her germline testing results were disclosed, therefore as it stood whether the mutation is inherited or not was unknown? Or should I disclose her germline results to clarify that it is indeed an inherited mutation based on these results, rather than the tumour testing results? In this ethically important moment with little time to consider how to manage the remainder of the interview, I decided that the most ethical approach would be to continue the interview following her beliefs and her narrative. I felt it was beyond my role as a researcher to disclose her germline results. Rather than correct her misinterpretation of her tumour testing results, what she believes and understands her results to be, whether correct or not, is an important part of this research. I was also reassured to some degree that she had an upcoming clinical genetics appointment where she would have both the time and expertise from the genetic counsellor to discuss and clarify any misconceptions.

## **8.7 Results**

### **8.7.1 Participants**

As discussed earlier in this chapter, the aim was to complete interviews with participants across different MTGT modes and with different outcomes. As shown in the table below, of the 18 participants who were interviewed, half (n = 9) had first line tumour testing, received no mutation identified results and required no further testing. Three participants who had first line tumour testing where MLPA failed and had follow-up germline testing completed an interview, including one patient who then received a RAD51C mutation result and another a RAD51C VUS. Four patients where a mutation was identified on tumour testing and then confirmed on germline testing were included in this sample. As described in Chapter 6 on the clinical outcomes of tumour testing, only three participants were found to carry BRCA1/2 somatic mutations; one completed an interview. One participant who had first line germline testing and was found to carry a BRCA1/2 mutation also completed an interview.

Table 8.3 Genetic testing mode and outcome of interview participants

<b>Participant</b>	<b>Initial MTGT mode</b>	<b>First MTGT result</b>	<b>Additional MTGT</b>	<b>Final MTGT result</b>
<b>MGT006</b>	Tumour	No mutation	No	N/A
<b>MGT013</b>	Tumour	No mutation, MLPA fail	Germline testing – extended panel	gRAD51C mutation
<b>MGT020</b>	Tumour	No mutation	No	N/A
<b>MGT021</b>	Tumour	No mutation	No	N/A
<b>MGT022</b>	Tumour	No mutation	No	N/A
<b>MGT029</b>	Tumour	BRCA mutation	Germline testing – specified mutation	gBRCA mutation
<b>MGT031</b>	Tumour	No mutation, MLPA fail	Germline testing – extended panel	gRAD51C VUS
<b>MGT032</b>	Germline	BRCA mutation	No	N/A
<b>MGT033</b>	Tumour	No mutation	No	N/A
<b>MGT019</b>	Tumour	No mutation	No	N/A
<b>MGT039</b>	Tumour	No mutation	No	N/A
<b>MGT042</b>	Tumour	BRCA mutation	Germline testing – specified mutation	gBRCA mutation
<b>MGT048</b>	Tumour	BRCA mutation	Germline testing – specified mutation	gBRCA mutation
<b>MGT053</b>	Tumour	No mutation	No	N/A
<b>MGT057</b>	Tumour	No mutation	No	N/A
<b>MGT059</b>	Tumour	BRCA mutation	Germline testing – specified mutation	gBRCA mutation
<b>MGT062</b>	Tumour	No mutation, MLPA fail	Germline testing – extended panel	No mutation
<b>MGT056</b>	Tumour	Inconclusive	Germline testing – extended panel	No mutation*

\*This participant was later found to carry a somatic BRCA1/2 mutation as identified on repeat tumour testing by Foundation Medicine

Three participants who were approached and invited to do an interview declined due to feeling too unwell. This included another patient with a somatic BRCA1/2 mutation, and a younger patient who was a germline BRCA1/2 mutation carrier. Two of these participants had recently relapsed, while another had progressive disease while on clinical trial treatment.

## 8.7.2 Themes

Each interview began with asking participants to recall how they had been diagnosed with ovarian cancer, and then to talk about their experiences since their diagnosis. Questions relating to genetic testing often flowed naturally from their stories of diagnostic journey and treatment.

Resulting themes fell into two streams: experiences around ovarian cancer, and experiences around genetic testing.

### 8.7.2.1 *Ovarian cancer experience*

#### **The signs and symptoms**

All participants began, unprompted, with their own recall and identification of their symptoms that eventually led to medical investigations and ultimately diagnosis of ovarian cancer. Across all the interviews, symptoms fell into several categories: digestive, gynaecological, urinary and systemic (fatigue, weight gain or loss, infection, pain). The majority of participants described experiencing at least one symptom, although multiple symptoms (either concurrent, or progressive) were also commonly reported. Symptoms were important to participants, as these were indications where they recognised something was not right.

The most commonly reported digestive symptom was bloating, which was initially intermittent and attributed to menopause, weight gain or IBS, before becoming persistent and increasingly uncomfortable. Systemic symptoms such as weight gain and weight loss were also associated with bloating. Some participants struggled with ongoing fatigue and persistent infections.

*All the while, my stomach was getting more and more bloated. I gradually found that I was having trouble fitting into clothes. [MGT059, TT + GT, BRCA+ve]*

*And I was going on holiday, I had another couple of attacks in between, they were so far apart and I just thought it must have been IBS or something like that. [MGT020, TT, no mutation]*

Gynaecological symptoms were typically bleeding. Participants found this to be a particularly distressing symptom; all the participants who completed an interview were post-menopausal either due to age or as a result of their ovarian cancer debulking surgery. This symptom was often the catalyst for participants to seek medical attention if they had not already. Urinary symptoms were described as haematuria and also prompted participants to visit their GP.

*Luckily, my eldest daughter had called in to see me, and I was crying. I said, 'I'm bleeding, I can't have periods at my age'. [MGT021, TT, no mutation]*

*So, he did a urine sample, and he said, 'Oh, yes, you've got blood in your urine. You've probably got an infection. I'll send the test to hospital, and it will be back within a week. You can phone.' I phoned, and they just said, 'Oh, no, it's not an infection, don't worry'. [MGT021, TT, no mutation]*

Only three participants described their experience prior to diagnosis as asymptomatic. However two participants experienced an acute period of digestive symptoms (vomiting) which led to A&E admission, while the sudden onset of PV bleeding for another participant did lead to medical investigations.

*I didn't have any clue at the original, I didn't have bloating and things that you're supposed to have, or going to the loo more often. [MGT032, GT, BRCA+ve]*

*Well I suppose I developed some post-menopausal bleeding which was at the beginning of last year but prior to that I'd had a little bit of constipation but not enough to go to the doctor, then when I got the bleeding, that was the reason I went. Then I was told it wasn't that typical for ovarian cancer, so in a way I suppose it was fortunate I did, because I felt fine, I wasn't ill at all. [MGT048, TT + GT, BRCA+ve]*

### **The diagnostic odyssey**

For the vast majority of patients, the process of diagnosis is perhaps best described as an 'odyssey'. Many spoke at length about their experience of the journey from symptom manifestation to eventual diagnosis of ovarian cancer. For most of the



participants, the diagnostic odyssey began with repeated visits to their GP, often over several months.

*So, after Christmas, I went back to the GP, maybe three times over the next eight weeks, something like that. I saw different people each time... For months of going to the GP, he was the first person to flag it up.*  
[MGT059, TT + GT, BRCA+ve]

*Yes. I didn't feel well, my stomach was so bad, it was so bloated and I went to the GP for a blood test and they didn't discover anything, nothing. So I changed my diet, that didn't do anything to me either. So I went back to the GP and she took another blood test and it wasn't right... So I went back, and the GPs, they don't want to know, and they just say 'No, go to A&E.'* [MGT039, TT, no mutation]

Delays were also encountered once a referral was actioned by the participants' GP. The process of diagnosis was sometimes protracted, with multiple investigations involving different medical specialties.

*I went through so many departments, I went through one department, then another, then another, then eventually ended up moving to oncology.* [MGT006, TT, no mutation].

*I: So once you went to the GP, what happened then?*

*R: I was sent for scan.*

*I: Straight away?*

*R: On a waiting list and after that, from one hospital to another hospital and I ended up in the best hospital.*

*I: And how long do you think that process took, once you went to the GP?*

*R: Half a year.*

[I = interviewer, R = respondent; MGT013, TT + GT, RAD51C+ve]

Once the diagnosis was confirmed, a number of participants reflected on their shock at learning they had ovarian cancer.

*I got the impression the doctor didn't quite know how to tell me, when I look back, he seemed to be twitching a lot and couldn't sit still, and didn't know how to say it, and eventually spilled the beans, and I was absolutely shocked. I just never thought it was cancer, completely shocked.*  
[MGT053, TT, no mutation]

*Well I don't know. I never suspected I had ovarian cancer. I was losing weight. That was it, I was losing a lot of weight and I just... That's right, I was sent to the [Hospital 1] and never in a million years did I think it was cancer. It was the biggest shock of my life when they told me that, absolutely shocked. [MGT042, TT + GT, no mutation]*

For some participants, there was a sense of self-blame about their delayed diagnosis; they felt they should have pushed their GP more or insisted on expedited investigations or referrals. Lack of recognition of symptoms was often blamed on menopause or IBS. Others spoke about the inherent sense that something was wrong, and the frustration to convince health professionals

*I'd never ever carried a belly like this in my life. I had been every size under the sun, so I knew what my body is capable of. But of course most of it got put down to menopause. The doctor says something, you're not medically trained, you tend to believe it. But I am quite intuitive and I've had this body for 60-odd years now. I know what it does, and no one would listen. [MGT057, TT, no mutation]*

*Okay, I've got a virus, there may be stomach problems, bloating, et cetera, because of antibiotics, maybe it could be, but there was a general feeling that something's not quite right. [MGT059, TT + GT, BRCA+ve]*

## **Ovarian cancer causation**

The aetiology of ovarian cancer is complex and still poorly understood; only a small proportion of cases can be attributed to inherited mutations which predispose individuals to developing the disease. Part of the interview focused on participants' own perceptions of why they had developed ovarian cancer, to explore if there was any attribution to family history or an inherited component. Some participants had never considered possible causality of their ovarian cancer diagnosis.

*I wouldn't even know. I hadn't thought about that. I accepted the fact that I'd got it [ovarian cancer] and wanted to deal with it really. [MGT029, TT + GT, BRCA+ve]*

*Well I suppose I don't really know. There are various things and I don't really know why, it's just unfortunately one of those things. [MGT033, TT, no mutation]*

*I don't think I've actually really thought about the cause, you just think well, cancer hits and that's it. [MGT020, TT, no mutation]*

A small number of participants felt ovarian cancer may have been linked to specific event in their life, such as exposure to x-ray in the pelvis, longstanding gynaecological problems, shock or stress. Others described cancer as occurring by chance. Five participants who received a germline mutation positive result during participation in this study were interviewed. Only one specifically commented on the link between family history, genetics and ovarian cancer.

*My attitude towards cancer I suppose when I hear about it is ouch, when people tell me that they developed cancer, I just feel very, very sorry. It's almost like a game of chance these days. Are you going to get cancer?  
[MGT006, TT, no mutation]*

*Just luck. It's a draw, some of us get it and some of us don't... So I didn't think anything about anything else that could be causing it. [MGT032, GT, BRCA+ve]*

*Well, certainly having had the genetic testing now and having five in a family of six I think there must be a genetic link somewhere. [MGT048, TT + GT, BRCA+ve]*

#### 8.7.2.2 The specifics of MTGT

##### **Initial offer of MTGT**

Participants were asked about the first time they could recall genetic testing was raised. One participant had genetic testing raised by her GP, because of a family history of ovarian cancer, although this was not followed up any further. A few participants had already taken the initiative to discuss genetic testing with their oncologist, although there was no further follow-up in these cases either. Instead for most participants, MTGT was first discussed during one of their oncology consultations and recruitment into this PhD study was typically a catalyst for that conversation. A brief explanation of genetic testing was provided by oncologists.

*Dr [name] when I saw her. I think it was when I came to have the first session of chemotherapy. I think it was then, and that was when she mentioned it to me... that it could be to see whether there might be a future drug available and see whether I would be eligible... Briefly she told me what it was, and I just thought well if it could help the future... It wasn't going to do me any harm, having it done, so I said yes, I'd go along with it. That's when she referred me to you. [MGT033, TT, no mutation]*

*Prior to that, I remember speaking with Dr [name] quite a long while ago, even before the end of the initial treatment, about the genetic testing being something that would be done in the future, but it was a case of, there isn't a rush for it now, looking at the age of the children as well. It would be after the initial treatment is all finished. But it certainly was mentioned, and I think we'd also asked about it, having a daughter as well as a son. [MGT059, TT + GT, BRCA+ve].*

### **Initial response to GT**

Overall, participants described a positive response when genetic testing was first raised. Participants were also quick to establish a link between genetic testing and risk to family members, with their first thoughts turning to female relatives. For a few participants, the offer of genetic testing was unexpected; they had not previously anticipated ovarian cancer could be inherited.

*My first thoughts were actually oh my god, I've got two granddaughters. I went home and thought about that, oh I've got two granddaughters... I was immediately thinking of family. I've got to do this because I want to know if there is a chance so I can warn them that things could happen. [MGT020, TT, no mutation]*

*My initial thought, to be honest, was, yes, I want to get it done, I'd like to help with the research. I realised how important it is for the future, for my children, for other peoples' children, and for treatments, for other people's treatments. So, I was always inclined, yes... [MGT059, TT + GT, BRCA+ve]*

*Well, I was a little bit shocked that that's what it could be. [MGT029, TT + GT, BRCA+ve]*

### **Using tumour tissue for genetic testing**

Participants had no concerns about the process of tumour testing, largely due to its non-invasive nature of using tissue which had already been removed during previous biopsy or debulking surgery. Using tumour tissue for genetic testing was seen as an action that was completely separate to them. Participants had a sense that if the tumour tissue could be used to benefit them in some way, then this was a positive course of action.

*But as far as your tumour testing, that's your job now. This is something that you've found that needs investigating. I don't even see why I was asked quite honestly... It's something you took out to stop me from dying,*

*so really I was glad to be rid of it... I would have thrown it away or burnt it [laughs]. If you guys need it still then knock yourselves out. [MGT057, TT, no mutation]*

*So, maybe, because feeling that it's a tumour that I've had, it's been and done. It's done the awful work already, so whatever you find out about it afterwards, it's a bit, helping with moving on for the future. [MGT059, TT + GT, BRCA+ve]*

*There was no physical process being done on me to genetically test me. They were testing the tumour that had already been taken out. I could see no reason to stress about that. It didn't make any difference where it was. That process was apart from me physically so it was easy. It's simple. [MGT020, TT, no mutation]*

### **Tumour vs germline testing**

Tumour testing is one mode of genetic testing to identify BRCA1/2 mutations that may or may not be hereditary. Throughout the interviews participants mainly used the term 'genetic testing' unless specific questions or references were made to using tumour tissue or tumour testing. Some participants demonstrated a good recall and understanding of the logistical processes of tumour testing, e.g. retrieval of stored tumour samples, transport to Germany for genetic testing, and return of testing results. They were also able to distinguish the different processes between germline and tumour testing, i.e. blood vs tumour samples. However very few participants had a good understanding that mutations identified on tumour testing could be non-inherited; only one participant was able to describe somatic mutations unprompted.

*I understood that you were going to test my tumour and that there was a chance that my tumour might have the BRCA gene, even if I didn't. So I thought that was a good thing... I did explain to her [sister] if there was something it won't prove because it might be just in the tumour, but then either I could organise a blood test or she could organise. [MGT022, TT, no mutation]*

*Obviously I'd already been asked about the tumour tissue, so I presumed that they would analyse that and then inevitably some sort of blood test would follow because blood seems to be integral to all this. [MGT048, TT + GT, BRCA+ve]*

*Well I'm surprised that it is, I just assumed I just was having the normal tests and it seemed appropriate to have had the tumour analysed first and then having a blood test. But I suppose... Are you saying with the blood test alone you can tell whether you have an inherited mutation?*  
[MGT048, TT + GT, BRCA+ve]

From participants' recall of genetic testing discussions with their oncologists, the language used reflects concepts related to germline testing such as risk for family.

*It was mentioned quite early on that it was something that one could take part in, and it was Dr [name] and she said some people choose not to, they don't want to know and they don't want their families to know, they don't want any onus on them.* [MGT006, TT, no mutation]

*'She said the same, like I said, 'We want to find out if it has something to do with your parents or grandparents, so it could affect your children as well' – along that way. She explained it to me, I agreed with her.*  
[MGT039, TT, no mutation]

During the course of the interview it emerged that two participants had forgotten they had tumour testing; they both incorrectly recalled giving blood for genetic testing rather than using tumour samples.

*So now this is really embarrassing, this is what I mean when I say I forget things. Did I have my tumour tested then? Did I have a tumour test?*  
[MGT053, TT, no mutation]

### 8.7.2.3 Experiencing MTGT

#### **Perceptions, expectations and motivations**

Perceptions related to the way participants regarded, understood and/or interpreted genetic testing. There was a perception that genetic testing was a positive action, with participants describing it as 'a good thing' to do. Most participants felt that genetic testing was primarily to benefit others, either family members or other ovarian cancer patients.

*Well, I knew vaguely what it would involve and I just thought well, if they can improve how treatment is done, whether it's just for the person who's having the testing or for other people, then I just feel it's a good thing to happen.* [MGT033, TT, no mutation]

*I didn't have any hopes for myself, I could see that it would benefit my family, having a daughter and grandchildren, granddaughters. I didn't think it would benefit me, I just thought it was a good thing to do, that it would benefit somebody. Not me. I never thought it would benefit me. [MGT032, GT, BRCA+ve]*

There was an expectation for some participants that genetic testing would provide an answer to why they had developed ovarian cancer.

*My only expectation was it would come back with an answer, what would the answer mean and that I wasn't sure of. So whether I had the genes or whether I hadn't the genes. [MGT062, TT + GT, no mutation]*

*I did actually think it would tell me one way or the other whether it was hereditary and I think most possibly because one of my daughters-in-law was particularly anxious about it, so I thought I need to know so that I can pass on the information. [MGT056, TT + GT + TT, sBRCA+ve]*

For almost every participant, their primary motivation to have genetic testing was for family. Genetic testing was perceived as being able to provide information for family members that could be of value. Only one participants expressed the possible personal benefit of tumour (or germline) testing, in terms of potentially accessing more treatment options.

*I suppose, there's two things really. Moving forward for family, I think, it's important that I should do it for them, even if we can be scared of the results [laughing]. Knowledge is power. It's empowering. That probably sums up why. [MGT059, TT + GT, BRCA+ve]*

*Well, because they said it could be passed on to the family. My son as well, and he's got three daughters. So mainly it was for them. I didn't know what it would mean for me personally. It's more they've got their lives to look forward to. [MGT031, TT + GT, RAD51C VUS].*

*If I was positive, it would open up more treatments for me, even though I didn't think I would be positive. [MGT022, TT, no mutation]*

Curiosity was another motivation for testing; participants were curious about what genetic testing might reveal and how it might inform their own understanding of ovarian cancer. Participants were interested in the possible outcomes of genetic testing, they 'wanted to know' what their results might be, whilst acknowledging it may be of little use.

*There was that curiosity, okay, there is this genetic thing, how it all fits in with the illness, what does that mean, why this one person who has the genetic mutation would get cancer? Presumably not everybody who has the genetic mutation will get cancer. I think I looked at it more from the curiosity point of view. [MGT059, TT + GT, BRCA+ve].*

*I just thought it was quite interesting. I also think I was quite interested to see that people might find out more about the illness, it might help other people, might help me anyway just out of curiosity. [MGT006, TT, no mutation]*

*I thought it would be interesting to know what the results were. There wasn't much I could do about it. But I would like to know. [MGT062, TT + GT, no mutation]*

### **Decision-making for MTGT**

Of the participants interviewed, they unanimously felt it was 'easy' to make the decision to have MTGT. Many described making their decision immediately, as soon as testing was offered by their oncologist.

*Well, I'd already made up my mind I was doing it. I discussed it with my daughter and my husband – I don't know if discuss is the right word, I just said I'm going to do it. [MGT032, GT, BRCA+ve]*

*To me, as I said to you, there wasn't any question about not doing it. There wasn't any question about not doing it, just the sheer fact that it was available and this sort of thing is important was enough. [MGT020, TT, no mutation]*

Some participants involved their family members in the decision-making process by discussing it with them prior to consenting to testing. For a few participants, it was a deliberate choice not to involve family members in the discussion and decisions around genetic testing, primarily to alleviate any worry or anxiety this may have caused.

*They were all very anxious about my health status and I didn't want to add anything else to their anxiety really until I knew the results because what I had learnt was that it could be, if there was the BRCA genes, if I had them, it could be passed from mother to daughters and to sons who could then pass it on to their own offspring and I didn't want to cause them that anxiety until I knew the answer. That's definitely why I didn't include them in my decision making. [MGT062, TT + GT, no mutation]*



As part of the interview schedule, participants were asked if they felt they had sufficient information and discussion with their oncologist to make the decision about genetic testing. Overall participants felt as if they had enough information and opportunity for discussion with their oncologists. Participants didn't seem to seek additional information from other resources. There was a sense that because of their illness and treatment, participants already had enough on their mind.

*I don't think I needed too much discussion about it. Dr [name] explained it to me, what could happen etcetera, and I just thought well, this is in important. So therefore you don't have to go on for much longer, I don't want every detail. [MGT020, TT, no mutation]*

*No, I wouldn't have liked any more information. If I'd have wanted information I'd have gone onto Google. [MGT042, TT + GT, BRCA+ve]*

## **Results of MTGT**

### *No mutation: What a relief*

The most common reaction to receiving tumour testing results was a sense of relief. For participants who received negative (no mutation identified) results, relief was associated with their perceived hereditary cancer risk to children and family members. Participants were also 'pleased' and 'grateful' that their results were negative. For most participants, once they received their mutation negative results there was little time spent ruminating on the outcomes.

*Yes, I felt quite relieved that I didn't have a disease I'm passing on. [MGT021, TT, no mutation].*

*I felt quite proud of myself [laughs], there you are then sort of thing. And yes, the funny feeling of relief I suppose. And I remember being quite pleased to say to the boys 'By the way there's no problem, you haven't got to go and all be tested, it's not a mutation.' [MGT006, TT, no mutation]*

*Well, the thing is when you're reading these stories about people in the family and all this, one daughter and another and another, grandmother, granddaughter, and they all have to be treated, if it's breast cancer or ovarian cancer, they get operated straight away, everything has to be removed, so you're quite happy that your girls don't have to go through that. They're only young. So that's a positive thing. [MGT039, TT, no mutation]*

A few participants recalled mixed feelings about their result, reflecting some ambivalence to the outcome because of the perceived lack of personal utility or benefit. One participant who was mutation negative, was relieved that there were no implications for her children, but had also been hoping that the results from genetic testing would expand her treatment options.

*As I said, in one way I thought good, I'm glad, it's nothing to do with that, so no problems there. And on the other hand because as I said I could have done something differently in treatment. But there you are.  
[MGT039, TT, no mutation]*

#### *Mutation carriers: The positives of being mutation positive*

During the course of the study, five of the participants interviewed learned they carried a germline mutation. Some of the participants had anticipated that their genetic testing results would reveal they carried a mutation, with two referring to a family history of cancer.

*I was expecting it to be positive because of my daughter. My husband wasn't, 'Oh, don't be stupid' [laughter]. But I did think it would come back, so when it did come back positive I wasn't surprised. [MGT032, TT + GT, BRCA+ve]*

*Well I was fairly confident that I would be positive. I would have a mutation given the history, so... I expected it. I wasn't the slightest bit... I wasn't surprised. [MGT048, TT + GT, BRCA+ve]*

Overall, participants felt that learning they carried a genetic mutation was in fact a positive outcome. There were perceived positive benefits in terms of their perceptions of the disease and understanding why they had developed ovarian cancer. For some participants, their results helped to alleviate feelings of guilt and self-blame. Perhaps the most striking impact of receiving a mutation positive result was for one participant who had blamed herself for developing ovarian cancer, and described her result as '...makes me feel more normal' [MGT013, TT + GT, RAD51C+ve].

*In some ways, getting re-diagnosed with the cancer and having the treatment, and then with the genetic thing, that there is the genetic link, maybe it's almost helped me come to terms with it a little, that this is going to be an ongoing condition that I will need to live with... and I almost feel that it's more manageable, mentally, moving forward, and it will make me stronger about dealing with it, rather than not. That might sound strange, but yes. [MGT059, TT + GT, BRCA+ve]*

*I think I felt quite happy about it, to be honest, because it was an answer to what I'd got and basically how I'd got it and it was an explanation, I suppose. [MGT029, BRCA+ve]*

*Yeah, because I blamed myself all the time, why did I inflict this illness on myself?... I was asked for another blood test which brought the conclusive results, and I understood that it wasn't my fault. This is the good influence of the research on me actually. I enjoy life more now. [MGT013, TT + GT, RAD51C+ve]*

When reflecting on what they felt were the positive and negative aspects of being a mutation carrier, participants largely felt there were no drawbacks. For most participants, the positive aspects of being a mutation carrier were actually related to their children, and how this genetic information would be of potential benefit to them. Only one participant explicitly spoke about a direct personal benefit in being able to access PARP-inhibitors.

*There are no positives, I don't feel, for me. But I do think it's fantastic for my daughter and all my granddaughters that I know they won't go through this. Well, they might do but they have a choice. They can choose to go down the path of being tested and making their own choices. [MGT032, GT, BRCA+ve]*

*I mean, the interesting thing was I thought all along it was purely the next generation who would sort of benefit or otherwise or they are the ones who need to take it forward, but it was interesting to know that from my point of view, I would be more responsive to the PARP-inhibitors should the need arise. [MGT048, TT + GT, BRCA+ve]*

*The only positive that I think is for the family because they've had the test, they can now be dealt with if they have actually got it... So if I haven't have had the test then none of these would have found out or known whether they'd got it or not. [MGT029, TT + GT, BRCA+ve]*

### *Results disclosure*

Participants were asked if they could recall receiving their MTGT results, in particular how they were delivered and what explanation was provided. Overall participants felt satisfied with how the results were communicated although some, both those who had received no mutation or mutation positive results, struggled to comprehend the meaning of the results.

*The person that I saw just said there's nothing there and handed me the sheet of paper [tumour testing report]. I think if I'd been worried or if it was positive I think that might have been a bit startling. I was a bit startled actually anyway, but I wasn't worried. [MGT022, TT, no mutation]*

*Yes. I don't have the BRCA genes...To be absolutely honest, I didn't really know what it meant in a way, I really didn't. [MGT062, TT + GT, no mutation]*

*So I don't know what the results mean for me. You tell me what they mean for me. [MGT042, TT + GT, BRCA+ve]*

## **Two unique cases**

There were particular aspects of two cases which due to their specific MGTG outcomes, germline RAD51C VUS and somatic BRCA1/2 mutation, did not reach inclusion within the thematic analysis and presentation of data. However their stories provide important insight into the genetic, tumour and germline, testing experiences of ovarian cancer patients which can help inform our understanding of these experiences and which may not be unique in other settings.

### *The unknowns of carrying a variant of unknown significance*

One participant, Janet<sup>2</sup>, [MGT031, TT + GT, RAD51C VUS] interviewed was found to carry a germline RAD51C VUS. First-line tumour testing did not identify any genetic alterations. However as the MLPA portion of testing failed, she had follow-up germline testing which reported a RAD51C VUS. She was the first patient in this cohort to be found to carry a VUS in this gene. Not only was Janet uncertain about what her result meant, so too was her oncologist.

*I had the initial letter. It told me that I wasn't carrying it and everything like that. So I was thrilled. I told them all that was fine, they haven't got to worry. Then I don't know at what point I saw [oncologist] and she said, 'There's this tiny bit of the bottom about something that's totally unknown.' She said, 'We know nothing about it. It's totally new,' and they're starting to look into it, and they've found this little bit of whatever this is, so I don't really understand it, to be honest.*

A referral had been made to the patient's local clinical genetics service, however at the time of the interview this was delayed and no appointment was forthcoming. As

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<sup>2</sup> Pseudonyms used

the participant describes in her own words below, her initial relief of not carrying a mutation then turns to worry and confusion. Reassurance from her oncologist provides little comfort, and she reveals her concerns about what this new, unknown finding might mean for her and her family. Until this patient was able to attend a clinical genetics service for genetic counselling, she was left feeling uncertain and anxious about her results.

*Over that bit now, yes, I do, because she [oncologist] said, 'It won't affect you and it won't change your treatment.' But obviously, you want to know everything's okay. As I say, it's only when letters come through and things are in black and white, which obviously I've got a folder full of them; that is when you feel concerned. I read it and feel quite sick, but I think thank god I am where I am and I just keep telling myself that I'm going to be alright.*

#### *When a positive tumour test result isn't that positive*

In this cohort of ovarian cancer patients, one participant, Leanne [MGT056, TT + GT + TT, sBRCA+ve], was eventually found to carry a BRCA1 somatic mutation after additional tumour testing (this is discussed further in Chapter 6). Leanne shared a similar narrative when reflecting on her experience of ovarian cancer diagnosis and treatment, motivations for genetic testing and decision-making. Despite the repeated tumour testing being undertaken specifically to determine trial eligibility, she was explicit in her lack of motivation to have testing for this purpose and still refers to testing to inform family members.

*I think I was more concerned about the possibility of it being hereditary and I thought if I could at least know one way or the other. I didn't really know about gene mutations or anything like that at the time, it was just can I... I thought is it like breast cancer where sometimes it's in the family and it's hereditary and I need to think about my children and my grandchildren and I suppose selfishly it was for those reasons as well, it was possibly a bit more knowledge for me. [MGT056, TT + GT + TT, sBRCA+ve]*

*To try and have possibly more information about whether it was hereditary or not. I know that's a selfish reason but that was the main reason for me. It wasn't so much that it would do me any good but I didn't expect anybody to say, "Hey, look, you'll be perfect for this trial, you've got all the right criteria, blah-blah-blah," it was really just to say, "Yes, your family, they need to be screened, they need to go for regular check-ups," or, "No, it's okay," sort of thing.*

Similar to other participants' experiences, Leanne spoke at her relief that her genetic testing results meant there was no hereditary implications for her children. Despite her lack of expectations, she also recalled being pleased that her results had meant she was able to take part in the clinical trial.

*So I suppose at the time, I was talking to the registrar before we started and he was explaining it, he said, "Well if you do the trial, you sort of get two shots, but if you decide just to go for chemo and then we find the chemo isn't working you can't then say, 'Oh well, can you put me on the clinical trial?' because the window will have gone by then". So yes. So when I knew that I did fit the criteria, I suppose I was glad, I had an extra chance at it.*

However, any hopes of the benefits taking part in the trial might bring were not met. Leanne struggled with the side effects of treatment and on reflection, wished she had not taken part. However she still spoke of her appreciation that she was able to take part in the trial thanks to having had tumour testing.

*Anyway, so the trial was a waste of time. For me, it was a waste of time. Whether it helps anybody else, I have no idea, but I had to have a transfusion because I just felt so low and my blood count was low. I just felt rubbish the whole time. I don't think there was a day when I didn't feel rubbish.*

*I wish it was different and I really would have to think if another opportunity came up, say... If I was here in a year's time and something else came up, I'd think very seriously about my quality of life before I made... I would then think carefully when I made my decision knowing what I'd been through this time. But I don't think... I'd still say I was relieved when I got the result that yes, I did fit the criteria and that wouldn't have happened if the tumours hadn't been tested, would they, really?*

## 8.8 Discussion

Targeted therapies are transforming oncology care where treatment can be increasingly individualised. BRCA1/2 tumour testing is one of many approaches to using genetic information to inform treatment decisions. For example Oncotype Dx has been recommended by NICE guidance to inform adjuvant chemotherapy decisions in early breast cancer, where gene expression is measured by extracting RNA from FFPE tumour blocks [298]. However there is an important distinction between BRCA1/2 tumour testing and other forms of gene profiling that are used in the oncology setting, in that the outcome of BRCA1/2 tumour testing has the potential to provide information about inherited genetic alterations.

In this cohort of participants who were interviewed, only one was found to have a BRCA1/2 somatic mutation, while five other participants carried a germline mutation. Given the vast majority of participants have a germline mutation and there is a paucity of literature around the patient experience of BRCA1/2 tumour testing specifically, this qualitative data will be considered mostly in the context of germline testing literature and will include somatic testing literature where possible.

Context has been an important part of this research. In Chapter 4 the context for this case study was defined as genetic testing in ovarian cancer, with the case (mainstreamed tumour testing) and the embedded subunits then bound within this context. The service evaluation in Chapter 5 and my experiences organising BRCA1/2 tumour testing in Chapter 6 were an invaluable part of developing my understanding of the overall context, in particular how genetic testing intersects with the oncology setting.

Over the months I spent in the clinic and with my participants, I was familiar with their cancer pathway and current treatment regimes. However I was much less familiar with their routes to diagnosis, and what their experiences of ovarian cancer had been prior to enrolling in this research. I wanted to try and understand the patient's own context in which MTGT would be taking place. Thus the introductory part of the interviews asked participants to tell their story of how they came to be diagnosed with ovarian cancer, and their experiences of treatment thereafter.

Whether it had been months or years from diagnosis, participants had very clear recollection of the events that led up to their diagnosis, even recalling exact dates and small details such as the weather on that day. The vast majority of participants had experienced diagnostic delay. This protracted route to diagnosis had had a significant

detrimental and long lasting impact. The diagnostic delay in ovarian cancer is well known and has been reported extensively [299]. Other qualitative studies of women's prediagnostic experiences of ovarian cancer have also reported their distress when concerns about their symptoms were dismissed by health professionals [300]. Part of the challenge of a timely diagnosis are the non-specific symptoms of ovarian cancer [299]. As one participant commented in her interview, 'I read ovarian is very silent, isn't it, a silent cancer. Is it still like that?' [MGT039, TT, no mutation]. As participants recounted their symptoms, they were related to gastrointestinal, gynaecological and general systemic symptoms, none individually being particularly indicative of ovarian cancer. Participants acknowledged that it was unlikely a more timely diagnosis would have had a significant impact on their prognosis, but they were frustrated that the signs that 'something wasn't right' were missed or ignored. The conviction that something was physically amiss within themselves, recognising their own embodied knowledge, has also been reported by other ovarian cancer patients [300, 301]. What their diagnostic experiences seemed to drive was a desire to prevent ovarian cancer happening not only for their own female relatives, but for other women in general. Scattered throughout the interviews were references to the need for a screening programme, in particular using CA125, to either prevent or detect ovarian cancer at an earlier stage. This may also have influenced their desire to have MTGT, seeing this as an opportunity to inform their family members of any potential cancer risks.

The experience of diagnosis was clearly a significant experience in these women's lives, triggering their cancer treatment pathway that would continue for many months and years. What became clear as the interviews progressed and the focus shifted from ovarian cancer to MTGT, was that genetic testing paled in comparison. As one participant put it succinctly, 'The worst thing had already happened: I'd got it' [MGT057, TT, no mutation]. The rich detail from their interviews emerged when participants were talking about their cancer diagnosis or treatment while their accounts of MTGT were fairly brief. Shipman et al reported similar findings after interviewing breast and ovarian cancer patients who had undergone TFGT, including some who had been tested via a mainstreamed model [292]. Women's accounts of their diagnosis and treatment were long and detailed, while their accounts of genetic testing were minimal with the authors concluding that genetic testing was not a concern in the context of ovarian cancer. For the majority of participants, genetic testing was just a brief interlude with little impact on their long and life changing journey of ovarian cancer.



Providing genetic testing during the ovarian cancer pathway also influenced how much participants were able to engage with it. Woven through the interviews was their narrative of managing the cycles of treatment and relapse. Focusing on cancer was the priority and at an already overwhelming time, MTGT could not be given the same attention. One participant encapsulated this, 'While you're dealing with everything that was going on, it didn't give a chance to put a lot of thought to it. I just got on with it' [MGT031, TT + GT, RAD31 VUS]. A focus group study of breast cancer patients who had genetic testing shortly after their diagnosis described the diagnosis of cancer itself as 'a great burden' (p.184) [302]. The tumultuous experiences of being diagnosed impacted their ability to fully absorb information and all that was happening around them. They were often preoccupied with thoughts and decisions related to their breast cancer diagnosis and treatment, making it difficult to focus on other issues like genetic testing. Liang et al reported similar findings in a cohort of advanced lung or melanoma cancer patients who had undergone somatic testing. Patients attributed their struggle with retention of information to cancer-related psychological distress [106]. In all these cases, the cancer context in which genetic testing was taking place was an impediment to engaging fully with the testing process.

Unlike other gynaecological cancers such as cervical cancer cases where the majority of cases can be attributed to the HPV virus, the aetiology of ovarian cancer is still relatively unknown. Only a small proportion of ovarian cancer cases, around 15%, can be attributed to inherited germline mutations [12, 75, 303, 304]. I was interested in exploring if participants perceived there to be a specific or underlying cause of their ovarian cancer, in particular if there was any attribution to genetic causes.

Many of the women interviewed had not previously considered what may have been the cause of their ovarian cancer. For some participants they did not speculate on possible causes, instead responding that they just did not know why cancer had developed. Despite being a participant in a study about genetic testing, there was little mention of any genetic or inherited cause to their cancer. Instead there was a sense that cancer was just 'one of those things', and their focus was on dealing with the diagnosis rather than trying to make sense of what had caused it. Other participants described their ovarian cancer as being down to chance or luck, implying the frequency of cancer as well as having little or no control over the development of cancer. In a qualitative study of Australian women's perspectives of gynaecological cancer causation shortly after diagnosis, women predominantly did not know why cancer had developed [305]. Similar to participants in this study, Manderson et al described women's beliefs about cause of gynaecological cancer as 'non-predictable',

likening it to the game of chance, roulette. For other women with a personal history of breast or ovarian cancer, they believed their diagnosis and the cancers within the family had an underlying genetic predisposition and genetic testing was a way to confirm their suspicions [127]. This may also reflect the impact of moving from the previous criteria required for BRCA1/2 testing to the unselected approach now used. Previously family history was one of the main criteria of eligibility for testing, which was reflected in Hallowell's paper where participants had a total of 119 relatives who had been affected with cancer [127]. In contrast, family history is no longer used as a and patients who are offered testing may be the only person in the family to have a cancer diagnosis.

This sample of participants included five women who had been identified as carrying germline mutations during the course of the study, however only one participant initially made the link between their family history and genetic testing result as having led to ovarian cancer. Even amongst a sample of women at high risk for ovarian cancer due to their family history or BRCA1/2 mutation status, participants described having little knowledge that ovarian cancer was also linked to BRCA1/2 mutations [306]. In a survey of Canadian ovarian cancer patients, more than a third (36.5%) of participants cited genes as being causative [307]. However the 'genes' were not specified as the high penetrance genes BRCA1 and BRCA2, more likely reflecting a general understanding of the role genetics plays in many diseases.

Most participants could recall when genetic testing was first raised by their oncologist. For one participant, her oncologist had already mentioned genetic testing at some point during their routine oncology outpatient appointment although testing was not undertaken. A small number of participants actually asked about the possibility of genetic testing themselves but again there was no further action. This reflected some of the observations from the service evaluation in Chapter 5; after MGT was implemented and BRCA1/2 germline testing was available for the majority of patients, genetic testing was offered at any point in the patient's clinical pathway. There was no systematic approach to MGT, with some oncologists choosing to offer testing shortly after diagnosis, while others preferred to wait for patients to settle into their treatment regime. As one participant recalled of discussing genetic testing with her oncologist prior to this study, '...It [genetic testing] would be after the initial treatment is all finished'. From a treatment decision point of view, based on the current criteria for olaparib results from testing would have little bearing until the patient had completed at least two lines of platinum-based chemotherapy. Therefore there is no clinical impetus for patients to have genetic testing during first line treatment, although

there may be benefit for unaffected family members. The timing of testing seems to be led by clinician preference, rather than an established timepoint or systematic approach.

For the remaining participants, genetic testing had not already been raised in their previous oncology consultations and the introduction of my PhD project was the first mention of testing. When participants recalled how MTGT was first offered, it was typically in the context of providing more treatment options or to identify if there was an inherited component. Participants made an instant connection between MTGT and potential familial implications, already highlighting that concern for family members was likely to be a primary motivation. Participants also described having an altruistic response, instinctively 'wanting to help' not only themselves and their families, but also others. There was a perception that they would be able to do so via MTGT and this research.

When recounting their initial response to MTGT, women often described making their minds up instantaneously that this was something they wanted to do. Despite at the time knowing little about what it involved, or the potential outcomes and implications, its perceived ability to be of benefit to female relatives seemed to be sufficient reason to agree to testing. In a recent study, TFGT was also received very positively by breast and ovarian cancer patients [308]. In this cohort there was a sense of familiarity with testing, either because it was something they had tried to pursue earlier or from general media highlighting celebrity testing experiences.

As tumour testing is still a new way of providing genetic testing to women with ovarian cancer, I was interested in how participants felt about their tumour tissue being used in this way. Participants had no concerns; as the tumour tissue had already been removed, how it was used after this point was of little relevance to them. Perhaps because of the non-invasive nature of tumour testing which did not involve providing a blood sample, it was seen as an external and separate process.

What began to emerge from the interviews as we discussed the process of tumour testing, was participants' struggle to distinguish between tumour and germline testing. In general participants had a good understanding of the logistics of tumour testing and how it involved using tumour tissue to look for genetic mutations. They could also recall that a blood test for further genetic testing may be required. However only one participant was able to specify that a mutation found on tumour testing could be somatic, and the purpose of germline testing via a blood test was to confirm the

inherited nature of the mutation. Two participants could not initially recall having tumour testing, and referred only to giving a blood sample for genetic testing.

Reflecting on some of the factors that may have contributed to this poor understanding of the nature of tumour testing, perhaps the explanations of tumour and germline testing that I and/or their oncologist provided were insufficient. The language we use to talk about genetic testing can be confusing. In this thesis alone I have used four terms relating to genetic testing (MGT, MTGT, germline testing, tumour testing) interchangeably depending on the specific type of testing. The term somatic mutation is specific to clinical genetics and oncology and would be very rarely found outside of these settings. The idea that genetic mutations, which until now have been associated with being hereditary, can be acquired and non-inherited is also novel. Furthermore I question whether it is possible to discuss tumour testing without germline testing, as a mutation identified on tumour testing requires germline testing to confirm whether it is somatic or inherited; in the main cohort of participants, more than half the sample went on to have follow-up germline testing. Thus this is both a new vocabulary and a new concept for participants to grasp. Compared to a typical genetic counselling session, in the MTGT context discussions about tumour testing took place in a much shorter timeframe and were often in addition to other clinical information about the participant's treatment or disease.

Because my research initially intended to capture participants offered either germline or tumour testing, the study documentation and questionnaires referred to 'genetic testing' as a way of encompassing both modes of testing. 'Genetic testing', when referring to germline testing, is much more familiar terminology that has become increasingly part of public discourse [108]. Any genetic testing previously discussed with their oncologist would most likely have referred to germline testing. References to their oncologists' description of MTGT revealed that their language often reflected inherited attributes.

*Yes, I think Dr [name], we had a chat and she mentioned it. It was before we met... It's a bit of a blur. She gave me the paperwork for it and I read through it and she just said 'Are you alright with that?' And I said 'Yes, that's okay.' She said the same, like I said, 'We want to find out if it has something to do with your parents or grandparents, so it could affect your children as well' – along that way. She explained it to me, I agreed with her. [MGT039, TT, no mutation]*

Furthermore participants in this study had already anchored notions of inheritance to the term genetic testing. As one participant's comments clearly describe the traditional model of genetic testing and counselling:

*What I knew about it was that I thought it was a blood test or saliva test and it was very hard to get it and it took a long time to get the results and you had to see a counsellor which I didn't quite see the point of.  
[MGT022, TT, no mutation]*

Terms that other research papers have used to distinguish germline testing from tumour testing include: 'Screening for somatic mutations in tumour', 'tumour profiling', 'genomic testing in cancer' and 'molecular testing'. This demonstrates the variability and inconsistency of language used to describe the same type of testing – genetic testing of tumour tissue to look for somatic mutations. With more personalised medicine options for cancer patients being encompassed into oncology, it is unlikely that the confusion between germline and tumour testing experienced by participants in this study will be unique.

Using the example of biomarker research for stratification in colon cancer which involved genetic testing to guide chemotherapy decisions, Perry et al described the concept of 'genetic misconception' whereby patients incorrectly assumed a hereditary component to testing [309]. Although this biomarker research did not involve germline testing, the physician's references to words typically associated with genetic testing for inherited mutations such as 'family', led patients to make incorrect associations with the term 'genetic'. The most striking example of genetic misconception in the interviews was the participant (MGT059) who discussed her tumour testing results (mutation identified) as if they were germline results, even though she had yet to receive these.

A qualitative study of attitudes towards personalised medicine and genetic testing also found misattribution of genetic testing; when cancer patients were asked to report the advantages and concerns related to somatic testing, they also listed those which are associated with germline testing [108]. The authors believe participants may have drawn on their existing understanding of germline testing, extrapolating these meanings to any type of testing that falls under the umbrella term of 'genetic testing'. Similarly in a sample of lung and melanoma patients with advanced cancer who were interviewed about their attitudes to somatic testing, a small number of patients indicated concerns related to heritability and incidental findings despite neither being relevant to the type of testing that was undertaken [106].

A recent study of physician and patient communication about molecular testing in cancer found that patients' top three preferred topics were benefits of testing (88%), how testing is used for treatment (88%) and implications for family (71%) [310]. Although there was significant overlap between physician and patient rated topics, familial implications was not listed as a topic by physicians. These findings highlight the importance of accurate communication about the differences between testing for germline and somatic mutations.

Perry makes the important distinction that '...genetics in this case does not necessarily entail heredity' (p.6) [309]. Genetic misconception is a significant misunderstanding in tumour testing and may have led to undue concerns about testing. However communicating this clearly to patients may present a challenge in an already busy and information laden oncology appointment. Gray suggests that visual aids and oversimplification of concepts may be necessary to improve patient understanding [108]. Different terminology may also be needed to clearly distinguish germline from tumour testing.

In an earlier chapter in this thesis, I proposed support for implementing tumour testing as a first-line genetic test with follow-up germline testing only when necessary. The rationale being that in this approach tumour testing could potentially alleviate concern and anxiety around the familial implications typically associated with genetic testing because the results would not initially reveal if a mutation was acquired or inherited; patients could then choose if and when they wanted to have follow-up germline testing. However the findings from this study suggest that the majority of participants responded to tumour testing as though it was germline testing, negating any potential protective factors of a two-step testing approach.

To some degree, tumour testing is an abstract activity for patients. As the tissue required for testing has already been removed, sometimes months or even years earlier, all that is required is providing written consent. The intangible nature of tumour testing may help to explain how two participants could initially not recall having tumour testing. Both made (incorrect) references to giving a blood sample, despite neither having been required to have follow-up germline testing. This may also reflect their existing perceptions of genetic testing, demonstrating prior knowledge that testing typically involves a blood test.

Participants voiced few concerns about genetic testing, perceiving testing to be a positive action. Although two participants mentioned the impact on treatment, the perceived benefits from genetic testing were largely felt as being for relatives rather than testing conferring any personal advantage. This was also reflected in participants' motivations for testing, with nearly every participant describing their primary reason as providing information to family members. This is an often cited motivation in the genetic testing literature, where testing is undertaken as an altruistic activity to benefit others rather than themselves [127].

Participants expectations for genetic testing was that it would provide answers, although as one participant put it, '...what would the answer mean I wasn't sure of' [MGT062, TT + GT, no mutation]. Other participants expected the results of testing to explain why they developed ovarian cancer, or if their cancer had an inherited basis. The perceptions and motivations participants described continued to reflect the genetic misconception of tumour testing, with concern for family clearly alluding to the hereditary implications of germline testing.

Despite the intention of MTGT to inform and potentially expand treatment options, this lack of perceived personal benefit may reflect poor communication about the potential treatment impact from myself and/or their oncologist. Conversely participants' perceptions of the familial nature of genetic testing and potential for cancer prevention may have been of more value, and therefore greater emphasis was placed on this. Despite well recognised and actionable clinical implications of BRCA1/2 germline and tumour testing, a recent qualitative study of breast and ovarian cancer patients who had undergone TFGT reported very similar findings [308]. Wright et al found that ovarian cancer patients' single motivation for testing was to prevent future cancers both for oneself and for relatives, rather than using testing for any potential personal or treatment benefit. In contrast, Meiser et al found that ovarian cancer patients who had already undergone or were reflecting on a hypothetical decision about TFGT most commonly cited motivations for testing to increase treatment options, followed by a desire to help family members [142]. The participants in Meiser's paper who had TFGT had done so specifically to determine eligibility for a PARP-inhibitor clinical trial, which is likely to have brought the focus of testing on to treatment. For the women in both my own and Wright's research, the point at which testing was offered was not to inform treatment decisions immediately, and therefore the focus may have remained more with familial implications.

At the time the interviews were undertaken, there had been no change to treatment based on MTGT results for the vast majority of participants. Thus there had been no direct, or tangible, impact of testing. The only change to treatment had been for one participant who became eligible for a clinical trial because of a somatic BRCA1/2 mutation that was identified on repeat tumour testing. Although tumour testing had given her the opportunity to take part in this trial, she suffered with severe side effects from the trial drug and eventually treatment was stopped. Our perception as researchers and/or health professionals is that by expanding the treatment options available for ovarian cancer patients via genetic testing, this is advantageous. What this participant's experience demonstrated is although genetic testing provided her with a new option for treatment, ultimately she felt her time on the clinical trial was detrimental to her health and expressed regret for having been part of it.

Of the participants interviewed, none of them disclosed any difficulties with decision-making. In fact, many described making an instant decision to have testing as soon as it was offered with one participant commenting, 'I didn't have any hesitation at all' [MGT062, TT + GT, no mutation]. In Meiser's study, ovarian cancer patients who had already undergone TFGT reported similar decision-making behaviour, needing little or no time to make their decision as '...there was no real decision to make' (p.155) [142]. Other research on RGCT for breast cancer patients found negotiating the decision process more challenging [302]. In Augestad's study, some women struggled with their decision, fearing the outcome of testing and the potential impact a mutation positive result could have on their children. However the ability of genetic testing to potentially prevent cancer for their children was also a priority; some women anticipated that the decision to have genetic testing would have been more difficult without this element.

Certainly in this study, there was a selection bias of participants who were interested in and wanted to have genetic testing so it is not surprising that participants experienced decision-making to be straightforward. To some degree this certainty in decision-making was reflected in the quantitative component of Chapter 7. From the survey data, total scores on the Decisional Conflict Scale were low overall (median 25.0), but did indicate there was perhaps greater struggle with the decision than participants recalled.

There was quite a dichotomous response in terms of whether family members were involved in the decision-making process. For participants who made their decision independently, there was a protective element of not wanting to cause additional



concern for family members, especially children. Meiser et al also reported a similar pattern of decision-making, with only half of the women who had already undergone TFGT involving other family members (apart from their partner) in their decision [142].

MTGT in this study took place following a mainstreamed model. As mentioned earlier, how much and how well oncologists impart information about tumour or germline testing is largely unknown. Although from a genetic counselling perspective (and my own bias) it may seem like there was insufficient time and information provided during the oncology consultation, perhaps what is more important is how patients perceived this interaction. Encouragingly, all participants who were interviewed felt that they had sufficient information and discussion with their oncologist to make the decision about genetic testing. In particular, participants did not want to be overloaded with information at what was already an overwhelming time. Reflecting this, participants did not seek additional information outside what was their own knowledge or provided by myself, their oncologist or the study documents. One participant noted how she relied on her existing knowledge about MGT to inform her current understanding of MGT:

*The other things, I suppose now that I'm thinking about it, now that you're asking me, I guess since I have got ovarian cancer I could perhaps have found out a lot more about the BRCA testing than what I did, which was nothing other than what I thought I already knew. [MGT022, TT, no mutation]*

This preference for brevity of information is shared by other ovarian cancer patients who have undergone or are offered genetic testing. A qualitative study of ovarian cancer patients regarding TFGT found that most women wanted to receive brief information verbally, with a slight preference to receive this from their medical oncologist [291]. Although women wanted to know about the familial implications of TFGT, they did not want detailed information unless they were identified as carrying a pathogenic mutation. Some women reported only needing information on treatment implications in order to make their testing decision. Advanced lung and melanoma cancer patients who had somatic testing to guide treatment wanted to receive verbal information preferably from their treating oncologist, with written information as a supplement [106]. Patients preferred less detail about genomic information, with a focus on practical and treatment-related issues.

It is difficult to comment on how oncologists discussed and provided information about MGT, and in particular tumour testing, to their patients without having been privy to

these conversations. Although patients' perceptions of having received enough information are encouraging, there are noticeable gaps in their understanding that indicate that communication could be improved. What was most striking is the lack of information participants received after their MGT results were disclosed. Recent research by Hallowell et al reported that oncologists felt confident discussing genetic testing with their breast cancer patients and they had sufficient experience and expertise to do so [311]. However other research on patients' views of TFGT noted that in reality '...there is little discussion of familial implications, or treatment implications associated with a PV<sup>3</sup> or VUS' (p. 463), although patients were provided with written information [308]. Other research has reported that non-genetic health professionals may be ill-prepared to discuss and provide genetic testing to their patients [312]. As noted in one paper, '...non-geneticists' unfamiliarity with specific requirements of genetic counselling may impair the quality of care for clients' (p.231) [313]. In a scoping review of communication about genetic testing with breast and ovarian cancer patients Jacobs et al acknowledge that there are differences between oncology and genetics health professionals that could impact the information that is communicated to patients [314].

A key distinction Middleton et al makes between the two specialties is the focus on the family by clinical genetics, while in oncology it is the individual [315]. Thus context may influence not only how information is delivered, but what content is disseminated. Although oncologists may lack specialised genetics knowledge, it is likely they share the goals, use similar language and communication style as clinical geneticists and genetic counsellors. Smets et al compared genetic counselling with non-genetic health care interactions and found both disciplines take a patient-centred approach, strive for shared decision-making and endorse an equal relationship between health professional and patient [313]. However, both face challenges to effectively address the patient's agenda and enhancing patient understanding.

Eleven participants who were interviewed had received results where no mutation was identified. Ten of these participants had tumour testing only, while one participant had also had follow-up germline testing because the MLPA portion of her tumour test had failed. Genetic misconceptions persisted throughout accounts of receiving results; most participants described feeling relieved at their results, as this had alleviated their concerns about potentially passing on a genetic mutation to their children. In a recent study of TFGT and mainstreamed testing, a sense of relief was

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<sup>3</sup> PV = pathogenic variant

also described by breast and ovarian cancer patients, with negative testing results also providing reassurance to family members [292]. In contrast, in the context of tumour testing for somatic mutations 'not having the gene' is more likely to be experienced as disappointment because of the loss of hope associated with not being able to access new or different treatment options [316].

Receiving a no mutation identified result appeared to have little impact, possibly because there were no implications for family or change to clinical care. Therefore it was often promptly forgotten, as one participant said, 'I've forgotten all about it, it's done now, ticked off' [MGT022, TT, no mutation]. However, because of the potential of genetic testing to expand the treatment options available, a few participants felt somewhat conflicted about their results. They were pleased that their MTGT results meant there were no implications to children and other family members, but there was also a sense of disappointment that that they would be unable to access PARP-inhibitors.

There have only been snippets of direct references to expanded treatment options attributed to MTGT throughout the interview, but this finding demonstrates there is some recognition that a different testing outcome could have led to different treatments. Rather than participants not realising the potential impact of MTGT on treatment options, perhaps their focus is more oriented towards what they perceive to be of more tangible importance, that is the prevention of cancer in their family.

Some of the literature around BRCA1/2 genetic testing has reported on the adverse psychosocial impact of receiving mutation positive results, in particular increased anxiety and cancer worry [110, 123, 133]. Even in the previous chapter I found that participants who were identified as mutation carriers had significantly more genetic testing-specific concerns.

Of the participants who were interviewed, four were found to carry a germline BRCA1/2 mutation while one participant was a RAD51C mutation carrier. At the time of interview participants appeared to be adjusting well to their results. Two described their results as being 'expected' because of a family history of cancer. None of the participants felt that their results came as a shock or a surprise, suggesting that they had prepared themselves to some degree that testing might identify a mutation.

It was interesting to find during the interviews that overall, participants perceived their mutation positive result to be a positive outcome, primarily by providing some explanation as to why they had develop ovarian cancer. It also alleviated self-blame,

highlighting to participants that this was something unavoidable. For one participant receiving her result of a RAD51C mutation had an almost transformative effect. She had blamed her diagnosis of ovarian cancer on herself, attributing it to her stressful lifestyle and poor diet. Learning that there was a genetic basis to her disease was a relief because she no longer felt guilt, but it also gave her a renewed sense of optimism.

The positive outcome of testing was less related to the impact on treatment, in fact the majority of participants could not perceive any direct benefit to themselves. As noted earlier in this chapter, only one participant had had a change to treatment based on her results (see vignette: Leanne). The clinical utility of carrying a mutation may become more evident for participants at a later date if they become eligible to access a PARP-inhibitor. The main advantage of mutation positive results was that it provided useful information for family members, with some relatives already choosing to have predictive testing to determine their own cancer risks.

In general, participants did not perceive there to be any disadvantages of their mutation positive results. One participant briefly mentioned the guilt she felt at having passed on the mutation to her daughter:

*I feel guilty that I've got it. Because my daughter's got it, I do feel a bit guilty about it, but I don't think there's anything else. [MGT029, TT + GT, BRCA+ve]*

From these interviews it appeared that overall participants were coping well with their results. There was no sense of heightened anxiety or distress as a result of learning they carried a mutation and no other concerns were reported.

In Shipman's research, these results also provided an explanation for cancer but also created uncertainty about risk management for themselves and relatives [292]. Similar concerns were not raised by participants in this study, primarily because participants were uninformed about what their results meant and the possible implications.

As we discussed MTGT results disclosure in the interviews it emerged that while for some participants communication had been sufficient, others were left feeling confused and unsure. From my own experiences in the clinic, the oncologists were usually unconcerned about results where no mutation had been identified and had a tendency to forget to disclose these results to patients. Participants' own recollection of results disclosure included little opportunity to ask questions or clarify any

implications of the results. While participants were reassured by the result itself, they still would have preferred more opportunity for discussion. There also appeared to be poor communication when results had identified a germline mutation, with one participant asking me to clarify the implications of her results during our interview.

Currently it is unclear whether oncologists did not have the information to provide to patients, or if they assumed that, in the case of mutation carriers, this would be discussed during their genetic counselling appointment. However as we have seen from the service evaluation in Chapter 5, there can be delays in referring patients to clinical genetics services which in turn have a long waitlist for appointments. In the meantime patients are left without sufficient knowledge. Interestingly none of the patients reported using other resources to try and understand their results, nor did they question their oncologist further.

*It was just a little bit odd, the way I was told the result, and I think if you'd been able to tell me the result it would have been more beneficial actually. [MGT022, TT, no mutation]*

Augestad et al proposed that cancer patients who have genetic testing outside the traditional face-to-face genetic counselling model may not have sufficient information or understanding prior to testing, which may increase vulnerability to stress [302]. Furthermore the authors comment that there are ethical challenges where testing is accepted without an awareness of the potential consequences. Although participants in this PhD research appeared to be poorly informed about the possible outcomes of testing and possible implications, for the majority of participants this did not seem to have a detrimental impact on their wellbeing. The fact that patients did not seek further explanation for their MTGT results suggests that in the context of managing ovarian cancer this was of less significance. However, Janet's RAD51C VUS result and the uncertainty about its meaning did lead to anxiety which was not allayed until her genetic counselling appointment several months later.

I agree with Augestad that a lack of clarity about what patients are consenting to and the possible outcomes is concerning. Despite the overall positive response to genetic testing and little psychosocial impact, as with any medical decision patients need to have information about the process, advantages and disadvantages and potential outcomes. The context in which MTGT took place was a 'pro-testing' environment where oncologists perceive there to be a real benefit from testing but patients need balanced information in order to make an informed decision, particularly as the opinion of their health professional has shown to impact testing choices [317].

I decided to include some of the experiences of the participants which were not shared across the group, so called 'negative cases', to highlight the diversity of MTGT experiences. These divergent cases emerged because of the specific genetic testing results that these participants received. One participant, Janet, had received a germline RAD51C VUS result while Leanne was the only participant with a somatic BRCA1/2 mutation who was interviewed.

Both of these participants would have benefited from genetic counselling shortly after receiving their (final) testing results. In Janet's case, VUS results are difficult to interpret even within the specialised genetics community; studies have shown oncologists struggle to interpret and communicate these results correctly and take appropriate action [318]. Compounding this situation was Janet's sister had also been diagnosed with ovarian cancer and died from the disease several years earlier.

I was only aware that Leanne had had repeat somatic testing when this was brought to my attention by her oncologist. I then happened to bump into Leanne the following week on her way to the Macmillan Cancer Centre and she agreed to meet me in the chemotherapy suite so I could find out a bit more about what had happened and invite her to take part in an interview. Leanne still had a poor understanding of what her somatic mutation meant and had only been told these results verbally. In the end I printed off all three genetic testing reports for her to read and briefly clarified that her final testing result showed an acquired, non-inherited mutation. In contrast to Janet, Leanne was relatively unconcerned about her genetic testing results, rather it was her experiences on the clinical trial that had had a significant impact.

## **8.9 Limitations**

One limitation has already been raised earlier in the chapter in relation to the language I used to refer to genetic testing during the interviews and over the course of the study which may have contributed to participants' genetic misconception.

The retrospective nature of the interviews means that for some participants many months had passed since they had received their MTGT results which can affect recall as well as introduce bias. As some participants said themselves, MTGT was often forgotten about. By the time the interviews were undertaken I had known some of these participants for nearly one year. Although familiarity can be advantageous in interviews as the participant feels more comfortable and already has trust in the researcher, shared knowledge and experiences between myself and the participant may have resulted in less detail shared and less detail sought.

Although the participant interviews have revealed novel and interesting insights into the patient experience of MTGT there is a distinct lack of awareness of what and how oncologists discuss testing. Interviews or observations of clinical encounters between oncologists and their patients are needed to fill this gap in our knowledge.

### **8.10 Summary**

Including participants' experiences of ovarian cancer prior to MTGT was to understand the context in which BRCA1/2 testing was taking place for them. For many participants their experience of the diagnostic odyssey had been traumatic and the effects had lingered. The ovarian cancer trajectory of treatment, remission and eventual relapse was their primary concern; genetic testing was a brief interlude into this context.

MTGT seemed to exacerbate existing concerns for family members, reflected in their motivations for testing, but was also perceived as a means of cancer prevention for unaffected relatives. Participants recounted their decision-making process for testing as easy and straightforward, and felt they had had sufficient information and discussion with their oncologist to reach their decision. However participants' recall and discourse about tumour testing reflected genetic misconceptions, attributing features of germline testing and outcomes. Disclosure and discussion of testing results could also be improved.

Although the intention of providing MTGT is to inform treatment options, this benefit of testing did not appear to be a priority and more value was placed on the perceived benefits of testing for unaffected family members. Participants who received no mutation results expressed relief because this alleviated concern about family members. Where a (germline) mutation had been identified, participants felt this was a positive outcome as it provided important information to unaffected relatives and assigned a cause to their ovarian cancer.

## **Chapter 9 Discussion and future plans**

### **9.1 Introduction**

We are witnessing rapid changes in the way genetic testing and genetic counselling is being delivered to cancer patients. Genetic testing is being used to inform surgical and chemotherapy decisions for breast cancer patients and to expand treatment options in ovarian cancer. Genetic testing is no longer only associated with testing for inherited predisposition genes, as we move to an era where acquired mutations can also play an important role in patient management. Genetic testing has also moved from the specialised domain of clinical genetics to become incorporated into mainstreamed medicine, facilitating the testing of more patients. Crucially, taking an oncology-led, mainstreamed approach to testing, removes the role of the genetic counsellor who has historically been responsible for information provision and psychosocial support.

With targeted treatments such as olaparib now available for BRCA-mutated ovarian cancer there is an impetus to identify more patients who carry somatic or germline mutations. MTGT offers a way to provide more testing to eligible patients while reducing the burden on clinical genetics services. Using a case study approach, this thesis aimed to explore the introduction of mainstreamed BRCA1/2 tumour testing in ovarian cancer with a focus on the patient experience and clinical outcomes.

To set the context of testing, Chapter 5 used a service evaluation to describe the current state of MGT in ovarian cancer at UCLH. Chapter 6 detailed the experience of implementing and providing BRCA1/2 tumour testing as well as reporting the clinical outcomes of testing. Chapter 7 and 8 used quantitative and qualitative methods, respectively, to explore the patient experience of MTGT. The key findings of each research question are addressed in the table below. This final chapter of the thesis draws together the key findings from each chapter to address the research questions posed in Chapter 4, for a holistic description of mainstreamed BRCA1/2 tumour testing.



Table 9.1. Summary of key findings in relation to research questions

Research question	Methodology	Results	Key findings
<b>How is MGT currently used in ovarian cancer?</b>	Service evaluation	<ul style="list-style-type: none"> <li>No systematic method of recording offers and declines of MGT</li> <li>Prevalence of germline BRCA1/2 mutations 14.8%</li> <li>Four BRCA1/2 carriers would not have met previous testing guidelines</li> <li>78.0% of patients with VUS not referred to clinical genetics</li> <li>33.0% of BRCA1/2 carriers accessed PARP-inhibitors after receiving MGT results</li> </ul>	<ul style="list-style-type: none"> <li>The prevalence of germline BRCA1/2 mutations is similar to published data</li> <li>Depending on timing of testing in cancer pathway, MGT may not have an immediate impact on patient management</li> <li>Non-referral to clinical genetics for patients with a VUS suggests oncologists are uncertain of clinical relevance</li> <li></li> </ul>
<b>What are the clinical outcomes of BRCA1/2 tumour testing?</b>	Provision of tumour testing, review of medical records	<ul style="list-style-type: none"> <li>Average turnaround time from consent to results reported 55 days; 42 days for retrieval and review of tumour blocks</li> <li>7 germline mutations identified; 6 BRCA1/2 mutations, 1 RAD51C mutation</li> <li>1 somatic mutation identified during MTGT; 2 more identified on repeat tumour testing</li> <li>52.6% of sample required follow-up germline testing</li> <li>58.3% of germline/somatic mutation carriers accessed PARP-inhibitor post-MTGT</li> </ul>	<ul style="list-style-type: none"> <li>Challenges to developing an efficient tumour testing pathway related to delays in retrieval and review of archived tumour tissue</li> <li>An 'inconclusive' result reported by Myriad was reclassified as pathogenic by a different genetic testing company reflecting the implications of different classification systems</li> <li>The majority of patients had testing during first line treatment where MTGT may have less impact on clinical management</li> <li>Given the number of patients who required follow-up germline testing, tumour and germline testing should be provided simultaneously</li> </ul>

**How do patients experience mainstreamed BRCA1/2 tumour testing?**

<p>Quantitative survey, three timepoints</p>	<ul style="list-style-type: none"> <li>• Distress and health related quality of life scores comparable to data of other cancer populations and general public</li> <li>• No significant change in distress or quality of life scores across timepoints</li> <li>• Most endorsed motivations for testing subscale related to prevention and medical care</li> <li>• At time of consent decisional conflict scores were low; post-MTGT decision regret scores were zero</li> <li>• Mutation carriers reported significantly more testing-related concerns than non-carriers</li> <li>• 8% incorrect recall of MTGT results</li> </ul>	<ul style="list-style-type: none"> <li>• Participants appeared to have ambivalent attitudes towards genetic testing</li> <li>• Overall this group of participants had good physical and psychological functioning which may reflect a selection bias</li> <li>• Although decisional conflict scores were low overall, the range of scores indicated some participants had substantial uncertainty over their decision</li> <li>• Participants reported having had sufficient time, information and support to make decision about MTGT</li> </ul>
<p>Qualitative interviews, post-MGT</p>	<ul style="list-style-type: none"> <li>• Experience of diagnosis traumatic</li> <li>• Genetics not believed to be cause of ovarian cancer</li> <li>• No concern about using tumour tissue for MTGT</li> <li>• Good recall of logistics and process of tumour testing, poor understanding of somatic vs germline mutations</li> <li>• Participants did not perceive much personal benefits from testing, rather for family members</li> <li>• Motivations for testing related to concern for family members</li> <li>• Poor understanding of MTGT results and implications</li> </ul>	<ul style="list-style-type: none"> <li>• In the context of facing ovarian cancer, MTGT is a brief, transient experience</li> <li>• Participants felt the decision for MTGT was easy to make</li> <li>• Genetic misconceptions of tumour testing were common and impacted participants understanding and perceptions of MTGT</li> <li>• A lack of explanation about what their MTGT results meant participants were confused and uncertain about implications</li> <li>• Receiving no mutation results was associated with a sense of relief related to concerns for family; receiving mutation positive results provided explanation for why cancer had developed and alleviated self-blame</li> </ul>

### 9.1.1 Research question 1: How is BRCA1/2 germline testing in ovarian cancer currently used in the gynaecological oncology department?

There has been increasing recognition of the need to move towards a systematic or universal testing approach for women with ovarian cancer as using previous criteria such as family history and relying on referral from oncology to clinical genetics was no longer sufficient to identify all BRCA1/2 mutation carriers [12, 63, 75]. With olaparib now licensed for use within the UK and other PARP-inhibitors available via clinical trials or managed access programs, there is a potential therapeutic benefit to identifying ovarian cancer patients with a BRCA1/2 germline or somatic mutation.

Across the UK, systematic genetic testing programs were implemented in Scotland in 2012, at the Royal Marsden and across East Anglia in 2013 [73-75]. The gynaecological oncology department at UCLH soon followed, introducing BRCA1/2 germline testing as a clinical service using an oncology-led model of MGT in 2015. Eligible patients would have a diagnosis of high grade non-mucinous ovarian cancer, unselected for age or family history. Over the first 12 months of MGT, 122 ovarian cancer patients underwent BRCA1/2 germline testing. The prevalence of BRCA1/2 mutations was found to be 14.8% (18/122), similar to other reported prevalence rates both in the UK and internationally [12, 73, 75, 304].

There had been a small impact on patient management with six of the 18 mutation carriers (33%) having been able to access a PARP-inhibitor treatment (typically olaparib) or clinical trial as a result of MGT. As the current eligibility criteria for olaparib requires patients to have completed a minimum of three lines of platinum-based chemotherapy, more patients are likely to become eligible for olaparib over time as they continue on their cancer pathway.

Reviewing the referral patterns of patients who received germline mutation or VUS results from MGT revealed only 22% (2/9) patients had been referred to their local clinical genetics service. This may reflect some uncertainty about the clinical utility of VUS results in ovarian cancer and a lack of understanding of the potential for these results to be reclassified as benign or pathogenic. Once this pattern was recognised, recommendations from the local clinical genetics service were introduced to ensure referral of appropriate patients.

By taking a mainstreamed approach, unrestricted by family history or age criteria, more ovarian cancer patients were able to access BRCA1/2 germline testing. After

family history was reviewed, four BRCA1/2 carriers would not have met previous testing guidelines and therefore been missed, demonstrating the importance of taking a more unselected approach to testing. The lack of a systematic record of MGT offers and those accepted or declined makes it difficult to ascertain the uptake rate of testing, or whether all eligible patients had been reached. Moving forward, the introduction of more rigorous record-keeping would help to ensure that eligible patients are offered MGT. Developing an in-house database may be a useful means of consistently recording MGT results which could be easily accessed by the oncology team.

A service evaluation of the second year of MGT would reveal whether similar numbers of patients were tested. BRCA1/2 mutation prevalence rates could be compared between the first and second years of MGT, particularly as the first year prevalence is likely to be slightly inflated due to the retrospective nature in which testing was offered. A second service evaluation could also explore further the variation in number of tests ordered across clinicians by comparing clinic case load and patient characteristics.

#### 9.1.2 Research question 2: What are the clinical outcomes of mainstreamed BRCA1/2 tumour testing?

With more data gathering about the prevalence of BRCA1/2 somatic mutations in ovarian cancer and the feasibility of using archived tumour tissue for testing, it is becoming increasingly likely that tumour testing will be offered alongside germline testing. Understanding the processes involved in implementing a new genetic testing service following a mainstreamed model will provide useful insight for other centres which are looking to introduce a similar testing strategy.

Despite specialist services and clinical expertise already existing at UCLH, such as the cellular pathology department and consultant pathologists, it was challenging to implement an efficient, streamlined tumour testing pathway. Retrieval of archived pathology material, reviewing and selecting relevant tumour blocks, cutting of new H&E slides all involved delays. For a busy and overstretched pathology service, tumour testing undertaken for research purposes was a low priority, despite the potential impact on patient management. If mainstreamed BRCA1/2 tumour testing is incorporated into the clinical service, sustainable processes would need to be in place to ensure that testing could be expedited.

A key learning point was that the physical amount of archival tumour tissue available can have an important impact on testing feasibility. Firstly, for some patients there was only a single tumour block from an omental biopsy, typically with only a small amount of tissue. The reluctance of clinicians to use the limited tumour tissue available was related to ensuring there would be tissue available for determining suitability for clinical trial participation, i.e. for additional tumour testing. Anecdotally, several participants expressed reluctance to undergo repeat biopsy if more tissue would be needed for testing, suggesting that there may be challenges to obtaining additional tumour tissue if required. Even patients with multiple tumour blocks may have insufficient tumour tissue for testing, particularly if the samples are from IDS where chemotherapy response may affect the quality of tissue and/or DNA. Thus the quantity and quality of tumour tissue may determine eligibility for BRCA1/2 tumour testing. Knowledge of the quantity of tumour tissue prior to consenting patients to testing could help to expedite the process.

Outcomes from this cohort identified one germline RAD51C mutation (prevalence 1.8%), seven germline BRCA1/2 mutations (prevalence 12.3%) and three somatic BRCA1/2 mutations (5.3%). Two of the three confirmed somatic mutations in this cohort were identified on repeat testing at a later date by a different genetic testing laboratory; one somatic mutation was identified in a patient where tumour testing had failed, and the other where Myriad had reported the result as inconclusive. Aside from the possible impact of IHT, tumour testing may not identify all somatic mutations in a patient cohort due to the use of different testing platforms and classification systems. Implementing a standardised tumour testing program across the UK would be a significant endeavour, particularly as there still remains variation in practice and access for germline testing [75].

There was a small impact on patient management as a result of genetic testing; of the participants who were found to carry a germline or somatic mutation, 58.3% had been able to access a PARP-inhibitor after receiving results. As testing was mostly undertaken during first or second line treatment, it is likely more participants will become eligible for olaparib over time.

In this PhD research tumour testing was provided as a first line genetic test, with follow-up germline testing when necessary. Capoluongo also recommended this strategy, suggesting that first-line tumour testing would lead to more focused germline testing [76]. However the perceived advantages of first-line tumour testing, such as

reducing the number of patients requiring germline testing and protective psychosocial impact (discussed further below), did not come to fruition. More than half of participants (30/57, 52.6%) went on to have second line germline testing, 19 due to testing issues alone. The two stage testing format also extended the testing timeframe; from initial consent to tumour testing to receiving final germline testing results took more than five months in some cases.

The experience of providing BRCA1/2 tumour testing and the outcomes of testing suggest that taking a concurrent approach to germline and tumour testing is likely to be a more time efficient means of delivering results. Logistics surrounding the process of tumour testing still need to be improved in order to deliver testing on a larger scale.

### 9.1.3 Research question 3: How do patients experience mainstreamed BRCA1/2 tumour testing?

This is some of the first research to explore the patient experience of MTGT, and in particular BRCA1/2 tumour testing. The quantitative component focused on three key timepoints of the MTGT pathway: attitudes and knowledge prior to testing, decision making when consenting to testing, and the impact of testing after receiving results. The patient experience covered more general topics such as distress and health related quality of life as well as measures specific to genetic testing. Participants were interviewed for the qualitative component after they had received their MTGT results, reflecting back over their testing experiences. To address the third research question, this discussion draws together the quantitative and qualitative data.

Context has been an important part of this research. For ovarian cancer patients who are offered MTGT, testing takes place physically within the oncology setting but also within their own experiences of diagnosis and treatment. As participants shared their narrative, it was evident that MTGT was a brief and relatively insignificant part of the long and challenging journey of being an ovarian cancer patient. Participants spoke in great detail about their diagnostic odyssey, recalling dates and names even if the events had passed years earlier. Overall MTGT seemed of little concern in the context of ovarian cancer.

Over the course of participating, many participants transitioned through treatment, follow-up and eventual relapse. Despite negotiating the cancer pathway, participants were of good humour and spirit and generally well. This was reflected in the quantitative data, where health related quality of life scores were comparable to other

published data in a gynaecological cancer patient cohort but also the general population. General distress scores were also comparable to other published data of cancer patient cohorts. Neither distress nor quality of life scores changed significantly over the three key timepoints on the MTGT pathway. As noted earlier in this thesis, the good physical and psychological function of participants may reflect some selection bias.

An important finding that emerged from the participant interviews, was the notion of genetic misconception, where patients incorrectly assumed a hereditary component to testing. Despite correctly recalling the process of tumour testing and what was involved, as well as being provided with verbal and written information about tumour testing throughout the study, participants' discourse about genetic testing reflected concepts associated with germline testing. For example when describing their expectations of tumour testing, participants often cited their desire to provide information to family members, in particular female relatives. For participants, the word 'genetics' is synonymous with the attributes related to germline testing only, as notions of familiarity and inheritance were anchored to this term. It is challenging to unpick this finding – to some extent the limitations of this research where study documentation referred to 'genetic testing', rather than 'tumour testing' are likely to have influenced participants' perceptions and understanding of the nature of genetic testing that was taking place. Furthermore more than half the sample of participants had in fact undergone germline testing as a follow-up after tumour testing, when notions of inheritance are correct and valid. Similar findings of misattribution of germline testing features to somatic testing have been reported [108, 309], indicating this is an important area for further research.

Genetic misconceptions were also reflected in motivations for testing, with 'family' named as the primary reason for deciding to have testing. Although it did not emerge as the main driver for testing, throughout the interviews were references to potential treatment benefits based on testing outcomes. This was also reflected in the quantitative data, with the most endorsed subscale relating to prevention and medical care items, suggesting that participants were interested in how testing could benefit them directly. Free text responses from two mutation carriers also made reference to increased treatment options as a result of MGT. More clarity about the purpose of MTGT and how the outcomes have the potential to impact treatment is needed for ovarian cancer patients.

From the quantitative data, participants appeared to have somewhat ambivalent attitudes to MTGT which may reflect poor understanding about the relative advantages and disadvantages of testing. To some degree this was also reflected in the interviews as participants did not perceive there to be any personal benefit from testing, but also did not mention any concerns from the testing process or outcomes. This identifies an area in the MTGT process which requires better information and communication so that participants are informed of all the risks and benefits prior to making their testing decision.

Decision-making for MTGT appeared to be a straightforward process. Participants described it as an easy decision, and one which was made with little hesitation. Participants felt they had received enough information and opportunity for discussion to make their decision, perceiving that more information would have been overwhelming. Perceived ease of decision making was also reflected in the quantitative data, which was collected at the point at which participants consented to MGT. Overall it showed that decisional conflict was low with a median total score of 25.0 (max 100). However the range of scores indicated that for some participants there was greater personal uncertainty about their choice which was not reflected in the interviews. Decision regret was measured at the final point of the MGT pathway after participants received their results. Participants reported little decision regret, with a median total score of 0. One participant with a somatic mutation was interviewed; the decision regret she expressed was related to taking part in the clinical trial, rather than regret about having had MTGT.

For participants who learnt that they did not carry a mutation (somatic or germline), these results provided a sense of relief from the concern about the hereditary implications for children. As there was no impact on treatment or family MTGT was often forgotten, to the extent that two participants were initially unable to recall having had tumour testing. Participants who learned they carried a germline mutation felt that this was in fact a positive outcome, providing an explanation as to why they had developed cancer as well as providing vital information for relatives. Despite participants voicing few disadvantages about their mutation positive results, in the quantitative component measuring the impact of MGT using a validated scale found that participants with a mutation had significantly more testing related concerns compared to those without a genetic alteration. It is important to ensure these individuals have relevant support which may be best provided within the clinical genetics specialty, rather than oncology.



For some participants, their experiences with MTGT results disclosure had been unsatisfactory with little explanation provided. This is of particular concern for participants with a germline mutation or VUS result. Oncologists may be relying on the clinical genetics service to clarify the implications of testing. Due to long waiting lists there is often a delay between when the referral is made and the actual genetic counselling appointment, during which time they may be left in a state of uncertainty or have misperceptions about their results.

Limitations in interpreting findings from the quantitative component due to the small sample size and the impact of language and wording of study documents must all be taken into consideration. However these findings suggest that MTGT does not have a significant psychosocial impact on patients. Patients and oncologists appear to have different agendas; oncologists are driven by the opportunity of expanding treatment options while participants' priorities remain with preventing cancer in their families. A key area for future research is how to improve communication and patient comprehension of tumour testing and somatic mutations, particularly in the context of BRCA1/2 genes which are already associated with germline testing. Addressing genetic misconceptions will be a priority as Blanchette notes, 'The distinction between somatic and germline mutations is fundamental' (p.3070) [109].

## **9.2 The future of genetic testing and counselling and PARP-inhibitors.**

An article published in 1997 highlights how much has changed over the last two decades in the provision of BRCA1/2 genetic counselling and testing [319]. Determining eligibility involved collecting, confirming and interpreting family history, considering ethnic background, deciding who to test and managing counselling issues that emerge from this information gathering process. Pre-test genetic counselling would discuss various topics including risks of having a mutation and possible results, cancer risks, benefits and risks of testing, logistics of testing and addressing any counselling issues that may have emerged during the appointment. These initial pre-genetic counselling session took an average of two hours. In the results disclosure appointment, the genetic counsellor would disclose the result while preparing for any psychological reactions, review any implications of the results as well as coordinate any follow-up appointments or services such as breast screening.

In order to meet the growing demand of genetic testing in ovarian cancer, this model of testing delivery is no longer feasible. Testing is increasingly being provided by other health professionals or without the traditional face-to-face format of genetic

counselling. There are some concerns with moving away from the expertise of clinical genetics. For example a survey of non-genetic specialist clinicians in the US who provide BRCA1/2 testing reported that while 57% spent up to 30 minutes counselling patients prior to testing and 61% discussed implications for family members, less than half discussed the psychological impact of testing and only 27% took a three generation pedigree [320]. The authors believed that inability to adhere to the current guidelines based practice could lead to harm for patients and their relatives due to incorrect test requests, misinterpretation of results and negative emotional impact. However other research has shown that testing without counselling can provide sufficient information [73, 284], does not cause undue psychological distress [144], and in fact patients may prefer this approach [283].

In taking an oncology-led mainstreamed approach to delivering tumour or germline testing, I believe the intention is not to attempt to replicate what is provided within a genetic counselling consultation. Instead it is about defining what information is crucial to making an informed choice in relation to testing and how this information can be delivered effectively to patients. Of importance will be the ability to identify patients who would either prefer or benefit from a referral to clinical genetics which has the advantage of more time and greater genetics-specific expertise.

There are also important changes coming to the provision of genetic testing within the UK which will impact what testing is available for ovarian cancer patients and how it is delivered. The NHS Genomic Medicine Service was established as part of NHS England's five year view to provide equitable access to genomic testing and technology, through a national genomic laboratory network and National Genomic Test Directory. The role of the Test Directory will be to '...specify which genomic tests are commissioned by the NHS in England, the technology by which they are available, and the patients who will be eligible to access to a test' (p.3) [321]. In the latest draft Test Directory for cancer published in July 2018, BRCA1/2 genetic testing in ovarian cancer will be commissioned for confirmed cases of high grades serous disease. Importantly, both somatic and germline testing will be available for patients. At this stage it is unclear what delivery model will be used in order to support this testing. More centres may be adopting a similar mainstreamed model of testing for cancer patients while testing for unaffected relatives remains in the domain of clinical genetics services. However there is an argument that the rapid advances in both genetic testing and targeted therapies have vastly overtaken accompanying

psychosocial research [316], and more evidence is needed on the potential outcomes and impact of testing before it becomes standard of care.

The findings from this thesis suggest that although using a mainstreamed oncology-led model of BRCA1/2 tumour and germline testing is feasible and appeared to have little detrimental impact on patients, it is a process that could be improved. An alternative to the oncology-led model would be to embed a genetic counsellor within the gynaecological oncology team. In this role the counsellor would attend weekly multi-disciplinary and pre-clinical team meetings to identify patients eligible for genetic testing (which may extend beyond BRCA1/2, for example endometrial cancer patients where genetic testing for HNPCC may be indicated). During the outpatient clinic, the counsellor would be available to discuss testing with patients, take informed consent and organise tumour and/or germline testing. Importantly the genetic counsellor is available to provide support in the oncology setting as needed, without lengthy delays for an appointment externally at the local clinical genetics service.

This approach was implemented at a central, tertiary hospital in Melbourne, Australia, where a genetic counsellor was embedded within the gynaecology oncology team [322]. Pre-test counselling was provided by a genetic counsellor during the patient's chemotherapy treatment or immediately after an oncology appointment. Results delivery and post-test counselling were provided in person or by telephone. This model of service delivery was undertaken using previous testing guidelines rather than an unselected testing approach therefore there was a much smaller number of patients (n=64) tested over a two year period.

Some adaptations may be necessary to meet the demand of unselected testing – for example patients could be offered the choice whether to have testing with genetic counselling, or directly via their oncologist. A study of breast cancer patients who could choose between in person genetic counselling and testing (DNA-intake) or receiving a testing kit at home (DNA-direct), found that 59% of patients preferred the 'direct' method of testing [283]. Patients who opted for DNA-intake had more decisional conflict and higher heredity-specific distress. In a sample of advanced cancer patients who were offered genomic testing in cancer found 34% of wanted formal genetic counselling before consenting to testing [109]. These findings suggest that patients who feel they need further support when facing a genetic testing decision may self-select for the approach that offers the potential for more psychosocial care.

The advent of PARP-inhibitors and data reporting increased efficacy in BRCA-mutated ovarian cancer has been the impetus for ensuring more patients have access to genetic testing [14]. At the time of writing, in the UK olaparib is licensed for use in ovarian cancer for women with a germline or somatic BRCA1/2 mutation after a minimum of three lines of platinum-based chemotherapy [191]. A request for extension to olaparib authorisation by the EMA means it may be licensed for use in the EU regardless of BRCA1/2 mutation status [97, 98]. Although this has yet to impact UK authorisation and licensing, it is important to consider the potential implications this may have for genetic testing. BRCA1/2 germline testing still provides important cancer risk information for unaffected relatives, regardless of whether it informs a patient's treatment options or not. But will tumour testing still be relevant if it is not required for determining PARP-inhibitor eligibility?

PARP-inhibitors are an area of rapid development, and olaparib is likely to be the first of many other targeted treatments to become part of standard clinical care for ovarian cancer patients. Genetic testing beyond BRCA1 and BRCA2 genes is also on the horizon, with three additional ovarian cancer susceptibility genes, BRIP1, RAD51C and RAD51D, already part of germline testing at UCLH. Although germline and somatic BRCA1/2 mutations are the most well-known mechanisms of HRD, up to 50% of high grade serous ovarian cancer cases will demonstrate HRD [323]. Ovarian cancers with germline or somatic mutations in other genes involved in the HR pathway have a similar phenotype to BRCA1/2 mutations, known as BRCAness [104]. Therapeutic approaches can now target HRD, broadening the potential use of PARP-inhibitors beyond ovarian cancer patients with a BRCA1/2 mutation.

With more targeted therapies comes the need to identify more patients who may be eligible for these novel treatments. As illustrated by the qualitative data, patients do not necessarily share the same agenda with oncologists in using genetic testing outcomes to expand treatment options. The potential clinical benefits of genetic testing for targeted therapies needs to be balanced against the potential psychosocial impact for patients. As Macfarland argues:

*...it is incumbent upon the oncology community to examine psychological and social implications of targeted therapy in order to provide an approach to patient-centered care with an eye toward improving quality.*  
[316]

### **9.3 Conclusion**

To the best of my knowledge, this thesis presents some of the first research to examine the patient experience of mainstreamed BRCA1/2 tumour testing. In this study BRCA1/2 tumour testing in ovarian cancer was a feasible but time consuming process. Overall testing did not lead to poor psychosocial outcomes in patients and was perceived to be a positive experience. Providing tumour and germline testing concurrently is likely to be a more time efficient and streamlined process. Given the challenges associated with distinguishing somatic and germline mutations, a concurrent approach which consents patients to both testing methods may help to reduce genetic misconceptions. Other deficits in patient knowledge suggest the need for improved communication and information provision from oncologists. There may be scope for a genetic counselling role in a mainstreamed approach to delivering tumour testing.

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# Appendix I

## PRISMA flow diagram for literature review

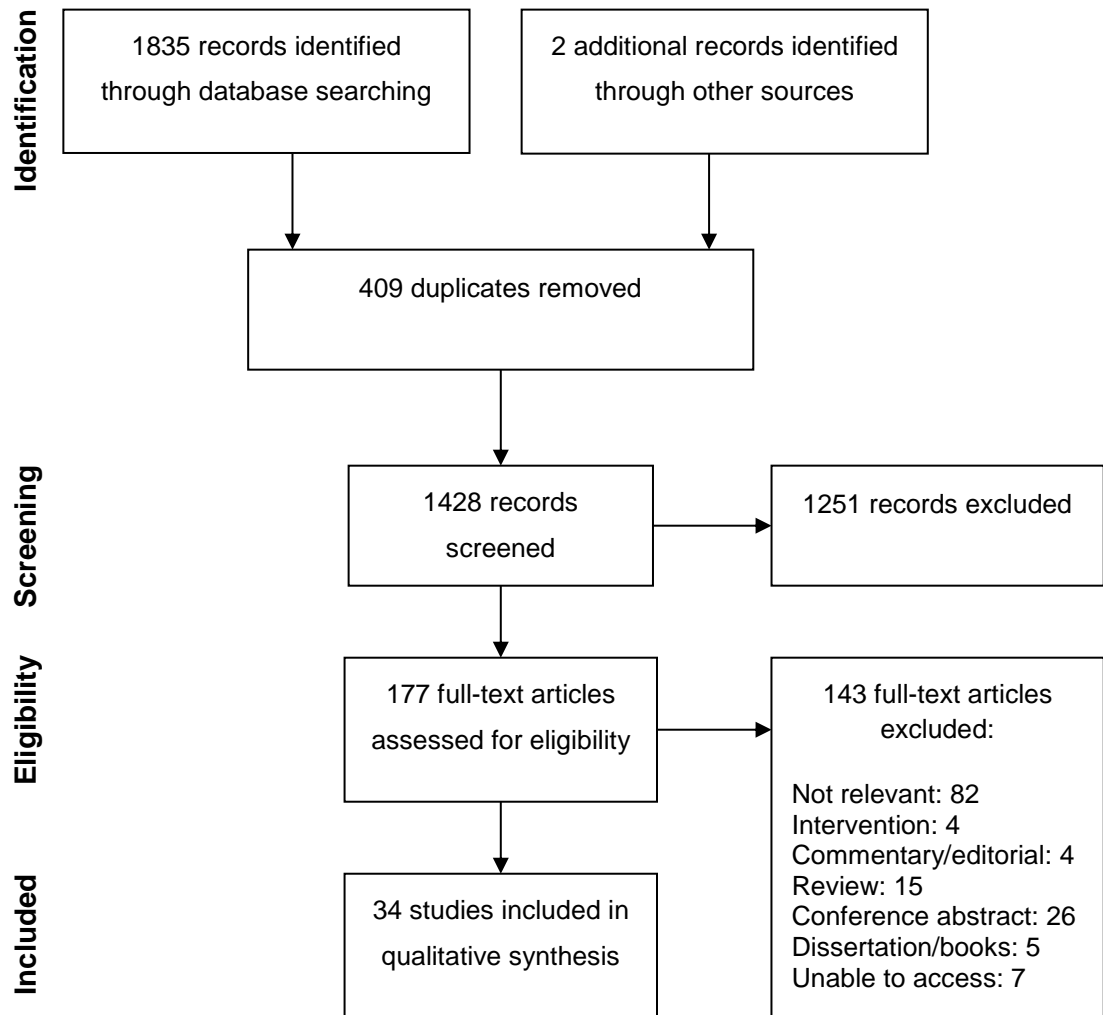


Figure 1 PRISMA flow diagram of stages of literature review

## Appendix II

### Data extraction tables of literature review

Table 1 Psychological impact of genetic counselling and/or testing in women with a personal history of cancer (affected): Qualitative studies

Study, country	Study design	Sample	Genetic testing	Outcome measures	Measurement timepoint(s)	Findings
Claes (2004), Belgium	Retrospective Mixed methods	62 affected 24 BRCA+ve 7 BRCA-ve 36 inconclusive	BRCA1/2	Evaluation of impact of genetic test results (interview, STAI, IES)	Median time between interview and GT results disclosure 17 months	BRCA carriers: 5 upset (increased risk developing second cancer), 5 afraid/ concerned (risk to offspring), 8 acquiescent (expected) 6 affected non-carriers: relief
Hallowell (2002), UK	Retrospective Semi-structured interviews	30 affected 10 BRCA+ve 12 inconclusive 8 awaiting results	BRCA1/2	Experiences diagnostic testing	1-9 years since blood draw for GT	Majority reported no emotional difficulties during testing and while waiting for results  'Non-event' when compared to cancer experiences  Receiving BRCA+ve results: costs and benefits, anxiety about self (future cancer), anxiety about relatives, disclosure of information  Receiving inconclusive results: relief, disappointment, acceptance, anger, disbelief



Hallowell (2004), UK	Retrospective Semi-structured interviews	30 affected 10 BRCA+ve 12 inconclusive 8 awaiting results	HBOC	Experiences genetic testing, accommodating risk	GT results disclosure between 2 months and 4 years ago	Majority took fatalistic approach for future cancer risks  In small group GT led to negative impact of perceived future (fear and uncertainty)  Overall GT not experienced as anxiety provoking or disturbing identity  GT insignificant in the context of cancer experiences
Kenen (2006), UK	Retrospective Focus group	13 affected All BRCA+ve	HBOC	Feelings and experiences of young affected BRCA carriers	GT between 2 months-10 years post-cancer diagnosis	Several women felt re-traumatised after BRCA+ve results  Effects of cancer worse than GT  Implications of testing more long- lasting  Anxiety communicating 'bad news' results within family  Some experience of relief (from guilt) and empowerment

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Table 2. Psychological impact of genetic counselling and/or testing in women with a personal history of cancer (affected): Quantitative studies

Study, country	Study design	Sample	Genetic testing	Outcome measures	Measurement timepoint(s)	Findings
Bjornslett (2015), Norway	Retrospective	354 ovarian cancer patients 32 BRCA+ve Remaining non-carriers	BRCA1/2	Psychological distress (IES, HADS); genetic testing-related distress (MICRA)	Mean time between questionnaires and GT results disclosure 31 months	14.4% of women had high MICRA score Carriers had significantly higher mean scores on MICRA compared to non-carriers No significant differences between groups on HADS or IES
Bonadona (2002), France	Prospective Mixed methods	23 breast, ovarian, colorectal or other cancer patients All mutation carriers	BRCA1/2 and MMR genes	Personal feelings and reactions before and after disclosure of positive genetic test results; general distress (HADS)	1 month post-GT results disclosure	52% no major emotional changes 35% distressed responses 52% felt reassured 91% reported no surprise at receiving mutation positive results Mean HADS score of 12 (range 2-20)
Bredart (2013), France	Prospective	243 breast cancer patients 11% BRCA+ve 74% Inconclusive 15% VUS	BRCA1/2	General distress (HADS); cancer-related distress (IES)	Baseline (at GC and blood draw) and 1 month post-GT results disclosure	Mean scores on HADS low to moderate 24% and 31% of sample had clinically significant anxiety scores at genetic counselling and post-testing Pre-test anxiety predicted by being on treatment compared to remission No association between BRCA result and distress

Claes (2004), Belgium	Retrospective Mixed methods Semi-structure interviews and questionnaires	62 breast and/or ovarian cancer patients 19 BRCA+ve 7 BRCA-ve 36 inconclusive	BRCA1/2	Distress (STAI, IES)	Median time between interview and GT results disclosure 17 months	No significant differences between carriers, non-carriers and inconclusive groups Scores on STAI comparable to population norms High levels of anxiety and/or depression found in 23% and 30% of patients
Hughes Halbert (2004), Canada	Retrospective	130 breast and/or ovarian cancer patients 25% BRCA+ve 40% BRCA-ve 35% AJ panel-ve	BRCA1/2	Trait anxiety (STAI); perceptions of stress (newly developed measure)	1 month post-GT results disclosure	Long-term survivors reported greater perceptions of stress Current cancer treatment not significantly associated with perceptions of stress, interpersonal factors, individual differences BRCA+ve reported significantly more perceived stress related to GT concerns
Wood (2000), USA	Prospective	35 breast and/or ovarian cancer patients 10 BRCA+ve 1 BRCA-ve 3 VUS	BRCA1	Distress (IES); anxiety and depression (Hopkins Symptom Checklist-25);	Baseline (pre-GC), post-GC and blood draw, and 1 month post-GT results disclosure	Significant decrease in anxiety between pre to post-test results – no differences between BRCA+ve or –ve BRCA+ve did not experience decrease in genetic testing specific distress Significant difference between women diagnosed <1 and those >1 year on cancer-related and genetic testing distress (but both decrease after GC/GT)

Qiu (2016)	Retrospective	67 breast cancer patients	BRCA1/2	FACT-B (Chinese version); Irritability, Depression and Anxiety scale (IDA); qualitative interview	10–13 months post-GT results disclosure	No significant difference in the QOL or IDA scores between mx carriers and non-carriers
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Table 3 Psychological impact of genetic counselling and/or testing comparing women with and without personal history of cancer (affected vs unaffected)

<b>Study, country</b>	<b>Study design</b>	<b>Sample</b>	<b>Genetic testing</b>	<b>Outcome measures</b>	<b>Measurement timepoint(s)</b>	<b>Findings</b>
Dagan (2004), Israel	Retrospective	138 breast cancer 138 unaffected 15% affected BRCA+ve 34% affected BRCA-ve 13% unaffected BRCA+ve 38% unaffected BRCA-ve	BRCA1/2 (AJ founder mutations only)	Mutation carrier vs affected status; distress (BSI)	3 months post-GT results disclosure	Mutation carrier and breast cancer history significantly affect psychological distress Having breast cancer and BRCA carrier status increases risk for psychological distress BRCA carriers without breast cancer reported highest levels of distress
Bosch (2012), Spain	Prospective	364 participants (57% affected)	BRCA1/2	Psychological distress (HADS)	3 months and 1 year post-GT results disclosure	Overall low distress 16% prior to and 14% post-testing scored above 10 on HADS Having a prior cancer diagnosis associated with clinically significant anxiety score on HADS at 3 and 12 months post-test results Genetic test result not associated with HADS scores
Croyle (1997), USA	Prospective	60 women (10 affected) 25 BRCA+ve 35 BRCA non-carriers	BRCA1	Psychological distress (STAI); test-related distress (IES)	Baseline and 1-2 weeks post-GT results disclosure	Post-testing, non-affected carriers showed greatest distress on IES Overall BRCA carriers showed more test-related distress (IES) and general distress (STAI) post-testing than non-carriers

Ertmanski (2009), Poland	Prospective	111 BRCA+ve (50% affected)	BRCA1 (3 Polish founder mutations)	Anxiety (STAI); distress (IES)	Baseline, 1 month and 1 year post-GT results disclosure	Anxiety stable between pre- and post-testing across both groups, decreases for affected at 12 months Overall, anxiety does not increase amongst BRCA carriers No differences in anxiety between affected and unaffected women Affected women had significantly higher levels of cancer-related distress at 1 month compared to unaffected (attributed to personal cancer history)
Graves (2012), USA	Prospective	464 participants 76% affected 31% BRCA+ve 56.1% inconclusive 12.9% BRCA -ve	BRCA1/2	Distress (IES, STAI, MICRA)	Median 5 years post-GT results disclosure	Affected BRCA+ve significantly higher levels of GT distress compared to affected receiving inconclusive results Same results found for unaffected group Affected BRCA+ve reported significantly more uncertainty compared to receiving inconclusive results
Hughes Halbert (2011), USA	Retrospective	167 participants (60% affected) 40% BRCA+ve 60% BRCA non-carriers	BRCA1/2	Genetic testing specific concerns (MICRA)	Mean 7.2 years post-GT results disclosure	Non-significant association between distress and cancer history (unaffected more likely to experience distress) Mutation carriers were most likely to experience distress than non-carriers

Lumish (2017), USA	Retrospective	232 participants (224 women) Affected+ve: 11 Affected+VUS:14 Affected-ve:104 Unaffected+ve:14 Unaffected+ VUS: 20 Unaffected-ve: 69	BRCA1/2; Multisite panels: Small (5–6 genes); medium (17–18 genes); Large (25+ genes)	Impact of Event Scale (IES); Multidimensional Impact of Cancer Risk Assessment (MICRA); Satisfaction with Decision Instrument (SWD);	12 months following genetic testing.	MICRA total scores greater in the Unaffected/mutation+ve group than in either of the mutation -ve groups or in the affected+VUS group No difference between groups for the MICRA uncertainty subscale Median IES total, avoidance, intrusion, and hyperarousal scores significantly higher in Unaffected/mutation+ve group than in any other groups
Mella (2017), Italy	Retrospective	91 women (88% affected) 13% BRCA+ve 87% BRCA-ve	BRCA1/2	Anxiety and depression (HADS); Profile of Mood States (POMS)	1 month post- GT results disclosure	HADS and POMS: No association emerged between being a carrier/non-carrier No difference in negative emotions or mood states between women who received mutation positive results and those with no mutation identified
Reichelt (2004), Norway	Prospective	244 unaffected (80 BRCA+ve) 43 affected (39 BRCA+ve)	BRCA1 (founder mutations)	Anxiety and depression (HADS), distress (GHQ-28), hopelessness (BHS), cancer distress (IES)	Baseline (pre- testing), at and 6 weeks post-GT results disclosure	No differences between affected and unaffected from baseline to follow-up GT and affected status not associated with increased levels of distress in short-term Type of GT result did not influence distress Affected women had higher levels of cancer- related distress

Reichelt (2008), Norway	Prospective	214 women (15% affected) 83 BRCA+ve 131 BRCA-ve	BRCA1 (founder mutations)	Distress (HADS, IES)	Baseline (pre-testing) and 18 months post-GT results disclosure	Affected/unaffected status or BRCA carrier status did not predict distress 18 months-post testing
Schwartz (2002), USA	Prospective	279 women (186 affected) 78 BRCA+ve 58 BRCA-ve 143 inconclusive	BRCA1/2	Distress (IES, HSCL-25)	6 months post-GT results	No adverse psychological outcomes for affected or unaffected women No differences between BRCA+ve and non-carriers
Tercyak (2001), USA	Prospective	107 women 38 affected, all BRCA+ve 69 unaffected, 31 BRCA+ve)	BRCA1/2	State Anxiety (STAI)	Baseline (prior to education session), at pre-test education session, and post-GT results disclosure	At pre-disclosure, unaffected women were more anxious At post-disclosure, BRCA+ve carriers were more anxious compared to non-carriers
Van Dijk (2006), Netherlands	Prospective	238 women 42 BRCA+ve (48% affected) 43 BRCA-ve (5% affected) 153 inconclusive (54% affected)	BRCA1/2	Breast-cancer worry; breast-cancer distress (IES)	Pre-test, post-testing and 6 months post-GT results disclosure	Affected women with inconclusive results had significantly higher levels of breast cancer worry and distress compared to unaffected women No differences observed between affected and unaffected BRCA carriers at any timepoints Worry and distress levels in affected BRCA carriers comparable to affected women with inconclusive results



Van Roosmalen, (2004), Netherlands	Prospective	368 women baseline, at follow-up 89 BRCA+ (23 affected, 66 unaffected)	BRCA1/2	Depression (CES-D); anxiety (STAI); cancer-related distress (IES)	Baseline (post-blood draw), 2 weeks post-GT results disclosure	<p>Women with BRCA+ve results only included</p> <p>Affected women had significantly higher baseline scores on depression and cancer-related distress</p> <p>No differences between affected and unaffected women across time on anxiety, depression and distress (all increased)</p> <p>At follow up affected women BRCA+ve diagnosed &lt;1 year had higher anxiety and cancer-related distress</p>
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Table 4 Psychological impact of genetic counselling and/or testing at diagnosis

Study, country	Study design	Sample	Genetic testing	Outcome measures	Measurement timepoint(s)	Findings
Baars (2014), Netherlands	Retrospective	Breast cancer patients 112 offered GC/GT during radiotherapy (3 no testing, 11 BRCA+ve, 7 VUS, 91 inconclusive) 127 usual care	BRCA1/2	Distress (HADS), cancer distress (IES), cancer worries (CWS)	Mean 10 years post-GT results disclosure	Follow-up study to Schlich-Bakker (2008) Low levels of distress No significant differences between groups Cancer worries not predicted by GT results Overall no long term impact of GC/GT during breast cancer treatment Some patients from both groups experience high levels of depression and distress in long term
Christie (2012), USA	Prospective	Breast cancer patients 87 post-surgery 16 pre-surgery	BRCA1/2	Cancer related distress (IES), decisional conflict (DCS)	Before GC session, and 2–3 weeks after pre-test GC	GT results not available Significant decrease in cancer-related distress from pre- to post-GC for before definitive surgery group Non-significant trend for after definitive surgery group
Hoberg-Vetti, (2016), Norway	Prospective	215 breast or ovarian cancer patients 26 BRCA+ve	BRCA1/2	Distress (HADS)	Baseline (GT offer), 1 week and 6 months post-GT results disclosure	HADS scores significantly decreased from baseline to 6 months post-GT results disclosure No significant difference in distress scores between mutation carriers and non-carriers

Meiser (2012), Australia	Retrospective (Qualitative)	Ovarian cancer patients  12 offered TFGT  10 control	BRCA1/2	Experiences and attitudes for TFGT	Not specified	Women receiving BRCA+ve result reactions of sadness (implications for relatives) and relief (more treatment options, cause of cancer explained)  Inconclusive results is relief (no implications for relatives) and no disappointment for ineligibility for targeted treatments
Meiser, Australia (2018)	Prospective	128 breast cancer patients  Strong FH n=74, no FH n=54  18 BRCA mx (50% strong FH)	BRCA1/2	Anxiety and depression: (HADS); Impact of Events Scale (IES) (breast cancer specific worry); test-related distress and positive experiences, Decisions Regret Scale (DRS) GT choice	Baseline, 1 week post-GC or educational materials, 2 weeks post-GT results, 6 months post- recruitment	DRS: When averaged across mx status, FH- women reported significantly greater decision regret regarding undergoing TFGT than FH+ women. For mx carriers, FH- women reported significantly higher regret scores than FH+ women (no difference in non-carriers)  Test-related distress: Significantly higher in mx carriers compared to non-carriers when averaged across family history and time. In mx carriers, FH- women reported significantly higher test-related distress scores than FH+ women (no difference in non-carriers)
Plaskocinska (2017), UK	Prospective	232 ovarian cancer patients  18 BRCA+ve	BRCA1/2	Depression Anxiety and Stress Scale (DASS-21); Impact of Event Scale (IES)	Post-results disclosure (exact timepoint not stated)	Measures completed twice: once anchoring to OC diagnosis, and once to GT  IES and DASS scores significantly lower on measures for GT compared to OC  Younger OC patients significantly higher intrusion and stress scores  BRCA mutation carriers had highest cognitive avoidance scores

Schlich-Bakker (2008), Netherlands	Prospective	402 breast cancer patients: 58 GT 118 no referral 44 decline 182 control	BRCA1/2	Distress (HADS, IES)	Multiple timepoints	GT results not reported No adverse effect from active approach for GC/GT during primary treatment for breast cancer No change over time up to 43 weeks post-approach for GC Increase in distress in subgroup of affected women: high baseline levels distress, not referred for GC, decliners
Wevers (2012), Netherlands	Retrospective	26 breast cancer patients 10 BRCA+ve	BRCA1/2	Psychological impact (self-developed scale); cancer-related distress (adapted Cancer Worry Scale, IES)	Mean 29.2 months between GT and questionnaire completion	54% reported RGCT caused additional distress above cancer diagnosis, 19% reported RGCT reduced distress, 27% reported no effect 23% of women had clinically relevant scores on IES; BRCA carriers significantly higher total IES scores compared to non-carriers
Wevers (2016), Netherlands	Prospective	Breast cancer patients 178 offered RGCT 87 control (usual care)	BRCA1/2	Cancer-related distress (IES); psychological distress (HADS); cancer worries (CWS)	Baseline, 6 and 12 months follow-up	Focus not on GT results No significant differences at short-term or long-term follow up for cancer worries, cancer-related distress, anxiety, depression between RCGT group and control Overall women had substantial distress at baseline which decreased over time (see supplementary data)

## Appendix III

### Ethical approval for PhD research

University College London Hospitals   
NHS Foundation Trust

**University College Hospital**  
Cancer Clinical Trials Unit  
1<sup>st</sup> Floor East  
250 Euston Road  
London  
NW1 2PG

Direct line: 020 3447 8818  
Switchboard: 0845 155 5000/ 020 3456 7890  
Ext: 78818

Email: [emina.hainsworth@uclh.nhs.uk](mailto:emina.hainsworth@uclh.nhs.uk)  
Website: [www.uclh.nhs.uk](http://www.uclh.nhs.uk)

Applied Health Research in Cancer Governance Group

25<sup>th</sup> July 2016

Dear Belinda,

**RE: Mainstreamed genetic testing: intentions, decision-making and outcomes**

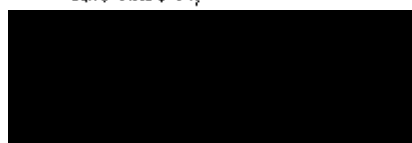
The Applied Health Research in Cancer Governance Group met on Thursday 21<sup>st</sup> July 2016. The group reviewed your study and is happy to provide approval for the project.

The following comments were made by the reviewers

- It is not clear where written informed consent will be taken (p22 protocol). Would it be possible to clarify?
- You are advised to attend the regular gynae research team meeting so that the wider team are made aware of the study

It would be helpful to provide the group with a response to the first comment and to take on board the second which might aid the smooth running of your project

We wish you the best for the success of your study  
Yours sincerely



Emina Hainsworth  
On behalf of Applied Health Research in Cancer Governance Group



Member of  
the UCL  
Group

Partnership  
with the  
University of  
London

Academic  
Clinical  
Hospital

Specialist  
Services  
and Diagnostic  
Centres

Specialist  
Services  
and Diagnostic  
Centres



## Health Research Authority

London - Hampstead Research Ethics Committee

Barlow House  
3rd Floor  
4 Minshull Street  
Manchester  
M1 3DZ

Telephone: 02071048127

**Please note:** This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

01 August 2016

Dr Anne Lanceley  
Institute for Women's Health  
Room 237c Medical School Building  
74 Huntley Street  
WC1E 6AU

Dear Dr Lanceley

<b>Study title:</b>	<b>Mainstreamed genetic testing in ovarian cancer: intentions, decision-making and outcomes.</b>
<b>REC reference:</b>	<b>16/LO/1226</b>
<b>Protocol number:</b>	<b>1</b>
<b>IRAS project ID:</b>	<b>199605</b>

Thank you for your letter of 27 July 2016, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Matt Rogerson, [nrescommittee.london-hampstead@nhs.net](mailto:nrescommittee.london-hampstead@nhs.net).

## Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

## Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

*Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).*

*Guidance on applying for NHS permission for research is available in the Integrated Research Application System, [www.hra.nhs.uk](http://www.hra.nhs.uk) or at <http://www.rdforum.nhs.uk>.*

*Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.*

*For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.*

*Sponsors are not required to notify the Committee of management permissions from host organisations*

## Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett ([catherineblewett@nhs.net](mailto:catherineblewett@nhs.net)), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

#### Ethical review of research sites

[Omit this sub-section if no NHS sites will be taking part in the study, e.g. Phase 1 trials in healthy volunteers]

#### NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

#### Non-NHS sites

#### Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Covering letter on headed paper [Cover letter]	1	14 June 2016
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [UCL insurance confirmation]	1	05 April 2016
GP/consultant information sheets or letters [Study 1 GP letter]	2	03 May 2016
GP/consultant information sheets or letters [Study 2 GP letter]	2	03 May 2016
GP/consultant information sheets or letters [Study 2 (Interview) GP letter]	2	03 May 2016
GP/consultant information sheets or letters [Study 3 GP letter]	2	03 May 2016
GP/consultant information sheets or letters [Study 3 (Interview) GP letter]	2	03 May 2016
GP/consultant information sheets or letters [Study 1 consultant letter]	1	01 June 2016
GP/consultant information sheets or letters [Study 2 consultant letter]	1	01 June 2016
GP/consultant information sheets or letters [Study 3 consultant letter]	1	01 June 2016
IRAS Application Form [IRAS_Form_14062016]		14 June 2016
IRAS Checklist XML [Checklist_14062016]		14 June 2016
IRAS Checklist XML [Checklist_27072016]		27 July 2016
IRAS Checklist XML [Checklist_01082016]		01 August 2016
Letters of invitation to participant [Study 1 invitation letter]	3	01 June 2016
Letters of invitation to participant [Study 2 invitation letter]	2	03 May 2016



Letters of invitation to participant [Study 2 (Interview) invitation letter]	2	03 May 2016
Letters of invitation to participant [Study 3 invitation letter]	2	03 May 2016
Letters of invitation to participant [Study 3 (Interview) invitation letter]	2	03 May 2016
Other [Case report form dropout]	1	21 January 2016
Other [Study 1 clinical data form]	2	03 May 2016
Other [Study 2 clinical data form]	2	03 May 2016
Other [Study 3 clinical data form]	2	03 May 2016
Other [Study 1 Questionnaire]	1	04 May 2016
Other [Study 2 Questionnaire]	1	04 May 2016
Other [Study 3 Questionnaire]	1	04 May 2016
Other [Project costs]	1	24 May 2016
Other [HRA statement of activities]	1	01 June 2016
Other [HRA schedule of events]	1	01 June 2016
Other [UCL insurance certificate]	1	13 July 2015
Other [Response to REC provisional opinion]	1	27 July 2016
Other [Study 1 Questionnaire (final)]	2	22 July 2016
Other [Study 2 Questionnaire (final)]	2	22 July 2016
Participant consent form [Study 1 consent form]	3	01 June 2016
Participant consent form [Study 2 consent form]	3	01 June 2016
Participant consent form [Study 2 (Interview) consent form]	2	03 May 2016
Participant consent form [Study 3 consent form]	3	01 June 2016
Participant consent form [Study 3 (Interview) consent form]	2	03 May 2016
Participant information sheet (PIS) [Study 2 (Interview) PIS]	2	03 May 2016
Participant information sheet (PIS) [Study 3 (Interview) PIS]	1	03 May 2016
Participant information sheet (PIS) [Study 1 PIS (final)]	4	22 July 2016
Participant information sheet (PIS) [Study 2 PIS (final)]	4	22 July 2016
Participant information sheet (PIS) [Study 3 PIS (final)]	4	22 July 2016
Referee's report or other scientific critique report [External peer review]	1	18 May 2016
Research protocol or project proposal [Protocol]	1.5	02 June 2016
Summary CV for Chief Investigator (CI) [CV for CI Dr Anne Lanceley]	1	01 July 2015
Summary CV for student [CV for student Belinda Rahman]	1	25 May 2016
Summary CV for supervisor (student research) [CV for Dr Lucy Side]	1	24 July 2015
Summary CV for supervisor (student research) [CV for Dr Rebecca Kristeleit]	1	22 April 2015
Validated questionnaire [Validated questionnaires]	1	03 June 2016

### Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research

Ethics Committees in the UK.

#### After ethical review

##### Reporting requirements

The attached document “*After ethical review – guidance for researchers*” gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

#### User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:

<http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/>

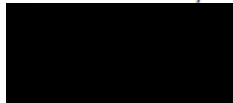
#### HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at <http://www.hra.nhs.uk/hra-training/>

16/LO/1226	Please quote this number on all correspondence
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With the Committee’s best wishes for the success of this project.

Yours sincerely



Signed on behalf of  
**Miss Stephanie Ellis**  
Chair

Email: [nrescommittee.london-hampstead@nhs.net](mailto:nrescommittee.london-hampstead@nhs.net)

Enclosures: “After ethical review – guidance for researchers” [SL-AR2]  
Copy to: Ms Tabitha Kavoi

## Appendix IV

### Description of the setting

The gynaecological oncology outpatient clinic is on the first floor of the Macmillan Cancer Centre, on one end of the large open atrium. Rows of seats face the reception desk, with the consulting rooms hidden along corridors. There are wall mounted stands for TVs which sit empty. A tall rack holds a few old magazines.

The clinic appointments start at 8.30 in the morning, but from 8.00 there will already be a few patients sitting in the waiting room even before the reception or clinical staff arrive to begin their shift. The waiting room is always too warm, even in the middle of winter. A large Dyson fan pushes warm air around the room. By 9.00 the waiting room will already be filling up with patients waiting for their appointments. The clinic still feels calm and quiet. Many of the patients have been coming to this clinic for years, and greet the reception team with a genuine warmth and friendliness.

At some point during the clinic, the waiting room will be completely full of patients and their family members. Some patients choose to stand, leaning against the wall under the empty TV stands. Others pace at the back of the waiting room. Inevitably the clinic will run late, sometimes up to two or three hours behind schedule. Some patients are unflappable, and wait patiently with a book or a newspaper. Others are restless with anxiety and boredom, going back and forth to the reception desk desperate to know when they will be seen by the doctor. The nurses and health care assistants run between the waiting room and clinic room, weighing and measuring patients before their appointments. The clinical trials staff duck in and out of their room, trying to spot their trial participants in the crowd of patients. Now the clinic feels chaotic, and a sense of frustration fills the air as patience (from everyone) begins to run thin.

Most patients look physically quite well, and despite the uncomfortable setting, able to navigate their blood tests and clinic appointments before heading home or on to the chemotherapy suite. At least one patient will be visibly very unwell, pale faced and breathing shallowly. There is such a lack of space for clinic rooms there is often nowhere else to go, and these patients remain seated in the waiting room, waiting their turn to be seen.

Once I was introduced to a patient who was interested in taking part, we often continued our discussion about my research on the chemotherapy suite. This is a

much larger space than the outpatient clinic, an expansive room with rows of beds on one side and large recliner chairs on the other. In the middle of the room are more chairs and a large, communal table with puzzles, magazines and craft activities. Patients with all different cancer diagnoses have their treatments here. It is much quieter, and cooler up here; intermittently a patient's name is called out across the room. Most chairs are occupied. Some patients are still waiting to start their treatment, cannulas already in place. Other patients have already started their chemotherapy infusions, IV drip stands holding bags of clear solutions. Many treatments span several hours and patients settle in to pass the time. Some come armed with reading material, kindles and iPads, while other patients sleepy from the 'pre-meds' (strong antihistamines), doze off.

## Appendix V

### Myriad Tumour BRACAnalysis CDx<sup>®</sup> technical specifications

Myriad GmbH: Tumor BRACAnalysis CDx<sup>®</sup> Technical Specifications

Effective Date: 31 Dec 2014

#### Description of Analysis

The Myriad Tumor BRACAnalysis CDx<sup>®</sup> test consists of sequencing and large rearrangement analyses of the *BRCA1* and *BRCA2* genes using next generation sequencing (NGS). This analysis is performed on genomic DNA isolated from ovarian, fallopian tube or peritoneal serous carcinoma.

#### **DNA sequence analysis**

**BRCA1:** Full sequence determination of approximately 5.400 base-pairs comprising 22 coding exons and approximately 750 adjacent base pairs in the non-coding intervening sequences (introns) is performed. Exons 1 and 4, which are non-coding, are not analyzed. The wild-type *BRCA1* gene encodes a protein composed of 1.863 amino acids.

**BRCA2:** Full sequence determination of approximately 10.200 base-pairs comprising 26 coding exons and approximately 900 adjacent base pairs in the non-coding intervening sequence (intron) is performed. Exon 1, which is non-coding, is not analyzed. The wild-type *BRCA2* gene encodes a protein composed of 3.418 amino acids.

The non-coding intronic regions of *BRCA1* and *BRCA2* that are analyzed do not extend more than 20 base pairs proximal to the 5' end and 10 base pairs distal to the 3' end of each exon.

#### **Large rearrangement analysis**

Genomic DNA derived from tumor is analyzed by NGS dosage analysis to determine copy number abnormalities indicative of deletion or duplication mutations. All coding exons of *BRCA1/BRCA2* and limited flanking intron regions are examined for evidence of deletions and duplications (see Limitations of method section for any exceptions). Large rearrangement detection utilizes the number of reads that map to each nucleotide normalized to the run median depth of coverage of the same nucleotide.

#### Description of Method

Acceptable sample types are formalin-fixed paraffin-embedded (FFPE) tissue from blocks or slides of ovarian, fallopian tube or peritoneal serous carcinoma. The portion of the tumor should measure at least 5x5 mm and contain at least 20% tumor cellularity determined using the adjacent Hematoxylin and Eosin stained (H&E) section. In cases where blocks are not available, one 4-5 µm H&E slide followed by four consecutive 10µm unstained slides are acceptable. Patient DNA is extracted and purified from the tumor specimen, assigned a unique bar-code for robotic-assisted

continuous sample tracking, and submitted for molecular testing.

**DNA sequence analysis by next-generation sequencing (NGS):** The samples are prepared through a hybridization-based target-enrichment strategy for subsequent NGS. Fragmented patient tumor DNA is ligated to specific adaptors and hybridized to biotinylated RNA library 'baits' for selective capture of *BRCA1* and *BRCA2*. The captured DNA is amplified, purified and diluted for loading on the NGS instrument. Samples are loaded on the NGS instrument, and the criteria for both sequencing and large arrangement calls is 99% of the bases must have  $\geq 100$  reads. Average read depth is approximately 425.

**NGS data analysis and confirmation:** A combination of commercial and laboratory-developed software is used for next-generation sequencing data processing, which includes base-calling, alignment, variant identification, annotation, and quality metrics. NGS dosage analysis for large rearrangement detection uses the normalized ratio of each amplicon compared across patients to identify regions of altered gene copy number. Genetic variants are reviewed by computer software and human reviewers. The minimum depth of coverage used for sequence determination by NGS is 50x per base. Clinically significant variants, deletions and duplications identified by NGS, and regions that do not meet NGS quality metrics are re-analyzed as appropriate.

#### Performance Characteristics

**Analytical specificity:** The incidence of a false report of a genetic variant or mutation resulting from technical error or errors in specimen handling and tracking is estimated from validation studies to be less than one percent (<1%).

**Analytical sensitivity:** Failure to detect a genetic variant or mutation in the analyzed DNA regions may result from errors in specimen handling and tracking, hybridization, amplification and sequencing reactions, or computer-assisted analysis and data review. The rate of such errors is estimated from validation studies to be less than one percent (<1%).

The analytical sensitivity of next-generation sequencing for genes in the Tumor BRACAnalysis CDx test is estimated to be >99.07% (lower bound of 0.95 C.I.), based on complete concordance of results from 42 individual anonymized tumor DNA samples collectively carrying 319 sequence variants which were confirmed by an independent laboratory (Myriad Genetic Laboratories in the USA). The lower limit of detection was determined to require a



minimum of 20% tumor content, based on a 'wild-type' cell line embedded in FFPE titrated with 50 known variants contained in six individual cell lines embedded in FFPE. All samples that were previously identified by alternative methods to be positive for deletions or duplications in *BRCA1/BRCA2* were correctly identified for large rearrangements using NGS dosage analysis.

**Test reproducibility:** Analytical validation studies included a reproducibility study for NGS. In a separate study, 10 samples were sequenced by NGS in triplicate across a total of 6 batches (i.e., 10 samples x 3 replicates each) which demonstrated 100% intra-run and inter-run reproducibility.

**Limitations of method:** Unequal allele amplification may result from rare sequence changes under hybridization sites. There may be uncommon genetic abnormalities such as specific insertions, inversions, and certain regulatory mutations that will not be detected by Tumor BRACAnalysis CDx. The detection of large rearrangement deletions and duplications is dependent on the quality of the submitted specimen. Large rearrangements restricted to the non-coding exon 1 or exons 1 and 2 of the *BRCA1* and *BRCA2* genes are not assessed by the Tumor BRACAnalysis CDx® assay. Other terminal duplications are reported as variants of uncertain significance. This analysis, however, is believed to rule out the majority of abnormalities in the genes analyzed.

#### Description of Nomenclature

All mutations and genetic variants are referenced to cDNA positions on their respective primary transcripts and named according to the HGVS convention (J Mol Diagn. 2007, 9(1):1-6). Transcript IDs are indicated on patient reports with their associated variants (*BRCA1*: NM\_007294.3; *BRCA2*: NM\_000059.3)

#### Interpretive Criteria

The classification and interpretation of all variants identified in the assay reflects the current state of scientific understanding at the time the report is issued. In some instances, the classification and interpretation of variants may change as scientific information becomes available

**“Pathogenic *BRCA1* or *BRCA2* Mutation Detected in Tumor”:** Includes clinically significant nonsense and frameshift mutations that prematurely truncate the protein. In addition, specific missense mutations and non-coding intervening sequence (IVS) mutations are recognized as pathogenic on the basis of data derived from linkage analysis of high risk families,

functional assays, statistical analysis, biochemical evidence and/or demonstration of abnormal mRNA transcript processing.

Deletions and duplications of an entire exon(s) identified by the Tumor BRACAnalysis CDx may also be interpreted to be pathogenic. Pathogenic large genomic rearrangements include single exon and multi-exonic deletions that are out-of-frame. Out-of-frame single or multi-exonic duplications are classified as deleterious if the orientation is determined to be in tandem and head-to-tail. In-frame deletions/duplications are interpreted on an individual basis and the specific evidence supporting the classification of these mutations is included in the individual patient report.

**“Suspected Pathogenic Mutation Detected in Tumor”:** Includes genetic variants for which the available evidence indicates a strong likelihood, but not proof, that the variant is pathogenic. The specific evidence supporting such an interpretation will be summarized for individual variants on each such report.

**“Variant(s) of uncertain significance”:** Includes missense variants and variants that occur in analyzed intronic regions whose clinical significance has not yet been determined, as well as nonsense and frameshift variants that occur very close to the normal stop codon, unless otherwise documented (Mazoyer S et al., *Nature Genetics* 1996;14:253-254).

**“No Pathogenic *BRCA1* or *BRCA2* Mutation Detected in Tumor”:** Includes genetic variants for which published data demonstrate absence of substantial clinical significance and truncating mutations in *BRCA2* that occur at and distal to amino acid 3,326 (Mazoyer S et al., *Nature Genetics* 1996, 14:253-254). Also includes variants in the protein-coding region that neither alter the amino acid sequence nor are predicted to significantly affect exon splicing, and base pair alterations in non-coding portions of the gene that have been demonstrated to have no pathogenic effect on the length or stability of the mRNA transcript.

There may be uncommon genetic abnormalities in *BRCA1* and *BRCA2* that will not be detected by Tumor BRACAnalysis CDx (see **Limitations of method**).

**Change of mutation/variant classification and issuance of amended reports:** Whenever there is a change in the classification of a mutation/variant within a patient's test result that has the potential to impact clinical management, an amended report will be provided by Myriad GmbH.

## Appendix VI

### Myriad Tumour BRCAAnalysis CDx information leaflet



Tumour

**BRCAAnalysis CDx™**

A companion diagnostic for ovarian cancer

## Patient guide to tumour BRCA testing



## Introduction to BRCA in Ovarian Cancer

You have been given this leaflet because you, or someone you know, have been diagnosed with ovarian cancer.

Ovarian cancer is categorized according to stage, which describes how far the cancer has spread; by grade, which indicates how quickly a tumour is likely to grow and spread; and by tissue type, which describes the specific type of ovarian cancer. In addition to stage, grade and tissue type, the cancer can also be classified according to BRCA status.

### What is BRCA?

*BRCA1* and *BRCA2* are genes involved with cell growth, division, and repair. The BRCA genes are found in everyone and play an important role in repairing damage to the DNA in our cells. When a mutation (a change or alteration in the gene) occurs in *BRCA1* or *BRCA2*, the gene can no longer repair DNA and so cell damage can accumulate. This damage can lead to a cell becoming cancerous.

Although they are most commonly associated with breast cancer, mutations in the BRCA gene are also seen in women with ovarian cancer.

### How does a BRCA mutation occur?

It is possible to carry a BRCA mutation which is either hereditary or somatic:

**Hereditary** (also known as germline) mutations are those inherited from our parents, meaning we carry them from birth.

**Somatic** mutations are those which arise spontaneously during normal cell division in the body and can occur at any time.

It is estimated that two thirds of ovarian cancer BRCA mutations are hereditary and one third are somatic. Either type of mutation can result in cancer.



## Why test BRCA status?

Not all ovarian cancers are the same. Approximately one in five women with ovarian cancer will carry a significant BRCA mutation.

Women with ovarian cancer who carry such a BRCA mutation (also known as 'BRCA-positive') have been found to respond better to certain types of drug therapy. This is because the BRCA mutation makes it harder for a tumour cell to survive when treated with such drug therapy.

A history of breast or ovarian cancer in the family is only one indicator that a woman could have BRCA-mutated cancer. That is why it is important that the decision to test BRCA status is independent of family cancer history.

## How are BRCA mutations detected?

BRCA mutations can be detected by testing a blood, saliva or tumour tissue sample. Testing a blood or saliva sample will identify **hereditary** mutations, while testing tumour tissue allows the identification of **both hereditary and somatic** mutations. The tumour tissue sample is usually provided from tissue that has already been removed at surgery.

Tumour tissue can be tested using the Myriad **Tumour BRCAAnalysis CDx** test.

## What is Tumour BRCAAnalysis CDx?

CDx stands for 'Companion Diagnostic' - a laboratory test used to identify patients who can benefit most from particular therapies. **Tumour BRCAAnalysis CDx** is a companion diagnostic tumour test for ovarian cancer to detect tumours with mutations in the *BRCA1* and *BRCA2* genes. A small section of tumour is tested to identify if the cells contain a significant *BRCA1* and/or *BRCA2* gene mutation.

## Why should I have this test?

The result of the **Tumour BRCAAnalysis CDx** test will determine if you may be suitable for a new ovarian cancer treatment option, known as a 'PARP inhibitor'. PARP inhibitors are a form of targeted drug therapy and have been demonstrated to be most effective in patients with a significant (pathogenic) *BRCA1* or *BRCA2* mutation. The drug, therefore, should only be prescribed to patients who have a significant mutation in either one of these genes.

As well as identifying if you may be suitable for a PARP inhibitor, the result also indicates whether your cancer is more likely to respond to platinum-based chemotherapy.

Knowing your BRCA status may help you and your healthcare provider make better, more informed decisions to create a personal treatment plan.

Please talk with your healthcare provider if you have any questions about PARP inhibitors.

## What are the possible test results for Tumour BRCA Analysis CDx?

There are two possible results for the test:

1. **Positive:** a pathogenic *BRCA1* and/or *BRCA2* mutation detected in the tumour
2. **Negative:** no pathogenic *BRCA1* and/or *BRCA2* mutation detected in the tumour

## What if my test result is positive?

If your test result is positive, based on your current cancer diagnosis, you may be eligible for treatment with a PARP inhibitor. Your medical management options and your complete treatment plan should be discussed with your oncologist. You should also consider genetic testing to determine if the mutation is hereditary or only found in the tumour.

## What if my test result is negative?

If your test result is negative, you are not eligible for treatment with a PARP inhibitor.

While knowledge of genetic mutations continues to grow, occasionally the test may identify a genetic change that has not yet been classified as positive or negative - this is known as a Variant of Unknown Significance (VUS). If your negative test result includes a VUS, you are not currently eligible for a PARP inhibitor.

Myriad continuously evaluates *BRCA1* and *BRCA2* gene mutations. If a VUS is subsequently found to be positive or negative, your healthcare provider will receive an updated report.



## Implications for family members

Testing tumour tissue identifies *both* inherited and somatic mutations but will not *specify* if the mutation was inherited or not. If a mutation is identified in the tumour tissue sample, then a blood test to look for the specific mutation is required to further determine if it is a somatic or inherited mutation.

Hereditary BRCA mutations may be passed on in a family. If you carry a hereditary mutation, there is a 50% chance your parents, siblings and children have the same mutation. Other relatives, such as aunts, uncles and cousins, may also be at risk to carry the same mutation. If your tumour test result is positive, your healthcare provider will offer you more information regarding hereditary testing.

If you have a history of cancer in your family and your tumour test result is negative for the BRCA mutation, there may be other mutated genes that could cause cancer to 'run in the family'. Your healthcare provider will work with you to consider further genetic testing and will help you manage your current treatment.

## Who will pay for my test?

Healthcare reimbursement and coverage for genetic testing varies greatly throughout the world. Please check with your physician, insurance provider, Myriad affiliate or distribution partner in your country for additional information.

## Will my results remain confidential?

Myriad is dedicated to offering high-quality laboratory services and is committed to securing your privacy through full compliance with international regulations. Myriad has an active privacy programme and discloses test results only to the requesting healthcare provider/designee, and to nobody else (including insurance providers) without your written permission. Additionally, Myriad does not provide results to patients directly, but only to their designated healthcare provider.

Myriad warrants that it has all necessary procedures and approvals in place to transmit and protect the patient data received.

### Notes

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Tumour  
**BRACAnalysis CDx™**

A companion diagnostic tumour test for ovarian cancer



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## **Appendix VII**

### **Study questionnaires**



## Attitudes to genetic testing

### Questionnaire Booklet

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Participant ID number:

Date:



Thank you for taking the time to complete this questionnaire. There are no right or wrong answers to these questions. The best responses to the questions are those that describe your situation.

Please carefully read the instructions at the beginning of each section. The questions can be answered by placing a tick clearly in the box that is closest to your views. Do not worry if you make a mistake or want to change your answer; simply cross out your previous answer and put a tick in the correct box.

Date of birth: \_\_\_ / \_\_\_ / \_\_\_ (DD/MM/YYYY)

Which of these best describes your ethnic group?

White	Mixed	Asian or Asian British	Black or Black British	Chinese/other
<input type="checkbox"/> White British	<input type="checkbox"/> White and Black Caribbean	<input type="checkbox"/> Indian	<input type="checkbox"/> Black Caribbean	<input type="checkbox"/> Chinese
<input type="checkbox"/> White Irish	<input type="checkbox"/> White and Black African	<input type="checkbox"/> Pakistani	<input type="checkbox"/> Black African	<input type="checkbox"/> Other
<input type="checkbox"/> Any other white background	<input type="checkbox"/> White and Asian	<input type="checkbox"/> Bangladeshi	<input type="checkbox"/> Any other Black background	
	<input type="checkbox"/> Any other Mixed background	<input type="checkbox"/> Any other Asian background		

Please tick the box which best describes your living arrangements:

<input type="checkbox"/> Own outright	<input type="checkbox"/> Own mortgage	<input type="checkbox"/> Rent from Local Authority / Housing Association	<input type="checkbox"/> Rent privately	<input type="checkbox"/> Other
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What is your marital status?

Single/never married	Married/living with partner	Separated	Divorced	Widowed	Civil partnership
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

What is the highest level of education qualification you have obtained?

<input type="checkbox"/> Degree or higher degree	<input type="checkbox"/> O Level or GSCE equivalent	<input type="checkbox"/> No formal qualifications	<input type="checkbox"/> Other
<input type="checkbox"/> A-levels or higher	<input type="checkbox"/> ONC/BTEC	<input type="checkbox"/> Still studying	

What is your current employment status?

<input type="checkbox"/> Employed full-time	<input type="checkbox"/> Unemployed	<input type="checkbox"/> Full-time homemaker	<input type="checkbox"/> Still studying
<input type="checkbox"/> Employed part-time	<input type="checkbox"/> Self-employed	<input type="checkbox"/> Disabled/ too ill to work	<input type="checkbox"/> Retired

Do you have children?

<input type="checkbox"/> Yes	<input type="checkbox"/> No	If yes, how many children do you have?
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Please read each item and tick the box that comes closest to how you have been feeling in the past week. Don't take too long over your replies – your immediate reaction to each item will be more accurate than a long thought out response.

**I feel tense or 'wound up':**

Most of the time	
A lot of the time	
Time to time, occasionally	
Not at all	

**I feel as if I am slowed down:**

Nearly all of the time	
Very often	
Sometimes	
Not at all	

**I still enjoy the things I used to enjoy:**

Definitely as much	
Not quite so much	
Only a little	
Not at all	

**I get a sort of frightened feeling like 'butterflies in the stomach':**

Not at all	
Occasionally	
Quite often	
Very often	

**I get a sort of frightened feeling like something awful is about to happen:**

Very definitely and quite badly	
Yes, but not too badly	
A little, but it doesn't worry me	
Not at all	

**I have lost interest in my appearance:**

Definitely	
I don't take as much care as I should	
I may not take quite as much care	
I take just as much care as ever	

**I can laugh and see the funny side of things:**

As much as I always could	
Not quite so much now	
Definitely not so much now	
Not at all	

**I feel restless as if I have to be on the move:**

Very much indeed	
Quite a lot	
Not very much	
Not at all	

**Worrying thoughts go through my mind:**

A great deal of the time	
A lot of the time	
From time to time but not too often	
Only occasionally	

**I look forward with enjoyment to things:**

As much as I ever did	
Rather less than I used to	
Definitely less than I used to	
Hardly at all	

**I feel cheerful:**

Not at all	
Not often	
Sometimes	
Most of the time	

**I get sudden feelings of panic:**

Very often indeed	
Quite often	
Not very often	
Not at all	

**I can sit at ease and feel relaxed:**

Definitely	
Usually	
Not often	
Not at all	

**I can enjoy a good book or radio or TV programme:**

Often	
Sometimes	
Not often	
Very seldom	

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	Not a lot	A little	Some what	Quite a bit	Very much
I have a lack of energy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I feel ill	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have cramps in my stomach area	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I feel fatigued	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am bothered by constipation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have swelling in my stomach area	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have control of my bowels	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am sleeping well	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I worry that my condition will get worse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have nausea	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am bothered by hair loss	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am bothered by side effects of treatment	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have been vomiting	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am bothered by skin problems	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am able to get around by myself	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am able to enjoy life	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am content with the quality of my life right now	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Genes are made up of DNA. Each with a specific function that helps our bodies grow and function normally. BRCA genetic testing is a blood test that uses DNA analysis to look for changes (mutations) in two different genes. These genes are called BRCA1 and BRCA2. People who have changes in these genes have an increased risk of cancer; in particular ovarian and breast cancer. Genetic testing usually takes place at a separate genetics clinic appointment with a genetics specialist. The statements below are about your attitudes towards BRCA genetic testing.

	Strongly agree	Agree	Neither Agree or Disagree	Disagree	Strongly disagree
Genetic test results would help my oncologist manage my health care	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Having a BRCA mutation would encourage me to live a healthier lifestyle	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Having BRCA test results would help me prioritize my life	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Genetic test results would give me greater control over my health	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Being found to have a BRCA mutation could lead to problems with my health insurance	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Being found to have a BRCA mutation could lead to problems with my life insurance	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am concerned about a false positive BRCA result	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I think my oncologist is unprepared to counsel me about undergoing BRCA testing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am concerned that if I have BRCA testing done my oncologist won't know what to do with the information	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
BRCA mutation could lead to problems with my job	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am afraid of the genetic testing procedure	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I don't want to know my BRCA test results	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

The following statements are about BRCA genetic testing. Please choose the best response for you: 'True' or 'False' or 'Don't know'

	True	False	Don't know
A father can pass down an altered BRCA gene to his daughters	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
A woman who doesn't have an altered BRCA gene can still get cancer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The BRCA gene causes about one half of all breast cancers	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
There are many different genes that cause cancer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
About 1 in 10 women have an altered BRCA gene	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
All women who have an altered BRCA gene will get cancer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
A woman who has a sister with an altered BRCA gene has a 50% chance of having an altered gene herself	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please think about whether or not you would have BRCA genetic testing if it was offered to you.

	Definitely	Probably	Unsure	Probably not	Definitely not
If you were offered BRCA genetic testing, would you choose to have this test?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
If BRCA genetic testing could be offered in the oncology clinic by your cancer clinician, would this change your decision?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
If you were offered a separate appointment with a genetics clinician to discuss genetic testing, would this change your decision?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

You have reached the end of this questionnaire booklet.  
Thank you very much for completing this questionnaire!





# Decision-making for mainstreamed genetic testing

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## Questionnaire Booklet

Participant ID number:

Date:

Thank you for taking the time to complete this questionnaire. There are no right or wrong answers to these questions. The best responses to the questions are those that describe your situation.

Please carefully read the instructions at the beginning of each section. The questions can be answered by placing a tick clearly in the box that is closest to your views. Do not worry if you make a mistake or want to change your answer; simply cross out your previous answer and put a tick in the correct box.

Please read each item and tick the box that comes closest to how you have been feeling in the past week. Don't take too long over your replies – your immediate reaction to each item will be more accurate than a long thought out response.

**I feel tense or 'wound up':**

Most of the time	
A lot of the time	
Time to time, occasionally	
Not at all	

**I still enjoy the things I used to enjoy:**

Definitely as much	
Not quite so much	
Only a little	
Not at all	

**I get a sort of frightened feeling like something awful is about to happen:**

Very definitely and quite badly	
Yes, but not too badly	
A little, but it doesn't worry me	
Not at all	

**I can laugh and see the funny side of things:**

As much as I always could	
Not quite so much now	
Definitely not so much now	
Not at all	

**Worrying thoughts go through my mind:**

A great deal of the time	
A lot of the time	
From time to time but not too often	
Only occasionally	

**I feel cheerful:**

Not at all	
Not often	
Sometimes	
Most of the time	

**I can sit at ease and feel relaxed:**

Definitely	
Usually	
Not often	
Not at all	

**I feel as if I am slowed down:**

Nearly all of the time	
Very often	
Sometimes	
Not at all	

**I get a sort of frightened feeling like 'butterflies in the stomach':**

Not at all	
Occasionally	
Quite often	
Very often	

**I have lost interest in my appearance:**

Definitely	
I don't take as much care as I should	
I may not take quite as much care	
I take just as much care as ever	

**I feel restless as if I have to be on the move:**

Very much indeed	
Quite a lot	
Not very much	
Not at all	

**I look forward with enjoyment to things:**

As much as I ever did	
Rather less than I used to	
Definitely less than I used to	
Hardly at all	

**I get sudden feelings of panic:**

Very often indeed	
Quite often	
Not very often	
Not at all	

**I can enjoy a good book or radio or TV programme:**

Often	
Sometimes	
Not often	
Very seldom	

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	Not a lot	A little	Some what	Quite a bit	Very much
I have a lack of energy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I feel ill	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have cramps in my stomach area	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I feel fatigued	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am bothered by constipation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have swelling in my stomach area	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have control of my bowels	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am sleeping well	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I worry that my condition will get worse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have nausea	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am bothered by hair loss	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am bothered by side effects of treatment	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have been vomiting	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am bothered by skin problems	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am able to get around by myself	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am able to enjoy life	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am content with the quality of my life right now	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Genes are made up of DNA. Each with a specific function that helps our bodies grow and function normally. BRCA genetic testing is a blood test that uses DNA analysis to look for changes (mutations) in two different genes. These genes are called BRCA1 and BRCA2. People who have changes in these genes have an increased risk of cancer; in particular ovarian and breast cancer. Genetic testing usually takes place at a separate genetics clinic appointment with a genetics specialist. The statements below are about your attitudes towards BRCA genetic testing.

	Strongly agree	Agree	Neither Agree or Disagree	Disagree	Strongly disagree
Genetic test results would help my oncologist manage my health care	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Having a BRCA mutation would encourage me to live a healthier lifestyle	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Having BRCA test results would help me prioritize my life	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Genetic test results would give me greater control over my health	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Being found to have a BRCA mutation could lead to problems with my health insurance	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Being found to have a BRCA mutation could lead to problems with my life insurance	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am concerned about a false positive BRCA result	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I think my oncologist is unprepared to counsel me about undergoing BRCA testing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am concerned that if I have BRCA testing done my oncologist won't know what to do with the information	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
BRCA mutation could lead to problems with my job	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am afraid of the genetic testing procedure	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I don't want to know my BRCA test results	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

The following statements are about BRCA genetic testing. Please choose the best response for you: 'True' or 'False' or 'Don't know'

	True	False	Don't know
A father can pass down an altered BRCA gene to his daughters	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
A woman who doesn't have an altered BRCA gene can still get cancer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The BRCA gene causes about one half of all breast cancers	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
There are many different genes that cause cancer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
About 1 in 10 women have an altered BRCA gene	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
All women who have an altered BRCA gene will get cancer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
A woman who has a sister with an altered BRCA gene has a 50% chance of having an altered gene herself	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Making the decision to have genetic testing. Please indicate how much you agree or disagree with each statement by ticking the box that best indicates your level of agreement.

	Strongly agree	Agree	Neither Agree or Disagree	Disagree	Strongly disagree
Learning my results will allow me to plan better for the future	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I want to know my results so I can get appropriate medical care	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
If I have an altered cancer gene, I want to know	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I want to learn my results, so I will know my child(ren)'s chances of getting cancer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Learning my results will help my doctor and me make a plan for monitoring for signs of cancer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Learning my results will help my doctor and me make decision about treatment	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Learning my results will help me live longer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
If I do not have an altered cancer gene, I want to know	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
It is important for my partner that I am tested	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
My partner does not want to know if I have an altered cancer gene	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
My partner will be upset if I have genetic testing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Having genetic testing is the responsible thing to do	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Knowing that <u>I do</u> have an altered cancer gene will help me live my life to the fullest	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Questions continue on the next page

Continued from previous page

Making the decision to have genetic testing. Please indicate how much you agree or disagree with each statement by ticking the box that best indicates your level of agreement.

	Strongly agree	Agree	Neither Agree or Disagree	Disagree	Strongly disagree
Learning my results will help my child(ren) make decisions about marriage and family	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Knowing that <u>I do not</u> have an altered cancer susceptibility gene will help me live my life to the fullest	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I do not know how I would cope with knowing that I have an altered cancer gene	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Learning my results will be upsetting to me	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Knowing my results will change how I feel about myself	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I will be fine emotionally regardless of what my results are	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
It seems wrong to have this type of testing. Time will tell if I have an altered gene	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
My doctor advised me to have genetic testing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I want to help research on ovarian cancer and genetic testing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Genetic testing might explain why I have cancer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



Making the decision to have genetic testing. Please indicate how much you agree or disagree with each statement by ticking the box that best indicates your level of agreement.

	Strongly agree	Agree	Neither Agree or Disagree	Disagree	Strongly disagree
I know which options are available for me	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I know the benefits of each option	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I know the risks and side effects of each option	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am clear about which benefits matter most to me	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am clear about which risks and side effects matter most	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am clear about which is more important to me (the benefits or the risks and side effects)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have enough support from others to make a choice	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am choosing without pressure from others	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have enough advice to make a choice	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am clear about the best choice for me	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I feel sure about what to choose	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
This decision is easy for me to make	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I feel I have made an informed choice	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
My decision shows what is important to me	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I expect to stick with my decision	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am satisfied with my decision	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

You have reached the end of this questionnaire booklet.  
Thank you very much for completing this questionnaire!



## Outcomes of mainstreamed genetic testing

### Questionnaire Booklet

Participant ID number:

Date:

Thank you for taking the time to complete this questionnaire. There are no right or wrong answers to these questions. The best responses to the questions are those that describe your situation.

Please carefully read the instructions at the beginning of each section. The questions can be answered by placing a tick clearly in the box that is closest to your views. Do not worry if you make a mistake or want to change your answer; simply cross out your previous answer and put a tick in the correct box.

Please read each item and tick the box that comes closest to how you have been feeling in the **past week**. Don't take too long over your replies – your immediate reaction to each item will be more accurate than a long thought out response.

**I feel tense or 'wound up':**

Most of the time	
A lot of the time	
Time to time, occasionally	
Not at all	

**I feel as if I am slowed down:**

Nearly all of the time	
Very often	
Sometimes	
Not at all	

**I still enjoy the things I used to enjoy:**

Definitely as much	
Not quite so much	
Only a little	
Not at all	

**I get a sort of frightened feeling like 'butterflies in the stomach':**

Not at all	
Occasionally	
Quite often	
Very often	

**I get a sort of frightened feeling like something awful is about to happen:**

Very definitely and quite badly	
Yes, but not too badly	
A little, but it doesn't worry me	
Not at all	

**I have lost interest in my appearance:**

Definitely	
I don't take as much care as I should	
I may not take quite as much care	
I take just as much care as ever	

**I can laugh and see the funny side of things:**

As much as I always could	
Not quite so much now	
Definitely not so much now	
Not at all	

**I feel restless as if I have to be on the move:**

Very much indeed	
Quite a lot	
Not very much	
Not at all	

**Worrying thoughts go through my mind:**

A great deal of the time	
A lot of the time	
From time to time but not too often	
Only occasionally	

**I look forward with enjoyment to things:**

As much as I ever did	
Rather less than I used to	
Definitely less than I used to	
Hardly at all	

**I feel cheerful:**

Not at all	
Not often	
Sometimes	
Most of the time	

**I get sudden feelings of panic:**

Very often indeed	
Quite often	
Not very often	
Not at all	

**I can sit at ease and feel relaxed:**

Definitely	
Usually	
Not often	
Not at all	

**I can enjoy a good book or radio or TV programme:**

Often	
Sometimes	
Not often	
Very seldom	

Below is a list of statements that other people with your illness have said are important. For each statement, please tick the box to indicate your response as it applies to the **past 7 days**.

<b>Physical well-being</b>	Not a lot	A little	Some what	Quite a bit	Very much
I have a lack of energy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have nausea	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Because of my physical condition, I have trouble meeting the needs of my family	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am bothered by side effects of treatment	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I feel ill	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am forced to spend time in bed	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Social/family well-being</b>	Not a lot	A little	Some what	Quite a bit	Very much
I feel close to my friends	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I get emotional support from my family	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I get support from my friends	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
My family has accepted my illness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am satisfied with family communication about my illness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I feel close to my partner (or the person who is my main support)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it please mark this box <input type="checkbox"/> and go on to the next section</i>					
I am satisfied with my sex life	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Continued on next page

*Continued from previous page*

For each statement, please tick the box to indicate your response as it applies to the **past 7 days**.

<b>Emotional well-being</b>	Not a lot	A little	Some what	Quite a bit	Very much
I feel sad	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am satisfied with how I am coping with my illness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am losing hope in the fight against my illness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I feel nervous	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I worry about dying	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I worry that my condition will get worse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b>Functional well-being</b>	Not a lot	A little	Some what	Quite a bit	Very much
I am able to work (include work at home)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
My work (include work at home) is fulfilling	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am able to enjoy life	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have accepted my illness	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am sleeping well	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am enjoying the things I usually do for fun	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am content with the quality of my life right now	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Below is a list of symptoms that other people with your illness have said are important. For each symptom, please tick the box to indicate your response as it applies to the **past 7 days**.

	Not a lot	A little	Some what	Quite a bit	Very much
I have a lack of energy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have pain	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I feel ill	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have cramps in my stomach area	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I feel fatigued	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am bothered by constipation	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have swelling in my stomach area	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have control of my bowels	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am sleeping well	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I worry that my condition will get worse	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have nausea	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am bothered by hair loss	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am bothered by side effects of treatment	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I have been vomiting	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am bothered by skin problems	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am able to get around by myself	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am able to enjoy life	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am content with the quality of my life right now	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



The statements below are some specific responses you may have had **after receiving your BRCA genetic test results**. Please answer Sections 1 and 3, regardless of whether you received a positive (BRCA gene alteration) or negative (no BRCA gene alteration) result. Please indicate whether you have experienced each statement *never, rarely, sometimes, or often in the past week*, by ticking the corresponding box.

*Section 1.*

	Never	Rarely	Sometimes	Often
Feeling upset about my genetic test results	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Feeling sad about my genetic test results	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Feeling anxious or nervous about my genetic test results	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Feeling guilty about my genetic test results	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Feeling relieved about my genetic test results	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Feeling happy about my genetic test results	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Feeling a loss of control	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Having problems enjoying life because of my genetic test results	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Worrying about my risk of getting cancer again	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Being uncertain about what my genetic test results means about my cancer risk	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Being uncertain about what my genetic test results mean from my child(ren) and/or my family's cancer risk	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Thinking about my genetic test results has affected my work or family life	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Feeling concerned about how my genetic test results will affect my insurance status	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Having difficulty talking about my genetic test results with family members	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

*Section 1 continues next page*

Please indicate whether you have experienced each statement *never, rarely, sometimes, or often in the past week*, by ticking the corresponding box.

*Section 1. continued*

	Never	Rarely	Sometimes	Often
Feeling that my family has been supportive during the genetic testing process	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Feeling satisfied with family communication about my genetic test result	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Worrying that the genetic testing process has brought conflict within my family	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Feeling regret about getting my genetic test results	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

*Section 2. If you have children, regardless of your genetic test results, please answer the next two questions. Otherwise please go to Section 3.*

Worrying about the possibility of my child(ren) getting cancer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Feeling guilty about possibly passing on the disease risk to my child(ren)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

*Section 3.*

Feeling that the genetic test results have made it <u>harder</u> to cope with my cancer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Feeling that the genetic test results have made it <u>easier</u> to cope with my cancer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please think about the **decision you made about BRCA genetic testing** (e.g. if you chose to have genetic testing, or chose not to). Please indicate how much you agree or disagree with each statement by ticking the box that best indicates your level of agreement.

	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
It was the right decision	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I regret the choice that was made	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I would go for the same choice if I had to do it over again	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The choice did me a lot of harm	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The decision was a wise one	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please think about your **experiences of BRCA genetic testing**. Please indicate how much you agree or disagree with each statement by ticking the box that best indicates your level of agreement.

	Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree
Did you have enough time to make the decision about genetic testing?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Did you have enough information to make the decision about genetic testing?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Did you have enough support about your genetic testing decision?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
My genetic testing result had a significant impact on my medical treatment	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I am satisfied with my experience of genetic testing	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I plan to share my genetic test results with my family members	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

My genetic test results (if unsure, please write 'don't know'):

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Any other comments:

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You have reached the end of this questionnaire booklet.

Thank you very much for completing this questionnaire!

## Appendix VIII

### Interview schedule

#### Ovarian cancer illness

- Can you tell me how you were first diagnosed with ovarian cancer?
- What have your experiences been since you were diagnosed?
- What do you believe was the cause of your ovarian cancer?
- How did you feel about your illness before this genetic testing process started?

#### Genetic testing – self

##### *Recall*

- Can you tell me how you came to be offered genetic testing?
- When genetic testing was first mentioned to you?
- Who first mentioned it to you?
- And can you remember what they [from prev. question] said about genetic testing?
- What were your first thoughts about genetic testing?
- Did you have any initial fears or doubts about genetic testing?

##### *Knowledge/understanding genetic testing*

- Had you heard about genetic testing before it was mentioned by [oncologist/registrar/HP]?
- If yes, what did you know/understand about it?
- What did you understand about genetic testing after your doctor first discussed it with you?
- What were your expectations of genetic testing?
- What were your hopes for genetic testing?
- What did you expect your results from genetic testing to be?

##### *Tumour testing*

- You were offered tumour testing as part of research. Could you tell me in your own words what this involved?
- What did you first understand about this approach/method of genetic testing?
- What do you understand about it now?
- How did you feel about taking part in research?

### Decision making

- Did you have enough information and discussion with your oncologist to make a decision about genetic testing?
- What were your reasons for deciding to have genetic testing?
- For you, what was the most important reason for having genetic testing?
- What, in anything, influenced your decision to have genetic testing?
- Was the decision to have genetic testing an easy one to make?

### Genetic testing outcomes

#### *Self – fact*

- What were your results of tumour testing?
- How were your results given to you?
- Did you receive any explanation about your results?
- What has happened since you received your tumour test results?
- Has there been any change to your treatment or treatment plans because of your results?

#### *Self – feeling*

While you were taking part in this study about tumour testing, you completed several questionnaires that looked at how you were feeling at different stages of the testing process, i.e. before testing, during testing and after you received your results.

- Could you tell me how you felt at the first part, before you signed the consent form for genetic testing?
- How did you feel while you were waiting to receive your results?
- How did you feel after you received your results?
- What was good about your experiences of genetic testing?
- What was bad about your experiences of genetic testing?
- At any point during the genetic process did you feel upset?
- If there is anything you could change about your experience of tumour testing, what would it be?

[Choose next questions based on genetic testing results]

### Tumour testing mutation negative

- When your oncologist told you the results from tumour testing, that they were negative and so you don't have a genetic mutation, how did you feel at the time?
- How do you feel now?
- For you, what are the positives of not having a genetic mutation?

- Are there any negatives of not having a genetic mutation?
- What impact did your results have on how you feel about yourself?
- What impact did your results have on how you feel about your illness?

#### Tumour testing mutation positive

- When your oncologist told you the results from tumour testing, that they found a genetic mutation but only in your tumour tissue, how did you feel at the time?
- How do you feel now?
- For you, what are the positives of having a genetic mutation only in your tumour tissue?
- Are there any negatives of having a genetic mutation in tumour?
- What impact did your results have on how you feel about yourself?
- What impact did your results have on how you feel about your illness?

#### Germline mutation positive

- When your oncologist told you the results from tumour testing, that they had found a genetic mutation on tumour testing and in the blood test, how did you feel at the time?
- How do you feel now?
- For you, are there positives of having a genetic mutation?
- Are there any negatives of having a genetic mutation?
- What impact did your results have on how you feel about yourself?
- What impact did your results have on how you feel about your illness?

#### Family

- What role did your family have (if any) in making the decision about genetic testing?
- What was your family's thoughts/feelings/expectations of genetic testing?
- Did they have any fears or doubts about genetic testing?
- What expectations did you have for genetic testing in terms of your children?
- What expectations did you have for genetic testing in terms of your siblings/other family members?
- Have you discussed your genetic testing results with your partner/children/siblings?
- [If yes] What was their response?
- How do you think they felt?
- [If no] Could you tell me why?
- Has your decision to have genetic testing, or your results of genetic testing, had any impact on your family relationships?

#### Future of genetic testing and ovarian cancer



- Currently, tumour testing is not available to all women with ovarian cancer. Do you think it should be part of standard care?
- What information would women need to have before making a decision whether or not to have genetic testing?
- If we were introducing tumour testing for every woman with ovarian cancer, what would be important for us to know?

#### Ovarian cancer illness

- When we started this interview, I asked you about what you felt was the cause of your cancer, and how you felt about your illness.
- Has genetic testing changed how you feel about your illness?
- Has it changed your beliefs about the cause of ovarian cancer or why you developed ovarian cancer?

#### Close

- Is there anything else you'd like to tell me about your experiences of genetic testing?

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