Mainstreamed Genetic Testing in Ovarian Cancer: Patient Experience of the Testing Process

McLeavy L[1], Rahman B[1], Kristeleit R[2], Ledermann J[2], Lockley M[2,3], McCormack M[2], Mould T[2], Side L[4], Lanceley A[1]

1 EGA Institute for Women's Health, University College London, London, UK
2 Gynaecological Oncology, University College London Hospitals NHS Foundation Trust, London, UK
3 Bart's Cancer Institute, Queen Mary University of London, London, UK
4 Wessex Clinical Genetics Service, University Hospitals Southampton, Southampton, UK

Corresponding Author:
Dr Anne Lanceley
237c Medical School Building
74 Huntley Street
London
WC1E 6AU
Email: a.lanceley@ucl.ac.uk
Tel: 02076796807

Co-authors:
- Dr. Belinda Rahman – EGA Institute for Women's Health, University College London, London, UK
- Dr. Rebecca Kristeleit – Gynaecological Oncology, University College London Hospitals NHS Foundation Trust, London, UK
- Professor Jonathan Ledermann - Gynaecological Oncology, University College London Hospitals NHS Foundation Trust, London, UK
- Dr. Michelle Lockley - Gynaecological Oncology, University College London Hospitals NHS Foundation Trust, London, UK/ Bart's Cancer Institute, Queen Mary University of London, London, UK
- Dr. Mary McCormack - Gynaecological Oncology, University College London Hospitals NHS Foundation Trust, London, UK
- Mr Tim Mould - Gynaecological Oncology, University College London Hospitals NHS Foundation Trust, London, UK
- Dr. Lucy Side - Wessex Clinical Genetics Service, University Hospitals Southampton, Southampton, UK

Highlights

1. The overall patient experience of mainstreamed genetic testing for ovarian cancer was positive.
2. The pathway did not appear to negatively impact the psychological wellbeing of participants.
3. Further psychosocial research is required prior to the expansion of the pathway.

ABSTRACT

Objective: Pathogenic *BRCA* variants account for between 5.8-24.8% of ovarian cancers. The identification of such a variant can have a significant impact on the affected individual and their relatives – determining eligibility for targeted therapies, predicting treatment response and granting access to disease prevention strategies. Cancer services are responding to the increased demand for genetic testing with the introduction of mainstreamed genetic testing via oncology clinics. The study aimed to evaluate patient experience of the mainstreamed genetic testing pathway at a tertiary referral centre in London.

Methods: Study participants were patients diagnosed with high-grade non-mucinous ovarian cancer, tested via a mainstreamed genetic testing pathway at the tertiary referral centre between February 2015 and June 2017. Eligible participants were invited to complete the retrospective study questionnaire. Five quantitative measures with additional free-text items evaluated the patient experience of mainstreamed genetic testing.

Results: The tertiary referral centre tested 170 ovarian cancer patients. Twenty-three pathogenic *BRCA* mutations were identified (23/170, 13.5%). One-hundred and six patients (106/170, 62.4%) met the study inclusion criteria. Twenty-nine of those invited (29/106, 27.4%) to participate returned the retrospective study questionnaire. Pathogenic *BRCA1/2* variants were identified within four respondents (4/29, 13.8%). Motivations for genetic testing related to improved medical management, and the ability to provide relatives with genetic information. Participants did not appear to be adversely affected by result disclosure post mainstreamed genetic testing. Two individuals with a pathogenic variant reported that the support provided by the tertiary referral centre post-result disclosure could have been improved.

Conclusion: Results of the current study support further psychosocial research into the expansion of the mainstreamed genetic testing pathway. The results although promising have also highlighted the importance of genetic awareness within the multidisciplinary team and the provision of timely psychological support from genetic specialists.

INTRODUCTION

Ovarian cancer is the fifth most common cancer in women across the United Kingdom,[1] with 1 in every 70 diagnosed in their lifetime.[2] Germline pathogenic variants of the tumour suppressor genes *BRCA1* and *BRCA2* account for between 5.8-24.8% of ovarian cancers.[3] Knowledge of mutation status is becoming increasingly important for affected individuals, with the exploitation of BRCA-associated tumour characteristics for personalised cancer therapies.[4] The presence of a pathogenic *BRCA1/2* variant can, for example, determine eligibility for treatment with a Poly (ADP-ribose) Polymerase inhibitor that induces targeted cell apoptosis. Olaparib was the first Poly (ADP-ribose) Polymerase-inhibitor licenced to treat mutation-positive individuals with relapsed, platinum-sensitive ovarian cancer.[5]

Risk assessment for hereditary ovarian cancer was previously limited to women with a significant family history of breast and/or ovarian cancer and those belonging to specific populations i.e. Ashkenazi Jews. Family history has been challenged as an effective predictor of *BRCA*-related risk, with only 56% of individuals with a pathogenic mutation reporting a family history that would warrant testing.[6] More recently, the National Institute for Health and Care Excellence recommended that genetic testing be offered to individuals with a ≥10% combined risk of carrying a pathogenic *BRCA* mutation.[7] Women diagnosed with high-grade non-mucinous ovarian cancer are therefore eligible under these guidelines. The demand for genetic testing has therefore increased, with an alternative model required to accommodate the rise.[8]

Individuals deemed eligible for testing under the traditional genetic testing model are referred from Oncology to a Clinical Genetics Service. Genetic counsellors are subsequently responsible for the organisation of the genetic test, the dissemination of test results and the provision of pre- and post-test counselling (Figure IA). Mainstreamed genetic testing is a systematic approach to testing, involving cross-departmental collaboration between Oncology and Clinical Genetics. Oncologists trained via the Mainstreaming Cancer Genetics Programme are responsible for test co-ordination and the dissemination of results.[9] Individuals with a confirmed pathogenic variant or variant of unknown significance are subsequently referred for post-test counselling with a genetics expert (Figure IB). In addition to the benefits associated with streamlining patient care, the pathway is also economically favourable and has been shown to significantly reduce resource requirements that in turn could save the NHS an estimated £2.6 million annually.[10]

METHODS

Study Participants

One-hundred and seventy patients diagnosed with high-grade non-mucinous ovarian cancer were tested via a mainstreamed genetic testing pathway at a tertiary referral centre in North London between February 2015 and June 2017. There were no age or family history restrictions applied. Genetic testing was provided within the Gynaecology-Oncology clinic. Oncologists had completed online training via the Mainstreaming Cancer Genetics programme.[9] Germline testing for pathogenic variants of *BRCA1* and *BRCA2* was performed by the North East Thames Regional Genetics Laboratories. Twenty-three known pathogenic *BRCA* variants (thirteen *BRCA1* and ten *BRCA2)* and eleven variants of unknown significance were identified. These individuals were subsequently referred to a Clinical Genetics Service for post-test counselling.

Individuals eligible to participate in the study were adult women diagnosed with high-grade non-mucinous ovarian cancer that were able and willing to provide informed consent. Oncologists at the centre reviewed lists of their patients and consistently applied the study inclusion and exclusion criteria. Sixty-four patients (64/106, 37.6%) were subsequently deemed ineligible to participate. Thirty-four patients (34/64, 53.1%) were deceased at study entry. Patients deemed "too unwell", either due to their treatment or disease (14/64. 21.9%) were excluded (based on clinician judgement) for example, those with clinically significant anxiety and those receiving palliative care. Patients without an understanding of the English language (9/64, 14.1%) were also excluded as the project budget did not cover translation of the patient-facing materials or additional interpreter services. The remaining seven individuals (7/64, 10.9%) were excluded as a result of absent records on the electronic patient record system.

Patients eligible to participate were subsequently sent an invitation pack through the post. Thirty-three of the invitees (33/106, 33.1%) returned their opt-in form at first request. Questionnaire booklets and consent forms were subsequently posted to the respondents. Twenty-nine of the respondents (29/106, 27.4%) consented to participate and returned the study questionnaire (Table I).

Measures

Patient experience of mainstreamed genetic testing was evaluation using a retrospective questionnaire entitled: Experiences of BRCA Genetic Testing. Four quantitative measures, commonly used in psychosocial research, were used to evaluate patient experience (Table II). Knowledge of hereditary ovarian cancer was assessed using the *BRCA* Testing Knowledge questionnaire, an adaptation of the original and validated Descriptive Statistics for Baseline Knowledge Measure.[11] The Motivations and Concerns for Genetic Testing measure consists of thirty-items scored on a 5-point scale from "strongly agree" to "strongly disagree". The items are categorised into five subscales (Medical Care and Prevention, Partner's Wish to Know, Future Planning, Ability to Cope with Results and Fear of Discrimination) that seek to understand patient motivations to pursue genetic testing (Table II). Items related specifically to genetic testing for cancer prevention were removed from the study questionnaire.[12] Decision regret was assessed using the validated Decision Regret Scale.[13] The Multidimensional Impact of Cancer Risk Assessment is a validated

measure to evaluate the psychological impact of result disclosure. The statements are grouped into five subscales (Distress, Uncertainty, Positive Experiences, Familial Risk and Ability to Cope) and scored (Table II), with higher scores indicative of greater psychological distress. [14] The fifth and final measure was a study-specific questionnaire designed by B Rahman. The measure explored multiple aspects of the pathway including informed consent, decision-making, patient satisfaction, impact on medical management and family communication. Free-text response items were incorporated to gain a more in-depth understanding of patient-specific experiences.

Statistical Analysis

Demographic and clinical factors will be summarised with counts (percentages) for categorical variables and mean (standard deviation) for continuous variables. The statistical significance of all tests conducted will be reported as p-values.

Comparisons were made between the respondent and non-respondent populations to determine whether chosen variables influenced the likelihood a patient would respond to the study invitation. An independent samples t-test was performed to determine the influence of age on the decision to participate. A Fisher's Exact test was conducted to establish the association between the stage of disease and study participation. The impact of mutation status on the decision to respond was assessed using a Chi-Square test.

A Multiple Comparisons test with Bonferroni correction was performed to determine which of the five Motivations and Concerns for Genetic Testing subscales provided the greatest source of motivation to pursue genetic testing. The number of items per subscale were non-uniform. Participant scores were averaged to account for this variation. Five participants (5/29, 17.2%) did not complete the measure and were therefore removed prior to the statistical analysis of this dataset only.

The qualitative free-text items were collated and analysed, with codes assigned to recurrent themes within the text.[15]

RESULTS

The tertiary referral centre offered 170 ovarian cancer patients mainstreamed genetic testing between February 2015 and June 2017. Mean age at diagnosis was 60.7 years (± 10.80, range: 28-88). High-grade serous ovarian cancer was the most prevalent subtype of ovarian cancer that affected 83% (141/170) of the tested population. Seventy-eight percent (132/170) had advanced disease (stage III/IV). Twenty-three pathogenic *BRCA1/2* mutations were identified, generating a mutation rate of 13.5%. Eleven variants of unknown significance were also identified.

Twenty-nine participants (29/106, 27.4%) returned the study questionnaire. The average age at diagnosis of the respondent population was 60.3 years (± 9.461, range: 42-78). Twenty-six participants (89.7%) had high grade serous ovarian cancer. Twenty-two participants (75.9%) were diagnosed with advanced stage disease. Cancer treatments were ongoing for half of the respondent population, with the other half in follow-up. Four pathogenic *BRCA1/2* variants (4/29, 13.8%) were identified within the participant population (3 in *BRCA1* and 1 in *BRCA2*). None of the respondents had a variant of unknown significance. Thirteen of the participants (13/29, 44.8%) received their genetic test result more than 12 months after their diagnosis of ovarian cancer. Twenty-one participants were also parents. There were only four participants (4/29, 13.8%) in employment, with three-quarters in retirement.

There were no statistically significant differences (demographic nor clinical) between those that responded to the study invitation and those that did not. An independent samples t-test revealed that there was no significant difference in terms of age at diagnosis (p=0.749). A Fisher's Exact test established a further non-significant association between disease stage at diagnosis and study participation (p=0.964). It was also revealed that mutation status did not influence the decision to respond (p=0.206).

The average *BRCA* Testing Knowledge score was 3.66 (± 1.675) (Table II). Participants gave correct responses to 52.2% of the items compared with 55% in the original questionnaire design study.[11] Peters *et al.* (2005) defined 'high knowledge' as a score of greater than or equal to six out of seven.[16] Six of the participants (6/29, 20.7%) were considered to have 'high knowledge'. Interestingly, the two lowest scoring statements were those that contained a statistic and led the patient to consider both mutation prevalence and risk estimation.

A multiple comparisons test with Bonferroni correction was applied to the Motivations and Concerns for Genetic Testing data, with 'Prevention and Medical Care' and 'Medical Influences' identified as the subscales with the greatest influence on the patient and their decision to pursue genetic testing. Statements within the 'Prevention and Medical Care' subscale evaluated the importance of genetic testing to inform treatment decisions and to provide genetic knowledge to the affected individual and their relatives. 'Medical Influences' explored motivations to advance the field of genetics through research and to increase our ability to understand the aetiology of the disease.

"Just to know it was inherited. It may have helped my children to look out for any signs in their own daughters" (PES07, Age 54)

"…being aware of the risk would enable them to take measures to be more alert as to the development of cancers." (PES33, Age 43).

The average participant scored 9.14 (± 12.397) in the Decision Regret Scale, with lower scores indicative of less decision regret. Fourteen participants (14/29, 48.3%), including two individuals with a pathogenic *BRCA* variant, reported no decision regret. All participants felt sufficient time had been given to consider the offer of mainstreamed genetic testing. There were two recurring themes within the free-text items. Firstly, that the decision to pursue mainstreamed testing was not one that required much consideration as the benefits seemed to outweigh the costs and secondly, that if anything there was too much time given to consider the offer.

"I decided as soon as it was offered and had the test that day. I already had cancer, so it wasn't a big decision for me" (PES25, Age 58).

"It was a no-brainer" (PES28, Age 62).

Participants produced relatively low 'Distress' and 'Uncertainty' scores in the Multidimensional Impact of Cancer Risk Assessment questionnaire regardless of mutation status; a trend towards higher scores was seen in those with a confirmed pathogenic *BRCA* variant. Nineteen of the participants that were also parents (19/21, 90.4%) expressed significant concerns over the possibility of their child(ren) developing cancer. Participants felt that mainstreamed genetic testing did not make it harder to cope with their existing ovarian cancer diagnosis. Three of the four participants with a pathogenic *BRCA* variant shared the view that knowledge of mutation status even improved their ability to cope. The vast majority of participants (26/29, 89.6%) felt adequately supported by the oncology department. Two individuals with a pathogenic variant (2/4, 50%) felt the level of post-test support could have been improved.

The Testing Experiences measure designed by B Rahman evaluated various aspects of the mainstreamed genetic testing pathway. One of the statements sought to determine whether the level of support provided, by the tertiary referral centre, when making the decision to pursue genetic testing was sufficient. Only two participants (2/29, 6.9%) felt that the pre-test counselling provided was inadequate. This was further explored within the free-text response items. As opposed to clear dissatisfaction, the recurrent theme was that of uncertainty amongst participants as to the level of support they should expect to receive and from which department. Similar comments were observed when participants were given the opportunity to feedback on the quality of support provided post-testing, with a small number of participants expressing the view that support was neither present nor absent. Twenty-six participants (26/29, 89.6%) were satisfied with their decision to pursue genetic testing. None of the participants expressed clear dissatisfaction. Family communication was also strongly supported within the population. The free-text items corroborated this result, with twenty-seven patients (27/29, 93.1%) discussing their decision to participate with at least one significant other.

DISCUSSION

This study sought to evaluate the experience of patients diagnosed with high-grade non-mucinous ovarian cancer that underwent mainstreamed genetic testing at a tertiary referral centre in London. Despite the potential benefits, treatment-focused genetic testing could be considered an additional burden on individuals currently facing a life-threating diagnosis and on-going cancer treatment.[17] Participants within the current study did not appear to be adversely affected by result disclosure. The results therefore support further psychosocial research into this expansion of this increasingly patient-focused pathway.

The percentage of correct responses given to the BRCA Testing Knowledge measure in the current study, although relatively low, is comparable to that reported within the original questionnaire study.[11]. The delivery of pre-test genetic counselling within the mainstreamed genetic testing pathway is the responsibility of the oncologist as opposed to the genetics expert. Oncologists at the tertiary referral centre had all undergone training via the Mainstreaming Cancer Genetics programme that offered teaching in human genetics and result communication.[9] Despite the similarities in training, what hasn't been explored is the way in which oncologists discuss genetic testing with their patients and how these conversations may differ when compared with those led by a clinical geneticist/genetic counsellor. It is also important to note that for the majority of participants significant time had elapsed between the initial oncologist-led discussion and questionnaire completion. Differing baseline knowledge levels and the time lapse from testing to questionnaire completion may partially explain the range of scores observed.

This study presents some of the first data looking at the long-term impact of result disclosure following mainstreamed genetic testing. Meiser *et al.* (2012) explored the motivations of ovarian cancer patients offered treatment-focused genetic testing. The most prevalent motivators were the potential to alter clinical management (89%) and the ability to provide one's relatives with the genetic information required to consider disease prevention (87%).[18] Analysis of the Motivations and Concerns for Genetic Testing data corroborates this with these themes present in the highest scoring subscales. Mainstreamed genetic testing provides patients with insight into the aetiology of their disease and the potential benefit of targeted treatment options. The importance of genetic knowledge to guide clinical management has increased following the introduction of Poly (ADP-ribose) Polymerase-inhibitors. Patient selection for treatment with Olaparib is dependent on the identification of a pathogenic *BRCA1/2* variant.[19]

Published research has shown that treatment-focused genetic testing has been largely accepted by the patient population, with very little evidence that there are negative implications to psychological wellbeing. Plaskocinska *et al.* (2016) reported that treatment-focused genetic testing did not alter patient distress levels beyond that experienced as a result of an ovarian cancer diagnosis.[20] Our results concur with these findings, with the psychological health of participants largely uncompromised by

mainstreamed pathway. Participants with a confirmed pathogenic variant of *BRCA1/2* generated marginally higher scores than those without. This is not surprising given the wider implications of a positive genetic test result. Despite this trend, the scores produced by such individuals remained consistently towards the lower end of the possible score ranges. Research conducted by Wevers *et al.* (2012) reported similar findings, that although there was a degree of additional distress associated with treatment-focused genetic testing, the majority of participants could appreciate the benefits of pursuing genetic testing.[21]

Over recent decades, patients have become increasingly involved in healthcare decision-making. Decision regret is a negative emotion associated with a reduction in satisfaction, quality of life, and physical health that results in a strained relationship between the patient and healthcare provider.[22] Decision regret was low amongst the study population, implying that participants were satisfied with their decision. This result is verified within the Testing Experiences measure, whereby 89.3% of participants either agreed or strongly disagreed with the satisfaction statement.

Individuals in possession of a pathogenic *BRCA1/2* variant have the added responsibility of communicating their genetic test result with family members. Dissemination of this information, when consequences are unknown, may be burdensome.[23, 24] Despite this, rates of communication are consistently high within the current literature, with 91-100% of individuals communicating their genetic test result.[25] This was true of twenty-seven participants (93.1) within the current study.

Patient experience was generally positive within the current study, with mainstreamed genetic testing described as both 'straightforward' and 'uneventful'. Only two participants expressed dissatisfaction with the provision of pre-test information. However this result, combined with the uncertainty demonstrated within the qualitative dataset, highlights the issue that the time pressures associated with the running of an oncology clinic may not allow for sufficiently detailed discussions surrounding the genetic testing process and the implications of test results. Two carriers of pathogenic *BRCA1/2* variants (50%) reported that improvements could also have been made to the support provided by the Gynaecology-Oncology service post-result disclosure. The post-test counselling of such individuals would have been largely provided by the local clinical genetics service. It is therefore important that this support is given in a sensitive and timely manner.

Limitations to the study included the multi-step nature of recruitment by post that resulted in a relatively low response rate. It is highly probable that recruitment directly from the oncology clinic would have improved response rates. However, project timelines rendered this recruitment strategy unfeasible. The small sample size and absence of a population tested by the traditional genetic counselling pathway limited the scope of our statistical analyses. The validity of the study may also have been affected by the heterogeneity of the cohort in terms of the time lapse from diagnosis to mainstreamed genetic testing. Nevertheless, the results produced remain informative of the patient experience of mainstreamed genetic testing and support further investigation into the expansion of the pathway within Gynaecological-Oncology departments, as well as further analysis of the psychosocial impact of this approach. Further investigations could seek to compare the experiences of patients tested within the clinical genetics setting compared to those tested in a mainstreamed oncology-led approach across different sites.

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Figure Legend

FIGURE I: A) Flowchart for the Traditional Genetic Testing Pathway. B) Flowchart for the Mainstreamed Genetic Testing Pathway.

Participant Characteristics	
Mean Age (Years) at Diagnosis, Range	60.34 (42-78)
Histotype	**Number of Participants (%)**
High Grade Serous	26 (89.7)
Endometrioid	2 (6.9)
Mixed	1 (3.4)
Disease Stage	
I	4 (13.8)
II	3 (10.3)
III	11 (37.9)
IV	11 (37.9)
MGT Result	
No mutation	25 (86.2)
BRCA1 mx+ve	3 (10.3)
BRCA2 mx+ve	1 (3.4)
VUS	0 (0)

Table I: Demographic and Clinical characteristics of the participants.

Measure	Subscale	Possible Score Range	Mean (SD)
BRCA Testing Knowledge	**N/A**	0-7	3.66 (±1.675)
Motivations and Concerns for Genetic Testing	**Prevention and Medical Care**	8-40	30.97 (±5.723)
	Partners Wish to Know	4-20	10.17 (±3.152)
	Future Planning	3-15	9.86 (± 2.900)
	Ability to Cope	5-25	13.48 (±2.849)
	Medical Influences	3-15	12.03 (±2.500)
Decision Regret Scale		0-100	9.14 (±12.397)
Multidimensional Impact of Cancer Risk Assessment	**Distress**	0-35	2.66 (± 4.108)
	Uncertainty	0-35	5.07 (± 4.154)
	Positive Experiences	0-20	3.36 (± 4.093)
	Familial Risk	0-10	7.05 (± 3.027)
	Ability to Cope	0-5	0.26 (±0.656) 2.46 (±2.134)

Table II: Summary of the quantitative measures used in the study questionnaire.