

Navigating brain tumours:
Uncertainty, fixing and the
production of possibility

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I, Henry Llewellyn, 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

This dissertation offers an ethnographic account of life for people with a brain tumour. It explores their understandings of disease and attempts to secure treatment amid progressive and unpredictable bodily decline. It asks how these people negotiate changing relationships with families and cope with their own emotional struggle and self-doubt as the effects of tumour manifest. It also examines how these people's lives are shaped by medical institutions and the changing formations of care. Above all, it is a study of navigation which explores how people with a brain tumour imagine and enact trajectories for their lives under conditions of radical change—bodily and institutional.

From October 2014 to May 2016, I undertook fieldwork at a hospital I call *The Warner*—a publicly-funded specialist hospital for people with neurological disease in the UK. Over these eighteen months, I interviewed and conducted long-term participant observation with sixteen people with a brain tumour to understand their lived experiences and approaches to medical decision-making. I worked intensively with thirteen of these people and their families as they struggled to understand their condition and plot the best course through care and treatment amid the shifting protocols of NHS administration, scientific knowledge and ailing bodies. I also worked intensively with healthcare professionals, observing routine practice across multiple settings including clinics, multidisciplinary team meetings, laboratories and radiology departments, and interviewing them about their work.

Building on an analytic of social navigation (Vigh 2007; 2009), my ethnography brings into view the multiple temporalities of a constantly shifting terrain of disease, care and treatment. Rather than examining scientific innovation, clinic contexts, and patient experience independently, I argue that studying the interactions between them is critical for understanding the condition of patients and their relations with families and clinicians as they live through disease and navigate care.

IMPACT STATEMENT

How people with brain tumours interpret promises of medical innovation, and how interpretations drive their decisions, hopes and struggles, is largely unknown. To date, no studies have investigated these relationships. With few exceptions, in-depth qualitative methods have not examined experiences of brain tumour patients. To my knowledge, no other UK-based ethnographies of adult brain tumours exist.

My ethnography of treatment and decision-making in brain tumours provides crucial understandings of relationships between science, technology and society, and how visions of good care emerge and are established throughout direct healthcare and policymaking. It provides ethnographic insight into the lived experiences of people with a brain tumour and how they navigate complex and changeable terrains of care and treatment. Only by understanding the diverse hopes, apprehensions and values of patients, families and clinicians can we grasp *what is at stake* in the lives of people affected by cancer.

My ethnography also provides early insights and people-centred forms of knowledge about the social consequences of innovation—especially the introduction of molecular biomarkers to diagnosis and treatment prediction. As a new era of medical innovation inspires new generations of patients, families, clinicians, policymakers and advocates to manage cancer, high quality, in-depth empirical research is *desperately needed*.

Analytically, my dissertation forwards a theory of navigation which attends to the interactivity between three main vectors—patients’ agencies, the social and structural formations of care and treatment, and the diseased body. As such, it gives key insights into how people with progressive and unpredictable disease approach situations marked by extreme social and bodily change. I hope this to be of significant analytical utility to other scholars in the fields of medical anthropology, medical sociology, health psychology and related disciplines.

The work has already led to one peer review publication, a book chapter, nine conference papers at UK and international conferences and workshops (including *Medicalisation of death and dying: systems, practices and politics workshop*, Université Libre de Bruxelles, Belgium, September 2018; *Foundation for the Sociology of Health and Illness, Researching end of life care from a social science perspective workshop*, Open University, UK, November 2017; *American Anthropological Association Annual Meeting*, Minneapolis, MN, USA, November 2016;

British Sociological Association, Medical Sociology Conference, University of York, UK, September 2015) and one lecture at *The Brain Tumour Charity*.

The project also provides foundational empirical and theoretical work for a successful grant application for a three-year study of the social consequences of integrated diagnosis and personalised medicine in cancer. This multi-sited ethnographic research project will further understandings of the social consequences generated by innovation in diagnosis and treatment and provide outputs to help patients, families and professionals anticipate and navigate new dilemmas generated by newer technologies. It will have real-world applications in future policy, treatment and outcomes in brain tumours and other cancers, given similar approaches to diagnosis and treatment prediction are happening across most cancers. This is a collaboration between scholars and clinicians at UCL, two UK hospitals, and Harvard Medical School, Boston, MA, USA.

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INTRODUCTION

Gabriel's wife, Cecilia, stands in the doorway of their terraced house wearing blue pyjamas and a long cardigan. She tells me it's her new look. She hasn't left the house in days. She tells me that Gabriel is being changed upstairs. We go through to the kitchen where Cecilia introduces me to Susan, a palliative nurse, and Sally, a district nurse. Hospital IDs hang from their trousers. I take a seat just away from the table in a low-slung armchair; I'm told to mind the needles. It takes me a second to realise what they are talking about. Ah, the small yellow box marked clinical waste. It lies balanced on the arm of the chair. Sally moves it to the bookshelf above me. On the table, there are paper charts and a tiny video monitor. It emits a dull sound. The screen is still and, at first, I'm not sure what I am looking at. Then, I can see Gabriel's bare legs and realise it's a live feed from his room.

Cecilia, Susan and Sally pay no attention to it. They talk about medications. Susan suggests dropping the steroids: "So that's one pill—" she says. Cecilia looks at her pointedly: "It's liquid. It's all liquid now. Everything." She remains pleasant, though Susan has clearly forgotten this detail of her husband's care. They talk about morphine. Cecilia momentarily forgets the dose and the carer who would know is asleep upstairs—Gabriel has private carers as well as palliative and district nurses. Cecilia says they give him half a bottle at a time and put a cup over the rest, ready for the next dose. Sally tuts and drops her head to the table in mock exasperation—they should use a new vial each time. "Do you want to see Gabriel?" Cecilia asks the nurses. Sally has to go, but Susan will see him. Sally says goodbye and tells Susan she'll call her later about another patient. Cecilia and I sit at the kitchen table. "Oh, she's forgotten it again," Cecilia says eyeing the yellow box of waste the nurse is supposed to take with her when she leaves.

I ask Cecilia how she is. "Okay," she says, "I'm just being swept along with it. It's tough. But I'm good at dealing with stuff like this." One of the private carers comes in the kitchen. Cecilia introduces me but forgets her name. "Anna," says the woman. She says she's been here a month. Cecilia apologises, saying she is so scatty at the moment. She asks Anna to heat some soup for Gabriel. Then we go and see him. I take the paper bag I brought with two whisky miniatures and follow Cecilia up the stairs onto the open landing. I once stood here when Gabriel was wearing overalls and painting the walls their deep green.

We enter their bedroom. Next to a large wooden double bed is a hospital bed, raised to the same height. Metal rails run full-length along on its outside edge. Here Gabriel lies. His chest is bare and uncovered by the white sheets that hide all but the narrow outline of

his waist and legs. A pile of white pillows props up his head, which lists to his left as if he is falling away in slow motion. His silvery hair and beard neatly cut. His eyes look straight ahead and left—they don't seem to focus. His face is pallid and I can see the bones in his chest as they poke through his pale skin. His shoulders, small, like two balls on either side of his thin neck. I feel an immense shock and sadness; a peculiar numbness. His eyes. Bright lights extend from the window across his legs and body. "Henry is here," Cecilia says, "you remember Henry." She sits on the bed next to him and strokes his hair. I reach across to his left arm, which he raises a little. I hold it and press the tips of his fingers.

"Henry's brought whisky," Cecilia says. I place the bottles in Gabriel's hand. He fondles them and draws them to his face. Everything is done slowly. I tell him it was tough choosing the whisky, knowing that Gabriel is such a connoisseur. He takes one of the bottles to his lips and holds it there as if drinking. "Would you like some, babe?" Cecilia asks, "We need a syringe." With this, she points me to a little table next to Gabriel on which a stack of pillboxes and small bottles sit next to a syringe and a glass of water. She tells me to fill the syringe with one-third water. Then she draws some whisky from the narrow bottle.

Cecilia points to the camera behind me and laughs that we'll be "found out" for letting Gabriel drink. "Just shuffle yourself left a bit," she says with a smile and I move to cover its view. "We should lift him up." She points to a controller attached to the bed by a grey coil. She tells me to press the blue button. Gabriel's chest and head lift slowly to the whirring motor. Then we ease him up. His skin is cool to the touch. Cecilia plumps the pillows to stop him from slipping down again and I pour the rest of the whisky between two glasses. We toast Gabriel. She places the syringe in his mouth and gently squeezes. Gabriel bites down on the plastic and she has to tell him to let go. "I'll give you some more," she says. Gabriel reaches for the other bottle. He is trying to get the cap off, but things are difficult one-handed. Cecilia asks if he wants help: "Oh, but you'll get pissed off with me if I do it." He perseveres but in the end, he doesn't manage. Instead he drops his hand and tucks the bottle under the covers.

Cecilia wonders aloud when Gabriel last had painkillers. "Have a look on the chart on the fridge," she tells me. I go downstairs. The chart, hand drawn and stuck to the fridge by magnets, runs hourly, midnight to midnight. The rows mark various medications and things like "agitation," "toilet." There is no cross against paracetamol. Upstairs, I tell Cecilia. "Oh, he could have some!" she says.

Soon Daniel, another carer, arrives with soup for Gabriel. Cecilia sends him for the paracetamol and calls after him that we need a syringe—"one with the units on, the writing's

gone on the one I have.” A moment later she calls down again. She has found one among various bottles on the table by Gabriel. The soup steams gently on a tall chest. It sits next to a boxed nebuliser. Daniel returns shortly and gives Cecilia a small brown bottle. She removes the cap and draws the chalky white liquid into the syringe. She pushes it softly into Gabriel’s mouth. He doesn’t hold onto the syringe this time.

When he has swallowed, Daniel passes Cecilia the bowl. She blows on a spoonful before tilting the soup into Gabriel’s open mouth. She asks me about the hospital and how other patients are doing—“We saw so many, but didn’t stay in touch.” She wonders whether Gabriel would be more comfortable sitting up and asks Daniel to raise his head so his back is more upright. Daniel reaches for the buttons that hang limply from the bed and presses, but this time Gabriel’s back folds rather than pivoting at his hips. Daniel tucks his hands under Gabriel’s arms and heaves him up so his hips align with the crease of the bed. Cecilia says it’s amazing how heavy someone is without any muscle tone. She continues to feed Gabriel, checking each time he has swallowed and once taking a spoonful for herself. Then Gabriel takes the spoon himself. At first, Cecilia supports him. Then he moves the spoon on his own, slowly. Daniel smiles and leaves.

Cecilia and I now sit silently on the bed next to Gabriel until a loud thump at the front door makes us jump. “Oh, it’s probably a delivery,” Cecilia says. We go down together and she opens the door to a man who stands outside with a clipboard and a large box at his feet. Cecilia signs and begins to handle the box. I go and help. The box is enormous. We pull it inward. “It’s got to go upstairs,” Cecilia says. I take it upstairs where Anna is waiting on the landing. “Where should this go?” I ask. She says in the other room, but she’ll take it. I put it on the floor. “What is it?” I ask. “More pads for Gabriel,” she says. She tells me that Gabriel is asleep—“Or maybe he just closed his eyes to get rid of us.” “Does he do this?” I ask. “I think so,” says Anna.

Cecilia comes up the stairs and meets us on the wide landing just outside Gabriel’s room. Anna suggests that Cecilia go in—“Maybe it’s just us, maybe he isn’t asleep,” she says. Cecilia opens the door a crack and whispers, “Hello baby.” I can see her walk over to the edge of the bed, climb onto it and move close to Gabriel. She strokes his hair and kisses his forehead. She turns to me and says I can come in. “Can I just say goodbye?” I ask. “Of course.” Gabriel’s eyes are open. I walk over to the side of the bed. I say it was nice to see him. I thank him. I say goodbye. I put my hand on his shoulder. It’s soft. I move in front of him, over to his left. We see each other now. He moves his left hand a little higher and I

take it. Clasp ing his fingers in my hand, I squeeze and say goodbye again. I walk out, peering back as I move into the lightness of the landing.

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This dissertation offers an ethnographic account of life for people with a brain tumour. It explores their understandings of disease and their attempts to secure treatment amid progressive and unpredictable bodily decline. It asks how these people negotiate changing relationships with families and cope with their own emotional struggle and self-doubt as the effects of the tumour manifest. It also examines how these people's lives are shaped by medical institutions and their changing formations of care. Above all, it is a study of navigation: it explores how people with a brain tumour imagine and enact trajectories for their lives under conditions of radical change—bodily and institutional—and how these trajectories must accommodate or resist the imminence of death. As such, this dissertation argues that medical decision-making is a distributed endeavour, fully comprehensible only through a consideration across multiple scales: the intimate debates of patients and families, hospital meetings and consultations, scientific fora, policy deliberations, and, ultimately, the invasion of tumour tissue.

From October 2014 to May 2016, I undertook ethnographic field research at a hospital I call *The Warner*—a publicly funded specialist hospital for the care and treatment of people with neurological disease in the UK. Over these eighteen months, I interviewed and spent time with sixteen people with a brain tumour to understand their lived experiences and approaches to medical decision-making. I worked intensively with thirteen of these people and their families as they attempted to understand their condition and plot trajectories for their lives. I observed their struggles as they unfolded over the course of disease, and I listened to their determinations, hopes, fears, doubts, justifications and disappointments as they grappled with treatment risk and benefit, weighed evidence, and contemplated the imperative to treat versus planning for a “good death.” I also worked intensively with healthcare professionals, observing routine practice across multiple settings including clinics, multidisciplinary team meetings, laboratories and radiology departments, and interviewing them about their work.

In the immediate weeks before Gabriel died, his sudden and rapid decline presented him and Cecilia with an onslaught of previously unthinkable dilemmas. They fought to keep up with the physical impacts of the disease's progression, which quickly affected Gabriel's

mobility and speech. They struggled to recognise stages in the disease's course and used a timetable Cecilia found online to make decisions about care—whether to undergo a scan or to continue with chemotherapy. When I visited them at home, they were besieged by the disruptions of the at-home care package, which, though it enabled Gabriel's preference to die at home, altered their lives fundamentally with the influx of new people and clinical technologies. These final weeks inspired new tactics for preserving privacy—blocking a video monitor, or feigning sleep—as Gabriel and Cecilia struggled to reconcile the intimacy of dying at home with the clinical rhythms of the care team.

Long before this, and for almost eight years, Gabriel contended with the severe and uncanny symptoms of seizures, visual disturbances, memory loss and difficulties speaking. He underwent multiple surgeries, treatments including chemotherapy and radiotherapy, which themselves exacted an extreme bodily toll. He and Cecilia often found themselves wracked by indecision amid a limited range of standard care options and the possibilities of private or experimental treatment, home or abroad. Mere weeks before Gabriel died they began to consult his doctors about access to clinical trials and second opinions for treatment alternatives.

I begin with observations about their experience because their story is particular, though not uncommon. There are many resonances with others presented throughout this dissertation. My account of Gabriel's last days illustrates that death is the inevitable end for most people diagnosed with a brain tumour and yet its timing and manner is unknowable. At stake was not simply the quality of Gabriel's death, but emotional and moral certainty: for him and Cecilia to know they did everything they could possibly do to delay death and allow Gabriel to live as well as possible up until his final moments. How did Gabriel get here? How did he and Cecilia decide to shift treatment in the palliative moment? What kinds of external pressure bore on Gabriel's decisions? What was it like to live with a disease that caused Gabriel to gradually lose his abilities to speak properly and make him unable to read? These are some of the questions I address in this dissertation.

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The people who I studied were affected by a range of brain tumours. Primary brain tumours—that is, tumours originating in the brain—are comparatively rare. They are not all considered to be cancerous, yet they are all potentially deadly and can cause major physical and cognitive disability. In any case, because brain tumours typically transform and become

more aggressive, so-called benign disease is often regarded by clinicians as “pre-cancerous.” It is estimated by the World Health Organisation’s International Agency for Research on Cancer that 296,851 people worldwide were diagnosed with cancer of the brain and central nervous system in 2018 (WHO 2018), though these figures are likely to be conservative given inconsistencies in cancer reporting. 11,432 new cases were registered in the UK in 2015 (Cancer Research UK 2018a). More than half of brain tumours diagnosed are cancerous and most of these are glioblastoma—a particularly aggressive form of the disease, which carries a “with treatment” prognosis of between 15 and 17 months (Liau et al. 2018). Less than one fifth of adults diagnosed with a brain cancer live beyond five years, regardless of its severity (Cancer Research UK 2018b).

Among cancers, brain tumours are a particular case. Because of their location in the brain, tumours frequently affect people’s personalities, speech, perception, memory, vision and movement. The people I met contended with these kinds of debility, yet what appeared most significant in their experiences was the fear that they would lose their sense of reality. Anticipated losses of perception and cognitive ability did much to disrupt patients’ understandings of themselves and their capacities for rational choice. Together with their families, patients worked hard to monitor their own mental conditions and to mend a sense of shared reality when they felt it at risk of being broken. Living with the anticipation of being unable to remember or speak, many improvised strategies, such as learning simple sign-language, or recording events in notebooks and drawings. Sometimes, however, these breaks were so overwhelming as to be irrevocable.

These statistics and descriptions of brain tumour symptoms set out the stakes facing patients and families after diagnosis. They also set the epidemiological terrain against which healthcare is imagined, commissioned and enacted. That brain tumours are rare is significant in how they are diagnosed. Most often people are diagnosed late and in Accident & Emergency settings (A&E) (National Cancer Intelligence Network 2016). A general practitioner (GP) in primary care might only see one case throughout his or her whole career and surveys suggest that over one third of people with a brain tumour see their GPs at least five times before diagnosis, as reported on The Brain Tumour Charity’s news page, in July 2016. During this period between the recognition of something untoward and the diagnosis of a brain tumour, patients might be given provisional and alternative diagnoses like stroke, migraine, visual or personality disturbances.

Research into brain tumours is historically and chronically underfunded. In 2014, brain tumours received just 1.5% (£7.7 million) of the £498 million UK national spend on

research into cancer, prompting experts to predict that “it could take 100 years to catch up with developments in other diseases” (House of Commons 2015; House of Commons 2016). Beyond deficits in funding, there is a lack of transferability of treatments developed in other cancers. This is mainly down to the specificity of the brain. The structure known as the blood-brain barrier—a diffusion tissue which prevents most compounds crossing from blood to brain—is commonly cited as a reason for the dearth of suitable treatments for brain tumours. There are only five chemotherapies commonly used in brain tumours. For comparison, there are more than fifteen commonly used in breast cancer.

During my fieldwork, a common refrain among both clinicians and patients was that treatment has changed little in 20 years. However, recent advances in molecular technologies might be starting to shift this moratorium (Louis et al. 2016). Described as a revolution in neuro-oncology, these innovations have stimulated a promising new research agenda and inspired both patients and professionals with new hopes for longer lives, freer of symptoms (Brandner and von Deimling 2015; Louis et al. 2014; Louis et al. 2016; Ritzmann, Grundy, and Rahman 2016; Thomas et al. 2017; Westphal and Lamszus 2011). A new manual for the diagnosis of brain tumours was published by the WHO in May 2016—my final month of fieldwork. In this, new molecular biomarkers were for the first time integrated in diagnostic practice and treatment prediction, making possible a previously unimaginable tailored approach to care. Clinical practice had already begun to shift at The Warner in late 2015 in anticipation of the manual’s publication. As I show in chapter 2, this had significant impacts on diagnostic routine and unanticipated downstream consequences for patients and oncologists. Immunotherapy trials were also being undertaken during my fieldwork and I heard patients with high-grade disease told that the benefits of these treatments could more than quadruple their life expectancies. Despite these promises, it is too early to determine the effectiveness of these technologies and their accessibility remains highly restricted (based on participation in clinical trials) and deeply contested.

Notwithstanding the low odds of treatment success and the significant debility associated with side effects, patients, families and clinicians continue to be seduced by the possibilities of biotechnology (DelVecchio Good 2001; DelVecchio Good 2007; Koenig 1988) and what has become a moral imperative of treatment over inaction (Kaufman 2005; Kaufman 2015). It is this imperative to intervene, combined with an impoverished range of treatments on offer, which makes experimental trials a key feature in the determinations of many patients. However, with the scarcity of trials places and the stringency of eligibility conditions, it is estimated that fewer than three percent of patients in the UK actually enter a

clinical trial; a figure much below other cancers (NCRI 2016). It is also perhaps one of the reasons why the benchmark of evidence might be lowered by regulators in their considerations over permissions for new therapies for brain tumours and their use in routine care, something I explore further in chapter 4.

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My ethnography brings into view the multiple temporalities of a constantly shifting terrain of disease, care and treatment. Rather than examining scientific innovation, diagnostic work, clinical consultations, and the “patient experience” in clinical and domestic spheres independently, I argue that the interactions between them are critical for understanding the condition of patients and the processes of medical decision-making. My focus on how patients rapidly change course and re-plot the trajectories of their lives amid embodied and technological change sheds light on the contingent and distributed nature of care. That is, the ways that different human and non-human actors (such as tumours) impose themselves with varying degrees of intensity at different times.

This broader perspective on the processes of knowledge production and decision-making moves the analysis beyond the binary of patient and clinician and brings other actors into play (Kaufman 2015). It deconstructs medical decisions, nuancing categories like “fact” and “value,” and reveals the imperatives which drive care. In my analysis of the “diagnostic fact,” for example, I show the many hands at work in its production, from radiologists, biomedical scientists, and pathologists, to neurologists, surgeons and oncologists, each of whom stand somewhere along the way, adding valence and, to greater or lesser extents, suggesting directions for treatment.

Bringing in a wider range of actors also helps to disrupt over-simplifications in the dichotomies of doctor paternalism and unchecked patient autonomy, and assumptions of a linear path of treatment. My ethnographic approach, which follows patients through institutional and domestic spheres of care, provides an account of the disjunctures between the institutional structures and ethical mandates of medicine and biology and the “local moral worlds” of patients and their families (Kleinman and Kleinman 1991; Kleinman 2006; Leonard and Ellen 2010). This acknowledges that disease unfolds both according to the metre of institutional time and through mundane domestic scenes (Kleinman 1995).

The research questions which guided my ethnographic investigation include: What networks of care emerge around brain tumours and how might these change in response to

new knowledge and political economies of care? How do patients understand treatment goals, risk, evidence, tolerability of symptom and side effect and how do these compare with the valuations of biomedicine? What kinds of lives do people envision for themselves after being diagnosed with a brain tumour? What kinds of constraint do patients encounter and how might they improvise ways around in their attempts to enact the trajectories they envision? How do the possibilities they envision interact with their bodies and the effects of disease?

CANCER NARRATIVES

With its place in the Euro-American imagination as the “emperor of all maladies,” cancer has attracted social science attention for more than forty years (McMullin 2016; Kerr et al. 2018). Yet it is really only in the last two decades that this attention has become significant and sustained, with cancer emerging as a key site of work on illness and the body. Anthropologists, sociologists and others have debated its multiple meanings and the social consequences of biomedical efforts to deal with it (Jain 2013; Lora-Wainwright 2013; McMullin and Weiner 2008).

Susan Sontag’s (1978) celebrated essay *Illness as Metaphor* set the terms of debate in much of the subsequent work on cancer by drawing out its pejorative metaphors and roles they played in making cancer a highly charged and stigmatised condition (Sontag 1978). Sontag named cancer the successor to tuberculous as the disease “that fills the role of an illness experienced as a ruthless, secret invasion” (1978:5), arguing that its characterisation as an evil and invisible predator did much to harm those afflicted with the condition¹. She further argued that cancer appeared as an affliction of the psychically repressed or else is the result of abnormal, chaotic growth, and therefore described in images that signify the negative behaviours of excessive consumption. These images, she argued, allowed for a set of discourses that prompted patients to be blamed for their disease: “Psychological theories of illness are a powerful means of placing the blame on the ill. Patients who are instructed that they have, unwittingly, caused their disease are also being made to feel that they have deserved it” (Sontag 1978:57).

Sontag’s essay is both a stinging critique of the abstraction of cancer experience and a rallying call to de-mythicise cancer of its especially de-moralising and imprecise images

¹ Reading metaphors for their temporal and spatial correlates, Sontag showed how cancer was marked as an *insidious, steady* and *implacable* threat to life, which *invades, infiltrates, creeps, spreads, diffuses* and *robs* people dying of cancer “of all capacities of self-transcendence, humiliated by fear and agony” (1978:17).

(Banerjee 2014; Lora-Wainwright 2013). Whether in attempts to free cancer of its troubling metaphors, supplant them with more empowering images, or trace cancer's many registers of meaning, this call has indeed been heard by subsequent generations of scholars and cancer activists, with wide reaching effects (for example, Banerjee 2014; Bell and Ristovski-Slijepcevic 2013; Hunt 1998; Jain 2013; Lora-Wainwright 2013; Ristovski-Slijepcevic and Bell 2014). Scientific theories of causation have also done much to displace earlier correlations of cancer with repressed emotions (Lora-Wainwright 2013). Diet, smoking, alcohol consumption, pollution, for example, have all been cited as causal factors—at least through the rubrics of epidemiology (Schottenfeld and Beebe-Dimmer 2005; Vineis, Illari, and Russo 2017). Genetic factors are also a key site of concern in cancer causation and new theories of “oncogenes” are doing much to shape ideas and practices in cancer diagnosis and prediction, relocating notions about causation and establishing new forms of sociality (Finkler 2005; Gibbon 2007; Gibbon 2008; Gibbon 2011; Gibbon 2013; Svendsen 2006).

Massive financial investment (Kerr et al. 2018) has shaped a very different biomedical terrain to that of the late 1970s when Sontag wrote *Illness as Metaphor*. With effective forms of treatment and management for many cancers, the intractability of disease and inevitability of death assumed in Sontag's analysis is no longer necessarily the case. These successes, while by no means consistent across cancers, have helped to inspire the hopes of patients, clinicians and publics, both in diseases for which effective treatment has arrived and those for which it remains elusive. This is not to suggest that cancer is no longer a stigmatised condition—far from it. It is rather that stigma and the moralising claims entailed take form against a very different social, biological and technical backdrop. The images and identities constitutive of cancer, and the possible futures available to many of those afflicted have therefore proliferated and include not simply identities and futures that are pejorative and desperate but those that can empower and inspire. Yet, given the correlates of these images in biomedicine and theories of causation which tie closely to the specifics of the body, they unfold very differently across different forms of cancer.

Unlike some other cancers, consensus around the cause of brain tumours is lacking (Philips et al. 2018). The only known cause is exposure to radiation, though the incidence of brain tumours caused by radiation is very small. Radiotherapy to the head therefore carries a risk of further tumours. There are no known links to behavioural factors and ideas about heritability are moot. This was clearly marked for me during fieldwork by the lack of origin stories patients had for their disease. Even when questioned directly, most patients would be unable to connect their disease to cause beyond the abstractions of fate or “Acts of God.”

Only Jamie, who we will meet further in chapter 3, offered a concrete account of cause: exposure to radiation caused by technologies like mobile phones. For Jamie, this origin story had a profound effect on his life. He moved out of the city and into a village, away from telephone masts, and dismantled the WiFi connection in his house. Each time mobile phones would be brought up in conversation, Jamie would tell me about SAR numbers, advise me to charge my phone in another room, and tell me that soon the story will break which will implicate mobile phone companies in a conspiracy to suppress the cancer risk they carry. For the rest of my respondents, however, the cause of their tumours remained mystifying. Without a known catalyst for their cancer, they also lived without some of the stigmas that can be associated with cancers of the lung, bladder, breast and liver. At the same time, however, the mystifying origins of and possibly surreal manifestations of a brain tumour (through personality disturbances, seizures or strange sensations called auras) do saddle those who are diagnosed with a brain tumour with a heightened sense of fear.

Many of these fears are intensified by social perceptions of brain tumours. As an unpredictable disease of the mind, it suggests that those affected might easily “lose themselves” or appear “weird” or “crazy” without self-awareness of these behaviours. Stories in the media do much to dramatise these concerns, depicting people with brain tumours as pathological, with unnerving symptoms. In a recent profile entitled *The Neuroscientist who lost her mind*, the Independent told the story of neuroscientist Barbara Lipska, who was diagnosed with a brain tumour in 2015. It quotes her as saying: “The tumours in my brain became inflamed, and it was this subsequent swelling that made me lose my mind. I was crazy for probably two months” (2 April 2018). The case of a man with a brain tumour arrested and sentenced to four years in prison for threatening women with a baseball bat made the press under headlines such as *Brain tumour survivor ‘wanted to kill blondes’*, (Daily Telegraph, 27 February 2018) and *Man with no previous convictions who became obsessed with wanting to kill blonde women following BRAIN TUMOUR surgery is jailed for four years* (MailOnline 26 February 2018, *capitals in original*). In these accounts, it is the image of a mass which appears full force—a mass which invades the brain and also the mind, assuming control of a persons’ thoughts, feelings and actions, often with malign intent and towards menacing ends.

Among clinical literatures and law, “mental capacity” is a term that refers to the ability to make decisions and is connected to the functioning of mind and brain. Those who lack capacity are “unable to make a decision for [themselves] in relation to the matter because of an impairment of, or a disturbance in the functioning of, the mind or brain” (Department of Health 2005:2.1). This might therefore include cognitive deficiencies

associated with comprehension, memory, analytical ability, and communication, commonly associated with brain tumours (Bernstein 2014). Mental capacity is defined in relation to particular situations, for example, the ability of a person to understand and engage in specific decisions about their care. The Mental Capacity Act (2005), for example, which provides the legal basis for the clinical management of individuals suspected of lacking capacity, differentiates between low-stakes decisions about what to wear or what to eat and high stakes decisions about whether to have surgery or move into a nursing home. Policy and guidance—for example, National Institute of Health and Care Excellence (NICE) recommendations on making decisions—therefore encourages routine assessment of capacity for those of suspicious mind and with pathologies known to affect the brain, and the use of established processes to legally record patients’ values and wishes in anticipation of further loss of capacity. These processes, not specific to neurological disease and often connected to end of life care, include Advance Care Planning, Lasting Powers of Attorney and Advance Decisions about care and treatment. However, these processes and capacity testing are reportedly rarely used by healthcare professionals (Bernstein 2014; Llewellyn et al. 2018).

Prominent advocacy groups, such as the Brain Tumour Charity in the UK and the National Society for Brain Tumours in the US, also define capacity as a key feature of brain tumours, more so than for other cancers. As the Brain Tumour Charity recently stated in their report *Losing Myself: The Reality of Life with a Brain Tumour*: “A fundamental difference between a brain tumour and a tumour in other parts of the body is the effect it can have on the mind and interaction with other people. Brain tumours frequently lead to the loss of the characteristics and faculties that make us who we are as individuals: personality, memories, cognition and the ability to communicate with others” (The Brain Tumour Charity 2015:4).

My account of people with a brain tumour focuses less on the clinical-legal modes of establishing capacity or what might fairly be described in such terms as a loss or lack of capacity. Rather, I note among my respondents the *fear* of losing capacity. As such, I discuss how the kinds of description detailed above bear on the lives of those with a brain tumour and how they understand themselves post-diagnosis. Early in my fieldwork, I met patients who had been turned blind by tumours, who had serious difficulty speaking, who could remember little beyond the simplest details of things, even forgetting the names of their families, who showed the excesses of hormones in enlarged facial features or a deepened voice, or who suffered such crushing headaches that they could barely raise their heads. Not all these afflictions affected the people with whom I had deeper engagements, though all had

suffered strange experiences like seizures and premonitory auras at one time or another. Grappling to situate their experiences, the people I met sometimes made desperate comparisons to diseases like Alzheimer's or to those in a vegetative state.

Many people were concerned about remaining reliable narrators and rational participants in the high-stakes care decisions ahead of them. They expressed worries that they were not making sense or that they had diverged from a reality they once shared with those around them. As I document in chapter 3, these concerns are produced through a nexus of sensation and diagnosis, the popular images described above, and the medical technologies that show patients their brains and the shapes of tumours therein. The intersection of these inputs with rationalist notions of autonomy and choice, contributes to deep self-doubt and even denial, as patients and families seek to reconcile their progression of the disease with practical decisions about treatment, care, and daily living.

CANCER CULTURES AND THE MEDICAL IMAGINARY

Recent scholarship usefully reminds us of cancer's sociality (McMullin 2016), marking out its distinct culture (DelVecchio Good 2001; Jain 2013; Lora-Wainwright 2010) and "carcinogenic relationships" (Livingston 2012:33). Julie Livingston, for example, writes how cancer happens *between people* and though it produces "moments and states of profound loneliness for patients, serious illness, pain, disfigurement, and even death are deeply social experiences" (2012:6). Across many geographic regions and forms of cancer, scholars show how living with cancer can produce new dependencies and how hopes are shared across networks of patients, families and clinicians (DelVecchio Good et al. 1990; Lora-Wainwright 2013; Mattingly 2010; Macdonald 2015).

No person I met during the course of my research was alone, but managed their disease as part of a family or community. They depended upon others who also depended upon them for practical and emotional support. The people I met also formed momentary or lasting patient-to-patient alliances, either via the prescribed networks of advocacy groups or online forums, or *ad hoc* in clinics. Sometimes they exchanged stories, encouraged each other through onerous treatment, or recommended articles on pioneering innovations in the long waits before appointments. Some met for meals, walks, exhibitions or did charity runs together. They attended funerals of other patients and made connections with their families. One person I met asked to be buried in the woods close to a friend she made on the ward who died two years earlier from the same tumour. I met two others who shared vials of an

unconventional treatment derived from essential oils and took it in turns to place orders for it from a laboratory in Italy. The connections and power of these peer-to-peer networks in rendering common experiences among people were staggering. They learned about disease and options for treatment together, hoped together, and shared sadness and disappointment. A key feature of these relationships was sharing the experiences that are unique to those with a brain tumour—auras, seizures and the feelings of being of another reality—things too abstract to be fully comprehended by most people. As I will show throughout this dissertation—and particularly in chapter 3—brain tumours, in affecting people’s minds and “capacities,” engender very particular kinds of sociality, placing awkward demands on patients and others as they grapple with discerning and mending a shared reality. By causing progressive debility, they also disrupt possibilities for intimacy between people, something I discuss more in chapter 5.

To confine the sociality of cancer to an analytic of care or intimacy, however, would be to obscure the many other relationships through which it is constituted. Arguing that cancer is more than simply an individual concern, S. Lochlann Jain emphasises the multiple permutations of cancer, suggesting we consider it—in Maussian terms—a “total social fact” (2013). Substituting “cancers” for the gift giving practices described by Mauss, she quotes:

These phenomena are at once legal, economic, religious, aesthetic, morphological and so on. [Cancers] are legal in that they concern individual and collective rights, organized and diffuse morality; they may be entirely obligatory, or subject simply to praise or disapproval. [Cancers] are at once political and domestic, being of interest both to classes and to clans and families. They are religious; they concern true religion, animism, magic and diffuse religious mentality. [Cancers] are economic, for the notions of value, utility, interest, luxury, wealth, acquisition, accumulation, consumption and liberal and sumptuous expenditure are all present (2013:13).

In her synoptic history of “cancer-in-action” (2013:7) that takes us through cancer’s metaphorical stand-in for anything scary or evil; the tobacco lobby and its curious links with progressive politics and activism; the deaths by cancer of the rich and famous; images of the autopsies of first world war soldiers killed by mustard gas and which led to the development of chemotherapy; the productive translational research between cancer and HIV/AIDS; and many other images, Jain thus draws out the many sites and practices through which cancer is constituted. She pays attention both to those that render cancer visible and those through which it is refracted and obscured. Cancer, she argues, has entered multiple domains and registers, not simply “an external threat to be battled” (Jain 2013:8), “a biological

phenomenon” (Jain 2013:14) or “a disease awaiting a cure,” but a “constitutive aspect of ... social life, economics, and science” (Jain 2013:4).

A crucial player here is the pharmaceutical industry and the multibillion dollar cancer industry, which comprises not just the obvious income generators of treatment and pharmaceuticals, but insurance, law, and research. Government and third sector spending on cancer is staggering. In the UK in 2012, cancer drew almost two thirds of medical research spending among four common conditions (cancer, coronary heart disease, dementia, and stroke) from governmental and charity organisations (Luengo-Fernandez, Leal, and Gray 2015). In 2016, a total \$5.2 billion was allocated to the United States National Cancer Institute (NCI), part of the national medical research agency the National Institutes of Health (NIH), comprising over 16 per cent of the US congress budget for all NIH activities (Kerr et al. 2018). According to IQVIA Institute for Human Data Science’s 2018 report *Global Oncology Trends 2018: Innovation, Expansion and Disruption*, global spending on cancer medications exceeded \$133 billion in 2017 and is expected to rise to \$180-200 billion in the next 5 years. While brain tumours receive a fraction of this spending, care and treatment is similarly configured according to financial imperatives. As I discuss further in chapter 4, financial imperatives operate with blunt force, exerting considerable influence on how care is evidenced, commissioned and accessed.

As Michael Fischer and others argue, “it is increasingly artificial to speak of local perspectives in isolation from [the] global system ... the world historical political economy” (Fischer 1991:526; Marcus and Fischer 1999; Petryna 2009). With its transnational networks of knowledge production, technology, markets and clinical regulation, not to mention the flows of patients in search of therapies, cancer is a prime example of this claim. This is not to say that biomedicine and clinical practice are not locally situated—recent work demonstrates how they most certainly are (Mol and Berg 1998; Livingston 2012; Street and Coleman 2012; Street 2014)—it is rather to assert that local meanings and social arrangements are always “‘transnational’ in character ... overlaid by global standards and technologies in nearly all aspects of local biomedicine” (DelVecchio Good 2007:385).

This was most certainly the case for the “brain tumour world” I saw in action at The Warner. Most notably, were the changing standards of diagnosis and experimental treatments, shaped by international consensus (Louis et al. 2014) and a global pharmaceutical industry which ran clinical trials across national borders. The local availability of staff, expertise and technologies are crucial to if, how, and when these get embedded and I learned there was significant variance between hospitals even within the same geographic locality.

When it came to establishing the molecular character of a tumour or its sensitivity to chemotherapy agents, for example, I was told decisions came down to whether a hospital had a means of doing molecular tests or at least access via another institution. The Warner, for example, will conduct analysis on tissue specimens for certain local institutions lacking means to do analysis themselves. This is largely due to the management of high costs associated with molecular analysis: by having fewer specialist centres to run tests for several hospitals, commissioners can save in the economies of scale that lie therein. When it came to experimental trials, I was told that portfolios were as much contingent on the curiosities and contacts of clinicians as on the availability of patients and dedicated personnel. Repeatedly, I heard patients told that there was nothing with proven benefit to the treatment of brain tumours that is not available at The Warner. Yet, what proven benefit means, and for whom, are very different things, as I show in chapter 4 through an analysis of a controversial treatment called *Avastin*.

The patients I met were wise to these differences and themselves developed ways of interpreting evidence. The disparate configurations of care—regionally and internationally—led a number of them to travel abroad or seek ways of getting treatment unavailable to them through The Warner. One patient—John—for example, recruited his local Member of Parliament to help argue his case to NHS England’s commissioning body after it ruled that his tumour was ineligible for a cutting-edge radiotherapy clinically recommended to him.² While he waited through unsuccessful appeals to the commission, he contemplated seeking the treatment abroad, collating scans from The Warner and sending them to centres in Spain and the Czech Republic. A key aspect of this dissertation, then, is how patients imagine and navigate terrains of care that extend far beyond the bounds of The Warner.

Medical anthropologist Mary-Jo DelVecchio Good cites hope as a binding sentiment that unites national and transnational actors in bioscience, biotechnology and society in their pursuit of new interventions. Hope, technological advancement, and the draw of financial interests are entwined in what she calls the *biotechnical embrace* (DelVecchio Good 2001; DelVecchio Good 2007). This entanglement is part of a *medical imaginary*: a concept which refers to the collectively imagined ideas and possibilities which galvanize medical innovation

² In separate consultations, John’s surgeon and oncologist had recommended ‘Gamma Knife’. Developed by surgeons in Stockholm in the 1960s and introduced to the UK in the early 1980s, Gamma Knife is sold by its marketers to replace the surgeon’s knife with multiple beams of radiation targeted to a specific area. As of August 2016, Gamma Knife became a routine option in the UK for people with haemangioblastomas, like John. The NHS England Specialised Services Clinical Reference Group for Stereotactic radiosurgery cited limited but sufficient evidence for its use. I have written about John’s case previously; see Llewellyn et al 2017.

and generate “constantly emerging regimes of truth in medical science” (DelVecchio Good 2001; Marcus 1995:3). Those living with disease are especially susceptible to the new hopes engendered by medicine’s imagination, however distant these hopes may be (DelVecchio Good 2001; Novas 2006). Patients and publics invest not just financially but emotionally with an “enthusiasm for medicine’s possibilities [arising] not necessarily from material products with therapeutic efficacy but through the production of ideas, with potential although not yet proven therapeutic efficacy” (2001:397).

In her ethnography of the increasingly decentralised nature and geographical spread of clinical trials, Adriana Petryna shows how trials are no longer regarded simply as hypothesis-testing instruments but “operative environments that redistribute public health resources and occasion new and often tense medical and social fields” (Petryna 2009:30). As such they become key means of treatment for many cancer patients reflected in demands for greater access to innovation (Biehl and Petryna 2011; Gibbon 2015; Keating and Cambrosio 2012; Kerr and Cunningham-Burley 2015). This is very much the case in brain tumours, where calls for greater access to clinical trials are increasingly made alongside attempts to embed the experimental as a universally available treatment option (Rhee et al. 2014; The Brain Tumour Charity 2015b). On one hand, this reinforces a collective sense of the possible (Novas 2006) giving access to treatments for a disease for which there is, frankly, little expectation of cure. Yet, on the other, it sets up a number of tensions in definitions of care and evidence-based practice, which I further describe in chapter 4.

Cancer is therefore not solely an individual experience but a complex arrangement of people, institutions, ideas and technologies, fastened in narrative, and in affective and financial bonds. Though patients are embedded in its imaginary, their experience is not simply determined by it. Rather, as I show throughout this dissertation, they interact with, resist, and navigate its dynamic social terrain.

NAVIGATING BRAIN TUMOURS, CARE AND TREATMENT

There is no avoiding the tragedy of a brain tumour diagnosis and the near inevitable possibility of death it foretells. And yet I watched how people with a brain tumour made extraordinary lives for themselves, approaching their disease and the burden of treatment with stoicism, humour and, ultimately, hope. They improvised new routes beyond institutional protocols and created new choices amid constantly shifting terrains of disease, care and treatment. While sometimes patients disagreed outright with clinical calculations of

risk, tolerability of symptom or side effects, at other times their complaints concerned the quality of evidence or medical opinion. Their actions often entailed a quiet protest against the “conventional”³ goals of standard care, seeking instead the more radical possibilities of a cure engendered by the medical imaginary.

...

To capture the tactical moves of people grappling with progressive and unpredictable disease, I deploy an analytic of navigation. I take my point of departure in Henrik Vigh’s work on social navigation (Vigh 2007; Vigh 2009). Vigh writes against ideas of gradual change which are often implied in analyses of social structure⁴, instead drawing our attention to the inherent fluidity of “structure.” Rather than focus simply on *how social formations move and change over time* or *how individuals move within their social environments at a fixed point in time*, he argues for the interactivity between the two. His concept of social navigation refers to “motion within motion” and captures “the act of moving through an environment that is wavering and unsettled” (2009:420). In Vigh’s words: “[W]e organize ourselves and act in relation to the interplay of the social forces and pressures that surround us ... social navigation designates the practice of moving within a moving environment” (2009:425).

The analytic offers a useful perspective on medical decision-making by accounting both for people’s movements through care *and* the changeable nature of biomedical formations and treatment options. These changes in the availability of treatment options might be due to changes in funding patterns or organisational structure, the start or close of a clinical trial, or, as I witnessed during my fieldwork, major scientific innovation and the redefinition of diagnostic parameters. While these changes work over different temporal rhythms and may be more or less predictable or obscure to clinicians, they are typically experienced by patients as extremely sudden and rapid. The analytic therefore captures the interactivity between patients’ movements within the social and structural formations of care and the changes inherent in these formations.

An analytic of social navigation also draws attention to the need for agents to be “flexible” or “preadaptive” in relation to “the dangers and possibilities of one’s present position as well as the process of plotting and attempting to actualize routes into an

³ Used by some patients to denote what they considered the prosaic or unremarkable quality of standard care.

⁴ Vigh specifically places his theoretical work in counterpoint to Bourdieu (1992), Goffman (1959) and Giddens (1984) who he argues take the foundational stability of our ground (or fields, arenas, structures) of enactment for given.

uncertain and changeable future” (2009:425). That is, actors move in the here and now as well as in relation to goals and prospective positions. Practices of plotting and actualising plotted trajectories operate in the present as well as in expectation of change.

A diagnosis of progressive and unpredictable disease recasts perceptions of the future and establishes in the present a peculiar sense of imminence—a future foretold in the statistical rubrics of prognosis yet unknown, since rubrics often fail to reliably map onto the real-world situations of people. It establishes what S. Lochlann Jain has called the condition of “living in prognosis”—a disorienting condition of severance in which we are cleaved from the ordinary ideas of a timeline and the typical ways we position ourselves in time—age, generation and life stage (2013). As Jain insightfully states: “Cancer exists in nonsensical time, and living in prognosis challenges individuals and institutions alike to conform to its hourglass. When one’s time is potentially limited, it takes on extra significance” (2013:103). The social goals and prospective positions hitherto taken-for-granted and placed in the ordinary structures of time or life course are suddenly and brutally disrupted⁵. This was painfully revealed to me through the ruminations of the people I met—Will I live to see my daughters graduate university? Will I live to see my grandson married? Will I live to see my niece born? Will I live long enough to make the trip we planned?

At the same time, patients, families and clinicians are informed by the technological ambitions offered through the medical imaginary. On the one hand, this imaginary drives an imperative to intervene in the destructive course of disease by the means currently available. On the other, it furthers future-oriented expectations for a possible cure. To live long enough for the next “magic bullet” treatment to arrive is often a key aim for care. And, if one is to go by the sensational headlines liberally scattered in the media and online forums, this “magic bullet” is always on the cusp of its arrival.

These investments in biotechnology and the looming presence of disease progression and death prime people’s hopes and fears and thus complicate their goals and prospective positions. Nowhere is this more poignant than at the grey zone between

⁵ See also Michael Bury on biographical disruption who similarly drew attention to the contingent and fragile nature of (embodied) existence, and the possibility of death, normally only seen as distant possibilities or the plight of others. Working with people with rheumatoid arthritis, Bury posited that expectations and future plans are de-stabilised and must be re-examined within the constraints of illness. These experiences culminate in “marking a biographical shift from a perceived normal trajectory through relatively predictable chronological steps, to one fundamentally abnormal and inwardly damaging” (Bury 1982:171).

treatable disease and irreversible disease progression, for here, are the high stakes choices between life-prolonging treatment and the preparation for death alongside a palliative approach to care.

Indeed, the changing body is perhaps the most radical of destabilising factors in the shifting terrains of treatment and care. To capture the particular instability of living and making decisions amid disease progression, I elaborate Vigh's original formulation to account *for the body* as yet another site in motion. My ethnography traces the effects of rapid bodily change and how it bears upon the plotting of trajectories and approaches towards decision-making. While the bodies of those with a brain tumour change through the build-up of pressure or complications of tumours which "infiltrate" the brain, they also change because of intervention. Chemotherapy, for example, depletes white and red blood cells complicating immunity and blood-clotting; radiation can cause further malignancy; surgery can weaken healthy tissue and damage blood vessels. Regarding clinical trials, the bodies of patients who have undergone treatments considered outside the standard logic of care are perceived by clinicians and trial practitioners as corrupted. Patients are deemed ineligible for standard treatments or experimental trials for the reasons that their bodies would not tolerate the side effects of treatments, that disease is considered no longer amenable to the effects of treatment, or that their bodies were not "treatment naïve"—the hypothetical zero point implied by measures of clinical difference to determine the treatment effect of experimental drugs.

The theory of navigation I propose in this dissertation thus attends to the interactivity between three main vectors—patients' agencies, the social and structural formations of care and treatment, and the diseased body. It therefore allows a broader and far more dynamic analysis of power and decision-making than hitherto offered by social scientific accounts of medical decision-making, which have tended either to focus on patients' agencies within a relatively static landscape of care or attempted to understand major structural change in the organisation of care. In conceptualising my approach, I attend to four main features. I consider *major scientific innovation* in brain tumour diagnosis and treatment, which is causing significant consternation among oncologists and others by changing patients' specific diagnoses, the relations between previous ways of knowing, and the treatment equations on which decisions are based. I consider how *experimental trials* feature in the lives of patients, how they open and close with sudden finality and how patients are excluded for what they consider obscure reasons. I consider the body and the unpredictable nature of *tumour progression* and the strange condition of being a person with a

brain tumour, whose diagnosis and experiences of uncanny feelings produces what I call a *subjectivity of negation*—a paradoxical displacement of self, characterised by spiralling frustration, anxiety and self-doubt and manifested in a serious questioning of one’s own rationality and conception of reality.

OUTLINE OF THE DISSERTATION

I present a more or less chronological account of life for people with a brain tumour which helps to evoke the experience of a progressive ordering of reality (Ingold 2007; Vigh 2007). I begin at diagnosis and move towards tumour progression and the ends of life. Following a short chapter on methodology, chapters are therefore arranged by themes related to power and contingency, which together shaped patients’ lives and their peregrinations through disease, care and treatment. Each chapter also focuses on a particular topical theme or arena of experience and foregrounds a particular type of actor in the field of neuro-oncology. The dissertation can therefore be read as a chronological, thematic, or theoretical account of brain tumours, always with people at the centre of analysis.

Methodology—details the methodological and analytical approach of my ethnography of care and treatment for people living with brain tumours. Situating my work as a form of hospital ethnography, I describe my field setting and its permeable borders, my attention to change and navigation, and make the case for empathy in a participatory approach to the study of lives *in extremis*. All the while, I take ethnography to be more than a method or toolbox, comprising both an epistemological orientation and embodied practice.

Chapter 1—*Diagnosis and Pathways*—examines the practices of diagnosis in action and the production of “care pathways.” I argue, following a navigational focus, that the diagnostic moment constitutes a *fixing of the terrain* of disease. I emphasise the ways in which modern medicine attempts to contain uncertainty and instability to enable intervention in the course of disease. Diagnosis makes disease navigable from the perspective of clinicians and patients by constituting a fixed terrain—or landscape—over which pathways can be routed. Yet, it is not a neutral terrain and the stability of diagnosis is only illusory. I argue that the production of a care pathways concretizes values concerning treatment goals, evaluation of risk, evidence and tolerability of symptom and side effects, which patients are expected to follow. The chapter therefore takes a critical approach to the “diagnostic fact” and shows

how facts and values are not as self-evident as claimed by biomedicine and healthcare policy.⁶ Chapter 1 also provides important exposition by mapping the sites of diagnosis like laboratories, so important to the direction of care, yet so often obscured from view. The key actors of this chapter are clinicians and biomedical scientists.

Chapter 2—*The molecular turn*—explores the initial social consequences of recent shifts in how brain tumours are conceptualised vis-a-vis molecular information. These shifts have challenged previously existing diagnostic techniques and are radically reshaping how care and treatment for people with a brain tumour is imagined. Drawing more fully on the concept of the medical imaginary, I trace how this turn has contributed to a promising new research agenda around personalised treatments, which is inspiring researchers and clinicians with renewed enthusiasm for the future and furnishing patients' hopes for longer lives free of pernicious symptoms. I also attend to the uncertainties given in this turn and the dilemmas it raises for clinicians and patients.

Chapter 3—*Spectre of a Mass*—addresses the affective dimensions of a brain tumour diagnosis. I focus on how patients' understandings of themselves are mediated through the notion of a disease of the mind and the uncanny experiences of symptoms like seizures and auras. I propose the analytic term *subjectivity of negation* to refer to the doubts patients harbour about their ability to make rational decisions about care and treatment.

Chapter 4—*The production and regulation of possibility*—explores the production of possibilities for intervention through experimental treatments. I begin with an analysis of patient and clinician accounts of experimental treatments and how they are narrativised in terms of “the cutting edge” or “salvage treatment.” Focusing on several trials underway in The Warner during fieldwork, I show the vagaries of opportunity for patients to gain places on a trial and the efforts they undertake to secure what they consider their right to the best available treatments. An examination of the case of a controversial treatment called Avastin brings together an analysis of biotech, drug regulation, patient advocacy, patients and clinicians, and the enduring possibilities of treatments which lack evidence.

Chapter 5—*Disease progression*—examines the nature of changing disease and transitions into the phase of care termed “end of life.” I describe the clinical terms of tumour progression and offer a conceptualisation of progression in social terms which goes beyond its usual biological characterisation. As such, I bring critical focus to notions of

⁶ See for example “shared decision-making”—a policy commitment and taught practice in healthcare which splits clinicians—as bearers of facts such as diagnosis—and patients—as bearers for values consistent with their life situations—designating roles and responsibilities accordingly. The shared decision is given in the interaction between these facts and values (Charles, Gafni, and Whelan 1999).

reversible and irreversible disease, the lived experience of imminent yet unknowable death, and the decisions—small and large—which constitute acquiescence or resistance to an underlying biological reality. I then focus on the moral dilemmas of families in caring for patients, situating these dilemmas in the capricious and continually unfolding terrain of disease and care.

In my conclusion—*Navigating brain tumours*—I draw together the experiences presented throughout into a theoretical account of navigation for people with a brain tumour. I argue for the need to take into account the “motion within motion” inherent in navigational praxis and hence the importance of considering the interactivity between patients’ agencies, the social and structural formations of care and treatment, and the diseased body in decision-making about care and treatment.

METHODOLOGY

In early conversations with my clinician collaborators, they suggested I study what they called “choice heavy points of the care pathway.” For a study on choice, as it was originally conceived, this seemed eminently sensible—focus on the forks in the road. I was concerned, however, that such concentration would miss much of what constitutes decision-making practices and indeed the temporal quality of the points themselves. If conceived in this way, decisions become confined to discreet moments—temporally located at points like diagnosis or disease progression, spatially situated in the consultation room, and socially configured in the relationship between patient and doctor. The lives and idiosyncracies of patients, those of doctors, the whole infrastructure of the hospital, the political economy in which it is set, and the things leading up to and away from those moments—things which have enormous bearing on their constitution—get lost.

Moreover, as I would later find, “choice heavy points” implies a sense of certainty inimical to the actual experiences of patients and practices of care. This motivated me to take a more expansive ethnographic approach which included a broader cross-section of spaces in the hospital—the laboratory, radiology department, clinic and so on—as well as in the domestic space of the home. It also entailed gathering data from a broader set of actors across multiple domains, including medical and scientific literatures, regulatory meetings and policy. By placing these multiple accounts in the same analytical space, my goal has been to provide an overall more dynamic and complex perspective than would have been possible had I collected data simply on the choice heavy points of the pathway and remained spatially bound to the clinic room. Moreover, by following the lives of a group of patients as they unfolded, I was able to glimpse how moments came into being and passed away, and especially how circumstances, which appeared intractable at the time, were not always inevitable (Biehl and Locke 2017).

These concerns motivated my ethnography of care and treatment for people living with brain tumours. In this short methodological chapter, I situate my work as a form of hospital ethnography, describe my field setting and its permeable borders, and make the case for empathy in a participatory approach to the study of lives *in extremis*.

THE WARNER HOSPITAL

The Warner Hospital is a tertiary care hospital funded by the UK National Health Service. It houses a specialist unit dedicated to the care and treatment of people with a brain tumour. This unit comprises a large neurosurgical team, neuro-oncology, neurology, neuropathology, neuroradiology and a whole gamut of care designated as “supportive” or “palliative,” and which is involved in counselling, rehabilitation and making adaptations to patients’ lives through, for example, manipulating their routines and the infrastructure of their homes. Not all of these services are dedicated solely to people with a brain tumour and within the team, professionals might have expertise in conditions like epilepsy or stroke, or techniques like deep brain stimulation.

While The Warner is publicly funded through the NHS, the hospital and brain tumour unit also receives endowments from private donors, most of whom have somehow been affected by brain tumours, and charities which have a specific cancer remit. Private patients also receive care here and though they are marked out from NHS patients by being privileged in terms of waiting times, facilities and access to treatments beyond “standard care,” they encounter the same practitioners and similar options of treatment. While private care is not of major interest in this dissertation, a number of patients I followed had private healthcare insurance. At times patients sought treatments through these policies or else found other ways to pay privately for care. In other words, a number of patients moved tactically between private and public modes of care so as to plot a course through disease, care and treatment they thought best. This might mean getting standard treatment sooner or experimental treatment outside a clinical trial.

As with many hospitals across the UK, The Warner constantly outstrips its 19th Century foundations. Behind its redbrick facade lie hi-tech treatment suites and glass-faced corridors (Starr 1982; van der Geest and Finkler 2004). With growing demand for its services, new rooms, wards and offices punch through its walls and up through the sky. The hospital is a peculiar bricolage; a testament to the episodic nature of medical progress and population swells over the past 150 years (Keating and Cambrosio 2003; Prior 1988). Major architectural changes were underway during my fieldwork in preparation for an increased oncology caseload: polythene wrapping and steel scaffolds hid the construction of state of the art surgical theatres, management offices and bigger wards, and patient appointments were sometimes re-routed to accommodate the works. The history of the Warner is further read on the wood-panelled walls of winding staircases from which 19th Century architectural plans hang alongside tall oil paintings depicting the late pioneers of neuroanatomy and brain

surgery. It is hard to mistake The Warner as anything but an elite institution with its own illustrious history.

The Warner is embedded in a larger local network of care sites, including a large general hospital and a specialised cancer centre. It also has service level agreements with international centres across the world meaning that some patients are given the industry standard even though the treatment is not available in the UK. This is often paid in part or fully by the NHS. There are other sites such as local hospitals and hospices which will become apparent through patients' accounts of care.

As a national and international referral centre, The Warner receives more than 700 brain tumour referrals annually from around the country, Europe and beyond. This figure is rising due to organisational changes across regional cancer services. It is highly active in research and many of its staff are leading experts in the field of neuro-oncology, contributing knowledge through basic and applied science and the formation of international standards and regulation for diagnosis and treatment. The Warner is therefore particular in being among a group of elite institutions in the UK with significant resources dedicated to research and clinical practice and espousing an approach to care and treatment which is “above” the standard and “ahead” of other sites of care in the UK. Very often, I heard doctors say to patients things like “there is no evidence-based treatment anywhere else in the world that we don't have available in this hospital or in the UK.” These kinds of statements also fill brochures and articulate its online presence. It is common in being administered through the broad structures of the NHS, subject to its changing bureaucracies and budgets, and located in the dominant frameworks of Western biomedicine. It is common by its participation in ever present calls to modernise according to shifting public concerns about patient choice and personalised treatments.

By participating in the lives of patients, families and clinicians as they underwent care and treatment, I engaged with a form of hospital-based ethnography. Much has been written about this situated mode of ethnographic engagement, not least how best to characterise hospitals as field sites (Street and Coleman 2012; van der Geest and Finkler 2004). Following recent formulations, I theorise The Warner as a core biomedical institution which is not simply an “island” separate from society (Caudill 1958; Goffman 1961), nor “mainland,” which directly reflects or continues it (Quirk, Lelliott, and Seale 2006), but simultaneously both. In this formulation, we see the particular social orders and conventions of biomedicine, the geographical and physical isolation of the hospital, yet also how it is made permeable in the flows of people and things, the short stays of patients, and the

extension of hospital staff responsibilities beyond the confines of the ward (Kaufman 2005; Quirk, Lelliott, and Seale 2006; Tanassi 2004; Vermeulen 2004; Zaman 2004). We see how hospitals are “necessarily constituted by multiple concurrent orderings of space” (Street and Coleman 2012:8): simultaneously open and bounded, familiar and strange; spaces that are both highly regulated, standardised and ordered by biomedicine and the bureaucracies that align disparate groups of people, technology, diagnosis and treatment, and adaptive to the complex and unpredictable “real world” of disease and the body.

CHARTING LIVES UNDER CONDITIONS OF CHANGE

In the introduction of their recent edited volume, anthropologists Biehl and Locke highlight the importance of ethnographies which are attuned to the “open-endedness of people’s becomings” (Biehl and Locke 2017:IX). They advocate an “ethnographic sensorium,” which foregrounds an analytical focus on “unfinishedness” and calls attention “to the plethora of existential struggles, improvisations, ideas, and landscapes that shape what life means and how it is experienced and imagined in splintering and pluralizing presents” (2017:5). This focus is extremely useful in understanding the experiences of people with cancer and other progressive and often incurable diseases. On the one hand, those who are dying face their becomings as located in the interstices of multiple temporalities of failing bodies, biomedical innovations, and institutional routines. These, in turn, operate as distinct-and-yet-related currents continually ushering forth new possibilities with new stakes. On the other hand, a focus on becoming provides a useful lens through which it is possible to view the nature of ethnographic work and the improvisations we must make as ethnographers when called upon to reimagine and enact new kinds of relationships with our interlocutors.

From October 2014 to May 2016, I was given access for the purposes of research to The Warner Hospital’s clinics and wards, chemotherapy and radiotherapy treatment suites, waiting areas, operating theatres, hospital laboratories, radiology departments and other sites of work, described in detail later. In 2012, I had conducted an earlier piece of research at the hospital and it was then that I sketched the faint lines of my PhD and developed an interest in the experiences of people with a brain tumour. However, this earlier project on advance care plans had focused on clinicians and lacked any patient input. The connections I made then helped me gain access for a larger scale ethnography and one surgeon in particular made my entry smooth by convincing others of the projects’ merits.

I gained formal access via the customary bureaucratic routes for all research, signed honorary contracts with the hospital, undertook good clinical practice refresher training, submitted lengthy applications and attended meetings for research ethics approval by the NHS. Ethical permissions were granted by London-Harrow Research Ethics Committee for 14-months in October 2014 and were subsequently extended allowing me to follow-up with some patients and clinicians at The Warner. A senior clinician at The Warner was appointed Principal Investigator and became an important advocate for the research on-site.

In my approved research protocol, I detailed procedures for recruiting patients, a process which entailed first contact by a clinician at The Warner, who would explain the study simply to patients and ask their permission to be seen by me one-to-one. I was introduced to these people variously as “a PhD student,” “our PhD student,” “a researcher,” “our researcher” and as someone interested in the care and treatment of people with a brain tumour and the process of decision-making. When I subsequently saw patients, I would explain the study to them in more detail and give them an ethics-committee approved participant information sheet for them to read. Several days later I would telephone them to inquire about their participation. I also detailed procedures for gaining the written informed consent of people participating in the study and how I would manage issues of mental capacity, which I detail further in chapter 3. Written consent was taken at a subsequent meeting with patients. I followed similar approved processes for family members who I approached directly with patients’ permissions. To recruit clinicians, the Principal Investigator first emailed members of the clinical team *en masse* to notify them of the study and my presence as a researcher. After several weeks of introductions, which included my presentation to the multidisciplinary team at The Warner, I became a familiar figure at various hospital meetings and could approach clinicians directly. Again, I used information sheets and sought their written consent to be interviewed and observed.

As the course of fieldwork unfolded, I undertook multiple strategies through which to observe routine care and ask questions about it. I undertook long-term participant-observation with sixteen people with a brain tumour and their families, who consented to the study, talking to them informally and during audiotaped interviews. First interviews were always semi-structured, as I took illness histories, asking them about diagnosis, what led up to it, their first encounters with medical institutions, and early decisions. Follow-up interviews were un-structured and responsive to what was happening for patients in the moment. I asked them about daily life, their hopes, aspirations, apprehensions, dilemmas and decisions, and we would discuss how things might change between our meetings. I also

accompanied patients to their clinical appointments as they met with surgeons, oncologists, neurologists, nurses and others to get clinical tests, discuss test results and treatment options, clinical trials, and receive various forms of standard and experimental treatments. I developed more involved relationships with thirteen of these patients and members of their families. As these relationships transpired during fieldwork, I was invited more and more into their lives and homes. I spent time with them at restaurants and cafés. We sometimes travelled together on foot, via public or private transport, through the city or their local neighbourhoods to make their appointments at the Warner, for example, or simply to find places to eat and talk. I also attended community meetings with patients—such as group meditations—or tended their gardens with them on sunny days. These interactions became analytically important, by extending my perspectives on their lives and revealing the subtleties of their conditions as lived day to day.

These sixteen people were aged between 32 and 70 years old, when I first met them. Most were in their forties and fifties, and most had been diagnosed with glioblastoma tumours very recently. Three patients had confirmed noncancerous tumours, though for one of these patients, her low-grade tumour crossed the threshold and “transformed” into one which was cancerous. One other was diagnosed with radiological scans and not with a tissue diagnosis—regarded as the diagnostic gold standard, as I further describe in chapter one. Though initially thought “high grade” and therefore cancerous by clinicians, her unusually positive response to treatment had them question this designation. Nine of the sixteen were women.

I also spent time with hospital staff outside the company of patients as they planned care, interpreted brain scans or slices of tumour tissue under a microscope, participated in multidisciplinary team meetings, or attended to miscellaneous administrative tasks. I attended public meetings and conferences about oncology and palliative care research, policy and practice. This meant moving between spaces like consultation rooms, the laboratory, the radiology department, and lecture theatres. In addition to numerous informal conversations, I conducted fifteen formal interviews with clinicians about their daily work and what future they saw lie ahead for the care of people with a brain tumour. I supplemented these with fifteen I had collected in 2012 as part of another research study, for which I was given permission to use by Dr Joe Low (Llewellyn et al. 2018).

While I had originally planned to spend 12-months in the field, I extended this by six months in order to better understand some of the social consequences of newly integrated molecular parameters in diagnosis, which were becoming a significant determinant in

treatment decisions. As well as spending more time in the laboratory with pathologists to understand the new practices entailed in diagnostic work, I made a more focused effort to trace how molecular data impacted the clinical teams working with patients. During these six months, I continued my engagements with patients with whom I had already met.

Overall, I spent many hundreds of hours observing and recording my observations in detailed field notes, which I typed up in longer narrative form soon after. I also collected fifty-two interviews with patients which I either transcribed verbatim myself or contracted to professional transcribers. I met and interviewed patients on multiple occasions allowing me to observe the changes in their daily lives, their experiences of disease, and their thoughts on care and treatment. The timing of these interviews was more or less *ad hoc*, according to the preferences of my respondents. Sometimes they would happen after a key event like tumour progression or the start of treatment and sometimes simply during the downtime between patients getting a blood test and seeing the consultant. Often, but not always, family members would be present during these interviews and would interject with important details. Conducting interviews with patients and families would do much to conceal as well as shed light on their shared understandings and emotional load. I found that accounts might differ between patients alone and in the company of another, but also how they stayed constant. An important analytical insight gleaned in joint interviews concerned patient-family relations and I resolved to be attentive to these dynamics and ask direct questions about the confluence of experience or the memory of events, when appropriate. I also conducted several one-to-one interviews with family members.

My interest in the nature and differing interpretations of evidence and shifting knowledge also took me to the neuro-oncology “evidence-base”—the thousands of articles which directly inform care. Sometimes I was given articles to read by patients (see chapter 4). John, for example, a fifty-two-year-old man with a low-grade tumour handed me a dossier at our first meeting which contained scientific articles and minutes from a national task force to establish eligibility conditions for Gamma Knife radiosurgery. He had compiled this in the hope of contesting a national regulatory committee ruling which had denied him the treatment which had been recommended to him by clinicians at The Warner. Clinicians also directed me to articles they or their colleagues had written—those foundational to current practice and those suggestive of change, such as the molecular diagnosis and personalised medicine (see chapter 2). While tracing the controversial decision to make Avastin available in the US and how this linked to the aspirations of UK patients, I also found verbatim transcripts from FDA meetings and investor reports from pharmaceutical

companies (see chapter 4). Healthcare policy was also a key data source given my interest in NHS care commissioning. While I do not read these from the expert position of a clinician, bioscientist, or care commissioner, and have little basis from which to appraise the scientific quality of these articles, they are useful as a source of data. Following scholars investigating the social consequences of science, technology and innovation, such as Adriana Petryna (Petryna 2002; Petryna 2009) or Sheila Jasanoff (Jasanoff 2004; Jasanoff and Kim 2013), I am interested foremost in what these articles and commentaries reveal about the social, political, ethical, and financial commitments built into research and innovation and how they are used by patients as a key technology to perform scientific literacy, communicate (usually off standard) treatment options to clinicians, or as sources of information that inspire their own hopes.

PARTICIPATING IN THE LIVES OF THOSE *IN EXTREMIS*

Fieldwork with people in the midst of an unpredictable and emotionally laden disease involves a complex and variable balance between being systematic and open to the serendipity of events. It also means being acutely sensitive to the sensibilities and practices of patients, families, and clinicians, ever conscious of imposing the formality of research and disrupting tense or precious moments. In practice, this meant following up observations and accounts as best I could, triangulating what I saw and heard with different people, tracing situations and conversations as they unfolded over weeks and months, and making connections within people's accounts as they too evolved through experience. Sometimes it meant stepping back, not demanding people's time and being absent from the action; at other times, it meant switching off the audiorecorder or keeping my notebook in my pocket. The guiding concerns are therefore ethical and analytical.

By emphasising emotional distance over intimacy, and "time away" over "time with," to avoid overburdening our interlocutors, the formal rules of engagement between "researcher" and "researched" seem out of touch with the practical realities and ethical grey zones that emerge when conducting long-term fieldwork with people *in extremis*—that is, in extreme conditions, such as those with an incurable disease (see Bourgois 1990; Bourgois and Schonberg 2009 for further commentaries). This is not at all to say they are unimportant, but that they are insufficient, leaving ethnographers underprepared for the thornier issues of involved fieldwork that is deeply relational and necessarily intimate. Indeed, what regulations or codes of practice could possibly foresee the ethical grey zones in

such situations of heightened emotion and existential uncertainty—when the stakes of “witnessing” (Marcus 2010) must be set against those of compromising particular precious moments in the lives of our interlocutors? As such, it is necessary to cultivate a kind of “ethical sensibility,”⁷ which is continually attuned to lively ethnographic moments and which is capable of balancing acute interpersonal and analytical sensitivity.

As ethnographers, we drop into people’s lives and we make relationships which can often be difficult to place. When we witness people suffer and resist—whatever its cause—we participate in the intersubjective space through which that suffering takes form (Kleinman and Kleinman 1991; McMullin 2016). At first, I was almost paralysed and utterly unprepared for how to respond to patients’ requests for assurance or for my opinion on treatment or to hear about the experiences of other patients. Often, I was asked by patients whether they were “making sense” or to promise to tell them if they “went cuckoo.” On several occasions, I was asked by clinicians to talk with patients about a trial—not, I hasten to add, to convince them one way or another but to be a sounding board after they had already been briefed with information. I learned from clinicians and by listening to conversations between patients and families to keep things open, to listen and to offer bland responses that erred on hope. However, I also learned this obsessive buoyancy might sometimes be inappropriate and gloss over patients’ situations and awareness.

There are many brilliant ethnographies which capture what it is to participate in the lives of those *in extremis* and the ethical dilemmas it presupposes (for example, Biehl 2013; Farmer 1990; Livingston 2012; Scheper-Hughes 1993; Street 2014). These show us what an engaged ethnography might look like—one in which the researcher does not simply stand at the margins looking on, but at times intervenes. They show us what it is to provide a deeply empathic account in which intimacy is a fundamental aspect of the research process. João Biehl’s extraordinary ethnography of life in Brazil in a what he calls “a zone of social abandonment,” for example, carefully reveals an intimate portrait of Catarina—a woman admitted and left in a ‘mental asylum’ for many years (2013:2). Through complex readings of “Catarina’s dictionary”—a poetic account of her thoughts and experiences—public policy, increased pharmaceutical activity, and the local politics within and between families, Biehl traces Catarina’s abandonment and “madness” at the nexus of failing welfare, pharmaceutical availability, and the common-sense designations of unproductive people

⁷ I want to credit Ignacia Arteaga with the term “ethical sensibility” as I use it here. We presented reflections on fieldwork with people in the midst of progressive and unpredictable disease, and who might be at the ends of their lives, in a joint paper entitled *Cultivating ethical sensibility in ethnographies of dying people*. The paper was given during the *Medicalisation of death and dying* workshop, l’Université libre de Bruxelles, 13-14 September 2018.

(2013). He relentlessly peels away the layers of Catarina's accounts and traces her life history through her medical notes, conversations with staff at the asylum and the distant members of Catarina's family. These investigations ultimately lead Biehl to a revelation about the reason for Catarina's incarceration, a revelation demanding his intervention. His account ends with Catarina testing positive for a genetic condition called spinocerebellar ataxia, a test that Biehl organised and one which ultimately links Catarina to her three brothers, who are similarly afflicted. He writes:

We made available to [Catarina's brothers] all the information we gathered. They likened this opportunity to 'divine grace.' Our work together, they implied, could at least halt the cycle of family denial and medical passivity vis-à-vis the disease that was costing them too much physically and emotionally ... Through the brothers' search for a diagnosis, Catarina's condition was being verified and a biological complex disassembled (Biehl 2013:283-284).

Biehl has returned repeatedly to his field site and to Catarina's family, continuing to trace how her story unfolds (Catarina died in 2003). After her death, he funded the engraving of her headstone (Biehl 2017), contributing to her memorialisation and continuing to salvage her abandonment in Vita—the institution which had, until his intervention, been her likely place of death.

Anthropologists Philippe Bourgois and Jeff Schonberg describe their participation in the moral economies of sharing and getting hustled during fieldwork with homeless communities in San Francisco. They describe how their feelings of betrayal and fears of coercion turned into recognition of a pragmatic need to participate to keep favour with their respondents and access to these communities. They also turned these sensibilities into an analytically useful way to understand the circumstances of those they engaged with and the social structural conditions in which these circumstances are perpetuated. "Participating in the moral economy," they write, "allowed us to understand its importance on an embodied and intuitive level and revealed its social structural and public health implications. We had to become sufficiently immersed in the logics of hustling to be able to recognise, through an acquired common sense, when to give, when to help, when to say no, and when to be angry" (2009:6).

Dropping into people's lives and becoming part of their life-worlds requires a deeply reflexive approach (Davies 1999). It demands that we do not look away from events and phenomena—like fluctuating capacities, dying or bereavement—that are hard to witness; to intervene when it is necessary; to learn and improvise appropriate levels of intimacy; and to render these experiences as analytically useful.

My fieldwork also meant stepping forward and intervening. Sometimes this might mean being an escort for a patient on the bus to chemotherapy appointments or through the maze-like corridors of the hospital, reminding patients what was said during a consultation, or interpreting the dense language of medical letters. At other times, it meant advising patients where to seek answers, which was mainly to refer them to their consultant or keyworker and perhaps to help them frame a question. These forms of participation are active in the sense that they perform a positive behavioural or communicative intervention and I would argue that withdrawal is similarly so. There is also a form of participation that is less obviously interventional—and this is how I would like to frame empathy. Here, I am not referring to its outward signs—a hand on an arm or an empathic word—but the feelings one shares with another. This means being attentive to hope, sadness, disappointment and so on as a matter of shared experience.

Of course, this sensory understanding pales in comparison to those actually going through illness or grief. As Julie Livingston says in her ethnography of cancer in Botswana: “Thankfully, I was never a cancer patient at [the hospital], so my participation was inherently partial. I cannot fully understand the ward from the position of someone lying in one of the beds. Nor was I a doctor or nurse charged with performing the skilled and difficult work of oncology” (2012:23). Instead, Livingston describes her experience as “diluted” compared with those of the patients and doctors she observed and interviewed (2012:27). Not overstating the stakes is a vital consideration in the interpretation of ethnographic intimacy and an emphasis should always be made on its partial nature. Yet, as multiple accounts of suffering attest, even such partial participation or diluted experience helps bridge gaps between self and other and can be a means to powerfully account for their suffering.

My point is fairly simple: participation is as much empathy as it is performed action. Participating via empathy, aside from being an ethical mode of doing research and perhaps truer to its experience, allowed me to better understand the stakes of emotions like hope and disappointment “on an embodied and intuitive level” (Bourgois and Schonberg 2009:6) and grasp the seductive qualities of the medical imaginary and its imperative to treat. This is consistent with the claim that doing ethnography is not simply about constructing and reflecting the world through other people’s experiences and narratives, but through our own, as ethnographers (Davies 1999).

COLLECTION, ANALYSIS AND REPRESENTATION

By now it should be clear that while I attend mainly to the practices undertaken within a particular site of care and treatment—The Warner Hospital—these, nor The Warner, are not my sole focus. Glimpsing biomedicine in action, how patients engage with it through their own interpretive frames, and how biomedicine is shaped by exogenous factors—both political and economic—entails an analysis which operates through multiple modes and across multiple sites (Marcus 1995a; Rapp 2000). To capture the movements of people through turbulent fields of disease, care and treatment I passed iteratively between “experience near” patient and family accounts of themselves, disease and treatment and their engagements with institutions of care (including but not limited to The Warner) and a more “experience distant” analysis of how care and treatment co-mingle with knowledge production and its implementation⁸. This approach employed long-term ethnographic engagement with people living and working with brain tumours, and attended to the broader backdrops of policy and scientific progress through a careful analysis of documents and expert opinion.

My analysis of interview transcripts and field notes happened throughout fieldwork and writing. I began simply by keywording field notes as I wrote them allowing me to refer quickly between them. Interviews I collected on audiotape, I listened to repeatedly and especially in preparation for follow-up meetings. I wrote references between field notes and interviews making connections between observations and oral accounts thereby allowing detailed narratives to emerge. I then wrote more analytic notes alongside these to keep track of preliminary ideas. Later on, I indexed interviews using open codes, allowing me to further develop themes and patterns across participants. I paid particular attention to personal meanings and values attached to disease, health, treatment and care and how these featured in decision-making. These were inevitably informed by etic categories found in the literature—hope, uncertainty, confusion, living in prognosis—as well as those particular to the experiences of people with a brain tumour—losing reality, scarcity of treatment, imminence.

As an analytic framework of navigation took shape during fieldwork, my analysis became more focused. I started to shift my attention to code for instances of change and collected further data on decision-making. I had spent a lot of time in the laboratory and radiology department and so diagnosis and prognosis were already key interests. Early on in fieldwork I heard about the epistemological changes that were coming to brain tumour

⁸ This attention to lived experiences and the micro and macro political processes of care is inspired largely by ethnographies like Joao Biehl's (2007) *Will to Live: AIDS Therapies and the Politics of Survival* and Sharon Kaufman's (2015) *Ordinary Medicine: Extraordinary Treatments, Longer Lives, and Where to Draw the Line*.

diagnosis and started to see some of the social consequences these might provoke—uncertainty being principal among them. Throughout fieldwork, patients would tell me about the uncanniness of their worlds after diagnosis, and I observed how strange symptoms like seizures and auras combined with biomedical interpretation and the imagery of brain scans to produce a subjectivity in which patients question their own competency and sense of reality. This too became a key area of focus. I saw how differently patients, families and clinicians approached the possibilities of treatment through clinical trials yet how their accounts would draw together in hope; how patients compiled dossiers of scientific articles and modified their course through care so as to present themselves as eligible and secure a trial place; yet how suddenly trials opened and closed and how strict their eligibility criteria were. Over the full course of fieldwork, I also observed the tragic fluctuations of patients' conditions, how quickly they could deteriorate and how unpredictably this could happen. These changeable phenomena—scientific progress, subjectivity, experimental trials and disease progression—would become my major themes and chapter headings. Navigation as theorised by Vigh therefore seemed an ideal metaphor in which to place the agentic movements of patients, families and clinicians within the changing structures of diagnosis, treatment, interpretations of self and disease; moreover, it allowed for their variable paces to be described. The very language of “pathways,” “plans,” and “navigating the system” neatly sutured with the terms used by clinicians and researchers to describe the molecular turn in diagnosis—“seismic change” and “groundbreaking.”

George Marcus describes ethnographic fieldwork as a process of bricolage—an assembling of parts gathered haphazardly and systematically into a whole (Marcus 2011). This image resonates strongly with my fieldwork, analysis and indeed my writing, which as I wrote above, moved between the opportunities and constraints of systematicity, serendipity and sensitivity. The situations I describe were undoubtedly mediated by my presence and participation in the ways I have detailed. Because of this, I present this dissertation as a first person account. I have also preserved as best I can people's individual narratives as they unfolded over the course of fieldwork and through their encounters as they plotted and re-plotted trajectories for their lives, and “[felt] their way' through a world that is itself in motion, continually coming into being through the combined action of human and non-human agencies” (Ingold 2000:155).

Like many ethnographies, I have selected particular cases and life stories to present. I have chosen these in service of the overall argumentation of the thesis and to be illustrative of the specific points at hand. Together, they represent a broad range of institutional

phenomena and patient and family experiences that are indicative of the opportunities and constraints encountered by patients and how they seize them or innovate ways around. It does not mean that these experiences are entirely typical in their specifics; nor do they represent the whole gamut of trajectories. And yet, I learned from multiple sources, such as the testimonies of clinicians, that they were common. In most instances, I have opted for long-form vignettes or quotations so as to illustrate the complex and contingent nature of experience. I also concentrate the thesis on a smaller number of patients than interviewed so as to delve more deeply into their life-worlds and illness trajectories. I used other cases to corroborate specifics as well as broader general patterns. Cases used in this way constitute a point of entry into the broader institutional processes, practices and discourses which organise people's lives and inform their subjectivities (Biehl 2013; Leonard and Ellen 2010). And this is just what I have sought to do: to follow these patients' courses through various layers of the medical institution and thereby trace how they are patterned by upstream processes, practices and discourses as well as how they might resist or avoid them.

Like many ethnographies, I have placed quotations around all speech; after Julie Livingston, I include an asterisk to mark speech when I am sure I have recorded someone's words verbatim (see Livingston 2012). In rare cases, I have removed some parts of ordinary conversation that were distracting—for example, “er” and “um”—although I have included difficult or irregular speech patterns in some instances when it connotes a deficit or irregularity in patients' speech, such as stuttering, and when it is relevant. I adopt a slightly different style of presentation in a large part of chapter 5. By including raw and minimally edited excerpts of field notes and interviews to story the last months of life for Rebecca, who died from a brain tumour several years after she was diagnosed. I do this to stay close to events as they transpired and to carry the passage of real-time. To maintain confidentiality, I have given pseudonyms to all people and places that appear in the text, apart from David Louis, the neuropathologist steering the integration of new diagnostic parameters. Louis is a known public figure in neuro-oncology and I had the opportunity to meet him. He gives permission for this use of his name and words. For the same reasons, I have also changed certain revealing features of people and places.

CONCLUSION

In my ethnography of care and treatment for people with a brain tumour, I engaged in a form of hospital ethnography, constructing a varied field sited across multiple arenas

(Marcus 1995a). I have drawn patient, family and clinician accounts of their lives and work as well as more abstract notions of scientific knowledge production, evidence and policy-making, using interview, participant-observation and documentary archiving as my principal forms of data collection. My practice in the field meant striking a critical balance between being systematic and sensitive to moments beholden by serendipity, during and after which I conducted an iterative analysis through modes of inductive and focused coding. Reviewing and presenting these disparate forms of evidence in the same analytical space illuminates how biomedicine shapes lives in complex ways and how the multiple temporalities of scientific progress, policy and disease disturb a terrain, field or landscape which, although continually in motion, is enacted as fixed. It allows us to glimpse the co-mingling of fact with value, and the sensible aspects of disease and care—experience—with the abstractions of diagnosis and pathway. Finally, it allows the experiences and first person accounts of patients, families and clinicians to be placed at the heart of analysis and richly contextualised in the political economies that shape their lives.

I have argued that participating in the lives of people *in extremis* means being acutely sensitive to the sensibilities and practices of patients, families, and clinicians, ever conscious of imposing the formality of research and disrupting tense or precious moments. It entails a form of empathy which, aside from being an ethical mode of doing research and perhaps truer to its experience, allows for a more nuanced understanding of the stakes of emotions like hope and disappointment “on an embodied and intuitive level” (Bourgois and Schonberg 2009:6). This, I suggest, is one of the unique contributions of ethnography and is consistent with the claim that doing ethnography is not simply about constructing and reflecting the world through other people’s experiences and narratives, but through our own, as ethnographers (Davies 1999).

CHAPTER I—DIAGNOSIS AND PATHWAYS

The diagnostic moment can often be a shocking one, marking entry into what Sontag called the “kingdom of the ill” (Sontag 1978:4). As discussed in the introduction, many people who present with a brain tumour follow a circuitous route to the gates of this kingdom and are typically admitted first to Accident & Emergency (A&E) after an accident and with no awareness of the underlying tumour. The vast majority of patients I spoke with told sensational stories of events before diagnosis—car crashes, bicycle accidents, falls, or collapsing over the dinner table. After the fact, patients recounted their gradual awareness of strange symptoms—periods of forgetfulness, headaches, blurred vision and provisional diagnoses of migraine, stress, depression or subtle personality disturbances. Often, they told me how they had made multiple trips to the GP and visited specialists like opticians or psychologists.⁹ These routes to diagnosis were further storied in case histories given in MDT meetings. They are borne out in survey estimates which report that almost two thirds of patients are diagnosed in Accident & Emergency (A&E) (National Cancer Intelligence Network 2016) and survey findings that many brain tumour patients see their General Practitioner (GP) more than five times before being referred or having a major episode like a seizure, as reported on The Brain Tumour Charity’s news page, in July 2016.

Before arriving at the ultimate conclusion of a tumour, therefore, most patients had moved through various layers of the healthcare service and experienced sudden, unusual and frightening events. The key feature of their stories was that “something had shown up on the scan,” either at A&E or secondary referral, after which they were fast-tracked to The Warner under the two-week wait—a national standard of care which stipulates those suspected of having cancer be seen by a specialist within two weeks. At The Warner, more scans, structured questionnaires and neurological assessments were done before decisions were made by the MDT about biopsy—to remove a small piece of tissue for analysis—and resection—partial or total removal of the tumour. By the time they see the neurosurgeon, then, the patient is already apprehensive. When I asked Mr Muldoon, one of the most experienced neurosurgeons at The Warner, how he would handle the sensitive task of discussing a brain tumour diagnosis he told me:

I tend to use that situation to walk through, talk through, what we jointly, patient and I, already know. To rehash it and bring us with a, not a blaze of trumpets, but ‘ta-rah,’ and ‘so now here we are and this is the

⁹ This also mapped onto case histories given in MDT meetings.

information.’ And then the last act, as it were, is to feed into and ‘where we go is—’ I don’t have the ability to look someone in the face and say, ‘By the way, the news I’ve got for you is that this is cancer.’ I can’t do that. I have to dig my own foundation every time I go through that conversation.*

This, then, is how the diagnostic moment is managed. It cannot help but be revelatory, but clinicians do their best to situate the news amid a sequence of events; to gesture towards “next steps” even as the future foreclosed in diagnosis sets in. The diagnostic moment settles the uncertainty that accompanied the patient into the doctor’s office and begins to lay out a route through which the patient can be managed and the disease treated. It is a moment in which the tragedy of progressive disease is narrated through and alongside hope, in reference to the efficacy of biotechnology and the imperative to intervene (DelVecchio Good 2001; DelVecchio Good 2007; Koenig 1988).

Diagnosis has long been an interest of social scientists studying medicine. In these analyses, it is key to establishing a direction for treatment, initiating and organising a cascade of medical processes (Smith-Morris 2016). It is therefore among the first instances which establishes the institutional field that shapes the lives of people with physical and mental illness (Biehl 2013). It is also a technology of surveillance and the organisation of society (Canguilhem 1991; Foucault 1973). These scholars have done much to unmoor the taken-for-granted status of diagnosis and given critical perspectives on the constitution of disease categories. In so doing they have robbed the distinction between normal and pathological of its supposedly natural character and provided a template for future work on power and medical authority (Mol 2002). Contemporary ethnographies of disease have moved these insights along and shown empirically the social practices that determine how things are “made visible, how things [are] *given* to be seen, how things [are] *shown*” (Rajchman 1988:91). They foreground the historically situated and distributed processes of knowledge production and the social exigencies that bear on the categories of disease (Hardon 2016; Koch 2016; Petryna 2002; Prentice 2013; Rapley 2008). It is in this spirit of analysis that I site this chapter, where diagnosis (and disease) is not a biological fact discovered in the world but a set of categories, highly contingent and achieved in multiple processes of enactment and negotiation (Mol 2002; Koch 2016): “a strategic event that is mobilized and transformed” (Koch 2016:47).

Nonetheless, as I observed at The Warner, the natural and neutral character of disease continues to be reified in medical practice. On entering the pathology department, for example, my interest in diagnosis was summarised by the head of the department as “an interest in facts”—facts which were objectively sought in routine diagnostic work. They

became unquestioned biological entities—naturalised and disclosed to patients in the language of certainty. At their most concrete, doctors spoke of “lesions,” “lumps” or “masses,” which would typically be classified into cancer or benign disease. Grades I to IV, an ascending scale describing the aggressiveness of a tumour, further characterised their descriptions, and remained an enduring scale upon which patients would be placed. As well as being a description of severity, grade is a fundamental determinant of treatment course. Unlike for other cancers, the clinical notion of “stage” is not regarded by brain tumour specialists. As a description of spread, stage is not relevant because brain tumours are extremely unlikely to spread beyond the central nervous system.

This chapter concerns professional perspectives on disease and the importance of diagnosis to the work of clinicians. I focus on the productions of diagnosis and the importance of the category of fact. Specifically, I attend to practices undertaken in three main sites at The Warner, which collectively might be considered the engine houses of diagnosis. These are the laboratory, the radiology department, and the clinical consultation. Each site corresponds to a particular way of knowing—histopathology, radiology and clinical history—ways which must later be coordinated in the efforts of producing a singular account of a patient’s condition (Mol 2002). I have chosen to present the MDT as a primary site in which coordination happens. While in practice these sites are not fully discreet, they do represent key locations and structure boundaries across which processes of translation in knowledge production happens (Bowker and Star 2000; Callon 1986; Latour and Woolgar 1986; Latour 1999). For my purposes, these translations happen as information passes through different mediums—for example, how flesh removed from a patient’s tumour became a pattern to be read beneath the microscope, or how a radiological scan became a typed report—and spaces—for example, from the laboratory to the clinical consultation. They are fundamental to how uncertainty is *managed* and *contained*, and how diagnosis acquires the stability of “fact” needed to direct the course of treatment events in patients’ lives.

The broader argument of this chapter—as with the rest of the dissertation—concerns navigation. Drawing from clinician’s own metaphors of establishing a “ground” or “foundation” for treatment to follow “pathways,” I foreground an analysis of the institutional work through which tumour diagnosis and therapy are premised. I use the concept of *fixing the terrain* to emphasise the ways in which modern medicine attempts to fix uncertainty and instability in relatively static landscapes as well as the implication to intervene in—or *fix*—the course of disease. As an analytical concept, it therefore captures at once the attempt at stability associated with diagnosis and that of intervention. This intervention, I

argue, is always present in diagnostic practice, as those who diagnose shape information in order to effect actions downstream. It is further manifested in relation to treatment pathways. Following a navigational focus, then, diagnosis is the process by which disease is made navigable, since it fixes the terrain over which care pathways can be mapped and routed (Llewellyn et al. 2017). This approach therefore gives serious critical attention to the navigational implications of locating disease in a spatiotemporal grid—“*now here we are*”—and looking ahead along a pathway of care—“*where we go is*.”

I begin with a close and technical analysis of the diagnostic processes and translations undertaken at The Warner in ethnographic snapshots of the daily work of biomedical scientists, pathologists, radiologists and clinicians. I then examine how these different forms of knowledge are dealt with and coordinated by the MDT showing how standardised pathways guide an imperative towards intervention (Berg 1998; DelVecchio Good et al. 1990; DelVecchio Good et al. 1994; Kaufman 2015; Kaufman 2016). Through this, I show the hospital as a fragmented space in which disparate groups of people, practices and material configurations stand at different points along the continuum of knowledge production and how they allow diagnosis to acquire stability. I also show the geographical, material, and linguistic borders between different professional communities—or epistemic cultures¹⁰ (Knorr Cetina 1999)—in the hospital and how these borders feature in maintaining a certain distribution of power. In so doing I hope to map out the common routes along which people with a brain tumour pass and some of the features and dynamics of power at play in decision-making, which might not seem so obvious and which, as I will show in later chapters, confer hidden accidental constraints on the aspirations and movements of patients.

CLINICAL HISTORIES

Clinical histories are an initial layer of information for clinicians based on structured questioning and standardised measures of function. Because my approvals did not extend to meeting and consenting patients prior to their diagnosis, I was not present for prediagnostic tests. However, in my long-term engagements with patients, I saw clinical histories and standardised tests done frequently. In this short ethnographic snapshot, I detail a clinical encounter between Dr Noyes, a neurologist, and Gabriel and Cecilia who I introduced in the

¹⁰ In her analysis of contemporary scientific knowledge production, Karin Knorr Cetina defines epistemic cultures as “those amalgams of arrangements and mechanisms-bonded through affinity, necessity, and historical co- incidence-which, in a given field, make up *how we know what we know*. Epistemic cultures are cultures that create and warrant knowledge, and the premier knowledge institution throughout the world is, still, science.” (Knorr Cetina 1999:1)

introduction. Although this particular encounter occurred towards the end of Gabriel's life and not at diagnosis, it illustrates well the structured questioning and tests used to establish clinical history. The appointment was made because Gabriel's eyesight was worsening and he was getting no answers from his optician.

Gabriel, Cecilia, and I sit in a row in blue plastic chairs waiting for Dr Noyes. Tall, Gabriel tucks his legs underneath so that the patients in wheelchairs can be pushed past. Other patients sit scattered in the rows behind us—some chat to each other, others watch the daytime TV that streams from the screen above. Cecilia clutches a bag out of which poke tattered pieces of white paper—"they're the GP letters," she tells me—a record of events. It is a routine appointment and Gabriel wants to talk about the problems he is having with his eyesight. "I've got these new glasses," he smiles, "but they're no good really. I saw the optician again, who doesn't say all that much, only that I have a bit of a stigmatism. He changes the prescription a bit but not much else." We don't wait long before Dr Noyes calls his name and jovially ushers us into the consultation room.

Inside, Dr Noyes sits at a computer facing Gabriel and Cecilia who sit side by side. "So I saw you about four months ago," Dr Noyes says, "and you had a scan recently—which wasn't great." He meets Gabriel's gaze. "Were you *aware* of this?"

Gabriel: "I think I was aware of something—I had a weird feeling."

Dr Noyes: "What type of feeling?"

Gabriel: "'A feeling'—it's difficult to explain. It was like it stopped working."

Dr Noyes: "So like a sixth sense."

Gabriel: "A bit."

Dr Noyes now looks at the two brain scans side by side on the computer screen. While he talks, he points to particular areas: "It's an odd thing because it's not particularly dramatic—I wouldn't necessarily expect you to know about it. This dark circle is where you had your surgery. So there's nothing really much more in there. But here you have some growth. And it's in a place called the cerebral peduncle which is in the midbrain. But you can see that this is no more squished here than here." Amongst other things, clinicians use scans to look for parts of the brain that appear squished—or compressed—and they compare scans done at different times for differences that imply change.

Cecilia: "What kinds of symptoms might Gabriel experience if it does become squished?"

Dr Noyes: “Often none—everything in oncology is to do with rates of growth. The brain can’t tolerate fast rates of growth. But if it grows slowly it can accommodate to a point.”

Gabriel: “The other day I had a seizure, well not a seizure as such—it kind of caught me in the street—I just felt a bit strange and then it passed. And last week I was so drained and kept kind of fainting—it happened four times in one day.”

Dr Noyes: “What exactly did you feel?”

Gabriel: “It was a very strange thing—I had to squat.”

Cecilia: “You said it felt like you were being drained from the head down.”

Dr Noyes repeats to himself: “The head down.”

Gabriel: “The rest of my body was fine.”

Cecilia: “You said you had a bit of tingling in your arms.”

Dr Noyes: “And these are exactly the same?”

Gabriel: “Yes I think so—they last about 30 seconds.”

Dr Noyes: “Tiny little seizures it seems like to me—and when was this?”

Gabriel: “Last Wednesday.”

Cecilia: “We called the emergency line and they told us to increase the keppra and start taking steroids.”

Gabriel: “Could this be causing the visual problems?”

Dr Noyes: “Steroids can cause transient visual disturbance. Did you have visual problems before taking the steroids?”

Cecilia: “Yes, before.”

Dr Noyes: “Then we can’t blame the steroids. Let’s see if we can find anything more objective.”

With this, he tilts Gabriel’s head upwards touching his chin and asks him to look at his nose. He then spreads his arms wide and asks Gabriel to say on which hand are his fingers are twitching. Gabriel calls out: “right—left—right—right—left.” Still twitching, Dr Noyes moves his arms up and down, in and out, as if tracing twelve spots in a grid.

“Okay fine. I think you might have a subtle defect here,” Dr Noyes says, placing his left hand to mark the spot on the imaginary grid in front of Gabriel, “but your central vision is okay. What about TV and reading?”

“Very frustrating,” Gabriel says.

Cecilia explains how Gabriel struggles with reading and how he can no longer read the TV guide on the screen—“it really seems like something is going on,” she says.

“We need to check this out,” says Dr Noyes, “I’m going to refer you to my colleagues in neuro-ophthalmology, who will do much more detailed tests.”

He asks Gabriel to stand with his back against the wall and read from an eye chart that hangs from the door, first covering one eye, then the other, with glasses and without. Gabriel gets the letters mostly right but he is slow and skips letters.

“That’s interesting,” Dr Noyes says sitting back down, “you’re accurate. You’re getting it, but—how about reading? Do you have anything to read here? A newspaper or a book?”

Cecilia gives him one of the letters from her bag and Dr Noyes asks Gabriel to read from it. Very slowly, he reads aloud one word at a time as if he is just learning to read, or unaccustomed to reading. He struggles on words—“chemotherapy” is one. At these moments he sighs, frustrated. Dr Noyes looks at him then at the page, then back again. After almost a minute of Gabriel persevering with the letter, Dr Noyes thanks him.

“This is not an eye problem,” he says, “you’re getting the words right, you can see them. But you’re struggling. Particularly on the word ‘chemotherapy,’ which is a long word but not a difficult word. Alexia—we call it alexia. What about writing?”

Writing is okay Gabriel says but he doesn’t write often and his spelling is terrible. Dr Noyes asks Gabriel to write out a dictation: “please refill my prescription as I am low on the antiepileptic drugs.”

Dr Noyes takes the piece of paper Gabriel has written on: “How do you spell refill?”

Gabriel: “R-E-F-I-L-E.”

Dr Noyes: That’s “refile.”

Gabriel: “Of course—the extra ‘E.’”

Dr Noyes: “And prescription?”

Gabriel: “P-E-R—”

Dr Noyes: “P-R-E.”

Gabriel: “It’s frustrating.”

Dr Noyes pauses. Then quietly and slowly, with space between his words, he delivers his verdict: “I can’t help feeling this is Mr. T. causing this—because it’s in a part of the brain that could affect this.” All of us in the room know that Mr. T is the tumour and we know the implications of this. He asks Gabriel about his job.

Gabriel is not working at the moment. Dr Noyes asks what he was doing a year ago. Private investment stuff, but even then he was handing stuff onto Cecilia. “And when did you stop reading newspapers?” Dr Noyes asks.

“A few weeks ago,” Gabriel says. He tells how Cecilia opens the post now, reads the newspapers, and tells him what is going on. He tells how he was an avid reader and when prompted by Dr Noyes names the books he liked to read—books about climbing, mountaineering, motorbike restoration. “So not detective thrillers,” says Dr Noyes before turning to Cecilia: “It’s often hard to spot because what you’ve done is moulded around him rather than pressing him to keep going. It’s very difficult with these things because they’re not immediately apparent. It’s not like you walk in here with a broken arm and in fact you said it was a problem with your eyesight. But it’s not your eyesight. It’s the processing of your visual information and when the opticians do their tests they don’t give you anything to read. And you can *see* things fine. So, they say your eyesight is fine and they don’t do anything. They might change the prescription but as far as they are concerned your eyesight is fine. But I gave you something to read and I can see—it’s not your eyesight. And this is not about pressure—we can see that from the scan. I think it’s infiltration.”

Infiltration is the word that clinicians use to describe the skein-like spread of tumour through the tangles of the brain. It is a point at which the tumour, once bounded and discreet in Gabriel’s case, now enters his body with far more serious effects.

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Dr Noyes writes in his letter to Gabriel’s GP: “His main deficit is not in his speech and language but in his vision. He has reported blurred and some difficulty reading for some time now but a recent visit to the optician did not suggest there was a primary refractive problem. On testing his vision, it was clear that he has normal visual acuity in both eyes (6/5 bilaterally) but he is missing letters and when I asked him to read a simple sentence this was very slow and he was unable to read one of the longer words (chemotherapy). His writing and spelling is also poor. I suspect that therefore what he is describing is a primary reading problem due to the involvement of the dominant posterior temporal lobe. This is most likely to be due to tumour infiltration particularly as he has been aware of it for at least a year or so but markedly over the last 2 weeks. I will refer him to Dr Jackson who runs a hemiopia clinic for his definitive opinion on this.”

To Dr Jackson, Dr Noyes writes: “I would be grateful if you would see this lovely gentleman with a progressive left posterior temporal glioma for which he is now on second line chemotherapy. He reports visual difficulties and problems reading and on testing I think he has alexia and upper quadrantanopia. I am sure he will benefit from your assessment.”

RADIOLOGY

Brain scans happen early in patients' journeys, after an event like a seizure or more subtle indications established during clinical histories. This often happens in A&E settings and subsequently at The Warner. Scans are also done throughout the course of disease according to clinically standardised temporal schedules—3, 6 or 12 months—or after a major event like a seizure or sudden worsening of a patient's condition. The most common scans are Computerised Tomography (CT)—which use x-rays to generate an image based on the different densities of tissue—and Magnetic Resonance Imaging (MRI)—which use magnetic fields and radio waves to manipulate and measure hydrogen protons. For brain tumours, MRI provides a safer and more detailed image. Brain scans are key technologies in locating symptoms and granting them a material basis in the body (Cartwright 1995; Dumit 2004). They provide an initial layer of information about tumour location and its composition, beyond patients' presentations and the versions of events solicited through structured questioning. In the UK NHS, radiographers work directly with patients and run imaging machines which are kept apart from other hospital equipment in lead-lined rooms which contain the radiation and large magnetic fields used to generate images. Scans are expensive and in high demand; it was common for patients at The Warner to wait weeks for an appointment.

The images produced by radiographers are digitised and uploaded onto a Picture Archiving Communication system (PACS) for all members of the clinical team to see. The move from film to digital image transformed radiology in several important ways, not least by giving new access to any medical professional from different locations and settings and allowing copies to be made easily and cheaply. Patients can pay £10 for a CD of their scans, which some patients I met did routinely. Those that requested them told me they did so simply to have another record or to send for second opinions. Despite this increased access to scans for other members of the multidisciplinary team, medically-trained radiologists have by and large kept the authority on the interpretation of scans—an endeavour which as we will see in the ensuing passages is a highly technical and specialised craft.

In the following vignette, I present Dr Chen, a young consultant radiologist, as she talks through her work. I attend especially to how Dr Chen writes her reports to persuade others and how dealing with uncertainty is a key part of this process. I also describe how radiologists talk about clinicians and how they see their roles as part of a clinical team.

These suggest how radiologists—as agents in the production of diagnostic information—place themselves in a hierarchy of knowledge and status, how they manage interpretation and objectivity, and ultimately how they shape information towards an outcome by its destination.

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The reporting room is dark—bright lights make the images harder to read. Dr Chen scrolls through the picture on the large computer screen in front of her. Another screen on her left shows the scan request form with the patient’s history written in this case by an oncologist. How much history there is varies. Sometimes clinicians ask specific questions—“question mark kinaesthesia,” “is it growing?” Sometimes Dr Chen loads a different image on this screen for comparison—a key practice in radiology, as she explains later. From time to time she pauses and you can see the rounded and frond-like outline of a brain. Two bright circles appear at the top of the screen. “These are the patient’s eyes,” she tells me, “we call them the orbits—they look bright because they are filled with fluid and on this sequence fluid looks bright. On other sequences they might look dark.”

Sequences are the scanning protocols that produce images. “Each sequence tells you something different,” Dr Chen says, “so this scan, for example, shows fat, blood, melanin.” Different sets of sequences are done for different suspected diagnoses. So, brain tumour patients are typically scanned to a certain standard. This helps to compare scans across time. Radiologists look at all sequences together so that they can get a fuller impression of the brain and any pathologies. They look at the images in different planes—top to bottom (axial), left to right (sagittal) or front to back (coronal). Using these three planes radiologists are able to work across three dimensions. Like different sequences, different planes show different things.

Dr Chen points to the middle of the scan. “I start here in the posterior fossa—the brainstem—it’s a good place to start. It’s easy to miss things here. You need somewhere to start to be systematic but you could start anywhere. A lot of people start with the brainstem. I start here at the base of the skull where the spinal cord joins the brain and move up through the head.” She moves slowly through each sequence paying attention to review areas—“these are risky areas or places where it’s easy to miss things—the orbits, blood vessels, the foramen magnum where the spinal cord passes.”

“I make a guess about what it is before looking at the history and seeing if there is already a diagnosis. I can see this is aggressive—it’s destroyed the bone. You can suggest a diagnosis by thinking about what grows in that region where there appears to be a lesion. So here adenoma and meningioma grow. And adenoma is more common. So we’ve worked out he has a skull based tumour and he’s had previous surgery. You can see surgery material here.” She points to a part of the skull that looks thinner. “This is where the surgeons went in.” Then she looks at the notes—“This time I guessed right. But it wasn’t a particularly difficult one.”

Using clinical information and patient histories is not simple and requires considerable thought. Radiologists told me about being “seduced” by other tests. They looked at scans blindly to avoid being swayed. Consultants also tell registrars to stick to what they can see and not to say something because that is what you expect. Sometimes patients might have multiple abnormalities and prior indications or diagnoses can be persuasive explanations: “as they say in the train stations in France, *‘un train put en cacher en autre’*—one train can hide another one,” I heard a consultant say to a trainee.

“I want to see if it’s growing,” Dr Chen says. She starts by looking at the most recent scan and then finds the patient’s very first scan. Then she looks at the next newest for comparison. This constant comparison allows her to see change. “It’s very helpful in assessing the behaviour of a lesion and whether you can leave it or not. If it’s mild growth over the course of year then it might be okay but if it’s over a month then it might be more aggressive.” She says that when she compares by eye she has to make sure the scans are the same size. “This looks a little bulkier, but I’m not sure. The sequences are slightly different on different scanners so comparison is a bit limited here. This one is running 2mm slices and this is running 5mm.”

“The last thing you can do is measure,” Dr Chen says, “but even though you may think it’s objective, it isn’t necessarily—it depends on what you measure.” The software she uses gives actual measurements in millimetres relative to its actual size. “Occasionally I might add measurements in the report,” she says, “where I think it’s relevant—if I want to say if it has changed a lot or a little or if someone specifically asks for it.” Other radiologists are more suspicious about measurement. One senior radiologist, for example, told me that clinicians don’t want measurement and he thinks it misleads—“I don’t like it because if you focus on the measurement then you stop thinking—you do all this measuring without noting the important bits.”*

Dr Chen continues: “I try to work out which portion of the tumour is larger. This helps the clinicians to know how the tumour is growing and in what direction—does it interfere with new structure of the brain? This is important—which areas of the brain that might be affected soon? So here it’s near the pituitary and the optic chiasm—where the optic nerves cross. It’s good to put that in my report. But I would see if it has been reported before. If it’s new then I would definitely report it but if it has been reported before then I would be more careful in how I would report it.” I ask her what she means, “You don’t want to panic clinicians. And you should remember your limitations. You can only ever be close in radiology—sometimes that’s close to 100%, sometimes it isn’t. The question is how to make sure you don’t panic the clinicians but make them aware of this. So, I’ll say something like ‘it extends relatively close to the optic chiasm. No sign of compression but optic tests are recommended.’ If it’s new then that can change decision-making.”

Radiologists are deeply aware of the implications of their work and their potential to change the treatment course. On several occasions, I watched radiologists write reports that radically altered this course. They take care with what they write, continuously revising the language in order to most constructively effect events downstream.

This is the moment when Professor Kandu, a senior radiologist, saw something new on a scan: “There is infiltration because it extends here. Oh, hang on, he’s got another meningioma. Oh, that is a miss, that is a miss from a previous study, that is clearly a meningioma.”* He dictates into a microphone: “this is a distinguished separate component,”* before correcting himself and changing the report to add detail but also a qualifier, “this may represent a distinguished separated mass which is separate from the pituitary adenoma.”* Off dictation he says to me, “this is ‘black belt radiology’ because we made a different diagnosis.” The previous report had missed the meningioma. He continues to dictate: “This is in retrospect present on the previous study. This causes only mild compression of the optic chiasm. Conclusion—there may well be two separate suprasellar mass lesions consisting of the pituitary and the meningioma.”* He turns back to me: “so this is opening up a new field. This will involve a new thing—its gammaknife radiotherapy now. This is where I earn my money—I’m making a difference now.”*

At other times, however, radiologists know that what they write will not change treatment. The same radiologist says another time when finding new brain metastases: “This patient has lung cancer. Her life is not going to depend on your report. The outlook is

already not good. So, it's a risk-free zone." The point is, radiologists are always aware of the context of their work. And this context always structures how they report.

They take care with what they include and how they write it, continuously making revisions. Like the requests radiologists receive, the reports they issue vary according to style and experience: "You can see the different styles of reporting here," Dr Chen says, "This is done by someone who is very experienced at this and who has been doing it a long time. So, it's very short—just two lines. But this is a longer report here." The other she shows me has three paragraphs, one of about 12 lines and the other two half as long. I ask her what clinicians prefer. She pauses. "I'd have to think about it. Different clinicians want different things. So, a surgeon versus a—well let's say a clinician from this hospital versus a clinician from a general hospital or a GP. I try to model it on their knowledge and needs. You have to be as clear as possible so that they understand the necessary information and whether it's positive and negative.

"I write my conclusion last and generally give some caveats. But it's a bit like the medical leaflet you get with medications. If you read all the side effects and the risks then you probably wouldn't end up taking the medicine even though you need it. It's the same with a radiology report. I wouldn't put every caveat in—it waters it down. You apply the evidence, your own personal experience and your subjective interpretation. For example, on this scan the slices are done in 5mm. That's routine on most scanners. I wouldn't put that—it's not useful information." I ask if clinicians are aware of the caveats. "It depends—some are. There are equivocal findings—radiology is not absolute. So, you have to think will there be the right amount of uncertainty—you need to think about differentials—what else it might be. You can give an actual diagnosis if it's pathognomonic—that's if it cannot be anything else—if you are certain."*

We see, therefore, that radiologists are highly aware of the implications of their work, of the uncertainties they encounter and the pitfalls they must avoid. Most see themselves as members of the clinical team and they know that how they style their reports has major bearing on what happens downstream. They think about whether they want to convince or temper, be gentle or direct. Their concerns are whether they have the "right amount of uncertainty" or have "watered things down," whether they are being "safe" or "brave." Information is *shaped by its destination*—who will read it and what it means to their work. Yet, even though they spend painstaking moments on writing reports, they are also well aware that clinicians might only read the conclusion and the name of the reporting radiologist. As

we will see later in this chapter, the caveats of scan production and interpretation are important in the coordination of information, especially when things are equivocal.

PATHOLOGY

While brain scans give an image of the brain and tumour in a relatively non-invasive way, histopathology works directly with tumour tissue after it has been removed by biopsy or surgical resection. It is the basis of “gold standard” diagnostic work—something I expand on shortly. Histopathology always follows brain scans but is not a diagnostic process used with all patients. This is because some operations—for example, if the tumour is too close to so-called “eloquent areas” of the brain like the optic chiasm or motor strip, which control vision and voluntary movements—are considered too risky. The key figures involved in the production of histopathological knowledge are surgeons—who remove suspected tumour material—biomedical scientists—who process the tissue and make diagnostic slides—and pathologists—who interpret the slides and write reports.

Like the radiology reporting rooms, the pathology department lies apart from the wards, clinic rooms and surgical theatres. Access from the main hospital is controlled by keycard locked doors; security guards monitor those who enter from the street. Inside, corridors are dimly lit and narrow, lined only with pin boards that are filled with the front pages of scientific articles. Titles give little away to the non-specialist—*“One Hundred and One Dysembryoplastic Neuroepithelial Tumors: An Adult Epilepsy Series With Immunohistochemical, Molecular Genetic, and Clinical Correlations and a Review of the Literature,” “Histological yield, complications, and technological considerations in 114 consecutive frameless stereotactic biopsy procedures aided by open intraoperative magnetic resonance imaging.”*

There are no waiting rooms outside its doors, no patients mill around. There are no beds, no nurses bustling up and down, no trolleys. The corridors are silent and empty and the doors that lie off are closed. Early on in fieldwork I’m told by a surgeon that the pathology department is a “black box”—he sends in a piece of tissue and waits for an answer. Like most other clinicians, he never visits the pathology department. Except when they are shown at weekly MDT meetings, the images made in the laboratory stay there and, unlike scan images, they are not digitised. During a talk by one of the pathologists, I learn of the pathology department’s proud record of completing timely diagnostic analysis—97% of samples taken by surgical biopsy are being processed in 7 days. The department processed 1070 samples for neurosurgery in 2013 and 1239 in 2014.

In the following passages, I describe what happens to tumour tissue after it has been removed by surgeons. I focus on how the tissue is processed and made into slides and how these slides are interpreted by pathologists. Like radiologists, pathologists also work to shape the directive character of their reports and this is something I foreground in this section. In an attempt to show the complexity and specificity of their work and the professional and epistemological borders bolstered in language, I keep many of the emic terms of pathology work. I begin at a workstation in the laboratory with Margot, a biomedical scientist as she works directly with the tissue. This tissue was removed from a patient by an operation and arrived in the laboratory the previous day.

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When tissue enters the laboratory from surgical theatres it must first be “processed,” “embedded,” “cut-up,” and then “stained.” It arrives in formalin but, if left too long, the cells will become poisoned. “Our job is to preserve the content of the cells,” I am told by Margot, “so we first dehydrate the tissue—this is *processing*—and then embed it in paraffin wax—this is *embedding*.” Like this, the tissue can be stored for hundreds of years. The wax also makes it a workable material. “We used to do this by hand but now we have machines,” Margot says. She opens up the machine to remove a metal tray in which small green and yellow cassettes are stacked. Inside the cassettes are pieces of tissue, already dehydrated.

She takes the tray to another machine and sits before using tweezers to remove a piece tissue the size of a pea, gently placing it into a small metal mould. She squashes down the tissue so it is reasonably flat and spread, though retaining its depth in the mould. She says she doesn’t squash it down too firmly—“you can damage it this way”—but she makes sure it lies flat so it can be cut in even sections. Once oriented correctly, she pours hot wax over it, places the empty cassette on top, and moves the covered mould to a frozen plate to cool. As it cools the wax turns opaque and the cassette becomes fixed in the wax. She says the tumour is from the pituitary. “Pituitary tissue comes in lots of tiny fragments because the surgeons operate through patients’ noses,” she says, “but pathologists prefer nice big sections to look at—bigger tissue is better for diagnosing because there are more cells.”

Soon a pile of moulds amasses on the frozen plate and I follow Margot to another room, much larger, in which three others work. Like Margot, they wear white smocks. She has brought the moulds with her and places them by a machine—“it’s called a microtome—but we call it the ham slicer—we use it to *cut up* the tissue.” She shows me the controls—

simple levers and wheels. She takes one of the wax blocks, removes it from the mould and places it on ice—“it cuts better when the surface is frozen.” Then she clips the block vertically onto a plate that she moves up and down against a blade. First, she gets rid of the layer of wax to reach the tissue. She does this quickly. Then she slows to cut a section off the block, in which a slice of tissue is embedded. “We cut this at four microns—that’s four thousandths of a millimetre.” It needs to be thin otherwise it won’t show much under the microscope; but too thin and the tissue does not stain well.

After cutting the section, she carefully lays it on water. “This is to make sure there are no wrinkles in the section—wrinkles make the slide difficult to read.” She leaves the section floating in the water bath for a moment before removing it to a glass slide and letting it dry on a heated tray. “And you can get artefacts on the slide if you don’t dry it properly.” Artefacts are made during the production process. They introduce uncertainty to diagnosis because they can be mistaken for features of the tissue.

While the section dries, Margot continues with another block, scraping away the layer of wax again, reaching the tissue and stopping. This time she removes the block with a dissatisfied “ugh.” She tells me you have to be careful about damaging the block and shows me how its surface is scored and smudged. “It’s caused by calcium deposits in the tissue—you can hear it on the blade.” She now has to “decalcify” the block with formic acid and soften the tissue with fabric softener. “Meningioma tends to be problematic here because these are tumours often close to the skull.” She says you have to replace the blade when this happens. She also changes the blade when a layer of wax builds up on it that cannot be removed. Wax built up on the blade can smear the surface of the block and make the sections misty—the blade has to be razor sharp.

Margot checks the sections she cuts against the blocks to make sure the pattern of tissue is the same. Then she writes the patient number on the slide. She tells me you have to be clean to avoid contamination, and tidy “for the perfect section.” Like the other biomedical scientists I meet, Margot takes pride in her work and she is aware of muddying the picture for the pathologists. She is not medically trained but she knows about tumours and follows the diagnostic outcomes of the tissue she works with.

When she has filled two racks with drying slides she takes me over to another station for the final stage of her morning’s work—staining the tissue. The floor is stained multi-coloured by many spills. “Staining is all about colour,” Margot says, “you want things at the opposite end of the spectrum, so if something is red then you want to stain the background with something blue. This is called counterstaining.” She explains how the different dyes

bind to different tissue components. The point is that in adding colour you make a *pattern*—or *script* as pathologists sometimes explained—that can be read underneath the microscope. In the case of the most common stain—Haematoxylin and Eosin (H&E)—the haematoxylin stains nuclei blue and eosin stains cytoplasm pink. Patrick, another biomedical scientist, joins us to help Margot get the slides out on time. He picks up on the conversation about colour. He says many of the methods they use now were found through trial and error, rather than knowing why something was happening, “we still don’t really know—it just works—the dyes came from the textiles industry and methods were gradually refined. The histochemical staining is slightly different because we know what’s going on, we know the chemistry of what’s happening. And the immunohistochemical stuff is very different again—it’s about antibodies affecting antigens.”

Patrick, who has lived through much of the recent history of pathology, explained as he dropped dye on tissue from a pipette—“This one is an original from Weigert, one of the fathers of pathology, modified over the last 100 years. H&E has been around since the middle of the C19th.” These are tinctorial staining methods. But since the 1970s immunohistochemistry has become more important and has expanded and occupied neuropathology. “We used to use horrible substances. The Holzer method. We used analine—very dangerous. It stains glial fibres. But now we don’t do that—the GFAP immuno has taken over from that. What I’m doing here is a tiny bit of what we used to do.” Margot says the immuno can quantify and this is the benefit—“All the tinctorial is qualitative—it’s interpretive.” What she says in essence, is that it needs more human input to make sense of it. As the immuno expanded, Patrick says, other more qualitative methods retracted—“but then again H&E probably won’t ever get replaced—all tests start from there—that’s what the pathologist will look at first.”

When Margot, Patrick and the other biomedical scientists have finished staining sections of tissue, they take them through to the pathologists. I follow Margot as she delivers them, hanging up my white coat as I leave the laboratory and cross the corridor. Once delivered, Margot returns to the lab and I stay with Dr Littleton, a young consultant pathologist.

...

Dr Littleton sits at a table in front of a large microscope with multiple viewing points. The room feels cramped after the large laboratory. Computer screens and stacks of thin card

trays holding slides crowd workbenches. Bookcases reach towards the ceiling and bend to the weight of the last four editions of the WHO's manual for the diagnosis of brain tumours, medical atlases, and several editions on artefacts and errors of slide production, which guide their work. You could have ten people look through Dr Littleton's microscope at the same time—at weekly review meetings they often do. He is doing an initial sweep of the slides that just arrived before meeting with Professor Lucas, a senior consultant. I sit opposite him and watch through the microscope while he moves the slide up and down, side to side, covering it fully. Every half minute or so he pulls away from the microscope to write notes on the referral letter—CD34, H3, Ki67—these are notes on which stains to order next.

He takes his time, sometimes pausing, sometimes using a marker to circle an area directly on the slide. He says that doing pathology is about recognising patterns and making comparisons—“scales, patterns and exceptions to patterns”—some research suggested good pathologists work more by experience and learning than aptitude, he says. Others have spoken to me about working “tacitly” and “intuitively” and having to get their “eye in,” especially when looking at slides made with new staining methods. Explaining this, one consultant pathologist used the analogue of sexing chickens—“It has to be done very quickly when they're chicks and when the differences between male and female chicks are so subtle. Even the people sexing the chickens don't really know how they do it.”

Professor Lucas enters the room apologising for being delayed. Dr Littleton moves to another viewing point allowing her to move the slide and direct the view we all see. While Professor Lucas adjusts her seat and focuses the microscope, Dr Littleton reads off the medical notes. Often, they get very little clinical data along with the tissue, something that Dr Littleton finds particularly annoying. It might simply say something like: “Right temporal tumour; headache and seizure—?GBM.” He says that radiologists get much more. The implication by the clinical team, he tells me, is that pathologists need less of a steer; that their work deals more with the biological facts (and hence singular truth) than the more interpretive endeavours of radiology.

“The patient was diagnosed two years ago with grade II astrocytoma and had a recent second surgery,” Dr Littleton says to Prof Lucas. “That's a shortish interval between two surgeries,” Professor Lucas replies. She talks as she slowly moves the slide—“The cells are being pulled a bit here, a bit more rounded there. I can't see any necrosis. I'm a bit cautious. There is a hint of oligo but it's been previously reported as astro grade II. There is some old blood in the tissue there—sometimes there can be a greater propensity for

bleeding at second surgery. It's IDH positive. But on the previous report from the first excision it was reported that there was an IDH mutation. There's no LOH 1p loss but LOH 19q loss. What about ATRX?" Dr Littleton has the previous report in front of him.

"Actually it's quite new so it probably wasn't done in 2013."* She tells me that ATRX labels neurones. It's a relatively new immunohistochemical stain—"It's very obvious when it marks so let's just say 'ATRX lost.' The capillaries are dark but," she pauses, "so ATRX mutated. We'll have to ignore all the oligo—that's in the history books now."¹¹* She switches slides. "So now we're just grading. This is H3 a type of marker which shows up mitosis. It should be negative because the tumour is suspected from the first analysis to be low grade. It's not high at all. Or is it? Maybe 5%—let's see about hotspots—it's pretty even. So it's a tumour without anaplastic features—grade II."*

Next case: "A woman in her late 30s,"* Dr Littleton reads, "previous smear suggested it was glial."* Professor Lucas has the slide in view. "It's diffuse in the bits we have—hypercellular—some necrosis—some endothelial proliferation—it's quite vascular—oh that's lovely."* She picks up another slide, places it under the microscope and sets the focus before placing the slide just reviewed back in the cardboard tray. "GFAQ looks brown—a scattered stellate pattern—ATRX in this case is quite dark in most areas—in most fragments—IDH1 is negative—what's CD34 showing?"* She switches slides again. "No—hmmm—not really—so this is negative—though this is tricky, hard to read—I would say probably negative."* Dr Littleton agrees and says that when you look at the control it's really dark.

Professor Lucas: "There's a vascular CD34 pattern but we don't know whether this sample is representative so we need to check the radiology."*

Dr Littleton: "But there's no loss of 1p19q."*

Professor Lucas: "This puts us in the GBM wild-type category."*

Dr Littleton: "So should we put something in comments? What's Dr Plank's phrasing? 'under-sampled GBM?'"*

¹¹ During my fieldwork, new molecular techniques were starting to be integrated with previous histological techniques to classify tumours. I describe this integration and some of the social consequences it entailed in chapter 2, but some explanation is needed here. One of major consequences was the reclassification of several tumours according to molecular data and their displacement or disappearance in the WHO's diagnostic manual (published in May 2016 subsequent to the interaction between Drs Lucas and Littleton presented here). Among the reclassified tumours was Oligoastrocytoma. On the basis of new molecular data, the 2016 manual recognized oligoastrocytoma as a mixed tumour with an astrocytic and an oligodendroglial component, and which was very difficult to define. A recent chapter by Mellai and colleagues (2016) summarised this simply in their title: "Oligoastrocytoma: A Vanishing Tumor Entity." Pathologists must now make a distinction and decide between whether the tumour is an oligodendroglioma or astrocytoma. This is what Prof Lucas means when she said, "We'll have to ignore all the oligo—that's in the history books now." See <http://www.intechopen.com/books/neurooncology-newer-developments/oligoastrocytoma-a-vanishing-tumor-entity>.

Professor Lucas: “Write something like ‘watch this—it may behave in a more aggressive way.’ Let’s do a high grade GBM panel—I would do lots of different stains.”*

Dr Littleton makes some notes and Professor Lucas sits back from the microscope. She says that this surgeon usually sends them particular bits for smears and other pieces for further analysis; others send the fragments all together and let them choose—“It’s a sign of experience and it tells us that he wants a diagnosis.”* Dr Littleton says that sometimes they get very little tissue to work with—“The surgeons will say we got 80% out of a 4cm tumour and then we get this.” He pinches his fingers together to indicate a fragment. ““So, where’s the rest?’ I think. It’s hard to interpret. But hard or not, it’s still useful. And if it’s not *morphologically* useful, it might be useful for other analysis. We’re always telling the surgeons to send everything to us. But the fact is we always act after the fact of surgery so we’re largely dependent on the surgeon. Some know we don’t work in a vacuum, others just don’t get it.”

This is a key point and relates the lack of clinical information they are given. Pathologists, as with all members of the multidisciplinary team, are situated along a chain of activity. Their work is contingent on the prior steps of surgeons who remove tissue and, as I have shown, biomedical scientists who process, embed, cut and stain it. Errors or choices made during the activities of surgeons or biomedical scientists therefore complicate the downstream practices of pathologists.

...

Pathologists, including Dr Littleton and Professor Lucas, told me they are at the endpoint of a “diagnostic funnel.” Everything that happens up until their involvement—the clinical histories, the radiological scans—contributes a working diagnosis. This means they have a particular epistemic authority in the diagnostic process and a responsibility to be categorical. They work directly with human tissue and they translate it into the bold text of a report. Pathology test reports are short, formulaic, technical and written as a definitive script with subheadings: Specimens(s); Clinical data; Smear/Frozen section; Macroscopic description; Microscopic description; Histological analysis. Pathologists say it is this final section which clinicians are most interested in—the diagnosis, for example, “Glioblastoma (WHO Grade IV).” And while they are titled with qualifier of “opinion,” they are artefacts which circulate with the status of fact.

This certainly accorded with my observations in multidisciplinary team meetings when reporting pathologists would sometimes be hurried to answer, “What’s the bottom line? What is it?”* Aside from this, clinicians might look at the microscopic description which might read something like:

All specimens show similar features and are described together. There is a malignant glial tumour which is highly cellular, predominantly composed of sheets of relatively small cells demonstrating astroglial differentiation. Occasional small rounded cells with uniform chromatin are noted in the CUSA fragments. Numerous intervening small vessels are seen, some of which demonstrate microvascular endothelial proliferation. Mitoses are frequently identified and there are many foci of pseudopalisading tumour necrosis. Immunohistochemistry for GFAP is positive in the majority of the lesional cell ad processes, with some cells demonstrating weaker staining. IDH1 is negative by immunohistochemistry and ATRX appears to be retained. The Ki-67 proliferative index is patchy, but is up to 15-20% in the most active areas.

INFLUENCE AND AUTHORITY

As these accounts of the diagnostic process show, producing knowledge about brain tumours in order to diagnose is extremely complex. It involves a number of specialists who work with particular technologies according to more or less standardised protocols in various sites in the hospital and yet with significant room for human interpretation and error. The practices undertaken in these sites significantly influence downstream decision-making and while the end result of a pathology report is a diagnostic fact, their work is anything but detached and neutral. Radiologists and pathologists took pains to structure their reports, writing for particular audiences, for example, whether a GP or oncologist, experienced in neuro-oncology or not, and in ways that intend to persuade others, temper uncertainty, or diffuse a potentially panic-inducing finding. Time and again, they told me it was important “to be helpful,” “to guide,” “to direct.” Their work is interpretive and part of that interpretation is to manage the downstream social consequences of knowledge and to direct or guide clinical decisions.

If we zoom out to consider the diagnostic stream across each of these cases and the various translations that happen along the way as narrative, sensation, experience, tissue, and image is reproduced in text and classified in nosology, we see, to paraphrase Adriana Petryna, how patients’ initial experiences of car crashes, seizures, headaches and difficulties reading, are refashioned and refracted through a series of technical strategies, errors, semiempirical models, approximations, informational omissions and international standards (Petryna 2002:215). Combined, these produce a picture of a known, circumscribed, and manageable

biological reality. In each case and at each translation, uncertainty, disagreement and qualification is somehow *lost* or *contained* within certain spaces: information becomes further reified towards the certainty of fact (Latour 1987; Latour 1999).

Take pathology, for example: Tissue arrives from surgical theatres, it is dehydrated, set in wax, sliced, stained, seen under a microscope, discussed and written about in particular ways. These reports are read by others also in particular ways, who, as I heard from multiple sources and observed in meetings, are interested mainly in the “bottom line”—the narrow band of diagnosis. This diagnosis circulates among the team and is eventually communicated to patients. The qualitative difference in how information is considered from laboratory to clinical consultation is do with the degrees of certainty and uncertainty and essentially, the difference between *opinion* and *fact*.

In this way, we could consider how uncertainty is *contained* in spaces like the laboratory, which as I described above, are geographically apart from the clinical space, secure, and very rarely visited by clinicians. And there are other structures which help to contain uncertainty. The slides, that is to say the material images used by pathologists to make their interpretations, are kept in the laboratory and rarely leave. For each patient, clinicians might only see one or two slides at weekly MDT meetings. And then there is the technicality of language used by pathologists to describe their work and the tacit level at which they make their interpretations. This corresponds to how pathologists receive new stains, talk about “getting their eye in,” and describe the intuitive nature of their work. It is about tacit knowledge and what medical historian, Lorraine Daston, calls in her essay *On Scientific Observation* an “all-at-once intuition:” “the condensation of laborious, step-by-step procedures into an immediate coup d’oeil [where] what was once a painstaking process of calculation and correlation—for example, in the construction of a table of variables—becomes a flash of intuition” (Daston 2008:108). Their knowledge, therefore is deeply contingent on developing a way of seeing. After I had spent a week in the pathology department, pathologists would sometimes joke that I had more training in their work than the clinicians. While this was exaggerated, it underlines the specialty of their work and, because of this, how challenges by others are highly unusual.

All this reinforces the authority of pathologists and “black box” their work, as the surgeon remarked and as Bruno Latour, and other scholars of science and technology, have theorised (Latour 1987; Latour 1999; Latour and Woolgar 1986). “Black boxing,” writes Latour, “is the way scientific and technical work is made invisible by its own success. When a machine runs efficiently, when a matter of fact is settled, one need focus only on its inputs

and outputs and not on its internal complexity. Thus, paradoxically, the more science and technology succeed, the more opaque and obscure they become” (Latour 1999:304).

To an extent, these descriptions hold for radiology. But as previously mentioned, the digitisation of scans has done much to democratise interpretation. As such, I saw on several occasions instances when clinicians would disagree with formal radiological reports and frame their descriptions of images differently to patients during consultations. Yet far more typically, the expertise of radiologists would carry their interpretation. Interestingly, this relates to the type of scan done and the familiarity clinicians and other members of the MDT have with them. There was, for example, only one radiologist with the requisite expertise to interpret images produced by a certain kind of perfusion scan. Clinical histories are further towards a democratic interpretation and openness to challenge than radiology. As I will show throughout the dissertation, they are more subjective and often reliant on patient and family narratives. As such, they do not hold the same epistemic authority and yet still they are a key form of knowledge about tumours and directive of treatment course.

DIVERGENCE AND COORDINATION

However, it is not quite so straightforward and a suggestion of simple progressive certainty through the diagnostic process would betray the contradiction and iterative quality of diagnosis-making. As other ethnographic accounts of diagnosis have shown, there may be different accounts of disease which contradict each other or misalign (see for example Mol 2002; Koch 2016). Given this, the stability which is acquired and received is not absolute. Here, my ethnographic case is the multidisciplinary team meeting. These meetings are a critical point through which information about patients is presented and discussed and treatment is planned. They are considered good clinical practice by the National Institute for Health and Care Excellence (NICE)—a means through which patients’ cases receive the input from a variety of professionals.

These meetings are weekly and attendance is mandatory for surgeons, oncologists, neurologists, clinical nurse specialists, palliative care physicians, speech and language therapists, radiologists, pathologists, an administrator and medical students. For 90 minutes, up to 40 members of the clinical team gather in a lecture theatre to discuss the current caseload of patients requiring clinical input (typically also around 40), diagnosis and treatment planning. They are highly structured starting with the seating plan, which, though nominally unorganised, is deeply entrenched in the dynamics of hierarchy. After my first

meeting, I was told by a surgeon that “you can almost see the diffusion of power as you move back up the tiered seats.”* Surgeons, oncologists and neurologists occupy the front two rows, with nurses, allied health professionals and palliative care next, and medical students at the back. The on-call radiologist and pathologist sit on stage facing the tiered rows and projected above and behind them are the huge monochrome images of brain scans or the coloured patterns of stained tissue. Although present, nurses, allied health professionals like Speech and Language Therapists, Psychologists, and Palliative care professionals, rarely speak.

Clinical histories are given first, again highly structured—age, previous medical history, symptoms—typically by a registrar or the patient’s consultant; radiology is then described by the radiologist followed by the pathologist’s description of findings. Typically, these descriptions proceed without controversy and within perhaps one or two minutes an image of a tumour type emerges that is continuous with patients’ clinical conditions, radiology, and pathology: they *align* (Mol 2002). However, there are also cases less simple, with divergent descriptions, and here, in the words of Annemarie Mol, different accounts of disease must somehow be made to “hang together” in coherent form (Mol 2002:55).

Coordination of these different versions happens through various techniques: by discarding or devaluing one or other account, for example. Most often this involved a hierarchy of knowledge in which clinical history defers to radiology, defers to pathology. Knowledge produced in the laboratory is the “gold standard” for diagnosis, I was told repeatedly in accounts that resonated with Dr Littleton's description of being at the end of the diagnostic funnel. The classification of brain tumours, standardised by the WHO, is based upon tissue diagnosis, with no input from radiology or clinical history aside from descriptions of correspondence and what to expect in radiology and symptoms. As Dr Littleton told me, everything up to pathology contributes a working diagnosis and as he further explained to me during an interview, they must make a call on discrepancy:

The defining piece of information that you need to call something in the case of an oligodendroglioma is [...] a chromosomal event. And that correlates very well—about 90 to 95% of the time to a particular histological pattern, which correlates about 85% of the time to a particular radiological pattern. So what happens quite a lot in the MDTs is one of the radiologists will say, “this looks like a glioblastoma”—and most of the time they’ll be right. But occasionally, they won’t. And so the challenge is then to ask: “Is what they’re seeing wrong? Have they misinterpreted what they’re seeing? Have they placed too much weight on one radiological feature, like calcification?” So often when the preoperative diagnosis is demonstrated to be wrong there’s a reason behind it. It’s either a slightly unusual manifestation or you can see with hindsight the radiological diagnosis is wrong.*

And yet, the hierarchy is not absolute: there are moments in treatment planning when lab knowledge is relegated to sit beneath radiology or clinical history, or radiology made to sit beneath symptoms. This happens in recognition of the specific practices of knowledge production and their proneness to error. The quality of knowledge produced in the laboratory is contingent on the amount, quality and location of tissue removed during surgery and the quality of slides produced. Cells can also be crushed during surgery, “poisoned” by formalin, over- or under-stained, folded on the slide, or contaminated by micro particles, during processing and slide production. This is why Margot and the other biomedical scientists work so carefully and why the pathologists consult books and articles on artefacts of slide production. Sometimes there simply is not enough tissue. Sometimes biopsies might be mistargeted meaning they collect tissue from a location with only a fraction of cell types, which end up being misrepresentative of the whole tumour. This is what Dr Littleton and Professor Lucas meant when discussing the radiology and how to frame a discrepancy of interpretation perhaps caused by an under-sampling of tissue. Consider the following exchange during one of the MDT meetings when one of the surgeons, Mr Fitzroy, presented a 58-year-old patient with multiple seizures.

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Describing the black and white MRI image projected over the room, Professor Kandu, the on-call radiologist, suggests that the tumour is “enhancing”—a radiological signal indicating tumorous tissue—and further that “it looks like a GBM—grade IV.” One of the other surgeons says it could also be an anaplastic grade III tumour—also cancerous. The radiologist agrees and Mr Fitzroy asks Dr Littleton, who sits at the microscope, for the pathology.

“It’s a slightly disturbed biopsy,”* Dr Littleton says, as he moves the pink and blue stained slide back and forth, which is projected overhead having replaced the black and white scan. “There are only occasional mitotic figures—less than 3 per cent,”* he continues, “It looks like an astrocytic tumour—morphologically it’s grade II.”* Professor Kandu disagrees and emphasises the enhancement on the scan which does not correspond to a low grade tumour: “This is not grade II.”* Mr Fitzroy adds rhetorically, “If you’ve got mitosis then wouldn’t that mean that it’s a higher grade?”* to which Dr Littleton responds that the WHO classification “is a bit woolly—it says ‘more than occasional mitotic figure’ for an anaplastic astrocytoma.”*

Mr Fitzroy counters, “As an amateur [pathologist] it looks quite cellular (another indicator of a higher grade tumour). I’m happy as an MDT to upgrade this to a grade III.”* The on call brain tumour pathology consultant, senior to Dr Littleton and who authorised the pathology report, says she is happy to upgrade the diagnosis but with the caveat that “on morphological grounds we cannot say this.”*

Mr Fitzroy says he would just treat on the basis of anaplastic astrocytoma, grade III tumour, which would mean a course of radiotherapy. The other surgeon agrees and suggests that if they could get more tissue, it could even be a glioblastoma—grade IV. Dr Anton, the oncologist who would receive the patient for treatment, says that, for her, the obvious and important difference is between grade III and grade IV—this would make a difference to how she treats the patient, with the addition of chemotherapy should the tumour be higher grade.

The radiologist says that they could also do a different kind of imaging more sensitive to grading tumours—it could be done in a week. He reminds the MDT that they had a similar situation before and when the patient was biopsied for a second time, it was shown to be grade IV by a second tissue analysis. The MDT agrees for the follow-up scan to be done and to treat the tumour as higher grade.

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The end result of this exchange was to treat the tumour as though it were higher grade than what was morphologically apparent in the pathology analysis and to rescan the patient to confirm the precise site of the original biopsy. If the new imaging showed that the biopsy was not done on the enhancing part of tumour, then the team might consider another biopsy before treatment. It is a rare example of how the ordinary gold standard of pathology is disrupted over concerns with under-sampling and a contrary radiological finding.

This exchange also introduces the algorithmic workings of the care pathway and the critical role of diagnosis in initiating and organising a cascade of medical processes (Smith-Morris 2016), to which I now turn.

PLANNING ALONG PATHWAYS

Care pathways (cf. patient pathways, clinical pathways, integrated care pathways, coordinated care pathways, protocols, algorithms) have become a defining feature of medical decision-

making (Zander 1991; Zander 2002; Ishikawa, Hashimoto, and Kiuchi 2013). Put simply, they are tools that map out chronologically key activities in a healthcare process (Allen 2009; Berg 1998). Although not new to medicine, it was only in the 1960s and 1970s that pathways were formalized to address problems of variability in medical practice and concerns that physicians' choices were often arbitrary and poorly explained (Berg 1998). Through its branching structure, a physician could “at long last, specify the flow of logic in his reasoning” so that clinical reasoning “can begin to achieve the reproducibility and standardization required for science” (Feinstein 1974). Echoing sociologist of science Marc Berg (Berg 1997; Berg 1998), the early rhetorical foundations of pathways were therefore science, reproducibility and standardisation, and the figures subject to their implementation were physicians whose practices needed to be brought into “greater compliance with standards based on current biomedical research” (Kanouse et al. 1989:XV).

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At the Warner, the pathway for brain tumours begins with the suspicion of a tumour, after a patient has been admitted through primary or secondary care, and routed through the various diagnostic processes described above. Thereafter, lie further decision points arranged along a more or less linear course and in a direction typically towards intervention. The guidelines published across several documents by London Cancer's Brain and CNS Tumour Pathway Board just five months before I arrived in the field in 2014 detail these decision points in descriptive passages and “management decision algorithms” set out in tables. I was sent the documents soon after arriving in the field by a nurse following a conversation about patient choice and standards of care.

The London Cancer documents clearly delineate therapeutic approaches recommended for different tumours and the influence of factors like age, performance status measured by the Karnofsky Performance Status (KPS)—a clinical tool which indexes physical function in categorical scores ranging from 0 *Dead* to 100 *Normal, no complaints, no evidence of disease*—and the outcome of surgery—for example, whether more than 90% of the tumour was removed during surgery.

Descriptions and algorithms for each broad category of tumour—for example, gliomas, meningiomas, schwannomas, pituitary tumours, ependymomas, chordoma and chondrosarcoma—are detailed in “tumour-type specific guidelines.” The text for high grade glioma tumours reads:

All patients with [high-grade gliomas] should be considered for radiotherapy. Radiation therapy is standard and has been shown to prolong survival by 3-6 months and improve quality of life, when compared to no radiotherapy. Treatment decisions should be based on known prognostic factors such as age and performance status. Patients with a poor prognosis may be better managed with active supportive care (London Cancer Brain and Spine Pathway Board 2014:3).

Beneath this, the algorithm details these decisions, set in tabular form:

KPS <40 plus <70 years = no treatment;

KPS <40 plus >70 years = no treatment;

KPS 40-70 plus <70 years = Palliative Radiotherapy;

KPS 40-70 plus >70 years = no treatment;

KPS >70 plus <70 years = Radical Radiotherapy +/- chemotherapy;

KPS >70 plus >70 years = Palliative Radiotherapy.

By and large, I watched these courses play out in the MDT meetings, with patients discussed in terms of prognostic features and risk—age, performance status, and so on—all of which would be scripted in clinical histories and adorned sometimes with more personalised accounts of “this lovely woman in her late 60s” or “this poor man with a history of grand mal seizures,” and the narratives of car accidents or incidental findings. While KPS score was sometimes given, clinicians were also more detailed in their accounts, contouring the descriptions coded in the KPS scores and especially at the points more clinically meaningful—40 *Disabled; requires special care and assistance*; and 70 *Cares for self; unable to carry out normal activity or to do active work*.

Most of the patients I followed up were diagnosed with glioblastoma grade IV tumours, less than 70 years old and deemed functionally able to tolerate aggressive treatment. After surgery, they were given chemotherapy and radiotherapy together for six weeks and temozolomide chemotherapy adjuvantly for six months. This has been the clinical standard for glioblastoma since a 2005 study showed a modest survival gain over radiotherapy alone (Stupp et al. 2005).

...

It was not simply the medical profession that advocated for pathways in daily care. Governments and hospital managers used them to wrest the inner workings of healthcare and make it subject to their administration (Berg 1997; Starr 1982; Timmermans and Berg 2003). In the UK, the shift away from individual discretion towards de facto rules that are capable of being audited (Pinder et al. 2005; Strathern 2000) accompanied the creation of ‘joined-up services’ (Ling 2002) and efforts to place patients at the centre of care (McCormack and McCance 2006; NICE 2012). In this reorganisation, disparate professional groups would cohere around a central matter of concern, avoiding the potential for professional conflict. It was assumed patients would be afforded new opportunities for equitable care and choice that hitherto had been the prerogative of physicians (Pinder et al. 2005; Stevenson et al. 2000).

Such discourses, however, obscure problems in how pathways have been embedded. Critics highlight how pathways assume an optimal path corresponding to every medical problem: the “widespread *illusion of a single answer*” (Berg 1997:1083, *italics in original*). This ignores the multiple overlapping modes of reasoning that characterise medical practice and the social lives of patients (Mol 2002; Pinder et al. 2005). Pathways end up being constituted by things—information, activities, people—that are easily codifiable (Berg 1997). Patients become defined by impairment and bodies essentialised (Pinder et al. 2005); “soft” or experiential knowledge is side-lined in favour of the “scientific state of affairs” (Berg 1997:1085); and care practices lacking an observable outcome become deprioritised or invisible (Allen 2014; Pinder et al. 2005).

All this reinforces tendencies to describe the management of patients’ journeys as a sequence of rational decisions (Berg 1997) and gives the impression of closure and linearity as patients are moved towards an end goal (Pinder et al. 2005). The implications of such approaches are clear distinctions between stages and orientations such as *radical*—an intention towards cure—and *palliative*—one that emphasises the alleviation of pain and symptoms (Timmermann 2012). There is therefore minor consideration of the blurred boundaries between stages and the contingent and improvised nature of care. Moreover, there seems in many cases an unduly optimistic and “can-do” attitude to management based around a technological imperative and medicine’s mandate to extend lives (Kaufman 2005; Kaufman 2015; Kaufman 2016).

Insurers have also established themselves as key players in the reification of pathways and the disciplining of care (Berg 1997; Kaufman 2015; Timmermans and Berg 2003). Sharon Kaufman convincingly argues that a chain of connections among science, politics,

industry and insurance organises the production of evidence and drives US healthcare (Kaufman 2015; Kaufman 2016). In this “medical industrial complex,” insurers make certain interventions, made *thinkable* in clinical trials, *doable* in routine practice by reimbursing for their use. This generates treatment standards that drive patients’ expectations about what is “normal” and “needed.” In 2016, the power of insurers to set pathways was revealed in the American Society for Clinical Oncology’s recommendations for pathways (Zon et al. 2016). These cited problems in “patient access, quality of care, and transparency in the weighing of information on clinical outcomes, toxicities, and costs in final pathway development” and reported oncology practices having to adhere to multiple pathways for the same type and stage of cancer “because of the different requirements of the payers covering patients” (Zon et al. 2016:262).

Although less obvious in state-financed systems, such as the UK National Health Service (NHS), insurers still contribute to the shape of care, not least in the global congeries of care and medical research in which treatment imaginaries and technologies circulate; for patients with private health insurance (11% in the UK, reported by King’s Fund 2014), the influence of insurers is clearly much greater. In the NHS, the particularities of pathways are locally configured. Yet, they must adhere to standards set by the National Institute for Health and Care Excellence who marshal evidence about technologies and interventions, as well as the Department of Health and regulatory commissions who determine what is fundable across disease groups according to logics of cost effectiveness (Shaw et al. 2013).

FIXING THE TERRAIN

Diagnosis and care pathways represent and embody a critical function in how care and treatment is imagined and practiced. They are the standardised expressions of Mr Muldoon, the surgeon’s, proclamations: *now here we are* and *where we go is*. They work in tandem to make disease *navigable*. Extending this navigational metaphor and paying serious critical attention to the implications of locating disease in a spatiotemporal grid, we might consider the diagnostic moment as one that *fixes the terrain* (Llewellyn et al. 2017). By this, I mean to emphasise the ways in which modern medicine fixes uncertainty and instability in relatively static landscapes. I also mean to suggest the ever-present implication to intervene in—or *fix*—the destructive course of disease. There is therefore an imposition of demand given in diagnosis, as it is a process already entangled in these attempts to intervene (Jain 2013; Rosengarten 2009).

As I have shown throughout this chapter, and as multiple accounts of diagnosis attest, diagnosis is a strategic event that is mobilised and transformed (Koch 2016; Mol 2002; Petryna 2002). We see this not least in the expressions of radiologists and pathologists and their attempts to be helpful and to direct. While they present the outputs of their work as opinions or facts and descriptions of the natural world, the practices of their work reveal processes of valuation. Behind this, as ethnographers and theorists of science, medicine and technology have repeatedly shown, lie the broader networks through which disease categories, experimental possibilities and standardised protocols are constituted (Timmermans and Berg 2003). Seen in this way, brain tumours, like all diseases, are not simply a biological event—natural and neutral—they are also fundamentally social, already and always entangled in the intentions to intervene. They are the first and key feature in the institutional fields that shape patients’ lives (Biehl 2013), and their power in organising a cascade of medical processes lies in how they constitute the foundation of medicine. In essence, the biomedical project makes diagnosis not simply a fixture in a landscape, but the ground itself. Through and over this ground, pathways can be routed, contoured always to the possibilities given in the diagnostic terrain and typically along a teleology of cure.

This ground and these routes are set according to parameters that unfold outside the lives of individual patients. Moreover, these are often unclear since diagnostic categories and pathways emerge from complicated histories and through the logics of multiple stakeholders. Far from neutral tools, they ascribe particular notions about risk and evidence, and impose sets of goals that circulate around ideas about longevity and quality of life, and what is tolerable regarding side effect and symptom. Importantly, these standards often differ from those of patients and families who, as I will show throughout the following chapters, enter new “arenas of constraint” (Inhorn 2003) yet attempt to find ways around.

CONCLUSION

Diagnosis is a fundamental classificatory tool in medicine—at once an act of naming and mobilising an impetus to act. It is therefore a vehicle of authoritative medical reference (Smith-Morris 2016). In this chapter, I have presented professional perspectives on disease and the importance of diagnosis to their work. By closely tracing the practices undertaken in the hospital laboratory, radiology department, clinical consultation, and the dynamics of coordination in the multidisciplinary team meeting, I have shown the distributed processes that lead to the diagnostic moment and the approach of clinicians, like Mr Muldoon, to

proclaim *now here we are*. Further, by presenting the care pathway as an archetype of modern medicine, I have shown the routes used to establish a direction of care—*where we go is*. Elaborating the navigational metaphor embedded in clinical and policy talk, I proposed the analytical concept of *fixing the terrain* to emphasise how modern medicine attempts to fix uncertainty and instability in relatively static landscapes as well as the implication to intervene in—or *fix*—the course of disease. This captures at once the attempts at stability associated with diagnosis and that of intervention.

I have also mapped out some of the spaces of the hospital, elaborating and peopling settings like the laboratory, the radiology department, the lecture theatre, and the consultation room and introduced some of the key technologies like scans, microscopes and clinical tools, as well as the professional actors involved in the care of people with a brain tumour—surgeons, neurologists, oncologists, nurses and allied health professionals—who meet with patients—and radiologists, pathologists, and biomedical scientists—who tend not to. It is across these spaces, the people in them, and the technologies they use, that diagnosis, decision-making and care is *distributed* (Rapley 2008). Entering the “kingdom of the ill” (Sontag 1978), then, means coming under a new authority of medical science and being newly located in its strange terrain—one terraformed by images, stained glass slides, algorithms, and the logics of statistics.

In the following chapter, I focus on the integration of a new *way of seeing* brain tumours, focusing on the social consequences of this integration and how it unsettles the diagnostic terrain. Thus, while this chapter has concerned fixity, the following chapter concerns a fundamental feature of fluidity in biomedical knowledge and its productions.

CHAPTER 2—THE MOLECULAR TURN

In May 2016, the World Health Organisation published a new manual for the classification of brain and central nervous system tumours with the statement that it represented “a substantial step forward over its 2007 ancestor” (Louis et al. 2016:818). This marked a pivotal moment in the integration of molecular genetic markers in the typing of brain tumours and set to establish a consensus amid controversy which had been waging for several years. While previously microscopic techniques were used, for the first-time molecular parameters were integrated and given primacy in the definition of tumour types. In simple terms, these new molecular features would allow for more objective tumour typing and prognostication and the ability to predict which patients are likely to respond to which treatments—a move towards *personalised* or *stratified medicine*. This personalisation and its increasing importance in directing decision-making was noted by London Cancer Brain and CNS Tumour Pathway Board in their 2014 guidelines—“Molecular analysis will increasingly be used alongside histopathological evaluation to characterise CNS tumours, providing information about prognosis and therapeutic response, and thereby facilitating patient stratification” (London Cancer Brain and Spine Pathway Board 2014b:5). The prescience of their statement anticipated NHS England’s vision for personalised medicine published two years later beneath the equally prophetic and optimistic title *Improving outcomes through personalised medicine: Working at the cutting edge of science to improve patients’ lives* (NHS England 2016) and 2018 guidelines for brain tumours published by the National Institute of Health and Care Excellence (NICE Guideline 2018).

Throughout my fieldwork the publication of the manual was hotly anticipated and a topic of much speculation among the MDT. Central to this speculation was the extent to which newly discovered biomarkers and novel techniques of identification would come to define tumour entities and what impact this would have on the treatment of patients. Repeatedly, I asked surgeons, oncologists, nurses and others about the impacts of molecular markers on their work and repeatedly I was told that the effects are still unknown—“we just don’t have the evidence yet—it’s still too early.” Others spoke about the change in terms of trust—“trusting the science,” “trusting experience,” “trusting pathology.” And still others emphasised the new hopes in the promise of objectivity and prediction. Pathologists, who as representatives of the community that diagnose and who are on the frontlines of knowledge change, characterised the debate as one between the forces of conservatism and progression. Unsurprisingly, they were far more conversant in the terms of change. Yet, together with the

rest of the MDT, they lived and worked in an unpredictable moment before these new procedures were fully established and *routinised* (Koenig 1988).

That things were uncertain and not yet fully integrated, however, did not mean that meaningful and instrumental change was not taking place in clinical practice. During fieldwork, I witnessed real changes in daily practice and in the tone and social dynamics of the MDT. Oncologists and surgeons alike, for example, emphasised the importance of pathologists not only in ordinary diagnostic work, but especially in the extraordinary times now unfolding. Again, using words like “trust,” “belief” and “faith,” they spoke of their deference to pathology’s assertion of the molecular over morphological and immunohistochemical features of tissue—hitherto the only means of diagnosis—and the need to update treatment plans accordingly. Relatedly, was the rapid expansion of a new research agenda and medical imaginary, inspiring new hopes for brain tumour communities amid a treatment landscape with extremely few possibilities for intervention.

In this chapter, I describe the unfolding importance of molecular genetic biomarkers to the projects of diagnosis, prognosis and treatment prediction. In the previous chapter, I described the routine productions of knowledge about brain tumours that were in place well before I began my fieldwork. While these same routines continued, they were joined—sometimes awkwardly—with new techniques in molecular genetics. Here, I present data on this integration and mark some of the social consequences that arose for patients and practitioners, in terms of a generalised condition of uncertainty, an increasingly algorithmic biomedical gaze and in the broader ethics of care. Moving once again between experience near and more distal layers of analysis, and also between time-points established in key moments such as the presentation of scientific findings, reports of various oncology consortia, and the on-the-ground introduction of biomarkers, I present a dynamic analysis of how local daily practice changes amid “scientific revolutions” (Kuhn 1970) and the major social consequences that lie therein.

I begin the chapter by detailing these diagnostic changes, using the accounts of pathologists given in interviews and debates in the scientific literature to story the changes in nomenclature (tumour typing) and diagnostic practice. Using these accounts, I draw out the promise of molecular technologies and describe the importance of *timely change* from the perspectives of those at the frontlines of their development and integration. Following this, I present a number of professional dilemmas entailed through a close hand ethnographic analysis of diagnostic routine, knowledge coordination, disclosure and treatment decision-making. Finally, I present some ways in which patients encountered, described and

negotiated molecular information. Analytically, I build on my analysis of navigation and terrain—established in chapter one—to suggest how changes in disease nomenclature, diagnostic practice, and increasingly personalised approaches to treatment, add a particular temporal and spatial fluidity. This we can think of as being akin to the movements of tectonic plates and major geological events such as an earthquake—events which cause sudden and radical shifts in the terrain to be traversed and the possibilities it affords for movements through and across.

A caveat is necessary: the changes wrought in the integration of molecular techniques are extremely dynamic. Both during fieldwork and after, significant change was happening (and continues to happen) at multiple levels. While shifting scientific knowledge and unfolding policy are more readily discernible through real time publication of commentaries, peer-review articles, guidelines and so on, the on the ground changes in practice have been much harder to capture since I left the field. Nevertheless, the key points of this chapter remain: scientific and policy change constitute a major current in the terrain to be navigated, provoking new and often unanticipated political, social, ethical and personal dilemmas.

SCIENTIFIC REVOLUTIONS

As noted in my introduction, brain tumour research is chronically unfunded and has seen very little change in approaches to treatment over the past twenty-years. The last therapeutic agent discovered to have a meaningful impact on tumour growth was the chemotherapy temozolomide in 1970s and, as I explain shortly, its efficacy for certain patients is now being seriously reconsidered. Given this moratorium on the field's development, it seems not unreasonable to refer to molecular technologies in revolutionary terms, as many have done. Within the neuro-oncology field, these commentators site the current moment as *groundbreaking* (Westphal and Lamszus 2011)—a turning point that takes treatment into a *new era* (Brandner and von Deimling 2015; Louis et al. 2014; Louis et al. 2016; Ritzmann, Grundy, and Rahman 2016; Thomas et al. 2017). It is an intervention arguably more significant than previous watershed moments including the introduction of immunophenotyping in the 1970s and 1980s, which allowed the detection of distinctive tumour antigens, and indeed the discovery of temozolomide, which was among the first drugs able to cross the blood-brain barrier.

The weight of revolution carries with it images of radical fracture, upheaval, social fallout and structural change. Studies of political revolution describe movement and patterns of resistance, once pocketed, now cresting forth and ushering a recalibration of the balance of power (Thomassen 2012). They describe a desire for transformation and the latent possibilities for change that lie within a status quo (Garcia 2017). Applied to his study of science, progress and paradigmatic change, physicist and philosopher of science, Thomas Kuhn, adapted this term to indicate the episodic nature of scientific progress amid legions of scientists and the battles waged between them. Kuhn similarly evoked a changing of the guard along with images of desertion, dissent, appropriation and consolidation. On the major turning points in scientific development such as those associated with Copernicus, Newton, and Einstein, Kuhn writes how each:

[N]ecessitated the community's rejection of one time-honoured scientific theory in favour of another incompatible with it. Each produced a consequent shift in the problems available for scientific scrutiny and in the standards by which the profession determined what should count as an admissible problem or as a legitimate problem-solution. And each transformed the scientific imagination in ways that we shall ultimately need to describe as a transformation of the world within which scientific work was done. *Such changes, together with the controversies that almost always accompany them, are the defining characteristics of scientific revolutions* (Kuhn 1970:6, *my italics*).

Importantly, Kuhn quickly dissociated revolution from the essential features of scale or range. That is, he insisted revolution be understood by the “specialists on whose area of special competence they impinge” (1970:7), however local. He further stipulated that the “assimilation [of new theory or method] requires the reconstruction of prior theory and the re-evaluation of prior fact, an intrinsically revolutionary process that is seldom completed by a single man and never overnight” (1970:7). As such he called forth the extended process through which revolutions operate.

Although criticised for adopting an overly relativist view of scientific knowledge (Worrall 2000), reducing theory-change to a matter of “mob psychology” (Lakatos 1970:178), and assuming the constitution of knowledge to lie in shared understandings (Keating and Cambrosio 2003), Kuhn’s characterisation of what constitutes revolution and revolutionary is a useful benchmark against which to consider the molecular turn. But rather than consider the epistemological debates within the scientific community, I am interested more in the social consequences they entail for patients and professionals working on the frontlines of care. What time-honoured approaches to treatment, for example, are being questioned? What new problems are available for scrutiny? What transformations are being

made in the medical imagination? To these questions, inspired by Kuhn, I would add something else: hope. It is hope by which revolution is fuelled and to which it in turn sustains (Garcia 2017). Indeed, molecular technologies have contributed significantly to the hopes of those with brain tumours: hopes for longer lives, freer of symptoms and the side effects of early generation treatments. What are these hopes and how do they manifest in individual and population-level decision-making?

THE MOLECULAR TURN IN BRAIN TUMOURS: PRINCIPLES AND ASPIRATIONS

The radical nature of incorporating new information into brain tumour diagnosis struck me in early 2015 during a presentation to the MDT by a pathologist at The Warner and crystallised in the phrase: “we think now that it does not exist as a biological entity.”* The pathologist was fielding a question about a notoriously hard to treat tumour, GBM-PNET: “this is a mixed bag—so it appears difficult to treat.”* Continuing, he explained how this is likely to be several different types of tumour considered as one. The oncologist next to me leaned over and whispered that this change and the whole discussion around using molecular data to diagnose is very important for her in terms of treatment and clinical decisions. To reiterate a point of the previous chapter: decisions about care are rooted in diagnoses. While her remark was perhaps obvious, the whole presentation was a reminder of how science moves at pace and how clinicians must make bold decisions in recognition of possible new ways of working. It was an indication that the very basic terms of engagement were changing. Like several other tumours, GBM-PNET was later dropped from the diagnostic lexicon and not included in the new classification (Louis et al. 2016:815).

In its simplest terms, the inclusion of molecular genetic biomarkers is an attempt to split tumour groups into finer, more reliably ordered entities. The following is a truncated account of the changes to pathology given to me by Dr Plank, a pathologist, during an interview in Autumn 2016. In this first passage, Dr Plank describes moves from a simple approach using stains to reveal certain features of the tissue under the microscope (morphology), to one capable of revealing more information about the tissue and cells, such as their origin.

Pathology has developed over the past forty years from a purely morphological approach and I would say until the mid 1980s all diagnoses were made based on the morphology of the cell—that is the shape of the nucleus, the shape of the cell, how the classical staining patterns appear and usually one looks at nuclei and the cytoplasm—

the processes of the cell, and then things that the cells can shed off which is things like amyloid material, collagen, and other material. So, people had a look at that overall appearance and then had to come to a conclusion [...] From the late 1980s onwards, people were now able to look at additional features of every single cell, which is the cellular origin. For example, the cell originating from the skin would have a certain molecule expressed but that wouldn't be found in a cell coming from the brain or from the soft tissue. And this technique was called immunohistochemistry and started in the 1980s to revolutionise the field of pathology (see chapter one). So we thought these should now be able to solve a lot of problems. And they did. A lot of the tumours that were unclear could now be solved [...] so that already is a very good and very consistent profiling that people did. And as the developments were going on, more and more of the cell signalling and disease specific mutations were discovered using molecular genetics.*

Note Dr Plank's use of "revolutionise" and his descriptions in terms of problems and solutions. He continued by explaining particular cellular processes and how specific mutations affect these before returning to their relation to brain tumours. In summary: a disease specific mutation often means a single genetic mutation; antibodies can be developed to recognise these changes. Mutations might change the metabolism of the cell, which is what eventually causes the tumour. He continued:

So we have then over the last eight or nine years identified more and more mutations and soon after that an antibody was generated to detect these mutations, such as IDH, and a large set of tumours was then looked at with this antibody. So in a way it is an antibody but it is also a molecular biomarker, this mutation, this mutant IDH1. And that meant that now we can look at a large number of cases and identify that some are mutant and others are non-mutant. Subsequently, four or five years later, another well-known protein to be often deleted in those tumours was identified and led eventually to the simplification of the tumour classification. Because until then it was always the case that these tumours were characterised simply by their appearance—how they look under the microscope (see chapter one).

So right now, we take into account also the combination of markers such as the mutant IDH, the loss of ATRX, and other markers that we can't look at under the microscope and that can't be done by an antibody but only by a molecular genetic test, such as the 1p19q co-deletion, which is the combination of chromosomal losses in oligodendrogliomas.*

According to Dr Plank, a pure morphological approach was complemented by immunohistochemical techniques which first allowed characteristics like cell origin to be detected and then for some molecular biomarkers to be established. Later, other techniques were developed which would more reliably detect these same mutations as well as others which are undetectable by immunohistochemistry. This new technique, real-time Polymerase Chain Reaction (RT-PCR), is a computer-based process which, unlike immunohistochemistry, does not rely upon the interpretation of stained sections seen by a pathologist under the microscope. It involves instead a quantitative technique and facilitates

the identification of precise DNA segments. As such, it is putatively more reliable and objective¹². Rather than detailed descriptions of PCR techniques, I want simply to mark some of the principles that are shaping practice and the main point here, in Dr Plank's words, is that “the accuracy of classifying better is even greater.”*

Beyond this, molecular genetic tests allow pathologists to further disambiguate groups such as GBM-PNET and distinguish more easily between similarly characterised tumours, as Dr Plank explained:

There are a lot of these tumours which are at the fringes [...]—those tumours that don't fit that classical appearance. They look alike but they also sway a little bit in the domains of another tumour, have features that could also be found in other tumours: *that is where the biomarkers come in. You define a tumour much more precisely. So using this approach we are now cutting down on the wastebasket*¹³. By knowing a little bit better we can say ‘this tumour belongs to this group,’ we take it out of the wastebasket and put it in the basket of well-classified tumours [...] that helps us, it gives us something more specific and something we can define, [we can say] ‘this tumour is a tumour with a certain signalling pathway alteration, and is going to respond to treatment in a certain way; or at least *more predictably*.’ So that's next generation diagnostics that we are now starting.*

Significantly then, the manual has included more features that are able to be detected by the techniques of immunohistochemistry and PCR. Most importantly, it has overhauled the diagnostic parameters of brain tumours, allowing many entities to be reclassified at a molecular level. This has led to the appearance of new groups of tumours as well as the disappearance or displacement of previously described entities such as oligoastrocytoma (Perry 2016), a diagnosis which reportedly “suffered from high inter-observer discordance, with some centres diagnosing these lesions frequently and others diagnosing them only rarely” (Louis et al. 2016:804).

The principles driving this turn are therefore precision, objectivity and predictability. A significant feature of this objectivity, and indeed an important strategy, has been the removal of subjectivity and relatedly the input of the human eye¹⁴. This was also the drive behind the development of immunohistochemistry and analyses which could be quantitatively described or even binary: positive versus negative.

¹² See Paul Rabinow (2006) for an excellent account of the establishment of PCR within the broader biomedical field.

¹³ Wastebasket is a colloquial term for tumours that are Not Otherwise Specified (NOS). That is, they fail to accord to a more clearly defined and consistent category.

¹⁴ Bruno Latour (Latour 1987; Latour 1999) and Lorraine Daston (Daston and Galison 1992; Daston 2008) among others have written extensively about the history of objectivity and removal of human intervention in scientific knowledge production.

In 2012, David Louis, professor of pathology at Harvard Medical School and lead editor of the WHO manual published in 2016 (and its 2007 predecessor), wrote an editorial in the prominent journal *Acta Neuropathologica* emphasising this aspiration and situating it in a broader history of neuropathology. The editorial—which ran a title inspired by an early book of Christian ethics, *The next step in brain tumour classification: ‘Let us now praise famous men’ ... or molecules?*—concluded:

We stand at a critical time in the evolution of diagnostic tumour neuropathology, with new objective techniques coming alongside comprehensive ‘-omic’ analyses of tumours. The era of the famous men has been a vitally important part of our history; indeed, the famous men have been our mentors. But, as the phrase ‘Let us now praise famous men’ states, the time has now come to take a big step forward and to allow the famous molecules (rather than more famous men) to be our legacy. (Louis 2012:762)

Earlier in the piece, Professor Louis contrasted an experiential system with one “far more objective,” again signifying new claims of objectivity:

[A]s the old aphorism states, ‘Good judgment is the result of experience; experience is the result of bad judgment.’ In other words, the system that we currently use has arisen from many trials and errors, and from a good aliquot of subjectivity infused with the convictions of our famous men.

For the first time in history, however, we now see the inklings of a system that offers far more potential for objectivity, and hence, less dependence on the vagaries of individual strong convictions. (Louis 2012:761)

These excerpts capture well the significance of this shift—evoking both a break with history and subjectivity, and driving the embrace of objectivity given in the molecular turn. I quote them here to illustrate the drivers and trajectory of the turn and the narrative of revolution. Next, I consider how these parameters were being introduced to clinical practice in ways which attempted to balance the gains in objectivity and specificity with the disruption they would likely cause to current routines. I focus on timing change and the metaphor of “layered diagnosis,” first at a global level, and then locally, at The Warner.

TIMELY INTEGRATION AND THE METAPHOR OF LAYERING

“If you are ten feet ahead of the parade, you are leading the parade; if you are ten blocks ahead of the parade, you are not part of the parade,” David Louis told me in June 2017. It was a quote he used later that month in a presentation at the 93rd annual meeting of the American Association of Neuropathologists, entitled *The 2016 CNS WHO—‘The morning*

after.” I met Professor Louis in his office at Massachusetts General Hospital, Boston, a leading centre for neuro-oncology. His laboratory was first to show that molecular approaches can classify (von Deimling et al. 1993) and predict therapy response in malignant glial tumours (Cairncross et al. 1998). I had emailed Professor Louis in 2016¹⁵, knowing I would be near Boston on a fellowship at Yale University soon after finishing fieldwork, and wanted to ask him about the WHO manual, which he has edited for the last two editions (2007 and 2016). He offered this maxim in response to my questions about his management of the pace of change.

In the years before the manual’s publication, Professor Louis and colleagues had undertaken a series of surveys and hosted colloquia to test the readiness of the field and establish consensus on the integration of molecular (and other non-histological) criteria to enhance typing and grading of brain tumours (Louis et al. 2014). These meetings aimed at establishing the relevance of molecular features to the international project and were framed by fundamental questions about the ontological significance of molecular features and the practice of their application across a variable global infrastructure of biomedical techniques. Such consolidation of knowledge is a key function written into the WHO’s constitution and critical to projects of universalising treatment approaches. Questions during a key 2014 consensus meeting in Haarlem, the Netherlands, included:

What is the relationship between diagnosis and grade? Can tumour type and tumour grade be separated from one another, as occurs in other (non-brain) tumour types? This also brings up the question of whether grade reflects natural history or likely prognosis after therapy. How does one make recommendations about the use of molecular testing? Is molecular analysis required or optional? If required, does molecular diagnosis become incorporated into overall diagnosis or is it added as an extra level to the histological diagnosis? Does one make recommendations about the type of test to use? How does one formulate diagnoses if some institutions use molecular tests and others do not? If one uses molecular parameters to classify tumours, what does one call tumours that have the histological appearance but not the defining molecular feature? And what does one do with a tumour that has the defining molecular features of one tumour type, but the histologic appearance of another? (Louis et al. 2014:431)

What is interesting about these questions is that they clearly demonstrate the potential for epistemological dissonance and differences in laboratory resources, pointing to

¹⁵ My intention was to meet with Professor Louis with a view to discussing his possible involvement in future collaborative work. However, during our meeting, it became obvious how relevant our conversation was to analytic themes I was thinking about for my dissertation. As such, our meeting was not a formal interview and not taped. Passages from our conversation have been reproduced with kind permission by Professor Louis. Apart from the “If you are ten feet ahead of the parade ...” quote, they are not verbatim but reproduced from notes I took following our meetings.

the stakes of tumour redefinition. In fact, the surveys had indicated a surprisingly positive uptake by respondents and broad accessibility to molecular tests (Andriuolo et al. 2016). But the variability of types of test was striking and the concern with imposing a narrow molecularly-driven classification was significant: worldwide, more than a quarter of laboratories still did not have onsite access to tests and this figure was determined on the basis of just 48 countries in mainly economically-developed parts of the world. In particular, Africa, South America and large parts of South East Asia were massively underrepresented, suggesting perhaps an overly optimistic estimate of global access. The authors noted this and suggested the response of the online survey “parallel[ed] active participation of (neuro)pathologists from these countries in congresses and publications in international journals” (Andriuolo et al. 2016:553).

Another concern was the known vagaries of general infrastructure across the world. That is, while institutions might have onsite access to molecular testing equipment, the national infrastructure of electricity and so on might compromise test results. Anthropologists Alice Street (Street 2014) and Julie Livingston (Livingston 2012) have written about this independently in two excellent ethnographies of Papua New Guinea and Botswana, respectively, and described how this structures the emergence and enactment of categories like “generally sick” in settings where laboratory infrastructure is present but unreliable. That is, an unreliability of tests structures an absence of specific disease categories. For David Louis and colleagues, mandatory molecular tests introduced prematurely might therefore have disturbed the global community, meaning that epidemiological analyses and clinical trials would not be comparable across sites. Interestingly, it was clinicians who were more enthusiastically in favour of change, with pathologists less so. Louis suggested this was because pathologists know the practical difficulties of changes in laboratory testing: clinicians just want to treat their patients; they are ready because they do not have to do the diagnostic work.

These factors led to what Professor Louis characterised as a “Goldilocks approach” over a Procrustean one. While the latter implies the subjugation to the world according to a more or less arbitrary standard, the former implies an approach which is adaptable to the on the ground realities of local settings, which differ in terms of available facilities: it is more *inclusive*. Accordingly, it means that different diagnostic information could be included alongside each other and diagnoses could continue to be made in the absence of molecular data. The molecular data simply adds a more definitive and specific diagnosis. In a related

passage on the intermediacy of integration in their summary of the new manual, Professor Louis and colleagues wrote:

The 2016 CNS WHO represents a substantial step forward over its 2007 ancestor in that, for the first time, molecular parameters are used to establish brain tumour diagnoses. While this has introduced challenges in nomenclature, nosology and reporting structure, and while it is likely that the next CNS WHO classification will view the present one as an intermediate stage to the further incorporation of objective molecular data in classification, the 2016 CNS WHO sets the stage for such progress. (Louis et al. 2016:818)

This therefore marks the current introduction of molecular techniques as not simply revolutionary, but transitional. And with molecular parameters being newly integrated alongside existing data and analytic techniques, new questions of knowledge coordination present. Here, a new metaphor of integration was established: diagnosis should be “*layered*.” Layering was a key concept advocated in the 2014 consensus meeting and based upon modern methods of digital mapping. As such, diagnostic information could be readily superimposed and hierarchically ordered providing a useful template for coordinating discrepancy and allowing for diagnoses to be made in centres without molecular techniques. This analogy was described to me by a neurologist during an interview at The Warner not long after David Louis had suggested it at the Haarlem consensus meeting:

Tumour diagnosis is going to become like a roadmap. So on a roadmap you might have, at one level, the roads and the motorways and then, at another level, you might have points of interest, and, at another level, you might have traffic information like traffic cameras or petrol stations. So in a similar way tumour diagnosis is going to have the actual histology—the gross histology was what informed the WHO up until now. The next level will be the presence of certain chromosomal deletions, for example, 1p19q, then they’ll be another level which will be in the mutational analysis—IDH and so on—and then maybe another level which will be the epigenetic analysis, in the future.*

While the constitution of layers differs very slightly from what was suggested in the Haarlem consensus, the implication is the same: information is multiple, it can be ordered, and while there can be absences of molecular information, if present, it should be seated at the top. Moreover, hematoxylin and eosin (H&E), a stain first described in the mid-19th century (Musumeci 2014; Titford 2005), would remain a vital first step in guiding subsequent morphological, immunohistochemical and molecular techniques. This was emphasised by many I spoke with, not least Dr Plank:

First, we have a look at the microscopic image, that gives an impression of what to do next, that's always the first thing, the H&E. Because you can do a lot of sophisticated tests but if you do it on the wrong material you are going to end up with a completely wrong diagnosis.*

The new manual has been well-received, selling unusually well for a WHO manual and much better than its 2007 predecessor, Professor Louis told me. This is because the 2016 book *is* so different, he continued: not many took major notice of the last one. However, there has been significant pushback from some communities, especially paediatric clinicians who argue that the manual did not go far enough in embedding a more molecularly-weighted approach to diagnosis. Another criticism is the lack of specific guidance on which reporting format and standardised techniques. Louis told me he gets a lot of queries from colleagues about the book. Why, for instance, does it not include MGMT status—what appears to be a critical factor in determining a patient's response to the standard first line chemotherapy agent, temozolomide? Among one of the most interesting things, he told me, are the new uncertainties brought by the manual: whereas previously error could be explained away as interpretation, now there was an objective basis to make a more categorical distinction. It is a real change in mindset for pathologists, he told me when we met: in the past people didn't get too upset by uncertainty; now they do. Showing me the title of a recent article in the journal *Human Pathology*, Louis quoted “*conflicting* IDH mutations.” Before it was much more subjective: there was *human bias*.

UNCERTAIN CHANGES IN PRACTICE

Arguably most challenging is the integration of knowledge into practice. In fact, this is what David Louis had intimated to me in reference to the translational “valleys of death”—the destinations of promising basic research findings that fail to emerge into (or out of) clinical trials and forego their chances of entering clinical practice (Meslin, Blasimme, and Cambon-Thomsen 2013). There are two key points, he explained, which constitute significant challenges to scientific progress and its clinical application: one between biomedical research and clinical science and knowledge; the other between clinical science and knowledge and clinical practice and healthcare decision-making. It is this second valley which is deeper and harder to traverse: it is where neuro-oncology is now. Louis told me the interesting thing is how there are different people along the way with different intentions: the bench scientist, for example, might not be thinking so much about application; it is at the second peak where application is considered more. At this point people will be thinking forward and looking

back, situated between bench and bedside. The final peak is the translation of research into clinical guidelines.

By mid-2015, molecular analysis was being done routinely at The Warner for a number of markers—1p19q, ATRX, IDH1 and 2, MGMT methylation, and EGFR. As a leading centre for neuro-oncology and with the capabilities of running PCR, the sheer numbers and types of marker tested was unusual across the UK. The Warner was also providing remote diagnostic services for other centres. Such agreements between services endure at the time of writing, with a number of specialist centres providing molecular analysis for neuro-oncology services around the country—a way of managing the new costs of molecular diagnosis in an economy of scale.

In late 2015, I put the question of change to a neuro-oncologist from a district general hospital outside London, who I met at a meeting part hosted by one the brain tumour advocacy groups. As we talked informally about care and diagnosis, I asked him to reflect on his career and how the integration of molecular parameters rated in terms of the significance of change. “This is a seismic change in brain tumours,”* he told me, “the molecular stuff is *big*.”* He continued, emphasising its newness and adding that nothing had really happened in brain tumours for twenty years. This I heard so often from clinicians and patients alike—something of a stock phrase that underlined an impoverished and static community; the humdrum of a fixed deficiency. In this particular conversation, however, it underlined the magnitude of change and the promise carried by molecular technologies. “Before we knew we had an apple—that’s the tumour,” he told me, “But now we know that apples taste different. So you have your granny smith or golden delicious—these are the many tumour subtypes and they all taste different.”

Others, who had enjoyed long careers in neuro-oncology, described these changes as the most significant event of their professional lives and some joked to their younger colleagues how all they had learned in their careers to date was becoming obsolete in the path of the new. In a particularly radical statement, one doctor told a lecture theatre of medical students:

Astrocytoma, astrocytes, oligodendroglioma, oligodendrocytes, astrocytic pathway, anaplastic. Familiar terms—it’s in your textbooks—the terminology, which I have clung onto over my career. It’s all nonsense! All this can go out the window! Throw out your textbooks! Now we’re interested in the molecular stuff. Now we talk about whether a patient has ATRX or 1p19q.*

These then, were further illustrations of a field in revolution: scientifically and clinically.

...

At The Warner, Dr Plank described himself as “the progressive mainstream” and I was told by other pathologists that he drove a department heavily weighted towards molecular analysis. When I asked him how these changes were being implemented across the MDT, he was emphatic:

Dr Plank: Early education is good and all it requires is to show one slide every year on the new developments and then keep it consistent with the reports—‘okay listen everyone, we are now doing the biomarkers in that way so this combination means that, this combination means that, and this combination means that’—give a three minute brief introduction in one of the MDT meetings and they are going to know what we are talking about for the rest of the year and particularly because it is perpetuated, reiterated every time and it is written in the reports, it is written in the comments. So it kind of settles in.

Henry: And is there consensus in the MDT about how much weight to put on the markers?

Dr Plank: Yes, yes. We tell them, we tell them: ‘In this case, it’s molecularly uninformative, so we can’t tell you further.’ Or we say, ‘there is this combination of mutations so this one is going to behave like a glioblastoma,’ for example, ‘even though it hasn’t got all the features we can obviously say that’ [...] All they need to know is: ‘positive/negative.’ We do the interpretation for them. They do not read that marker but they trust us—if we tell them it’s IDH negative, it’s negative; or if it’s IDH mutant. They know they can trust us.*

This, he told me in 2016, after the publication of the manual. Yet, the reality I saw during my earlier fieldwork in the clinics and heard in my conversations with nurses, oncologists and surgeons contradicted this. Moreover, when it came to communicating the changes to patients or changing the course of their treatment, things were even more complicated. Consider a nurse who told me in passing how “it’s really changing things for us. It’s so complicated and if I don’t understand it then how are patients going to understand it?”* She said that patients were reading about the tests and two had recently requested tests:

What we say is: we have additional information that helps us to treat them. But we’re not sure about it, and if I don’t know it yet in my clinical experience then it makes it harder—I should trust the science shouldn’t I?—I am just

the nurse and if the medics are saying we should do it, then we should trust them—but we’ve not had the ten years we’ve had with the Stupp Protocol¹⁶.*

Consider also Dr Anton, an oncologist, who told me how “Dr Plank is being quite militant about treating certain cases as GBM. But maybe they aren’t—it’s a major dilemma.”* She emphasised the big differences in treatment from radiotherapy to radiotherapy plus chemotherapy and continued, “But it’s quite uncomfortable because we’re not totally sure—there is not the evidence yet—a lot of it is anecdotal—it’s so new.”*

Interestingly, she drew a comparison with radiology: with radiology she could see the images and understand—“Oh yes, we see that”—but with the pathology it was different: “It’s kind of pointless them putting up the slides and the reports. They’re so long. The pathologists love it; but we really just go straight to the bottom line: ‘what is it?’”* This last point echoes many interactions I saw in MDT meetings, and my report in chapter 1, where clinicians would demand specificity and finality in questions—for example, “What is going in the report?” “What is the bottom line?”—and defer to pathology for an answer. Dr Anton finished by saying: “If the pathologist says it’s a GBM based on molecular analysis then we must treat it as GBM.”*

It seems therefore not simply a matter of communication but of the stakes of treatment and having trust and enough direct experience with new ways of working. While Dr Plank told me that the rest of the MDT get it and need only a slide per year to be briefed, clearly the feeling at the clinical interface was very different. And while clinicians routinely seek the bottom line, privately they remained equivocal about change. At stake therefore, was whether or not the changes would have meaningful effects on patients’ lives and whether there was enough evidence for them to change their approach.

...

Adding complication, the timing of the new tests was out of sync with microscopic analysis by a matter of weeks. This posed a problem for the communication of diagnosis: should it be a two-stage process with a provisional microscopic analysis and definitive integrated diagnosis including molecular parameters? Or should clinicians hold off communicating the microscopic readings and give a one-off integrated diagnosis? Another issue was how to

¹⁶ The standard therapy for glioblastoma set after a 2005 article by Roger Stupp and colleagues (Stupp et al. 2005). It is informally referred to by clinicians (and some patients) as the Stupp Protocol.

quicken the molecular process in an understaffed pathology department with a huge throughput of patients. At the time, only one biomedical scientist was preparing the molecular tests; the department had made multiple requests for further funding to support more staff. On top of this, was what to do about patients recently diagnosed but in advance of routine molecular testing¹⁷.

I was told that these questions were being asked throughout neuro-oncology departments nationwide. The Warner was spearheading integrated diagnosis in the UK and I was told that not all centres would be doing molecular tests at the same level. David Louis had also mentioned timing when I met him almost two years later telling me that while MGH now had a 24-hour processing time for molecular analysis, more broadly these kinds of glitches would be smoothed out in five years.

As with other centres around the country, the significance of predictive factors like MGMT in guiding treatment in The Warner was still very uncertain; I return to this shortly. For now, I want to focus on the implications of changing diagnostic categories. Remember, too, how the importance of molecular parameters and method of integration had yet to be concretised by the WHO and the neuro-oncology community at large was far from reaching consensus. It was not until May 2016 the manual finally arrived and I would later learn this did not fully settle the issue with hospital (and perhaps others)¹⁸.

In the meantime, with a time difference between microscopic and molecular analyses and amid discrepancy between tests and an ever-growing pressure to weight diagnosis towards molecular data, I heard of a small but growing number of patients who were being recalled for special consultations and having their diagnoses changed. This caused significant consternation within the MDT, especially for oncologists who would usually be the messengers of change—re-determining treatment and telling patients about it. The following field notes taken during an MDT meeting are worth presenting for they capture some of the fraught social dynamics at play during the transition into integrated diagnosis.

¹⁷ For patients diagnosed before the routine application of molecular tests, diagnoses typically remained the same, even for those with oligoastrocytoma or PNET tumours. Only for those with progression incommensurate with a presumed disease profile or who had been re-operated were the additional tests done. This effectively meant the existence of groups of patients with different diagnoses even though they might have had the same underlying pathology on the basis of one test or another.

¹⁸ Marc Berg and Annemarie Mol, among others, have written extensively about the global travel and local configuration of diagnostic practices (Mol and Berg 1998). Yet this has commonly been exemplified with examples from countries with low economic development and framed by the characterisation of lo- versus hi-tech economies or resource poor and elite settings (e.g., Livingston 2012; Street 2014). What is interesting here is the dissonance between elite centres.

A new patient is presented by Dr Anton who she told me about yesterday in the radiotherapy planning meeting. The patient was thought to have an anaplastic glioma, possibly a grade III oligo and was presented in a previous MDT, but 1p19q analysis was pending. Dr Littleton, who is at the microscope and talking through the pathology, says they need to revise the pathology. To recap, he says, the tissue fragments show no necrosis and no microvascular proliferation. These are features of a GBM and hence if present indicate a GBM diagnosis. This therefore suggested the diagnosis of anaplastic oligodendroglioma—a grade III oligo, which was the initial diagnosis. However, there is no IDH mutation and no 1p19q on the molecular analysis. These *are* features of a GBM.

Dr Littleton speaks quickly: “Five years ago, we would have diagnosed this as oligodendroglioma grade III. Now with the molecular analysis, the tumour appears not to be oligodendroglial.”*

Pathology is repeating the analysis to confirm. There is a frenzy of voices in the meeting and an edge to them. Dr Fiennes, who is chairing the meeting, asks what pathology will put on their report: “what will go down on the path report?”*

“GBM,”* Dr Littleton reports.

“Right, let’s move on.”*

Dr Plank says that we will see more of these as we see more molecularly-supported diagnoses. Explaining the discrepancy, he says there are two possibilities: the first is that there is an under-sampling of the tumour by the surgeons meaning that they only took cells from a part of the tumour which was not representative. But that would be unfair on the surgeons. Before he gives the second possibility, someone asks about the scan. The on-call radiologist says she would not confidently call this a GBM. Dr Fiennes says that at over 70-years-old, it’s likely to be a GBM. The plan is made to treat the patient for a GBM. Dr Anton will see the patient later in the week and will inform her of the change. Fortunately, the patient has yet to begin treatment.

While a scientific field moved towards resolution, uncertainty still plagued the integration of molecular parameters in clinical practice. These changes had to enter a neuro-oncology service which continued to run with a high throughput of patients. Busy practitioners had to learn new tumour categories and techniques of differentiation fast and *trust*. There could be no pause in care; everything happened on the move. The on the ground difficulties in integrating new (and uncertain) information did not simply play out in laboratories, MDT meetings, or other interactions between members of the clinical team in how negotiating diagnosis and treatment, but with patients: how to frame an admission and break the news that “it’s worse than we thought” and how to disclose uncertainty. In the following section, I reflect on these dilemmas, recounting an encounter at the doctor-patient interface.

DISCLOSING UNCERTAINTY: THE CASE OF SARA

After the meeting recounted above, I spoke with Dr Anton about the change in diagnosis and asked if I might come to the consultation. She checked with the patient at the centre of this uncertainty, Sara, who agreed and who I would come to know well.

Days later, on the morning of the consultation, I sat in a clinic room with Suze, the nurse, and Dr Anton who said in a strangely reassuring way: “It’s still very uncertain.”* Suze had worried that the consultation was going to be challenging given the new prognosis and direction of treatment. Given the change in diagnosis, the patient’s prognosis had been radically shortened: from years, to months. Treatment would now include a long course of chemotherapy in addition to the radiotherapy Sara has already consented to. Dr Anton explained what I had gathered from the MDT meeting; that on the scan the tumour did not look like glioblastoma and that under the microscope it has the appearance of an oligo—a far less severe tumour.

Sara had been diagnosed almost two weeks previously with an oligodendroglioma. “But she has no IDH mutation which according to Dr Plank is more suggestive of glioblastoma,” Dr Anton said, “I’m not so sure. But ATRX is retained, suggesting astro rather than oligo. Pathology was waiting for 1p19q which was also retained, meaning it was not mutated, and Dr Plank has said the molecular profile is of glioblastoma. But it’s confusing: the scan doesn’t look like a glioblastoma.” This discrepancy she repeats several times in our conversation. “If she has oligo features would the prognosis be better?” Suze asks. “The fact of the matter is, we don’t know how well patients will do—we have no actual evidence,”* Dr Anton says.

She runs through Sara's other characteristics: “She has no MGMT methylation which isn’t good—patients do better on temozolomide if they have methylated MGMT promoter. But she has had seizures which is a good prognostic feature and the scan doesn’t look like glioblastoma: these are factors which are good.” Her reasoning carried through to a conclusion that Sara's tumour might behave like a slower-growing oligo. She went on: “But now the plan is to treat as a glioblastoma—chemoradiation and adjuvant chemotherapy—and possibly it will respond better than a classic glioblastoma. But what’s so confusing is that radiologically it does not have the appearance of GBM—so that suggests that it’s not a *dreadful* GBM.” She turns to me and says that in the past (before integrated diagnosis) they would have treated Sara with radiotherapy and held chemotherapy in reserve: “It would have been diagnosed as an oligoastrocytoma, grade III. But these tumours don’t *exist* anymore.

So now these patients are likely to do better [with the more aggressive treatment] than a year ago.”*

...

Not long after this conversation, Sara was sitting with Robbie, her husband, listening attentively to Dr Anton who now explains the situation to them. Sara looked in her fifties but later told me she was in her seventies; she was smart and well made-up. After pleasantries and introductions, Dr Anton moves to the reason for the consultation:

We would usually wait until the next appointment at radiotherapy but we discussed you yesterday at the MDT. Now we have looked at the full pathology with the full molecular analysis, we agreed that you would do well to have chemotherapy at the same time as radiotherapy. So there has been a slight change of plan to treat the tumour like a glioblastoma.

She explains that the molecular analysis is really very new, how under the microscope and on the scan it looks like an oligo, grade III, but with the molecular analysis it would be better to treat it like a glioblastoma, which would be radiation and chemotherapy; the side effects of the radiation will stay the same but chemotherapy included sickness and might affect her bowels: “some people have flu-like symptoms and your sense of taste can be a bit strange.”

“I think it’s a good thing,” Robbie says, “another weapon in the armoury—some people don’t even get offered the chemotherapy, if they don’t have the numbers.”* Dr Anton says until recently, they only had two options with regard to these tumours, radiation long course or short course and radiation with adjuvant chemotherapy if we felt it would work. “We always thought that you would do better on the longer course radiotherapy anyway, because you are fit and your biological age is less than your actual age.”* Sara asks her about its success. “We don’t know—we really don’t know,”* Dr Anton responds slowly, drawing out the words and forming them roundly, “we hope it will be better than just the radiotherapy alone.”*

...

While this scenario was relatively rare (I heard of only several cases during fieldwork) and while the MDT was working hard to avoid further discrepancy, it reveals the stakes of

change and the uncertainties of the clinical team. This is not to say however that diagnoses were not “upgraded” before being given to patients: indeed Dr Plank told the MDT in mid-2015 that they would be seeing more and more molecularly-supported glioblastoma, that is tumours which look grade III (or lower) under the microscope but which have the molecular profile of glioblastoma, grade IV.

The key thing I want to focus attention to here is how the conversation revolves around treatment, not diagnosis. It is about “what we are going to *do*” rather than “you *have* this” or “you *are* this.” Diagnosis in fact remained ambiguous in correspondence to Sara’s GP, described differently throughout the months following this meeting—sometimes “grade IV oligodendroglial morphology,” at others “grade IV anaplastic astrocytoma with oligodendroglial morphology,” “grade IV glioblastoma with oligodendroglial morphology,” or simply “grade IV glioblastoma.” While this could of course be down to human error (letters are dictated by clinicians and later typed up by secretaries), I suggest that it further belies an enduring uncertainty among clinicians.

This tracks the conversations in MDT meetings and the split registers of tumour *type* and tumour *behaviour*. It is tipped towards intervention and options, interpreted as “another weapon in the armoury.” This split is mobilised within the context of uncertainty as a way to manage it. I also want to point to the extension of the distributive process detailed in chapter one and how it manages uncertainty. Here, uncertainty is present and shared—yet this sharing is fast subsumed within the process of planning. It is, moreover, converted into hope and the common investment in a biomedical solution, as suggested in Sara and Robbie’s response to having a more aggressive treatment regimen.

Once Sara and Robbie left the consultation, Dr Anton told me she’s never sure what to say around the likely success of treatment, but thinks it better to keep it open and not sap hope. She thinks with Sara and Robbie it would be better than being “doom and gloom,” sitting them down and saying, “look things are worse than we thought.”

...

Several months after the consultation, Sara told me how she had been hit when she heard it was higher grade, how she “didn’t believe it would be as bad.” But nearing the end of treatment, which was ultimately cut short owing to side effects and the clinical reasoning that there would be little value added by its completion, she and Robbie were sure that more treatment had been the right decision. Later, in an interview ten-months after we met, I

asked them about the consultation with Dr Anton and those they had with other clinicians at the time. Sara told me about Dr Noyes, the neurologist originally in charge of Sara's care:

Sara: They have done nothing but what they can do for it. And Dr Noyes when I went to see him after [my surgery] he said they say it's a grade III but I'm treating it as a IV.

Robbie: He said they're going to throw everything we've got at it.

Henry: How did you take that when he said it?

Sara: I thought yeah do it. I thought that would probably give me more chance of giving and going on in life. And I thought yeah do it. I thought even if he has to treat a size ten—I know that there is no ten—but you know what I mean—you know just give it to me.

Henry: And did he give a reason for why they would treat it like that?

Sara: He didn't really did he. Did he to you?

Robbie: Well I think the impression I got was behind every III is lurking a IV. So I think he thought we're going to give you this treatment. As he said we're going to give you everything we've got. We're going to throw everything we've got at it. And my impression was, and I'm sure yours [Sara's] was as well, we'd rather them throw everything they've got at it. And with the chance that they'd gain some success than if it would come back again and they say oh well it is a IV.

Sara: Because another doctor said we won't operate on it because it's only a tiny one. We'll just see how it progresses. And I thought, oh okay. He knows what he's doing. And he was supposed to be the one that knows what he's doing.

Robbie: But apparently, of course Dr Noyes, he's the clinician that gives the go ahead, and whether he's experienced.

Sara: He asked me an *awful* lot of questions didn't he. Yeah like, he just sat back in his chair and said, "Tell me your life. What you do? What you don't do? How did you find out you had this?" And I had to explain that to him. And he said, "Well what do you do?" And I said, "We travel a lot. I said we go on holiday quite a lot and I said we go abroad about twice a year. But then for the rest of the year we go away for weekends, we go dancing, we do gardening, we go off to look at gardens and things. And we've got grandchildren who have and we look after." [...] And after I told Dr Noyes this, he said, "Right, I'm taking you on." I said, "What do you mean you're taking me on—I thought I was already on." And he look at my age and said it's quite a lot to go through. And I said well you might have 70 on that form but really I'm only 50.

Robbie: And he said well we've got a big fight on our hands then.

Sara: And I said put whatever you want through me and I'll get over it—we're in this mood now! And he might have thought "Well she's a nutter—she might just do it." But I've got this far. And Dr Anton said to me he's been saying "no she'll do it."

Robbie: Dr Anton said Dr Noyes is really in your corner. I think there must have been some discussion about age.

Sara: Well I suppose if you're not strong then you can't do it. But in here, in my head, I know I could go another load if I had to.

Robbie: Really?

Sara: I might moan a bit. I want to see my grandchildren grown up. I want to see them married. So I think if it's all up here (points to head).

Robbie: You've got confidence in the doctors, you've got confidence in the treatment. I think if you've got great confidence then you're half way there. I believe that if you're positive then positive things happen.*

REINTERPRETING EVIDENCE, RE-DETERMINING TREATMENT

Sara's treatment changed because her diagnosis changed. Yet by offering more nuanced information about individual patients' tumours, molecular technologies have also led to new interpretations of landmark studies in neuro-oncology as regards *treatment prediction*.

Molecular techniques are therefore not simply changing the nomenclature—that is, how tumours are typed and classified—but understandings of how tumours will respond to treatment. From the perspective of patient care, prediction presents an obviously more contentious set of challenges because it more readily hinges on ethical questions around treatment access. Consider, for example, the case of temozolomide.

Discovered in Birmingham, UK, in the late 1970s and trialled clinically in the 1990s, temozolomide is among the few effective chemotherapies for use with brain tumours because of its ability to pass through the blood-brain barrier. It is now the standard first line chemotherapy treatment for newly diagnosed glioblastomas (WHO grade IV) and grade III tumour progression across most more economically developed healthcare systems. However, since the publication of a 2005 article in the *New England Journal of Medicine* (Hegi et al. 2005), and subsequent others, which detailed the role of changes in the MGMT (methylguanine methyltransferase) gene in determining the treatment effect of temozolomide, its therapeutic value for a large number of patients is increasingly questioned (Weller et al. 2013).

In short, MGMT is a DNA repair protein that allows tumour cells to restore DNA and continue regrowth after temozolomide. However, its expression is mediated by MGMT promoter methylation—which essentially has an inhibitory effect on MGMT. If a tumour lacks the promoter methylation, it means that MGMT functions uninhibited which effectively neutralises the effect of the chemotherapy. There is now an emerging population of patients with tumours like this, which are essentially temozolomide-resistant (Lee 2016; Taylor and Schiff 2015). This is highly significant because it unbalances the treatment equations on which individual and population-wide clinical decisions are based. It creates doubt and recasts relationships between the tolerability of symptoms and side effects, the potential for risk and treatment benefit, and fundamentally the goals of care. At the heart of this is whether patients with particular molecular profiles should continue treatments known

to be ineffectual or forego them altogether (Taylor and Schiff 2015; Weller et al. 2010).

Relatedly, is the question of who should decide?

I further observed the ambiguity of using MGMT promoter methylation to steer treatment decisions during fieldwork. While patients were routinely tested for methylation status, clinicians appeared apprehensive to discuss methylation status with patients scoring low. A cancer doctor speaking with newly qualified doctors summarised the stakes and challenges associated with translating the new information into routine clinical practice:

Would we still use temozolomide if a patient does not have the MGMT promoter methylation? Good question. Even though these patients might not do well with temozolomide, comparatively, are we going to deprive them of the one drug that might help them based on their genetics? No.*

Another told me:

If methylation is present or not it's only suggestive about whether they'll be more responsive to chemo or not—it wouldn't make you decide to give it to them or not. You would hope they would do better but it wouldn't necessarily make you do it.*

The controversies around using MGMT status to determine treatment decisions carries through in scientific literatures and clinical guidelines, often marked by disclaimers, such as “remains controversial” (Weller et al. 2017). It is a dilemma in which probable treatment effect has to be rationalised against the distribution of funds, hope, and the fact that it is “difficult to withhold an approved chemotherapy from those with the poorest prognosis” (Taylor and Schiff 2015:4). It is also a dilemma compounded by there being few treatment alternatives and repeated estimates that up to 60% of tumours might be temozolomide-resistant (Taylor and Schiff 2015; Weller et al. 2013). As scientists and clinicians either side of the issue debate the terms and strengths of evidence, many now call in varying degrees for the personalisation of temozolomide use on the basis of MGMT status (Taylor and Schiff 2015; Thomas et al. 2017; Weller et al. 2013; Weller et al. 2014; Weller et al. 2017). The strength of this call has been especially strong for older patients (>70 years) and those younger, without functional status (Taylor and Schiff 2015; Weller et al. 2014). New European guidelines now advocate for personalisation across a number of aggressive tumours, regardless of age (Weller et al. 2017). The UK regulatory body, the National Institute of Health and Care Excellence, has recently followed suit, also advocating for personalised decisions (NICE Guideline 2018). It is notable that these updated

guidelines are the first to emerge in more than a decade: the last were published in 2006. Other biomarkers are likely to join MGMT in steering patients towards particular treatment regimens given the growing consensus around the roles of additional DNA repair mechanisms in determining chemotherapy sensitivity (Thomas et al. 2017).

Together, these observations indicate how the promissory advances of molecular technologies and personalised approaches lie within the condition of deep uncertainty. As yet, firm evidence, effective guidelines and viable infrastructures to translate scientific findings into clinical practice are still lacking (Ritzmann, Grundy, and Rahman 2016). Neuro-oncology appears to be caught in an ethical grey zone in which calls are made on scientific communities to rapidly validate findings using “creative clinical trial designs” that incorporate both clinical and molecular factors (Ritzmann, Grundy, and Rahman 2016; Weathers and Gilbert 2017:263). As this evidence sharpens, the need for resolution will likely increase and healthcare commissioners will soon have to weigh in and make tough decisions about care provision and the equitable distribution of treatment funds. Such decisions constitute what medical anthropologists Barbara Koenig and Sharon Kaufman describe as closing the ethical gap (Kaufman 2015; Koenig 1988): when innovative modes of care and treatment become routine.

For the time being however, questions remain: What kinds of scientific programme will develop in the growing lacuna of effective treatment for those with temozolomide-resistant tumours? What logics will guide policymakers and commissioners as they steer a course through such uncertain, ethically contentious and emotionally charged terrain? How will “treatment as hope” feature in these logics? How will these logics be shaped by the other (often financial) imperatives of groups like insurance companies? I return to such questions and the logics of hope in chapter 4, in an analysis of the regulatory disputes around Avastin, a controversial treatment for brain tumours endorsed by the FDA in the US and lacking approval in Europe.

A NEW IMAGINARY

In addition to impacting standard care, the molecular turn is having major effects on experimental trials, contributing to a research agenda geared around personalised medicine and controlling trial entry criteria. It was also causing some consternation at the hospital that currently recruiting trials based on histological data (without molecular data) might be confounding study samples by including patients, like Sara, who were histologically grade III

but molecularly grade IV. This latter concern was raised in scientific literatures with the acknowledgement that “so far [trials] have been hampered by the biological heterogeneity of the tumours collected under the same designation” (Schittenhelm 2017:83).

The case of EGFR—or Epidermal Growth Factor Receptor—provides a useful example. Briefly, mutations in the EGFR gene commonly occur in cancers, including primary and secondary glioblastomas. It is considered prognostically relevant and, given its role in pathogenesis (disease development), experimental trials were being designed to test potential interventions which might target it. In late 2015, I heard that patients were increasingly asking for EGFR profiling following recent developments of EGFR-targeted therapies for recurrent high-grade tumours: “with all the work on EGFR patients are wanting to know and they want to be tested early so that they don’t delay if they need treatment,” one nurse told me. During my last months of fieldwork a new trial opened at the hospital and patients newly diagnosed with glioblastoma were then routinely offered screening for EGFR, in anticipation of tumour recurrence¹⁹. It was framed as an option for the future and a matter of preparation. For example, one oncologist said to a patient during a consultation:

We’re always thinking of the future. And if in the future the treatment doesn’t work and if your tumour starts to progress, which we hope would happen in a very very long time, we are trialling a new treatment for patients who have something called an EGFR mutation. About half people have it and the test takes a few weeks or even months to get the results. So we want to test people now so that we already know if anybody has the mutation. So it’s for a trial for treatment in the future.*

Without the mutation, patients tend to do better, living longer and responding better to chemotherapy. But these patients would be ineligible for a whole group of trials, structuring a curious dynamic of hope and disappointment, as revealed in this short exchange between two oncologists:

Dr James: About a third of patients are thought to have the EGFR mutation, although only about 10% of the patients they have tested at the hospital have it.

Dr Anton: So two thirds of the patients will be disappointed.

Dr James: Well, some studies have shown the mutation to be a ‘negative prognosticator.’*

¹⁹ While patients were already now routinely tested for EGFR as part of standard practice, trial sponsors required the test to be done in a central laboratory. Centralised testing is usual practice for trials and is done to mitigate errors caused by differences of interpretation between technique and personnel.

It is a case therefore which shows two aspects of the molecular turn and how hope is implicated: biomarkers govern access to therapy, and hence reinforce hopes in intervention; they are also prognostically relevant and might indicate greater chances of survival or response to standard treatment. In cases when these two hopes oppose and hinge on the basis of single biomarker, such as with EGFR, patients are placed in the predicament of making complex evaluations about hope, with extremely limited information and inexact calculations of risk and probability. For example, the figures quoted by clinicians differed quite significantly, and the hospital's own records showed another figure altogether. These discrepancies also feature in the clinical literature. More significantly is whether these trials will yield the rewards that have been promised; another contentious issue (Westphal, Maire, and Lamszus 2017). Finally, the prognostic value of EGFR is still unclear (Chen et al. 2015). So, from a patient's perspective, is it better to have more options in the armoury or be placed in a generalised category of better responder to standard treatment? I saw several patients broach this evaluation while being approached for testing.

I will discuss patient's relationships to trials in greater detail in chapters 4 and 5. For now, I simply want to mark how biomarkers are a critical intervention into their design, governing access, inspiring new increasingly personalised approaches, and questioning the conduct and meanings of previous (and some current) trials which use eligibility criteria based on histological data. Biomarkers envision a new future for treatment, which is tantalisingly close. Patients desperate for cure and clinicians share in this and are subjected to a new "regime of truth" which orders a new reality and set of possibilities (DelVecchio Good 2001; Marcus 1995b). Through this new regime, life is continually visualised at the molecular level in terms of genes, molecules and proteins; a "molecular gaze" ... enmeshed in a molecular style of thought about 'life itself', which has seen the body fragmented and reconfigured in new ways" (Bell 2013:126). This inspires new yet still ambiguous hopes for longer lives, freer of symptoms, structured by experimental trials and the possibilities they carry. These are the affective concerns dredged up and informed by the imaginative dimensions of biomedicine; they envelop patients, clinicians and the public in a "biotechnical embrace" (DelVecchio Good 2001). Within this, we see how those with disease are especially susceptible to the new hopes engendered by medicine's imagination, however distant these hopes may be (DelVecchio Good 2001; Novas 2006).

LOCATING PATIENTS

The molecular turn bears significantly on the location of patients in medical decision-making. As I stated at the outset of this chapter and illustrated with the example of MGMT promoter methylation, the integration of new molecular features in treatment prediction constitutes a move towards *personalised medicine*. This personalisation, anticipated by London Cancer Brain and CNS Tumour Pathway Board in their 2014 guidelines and confirmed in 2018 NICE guidelines for brain tumours (NICE Guideline 2018), is a key example of ambitions set out in NHS England's recent vision of care (NHS England 2016). Like the rhetoric of the molecular turn in brain tumours, the rhetoric of NHS England's vision and strategy is striking for its evocation of imminence, revolution and moves into a new era:

[W]e stand on the brink of a new era of medicine. Across the world, we are witnessing a healthcare revolution driven by scientific and technological advances—in genomics, informatics and bio nanotechnology to name but a few—which are enhancing our ability to more precisely diagnose illnesses and target treatment of disease. (NHS England 2016:4)

With images of newness and radical change, a shared journey and public ownership of a healthcare service, which “belongs to the people” (2016:4), patients are defined by their uniqueness. According to the strategy, personalised medicine means:

A move away from a ‘one size fits all’ approach to the treatment and care of patients with a particular condition, to one which uses new approaches to better manage patients’ health and target therapies to achieve the best outcomes in the management of a patient’s disease or predisposition to disease. (NHS England 2016:6)

It is an approach which turns traditional medicine “on its head” and while traditional approaches were built around clinical teams focusing on one organ or site in a generic body, working back from symptoms to diagnosis, personalised medicine recognises that:

One disease may have many different forms, or ‘subtypes’, resulting from the complex interaction of our biological make-up and the diverse pathological and physiological processes in our bodies. These will not only vary between patients who have the same disease but also within an individual patient as they get older and their body changes. (NHS England 2016:6)

While the precise nature of personalised treatment in brain tumours remains unrealised and even controversial across guidelines and medical communities, its course towards standard treatment appears set. New research agendas are increasingly driven by questions of individual specificity and the goal of determining treatment protocols based

upon the genetic composition of patients' tumours (Schittenhelm 2017; Weller et al. 2010). Brain cancer was one of five cancers highlighted by the strategy, among others with a longer history of clinical biomarkers, notably leukaemia and breast. In fact, cancer is the paradigm case and reference for other diseases which seek to emulate the integration of biomarkers. Across oncology, an entire infrastructure of government, private and charitable funding schemes, university research departments, pharmaceutical companies and so on is being redirected to support a previously unimaginable "tailoring of patient therapy" (Keating and Cambrosio 2012; Louis et al. 2016:818; NHS England 2015; NHS England 2016).

As I observed during fieldwork, personalisation was entering daily care, albeit with the ambivalences described above. While MGMT methylation was not yet a determining factor in treatment, as now advocated in some patients by NICE guidelines, options of experimental treatments were already delimited by genetically-determined trial exclusion criteria. Clinical teams were getting familiar and gearing up for an approach to decision-making based on the presence or absence of specific biomarkers.

The language of these developments is intriguing and familiar—"personalised," "personal," "tailored." These are terms which resonate with discourses of patient choice (Coulter 1997; Coulter and Collins 2011). Yet, crucially, the notions of personalisation, specificity, tailoring and individuality articulated in programmes of personalised medicine differ to how they are embedded in the person-centred care policies of the UK NHS and the healthcare systems of other neoliberal democracies. At the core of this discrepancy is how individual patients—as the figures to which treatment is tailored or personalised—are being defined and embedded. Through discourses of patient choice, patients are listed as consumers, customers, clients or citizens with jurisdiction over their bodies and lives and able to exercise their right to choose treatments that befit their life situation (Mol 2008; Mold 2015; Rose 2013). In variously open or constrained ways they are configured as individuals biographically rooted in cultural histories with aspirations and needs, relationships and responsibilities. They are entitled to rights of autonomy, dignity and respect. Within the realm of personalised medicine, however, patients are defined by the molecular constitution of their tumours—the growing list of slim and anonymous acronyms of biomarkers—ATRX, IDH1, IDH2, MGMT, 1p19q, EGFR. Despite appearances, the scale, referents and overall substance of these discourses is therefore radically different, and while discourses of choice assume tailoring to an individual's personal and social circumstances, personalised medicine tailors to their body.

Exactly how this might affect the way that decisions are made is hard to predict. On the one hand, there is a risk that autonomy and choice are undermined as biomarkers effectively stand in for the agency of patients and drive the direction of treatment. But on the other, a new research agenda and healthcare infrastructure consolidated around new molecular data and an injection of funds to brain tumour research might mean an increase in the numbers of treatments and clinical trials available for patients to choose from, albeit on the genetic basis of their tumour. It might also mean both: a proliferation of options but one “true” choice as patients are encouraged to choose the option already chosen.

Key, is how brain tumour patients will respond and attribute meaning to biomarkers. Anthropologist Kirsten Bell has drawn attention to this shift in how bodies are described and imagined focusing on the semiotics of the molecular gaze in cancer (Bell 2013). She speculates on the meanings people living with and beyond cancer attach to risk and its realisation, emphasising biomedicine’s inability to control the so-called objective meaning assumed to lie within biomarkers. Rather, people make their own attributions. And yet what is different in this molecular era is the assumption of objectivity and the “relative clarity they may provide amidst cancer’s semiotic ‘din’” (Bell 2013:134). For Bell, biomarkers represent a step further along the numerical technoscientific trajectory of biomedicine, rendering images of disease which are at once graspable and yet obscure: a new style of thought about “life itself” (Rose 2007). Highlighting the fuzzy pictures of CT scans and biopsies, which must be interpreted by specialists, she writes how:

In a sea of floating signifiers, biomarker numbers may provide a reassuringly concrete buoy for patients to cling to, providing a sense of control and empowerment amidst the onslaught of information and decision making that now characterises the ‘career’ of the cancer patient. (Bell 2013:135)

The semiotic power of biomarkers furnished Bell’s respondents with new powers to challenge clinicians’ decisions as they claimed objectivity against clinicians’ dismissals of their subjective sense of disease. As I mentioned previously, I heard that some patients at The Warner were beginning to ask about molecular markers. But those I met were less proactive in seeking profiles. Instead, their encounters were more oblique or passive as they received a molecularly-defined diagnosis, like Sara, were told their MGMT methylation was a good sign that treatment might work, or were approached about trials with access governed by biomarkers. The empowered positions assumed by Bell’s respondents were therefore not resonant with mine, and while there was a certain clarity in the accounts of some patients, this clarity simply echoed what they were told by clinicians.

...

Relatedly, molecular tests might be intervening in clinical jurisdictions. In their ethnography of breast cancer genomics, Pascale Bourret, Peter Keating and Alberto Cambrosio argue that these tests embody (non-human) clinical-diagnostic agency by shifting the “content, contours and tools of diagnosis, and by establishing a direct connection between test results and therapeutic choices” (Bourret, Keating, and Cambrosio 2011:822). As such, they suggest a possible shift in the locus of clinical judgement and decision-making as these technologies disrupt long-standing social arrangements between clinicians and pathologists. One possible consequence is a relocation of the treatment decision from the clinic to the laboratory as tests are increasingly linked to treatments. In a clinical environment in which decisions are already prefigured in treatment algorithms (Berg 1997; Pinder et al. 2005), this is increasingly likely.

While I did not witness a major or obvious shift during fieldwork and while my fieldwork was undertaken before personalised treatment has become clinically standard, there did appear subtle slippages in power and repeated reports from clinicians that pathology was certainly becoming “more vocal” in weekly multidisciplinary team (MDT) meetings, “insistent” or “militant” on the course of treatment. Pathologists advocated hard for these parameters to determine the diagnosis, even when histology and radiology suggested differently. A phrase I heard repeatedly from pathologists was: “this is likely to *behave* as a GBM.” In these cases, they would recommend that oncologists “accept these are high grade tumours” and “treat them more aggressively.” On numerous occasions, pathologists would emphasise the increasing likelihood for these schisms and how they had run molecular tests on biopsies of deceased patients originally diagnosed with lower grade tumours to find that under the new diagnostic guidelines a large proportion would have been upgraded. While this is to do with *diagnostic* shifts rather than the *predictive* promise of personalised medicine, it shows us what might be a rise of the pathologist and, moreover, the authority they are accorded in the relative inaccessibility of their work.

These changes contribute new configurations of patients and practitioners and might position patients further towards the edges of clinical decision-making. And as I showed in chapter one, the production of knowledge and its communication is a distributed process: pathologists do not meet patients. On one hand, personalised medicine offers new inevitabilities in the treatment course along with the allure of tailored therapies. On the

other, shifting the locus of decision from the clinic further into the “black box” of the laboratory risks reconstituting medical paternalism and complicating the opportunities for patients to question the values, risks, assumed tolerances of symptom and side effects, and goals of care embedded in treatment protocols. This relates to the paradoxical nature of biomarkers, which Bell highlights: the comparative unambiguity of their meaning alongside the obscurity of their production.

How will pathologists, clinicians and patients negotiate new positions in the context of new non-human clinical-diagnostic agencies brought by the molecular turn? How will discourses of personalised treatment and person-centred care interact? How might they diverge and become distinct or conflated and confused? How might clinical commissioning groups and insurance companies steer treatment options and the capacities of patients as choosers? And how will these new scenarios affect patients’ choices?

TEMPORALITIES OF KNOWLEDGE REVISITED

In chapter one, I wrote how the different accounts of disease given in histology, radiology and clinical knowledges are temporally bound and that this temporality factors into the legitimacy they carry in establishing the state of affairs and directing the course of treatment and likely disease progression. As we have seen in this chapter, a deeper and more foundational temporal current also operates. This deeper current concerns the very conceptual and technical apparatus which brings categories of tumour into the world. As such, it sets new expectations and investments in the legitimacy and authority of knowledge, and moves patients and practice along accordingly. At this deeper level, the very terms of engagement are redrawn. Topographically, we might consider this the bedrock of care upon which all else rests. Like bedrock this is relatively stable and much slower moving in comparison to other vectors which we will see later. But it is similarly prone to episodic and radical shifts, akin to the movements of tectonic plates—“seismic shifts,” as the oncologist at the district general hospital told me. These foundational knowledge platforms are therefore only ever temporary structures, never transcendental (Keating and Cambrosio 2000; Keating and Cambrosio 2003). Their rupture and replacement is experienced as revolutionary, era-defining, groundbreaking, seismic change by virtue of their capacity to reframe the very nature of disease along with the re-imagination of routine and possibility. Both hope and uncertainty are highly characteristic.

Medical historians Peter Keating and Alberto Cambrosio have described these transformations as movements between platforms. For them, biomedical platforms are “material and discursive arrangements, or sets of instruments and programmes, that, as *timely constructs*, coordinate practices and act as the bench upon which conventions concerning the biological or normal are connected with conventions concerning the medical or pathological.” (Keating and Cambrosio 2000:386, *my italics*). “As a site where the normal and the pathological are articulated, platforms connect population data with diagnostic and prognostic singularities. We can resort to this new category—the biomedical platform—to account for the transformations of contemporary biomedicine, and thus for the present-day biomedical enterprise.” (Keating and Cambrosio 2000:386).

Returning to the theme of navigation and temporality, and Henrik Vigh’s image of motion within motion, unstable and changing knowledge constitutes a significant and irregular temporal current which ushers people along in particular often unknown directions. It is characterised by uncertainty, imminence, and perhaps disruption and while stewarded by scientific and regulatory apparatuses, unfolds in ways which might be hard to anticipate. Patients and clinicians are called on to reimagine possibilities, envision trajectories, and adjust their plots, by attending to these currents. Yet this is done amid imperfect knowledge. As Bell forecasted, this might offer patients new possibilities for empowered action, such as, insisting on tests or trial entry. But as treatment decisions become increasingly biomarker-driven, it might also shackle them in new constraints and further dislocate them from conversations about treatment. What might happen to the lives of those newly designated treatment-resistant remains to be seen.

CONCLUSION

Continually framed and reframed as “emergent,” “revolutionary,” “next generation,” “groundbreaking,” “seismic,” and “era-defining,” the integration of new molecular biomarkers works at an ontological level. The new focus shifts the scale of view and the classificatory parameters that determine what constitutes specific biological entities. It brings new objectivity and specificity to disease nomenclature and diagnostic practices and allows for a new research agenda and treatment armoury to be *imagined*. In this, new hopes are given. But these changes are also provoking new ethical dilemmas around individual and population-wide treatment decisions, equity of treatment access, and the social arrangements of care.

Studying the social consequences and new social configurations materialising around infertility and assisted reproduction, Rayna Rapp coined the term “moral pioneer” (Rapp 1988; Rapp 2000). This described women’s uncertainties as they moved through previously uncharted terrains of prenatal testing. She writes: “at once conscripts to technoscientific regimes of quality control and normalisation, and explorers of the ethical territory its presence produces, contemporary pregnant women have become our moral philosophers ... when viewed collectively, all the women using or refusing the test can be seen as moral pioneers ... participating in an impromptu and large-scale social experiment” (Rapp 2000:307-310).

This term is apt for capturing the positions of people like David Louis, who coordinate the terms of knowledge integration globally, and Dr Plank, who does so locally, as well as those institutional actors which determine guidelines for best practice. It also captures the new positions of patients and families, who are momentarily taken to share in the uncertainties which characterise medical knowledge and which cannot yet be fully contained or fixed in the terrain. The terrain is made unstable, fractured amid seismic change. As with Rapp’s women, the decisions made now by these various people contribute to the medical imaginary in brain tumours and set ethical precedent to be embedded in new routines. In the meantime, lacking certitude and the cultural scripts to guide them, they approach dilemmas with the trepidation of pioneers on a revolutionary frontier: hoping for the means to lengthen and better their lives or the lives of those they care for but unsure of the nature of change. Doctors and nurses, not yet with the experience and “feeling” (Koenig 1988) of new meanings and techniques, must trust those with the conviction of change.

The social impacts that happen along the way of progress are many and diverse. They are likely to continue. In an interview published in the *Annals of Translational Medicine* regarding personalised (or precision) medicine, a prominent neuropathologist was clear about its relative infancy and continuing rollout:

In my opinion we are just entering the era of precision medicine. I think as yet we are far away from the rollout of precision medicine. As for now, neuropathology has just identified diagnostic biomarkers (most developments happened the last 10 years) and it will take another 10 or 15 years for the oncology community to develop drugs that can target these pathways. The advance of epigenetic profiling will have to be combined with confirmatory testing for druggable targets (single mutations or pathways) and this will form the basis for precision medicine. (Lu 2018)

Given this continued cresting of change, the ethical instability is likely to remain open and “in the making” (Biehl and Locke 2017:5). The fundamental question is how

might biomarkers change the everyday ethics of brain tumours care and treatment. More immediate questions concern those patients, like Sara, who are caught in the crosshairs of change and how to deal with the uncertainties implied in epistemological change.

In the following chapter, I further consider how patients interact with medical knowledge and imagery, focusing especially on how patients imagine themselves and the world around them in the context of having a progressive disease of the mind.

CHAPTER 3—SPECTRE OF A MASS

I entered the field with an expectation of witnessing sudden and radical changes in patients' cognitive capacities. In fact, a large part of my pre-fieldwork preparation was based on this expectation and I had developed detailed protocols through which to monitor participants' senses of themselves, the project, and to re-establish consent in moments of compromised cognition. This was key to me obtaining the ethical permissions that would allow me to undertake the study and it involved a somewhat convoluted process. "In cases where a patient's capacity is questionable, as indicated by clinicians," I wrote in the final study protocol which was granted ethical approval by a central NHS research ethics committee, "the researcher [me] will conduct a brief and structured assessment of their capacity to consent to the study based on the criteria outlined in the Mental Capacity Act (2005)."

If, after this assessment, patients were assessed to lack capacity, a four-step plan would follow. Assent would first be sought from "a patient's next of kin, family carer or someone close to the person (who does not receive remuneration for this role) who will act as a 'personal consultee' (identified by the clinical team responsible for their care)." And in cases where a personal consultee could not be identified, a professional consultee would be sought, defined as a "senior experienced health or social care worker who is not directly involved in the research or care of the patient." This plan was based on previous studies with people with dementia undertaken in my department and it adhered closely to advice from ethics committees and the MCA (2005). It lays out some of the social actors implicated in structuring incapacities—families, carers, someone close, a professional—and establishes them as neutral—uninvolved in direct care and without remuneration.

I took pains to emphasise the provision of appropriate guidance for consultees—personal or professional—and especially for them to note conflicts of interest, make considerations with impartiality as best they could, and act in patients' "best interests." However, in spite of this preparation I remained nervous about these encounters not least because of the vagueness of concepts like "capacity," "best interests" and "conflicts of interest," which although mainstay principles in the MCA (2005), lack both conceptual precision and real-world clarity.

Lacking mental capacity is a defining feature of how clinical, research and lay communities imagine brain tumours and dealing with it has become a prime concern within psychology, psychiatry and health services research literatures (Bernstein 2014; Kerrigan et al. 2014). It is also a key feature in the advocacy literatures and fills the threads of online brain

tumour forums. As such, “losing myself,” to borrow a phrase from The Brain Tumour Charity’s report on brain tumour experience (The Brain Tumour Charity 2015a), is a primary fear for patients and for their families, represented as a terrible mystery and an ever-present concern.

Given these experiences pre-fieldwork, I had therefore not unreasonably expected to see patients lacking capacity and rendered so through routine capacity assessments. And I had assumed that I would at some point face dilemmas in re-establishing consent through the processes described above. However, I quickly understood that while administrative protocols are in place, they might not be used routinely. And while patients greatly feared the losses of mind suggested in popular conceptions of a brain tumour, formal ascriptions of incapacity seemed rarer than imagined.

I was told that while assessing capacity is a collective responsibility and mainly under the remit of the decision-making team (typically, consultant surgeons and oncologists), it is rarely done. “The problem with capacity,”* I heard one clinician say to a colleague, “is that it’s only you and me who are doing assessments.”* This mapped onto my experience in the field where I never witnessed clinicians doing assessments and only once saw a formal assessment form in patients’ notes. While I do not want to surmise from this that capacity assessments are systematically avoided, I do want to mark how it is rarer than I had imagined after reading the literature on brain tumour symptoms and popular accounts.

I did, however, commonly hear words like “confused,” “confusion,” to describe patients who were “not themselves;” words which are arguably less loaded and within an everyday parlance shared by patients and families alike. I also want to state the obvious: mental capacity is a hugely complex issue, rendered through complex intersubjective practices. In practice it is a “balance of probabilities” (Department of Health 2005:2); or in the parlance of clinicians: “Your best guess;”* “Something that is never clear cut.”* As such, patients of suspicious mind were more likely to be placed in everyday vocabularies of confusion than the formalised measurements of capacity.

In this chapter, I explore these ambiguities and assumptions from the perspectives of patients. In chapter 1, I outlined the productions of diagnosis and treatment planning only to show in chapter 2 how these routines are being destabilised with the introduction of new technologies. Nonetheless, both chapters concerned mainly biomedical knowledge production, from the perspectives of scientists and clinicians and more broadly “behind the scenes” of the hospital. Here, I explore how patients receive these biotechnical facts and what this means in terms of how they see themselves. Through these diagnostic processes,

patients are given new explanations for the strange events of their last weeks or months. Migraines, headaches, personality disturbances, seizures or more subtle things like the auras and tiredness are renarrativised and redefined as symptoms: the spectre of a mass comes into full view.

Specifically, I deal with the development of *an anticipatory loss of self*: a subjectivity and an interpretation of oneself—mind and brain—produced in the intersubjective encounters between patients, their families, clinicians, biomedical technologies, and the physical sensations that emerge as tumours develop and patients undergo intensive monitoring, surgery and therapies. I argue that this anticipatory loss of self is not merely an emotional state, but a mode of being that establishes a frightening imagined reality and through which one questions physical sensations, the nature of reality, and ultimately *one's own capacity as a rational agent*; that is, one capable of making significant decisions about care. Mental incapacity is not an inevitable consequence but it is one that patients think about frequently and attempt to manage or resist through narrative and practical strategies to reaffirm the self.

I begin the chapter by elaborating an important conceptual foundation: the specificity of neurological disease and the location of self in a prevailing Western materialist ontology (Vidal 2009). The tight binding of mind and brain given in this ontology is, I argue, what grounds patients' conceptions that damage to the brain equates with loss of self. It is an ontology embedded in contemporary neuroscience and which also circulates freely in popular culture (Williams, Higgs, and Katz 2012). As patients become diagnosed, see images of their brains, watch videos of neurosurgery and so on, these popular ways of locating the self become further reified: the brain further becomes a site of key significance. Following this, I document patient encounters with strange and uncanny feelings. I then show how these combine with biotechnical explanations to produce an orientation in which these encounters become the harbingers of a new fate—the anticipatory loss of self. In the next two sections, I examine how patients strategise to counter the instantiation of these losses, tracing their efforts through narrative, modes of documentation, and the appropriation of biotechnical imagery. In the final two sections, I suggest a theoretical account of what I call a *subjectivity of negation*—a paradoxical displacement of self, characterised by spiralling frustration, anxiety and self-doubt—and conclude with a reflection on contested agency.

CONCEPTIONS OF BRAIN, MIND AND SELF

In understanding how people with a brain tumour come to see themselves, it is key to reflect on the specificity of neurological disease and the location of self in a Western materialist ontology (Vidal 2009). In this, I follow sociologists Simon Williams, Paul Higgs and Stephen Katz in positing the recent emergence of a neuroculture constituted by “mutually reinforcing fields connecting ongoing debates about mind and body, consciousness and intentionality, and nature and culture with new technologies, knowledges, subjectivities and cultural imperatives” (Williams, Higgs, and Katz 2012:64).

As others have documented, neuroscience has increasingly provided “proofs” that the brain is the seat of the self, documenting first brain structure and now function, through increasingly sophisticated means (Dumit 2004; Rose and Abi-Rached 2013; Vidal and Ortega 2017; Williams, Higgs, and Katz 2012). We now have the means of “picturing personhood” (Dumit 2004), able even to disentangle ephemeral feelings like pleasure and to see them as biological events (Cohn 2008). Not only this, but through psychopharmacology and other means to effect brain function, we have learned to understand and manipulate our troubles, desires, affect and even moral reasoning by way of the inner “organic” functioning of the body (Rose 2003). As Nikolas Rose summarises: “While our desires, moods, and discontents might previously have been mapped onto a psychological space, they are now mapped upon the body itself, or one particular organ of the body—the brain.” (Rose 2007:188). The contemporary belief that “we are our brains,” though not new, is continually reaffirmed and relentlessly pervasive (Vidal 2009; Vidal and Ortega 2017).

While certainly these beliefs circulate freely through popular discourses of brain and self (Williams, Higgs, and Katz 2012; Pickersgill, Cunningham-Burley, and Martin 2011), I want to emphasise how people with a brain tumour are further brought into understanding themselves in this materialist way. As I documented in chapters one and two, patients are brought under a new biomedical authority. New explanations are concretised around what were, for many, the strange events that led them to A&E or being referred for a brain scan. They literally learn new ways of seeing themselves.

This happens through repeated scans, while patients lie in the tunnels of MRI machines and afterwards “see themselves;” the precise planning of surgery and radiotherapy, which mark out the brain in terms of “eloquence” and “essential functioning;” and through some operations themselves when patients are awake and called on to respond to structured questions while surgeons use electrodes to stimulate parts of the brain to localise function and establish what is safe to remove. Some watch videos of neurosurgery on YouTube and

see for themselves how a touch from a charged titanium probe to the brain makes someone slur their words, stutter or stop shaking their arms. They learn the idiosyncrasies of their brains: the specific neural patterns which shape whether they are left or right-handed, or the precise location of their motor strip²⁰, and they are told that this is the site that makes them smile, frown or move their fingers. Patients become aware of *their* brains through these processes and they are often curious. Chloe, for example, was curious to know how her brain looked during an operation, which I witnessed. When I visited her on the ward during her convalescence she persisted in asking, “How was it? Did you see it? Did you see my brain? What did it look like?” These specificities are further drawn in repeated consultations as patients learn that their tumour is in a part of the brain which affects memory, speech, or vision, for example.

That the brain becomes a site of particular significance for people with a brain tumour accords with numerous accounts of the body in disease, where it is no longer “absent” from experience (Leder 1990) or taken-for-granted, but rather present and objectified as the very site of experience (Bury 1982; Scheper-Hughes and Lock 1987). Such objectification has been noted previously in contexts of the brain. Martyn Pickersgill and colleagues, for example, document the new awareness of the brain given in neurological diseases like epilepsy and stroke; Margaret Lock does similarly in her analysis of Alzheimer’s Disease, where people learn to understand themselves not simply through scans but at a neuromolecular level (Lock 2013).

So how do conceptions of brain, mind and tumour come together? And what does this mean in terms of how patients see themselves? In the following four sections, I explore patients’ encounters with strange new events, their experiences and interpretations of scans and biotechnical explanations, and how these coalesce in new subjectivities and harbingers of a new reality. I lay out some of the coordinates of an intersubjective space—a space of intersecting conceptions of mind, technologies, and affects—which allows new possibilities for understanding one’s sensations and experiences in particular ways. It is through this space that patients ultimately come to understand themselves. I therefore argue that an illness subjectivity is not an inevitability, received from biotechnical truths, but is co-constructed by patients, families and clinicians in often creative and unexpected ways.

²⁰ The motor strip is a part of the brain which controls the voluntary movements of skeletal muscles.

ENCOUNTERING THE STRANGE

During my first week in the field, I saw and heard about patients turned blind by tumours which had crushed their optic nerves, who had major problems speaking, who could remember little beyond the simplest details of things, who forgot the names of their families, who exhibited the excesses of hormones like growth hormone because their pituitary glands had been radically disturbed, or who suffered such crushing headaches that they could barely raise their heads. Not all these afflictions affected the patients with whom I had deeper engagements, though all had suffered strange experiences like seizures and premonitory auras at one time or another. Sara, who I introduced in chapter two, began suffering more serious seizures sixth months after she was diagnosed. Midway through chemotherapy, she was rushed to hospital by ambulance after a particularly heavy seizure late at night and spent the next six days under close observation. She had been out of hospital only a week when we met at the chemotherapy clinic.

It had been a traumatic time and scary for Sara and Robbie, her husband. Sara had wanted to continue with treatment soon after returning home and the doctors were also keen to proceed. We had seen each other fairly frequently over the six months since her diagnosis and I had grown to understand some of the nuances of her relationship with Robbie. Though married for almost fifty years, they had the affection of newlyweds: always holding hands, always flirting. For several weeks after Sara was discharged, she and Robbie came back to the hospital each week for blood tests and to see the oncologist. She had finished radiotherapy months back and was now midway through chemotherapy. Blood tests are done to test for things like platelets and white blood cells, both of which can be depleted by the treatment. It was because her platelets were down that Sara returned each week: low platelet counts make chemotherapy too risky; wait a week and they might come up.

We met in the hospital foyer, as usual before her appointment with the oncologist. I was surprised to see Sara looking so well—Robbie had told me about the seizure over the phone—she was bright-eyed and with flushed cheeks. But her hearing had worsened suddenly after the seizure and Sara told me she was finding things very confusing. The clinic was on the lower ground floor, unlike usual, and this was hard for her to reconcile. “In my head we should be going up there,” Sara kept saying, pointing upwards to the 4th floor, “It’s so confusing.” Consistent with the experiences of almost everyone I spoke with, these small changes to routine could at times be unsettling in the extreme.

Over the course of these weeks, I watched Sara's slow movements through her confusion and the emotional toll it took on her and Robbie. It began with strange episodes

when Sara kept thinking she was in her parents' house: "It's really weird: when I'm upstairs I think I'm with my mum and dad and when I'm downstairs I'm back home with Robbie." These thoughts would be extremely affective and laden with the details of old memories of her childhood. But as Robbie later told me, Sara's parents had both died more than twelve years ago.

A week later, Sara told me how she was determined to get back to her routine, especially cooking, which by her account had suffered under Robbie's management. Although she felt lifted with more energy, she remained confused by where she was, and was now plagued by other old memories as well as the enduring fiction that she was in her parents' house. "I was looking for something and I couldn't find it,"* she told me, "and I was asking Robbie where it was, did he move it?—it was flour or something—'No,' he said. And I thought it was where I always had it, but it wasn't there. And then I realised it wasn't there because it wasn't the same kitchen. I was thinking I was in my old kitchen."* While these thoughts and disorientations were distressing and frustrating, for Sara, forgetting the names of her grandchildren was hardest to handle: "It's sad,"* she said, "I'd hate for them to know."*

Throughout these weeks, Robbie and Darren, one of their three sons who sometimes came to the clinic, would try to give perspective to Sara. They called the seizure her "blip" and would say how everyone forgets things: "It's just your blip, Mum. Everyone else in your case will have blips too; it might not be a seizure but it'll be something else. And that's what the doctors call it: a blip."* Robbie, ever gentle and with near unsinkable hope, would hold her hand in his and test her on the names and ages of their grandchildren: "Well done babes, see you're getting them now,"* he would say if she answered correctly or would steer her to the right answer with clues if she guessed wrong. Following their lead, I too sought to play down Sara's symptoms. Though, in a moment of frustration, I saw how she was losing patience: "Don't make excuses for me,"* she told me, when I told her that I too lost track of time, made mistakes and forgot things, "it's the trauma."*

The doctors would explain things in different terms. Rather than place her experience within a more generalised framework of 'it happens to everyone,' they would explain her symptoms through the clinical registers of diagnosis, treatment side effects, and the general constellation of factors like tiredness. "It's not surprising for you to have some problems with your memory because of where the tumour is,"* her oncologist said two weeks after the seizure, "And the surgery and the radiotherapy—they all make it worse—and

the fatigue too. This is usually what happens around this time—it's consistent with treatment—which is why I am not too worried. You look well.”*

The MDT had concluded in its previous meeting that the enhancement seen on a scan done soon after the seizure should be attributed more to treatment effects than tumour progression: Sara should therefore continue treatment. As such, the doctors upped her anti-seizure medication and rescanned her: an unusual practice at this stage in treatment because scans are difficult to interpret so soon after surgery and radiotherapy. As predicted by her oncologist, it gave a mixed picture: “Now there's no definite evidence of progression but there is some more enhancement. This could be other things like blood products but it can be difficult to differentiate these from progression. So what we'll do is continue treatment and then rescan you.”*

...

I would sometimes ask people to try to tell me what they saw and how they felt—what an aura is like, or a seizure, or indeed what they saw in ordinary moments—not to worry how weird and wild it sounded, which was sometimes a concern, but just to tell me what life was like for them after being diagnosed with a brain tumour. Describing her eyesight, which had seriously deteriorated after her surgery, Fay told me, “It's so confusing—so disorientating.”* This was hugely distressing for her. She lived alone and so these kinds of incapacity were especially significant for her. At first, her oncologist hoped that things would get better with her eyes. He attributed it to swelling caused by surgery. But instead, it continued to deteriorate and Fay was eventually registered partially-sighted. When I asked her more specific questions about what she saw, Fay told me:

Fay: If I'm looking at your face—I can see the whole of your face—but I can't see what is at the side of you, I can't see the door, I can't see the door opening, I can't see the end of the sofa. I can see the picture—well I know the picture is above your head, I can see the outline of the bottom part—but I can't see if—I can't see the whole of the picture—

Henry: And what about to your right?

Fay: Yeah I can see the television, the TVs there. I can see Dennis's [Fay's cat] blankets on the floor. I can see the chair.

Henry: And what does it actually look like, I mean the stuff that you can't see, what is there instead?

Fay: Nothing, it's black—it's empty space, it's like it's not there.*

Later on, what Fay saw developed into bright colours which zigzagged down her eyes across whatever it was that she was looking at—a kaleidoscopic film which played over the world. This shifted her entire physicality: how she walked, for example. Her sister Maria worried that Fay looked an easy target in the street given her disorientation was plain for all to see.

Describing auras—perceptual disturbances that may or may not precede a seizure—Jim told me:

It feels just a bit like too much information in your head that you can't process. Let's say if you're working on something—and this is what would happen to me at work and another thing that I noticed for over a year before maybe—is that I'd be working on something late into the night and I wouldn't be able to get it out of my head and that's exactly how the seizure started. It just felt like an overload of information in my head. Like a buzzing sensation and then I just felt the buzzing sensation just take over and then spread from one side of my head to the other. So now what I fear is just that overload of information, like I'm staring at something too intensely. My mind can't get rid of the information. That's what it feels like to me.*

Jim was thirty-five when we met and married to Tina. Together, they had two young children. He had worked successfully as a computer software designer before being diagnosed with a glioblastoma in late 2014. After the rare event of a stroke during surgery, he had almost completely lost the power down his left side and was unable to walk. He told me how his frequent seizures were difficult to control and would make him feel as though he was losing track of hours, days sometimes. He sometimes fitted at night making it harder for him to place himself in time. Like others, Jim told me about the peculiar feeling of time lost to seizures and when I first met him, shortly after surgery, he relied on his wife to fill in the gaps. He found it hard being in groups, finding conversation difficult to track with, as he put it, “trouble finding the right words and responding quickly enough: I'm generally just slower at talking and thinking.” Most of all, he was concerned with not making sense and doubting his reality, as this exchange between Jim and Tina, a year later, shows:

Jim: Distinguishing the causes of symptoms—it's very hard. People keep asking me how I feel or do I feel different. I don't know. Or am I doing that? You keep questioning my sanity—

Tina: [laughing] I don't—it's because he was having a conversation in his sleep last night, saying that had I paid the tennis instructor—I said, “You haven't been to tennis.” And he said, “yes I had.” And I said, “Maybe it's for Tom”—our little one—and I said, “but Jim, you can't walk.” And he said, “nonsense” and went back to sleep—

Jim: That was actually a joke—

Tina: I wasn't questioning your sanity!

Jim: That was a joke. I'd woken up. I just been dreaming and was just a bit out of it still. You keep trying to ask me if I feel like I did when I had the infection—

Tina: Which infection?

Jim: You know when I was behaving strangely. But I just don't know. I don't know if I'm making sense now. I assume I am but—

Tina: [tenderly] You're making complete sense—

Jim: But I don't know—*that's the point*. So if I'm having a seizure then I know I'm having a seizure. But I don't know with you. I don't know how I'm appearing to everyone else. I really don't want to be stuck where everyone else is talking about me and I'm out of it, obviously, knowing what's up but—it's like when I've had the seizures before I can see everyone else's reaction. But I can't talk, which is disturbing. Or when I was about to have one—

Tina: You're frightened of the boys seeing you aren't you.

Jim: Yeah, I don't want the children seeing it—or when I'm having the aura and I know it's about to happen. And I see other people panic. That makes me more—whereas one time when you were there. It was okay. It didn't happen. That's how I want other people to behave but if I can't talk it's very stressful. I can't say, "stop panicking everyone." Because I'm shaking and—I think it's weird being aware of what's going on around you when you're having that seizure. Everyone says that you can't—that you should be unaware. But actually each time I've had one I've been awake and aware of what's going on around me. And my arms start moving. And I can see everyone else's reaction. But I can't communicate. It's weird. That's quite unpleasant. That's why I'm so nervous about having one. I just want to tell everyone to calm down.*

As well as receiving popular conceptions of brain tumours and fears of losing themselves, patients learn to make more specific attributions through biomedical knowledge. Efforts to understand the significance of strange experiences become imbued with biotechnical explanations. Patients learn to see themselves and strange events through a clinical register, and as such, these can become harbingers of a new reality. Here, a new orientation and interpretive frame in which to situate the uncanny is acquired and established.

HARBINGERS OF A NEW FATE

Jim's concern with making sense was by no means unusual. In fact, it was an enduring feature of many accounts. And it was not simply in people's interpersonal relationships, but in their broader relationships with the world around them.

Consider Fay's explanations for a peculiar find in her garden. Fay lived alone after caring for her parents who both died of cancer. She was forty-nine when we met and, although unmarried and without children, her family was large and ever present. Her four sisters would sometimes cram into the consultation rooms at the hospital. She had another

living in the US and a step-brother who lived close by and sometimes stayed with her. After her mother's death two years before, Fay had moved into a smaller place with a small garden. At once her sanctuary and freedom, this garden occupied her days off from the hospital routine and her many family commitments. Many times she told me how it was her "cancer-free zone." Sometimes we would stand among the pots and she would point out the new shoots coming up or the freshly tilled soil hiding bulbs she had planted: "Every day something changes," she would say. At other times, we would sit and talk in her sitting room and watch the birds flitting to and from the nuts she scattered on a high table. A few times we would garden together and let my audio recorder run. A year after we met she told me this story while scratching away in one of the pots:

Guess what happened? A few weeks ago, I was out here planting some new seeds and I could see this little pink thing sticking out of the soil. I thought it was a big fat bud, so I dug around it to see. And Maria [Fay's sister] was with me and I asked her, "Did you plant a carrot out there? Did you seriously plant a carrot to wind me up?"—because that's the sort of thing Maria would do—but then she said, "Fay, that's not a carrot; it's a frankfurter!" I'm not kidding! It looked like it had been pile driven straight down into the soil. So, I'm saying to Maria, "Are you taking the piss?!" I said, "Maria—," I said, "Please don't!"—Because I thought well maybe I planted it and then forgot or—And she said, "I promise you"—she was rolling around laughing—"Fay, I promise you it wasn't me." And I said, "Someone's taking the Mickey,"—you know whether it's the neighbour, or kids, I thought—So she says, "I wouldn't do that because I know how confusing you find things." So anyway, a few days go by and I was sitting in the garden and this squirrel came bounding across the shed. And it jumped down into those plants that are in the basket by the wall. Then it lent down, grabbed one of the plants with its little hand and yanked the whole thing up—the whole plant—and then it planted a great big wedge of cheese—I'm not kidding you—a great big wedge of cheese! Then it stood on it and stamped down on it and patted the soil with its hands. And then I'm thinking, okay now I believe it wasn't Maria and it wasn't me: it was the squirrel! And then last week Maria was in the garden and she said, "Fay, come and look at this." A whole egg! In its shell! She found a whole egg! And I said how can a squirrel carry an egg? How can he get it over the fence?! I thought I was losing it.*

When she told me this, Fay was laughing. She was incredulous at the sight of a squirrel with a frankfurter, a piece of cheese and an egg. But there is a deeper narrative running through the story and this has to do with the alternatives Fay gave by way of explanation: if not Maria or a neighbour's practical joke, perhaps it was her. In fact, this was something of a common theme for Fay. She was terrified of "losing it."

To anchor the significance of this story, we need to return to her earlier accounts where she spoke more explicitly about her doubts. The following passage is from six months earlier, days after Fay had defended her sovereignty from two of her sisters who, in

her words, “went behind my back,” for a special consultation with the doctors without her. The consultation never happened but Fay was furious nonetheless:

Fay: It’s like I’m not part of my life anymore—I did feel like it wasn’t my life. It was like everybody else was making decisions for me. And I said to them, “I’m not stupid, I’m still here, I’m still Fay, you know!” I felt like they’ve just taken it out of my hands and it did upset me. I felt betrayed by them both ... I just think to myself, “I’ve got this, this is happening to me,” and I’m doing my best to—not get over it because you can’t get over it—but to get on with it. And I felt when they did that, it kind of put doubt into my mind that I’m not capable of making my own decisions. And last night I lost my keys and I cried my eyes out because I’d thought I’d put them somewhere. My memory is not great, I’m not going to say it is: it’s not great. It was the sheer frustration. I was so upset and it just makes me doubt myself. I think I’ve put my phone here and I haven’t, it’s over there. So I’m looking over here for it. And I’m like, “where is it?” I put it there. Like I said to Maria this afternoon: people with Alzheimer’s, how frightened they must be. Maybe they’re clear the one minute and then suddenly they don’t know where the hell they are. I don’t want that to happen to me. Sometimes I wake up and I think, “where the hell am I?” I look around and I think to myself, “I don’t know where I am.” And then it will suddenly come back, “you’ve moved.” And then I remember everything.

Henry: When did you start to have these kinds of thoughts?

Fay: Ever since I came out of hospital, but my memory has got worse since I’ve been home, since I had the radiotherapy and all of that lot, it has been worse. And also because my eyes are so bad. But I don’t think, “oh maybe I put it somewhere else.” I’ve convinced myself that’s where I put them so I say to myself, “why isn’t it there?” I don’t know what happened last night, I was really upset. Why was I crying over a bunch of keys? ... In the future, whether it’s a week or you know, five years, I do not want to be dismissed by anyone. Not just the doctors. I don’t want to be dismissed by my family—not that they would do it deliberately ... I wouldn’t even have Lee’s children last week because Maria wasn’t going to be around. One is ten and the other is eight, so they’re not babies. And the counsellor [Fay was seeing a counsellor at the recommendation of her oncologist] asked if it was because I was scared that I was going to have a seizure or something like that. And I said I was scared because I didn’t want the children to be scared if anything happened. I think it was the counsellor I was talking to about that, or it might have been Sherri?

Henry: I think it might have been because I remember, I was with you—

Fay: It might have been Sherri—do you see what I mean about my memory? I remember saying things but I don’t remember who I said them to—But yeah, I’m not afraid about things happening to me, I’m afraid of frightening the children. I’d love to have them, I’d have them every day of the week if I could. I just don’t want to end up the batty aunt that no one wants to come and see.*

Over the course of nearly two and half years, Fay would tell me of these strange events. We continued our friendship, speaking on the phone when I was in America and seeing each other after I was officially ‘out of the field.’ Whether she had lost her keys, mistakenly used someone else’s toothbrush, forgotten someone’s name or the details about a consultation, she would invariably chalk these up to the tumour. For her, these events would signal a descent into unawareness. She would often stop during interviews and in general conversation to check in, “I mean I’ve said to you before I think—Am I rambling? Am I making sense?”* It became somehow inevitable for her, though with uncertain timing; the

image of a lone Aunt, dismissed and unknowable, who no one wants to come and see. Seeking a more detailed forecast, she asked her oncologist:

I asked him, "What are the later stages, what happens?" And he said, "Oh, your memory gets a bit worse and confusion and things like that." I was starting to freak out about it because, like I said, I mean crying over lost keys was ridiculous—I've lost my train of thought again, it's just ridiculous—I was just so scared when he said, "Oh your memory can be a bit, you know—" And also he said, which frightened me even more, he said, "Oh I'm not so sure you'd be able to live alone!"*

Gabriel (see introduction and chapter one) spoke of premonitions. Recounting the moments before he was diagnosed, he told me:

Very strange. I'd given up my job and I was travelling and I just got a 'mad feeling.' And thought, "I need my brain scanned." There was no straight reason it just was a message my head was telling me. So very strange—it just came out of nothing. So I carried on travelling for another—probably six months after that. And as soon as I got back I started asking—I think it was the sinus guy I was telling the problems to—and I said to him I wanted a scan of the head. And it got into a bit of a discussion; the possibilities of why I felt that. And then he asked me about the first migraine I'd had. And I described it as stars. I had migraines after that, but they were all different—lines—normal sort of lines that people get from migraines. But the first one was very different. He said right, "We'll send you for a scan." And that's where it started ... [And with the recent progression] there were other things I didn't understand—because I'd started running again—I started fine, but after about three or four weeks I had to stop certain exercises which I did in the middle of the run. I'd have to stop because I started feeling—dizzy, I suppose—I wasn't necessarily going to fall over but it felt like a strong dizziness.*

Gabriel, was forty-nine and had long history of disease, having been diagnosed 14 years before. He was initially diagnosed with a grade II tumour and was told, given its size, he might have had it since he was twelve years old. Not long before we met, he had undergone a third operation which had returned a new and more aggressive diagnosis of grade III astrocytoma. Speaking about tumour progression he told me, "I've had [a brain tumour] for a long time. So now if I get a weird feeling—if something weird happens—that's the direction my thought goes."*

These are the subjective turns that are produced by changing conceptions of mind: when patients become the subjects of their own doubt and when certain kinds of experience would be equated with a loss of self. To greater or lesser extents, these turns happened consistently across patients I spoke to and would recur over the duration of disease. Old memories that impose themselves, disrupting daily tasks, and returning feelings of nostalgia to the present, seems obviously strange and understandably frightening. Yet even things like

losing keys that seem innocuous and quotidian on the face of it could induce major anxiety and doubt. While they might be a little out of sync with the habits of everyday life they are also very much a normal part of it; usually an explanation soon appears and the uncertainty felt before it does is not typically threatening. But time and again I listened to how these experiences—big and small—would be chalked up to the tumour. They would be interpreted as symptoms and narrative proofs. In these narratives, strange events became harbingers of a new fate: “I really don’t want to be stuck where everyone else is talking about me and I’m out of it,” as Jim said.

DOCUMENTING REALITY

Strategising ways to counter the frightening anticipation of losing oneself was also common among those I spoke with. While these would sometimes be simple affirmations—as in Fay’s, “I’m still Fay, you know!”* and Tina’s, “You’re making complete sense, Jim”*-or narrative modes of establishing continuity—as in Robbie’s, “It happens to us all, babes”* and Darren’s, “It’s just your blip Mum”*-they would also be more elaborate and calculated.

George was sixty-six and recently retired from a life on the railways. His wife, Phoebe, told how this work had a life-long effect on his sensibilities towards marking time. His life was lived by “minute-to-minute” punctuality, a temporal grid which kept things precisely in place. Since the tumour, though, he started to lose track of the details which ordinarily he took for granted. So, he devised a ledger in tall red book. I asked him to bring back the book one time and read from it, which he did: “0558 up in the morning; headache; 0604 toilet; 0632 made cup of tea; 0708 went back to bed; 1057 woke up again.”* This book, which revealed a life measured out in small daily tasks, became a key means of establishing reality for George. He would sometimes read from it if he felt he was out of touch: “that will ease my mind—because then somewhere I can remember.”*

Over time the log became more sophisticated—different colours, bracketed comments, thoughts, feelings:

I write down everything and then on the next page I’ll write down the things that are relevant to me ... it’s part of the process [I’m] going through to try and understand it—to have some sort of an idea, a log, to understand how we’ve ended up somewhere.*

These he wrote down as soon as he could, lest he forget but sometimes events took over and distractions kept him from doing so. He would then ask his wife Phoebe to fill in the gaps. “He’ll ask me what did we do today,” Phoebe told me:

“What time did we do that? Who came? Did we do this today or did we do it yesterday?” And I’m kind of saying to him, “if you can’t remember then it’s not a true log. If you’re having to ask me to tell you what we did and then you’re writing it down then it’s not a true log of what happened.” A true log is how it is for him. So if I’m telling you then you need to put my name in different colour or put my name in brackets to say, “Phoebe told me that this is what we did.”*

On another day while waiting to see his oncologist, the three of us sat and at George’s request drew a map of the head: “that would be good wouldn’t it—then I’ll know—I can put 5 for a really bad headaches, 1 for less bad.”* It was another iteration towards establishing a more accurate account of what George called “fleeting pains and feelings.”* Phoebe elaborated:

He’s struggling with the translation of how to tell you how he’s feeling and what kind of—he doesn’t understand how to express, it’s like—I ask him: “is it a sharp pain? Does it last long?” And he says, “I don’t know, I can’t explain it.” So it gets frustrating on all sides. But you can’t—it’s like a child. You know they’re crying for some reason but they can’t explain it to you. I didn’t mean that derogatorily, but you know they can’t explain to you what the problem is, so therefore.*

Together, we drew the outline of a head in the red book and divided it into regions where George said he was having headaches. The next time I saw him, he showed me the outline which he had marked with jottings and numbers and described the route his headaches had taken the previous day, moving from front to back and gradually getting less severe. While serving the same basic function to establish a memory of events, this was also a technology of communication for George, a bridge between Phoebe, the clinicians and himself: “that way I can tell them what’s what—to give them an overall picture that they can relate to.”* It supported a two-way channel allowing him to articulate sensations and know how to order them into symptoms and descriptions of tumour activity. He and Phoebe had learned, for example, that headaches early in the morning are more cause for concern and when it is severe and throbbing.

Jim also revealed to me his strategy for managing change. As told through his accounts above, Jim was experiencing a strange dissonance where he would be conscious through seizures, seeing others around him and yet unable to communicate with them: “it’s

weird being aware of what's going on around you when you're having that seizure.”* As I was leaving his home after an interview in which he told me this, I saw above me a camera trained on the middle of the room. He told me that he had it installed so he could play back the footage and see a true account of his next seizure: “I want to see exactly what is happening.”* It was his way of reconciling the difference in what he experienced and what others told him about being unaware during seizures.

Like the brain scans which render images of the brain and tumour, these everyday means of recording reality are sense making technologies. Though rather than establish difference, they are part of attempts to bridge gaps between self and other, and help to mend a shared reality. It is in this way that these are effective sense making techniques that restore continuity and sense of self. While patients' doubts are powerfully refracted through their social relationships and interpersonal interactions, so too are their reaffirmations.

APPROPRIATING IMAGES

The imagery of disease is not always taken as stock; complex interpretations turn biotechnical explanations into new, unexpected and positive framings. This is well illustrated in Jamie's accounts. Jamie was fifty-five when we met in 2014, a retired fireman. He had continued working after being diagnosed with a grade III tumour in 2009 but had taken early retirement in part because his managers were losing sympathy for his condition. He and his wife Mel lived between their London home and their retreat in the south of Turkey. Jamie was a practicing Buddhist and heavily involved in his local Nichiren community. I would sometimes accompany him to his frequent meetings and ritual chanting where I would hear how Jamie's recent positive scans were “proof of the power of chanting.”

Chanting was something Jamie practiced daily and during each session he would visualise his tumour. It became an enjoyable part of our conversations when Jamie would tell me about his visualisations. Often he would warn me that I would laugh, and invariably I did:

It's all black—a black blob with white eyes. And what it does is it spreads its tentacles ... and then the tentacles are growing and these little Buddhas are chopping them and pushing them away, chopping them and getting back to the core. And then—I don't mind if you laugh cos its quite funny—I've got this group of people who are martial artists—because I used to do Tae Kwan Do. And they've got my tumour in a corner and when it tries to escape they punch and kick it, punch it and kick it. But then I heard people say that you need to love your tumour. So what the ninjas now do is punch and kick it and keep it in place. And they tie it up. And then they comfort it, once it's all tied up. And they comfort it and say “right, you now have to leave this body, sorry, go away.” And then they put it,

they literally put it on this set of stairs that goes out to the toilet. And they lock the door and then of course I go to the toilet and flush it away—that’s my visualisation—and it goes into the sea. And then after that there’s another group—a great big group of people all around my brain and its glowing and they’re chanting to it and there’s nothing wrong with it, it’s perfect—that’s my visualisation. And then I’ve got my oncologist and my surgeon there too, and they’re saying, “thumbs up, Jamie you’re alright now”—I’ve got that visualisation—“Jamie, you’re alright now, go away, stop wasting our time!”*

Another time, Jamie told me that the Buddhas now had motorcycles. He imagined a desert-like scene in the US and a lost highway stretched out to the horizon. The tumour, bound and gagged, now rode on the back of one of the bikes, flanked either side by a motorcade of Buddhist ninjas and riding off into the distance.

Three months after this and following a scan, which had been reported very positively by the radiologist, Jamie told me how the visualisation had changed. He recounted a joint consultation with the surgeon and his oncologist:

At the review Mr Fitzroy showed me the scan and he said, “you can see the difference.” And it wasn’t making sense to me. And I asked which one is he showing me? He goes, “well look at that one, the latest one, look at the one from February.” And he says, “Now I can’t really see any evidence of any tumour.” And I’m like, “I’m not getting it.” I wasn’t getting it. Phil was with me, my good friend, and Mel. They got it; I didn’t get it. I couldn’t comprehend what they were telling me at the time. It was only once when we went outside and I said to Mel, “what are they telling me? I don’t understand what they’re telling me?” She said, “They’re telling you that they can’t see it—they cannot see it in your brain. They cannot see evidence of a tumour in your brain anymore.” So, it was then that I started to realise, actually its really gone down. All the chemo had really worked and all the other stuff that I do really worked. And because I had been doing quite a lot of intense chanting as well, with the visualisations. And my visualisation has changed a bit now. Because I’ve been told its smaller, it’s now become smaller in my visualisation. It’s like a rat now.

Henry: What you see it as a rat?

Jamie: Yeah, I see it as a rat. And what the Buddhas in my head do is they shrink in size and they go to the rat and start beating it up.*

Jamie’s images became more and more elaborate and though he has a particularly brilliant and inventive imagination, what I want to suggest is a serious point about the intertwining of biotechnical imagery, sensation, and everyday living, that was common among many of those I met. These images of his tumour—dark, daemonic, monstrous—were also common. They map straight onto the descriptions received in the clinic and the black and white imagery of the scan, which, as some remarked, look weird and ghoulish. Yet people also envisaged goodness and something positive to usher into the world; instrumental acts and powerful actors.

For Jamie, visualisations even included the avatars of his surgeon and oncologist and co-mingled with his lifestyle choices like taking huge amounts of nutritional supplements and drinking juices, his Nichiren community and spiritual iconography, the things he read and was told by others, exotic portrayals of ninjas, motorbikes and highways taken from his experiences (Jamie had driven across America in the '80s and told me of the expansive highways and “deserted plains of Nevada”). The size and characterisation of the tumour—whether a white-eyed blob or shrunken rat—corresponded to clinicians’ reports and the clear presentation of increase or decrease in scan enhancement.

Like Jamie, Amanda had a strong visualisation. Because her tumour was so deep and in a region of the brain deemed too risky for surgery, she had never undergone an operation or had a tissue diagnosis. The radiological diagnosis—which as I described in the previous chapters provides a lesser description of the tumour—suggested grade III. Though now, because she was doing so well clinically, doctors were informally suggesting it might be benign. In this positive light, Amanda, thirty-two when we met, and her husband Mark were considering a second child. Towards the end of our first formal interview at her home in early 2015, I asked her about the scan of a healthy brain she had pinned to a board above her desk, reminiscent of the ultrasound image expectant parents might carry of a child in the womb. She smiled as she told me:

That’s not mine. It’s part of my therapy basically. Because like I mentioned to you, I like to think positively. I read a book about this—and this really helps me—one of the things from this book was to print out the pictures from your dreams—so your purpose in the future, what do you want, these kinds of things. So I printed a healthy brain. The book said that you should look at this picture every day and visualise this picture and think that this is yours—that this is your dream—and it’s going to come true and this is basically part of my therapy. So when I look at the calendar and see it, I say “yeah, this is going to be my next scan.”

Henry: And do you have other pictures?

Amanda: I think that’s the only one. And the one with my dreams [laugh]. This is going to be my next scan basically: this is how it’s going to look.*

What I find interesting about Amanda’s account and Jamie’s is both their reliance on biotechnical imagery and their appropriation of it. In Jamie’s case, his visualisation transformed the black and white scan into an enemy which he could apprehend and stall through attacks or diplomacy. It gave a story and a logic to his real world approach. Amanda appropriated the imagery to give substance to her dream and usher in a more hopeful future. Their visualisations, I argue, do more than simply make abstract biotechnical truths intelligible: they establish a narrative agency, self-actualisation, and thereby a kind of

mastery over disease. When I put this interpretation to Jamie in another interview, he responded in this way:

I believe visualisations have had just as much influence as the chemo. But I do understand the chemo plays a part too. And I have been told that sometimes you can have chemo and it can later on come back again. So I'm not stupid enough to think "oh I can stop everything now and go back to normal." I'm still doing my Buddhist chanting, I'm still eating healthy foods and I'm still doing my regular exercise. And doing all the things I should be doing: to keep taking my supplements and doing everything—all of it. And personally believe I'm gonna keep it at bay.*

SUBJECTIVITIES OF NEGATION

In his analyses of symptoms, technologies and subjectivities among people cast as mentally ill (Biehl 2010; Biehl 2013) and those diagnosed with or at risk from HIV infection (Biehl 2007a; Biehl 2007b; Biehl, Coutinho, and Outeiro 2001), anthropologist João Biehl deftly weaves the layered productions of people and how they consider themselves. He points to the technoscientific and medical developments in which people and social interactions are constituted and hence the social and technological embedding of subjectivity.

As part of his analysis of public health programmes regarding HIV in Brazil, for example, Biehl highlights the mediating roles of biologically based identities and rational-technical health management concepts, including free HIV tests, which he suggests produce “a population of ... an *imaginary AIDS*” (Biehl 2007b; Biehl, Coutinho, and Outeiro 2001:99, *italics in original*). This population comprises people at low-risk of infection who complain of AIDS-like symptoms and demand serial HIV/AIDS testing, only to be returned each time as sero-negative. Biehl suggests that their anxieties and somatic responses are as a result of how they have absorbed certain biotechnical truths and developed a morbid and anticipatory subjectivity.

In a particularly insightful passage he discusses what he calls *technoneurosis*—“the confused and painful experiences [that are] somewhat technically engineered” and which establish a kind of “neurotic ‘fate’” in people who come to see themselves as being at risk (Biehl 2007b:270). Biehl highlights this as a neurotic disposition that is characterised by the symptoms of an imaginary AIDS rather than a biological reality. He thus draws attention to how certain kinds of predictive profile are lived as realities by the people they define, even though these people do not have the virus. He therefore sites biotechnology as a “complex intersubjective actor,” determinative and capable of producing radical transformations in people’s subjectivities (Biehl and Moran-Thomas 2009:280).

I find this particularly useful in understanding the predictive quality of biotechnical explanations and technologies like brain imaging as they are interpreted by Fay, Jim, Gabriel, Sara, George, Amanda, Jamie and the others I spoke to, all of whom suffered the feelings of what might be termed a “fate” of confusion. Although I do not wish to term these experiences neurotic and while clearly the situations of undiagnosed populations with an imaginary disease and people actually diagnosed with a brain tumour are substantially different, their experiences of inevitability and interpretations of sensations and events as signifying a new imagined reality are strikingly similar. With their fated existences, as they saw them, my respondents framed new sensations and certain experiences as strange and co-extensive with the biotechnical fact of a tumour, and would each time identify these as the harbingers of a new imagined reality—one they could not know. These were experiences that at once embodied and ushered forth a terrifying loss of self.

This brings me to suggest the paradoxical subjectivity that is particular to people with a brain tumour and perhaps—as Fay indicated in her comparison above—people with neurological diseases, like Alzheimer’s. As biotechnical truth is internalised and worked as an interpretive frame through which to see experiences and cast them as strange, patients are led through spiralling doubt into inconsolable frustration and upset and to convince and imagine themselves as the “batty aunt”* or “out of it;”* stuck in a void of their own and dismissed by everyone around them. It is a subjectivity of their own negation. The deep ambiguity and paradoxical nature of this negation is radically disturbing; the very point Jim made when comforted by Tina that he was making sense: *“But I don’t know—that’s the point.”**

However, it is misleading to portray a linear evolution from preclinical explanations through the acquisition of biotechnical truth to an orientation that continually remakes the world conform with diagnosis. Such overly determined subjectivity, which might be figured through a Foucauldian analysis of power and subjugation, denies the role of patients’ own interpretations and experiences outside the imposed conditions of certain kinds of biopolitical regime, giving undue power to biotechnical accounts (Biehl, Good, and Kleinman 2007; Fischer 2009; Good 2012). Rather, as I have demonstrated through the accounts above, there are multiple frames which mediate the world and render experience continual with a brain tumour, coincidental or discordant—this is the friction of experience and how it is interpreted.

Martyn Pickersgill and colleagues, to whom I earlier referred, have suggested a bricolage-type quality to subjectivity in how people assemble biotechnical explanations among others in understanding themselves. “Neuroscientific concepts,” they write,

“compete with, integrate into, and only occasionally fully supplant, pre-existing notions of subjectivity” (Pickersgill, Cunningham-Burley, and Martin 2011:346). There is therefore no simple and inevitable causality of “biotechnical truth,” but rather these coalesce with sensation and alternative explanations.

Over the long periods I knew patients, I learned how the bricolage of people with a brain tumour happens through a complex and evolving intersubjective space and is a constant choreography—new sensations; new explanations; new biotechnical portraits; new relationships and ways of relating; narrative oscillations; new affirmations; new ways to normalise; new appropriations; new improvised techniques and more sophisticated means of mending shared realities. Patients and those around them move through this space sometimes awkwardly, sometimes constructively, and, though fundamentally ambiguous, they attempt to retain and realise different possibilities of being.

CONCLUSION

I started this chapter by reflecting on mental capacity and my expectations of encountering patients with dubious mental states and their renderings as “non-agents” in decisions about care and treatment. This did not bear out in fieldwork. Where I had intended to see routine capacity testing, I saw none; instead, I saw patients placed, by clinicians and their families, in ordinary registers of confusion. In my expectations, I shared the assumptions of many patients that the tumour would necessarily produce incapacity. What I found during fieldwork, were patients who lived to greater or lesser extent in the grip of an anticipated loss of self—a subjectivity of their own negation wrought in a complex intersubjective space of intersecting conceptions of mind, technologies, affects, intimacies and professional relationships. By using this formulation of negation, I am deliberately highlighting the complicity and contradiction in patients’ constructions of their own denial and self-doubt. It is this subjectivity, I argue, that, in correspondence with rationalist notions of autonomy and choice, contributes to patients’ contested agencies in decisions about care, treatment and daily living. Although it is by no means inevitable, and while patients engage actively in modes of resistance and appropriation, it is certainly a hallmark in the condition of being a person with a brain tumour.

While this chapter has concerned how patients resist, accept and create conceptions of themselves vis-a-vis biomedical knowledge and imagery, the following chapter explores how biomedicine informs their hopes. I explore the production and regulation of possibility,

taking clinical trials as an example of the medical imaginary, par excellence, and how patients engage in their navigation.

CHAPTER 4—THE PRODUCTION AND REGULATION OF POSSIBILITY

Several patients sit in an open hospital ward looking onto the curious scene before them. On one of the beds, Fay—whom I introduced in chapter 3—sits swinging her legs inches above the ground. Fay’s tumour lies, depleted by treatment, in a part of the brain known to correspond to memory and speech. A thin scar curls above her ear and around the side of her head. The scar marks the place where, months before, surgeons removed a small piece of her skull, sliced through the bluish gossamer-like layers of dura that concealed her brain and lifted multiple pieces of reddish brown and beige tissue that together had amounted to the size of a snooker ball. Her greying hair is slowly covering the scar—fuzzier than when it was before she had radiotherapy. To her left, a large metal urn, covered in bright stickers that instruct careful handling and reveal its overseas travel, stands reaching the height of her knee. A nurse wearing thick elbow length gauntlets prises open the urn and clouds of nitrous oxide spill onto the shiny linoleum floor. Surveying the craned necks of the patients, Dr James, the oncologist beside me jokes about selling tickets to the next performance. It is certainly a performance befitting of what many are calling “the treatment of the future.”* We watch the nurse as she slowly and carefully removes a canister from the urn, and from the canister, a small vial of fluid perhaps two inches long. She draws the fluid into a syringe, pushes out bubbles of air and twice flicks the needle, which is now poised before Fay’s arm.

This is the intrigue that has produced the chattering among patients on the ward and a general verve throughout the hospital. The liquid about to be injected into Fay’s arm contains, she hopes, one of the most promising innovations in the recent history of brain tumour treatment—a vaccination tailored to her tumour by combining her immune cells with the cancerous tissue removed from her brain. Because Fay is having the vaccine through a double-blind randomised control trial, she doesn’t yet know if she is getting the vaccine or a placebo. Her hope is to live ten more years—ambitious because three quarters of people with glioblastoma tumours do not survive beyond a year, but a hope shared by her oncologist, the trials team, and countless other patients desperate for innovation in a treatment landscape that has changed little in 20-years. Once, when looking at a brain scan, Fay asked her oncologist if her tumour might disappear completely; she was told that with this treatment it might.

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Given the lack of effective treatments, experimental trials are often a key feature of care for patients with brain tumours. For many, trials offer hope in what some characterise as a treatment wasteland: one barren and devoid of effective therapeutic options. They are the example par excellence of the medical imaginary, structuring practices that lie at the complex intersections of hope, industry and care (DelVecchio Good 2001; DelVecchio Good 2007; Kaufman 2015; Keating and Cambrosio 2012). Experimental treatments are putatively an addition to the “standard of care.” Almost by definition, they are not available to all.

While advocates and others call for greater opportunity and choice regarding clinical trials, in reality, they are the privilege of the few. Less than three per cent of people with a brain tumour enter a clinical trial (NCRI 2016). This presents patients with significant dilemmas as they attempt to plot and actualise new courses around the impasses caused by strict eligibility criteria, extortionate costs and the broader bureaucracies of care. These patients, together with advocates, regulators and others, seek to access the cutting edge of treatments now, rather than wait for them to trickle down through the complex infrastructures of knowledge production and regulatory action. Moreover, the reality of being on trial is often far from imagined as patients are subject to new constraints, an increased schedule of appointments and what can be gruelling new interventions. They live and navigate new and heightened hopes that may be more promising than standard treatments but might also disappoint more dramatically. As Cheryl Mattingly writes of the paradox of hope: “[It] is on intimate terms with despair. It asks for more than life promises. It is poised for disappointment” (Mattingly 2010:3).

In this chapter, I trace the dynamics of clinical trials and treatment regulation in brain tumours, how they feature in patients’ lives and the work of clinicians, and how they relate to the political economy of brain tumour care. While the previous chapter showed how biomedical knowledge and intervention mediate a frightening loss of self, this chapter concerns how it equips patients with hopeful possibilities of living longer lives and being freer of symptoms. I focus especially on the hopes that arise in the tightening of the “biotechnical embrace” (DelVecchio Good 2001), as the promise of medical innovation creates new patient aspirations. In so doing, I map out a real and symbolic infrastructure in which hope can be *practiced* (Mattingly 2010) and show the dilemmas and uncertainties faced by patients either side of the line of trial access. I also contextualise their experiences among a broader decision-making process bringing in the voices of clinicians, regulators, advocates and others influential in the stewarding of innovation. By jointly attending to how oncologists, trial practitioners, drug regulators, and pharmaceutical executives define

treatment, experiment, evidence, uncertainty and risk, and how patients and families do so, as experimental subjects and people fighting for survival, I seek to present a more nuanced picture of experimentation, evidence, access, and the politics and production of possibility.

THE POSSIBILITIES OF TRIALS

In May 2018, ClinicalTrials.gov, a registry of public and private trials across the globe maintained by the US National Library of Medicine and which feeds to the UK Clinical Trials Gateway, listed 408 actively recruiting trials for adult glioma worldwide, 270 of which were for glioblastoma. Fifteen of these were UK-based, seven of which were for glioblastoma. In the US, the numbers were 285 and 176, respectively, and in Europe, 84 and 50. Within the UK, the numbers of clinical trials are therefore relatively small meaning that patients often look abroad for trial places. The dizzying plethora of hope given in this global landscape of trials provides a *raison d'être* for recruitment companies such as *Cure Forward*, which attempt to steer patients through an international landscape of experimental treatments by advertising trial places and hosting mailing lists with promises of access and assistance. These companies help drive the promise of innovation and communicate strong messages of hope towards those with a disease without cure: “Clinical trials can open up your options for breakthrough cancer treatment,” as the website *Cure Forward* states, “Our clinical trials navigators will help you access them.” As such, they are key players in structuring expectations and what sociologist of science and technology, Paul Martin, calls the “*capitalisation of hope*”—that is, how expectations and speculation in the biosciences are translated directly into economic value (Martin 2015; Martin, Brown, and Turner 2008).

The UK government, conscious of a historic lack of public funding into brain tumour research, announced a doubling of its initial £20 million funding pledge for brain tumour research announced in February, to £40 million. This announcement came in May 2018, following pressure from advocacy groups, such as the UK-based Brain Tumour Charity and Brain Tumour Research, and was given in special honour of former Labour cabinet minister, Tessa Jowell, who died days before the May announcement and whose immunotherapy treatment in Germany highlighted the dearth of current NHS treatment options. It was, in many ways, her case which led to this release of funds having contributed a public face to the lived experience of brain tumours and a powerful ally to the advocacy cause. In a moving and widely reported address to the House of Lords on 25th January 2018, Baroness Jowell said that what every person with a brain tumour wants to know is that “the

best, the latest science was being used and available for them, wherever in the world it was developed, whoever began it.” With the backing of advocates such as the Brain Tumour Charity, she had called for greater global collaboration through programmes such as the Eliminate Cancer Initiative²¹ and for doctors and scientists to band together to learn from and support each other, “much as patients do.”

While this most recent intervention supported by Baroness Jowell came after I left the field, the campaign has been underway much longer. At an All Party Parliamentary Group Meeting in the House of Lords I attended December 2015, innovation and trials were among the points most consistently raised by clinicians, patients, and advocates. Both billed speakers and audience members repeatedly emphasised the need for increased access, lack of funding, structural deficiencies in the NHS preventing clinicians from engaging in programmes of research, and a pharmaceutical industry which has failed to invest in brain tumour research. The implication is always that people with a brain tumour need increased access to trials because the current standard of care fails in offering adequate outcomes.

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After her death in May 2018, less than a year after her diagnosis, Baroness Jowell’s husband, David Mills, quoted her on the BBC’s flagship current affairs programme, *Today*, saying, “If I can just survive two years at a time, or even a year at a time, new things will come along and it’ll give us new hope.” This sentiment echoes the hopes and aspirations of many of those I met. It poignantly illustrates the stakes of diagnosis and the promise of innovation.

For the many people I encountered in fieldwork who continually tracked clinical trials and the extending horizons of discovery, the imaginary was at once a practical resource with the promise of a trial place and a beacon of hope that things might change in the future. These patients kept detailed dossiers on media articles, research findings, eligibility criteria, and the movements of clinical trials groups; grappled with the implications of new and complex information about their tumours, such as the molecular profile of their tumours, which had been introduced into diagnosis and which was beginning to feature in treatment decisions and define trial eligibility. They asked their doctors at each consultation for the scoop on the future promises of care; emailed trial practitioners and experts in the field *ad*

²¹ The Eliminate Cancer Initiative is a global programme announced in May 2017. Philanthropists Andrew and Nicola Forrest pledged more than \$50 million as planning capital to reward collaboration, accelerate and promote research breakthroughs and improve prevention, detection and treatment for cancer patients including access to clinical trials through the establishment of a global collaboration framework.

hoc; joined forums and networks and signed up to discovery alerts. Given experiences of exclusion, some of these people also learned to make decisions in the present to avoid being denied access to existing or future trials. In the following sections, I outline some of these experiences as they unfolded in the lives of several patients, illustrating some of the diverse ways in which trials featured in experience. I begin where I left off with Fay, on the ward and with the nurse poised to inject.

NEGOTIATING INCLUSION I

Fay squeals when the vaccine is given, her eyes closed and squeezing her sister, Maria's, hand whose finger tips turn white. It takes a minute per injection and there are two of them. "At least we know it's going in properly,"* the oncologist says. The nurse bends the needle of each empty syringe and puts them in a tray. She completes some paperwork and calculates the volume of vaccine going in. Maria tries to get Fay to eat but Fay is now distracted with a patient across the room. I hear snippets of their conversation. "How long does the trial last?" "We saw it on TV." "It's for brain cancer." "You've got to be thankful there's someone somewhere out there with the brains to make it,"* Fay says.

Fay was one of several hundred patients recruited across Europe to a clinical trial testing the vaccine. It is also available for those who can pay £300,000 per year to have it privately. One of a growing group of cancer treatments called personalised immunotherapies, the vaccine is made with antigens taken from patients' own tumour tissue which is harvested by surgical operation and processed with dendritic cells—the so-called sentinels of the immune system—removed from patients' blood. In contouring public understandings of immunity and the "flexibility" of bodies (Martin 1994), its rationale is easily understood by patients: by combining *their* tumour tissue with *their* immune cells, the vaccine equips *their own* immune systems with the capability to recognise and target *their own* tumour—a way to enhance the body's "natural defence" against cancer. Having drawn significant gains from advances in immunology and the molecular technologies I described in chapter 2, personalised immunotherapies hold considerable promise among brain tumour communities and are being touted across multiple arenas as the future of oncology (Preusser et al. 2015; Reifenberger et al. 2017; Sims et al. 2015; Huang et al. 2017; Gotwals et al. 2017). But without reliable phase III and IV trial data their potential remains uncertain.

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Fay was undecided about the trial when we first met, almost a year before the scene described above. She had only been operated on two weeks before our first meeting and the news of her tumour was days old. We met in clinic as she discussed chemoradiation (chemotherapy plus radiotherapy) with her oncologist—the clinical standard for glioblastoma since a 2005 study showed a modest survival gain over radiotherapy alone (see note 16). She was shell-shocked, yet trying with her five sisters to quickly assemble information about the high-stakes of intervention or inaction and whether to enter the trial. She had been approached about the trial by another oncologist even before her surgery and when there was only a suspicion of cancer from a scan. Her consent to the early stages of the trial had to be taken early to allow a different method of processing the tumour tissue removed during the operation. When we first met, though, she was undecided: I followed her through the first few weeks of uncertainty as she moved between wanting to do the trial and not.

Her decision was complicated by a number things, not least the added hospital appointments and the burden it might place on her sisters who would have to help her to the hospital, at least in the early months. She also suffered excruciating pain from repeated failed attempts at drawing dendritic cells from her blood by a process called leukapheresis, worries she was being messed around by The Warner with little information and treated more as a guinea pig than patient, and thoughts that it might be all for nothing. At times these threatened to completely derail her decision or take it out of her hands altogether which contributed another layer of anxiety. She also worried about delaying radiotherapy, which was momentarily on hold for reasons to do with the trial sponsor and obscure to Fay. The hospital needed an answer and clinicians, behind the scenes, were concerned that she might not be the “reliable subject” they first had thought. With increasing pressure to make a decision and under a 4pm deadline one day, weeks after being first approached, Fay fully consented to the trial, as she explained to me during an interview:

Because when I first started the vaccine trial I said to [my oncologist], what’s the outcome? I just came out with it. I just said how long have I got? And he says, oh probably with the vaccine years and years—10-years—it had great results from America and everything. And I thought okay. And then he said, without it, 18-months. And I thought oh crikey there you go from 10-odd-years to 18-months and I thought well I’m gonna start living now. If I’m not getting the vaccine I’m not sitting here waiting to get it, if you know what I mean. If I want something, or want to do something I’m going to do it ... Anyway, [the oncologist] said [during the consultation], “Go off for a few minutes and talk to your family about it.” And I’m thinking it’s got nothing to do with them. It’s my decision. It’s not, “oh everyone can make their mind up for me.” They can support me either way, or they can say “Fay I don’t think it’s a great idea,” but it’s still my decision whether I want to go through with it. I went outside and I said, I think it was to

Maria. I said to her, “you know what Maria—I’m doing this, I’ve come this far and without it, it could be 18 months. With it, it could be 10 years or more.” And she said “Fay, you do what you want to do.” And I said, “I’m doing it.” So I went straight back in and I said, “I’m carrying on.” I signed the papers and [the oncologist] was like, “are you sure about this?” I said “yes.” What am I going to do? Just sit at home and wait to die? Or am I gonna try and fight it?*

NEGOTIATING INCLUSION II

The relationship patients had to clinical trials could be extremely fraught and the relationship trials had to standard care equally complex. Rebecca and Sam’s experiences, as patient and husband, were emblematic of those who placed trials at the top of their hopes for cure. “The target is to survive until that brilliant drug is found that will help prolong your life a little bit more without the after effects,”* is how Sam had put it. And yet he and Rebecca remained passive when it came to making demands on the clinical team, making rare suggestions: “You get little snippets of things from all of the programmes and little bits of different information: sometimes you feel like suggesting something. But I always think well the doctors must have thought about this already,”* Sam said. Only once in all the meetings I observed between them and the clinical team did they make a suggestion about something off the table: when Rebecca was dying and they were desperate. Their passivity and trust in the doctors contrasted strongly with Alice’s scepticism and immediate recourse to ask about trials. While many saw trials at the back end of treatment, Alice wanted to begin straightaway.

I met Alice first at a consultation with Dr Anton, one of the oncologists, when Alice, her husband and daughter, had fired question after question about standard treatment. I had already heard the rumours of a young patient recently diagnosed with a glioblastoma questioning the treatment—Alice was barely in her forties when we met, a mother with three children and on sick leave from her work in social care. Even so, this particular appointment had been described to me as routine and for planning the schedule of chemoradiation; in fact, Alice had already signed a treatment consent form the week earlier. But with the appointment underway it was immediately apparent just how strong her opposition to standard treatment was. The consultation ran as though Alice and her family were interviewing Dr Anton for a job, beginning each question with “if we went for you”* and listing the other appointments they had scheduled with several “alternative or complimentary therapists.”* She was also interested in finding out about experimental treatments and, like others, had been looking online. She left the appointment still undecided and with another booked for fitting a radiotherapy mask. However, she later called off the fitting and

cancelled the treatment.

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Clinicians at The Warner reacted quickly to Alice's decision to withdraw from treatment: they scheduled an extraordinary meeting led by her surgeon and Dr Anton. Alice arrived with her husband and daughter, anxiously clutching a stack of papers and adamant she would not have radiotherapy or chemotherapy before she went into the appointment. I attended the meeting with her and on several later occasions we spoke about it. What appeared crucial at the time and in her later reflections was not simply how alternative treatments were considered and described by the clinical team, but how clinical trials and access to them were framed. As the surgeon had said during the consultation:

I'm open to alternative treatments. But I'm concerned with having them in the absence of what we know works. And I'm wary of trials that take you away from conventional treatment. Because if it doesn't work then you've lost a second line option—people who have alternative treatments might not be eligible for these trials. Because in a trial, you're trying to get 100 people as close to each other as possible so you eliminate possible effects of other things—so there are potential ramifications downstream as well.

From the beginning, Alice had been interested in trials and the stack of papers she carried included reports of experimental treatments. Standard treatment—or conventional treatment, as she routinely described it—represented something retrograde. Like others, she emphasised the dearth of effective treatments for brain tumours and could not reconcile the stagnation of possibility with what she read online about new discoveries in programmes like the immunotherapy vaccine Fay was trialling: “I think the fact that our standard treatment is chemo and radiotherapy is just crazy when you look at all the ways that medical treatment has advanced,”* she said. The essential argument being made by the clinical team, and what became the dilemma for Alice, was that foregoing standard care or having alternative treatments might mean foregoing the possibility of clinical trials now or later. Because without standard treatment, Alice would have been considered different to the other patients on the trial, and therefore ineligible. The meeting with the surgeon and oncologist lasted over an hour. Alice left with the treatment back on and another appointment to plan radiotherapy.

I saw others weigh similar dilemmas. The intent for patients “to be ready” for trials is strong, not least in the dominant idea that a cure is always around the corner or on the

culp. The aim for many, therefore, is to live long enough for this cure. The hope given in trials not only prevents patients from seeking alternatives, but turns back on decisions to have standard care; hence trials themselves turn patients around to the norms of chemoradiation.

EXCLUSION

While Fay and Alice experienced and considered inclusion in clinical trials to be a viable option, most others cannot. As I have emphasised, less than three per cent of people with a brain tumour enter a trial in the UK (NCRI 2016); the proportion of patients entering a trial in other cancers averages 7%. As a crude comparison, there were more actively recruiting trials for breast cancer in Europe registered on the ClinicalTrials.gov database in May 2018, than worldwide for brain tumours, and almost four times as many trials in lung cancer. The explanation for this lack of opportunity given by lobbyists and the clinicians I spoke with is the relatively minuscule amount of funding put into brain tumour research and, as I explain shortly, advocacy groups are attempting to intervene in this. It is also down to the brain itself: an immune specialised site encased in a semi-permeable structure controlling the flow of substances to the brain, which complicates the action of certain therapeutic agents—the blood-brain barrier. Because we know less about the brain, biomedical scientists, pathologists, and medical oncologists (who are the main proponents and deliverers of trials) are less able to progress to human trials or take advantage of treatments developed for cancers in other parts of the body. While obviously, trial participation figures can be used to support multiple perspectives on equity and access and, for example, might be set in context with disease incidence and availability of effective standard treatments, from the perspectives of people with a brain tumour, they describe a trials landscape with many fewer opportunities, as evident in this exchange between Matthew and his wife Pam:

Pam: You've also got to remember only 2 percent of brain cancer patients get a trial. Its tiny—

Matthew: Yeah seem to be lots of trials for other cancers—well breast cancer in particular I think

Pam: Well it seems there's just more possibility for other things

Matthew: Yeah, there seems to be very few possibilities for brain tumour patients.*

This sets a disposition for patients not only of hope but of desperation. I met Matthew when he was 50-years-old at an information day organised by a prominent UK cancer charity. Pam, his wife, had given a talk on the *The Experience of Being a Carer*. She had

spoken authoritatively about Matthew and the nature of cancer care. Each embodied an almost ideal type of “patient expert”—highly educated, medically savvy, with a presence of mind and determination for inquiry and insistence. “Don’t believe your oncology team know everything,”* Pam told an audience of new patients, “they are human too.”* Pam had cared for her sister who had died of a brain tumour twenty years before. I was struck by the tragedy of her experience and the lengths she and Matthew had gone in their quest for cure. Another striking thing in her presentation was what had struck her: in almost twenty years between the death of her sister and Matthew’s diagnosis “there is almost nothing new”* and “very little research.”*

“It seems to really discourage initiative,”* Matthew said several weeks after Pam’s lecture while talking about trial design and how he was continually cast as ineligible. He and Pam searched for trials through multiple platforms, though grew increasingly cynical: “The first thing we do is look down the exclusion list and I’ll be excluded by something *always*.”* The design of trials contradicted their ideas of equitable care and, moreover, what a patient should be—*proactive*. As Matthew explained:

We have a family friend with a rare form of bone cancer. *Now he’s on a trial*. I don’t *know* but I suspect he’s not as proactive—he’s just gone along, had his standard treatment or whatever the doctor says. He hasn’t been doing what we’ve been doing which is trawling the internet, trying this, trying that. He’s just sat there and taken what doctors have doled out. But because of that he’s qualified for a trial in Belgium. It seems very unfair to me—we’re the ones really trying and yet by doing that we’re excluding ourselves from trials.*

...

Like Fay, Matthew underwent the eight-month standard therapy for glioblastoma the year before we met. This had been relatively trouble free, with the exception of missing several chemotherapy appointments because of low blood counts—that is, when levels of white or red blood cells, depleted by chemotherapy, become dangerously low to give further treatment. Although common, these “blips,” as clinicians call them, can worry patients and force them to reconsider their response to treatment. Matthew’s response was to think of a tumour left untreated and, like so many I spoke to, his instinct was “to keep attacking it.” This is when they first encountered the immunotherapy which Fay was trialling.

“‘The future’ was immunotherapy,” Pam explained, “Everywhere we turned, that’s what people were saying. And funnily enough I’d even asked [Matthew’s surgeon] before his

surgery two years ago. I'd said to him, what's the future? What should we be looking at? He said 'immunotherapy.'" But there was a problem, as Pam continued:

I was infuriated. No one had alerted us to the vaccine trial before Matthew's surgery. It would have been a lot better to have had the option to have Matthew's tumour frozen because then it could have been used for future trials. And no one ever said that to us either. So it was just done in the standard petroleum wax which means it's pretty useless. If we could go back two-years, what would have been incredibly helpful at that point would be to have had someone who knew the breadth of the situation, the circumstances, and could say: "These are some of the things you need to think about—is it operable? Okay its operable. Well consider having it frozen—it might cost you some money—but it's a good choice for down the line. Have you looked at all the trials *before* you go into surgery?" You needed some kind of mentor or advocate—someone who could help open up your horizon.*

Matthew agreed:

People weren't at all forthcoming with information. We didn't know. We didn't even know about freezing tissue—nobody said anything about that to us. That set how we're now used to it: we're used to options being closed to us. Especially trials because of something we've done in the past without realising the implications—that's very frustrating.*

Matthew was excluded because his tumour had been processed according to the routines of the pathology laboratory. As I described earlier, tumour tissue must be processed differently for the vaccine. Tumours are typically set in wax because this makes the tissue into a workable material, which can be sliced wafer thin and stored for decades. However, the wax also changes the tissue in ways that make it permanently unusable as an ingredient in the vaccine. To be used in the vaccine, tumours must be *frozen*: tumour tissue must therefore be handled by pathologists in ways that contradict standard laboratory practices across the world. Given tissue is processed almost immediately after surgery, decisions about the trial must be made *before* surgery, and given surgery happens often within two weeks of a tumour being suspected, this decision is made in the midst of a confusing and frightening time, when patients are typically naïve about the possibilities of trials and how to navigate them.

...

After failed attempts to get Matthew on an immunotherapy trial, he and Pam found and self-funded a different immunotherapy in a private hospital. Unlike the one being trialled, this did not require Matthew's own tumour tissue for the vaccine's preparation. But he would

have to travel for it and each month for almost a year he journeyed overnight to a city in central Germany by plane, train and taxi until routine MRI scans in the UK suggested his tumour had grown again and he became too exhausted for the monthly visits. He then found another trial in the UK for recurrent glioblastoma. This was for Avastin, a drug that affects blood flow to tumours and which has come under intense scrutiny for reasons I describe shortly. As Matthew explained, however, his treatment in Germany had added a complicating factor:

I've been a Judas and had immunotherapy. My immunotherapy in Germany, apparently it excluded me from the trial. Now we get more cynical and questioning of these consultants' decision-making and I actually suspect he made that up, or at least he could have easily bent the rules and let us in the trial [...] and that's just been our experiences all along with the trials. First of all it was, 'well the tumour isn't frozen.' And now this.*

The effects of exclusion were profound as Matthew and Pam now thought carefully about making decisions in the present to avoid being excluded from future trials. Had he known about the vaccine before his first operation, Matthew said he would have insisted on his tissue being frozen. I met others who shared this disappointment and lamented the fatefulness of an operation after which their tissue was not frozen. The urgency of conditions under which operations are done further complicates the dynamics of these decisions as patients and families are confused, frightened, and unable to grasp the stakes of the situation let alone understand the implications of things like tissue handling. Importantly, the stringency of trials and biomedical obsession with treatment naïve bodies impose a particular politics of exclusion as upstream decisions impact radically on options for future care.

In some ways, the experiences of Alice and Matthew were similar: both looked for hope in trials and encountered constraint in accessing them. The radical difference was timing and how constraint was configured. For Matthew, constraint happened because of what he had done in the past; for Alice, it was what she might do now in view of the future. They learned to be concerned that their bodies be kept “treatment naïve” or “as close to other bodies as possible.” The great irony for Alice was that preparing her body for the possibility of future trials meant, in her words, “burning it and poisoning it with toxins.”*

OPPORTUNITY AMID SCIENCE AND SCARCITY

When I spoke to clinicians about trials, I got a strikingly different story:

I mean I'd love to—we'd love to offer all our patients trials but there isn't the [funding]. Brain tumour is relatively underfunded compared with other cancers and trials are expensive. And they're expensive because of the amount of time they take, because a lot of data needs to be collated and analysed and that means that logistically you can't run that many trials without a large number of staff—and if there's no funding for it then the trials can't happen.*

Dr James told me this in an interview when I asked him about cases like Matthew's and lobbyist's calls for universal opportunity to participate in trials. But as he continued it became clear that it is not simply down to lack of funding at the level of government and industry, which is, broadly speaking, the narrative of lobbyists. It is also about what is feasible for individual centres, both fiscally and practically, as well as a whole host of other reasons which determine access including the nature of trials themselves. Asked how The Warner selects trials, he said:

That's really about the relationship between a centre or a consultant with whoever's running the trial. So it might be, trials can be run by different institutions, they're called sponsors in the sense of trials, and the sponsor might be the drug company whose drug is in the trial. It might be a university who have academics or clinicians who thought this is an interesting trial design: 'let's see if we can get some external funding perhaps from a charity like Cancer Research UK or the Brain Tumour Charity and let's do a trial on it.' Or it can be a consortium. There aren't so many in the UK but in America there are big consortiums of academic and hospital institutions and they run trials with each other. And it's really just a mix of people that are interested in the specific question that this trial is answering and knowing who those people are and approaching them. And then within a centre you've only got so many patients so you need to decide what's feasible—how many trials are feasible to have.

Henry: And what's that for you? Josie was saying seven or eight at one time—

Dr James: Yeah probably. And the thing is: trials open and close, often quite unexpectedly. Nowadays they're pretty much all multinational, multicentre, they've got a set recruitment target and trials just suddenly close, and that might be a trial that has been open for years or it might be a trial that actually you'd only opened in your centre a month or two ago and they take, you know often, between three and six months to set up the trial. Sometimes even longer, up to a year or longer than that and then it might only be open for a few months and it's difficult to know during that set-up period how long the trial's going to be open for. So you need to rationalise and maybe hope to have a few more trials than you've actually got the patients for.

Henry: Yeah, absolutely. And how do they keep you in the loop with the number of places they still have on the trial?

Dr James: So most of the early phase trials are a bit more selective—particularly the phase I—the dose finding trials where they really only have a handful of patients and that's very close in terms of your recruitment might be actually literally you've got to find one patient and you've got two weeks to find it. The large trials, like the phase III trials that have hundreds of patients on, it's generally you're just allowed to recruit and then you'll get an email saying, 'we've hit our target, stop recruitment.' And if you've recruited someone a second before you read that email then generally it's okay. You know there's a bit of leeway, you know there's an acceptance that these are *not experiments*,

they're *human patients* and you have to have some leeway to allow for the fact that patients want to try the trial and you should let them join it.*

Dr James was a young oncologist attached to the trials team; attentive and down to earth with patients, and a dedicated researcher. His thoughts on treatment were progressive yet very much within the biomedical rubric: I had once bumped into him fuming because the MDT had voted against adopting a new treatment protocol for low grade tumours on the basis of lack of evidence. “They’re all wrong,” he told me, “they’re doing it right now at Mass Gen.”²²*

The trials team at The Warner worked to curate a portfolio of trials across tumour grade and disease trajectory including options for newly diagnosed and recurrent tumours, nursing and palliative care. They ran studies on chemotherapies, radiotherapies, targeted vaccines and immunotherapies, negotiating these alongside workload and capacity, and each new study (including mine) must find broader agreement within the MDT. Trials require infrastructure and people and as Dr James told me they are expensive. These things would be brought up during research rounds meetings where, more broadly, the trials team would discuss the trials portfolio, accrual, training and delegation, workload and capacity, monitoring and audits, report on serious adverse events and data quality.

The team were conscious of access and trials as treatment options and worked to negotiate scarcity. During one of the monthly research rounds meetings, for example, they discussed closing a trial because its inclusion criteria were so strict, denying patients of treatments. This would have allowed them to open another trial earlier. They also spoke about the overlap between treatment modalities suggesting that competing trials offer fewer distinct options and hence possibilities for care. On a more micro level, trial access can be determined by the accreditation and bureaucratic legitimacy of the consultants in charge of patients. Once, for example, at the close of a meeting, one of the oncologists reminded the team to make sure surgeons have submitted their financial disclosures and are up to date with their GCP (Good Clinical Practice) accreditation: “You might remind them that they cannot take part in the trials if they don’t have these things in place. It doesn’t hurt. *Because if they want their patients in trials then they need to do this.*”*

So the numbers and types of trial run are contingent on numerous things over and above the bottom line of money. Institutional workload, the impulse to vary options, consultant accreditation, and the sheer interest of clinicians, all contribute to the constitution

²² Massachusetts General Hospital in Boston—a leading light in oncology research and practice.

of the institutional portfolio and how available it is to patients. On top of this, research sponsors and regulatory committees, both of which might be in other countries, can suddenly put recruitment on hold or stop it all together. Trials are a moveable feast.

SCIENTIFIC ADVANCEMENT, PATIENT RIGHTS, AND AN ETHICS OF EXPEDIENCY

These tensions between person, patient and experimental subject are enduring ones, which have been discussed at length within medical anthropology, sociology and science and technology studies literatures (Abadie 2010; Biehl and Petryna 2011; Cooper and Wald 2014; Keating and Cambrosio 2012; Petryna 2009; Petryna 2013). They characterise the relationships of consent, acquiescence, expectation and demand between patients and clinicians. Fay, for example, often told me how she felt like a guinea pig or experiment. This she attributed to the comportment of doctors and how much they asked about *her*, whether they would “come off the page” and make eye contact with her during consultations or run down the column of trial report forms—“tick tick tick tick.” But even as she criticised the doctors’ cursory treatment, she would recount her hopes that the trial would help not only her but someone else if for her it failed. As she oscillated between accepting a trial place and withdrawing, she spoke about her desperation yet made (entirely legitimate) demands on the trials team to meet her at times she chose and stick to them. The doctors articulated similarly conflated and confused feelings, negotiating the contradiction of an unproven treatment.

The lack of trials puts patients with low incidence disease at a loss with little to choose from and doctors in an awkward position being unable to offer trial places to their patients. It drives the rigid application of “soft criteria” designed to distinguish those that can stay the course from those unlikely to adhere. Clinicians debated the suitability of trial candidates frequently in MDTs, using little but their few meetings with patients to go on, demographic qualities like age, and informal descriptions of “performance status”—a term, like quality of life, which has been lifted from standardised measures of function and which now circulates freely alongside qualifiers like “poor,” “good” and “reasonably good.”

I asked Dr James to explain the application of these criteria:

It’s about knowing the patient’s personality—you know some patients are very keen to try experimental options and some patients you know aren’t. Often the main thing that patients don’t consider is that the trials often take a lot more of their time than standard visits, than standard treatments. They have a lot more visits to the

hospital. They often have to do a lot more tests, things like questionnaires on their symptoms. They take hours and they wouldn't have to do them if they weren't doing the trial. And it's about knowing if patients, if you think patients would strongly dislike that then you've got to decide do you think they'd be a suitable trial candidate. But also you need to be able to trust that the patients will report any side effects of the drug to you. Some patients aren't very—I'm not sure why it is—they're reluctant to come into hospital, understandably because they want to get on with their real life. They want to have treatment but essentially they want to forget about and you need to decide is this going to be the right person for the trial and is it going to be safe for them, because you don't want someone to have a horrible side effect and not tell you about it. But also some patients are worried that if they tell us about horrible side effects then they'll stop the drug. And that's dangerous for them but also it's dangerous for the future patients of the drug because we need to know what's happening.*

This kind of reasoning was frequent and marked the complexity of trials—whether treatment or research—and the rationing of trial places where in effect patients are pitted against each other for access. During my fieldwork, Fay was the only patient I met to be involved in any kind of trial and the only patient at The Warner to be involved in the vaccine study.

Crucially, advocacy groups for brain tumour patients and families are dedicated especially towards enhancing access to trials, as well as redirecting funds to brain tumour care and research more broadly (Rhee et al. 2014). These groups are explicit about attempting to shift the trajectory of care and possibility by “stewarding” research and creating positive change within a government or regulatory system to bolster drug development for neuro-oncology communities and they are doing so in inventive ways. This has included innovating new roles for themselves as resource hubs for academics and pharmaceutical researchers—providing patient registries and biobanks—and positioning themselves as funders of “high-risk, high-return” research unlikely to be sponsored by conventional pharmaceutical companies and venture capitalists (Rhee et al. 2014; The Brain Tumour Charity 2014). Under a narrative of “filling the gaps” (Rhee et al. 2014) and bridging the epistemological distance between patients and researchers, these groups are therefore intervening in the imaginary and attempting to increase the pace at which new treatments enter mainstream care. Paraphrasing João Biehl and Adriana Petryna, a key point here is that patients and advocates are not just waiting for new medical technologies to “trickle down”—they are lobbying governments, financing research and attempting to change public discourses on experimental treatments to gain full access now (Biehl and Petryna 2011; see also Epstein 1996).

By increasing demands on the designation of clinical trials as an extension of the clinical setting, patients and advocates mobilise rights discourses and elevate expediency as an

ethical principle (Fortun 2008). Such calls cast experiments as social goods with legitimate demands on public resources, no longer regarded simply as hypothesis-testing instruments but “operative environments that redistribute public health resources and occasion new and often tense medical and social fields” (Petryna 2009:30). This is very much the case in brain tumours where calls for greater access to clinical trials are increasingly made along with attempts to embed the experimental as a universally available treatment option. On one hand, this reinforces a collective sense of the possible in the “practice of hope” (Mattingly 2010:37; Novas 2006; Novas 2007), giving access to treatments for a disease for which there is, frankly, little expectation of cure. This is especially important given recent doubts in standard care. However, it also sets up a number of tensions in definitions of care and evidence-based practice.

Clinicians and scholars alike have drawn attention to how the realignment of experimental treatments alongside standard care normalises them and shifts the frame from extraordinary to ordinary. I was repeatedly told by clinicians, for example, that they saw their patients obsessed with trials and as a way out. “But the thing about trials, you’ve got to remember,” Dr James reminded me, “is that trials are trials for a reason. We don’t know if [the treatment being trialled works].” He went on to explain:

The presumption of the patient is always that the new treatment is better. They almost always think that. Whereas actually if we look at glioblastoma—I don’t know how many trials have been published since 2005, when the paper came out saying Temozolomide prolongs overall survival in glioblastoma when added to radiotherapy, and that was the last trial that was positive in glioblastoma—I don’t know how many, but dozens: dozens and dozens and dozens of negative trials. And they’ve not all been worse than Temozolomide but a lot of them have; [that’s] when the new arm actually did worsen the control arm. Most of them showed similar results. So you’ve got to remember that not everyone should be on a trial because they’re not necessarily getting better treatment [by being on a trial]. And they’re having their time taken away from them. So I think it certainly shouldn’t be the default option that a patients go into trial but it should be an option for patients that want to enter a trial, should have a trial that they want to go on.*

Such investment, though entirely understandable, risks obscuring uncertainties and the potential for harm inherent to experimental models and, by strengthening the allure and miraculous promise of high-technology, forces a situation that has made it “difficult, if not impossible, to see the line between *enough* [intervention] and *too much*” (Kaufman 2015:2, *italics in original*). The potential to benefit patients notwithstanding, some worry that eliding the experimental with standard models of care and setting new discourses of patient rights to trials, principles such as informed consent are in jeopardy (DeVecchio Good 2001;

Petryna 2009). They fear that patients' understandings of the burden of trials—increased appointments, increased tests, less than perfect dosing, and the unfathomable odds of success and harm—are poor and overlooked by patients and clinicians in the collective obsession and complicity with progress. And yet it is not just patients who are weighing the odds of risk and benefit in favour of ushering in innovation. I now shift the frame a little to think more explicitly about regulation, how experimental drugs make it into the market, and how this raises patients' expectations. I focus on the case of the controversial drug Avastin (Bevacizumab).

REGULATING POSSIBILITY

As I learned during fieldwork, Avastin represented an extremely promising approach for many patients and not least because it had gained wide approval in the US. Matthew, for example, had read about its successes in the US market and was keen to try it after being excluded from the vaccine study. Yet, for clinicians at The Warner, it was held with much suspicion. To better understand this state of contradiction, I traced Avastin's progression through multiple arenas—scientific, regulatory, financial—and in popular media. Its history is long and waymarked with controversies; yet, according to annual profits, it remains one of the most lucrative drugs ever produced. It is a case which gives further insight into the complex and competing logics of the production and regulation of treatments and how evidence is considered and “cultured” by multiple actors along the path of production. As such, it is worth examining in some detail.

Avastin, is an “anti-angiogenic” therapy. It is designed to block VEGF (vascular endothelial growth factor)—a protein involved in the growth of new blood vessels—and is thought to limit the blood supply that feeds tumours with nutrients and oxygen. Unlike chemotherapy it is not cytotoxic, meaning it does not attack and destroy cancer cells. Early hypotheses that anti-angiogenesis might be an effective anticancer strategy developed in the 1970s (Folkman 1971; Gullino 1978). However, the promise of angiogenesis inhibitors in the treatment of cancer only became realisable after the recognition of VEGF in 1980s as regulator of normal and abnormal blood vessel growth (Senger et al. 1983; Ferrara 2004). Less than a decade later, a monoclonal antibody targeting VEGF showed dramatic suppression of tumour growth in mice (Kim et al. 1993). It was this which led to the eventual production of Bevacizumab as a humanised variant of this antibody and, more importantly, its place as an anticancer agent.

Avastin—the registered trademark name for Bevacizumab—was the first angiogenesis-inhibitor to be engineered, trademarked and approved by the FDA. It was developed by Genentech, the biotech division of the Swiss pharmaceutical company Roche in 1997, who had funded early mouse models, and trademarked in 2000. The FDA first approved its use in metastatic colorectal cancer in 2004 and it received accelerated FDA approval for brain tumours in March 2009 on the basis of two phase II trials: AVF3708g, sponsored by Genentech Inc. and NCI 06-C-0064E, sponsored by the US National Cancer Institute. However, its licence was limited to previously treated recurrent glioblastoma.

Accelerated approval by the FDA allows drugs for serious conditions to be approved based on a surrogate endpoint that is likely to predict clinical benefit. These markers are used in place of the “gold standard” of overall survival in cases where a disease lacks effective treatment and when overall survival data is unavailable. It is a regulatory pass designed to shortcut the bureaucracies of trials and make potential treatments available quicker and it is generally granted on the condition of further phase IV studies and future availability of survival data. In the case of Avastin, these surrogate endpoints were objective response rate²³ and progression-free survival²⁴, both of which had been reported positively in the two trials. Radiological findings were used to determine these endpoints in the FDA’s Oncology Drug Advisory Committee (ODAC) ruling, despite the strong advice of its own briefing reports and published data on the ambiguity of radiological readings, a key point to which I will return shortly. The approval received support from patient advocacy groups and industry alike. At the time, Harriet Patterson, director of patient services for the US-based National Brain Tumor Society was quoted by Roche as saying: “Until now, people with relapsed glioblastoma have *had almost no treatment choices and little hope*,”²⁵ signalling the charity’s support for Avastin, which has continued in spite of its more recent failures.

When it entered the US market, Avastin was priced at \$100,000 per patient per year. Shortly after, Genentech was in the headlines for justifying charging the highest market rates for Avastin on the basis that if society wants benefits it must be prepared to spend more (Jain 2013). “As we look at Avastin and Herceptin²⁶ pricing, right now the health economics hold up, and therefore I don’t see any reason to be touching them,” William M. Burns, the

²³ Objective Response Rate is defined by the FDA as “the proportion of patients with tumour size reduction of a predefined amount and for a minimum time period.”

²⁴ Progression Free Survival is defined by the FDA as “the time from randomization until objective tumor progression or death.”

²⁵ *My emphasis*; Quote by Harriet Patterson can be found here <https://www.roche.com/investors/updates/inv-update-2009-05-06.htm> (accessed 1st September 2018)

²⁶ Herceptin is another high cost cancer drug produced by Genentech

chief executive of Roche's pharmaceutical division and a member of Genentech's board told the New York Times in 2006 in an article titled *What price for health and drugs?* "The pressure on society to use strong and good products is there." According to Roche's 2004 annual report, Avastin generated more than \$700 million less than 12-months after entering the market, and increased dramatically year-on-year until 2015 when sales started to plateau. In 2016 and 2017 the drug generated almost \$7 billion in global sales, providing almost one fifth of Roche's total revenue from pharmaceuticals and helping its claim to be the largest cancer biotech company in the world; it is the third largest according to Nature Reviews Drug Discovery (Urquhart 2018). According to several polls²⁷, Avastin was the most sold cancer drug globally in 2014 and 2015, second in 2016, and fourth in 2017. In 2017, it was fifth among all drugs (Urquhart 2018). Critics have consistently argued that patients are being priced out of the Avastin market contributing significant inequities within the US healthcare system.

What is more interesting, perhaps, is Avastin's success given its relatively minimal evidence base and controversy around endpoints. How does it happen, that a drug with such contentious evidence can generate such massive profits? Why do advocacy groups such as the National Brain Tumour Society continue to support FDA approval of Avastin despite the contraindications of recent RCTs? Why does the FDA not revoke its decision given the recently reported survival data and further why does it approve the production of biosimilars? Why do clinicians continue to prescribe in the midst of deep uncertainty? Why do patients continue to yearn for these medications and how much do they understand? The answers to these questions are complex.

A story I got separately from two oncologists was about the pharmaceutical company behind Avastin: Roche. They cited money and the sheer numbers of indications listed on the bottle and included in trials. According to their accounts, Roche was pumping in huge sums of money meaning that trials were being done in multiple cancers. "Avastin has been trialled in pretty much every cancer you can think of," one told me, "because the company that made it, invested a lot in it and they throw it at everything." Others told me it was to do with the US market and the accelerated approval by the FDA. Both these explanations are plausible and likely reasons for success. We know from countless examples and ethnographic work that pharmaceutical companies lobby hard and spend enormous sums on advertising (Biehl 2007a; Dumit 2012; Rajan 2017; Hardon and Sanabria 2017). Company spend on marketing is reportedly twice that of drug development and safety testing (Angell

²⁷ Polls include IgeaHub, Genetic Engineering & Biotechnology News

2004). It stacks up empirically, as Avastin has now been approved in the US for use in eight conditions with applications for further indications in process.

CULTURING EVIDENCE

But there is more to Avastin's success than the pharmaceutical lobby and these factors cannot explain fully regulators' decisions and their approaches to evidence. When I asked oncologists about Avastin early on in fieldwork they repeatedly told me how it made MRI scans "look great" without making a difference clinically. The problem was that Avastin was confounding the production of scan images²⁸. This was corroborated in a 2013 interview at the American Society for Clinical Oncology (ASCO) annual conference with Mark Gilbert²⁹, the investigator who led the 2014 RTOG study reporting no survival benefit, and who had previously been involved with early trials. In the biomedical literature, I read how the lack of reliability in MRI had in fact been consistently reported since at least 2006. What is more, is that the NCI sponsored study used to support the application for accelerated approval had also reported this issue and had been published the month before the ODAC meeting in March 2009 (Kreisl et al. 2009). In fact, it had been reported in the FDA briefing that went to ODAC members for the March 31st 2009 meeting and presented at the meeting itself when a clinical reviewer for the FDA was minuted saying, "Response rate assessments may be complicated by a drug that has an effect on medical imaging. By modern standards, response rate has not been accepted as a surrogate endpoint for accelerated approval in GBM" (FDA 2009:30).

Despite the awareness of these caveats, and significant uncertainty expressed by committee members during the March 31st meeting, objective response, based on MRI, was included as a primary endpoint for the consideration of accelerated approval for Avastin use

²⁸ The reasons for the questionable relevance of MRI as an indicator of Avastin treatment efficacy are twofold. First, there is an inherent difficulty measuring GBM given their variability and the nature of infiltration which troubles a simple measurement of diameter (Cohen et al. 2009). This is not specific to Avastin but it was underscored by an almost 50% disagreement between independent radiologists in the FDA's review of radiographic materials provided by Genentech (FDA briefing 2009). Second, is the physiological response to anti-angiogenesis itself. Avastin temporarily stabilises the blood-brain barrier (ordinarily disrupted by tumour infiltration) meaning that vascular permeability is decreased. The decreased vascular permeability results in an improvement in oedema and a decrease in gadolinium enhancement (the dye used to highlight tumour tissue) on MRI, both of which are associated with brain tumours (Cohen 2009). As one of the oncologists I spoke to had put it more simply: "Avastin makes scans look better without necessarily affecting tumour growth."^{*}

²⁹ The interview with Mark Gilbert was conducted at the American Society for Clinical Oncology in 2013 by IMNG Medical Media. It is available online at <https://www.youtube.com/watch?v=KoKJPrXgzE0> (accessed 1st September 2018).

in glioblastoma³⁰ by the FDA. In fact, it was given unanimous support from ODAC members (FDA 2009) who ultimately reasoned that the response was “of significant magnitude, that is, clinically meaningful to serve as a surrogate reasonably likely to predict clinical benefit for the purpose of accelerated approval in refractory glioblastoma” (FDA 2009:172). While this appears hardened by evidence, the transcript from the March 31st meeting and summary of minutes, both publicly available from the FDA’s website, suggest an important and intriguing context for this decision. This has to do with the influence of public testimony.

In an open public hearing, after presentations from the FDA’s scientific committee and Genentech, and questions from the board, the committee heard testimonies from people with a brain tumour, their husbands, wives or parents. Some of these patients had been given Avastin privately or as part of a trial. The stories told were intimate, highly affective and strongly resonant with the stories of those I met at The Warner. Across all accounts, the Avastin narrative was unequivocally positive: that Avastin had offered hope where there was none, that it had improved quality of life, that it was one among few options for people with a brain tumour and possibly one that could extend lives enough for a cure to be found. “I’m asking you, in memory of my daughter, and all of those who continue to fight this disease,” one father said, “[for] accelerated approval of Avastin. It restores quality, lengthens lives of brain cancer patients, and allows them to continue being productive members of society” (FDA 2009:146). “Please approve Avastin,” a mother with a glioblastoma said, “I may need it again. It has given me more precious time with my children” (FDA 2009:151).

Several advocacy groups—small and large—also spoke on the behalf of the broader brain tumour community. One group had set up what they called the Brain Tumour Virtual Trial—an ongoing registry recording outcomes of people with a brain tumour taking Avastin. Speaking with the express permission of 1,702 people (three quarters of whom had written letters to the FDA in support of Avastin), Al Musella of the Musella Foundation for Brain Tumour Research and Information Incorporated said their virtual trial “confirms that Avastin really works in the real world, not just in these clinical trials” (FDA 2009:150).

³⁰ The committee reasoned that radiological findings were likely to be clinically meaningful given the magnitude of change. This decision they rested on an earlier ODAC meeting on the relevance of objective response in glioblastoma (12 January 1999) and a public workshop on clinical trial end points in primary brain tumours held in January 2006. During this earlier meeting, the ODAC stated: “objective response could be an adequate surrogate for clinical benefit under the proper parameters. The response must be well-defined and of sufficient magnitude to overcome the noise level resulting from other variables” (see Cohen 2009:1136). Scientists and clinicians, such as Mark Gilbert, now disagree, yet this seems to have impacted little on regulatory decisions.

Outlining the stakes of regulation and possibility, Harriet Patterson of the National Brain Tumour Society said:

We know that Avastin is not the silver bullet that's going to cure this disease, or even maybe turn glioblastoma into a chronic condition, but it does represent a marked improvement in quality of life for patients; and it is doing so in a landscape where there has been little hope, where prognoses are grim, and where adding just a few months of life actually is a significant improvement in life expectancy. Despite some of the issues that people talked about this morning, we believe patients are clamouring for Avastin because it offers legitimate hope and a meaningful extension to their lives where no others exist (FDA 2009:137).

Following these testimonies, and after offering a long explication of the caveats outlined above, one committee member said:

But with all that, and that benefit, I think I share what others have said. Putting it in context of just about everybody else's experience, both anecdotal and in series, reporting the literature, we seem to be seeing something that's considerably different. And I think the problem of not approving it or not recommending approval may outweigh many of these uncertainties, and they are many, about the quality of the data that's before us (FDA 2009:166).

Another committee member said:

I think those of us who deal with this more or less on a daily basis, in patients who have seen enough patients treated with this drug, can say for sure that the drug is having an effect. That effect is not necessarily the effect that we used to expect from these drugs ... I think it's unfortunate that we seem to be unable to capture that in numbers or in graphs, but I think it really does happen not universally to patients treated with this agent, but very commonly. I think it would be nice if we knew ahead of time who was going to [derive] that benefit and who was not. Whether or not that's going to lead to longer survival, my suspicion would be that it may. But I think if the objective is both longer life and better life, I think clinical experience strongly suggests that many patients have a better life because of the agent. Whether that life is going to be longer it's obviously going to have to await Phase III trial" (FDA 2009:160).

Later, in a concluding discussion, acting chair, Wyndham Anton, M.D., said:

I think the point that I'm getting at is that I think the totality of the evidence would suggest that there is some clinical benefit here. But if you were to say, well, what is the likelihood there will be a survival benefit here, I have to say that I have a much lower index on that. And so, that's why I bring up these other issues [about quality of life outcomes in a future phase III trial] because if we are, in fact, looking at there being the likelihood of clinical benefit and many of us think that's primarily going to be in quality of life—and, again, we obviously don't have a

crystal ball here—[but] one would hope that a confirmatory trial would end in a prospective manner, have that built in (FDA 2009:169).

Time and again, therefore, anecdotal evidence and clinical experience was raised in support of Avastin, relocating the evidentiary basis here, rather than what was reported in the two studies originally intended to support the FDA's decision. In fact, quality of life was never reported in either study. And yet quality of life on the basis that Avastin might alleviate symptoms, in much the same way as steroids, was a defining influence on the decision to use the radiological data as an index of efficacy and ultimately grant Avastin accelerated approval. In other words, the accelerated approval was granted not simply on the basis of the response reported by the two phase II clinical trials, as reported in the subsequent press releases, but also (and perhaps more so) on the basis of anecdotal and clinical experience and in the hope that Avastin would improve quality of life. Hope and possibility appeared more important than the evidence of the trials, even though the evidence from the trials was reported as the basis of accelerated approval. And as one of the public testimonies ended: "Quality of life is all about options" (FDA 2009:147).

This meeting is a crucible for the culturing of science—it reveals the power of testimony and the power of advocacy groups to mobilise this testimony. It is an example of the influence of civic epistemologies and how evidence is cultured and technology is peopled (Fischer 2013).

...

The ODAC decision was reported online to Roche/Genentech investors the same day by Genentech under the headline: "FDA Advisory Committee *Unanimously Recommends* Accelerated Approval of Avastin for Previously Treated Brain Cancer (Glioblastoma)" (*my emphasis*). They said:

[T]he U.S. Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee (ODAC) voted unanimously that the response seen with Avastin® (bevacizumab) in people with previously treated glioblastoma is of sufficient magnitude to be reasonably likely to predict clinical benefit. The FDA is expected to make a decision whether to grant accelerated approval of Avastin *for use in this most aggressive form of brain cancer* by May 5, 2009 (*my emphasis*).

The decision to approve Avastin for use in previously treated recurrent GBM was forthcoming and has remained unchanged. On the day it was granted, Roche quoted

Timothy Cloughesy, M.D., director of the Neuro-Oncology Program of the Jonsson Comprehensive Cancer Centre at the University of California, Los Angeles, in their online press release: “People with this type of brain cancer have had no new treatments in more than a decade. After so many years with little progress in this field, Avastin was associated with a durable tumour response and doctors now have a new medicine to offer patients.”

The ODAC statements about lack of other treatments and need for options are significant and key to understanding how the FDA appraises evidence and context. In the case of the accelerated approval of Avastin in glioblastoma, contentious radiological data was accepted as a way to increase the availability of options for patients and practitioners. The bar for good evidence was therefore lowered. As such, what was described as “*objective response*” was given valence by the lack of known treatments. It is the biotechnical embrace and the investment in hope writ large. It is also an acute demonstration of the power of patient choice: a principle made paramount in numerous position statements across advocacy, regulatory bodies and the pharmaceutical lobby. The US National Brain Tumour Society, for example, who publicly supported Avastin on its approval and continued to do so following the publication of evidence suggesting no gain in survival in 2014 (Chinot et al. 2014; Gilbert et al. 2014), published the following statements on its website:

[Avastin] is approved for the treatment of patients with recurrent glioblastoma multiforme (GBM), the most aggressive and deadliest form of malignant primary brain tumours. However, some doctors have been known to use it to treat newly diagnosed GBM patients, as well as patients with other brain tumours, such as astrocytomas due to the molecular similarities to GBM. *Avastin has significant meaning to some of the patients and families who are facing and have fought GBM. For some, it has brought them a better quality of life during the last few months of survival. Currently, Avastin is only conditionally approved by the FDA through its accelerated approval program. Continued approval is based upon the results of studies aimed at demonstrating the effectiveness of the drug. As the largest nonprofit organisation in the U.S. dedicated to the brain tumour community, the availability of effective therapies is a top priority for the National Brain Tumour Society ... There have only been four (4) FDA approved drugs for brain tumour patients in the past 30 years. If Avastin were to ever be withdrawn as a treatment for GBM, it would reduce this number to only three (3) (2014, my emphasis).*

And earlier:

Avastin is an important part of the current limited treatment landscape for many brain cancer patients. National Brain Tumour Society understands that *Avastin has helped some brain cancer patients have a higher quality of life in their last months, and as such we think it is important that it remains an available treatment option for patients and doctors (2013, my emphasis).*

...

The conversation around Avastin efficacy within oncology communities remains open in spite of the two large RCTs published in the prominent *New England Journal of Medicine* (Chinot et al. 2014; Gilbert et al. 2014), a recent Cochrane systematic review of anti-angiogenic therapies in high-grade glioma (grades III and IV), including seven trials (4 of which included Avastin) and 2,987 patients, all of which reported no benefits to overall survival and an unclear impact on quality of life (Khasraw et al. 2014). Interestingly, the two studies used to support the FDA approval were excluded from the Cochrane review on the basis of trial design. An edited volume by Chen and Chamberlain entitled *Controversies in Neuro-Oncology: Avastin and Malignant Glioma* and comprising 25 chapters by leaders figures in neuro-oncology was published in 2010 in the hope of developing better understanding on the problem. Yet, it seems that this too did little to settle consensus. While randomised trials uniformly show overall survival does not improve with Avastin, current debate continues on establishing an appropriate endpoint to assess efficacy as well as dosing, safety, the exact mechanisms of physiological action and resistance, and clinical use, with some now suggesting a role for Avastin in surgery (Tamura et al. 2017).

The FDA has not only stuck with its decision on provisional approval but granted full approval for Avastin in December 2017, despite what might appear its contradictory action to revoke Avastin's licence of use in metastatic breast cancer licence on the basis of poor overall survival. In the case of breast cancer, Janet Woodcock, then head of the Centre for Drug Evaluation and Research at the FDA, said in 2010:

We did this because of the results of the confirmatory studies that showed that Avastin when it was added to the standard chemotherapy for medicine that if breast cancer did not improve survival and there was no evidence that the patients had clinical benefits, for example, on symptoms; therefore, we are proposing to remove the indication because the original promise of benefit was not confirmed in these subsequent trials.

Roche and supporters of Avastin move within the margins of uncertainty, optimistic of its efficacy: they continue to describe Avastin in marketing materials as a “tumour starving therapy” which “can stop the tumour from growing.” Avastin is now licensed in Japan for use in newly diagnosed glioblastoma. As others have shown, the possibilities of new drugs do not arise as if simply discovered, but rather are given in complex arrangements of social practices, market interests, and experimental regimes (Hardon and Sanabria 2017). These are some of the features and activities which constitute what Mary-Jo DelVecchio Good, Carlos

Novas and Nikolas Rose have each called *a political economy of hope* (DelVecchio Good 2001; DelVecchio Good 2007; Novas 2006; Rose and Novas 2005).

PROMISES OVERSEAS

European regulators have been more cautious in continued efforts by Roche to gain approval for Avastin use in GBM. The Committee for Medicinal Products for Human Use (CHMP)³¹ continues to disallow GBM, recurrent or otherwise, to be listed as an indication for Avastin, citing lack of evidence (European Medicines Agency 2014). In their most recent review, the scientific committee noted no effect on overall survival, no benefit in terms of quality of life, and potentially detrimental neurocognitive functioning as a result of Avastin. They also noted a lack of radiological clarity, an overestimation of progressive disease in the placebo controlled arm and an underestimation in the Avastin arm. In their words: “[Roche] did not convincingly show that the sensitivity analyses performed were able to mitigate the risk of systematic biases in the evaluation of PFS [progression free survival] and were adequate to provide sufficient reassurance that bevacizumab produces a PFS increase of clinically important magnitude” (European Medicines Agency 2014:5). Avastin had in fact been contraindicated in patients with untreated central nervous system (CNS) metastases in 2004 based on a single case of fatal intracranial bleeding in a patient with metastatic hepatocellular carcinoma who was enrolled in a Phase I study of bevacizumab. This was lifted in 2009 following new safety information and risk review (European Medicines Agency 2009). The European Union approved Avastin for use in cancer of the colon or rectum in 2005 and subsequently in breast, non-small cell lung and renal cancers. The UK National Institute for Health and Care Excellence (NICE) has consistently deferred to these opinions having suspended its own review of Avastin in GBM in 2010. Although Avastin has not been approved for use in brain tumours in either the EU or the UK, brain tumour patients in the NHS continue to ask for it. As I explain now, the US scenario is a crucial part of their stories and the work of practitioners.

...

³¹ The Committee for Medicinal Products for Human Use (CHMP), formerly known as Committee for Proprietary Medicinal Products (CPMP), is the European Medicines Agency's committee responsible for elaborating the agency's opinions on all issues regarding medicinal products for human use.

By the time I entered the field, clinicians were already cautious about Avastin. In fact, I had interviewed a neurosurgeon in 2012 who had told me Avastin “is just a very expensive steroid, basically.” At that time, I was unaware of the significance of his statement and knew nothing of the drug which would feature prominently in my later fieldwork. He had used the case of Avastin to illustrate global differences in care, evidence and the allure of overseas treatments:

We see a lot of [patients with very strong hope] and we never dissuade people from doing whatever they want to do. If they want to go off and take jungle juice, that’s absolutely fine by us, and I do emphasise that there’s no evidence-based therapy treatment that we don’t have available in this hospital, or in the UK. So, a lot of patients will immediately start fundraising to go to America, and we try to discourage that, saying, ‘There’s nothing over in America that you can’t get here. If there is, people are taking money off you, basically.’ There’s a huge financial incentive for doctors to tell untruths over in the US. [These situations are hard to manage] because the patients that do go over there and get second opinions, it’s usually not mainstream—not mainstream UK—and the treatment options are ... For instance, this drug, Avastin, that you may or may not have heard of, which is very expensive, they give it away like Smarties in America. But it costs £100,000 a year to give it, and you can’t get it on the NHS. So, some of these patients have gone over and started Avastin in the US and then expect to come over here and for us to prescribe it to them. And they get a bit shocked when we say, ‘Sorry we can’t, you’ve got to pay for it yourself.’*

Like many clinicians I would later speak to, the sheer cost of Avastin was a key factor in his description. In 2012, his statement was even before the overall survival data had been published and more than two years before I began my doctoral fieldwork. Over these two years and throughout my time in the hospital, numerous commentaries cautioned its use and a succession of reviews were added to the Gilbert and Chinot articles published in 2014. Yet this has done little, it seems, to diminish Avastin’s appeal among patients where it remains a durable treatment option. I heard about it again in my first week of fieldwork in October 2014 when a patient had mentioned it to Dr Anton. Although she had listened attentively, her answer to the patient was clear: “there simply isn’t any concrete evidence yet.” Further, and in contradiction to the ODAC committee meeting, she said that anecdotal evidence has not been great, “even though the first scan often looks good.” I learned this kind of response was pretty standard for experimental treatments and especially Avastin, which appeared frequently in media headlines and promising stories.

In fact, Avastin was being trialled with another drug—Lomustine—at The Warner during my fieldwork. But results had not been that promising and when out of patients’ earshot, Dr Anton would say, “it’s very hard when trials don’t work.”*

MATTHEW

When Matthew had been excluded from joining the Avastin plus Lomustine trial he had logged it among the collection of other trials beyond reach. He was angry at the hospital and had lost some faith in the oncologist who told him he was ineligible. He could not understand why they could not bend the eligibility criteria. He and Pam now used the term “health refugee,” which they saw on one of the patient forums, to describe their situation and looked to America as a potential source of Avastin. Reflecting on how they now saw the role of the NHS in Matthew’s care, they said:

Pam: I think with clinical commissioning and the choices that are made locally as well national level on choices to fund treatment or not fund treatment, absolutely I see it’s part of it. That puts you in a whole new arena in thinking about your health when you know that you go to your GP and you say I need this treatment, I need Avastin, will the local commissioning body approve it and they won’t? We know that NICE don’t—

Matthew: Avastin is so expensive—

Pam: We know that the cancer fund that was set up has now taken Matthew’s treatment off. We understand that it’s by and large economic—although some of it’s about the controversy over Avastin for Glioblastoma. I think we get a general view that there’s a cost-benefit equation made all the time—and I understand that. But they seem to be quite tough when it’s end of life decisions.

Matthew: And I think this dilemma is going to get bigger as people live longer. Cancer treatment seems to be prolonging people’s lives and I think they are getting into these more esoteric and expensive leading edge treatments. And the NHS to be fair is not a bottomless pit and needs funding. But with Avastin, didn’t the manufacturer sponsored a huge trial? It’s very odd—because we’ve been talking about it like it’s the holy grail and the magic bullet. But they conducted this huge trial which reached the opposite conclusion. They sponsored that for years, trialled hundreds of cancer patients—

Pam: It’s very controversial—

Matthew: And the conclusion of the trial was it didn’t prolong patients’ lives sufficiently to justify the cost. If at all—which seems totally against the anecdotal evidence. But apparently it’s to do with the fact that most of the cohorts were first line treatment and for some reason it only seems to work well for people like me, with recurrent Glioblastoma. But 80 percent or something of the hundreds of patients involved in the trial were first line treatment and apparently it has little or no beneficial effect. So Roche shot themselves in the foot there, slightly. And I think they’re just trying to claw back as much money as they can now.*

Matthew and Pam knew that Avastin was controversial. Matthew’s oncologist had told them and they had read about it. In Pam’s words, the oncologist had said: “it’s a slippery slope if you come off it” and had told them he could not predict how long it would last: months or years. But he had also said that the standard second line chemotherapy—PCV (Procarbazine; Lomustine; Vincristine)—would not work quickly enough now, as Matthew said:

He was like: ‘you are really ill and I think if you have the PCV NHS treatment you are going to die. It won’t work quickly enough.’ And I felt so awful by then. I wasn’t gonna disagree; well you don’t disagree with consultants anyway. I certainly went totally along with that opinion.*

He and Pam now mistrusted evidence produced by trials, instead relying on anecdotal forms of knowledge. They had rid themselves of the idea of a “magic bullet” and described instead a layered approach to treatment which they called “Matthew’s cocktail.” They accepted slim odds and small gains, so while they knew that Avastin had a “shelf life,” they also had faith that it would contribute at least slightly. Having made the decision to try Avastin, they had to find ways to pay for it. Matthew joked about making Avastin in his shed in the garden, comparing himself with a character in the US TV show *Breaking Bad* who makes crystal meth in a makeshift lab. In harrowing detail, Pam described their dilemma:

Pam: I very innocently said to [the oncologist], well if [our insurance] won’t pay for it how much will it cost to self-fund? And he was very derisive: “What do you mean? It costs a hundred thousand pounds each year!” And I wasn’t particularly thrown by that, given we’d already been funding the treatment in Germany—those possibilities didn’t feel brand new ... so we made the decision that we would pursue [Matthew’s insurance] for covering the cost. He said Matthew needed to be in on the Monday to do all the paper work, ready to start Avastin on the Tuesday—

Matthew: I was worse then wasn’t I—

Pam: Yeah ... so I was even more concerned about Matthew and I spent most of the next day fighting and arguing with [the insurance company]—they gave me the runaround most of the day and then said they wouldn’t fund it. So I think this is one of the critical points of decision making: sitting in that hotel with you really unwell, with me being told this treatment tomorrow is probably the treatment that’s going to give Matthew length of time and quality of time. Or you go back to PCV. It felt like the most impossible situation I’d ever been in. And [the insurance] are saying no. And I’m thinking, “Well how are we gonna make this work then?” You know, I knew how much it was going to cost. So I really had to keep quite a cool head and get the support I needed to think through how to make that decision. So speaking with a friend of mine and with Matthew because I said, “Matthew, we need to brainstorm how we solve this problem. We need to think out the box what we’re going to do, short of robbing a bank. How are we going to pay for this?” ... and Matthew was saying, “I’ll just have to go back on PCV.” And I was like, “that’s ridiculous—you have to have this best in class treatment that’s available in the UK, but you have to pay for it.”*

They managed to get a loan from Matthew’s work and eventually, and with the backing of friends, Matthew and Pam raised more money through crowdfunding:

Pam: All of a sudden there was this industry behind us that was communicating, that was telling people about the situation. Friends were then doing things to raise money, like charity gigs, runs, all sorts of things.

Matthew: There was a Justgiving page and an American equivalent of Justgiving—the American one was started by someone living in the next road—it was all friends around here.

Pam: So we were able to—I can't think what the word is—*accumulate* enough money to keep Matthew going for a few more months until this year ... there's a reserve to cover Matthew for the winter into spring. But now, even with the best of intentions—there still is hope for people to donate and do fundraisers and all sorts—but for the long term that doesn't feel sustainable.*

...

Matthew and Pam continued looking at other trials throughout this, fully conscious that it was now Avastin which closed off other avenues and they never let go of the possibility of the vaccine. When I saw them again a month later, days before Matthew was due for a scan, they were nervous as always. But unlike the usual fears of new growth, new growth was precisely what they hoped for. They hoped for his tumour to grow enough for a second operation to harvest more tissue for the vaccine being trialled at The Warner to be made privately; such were their hopes in the trial and such are the paradoxes of tumour harvesting. When I later spoke with them, they told me that Matthew's tumour had in fact grown. But it had grown skein-like through the tangles of Matthew's brain and was no longer operable.

...

The production and regulation of possibility is a global affair, as scholars studying science and technology attest (Mol and Berg 1998; DelVecchio Good 2007; Fischer 1991; Fischer 2009; Fischer 2013; Marcus and Fischer 1999; Petryna 2009). Not only did the decision by the FDA make Avastin a legitimate option for brain tumour patients and clinicians in America, but it did so for patients and clinicians in the UK. While it is true that European and UK regulators did not support Avastin by approving it for use in brain tumours, it became an option nonetheless for people with an eye on private or overseas treatment and a piece on the board which could be moved to support a claim to its use. The FDA decision gave Avastin legitimacy abroad in establishing a new symbolic value. By contributing a new semiotics of hope, it was this symbolism which reinforced the aspirations and decisions of patients like Matthew and also troubled doctors working in a healthcare system without recourse to the treatment.

ALICE

Alice began chemoradiation shortly after the extraordinary consultation I described above. However, after one week she abandoned it due mainly to the side effect of sickness and the fear of losing her hair. She wanted to feel well enough to spend quality time with her young children. Instead, she began a series of treatments, which she called alternative. One was given to her by a Brazilian neurosurgeon who had developed *perillyl alcohol*—a natural substance isolated from the essential oils of lavender, peppermint, spearmint, cherries, celery seeds, and several other plants—for use in glioblastoma. She had had the surgeon flown from Brazil to meet with her and ended up placing bulk orders of the *perillyl alcohol* from a laboratory in Italy, which she shared with another patient.

FAY

I went to see Fay again after coming back from America. It was late summer in 2017 and she had been admitted into the hospital after a seizure and having fallen. We had kept in touch while I was away and so I had kept abreast of things. I knew that her scans had been bad from the weeks before and for the first time—like her—I knew for certain that she had been given the vaccine and not the placebo. After progression had been apprehended, she had been taken off the vaccine trial and offered the second line intravenous chemotherapy, PCV.

She lay in bed, her eyes closed and when I approached she gave a muted hello. We hugged and sat in silence before the story of the last few weeks tumbled out. The trial hadn't worked, the chemotherapy she had started a month ago was on hold, her eyesight had worsened, and she had just been told she “might never need to go home.”* Her mood was flat, her voice empty of its usual energy and spirit. I can't recall a time so desperate in any of my meetings with her. As we talked, she kept circling back to the trial, to the sadness, to how her “world has come crashing down.” Everything now was at a hiatus.

When hope fails, narratives must shift and new futures imagined. We talked about possible moves from the hospital and about Fay's home. She told me that the hospital would not discharge her until there was a care package in place. She already had people coming morning and evening, so now it was just finding someone for the rest of the time. “I can't just walk out of my life,” she said, “I've got bills to pay. All my things. It's my home. I can't just leave it.”* Walking out of a life—to abandon what you know and the loose threads of living—it sent a shiver down my back. “I want to go home,” she said. I asked her about Dennis, her cat who used to drape himself across her shoulders and chew through her boxes of green tea, which she swore was cancer beating. “He's with Maria. I know he'll never

come back with me now.”* This was somehow the most crushing thing. Dennis was her companion and confidante: the ginger prince who stole her attention and returned it with his playful pawing. It was a sign of imminence and inevitability—the first major admission and a break with hope that would lead her along another path.

When I left the hospital that day, I realised that I too had invested deeply in the trial and its possibilities—broken hope and a fate all but sealed.

...

When the failure of experiments is framed at a collective level, such as I described in the case of Avastin, it is an abstract failure (or not a failure at all—edited out of official investor accounts—or repurposed as a steroid; useful at surgery). It is a setback but not the end of progress: something will give; a discovery is somewhere on the horizon. But when a treatment fails for a patient, you realise what is truly at stake. It is not simply a setback in a world that goes on, but a tragedy in which a world comes crashing down. Although the immunotherapy vaccine ultimately did not live up to Fay’s hope to live ten more years, a May 2018 article published extremely promising interim results with a 6-month increase in survival over standard treatment (Liau et al. 2018). The Brain Tumour Charity issued a statement immediately after publication of these results and heralded a possible “paradigm shift in the treatment of brain tumours” (The Brain Tumour Charity 2018). Another charity countered with concerns over the high cost of the vaccine and the ethics of making treatments available for private use, if they are not publicly-fundable (Brain Tumour Research 2018).

CONCLUSION

Trials are not simply hypothesis testing instruments but “operative environments that redistribute public health resources and occasion new and often tense medical and social fields” (Petryna 2009:30). As I have shown throughout this chapter, it is in these new fields that patients and families find a real and symbolic infrastructure through which hope can be *practiced* (Mattingly 2010). However, limited funds and the sheer difficulty of intervening in a disease of the brain, means that trials for people with a brain tumour remain the privilege of the few. Those with access to trials live and navigate new and heightened hopes that experimental drugs may be more promising than standard treatments but might also

disappoint more dramatically. Those who are excluded attempt to find new ways around, drawing resources through platforms such as crowdfunding and travelling overseas to access innovation now. Advocacy groups are key actors in shaping the social field of innovation, effecting both the production and regulation of possibility through programmes of lobbying and direct funding of research (Epstein 1996; Novas 2006).

Whether trials—as the pinnacle of innovation and primary example of the medical imaginary—are considered as patient right or the province of scientific advancement with little direct responsibility to individual patients, is therefore extremely unclear. In truth, they are both and, as such, a complex set of dilemmas plays out in the improvised spaces of the clinic. The example of Avastin shows how evidence is shaped in these dynamics and given valence in contexts of hope, desperation, and the production and regulation of possibility. Overall, the case of brain tumours further shows how treatment possibilities are shaped according to multiple logics, not least the logic of the market. To repeat Cheryl Mattingly: “Hope is on intimate terms with despair. It asks for more than life promises. It is poised for disappointment” (Mattingly 2010:3).

In the next chapter, I continue the themes of hope, despair and disappointment and follow patients and families into a new phase of care. Focusing on disease progression, I also bring out the sense of imminence which characterises the experience of brain tumours; imminence not just in the discovery of cure, but the coming of death.

CHAPTER 5—DISEASE PROGRESSION

A Return to Gabriel.

After I said goodbye to Gabriel lying on his bed, Cecilia and I sat in the kitchen and talked.

“It was all so quick. That’s what was so difficult,” she said, “Around Christmas we came for our scan but I got the day wrong—I was so scatty around then—we were a week early. At that point, Gabriel could walk to the car and from there to the hospital. But a week later, when we should have gone for the scan, he couldn’t walk. It was that fast. And so we decided not to go for the scan because it wouldn’t show anything new—anything we didn’t already know.

“Quite a change, isn’t it? It’s been so sudden. So hard to know what to expect. No one seems to know—to be able to tell you anything. I found this timeline online about the final weeks of a brain tumour—what happens. It’s been really useful. And Gabriel seems to be following this. Most of the time he’s pretty out of it but sometimes he’s lucid—today he’s with us.” She sent the timeline around to family, “I was having all these phone calls especially around Christmas and I didn’t know what to tell anyone. They were asking ‘well is this it? Should we come and see him?’” She tells me that Gabriel’s mother is in denial and thinks Gabriel will get better. “His parents find it very hard. I’m now next of kin, which is a good thing. I want them involved but they can’t talk about it.”

Gabriel is now managed at home by a local palliative team and private carers, which Cecilia coordinates. His contact with The Warner is limited, reduced to Cecilia's telephone conversations with Gabriel's nurse and key worker, Suze, and the few updates she sends. Cecilia says it's difficult managing all the community teams: “So many people. We had nine people here the other day, including family. They all have different ways of doing things, different things they will or won't do. Some of them question giving him sedatives. But it's not as if we're drugging him up.” She says, “it's a battle and we're the ones on the frontline.”* Sometimes she spends all day on the telephone trying to get more help. “It's hard to know what to do. It's hard to know when he's in pain. He makes small signs and I'm getting some of them. I spoke to a palliative care consultant—that was reassuring. She told me about caring for Gabriel at home and how it can be emotionally. She asked about the hospice but we wanted to stay here—we resisted a hospital bed for a while but then it became too much. And here we are.”

...

The last year of Gabriel's life was marked by a deep uncertainty. Several months before his death, he was complaining of troubled vision and been unable to read. Return trips to the optician did nothing to bring resolution and only after a consultation with the neurologist did an answer finally arrive: Gabriel's tumour had grown and become more aggressive. In the vernacular of the hospital and echoed in the tragic yet ambiguous inevitability felt by Gabriel and Cecilia, Gabriel's disease had *progressed*.

In the moments discussed in the literature as “end of life,” time is the most precious commodity and the biggest unknown (Bluebond-Langner 1978; Borgstrom 2015; Glaser and Strauss 1965; Glaser and Strauss 1968; Kaufman 2005; Kellehear 2007; Kellehear 2014). Families live in nervous anticipation of the “last moments” with little clinical certainty regarding the pace of disease progression and the imminence of death. While the broad goals of care shift from prolonging life to controlling symptoms via palliative means, the lived experience of disease progression is plagued by a lack of moral certainty, doubt, and what some might characterise as denial (Kaufman 2005; Round and Llewellyn 2016).

From a biomedical standpoint, death from a brain tumour is typically the consequence of a build-up of pressure in the brain caused by the mass of a tumour or complications resulting from the infiltration of tumour tissue into brain tissue. It is the implied endpoint of *tumour progression*, where *progression* describes the growth, spread or transformation of a tumour into a more aggressive form of disease. In this way, tumour progression is characterised as the natural history of disease: an empirical and biological fact of the inevitable proliferation of tumour cells. In the care of patients, tumour progression is apprehended through snapshots of successive diagnostic moments which are narrativised over time. These moments are rendered typically through brain scans and less typically through samples of tissue taken at repeated operations; they are experienced in the manifest symptoms of patients.

Establishing tumour progression is therefore an interpretive effort and, as I have shown throughout this dissertation, the timing of scans, operations, clinical appointments and so on is the result of complex negotiations, contingencies, and *ad hoc* schedules. By locating the evolution of disease, progression serves the clinical role of marking key moments in its management by the interventions of surgery, radiotherapy or chemotherapy, or to consider experimental treatments. As such, it is a call to action. And yet it is also one

that can presuppose inaction. Here, tumour progression marks a new point—entry into the phase of care termed “end of life.”

While tumour progression is narrated in the clinic as a biological phenomenon, I argue in this chapter that it is productive to view tumour progression as equally “social.” Such a focus lifts tumour progression from its placement as an inevitable point on the pathway—a mark in the cold narration of disease course—and re-sites it in the hopes and fears of patients, families and clinicians, and the dilemmas and moral ambiguities of their lives and work. By establishing a space in which to consider the social and biological constitution of tumour progression, I hope to bring critical focus to notions of reversible and irreversible disease, the very real social consequences of a biotechnical embrace (elaborated from the previous chapter), the lived experience of imminent yet unknowable death, and the decisions—small and large—which constitute approaches of acquiescence or resistance to an underlying biological reality.

I begin the chapter with a discussion of end of life care policy and the fraught transition from treatments variously termed “radical,” “curative,” “life-extending,” or “life-prolonging,” and which support a narrative of fight or attack, to care considered “supportive,” “palliative,” “comfort,” or “end of life.” I discuss the administrative and ideological struggles that characterised this “phase change,” both in and outside the hospital setting, and the ways in which the rapidity and volatility of brain tumours, specifically, posed a challenge to administrations such as Advance Care Planning. I then present a timeline of disease progression for Rebecca, a patient whose experiences demonstrate that pivotal moments are not always regarded as such at the time, that the extent of progression of the disease is not simply a biological fact. Rather, the end of life for people with a brain tumour is full of difficult choices about not only how to live, but when to act. I show how dynamics of waiting, delaying and “buying time” loom large as time remaining shrinks. Finally, by presenting the cases of other patients in the final weeks and days of life, I argue that the “progressional ordering of reality” (Ingold 2007:88) about the nature and extent of disease creates conditions of doubt, where each moment that comes poses utterly new challenges without precedent. Though the dilemmas that accompany physical deterioration may seem inevitable “after the fact,” I show how they were experienced in the moment as utterly new and *potentially* transformative. At stake for patients and families, was the quality of their lives up until the end, the moral approbation of those that care, and the feeling that they did all they could.

EXPERIENCES AT THE END OF LIFE

As with all phases of care, people are encouraged to make choices about care at the ends of life. This is written into the UK's End of Life Care Strategy (Department of Health 2008; NHS England 2014), which focuses on choice as a key premise, expecting people to make decisions on where they wish to die, who they wish to care for them, whether they would wish active treatment (e.g., for infections), and the circumstances in which they would wish to be resuscitated (Borgstrom 2015; Borgstrom and Walter 2015). While previously the strategy focused on place of death as a key choice and determining factor in the “quality of death,” the more recent ambition is to ensure that living and dying well is the focus of end of life care, regardless of place (NHS England 2014:4). As such, a broader notion of “experience” is taken to be the primary aim, made clear in the introductory statements of NHS England's white paper *Actions for End of Life Care: 2014-16*: “Importantly, we signal a shift in focus from ‘place of death’ to the broader ‘experience’ of end of life care. Wherever people are, we want to enable them to live and die well” (NHS England 2014:6).

Founded on quality standards set out in the NICE Quality Standard for End of Life Care for adults (2011) and aligned to a narrative of “Every Moment Counts,” this document provided the template for NHS England's “House of Care”—what might broadly be described as a community focused approach to person-centred care. As the document explains:

The ‘walls’, ‘roof’, and ‘foundation’ of the House of Care represent four interdependent components which, if present, provide the greatest opportunity for person-centred and coordinated care. The framework assumes an active role for patients and carers in individual care planning, working with health and social care staff, services and other support agencies.

These interdependent components—Engaged, informed individuals and carers; Health and care professionals committed to partnership working; Organisational and supporting processes; and Commissioning—therefore represent key domains in a dynamic system overseen by regional level Clinical Commissioning Groups. End of life care is locally commissioned and locally provided meaning that Clinical Commissioning Groups and local organisations are responsible for developing local vision and strategy, gathering information about their locality, planning and procuring services and monitoring their work. While direct care might be provided by NHS employees, such as in the case of specialist palliative care nurses, the state also contracts care out to private companies. Charities, such as Marie Curie

Cancer Care and Macmillan Cancer Support, provide significant resource including community nursing and hospice care. The institutional and social formations of care are therefore extremely complex.

Recent policy and the move to a broader notion of experience developed in a turbulent time. End of life care provision had been reported as perpetuating gross inequalities with, for example, spending discrepancies on specialist palliative care ranging from £186 to £6,213 per death across Primary Care Trusts in the UK (NHS England 2014). Ahead of my arrival in the field, end of life care was under significant media scrutiny, decried under the headlines of *'Brutal and Callous' NHS Treatment Exposed* (Telegraph July 15 2013), *Euthanasia by the Back Door* (Independent January 9 2013) and *The Most Corrupt Practice in British Medicine* (Mail November 4 2012) and reported as “allowing patients to suffer days of dehydration, or to be sedated, leaving them unable to even ask for food or drink” (Telegraph December 1 2013). The Liverpool Care Pathway—hitherto the guiding framework of care in the last days and hours of people’s lives—had been singled out as contributing to a callousness and a tick box approach to care, and, in some ways, became emblematic of wider care failings. An independent review of the pathway published in July 2013 with the standfirst of “More Care Less Pathway” suggested the pathway be rapidly phased out. Instead, a less generic, more tailored approach should be adopted (Department of Health 2013).

The initial system-wide response to these criticisms by the Leadership Alliance for the Care of Dying People—a group of 21 national organisations including Government bodies like NHS England, Public Health England, NICE, and charities such as Macmillan Cancer Support and Marie Curie Cancer Care—was *One Chance to Get it Right: Improving People’s Experience in the Last Few Days and Hours of Life* (Leadership Alliance for the Care of Dying People 2014). This was set around five key priorities that together emphasised timely planning, clear communication, sensitivity and choice. Adopting a new approach to inspection and regulation of end of life care, the Care Quality Commission—the independent regulator of health and adult social care in England—began to focus on markers that were purported to “get to the heart of people’s experience of care” (2014:38). Though focused on the last few days and hours of a person’s life, recommendations rested on the foundation of “planning ahead as much as possible” (2014:24) where “the principles of palliative and end of life care apply from a much earlier point in a person’s life-limiting illness” (2014:76). This marked out a broad temporal frame for end of life care and was intended to encourage practices such as Advance Care Planning—a recommended mode of

discussing and documenting patients' values and wishes for future care in the anticipation of physical deterioration that might complicate decision-making—and Advance Decisions—more formalised advance statements of preferences and wishes as well as legal processes such as lasting power of attorney and advance decisions to refuse treatment.

TIMELY PLANNING AND THE IRREVERSIBILITY OF DISEASE

It is no surprise then that timing should be a major feature in clinicians' accounts of end of life care. In 2012, two years before I started fieldwork, I was part of a team investigating how clinicians working with people with a brain tumour understand and engage (or not) in the practices of Advance Care Planning (Llewellyn et al. 2018). As part of this project, I interviewed surgeons, oncologists, neurologists, nurses, and allied health professionals at The Warner and I have kindly been given further access to these interviews by the team under Joe Low. It is striking for me to revisit these materials and listen to the voices of those who would become key participants in later fieldwork; their words now contextualised in the dailiness of their work.

The key ideas that came from these early interviews centred on the lack of Advance Care Planning practice in brain tumours and reasons were multiple. A salient factor among those I interviewed, was the need for lengthy conversations amid the pressures of routine. Health professionals, for example, spoke of the need to account for their work and the difficulties in having such conversations recognised as legitimate. It was as if these kinds of activity fell out of a bureaucratic gaze and as such slipped down the list of priorities, displaced by those that were more measurable or at least legible to such a gaze. This statement, given in 2012 by a clinical nurse specialist, aptly captures a broader predicament and, moreover, foreshadowed what I would later observe in the work of others:

It's hugely emotive and hugely time consuming to engage in these conversations. So, bearing in mind we're in an environment at the moment where everybody wants to know that what you are doing is either generating income or cost effective, justifying that amount of time on having a conversation to enable someone to come to a good decision. I know it's good quality care, but that's in amongst 101 other things that also have to be done, which are more clinically measurable, have a better outcome in terms of ticking a different type of box.*

This is clearly extremely concerning and compounded by workforce disruptions due to continued budget cuts and administrative reconfiguration. During the 2012/13 interviews, for example, there were four clinical nurse specialists, yet, for most of my

fieldwork there were only two. While this was in part due to circumstances beyond budgetary distribution and workforce management, the result was effectively a double workload for already overstretched nurses. After long consultations and the final recognition of a thinly stretched service, the case was successfully made to recruit a nursing staff of five, which was in place by the time I left the field in May 2016. But this was also in preparation for a major increase in brain tumour patients owing to wider regional reorganisation of cancer referrals across London.

Although key to whether particular practices are done, workforce factors like these are not my main concern here, nor is the need to have more time *per se*. The most salient feature of these interviews is, I suggest, the *timing* of end of life conversations vis-a-vis disease progression and the perceived receptiveness of patients, families and clinicians to conversations about dying and palliation. In effect, the social inputs that inform notions of disease progression.

A significant critique of End of life Care policy and its ideological foundation of a good death is its reliance on relatively predictable trajectories and markings of transitions (Borgstrom 2015). Diseases that fall outside the natural histories of certain cancers are problematic because they fail to accord with a trajectory of gradual decline. This was something revealed to me in the interviews. In brain tumours, the decline towards death can be sudden and rapid and it is confounded at times by compromised capacity, which, as I have shown in chapter 3, can be both imagined and real, formally described and diagnosed, or suspected. As a neurosurgeon told me:

There is a huge problem in communicating all of this information to a patient who doesn't have clarity of thought, doesn't have comprehension, verbal comprehension, because this has usually evolved so rapidly.*

This is how a nurse described to me:

There are other things that are problematic with this patient group in that sometimes the person to whom it's happening, who's got some cognitive impairment, has absolutely no insight into it. So although they have capacity to initiate a Lasting Power of Attorney, they could rationally think about it and make a decision to do it, they don't detect that they have a problem. But you couldn't then force [an advance plan] on them because they do have capacity. So there's a very grey area, very, very grey area with regard to their insight into the problem. If that's part of the cognitive process—that they can't see, that they're behaving a bit strangely, or that they're not willing to accept that there will come a time where they can't act for themselves, be that because they are no longer able to think straight, or verbally communicate, or that they are moribund in a bed, unable to wake up to do stuff.*

Several brain tumour specialists I interviewed in 2012/13 told me that community palliative care teams had only recently started taking referrals for people with a brain tumour because the disease was so unpredictable and rapid, and historically end of life care needs were under-recognised. While they described a changing landscape for palliative care in brain tumours with greater recognition of the complex needs of patients and families and structural changes like the appointment of the first palliative care consultant in the country with a specific remit in neuro-oncology, problems endured. The predicament they outlined was one of timing. Even if they made referrals to community palliative care teams for local support, these teams returned them because patients, being relatively well, were not yet eligible for specialist palliative care. “They fall through the gaps in the net,”* one nurse told me:

Some [patients] are not eligible for palliative care because they are not that bad yet, but we’ve got nothing more to offer them so they know that they’re facing disease progression at some point where they will decline. But irrespective of that, there’s never going to be any treatment for them and they fall through the net a lot—because palliative care wouldn’t pick them up.*

Another told me it was about knowing the ropes and had learned to write the forms in such a way to get patients access to the services; “And I always send them a referral and say, ‘Please call me to discuss this patient.’ And we always have a long conversation where I explain the story because it’s quite hard to write the story particularly in a referral form,”* she said.

I was also told that practices like Advance Care Planning were extremely rare in brain tumours. A major problem for clinicians was identifying the right time to engage in conversations about end of life care, something I return to later. This maps onto the results from a nationwide survey of almost 1000 people with a brain tumour published in 2016 by the Brain Tumour Charity. The charity reported that less than a third of people self-described as having a terminal diagnosis had received appropriate information about end of life care, while only one fifth had been given choices around end of life care (The Brain Tumour Charity 2016). Complicating matters, some patients who had received information said it had been provided in an insensitive way with offers of end of life care made too early.

The Warner had its own palliative care team. During fieldwork, I was concerned mainly with people soon after diagnosis, who were undergoing treatment and who, though symptomatic, were living in relative wellness. I witnessed at close hand the deaths of George and Gabriel who both died at home and Rebecca and Fay who died in a hospice, seeing them

days before. In addition, I attended care planning meetings for Karen, another patient who died very soon after diagnosis and with serious complications after treatment. Matthew, Sara and Penny also died, shortly after I left the field. I spent little time with the hospital based palliative team, though twice interviewed one team member and attended a number of meetings at which the team was present. The overall narrative I got from these interviews and which accorded with my observations was one of a service struggling for legitimacy at the margins of a treatment focused environment. Managerial structures dictate that palliative care is only involved with patients via referral and, in most cases, I was told that the service was reduced to discharge planning.

This marginality extended beyond the hospital. At an information day I attended, organised by a prominent brain tumour charity and designed to mark out the “way ahead” for people with a brain tumour, palliative care had been included in the programme, but only just. One of the nurse organisers told me she had to fight hard for it: “It goes against the charity’s message of hope—but it’s so important to patients’ journeys,”* she told me.

In an interview with a palliative care consultant, I was told that it’s “a lack of understanding”* across the board, where death and dying are figured as the “worst outcome possible.”* Reflecting on the place of palliative care in neuro-oncology early on in my fieldwork, he explained:

It’s a clash of cultures—at two levels—one to do with, as I said, the doses and the drugs but one behind that to do with what are we trying to achieve. So, a biomedical model versus a much more biopsychosocial model. And most people in medicine feel themselves to be trying to prolong life and death is the enemy. It’s almost clichéd this stuff but there’s a truth to it. Whereas if death isn’t the enemy, if it’s normal and the circumstances in which it’s normal is when it is irreversible, as a broad characterisation, then recognising when it’s irreversible is the trick. And if you are not used to thinking in those terms then you’ll never recognise that it’s irreversible—you’ll try and try and try.*

This certainly accords with my experience in the field. As I have shown throughout this dissertation and especially in chapter 4, care among people with a brain tumour is driven by a strong embrace of biotechnology and imperative to treat. Fay, for whom experimental treatments ultimately failed, continued to place her hopes in the wonder of treatment right up until she was admitted into a hospice and died eight weeks later. Matthew, continued his visits to Germany for treatment including dendritic cell therapy and sought other therapies in the UK until one month before he died, having stopped Avastin two months prior. I observed the intent to treat up until the last moments of life across those who died during fieldwork, who by and large sought ways to eke out more time.

And yet there is a paradox. While it is certainly the case that care is driven by this imperative to treat, clinicians are also aware of its futility. I was struck by repeated descriptions of “radical treatment” in conversations between clinicians, its mention in MDT meetings and occasionally in the headers of letters. “Radical” in the context of medicine, I was told, means treatment “with intent to cure.” It is opposed to “Palliative,” which orients care around a focus on symptom control and is meant to imply a more holistic approach. In the context of brain tumours, however, these terms take on different meanings. Most brain tumours, regardless of grade, are incurable. “Radical just means higher doses and longer courses of treatment,”* one oncologist told me, “Really all the patients we see are palliative.”* The difference between Radical and Palliative in this context is that radical treatments maximise the impact on the tumour and delay its progression; palliative describes a schedule that is shorter and is for patients with low performance status or who are considered to be elderly. While oncologists do not typically use the word “Radical” in communications they know patients will see, I was told that they are supposed to use the term palliative if a patient is deemed to be progressing. The use of the word radical, I was told by one nurse was further proof of “a death denying environment”* in oncology, something Mary-Jo DelVecchio Good and others have alluded to (DelVecchio Good et al. 1990; DelVecchio Good et al. 1994). The nurse told me:

The average prognosis for the majority of these patients is 14 months. The whole fact that [oncologists] will call the treatment radical treatment—and the debate I’ve had with the consultant who gives the radical treatment—I’m saying, ‘It’s not radical treatment, the vast majority of patients it’s palliative treatment, they are not going to survive this.’ But it’s termed radical treatment. And he’s saying, ‘Well because that’s our goal.’ And I’m saying, ‘But it’s the goal for, like, 5% or whatever!’ We know for the vast majority, we’re not going to cure them, so you know, I find it incredible. But actually those cancer centres are such a death denying environment. It’s amazing, because I never realised it until I worked in it, now. I always thought, because you would have conversations with clinicians who, interestingly, will have conversations with professionals about, ‘Oh the prognosis is this, and we don’t think—’ Like I say, they’re never very accurate on their prognoses, but they may have those conversations with professionals, but they won’t have those conversations with patients ... You would think of all environments, as opposed to a respiratory, or cardiac, or whatever, that an oncology centre would be more acknowledging and maybe more open about it; but they’re not.*

So strongly woven into the work of the hospital, this intent to treat is perceived as constitutive of the identities of surgeons and oncologists. I heard this from clinicians and patients alike and it was described as a core reason for clinicians’ discomfort in bringing up Advance Care Planning. As such, it is assumed that palliative care as a speciality is most appropriate to engage in conversations about planning for the future. In the 2012/13

interviews, only one person of fifteen interviewed had completed an Advance Care Plan and she had a strong pedigree in palliative care. Yet, as I described earlier, if patients are not referred, then they will not see palliative care. Out of those whom I saw die, only Karen and Fay had contact with the hospital palliative care team having been admitted as inpatients. The others told me they had no consultations and I found no record of contact in their electronic notes. Instead, these patients had by and large been referred to locally-based community palliative care teams in the immediate months before they died, with a few telling me they had had contact earlier. And even if they are referred earlier, referrals might “bounce” because patients are too well and, in any case, might not be acted on or used as a means to plan for the future; patients and families, too, invest in the hopes of treatment. Planning ahead for the end of life, as it is advocated by policy, is often deferred.

Reading policy for its focus on timely preparation and clinicians’ accounts for their descriptions of difficulties undertaking advance care planning—when timing a conversation or referral to palliative care is a critical factor in determining whether planning is done—it is clear that time is of major significance. But when is the right time? When is appropriate for palliative care to become involved? What kind of lead in is required for the adequate preparation of end of life care? When is disease irreversible? And when do patients begin to think about irreversibility? In the next section, I focus on these questions from the lived perspectives of patients and families by examining the case of Rebecca in detail. In this, I hope to chart the social constitution of disease progression.

REBECCA

I met Rebecca and her husband Sam in March 2015 when Rebecca was forty-eight. Rebecca died in April 2016 almost four years after being diagnosed in August 2012 with a glioblastoma. Although Rebecca lived well beyond the expected prognosis for glioblastoma, in other ways her life with a brain tumour was typical. Rebecca had undergone three major operations at The Warner, radiotherapy and chemotherapy in her first year after diagnosis, and received multiple interventions for her worsening eyesight and seizures. Up until she was diagnosed, she had worked at a primary school and had cared for Sam while he was dialysed for kidney failure and underwent a transplantation several years before. When we met, Rebecca was in the beginning weeks of second line PCV chemotherapy which she finished in August 2015. Here, I focus on the last months of Rebecca’s life.

Over these months, I met with her and Sam at clinic appointments, at their home, and at hospital frequently. Sam and I also messaged each other and spoke on the phone to arrange visits, check in with each other and debrief about Rebecca. A few times during these months the three of us would sit down for informal taped interviews, at other times we would just spend time together and after seeing them I wrote up our interactions in detailed field notes.

By presenting their story through raw and minimally edited excerpts of field notes, interviews and phone conversations, I stay close to events as they happened and chart several important things. I show the timescale over which tumour progression occurs and the frequency and nature of hospital contact. I mark how disease asserts itself in radical ways, what this does to capacities to act, and how the limit possibility of death dictates the terms of action through an imperative to treat. Most of all, I present the daily challenges and utter confusion which characterise progressive disease and the descent into death, when everything appears without precedent. In what follows, I refrain from an overly thematic account, using instead time as a simple ordering device and thick description to present the unfolding nature of disease and transition.

I begin seven months before Rebecca died, as she and Sam arrived for a routine scan. I have changed dates slightly to avoid revealing the identities of Rebecca and Sam and others mentioned. But I keep the intervals between events.

4 September 2015

Field notes from Rebecca's MRI scan at The Warner—Rebecca shuffles into the waiting room well wrapped in a winter coat, scarf and hat. “It’s cold,”* she says. They had to get up at 0630 to get here on time and got “bashed about”* by commuters on the underground. The three of us sit and Rebecca takes off her hat. Her black hair shines in the glare of the overhead lights. It’s messy beneath the hat and though thin it covers her head all over. She has colour in her cheeks.

Rebecca tells me that yesterday she had a kind of seizure, “I don’t know if it was definitely a seizure but a funny feeling. Sam came in and I was trying to talk to him, but I couldn’t speak. I had the words in my mouth, but I couldn’t speak.” Couldn’t speak, she repeats over and over. “We were really scared. It lasted half an hour.” They didn’t tell the doctors. Sam tells me later there would be no point: “I know what they’d say,” he says, ““Wait until you have the scan.””

When Rebecca is being scanned and Sam and I are alone, he tells me how Rebecca has been more tired than usual: “We can’t really go out because she’s so tired.” She can only do ten minutes on her exercise bike now, usually a key part of her day and an important strategy for keeping her fit after chemotherapy. “She’s really down, I’m not sure what to say to her. You can’t keep going ‘everything is going to turn out okay’ when you know it isn’t.” Rebecca is terrified about going to sleep. “A good friend of hers died in her sleep,” Sam explains, “she was diagnosed around the same time with the same tumour—and it was roughly in the same place—she went to sleep one night and never woke up. Rebecca is really afraid of that. She makes a point of always saying goodnight to the girls.”

“I don’t know how she does it,” he says, “I was looking at her the other day and I just thought to myself, ‘oh shit, how can she carry on with this?’ Not knowing what’s going to happen or when—I’d go mad. But it’s very difficult having these conversations with her—she doesn’t like to talk about it—we just carry on doing things day by day.”

I ask Sam if he wants to talk about things—about the future. “I would,” he says, “I’d like to know what is going to happen, but it’s really difficult. All we can do is what the doctors say.” I ask if moments like yesterday prompt them to talk. Not really, he says, “they remind you of it. But we don’t really talk about it. She has been under a lot of stress lately with the girls going off to university—I think it is difficult for her.” Sam says that when the girls are gone he is going to paint the house. He bought paint two years ago but hasn’t had a chance. “It’ll keep me occupied but it’s a big job and I’ll only do it if Rebecca is well enough—I don’t want to turn the place upside down when she’s not feeling good.”

17 September 2015

Field notes from clinic with Mr Fitzroy, Mr Caine and Suzie—Rebecca has come in for the scan results. It’s good news, she is told by the surgeon, Mr Fitzroy. She looks tired and not especially overwhelmed by the news: “Oh good,”* she says. She wants to see it on the computer. Mr Fitzroy turns the computer towards her and Sam and explains:

“So this is where you had your surgery,” he says, “And nothing is picking up any contrast.” He points towards a dark area—a circle on the right of the image. The boundaries are sharp, the circle black with its edges going into grey. There is no white, which would indicate enhancement and therefore cancerous tissue. Mr Fitzroy pulls up another scan, “For comparison, this is your scan last November with some tissue picking up the contrast here.” He runs his finger along the white lines around the circle. “This is when we

thought we'd give you some more treatment. And this is another scan done midway through your treatment in March." This time he runs his finger along a thinner white line around the tumour. "And here is now." He pulls up the latest scan again with a kind of "Ta-da." It seems convincing evidence that the tumour has been contained.

Rebecca says she's pleased but sort of surprised because of the headaches she has been having. "Well there's no sign of anything untoward," Mr Fitzroy says, "I'm afraid headaches come and go and there's often very little explanation for them. But there's nothing untoward on the scan." Rebecca tells him about having a seizure, "although Sam says we shouldn't use that word—it's kind of a seizure maybe. I had one in July and August." Prompted to describe it, she explains that her right hand goes numb and she can't speak, that it lasts for about half an hour. She is worried because it happened recently twice in a row. Her GP thinks it could be migraine. After a brief discussion about seizure medication, Mr Fitzroy suggests referring her to the neurologist. Sam turns to talking about the scan, has it shrunk or is it just not visible? "It's not visible on the scan," Mr Fitzroy says, "that doesn't mean that it's not there but it's not on the scan."* Sam says they've been erring on the negative side because of "all the symptoms." When he says Rebecca's energy is flatlining, Suze, the nurse, says she thinks it could be all the treatment: "it has just knocked you for six—it's still early on after the treatment." Sam says they did manage a brief holiday though to Bournemouth. Mr Fitzroy says that's good: "take more!" They schedule the next scan for six months.

Outside in the corridor, Sam is jubilant—he'll celebrate tonight with a beer. Rebecca is more reserved. She smiles but her reaction seems mixed. "It's strange," she says, "when I feel like this and with the headaches. It's good. But I am so tired."* Sam jokes he'll give me a paintbrush the next time I see them—he wants to start decorating.

13 October 2015

Interview with Rebecca and Sam at home—A month after getting Rebecca's results I meet with her and Sam at their home for an interview. Rebecca is still tired and keeps losing track of her thoughts. Listening back to the interview I hear how much of an effort speaking is. Even so, we talk for more than two hours straight.

When I ask about the consultation in September Rebecca tells me about the letter they got from the doctors the week after. She fishes it out from a filing cabinet where she

keeps important things from the hospital and hands it to me. She was hoping for something more effusive: “it just says she had good response and that’s it.”*

“There isn’t much more they could add to that,” Sam says, “You could flower it up as much as you like but the core of it is that the scan shows that the tumour isn’t there, that’s all they could say.”* Overall, she and Sam have mixed feelings about the scan but Rebecca is more circumspect, “I’m not convinced at all—I refuse to believe it.” Sam thinks it’s almost like Rebecca wanted them to find something: “I’ve spent every day telling her, ‘It’s really good news—it’s positive news—we’re going in the right direction!’”* But Rebecca counters:

It can spread very quickly. That’s why I’m always conscious about it, why I get worried about things. Last time I was well after six months and then suddenly I’m not. Can you imagine that? Imagine that time span: it’s very short. That’s why sometimes I get worried or get scared. Like today, I wasn’t feeling well in the morning and I said to Sam, “it seems like I’m going to have another seizure.”*

Whatever happens Rebecca says she’ll fight:

If they say, “Your tumour’s come back,” I will tolerate it. I know it’s difficult to get rid of it. But if I have to do another chemo it’s fine because I know I’ll be fine. I’ll carry on fighting ... I’m quite positive in that way. And I’m trying to be fit and to do things—sometimes I do get problems with my brain—like it just decided to say, “You can’t walk today.” But then I will crawl up the stairs and I will still go up and down the stairs, things like that because otherwise you just sit down there and you waste yourself.*

Sam is encouraging Rebecca to get out more before the Autumn sets in and is planning another trip. He hasn’t started decorating yet. Rebecca is planning a 10km run with her friend for the Brain Tumour Charity: “My biggest aim is to do the marathon,”* she says.

18 November 2015

Telephone conversation with Sam—I was due to see Rebecca at home today but Sam has called off our interview. He tells me Rebecca had some sort of paralysis: “Yesterday she wanted to go upstairs to lie down and on her way up she fell and banged her head.”* Sam called the ambulance and Rebecca was taken to Whitefield (the local hospital)—they got back home late last night. He is waiting to hear from The Warner now but the doctors at Whitefield can see that she has got some oedema on her brain. He tells me Rebecca had the option of

staying in the hospital but she didn't want to, so he brought her home—he can always take her in if they need to see her. “It's a bit grim at the moment,” he says, “but we'll survive.”*

24 November 2015

Telephone conversation with Sam—Sam says things are still not good. He says the doctors at The Warner still think it's migraine and have given Rebecca a different migraine medication—propranolol. They've also increased her anti-seizure medication. Sam had to go to The Warner to collect the new drugs on Friday and Rebecca started taking them that day. But the following morning she had another attack and another on Monday: “They seem to be getting less severe but more frequent,” Sam says, “but it's still worrying.”* Rebecca has now lost movement in her right hand. She is exhausted.

Sam is struggling to make sense of things. “I don't know what to do,”* he says, “I don't think the doctors know what to do. I thought they'd want to see her so they could see how severe it is. But they seem reluctant to see her.”* Apparently the CT scan she had at Whitefield looked alright.

He says I should come and see Rebecca but I say I don't want to impose if it's a difficult time. “We've spoken about it,” he says, “We think it's a good idea you come so you can see what she's like—what's been going on.”*

25 November 2015

Interview with Rebecca and Sam at home—Sam answers the door and immediately starts telling me what is going on—he just got off the phone to Suze, the nurse. He says it is difficult since being back from Whitefield, “In hindsight we should have stayed in.”* He takes me to Rebecca in the sitting room. She is slouched in a large comfy chair, covered in blankets and wears a grey woolly hat. The heating is on full, Sam tells me. I sit with Sam on the sofa opposite Rebecca.

Rebecca tells me she had another attack last night, milder than before. Several times she tells me she is ready to give up and speaks more slowly than ever it seems. She is tired. Sam fills in more than usual though she sometimes corrects him and I get the sense that they disagree on some details—who they talk to, what they said, when they said it. They agree on “feeling lost”* and waiting for answers. The clinicians at The Warner, Whitefield and

Rebecca's GP are coordinating things, but it is uncertain who is taking the lead at The Warner, whether Mr Fitzroy, the surgeon, or Dr Bond, the neurologist:

Sam: When the chain is broken, when someone is away, then it's a problem to get an answer. But I really don't know, even to this day, what the solution is. Suze thinks maybe we should have an MRI scan and I think an MRI scan might give a clue as to what's going on in there—at least it will eliminate certain things. I know it's quite expensive and we have to get up there and everything else. But for me I don't care how much it costs, I'll go down there and do it. And then actually it would be good if they saw her—her state—from what she was before to what she is now. You know just to see her walk, talk, watch her hold something—even to hold something she has to concentrate on how to do it. Her dates have gone wrong and now even her spelling—it wasn't like this a month ago.

Rebecca: No—I've had more of these issues haven't I—

Sam: Yeah—with each attack it seems to have—she loses a little bit more, the edge goes. For her it's very frustrating. She just about managed to shower this morning and I helped her put cream on and get dressed—

Rebecca: This morning was bad—it's horrible—I don't know—I try to sleep—I can't do much (she laughs). Yesterday was okay—I was able to do my puzzle. But the last few days I wasn't able to do anything ... last night—I don't know what time it was—you were awake, no you were sleeping—and something wasn't right. And then my hand starts jerking—and I can't do anything. And I said to myself, 'you know what f-f-f-f-forget about it—go back to sleep.' Because there's nothing I can do. I should have w-w-w-woke woke you up but I didn't. I couldn't move a lot, especially on this side. I was so tired. And I am hoping that everything is okay—because sometimes you don't know.*

Not knowing is difficult. Sam now keeps a diary, day-by-day to keep track of things. Between them, they have devised a scale to rate the severity of attacks one to ten. But no one, including the doctors, knows what the attacks are and Rebecca and Sam are struggling in this void. Sam says that, "If they could find out, actually pinpoint what it is and say, for example, this is definitely migraine problems it would help massively."* He says there are other possibilities too:

It could be a TIA—a stroke—I mentioned that to Suze. Because the ambulance guys that just came along said it looks like a TIA. I read it up just now actually. And it just mimicked those same symptoms. But when we spoke to Dr Bond he said that the way a seizure looks and the way a migraine looks, that the seizures will have what's called a positive—you'll do something like flicking your arms out or you'll tremble or you'll do something outward. But with a migraine it's a negative impact on the body. So, you lose feeling in your arm and legs and so on. But when you look on the NHS sites about migraines it tells you about the ones that Rebecca has had. And it says that it looks like a stroke. So it's very close and I don't know if there's any way of differentiating post-attack—like if they could put electrodes on your head and say, "you've had a stroke."*

It is especially hard given the profound dissonance between how Rebecca is now and the scan results in September.

Sam: When we had the news about the scan that everything was looking good—

Rebecca: I never said that—

Sam: And then from that day it actually seems to just go downwards—

Rebecca: I never thought “this is good.” Because I never believed it. Because—I don’t know—

Sam: She’s very sceptical—

Rebecca: Because it can’t be. Because the tumour is so—it’s so difficult. How can the tumour have gone away? That’s why they never say anything about the tumour.

Sam: The only thing they said was it’s not visible on the scan. And she was unconvinced by that—because leading up to that she’d had seizures and we were expecting a bad scan—you know that the tumour has grown. But to say that it’s a clear scan, well, I was shocked, absolutely shocked. And then I suppose the reasoning was go and see the neurologist, which we did on November 3rd. We’re waiting for his letter and his conclusion. The jury is still out on this—what is it? What can it be? Is it stroke? Or migraine? But why isn’t she recovering from the attacks? She still got this speech difficulty and numbness down her right side. It follows that same pattern every time ... We’ll have to see—I told Suze this—I spoke to her for about three minutes and she thinks get another scan. But that was overruled by the doctors I think. They seem to think just change the medication and see how that goes.*

Sam wants to get in touch with the local Macmillan team (with whom they have been in contact every three months since diagnosis) and start thinking about getting a stairlift and chair for the shower. But they are also reluctant to get more people involved, “unless it’s absolutely necessary.”* As ever, they are aware of an overstretched NHS and other people in need.

We speak for almost two hours and though I’m conscious that Rebecca might be tiring or restless, she wants to talk. At one point during the interview she stands very slowly to walk across to the window and back and Sam stands close by in case she falls. It is a distance of about seven metres but it takes minutes for her to shuffle a few inches at a time, her feet barely lifted. She rests for a little while on the arm of the sofa before returning to the chair. As we talk she changes position a few times, making her torso higher up the back of the chair before it slumps back down. She moves her feet out from under the blanket that covers them and then back under. They look tight and reddish brown; darker than the rest of her.

When I leave, Rebecca insists on standing to say goodbye.

7 December 2015

MRI scan at The Warner—Urgent MRI requested by Suze on 30 November is done. I’m not there.

10 December 2015

Field notes from clinic with Mr Fitzroy, Dr Anton and Suze—Today there is resolution to the past weeks' uncertainty of Rebecca's condition with news of tumour progression. Rebecca consents to a third course of chemotherapy, this time it is temozolomide. Her condition is worse than when I last saw her at home two weeks ago; she arrived to clinic in a wheelchair having taken hospital transport and wrapped head to toe in winter clothes, all black with her shoelaces a flash of neon pink. "Four weeks ago we took the tube," Sam says as we wait for the consultation, "It just shows you how quick. And whatever degree of independence she has is rapidly eroding."*

Rebecca moves her hands strangely as if caressing something in front of her and then she purposefully grabs the air, all the while watching intently as if it is no longer her hand. Her head nods in jerks, stays still for a moment and then jerks again. As if a puppet, she moves like this. At one point, Sam tenderly takes her hand in his and rests them together on the arm of his chair. His feet touch her feet as he angles himself towards her as if in embrace. He sometimes reaches across Rebecca to rearrange her hat and tuck her hair around her ear. Rebecca stays there motionless while he does this and Sam speaks in an unbroken flow. He tells me that Macmillan have been very good and an occupational therapist has been to the house: "We now have handrails around the house and we're mainly upstairs."* Rebecca sometimes interjects to corroborate or correct details. Suze soon arrives to escort us to the clinic room.

It is not long before Mr Fitzroy tells Rebecca and Sam about the progression: "Unfortunately, it's what we thought"*—there is space around the words, clear and unambiguous—"And I am afraid that more surgery isn't a good option."* Rebecca stares blankly for a moment, her eyes beginning to wet. Sam takes her hand and he too has wet eyes which he wipes dry. Dr Anton says there are two types of chemotherapy—"the temozolomide that you had before or the carboplatin which is intravenous."* "Her veins are shot to pieces,"* Sam says. The team agree and Dr Anton suggests temozolomide, taken orally.

Suze asks how things are at home and Sam updates: "She can't enjoy life anymore."* He asks if the tumour has spread through the brain or only in the same place. Mr Fitzroy says it's both. Sam asks if treatment would allow Rebecca to get stuff back and is told it depends how she responds. Rebecca says she could try more chemo. "How ... how ... how long is tumour for me to survive ... if didn't take ... med ... me ..." She stammers.

“Without treatment?”* Sam asks. She nods. The bluntness of her question is emphasised in how it is haphazardly constructed. “We never know,” Mr Fitzroy says slowly, “but given it changed a lot over three months—you might find you are sleeping an awful lot more as the tumour starts to take effect. And maybe this would start to happen over a similar time.” Okay, Rebecca says. It still seems fairly open or covered somehow, but Rebecca does not probe and nor does Sam. She signs the consent form which Dr Anton has been preparing and Suze then leads us out into the waiting room.

For several minutes after the consultation, no one says anything. Sam makes another appointment at reception and then Rebecca turns to me: “I’ve reached the end of my run.”* I ask her what she means. “Now it’s time to go,” she replies, “I will do the treatment—maybe it will give me another year.”*

The three of us go to get Rebecca’s bloods done. She says she will start to think of the things she wants to do. She wants to go to New York—she has never been—“And I want to go home to Malaysia to see my family. I want to see my mother.” Rebecca has not been for years and her mother has never visited.

After blood tests, we sit and wait for the transport ambulance to take Rebecca and Sam home. They try to make sense of the news. “It’s a game changer,”* Sam keeps repeating. They talk about how to tell their daughters and who to tell after, before Sam goes to collect more steroids from the pharmacy. Rebecca and I continue talking. She moves between the sadness, the surprise—“they thought it was migraine!”*—the rapidity—“three months!”*—and the absence of cure—“there’s nothing!”* She tells me about plans small and large—“Maybe I will have a drink—I haven’t drunk for four years.”* Once she says, “If I go cuckoo, let me know.”* But her resolve to treat is solid: “I will try the treatment. If that’s what they say. What is the point in not? I think I have been lucky—I was told this tumour only lasts one year.”*

Sam returns from the pharmacy and as the transport arrives we are joined by the mother and daughter who came with them in the transport ambulance. They ask how it went: “Not good,”* Rebecca says. “The tumour has come back,”* Sam elaborates starkly, “She can have chemotherapy but it only buys time. That’s the thing with this—you can only ever buy time. Eventually it will catch up with you. You can’t outrun it.”*

Field notes from first chemo clinic with Dr Anton and Suze—It's Rebecca's first chemo appointment since the bad news last week. It runs 30 minutes, longer than usual, and there is a lengthy discussion about the benefits of chemo. Sam takes the lead by saying they have spoken a lot about it the past week: "We know there's not much time no matter—the big thing is whether the chemo would help with Rebecca's symptoms."* Dr Anton and Suze listen patiently while Sam explains that Rebecca is "progressively getting weaker and weaker, even since last week."*

Rebecca listens too, nodding her head as before, then she says: "For me, it's to see through my daughters."*

She stops and Dr Anton asks if she is worried about the side effects "knocking her."* Sam fills in, saying their daughters are back for two weeks: "Her ultimate goal is to see them through their first year of uni, which is until June."* Rebecca says she doesn't think she will make that.

"So the decision about the chemo," Dr Anton says, "That's absolutely right. We don't know if it will have a good response, or a quick response, and it has to be weighed against the possible side effects. You coped well last time and the side effects are different, but not hugely different."* She thinks Rebecca should try the chemo, "You'll always wonder if you hadn't. I've known you a long time and think that's probably what you're feeling."*

"I'm up for it,"* Rebecca says.

"You can try one lot," Dr Anton says, "just one—and if you tolerate that, then go on."* She tells Rebecca that her weakness is in her a physical condition, but in yourself you're a very strong person: "It's not often I try and push someone with chemo."* I catch a smile on Rebecca's face. Sam agrees and says in a chipper way, "A little bit of a plan, eh? She's a very stubborn person—one last try—to satisfy what she feels."*

The last minutes of the consultation is directed by Suze who asks about palliative care and "making the home safe."* Suze has been in touch with Macmillan and Rebecca and Sam will meet her to talk about options and what happens in the home: "The stairs are going to become a problem. We've thought about going down one level. The other option is coming down to the bottom—we've got a sofa bed—and a hospital bed when that kicks in."* Suze asks about medication too. Sam tells her types and doses of steroids, antiseizure and the propranolol, which Dr Anton remarks is a high dose and Suze notes was prescribed "when it was thought migrainous."* Sam repeats, "That was when everything was based

around migraines, when it wasn't."* They drop the dose and Rebecca and Sam leave clutching a prescription for the first dose of chemotherapy.

"I haven't given up hope," Rebecca tells me when Sam is handing in the prescription, "It's nice to have Dr Anton's guidance."* She says she is sympathetic and feels Dr Anton knows her. They have told one daughter, not the other—they are waiting for her to come home. Rebecca tells me about her bucket list again. She spoke to her friend about getting tickets to see a Spurs game—"I've never been."* She mentions New York again. I also say I have noticed how she sometimes holds her hand in front of her face and ask her why she does this. She says it's because she cannot really feel it—"it feels so strange."*

23 December 2015

Interview with Rebecca and Sam at home—Rebecca and Sam have started talking about the future and making plans. The uncertainty is different now. They have an explanation for the attacks and Rebecca's progressive weakness, and a plan for what to do. Sam says:

It was a relief to know what it is because of the uncertainty. This migraine thing was coming on and on all the time and you know we were trying to work out, well it can't, there must be a way of treating this. We couldn't figure out why she'd been taking all this medication and it's just not working, she's still getting ill. And then when we had the final, that scan and it showed the tumour was back, then you think "oh yeah, well that's the reason why, it's nothing to do with the migraine." So yes it was a relief to know what it was.*

But whether the plan will work and what will happen remains unknown. Rebecca has told their friends to come and see her now, "because I don't know what will happen tomorrow or the next day."* She moves between this and saying, "This is it."* Some of friends really get it—"they are fellow cancer sufferers"*—others don't and are busy so Rebecca hasn't told them yet. Their daughters both know now.

Seeing Dr Anton and Suze last week has reinforced their commitment to treatment, Sam Says, "It's something for Rebecca to cling onto."* Rebecca agrees but says she sometimes sways:

Sometimes I think I want more, I want another day, I want to see the girls at least go through the first year of uni and I haven't had my bucket list (laughs)—there's a lot of things that I want to do. So in one way I'm quite determined to go through another half a year of chemo. And there are days that you say, "Sod it! I don't want to—I've had enough." But then there are some days and I'm thinking, "Oh shit—I haven't finished [living] yet!" So then I'm more determined to get on with it. So every day I wake up, "yeah I'm fine, I'm good" even though if I have to sit

near the window just listen to music. I listen to music a lot because there's a lot of things I can't do anymore so it's quite nice actually and then I watch a bit of TV and things like that—that's my day. So it's okay ... The thing with this tumour is: I don't know what's going on. It's like every day I wake up, "Right I'm still here". And then it might not be the following day ... I want to be still around for a little bit longer and I keep telling myself I'll be fine. I want to stay a bit longer and hoping that the chemo works. So it's difficult. Every day I wake up and think, "Yep I'm still here, I want to do things." I still want to do things.*

Rebecca and Sam are planning a holiday but will wait until mid-January to see how the chemo affects Rebecca. Sam also tells me they have arranged a meeting with the bank to talk finances and with Gabriella, a Macmillan coordinator, to talk palliative care and things like Power of Attorney, funerals, organ donation. "Unsavoury things,"* he calls them.

15 January 2016

Field notes from second chemo clinic with Dr Anton and Suze—Rebecca looks so much better today. Her face is full and round due to the higher dose steroids but she has more of a glow and her speech is better. Sam tells Dr Anton and Suze that Rebecca is able to get around more using her walker. They've turned the heating off, which is better for Rebecca: "We've found that temperature really affects her,"* Sam says. They have "more things to think about"* after speaking with Gabriella. The occupational therapist has helped position things strategically in the home for Rebecca to grab on to. Rebecca says she has been spending more time with her daughters. She asks to see the scan from 7 December; they didn't see it before.

For the first time, Sam asks about trials: "Experimental drugs—I'm sure you've already thought about it."* Dr Anton says they have and smiles. Sam takes the cue and asks why they cannot operate. This time Dr Anton responds more fully and explains that they hope to reverse the disease with chemo, which the surgery wouldn't really do in Rebecca's case. She says they can operate but the risks are quite high and might make things worse. "We always think that removing a tumour is a good thing, but it's not always," she explains, "Because of the infiltration you only really remove part of the tumour. And often it grows back to fill the space, unless it's an anticancer treatment and this is the advantage with chemo. And it looks like it's working."*

Rebecca is certainly more upbeat than three weeks ago.

12 February 2016

Field notes from third chemo clinic with Dr Anton and Suzie—Rebecca has improved again, her speech is more fluid and she is much more animated: “I have been doing my puzzles, and reading and doing some writing,”* she says. Sam agrees: “And she can watch the TV and follow what’s going on.”* She has been writing “for my girls;”* for when they are older—things she might not be able to tell them later. Sam says she is much more independent, having physio three times a week and reclaiming some of the things she lost. Dr Anton is visibly moved and extremely positive. She says how they were worried about her and about trying the treatment, “But it seems to have been the right decision.”* They will do a scan between now and the next appointment, “To see what’s really going on.”* Sam is looking forward to it, he says.

27 February 2016

Telephone conversation with Sam: I can immediately tell something’s up: Sam’s voice is flat. “Rebecca is in the local hospital,” he says, “I’m just on the bus going there now.”* He tells me she was having more and more seizures so he called 999 on Monday; they wanted to get her into Whitefield. They’ve boosted her steroids now and they are in touch with The Warner trying to work out what to do. The choices are either to send her to The Warner or keep her at Whitefield with input from The Warner doctors. “We’re kind of in a difficult situation and she’s losing a bit of herself after every seizure,”* he tells me. He asks if I’d like to come and see her: “It might be good for you to see—she’ll probably be here until at least Wednesday. Next week they’re making a plan. It’s basically down to the neurologist and what he wants to do—that’s where it all hinges.”* He explains that if it is simply a case of changing the drugs and discharging her, then he will take Rebecca home and Macmillan “will kick in their processes.”* Sam asks me to call on Monday, “Right now we don’t know what’s going on—we’ll have more of an idea then.”*

29 February 2016

Telephone conversation with Sam: “Things are not good at the moment,” Sam tells me, “You almost can’t have a conversation with her now. She’s too tired and bed bound.”* He says if I came that, “We’ll be talking about her rather than with her.”* But again he thinks I should come: “It will be good for you to see her.”* The team at Whitefield are trying to get her into

another ward—“actually it’s a Macmillan room. I need to get in touch with Suze to see if we can get her over to The Warner too—they haven’t seen her—they’ve just increased her medication.”* He says he is coordinating with the doctors here at Whitefield and at The Warner to make decisions. He tells me to come for half hour not to tire out Rebecca: “It will be nice to see you.”*

1 March 2016

Field notes from Whitefield Hospital—The ward is huge and open, high ceilings with maybe fourteen beds and large windows between them—I don’t count. Several of the beds are hidden by curtains. Rebecca is lying at the far end of the ward and I hear my steps on the wooden floor like the slow ticking of a clock as I approach her. Sam stands to shake my hand: “It’s the first day she’s started to pick up,”* he says. Rebecca turns her face towards me, her skin shiny and taut like a balloon because of the steroids. Her legs, bent over to her left, and her feet protruding out of the blue covers are swollen also. Her arms are pale and dry; she looks tired. I ask how she’s been? “I don’t know,” she says, “I don’t know what happened.*”

Sam fills me in. She was admitted eight days ago. The Warner are directing things; he was just on the phone to Suze. He says that he is waiting for Rebecca to get well enough so that she can go home, “But at the moment she can’t even sit up.”* He says he has been in touch with Macmillan downstairs, “They’ve got a place a bit like a hospice and it’s just across the road. It’s called the Mary Centre.”* It’s easy for him to get to and they do 24 hour care, “Which is more than I can do at home—I need to sleep at some point and I don’t know anyone who can give me a night off.” He thinks it is good if Rebecca could go there while he sorts things out at home. Suze told him to make sure that a care package is properly in place before she is discharged—he is hoping to get carers coming in four times a day. His phone goes and he excuses himself to answer.

I ask Rebecca how the food is. She turns up her nose and shakes her head. I look over at the tray suspended above the bed to her left. It has crisps and Fanta and a tub of jellybeans. I say to her, at least you have your jellybeans (a favourite of Rebecca’s). “Yeah—but he didn’t bring enough,”* she says slightly crossly. I can hear Sam on the phone arranging visits, coordinating his daughters and friends of theirs. I hear things like, “The girls will only be here an hour—that’ll be enough for them” and “You guys come in an hour or so.”* When Sam is off the phone he explains that their friends from Sweden just flew in.

They are staying until Friday, “On Sunday I didn’t know what was happening, so I called everyone and said, ‘you better come and see her.’ So my mum came and my sister and I called the girls back from uni.”*

Rebecca looks off into the distance. I ask her if she is a bit fed up being here. She pushes her lips together and nods a little. It gets noisy, Sam says, but the staff are great.

1 April 2016

Telephone conversation with Sam—Rebecca is now in the Mary Centre—they found a bed. She has been there a week. She is still awake but things are “not brilliant.”* “She had quite a big seizure on Friday,” Sam explains, “It took a lot to get her out of it but we finally did. Every seizure leaves its mark on her but we’re cracking on. We’re trying to get her to Coombs House (a local care home) but they’re quibbling over costs now. She’s been accepted but the commissioning group says one thing and Coombs House another. The doctors here say don’t rush and we’re going to see over the weekend.”*

5 April 2016

Telephone conversation with Sam—Rebecca is still at the Mary Centre. Sam explains: “Well I think they’ve decided on a way to go. They’ve decided to stop the steroids completely—8mg to zero—and I think it’s going to be quite catastrophic. We’ll see—it’s all been done in consultation with Rebecca.”* I ask, why now? “Well—she’s not getting better. She’s slowly losing everything and even her dignity. She’s not in a good place so this will speed things up to put it bluntly. She can think and talk but she can’t communicate that well. She’s basically locked in—that’s the only way I can put it. She can say, ‘Okay, I’m okay,’ but that’s about it. I spoke to Suze but I think I misled her. I said they were going to drop the steroids by just 2mg and taking it down slowly. I wasn’t aware they were going to drop it so fast—I think it will take her into a kind of—” He does not finish this sentence, and then: “Her body won’t have enough time to build up its own steroids and I think it’s about preparing Rebecca for the outcome. It’s in a way trying to control things. I went to the funeral director.” He pauses again and says it is weird to talk so bluntly. Another pause. He tells me their daughters are home and they are bringing Rebecca food. “It’s just so sudden—there’s no pain and they’re prepared for any pain that would come—they’ve got mechanisms for that.

And she knows what's going on.”* He says I should come as soon as possible: “We don't know how long now.”*

6 April 2016

Field notes from The Mary Centre—I arrive soaked through after cycling in the rain; I feel a mess and I make the best I can. But soon I feel how irrelevant all that is. Sam is at reception looking under slept, his near black eyes glistening in the harsh florescence of the light above him. He wants to update me before we go and see Rebecca. We walk past an open door and I see Rebecca lying on a bed facing the door, her eyes closed. We walk straight past without Sam mentioning she is there and turn into another room, light and open, with three large low slung sofas and two book cases. There are large windows running parallel along opposite walls: one set looks onto the corridor, the other overlooks the road outside and onto the red brick of the main Whitefield hospital. There are books in the bookcase—thrillers like *The Da Vinci Code*—a fireplace with no fire; a mantel piece with a mirror; flowers; Thank You cards to the centre. A kitchen signed “For Visitors” to make tea and heat food in a microwave and stacks of chairs in the corner. On the pale walls there are photographs of flower details and ponds, the kinds of things that are supposed to still the mind. “I've spent a lot of time in here,” Sam says, “I only really go home to eat and sleep. It begins to feel a bit like home—I sometimes eat here.”*

“The situation is this,” he says, “they've dropped Rebecca's steroids right down in one go—from 8 to zero—I didn't know they were going to do that at first. I thought they were going to do it gradually but it's down to zero. And it seems to be having an effect already—yesterday I was talking to her and today she won't wake up. Actually, she was awake a little in the morning; she ate a banana—part of it—but now I can't wake her. They think she's having trouble swallowing. So this is it really—this is how it is. You can never really prepare yourself for it—but this is it. She was aware of what it would do. It was just so frustrating for her. She was basically locked in. Watching her struggle to say something—exhausting herself—she was just so tired. And she was so frustrated with me for not getting it—last night she told me off—she mustered all she had so that she could tell me off.”

He tells me how he usually brushes her teeth in the evenings, “She likes to have clean teeth before going to bed.”* But he'd forgotten and she was trying to tell him; that's when she managed to tell him off. It is one of the last things she said to him and now Sam says he doesn't know if she will wake up again. Perhaps it is why he now uses the past tense to

speaking about Rebecca. He tells me about their relationship, about her determination and the difficulties with her family in Malaysia, until we are interrupted by a phone call from the care home where Rebecca might have gone.

He tells the person on the phone that Rebecca would have loved to have died at home, but that the care they sent was not adequate, that they didn't have the experience: "My wife is a very complex case—they didn't know how to deal with her—and they couldn't have used the medications she needs."* He tells the person on the phone that things have suddenly changed: "My wife is very seriously ill now. This is why I was saying this has to be done fast."* He says the best thing to do is for the care home to get in touch with the doctors here so that the doctors can update them. When he is off the phone he says it has been hard and frustrating sorting this out.

The care home is very nice and close to the house, but they were quibbling over costs: "Usually it's £1,250 a week, they were trying to negotiate £850." He says she wanted to die at home. He says they wanted to get Marie Curie nurses or Macmillan nurses at home. He is not really in touch with The Warner now: "I think they are more focused on treatment,"* he says. He calls only to update them.

There is a lament in Sam's words and a bitter sadness that things have come to this. He shares fond memories of Rebecca and some tinged with regret: "You can never prepare yourself for this,"* he says again.

When I see Rebecca, she is asleep. I tell Sam not to wake her. "She knew you were coming," he says, "I asked her and she said it was fine."* I stand by Rebecca's head, facing her. "Henry's here," Sam says. She doesn't register but sleeps silently. "Henry's come to see you," Sam says again. He stands at her feet, leaning against the wall. The room is small and the distance between the toe of the bed and wall is just enough for a person to pass through comfortably. We stand in silence looking at her small movements as she breathes. The cover is pulled up to her shoulder; the white dotted gown up to her neck; her head large from the steroids. I say she looks peaceful. Sam says she does: "They say she won't be in pain."*

We stand silently for maybe a minute. I feel paralysed a little, but calm. I would like to say something to Rebecca, but it feels strange. I go several times to open my mouth and speak. Eventually I tell her thanks: thank you for being so generous in allowing me to come and see you, and always being so open. Thanks for letting me in. I look at her as if for a reaction, but none comes, none that is visible. She sleeps.

15 April 2016

Rebecca died at the Mary Centre today, not yet fifty. It is just over four months since the scan signalled progression and eight weeks after her last chemotherapy appointment. It is seven months since the positive news of her scan in mid-September. It is 3 years and 258 days since Rebecca was diagnosed with a brain tumour.

DISEASE PROGRESSION AND ITS SOCIAL CORRELATES

Reading back, it is all too easy to fall into an ordered comprehension that comes “after the fact” of Rebecca’s death. We risk seeing things as inevitable and being seduced into feeling as though we know the junctures and turns she and Sam might have made in their situation. In so doing, we obscure the lived realities of patients and families. By using the contemporaneousness of field notes to carry the passage of real time, I hope to have captured some of the features of care and the stakes of decision-making as they appeared for Rebecca and Sam. My aim has been to evoke how their hopes, excitements, numbness, doubt, sadness, anxiety, determination, resignation and acquiescence commingled in their attempts to plan and how these plans rose and fell amid the institutional orders of hospitals, the economic rationality of care commissioners and private care homes, the effects of treatment and rapid surges of Rebecca’s tumour.

While Sam was calling people to come and visit Rebecca and thinking of ways to broach conversations about what he called the unsavoury details of the future, he was supporting Rebecca in relentlessly pursuing treatment and asking about experimental treatments. He framed bad news as “a game changer” yet would later look forward to the next scan confident it would show an improved state. While Rebecca was adding to her bucket list, hoping to see her daughters through their first year of university, and planning for a marathon, she would also say that she would not live to complete her treatment. She was ready to give up as she was ready to fight. Plans like redecorating the house were put on hold or set in action amid the oscillations between doubt and resolution, the enduring possibilities to prolong life through treatment, new symptoms, and the imminence but unknowability of death. At stake, all the while, were the interpretive shifts in how Rebecca and Sam regarded time and time-remaining: the strange condition of “living in prognosis” and being severed from the ordinary markers of life-course (Jain 2013:103).

I find Tim Ingold’s insights into how we inhabit and navigate the world especially generative for thinking about the movements of Rebecca and Sam, Gabriel and Cecilia,

George and Phoebe, Fay, Maria and their sisters, and the other people I met, through fields of disease, care and treatment, when things are continually in flux.³² Considering the relations between movement, knowledge and description, in social life and experience, Ingold imagines the figure of the wayfarer³³—he or she who is continually on the move and who must “sustain himself [or herself], both perceptually and materially, through an active engagement with the country that opens up along his [or her] path” (Ingold 2007:76). It is in the course of the movements through his or her environment that the wayfarer comes to know it; a knowledge forged in the passages from place to place, point to point, and the continually changing horizons along the way (Ingold 2000; Ingold 2007; Ingold 2015). Conceived as such, Ingold suggests that the practices of wayfaring most faithfully represent how we inhabit and come to know the world, for it is as wayfarers that we experience “a ‘progressional ordering of reality,’ or the integration of knowledge along a path of travel” (Ingold 2007:88).

Just as with the wayfarer, the experience of navigating or negotiating terrains of disease and care happens *along the way*. Although there are broad schemas to understand disease course or treatment in pathways, as Ingold insightfully states, these kinds of representation are somehow illusory. The illusion is that the terrain or surface of the world is fixed ahead of the journey being made, which simply is not the case. As Ingold explains:

This distinction between trail-following or wayfaring and pre-planned navigation is of critical significance. In brief, the navigator has before him [or her] a complete representation of the territory, in the form of a cartographic map, upon which he [or she] can plot a course even before setting out. The journey is then no more than an explication of the plot. In wayfaring, by contrast, one follows a path that one has previously travelled in the company of others, or in their footsteps, reconstructing the itinerary as one goes along. Only upon reaching his [or her] destination, in this case, can the traveller truly be said to have found his [or her] way (Ingold 2007:15-16).

Tumour progression, then, is just that—a *progression*. And while it is apprehended by clinicians as a point on a pathway, it is lived *along the way* of a journey. Rebecca’s tumour progression unfolded through a *progressional ordering* of new moments, missed opportunities, positive characterisations of growth, spread, transformation and infiltration given through

³² I am indebted to Henrik Vigh’s work on social navigation and his reading of Tim Ingold and also to Ruth Pinder and colleagues for their deployment of Ingold in critique of care pathways. However, I have so to speak, gone back to the source and read Ingold’s more recent work which was unpublished at the time of Vigh and Pinder’s excellent work.

³³ Wayfaring, for Ingold, is the most fundamental mode in which we inhabit the world, and the wayfarer is one who “participates from within in the very process of the world’s continual coming into being” (2007:81). While Ingold begins his theoretical overture with the notion of wayfinding (2000), he shifts to that of wayfaring (2007; 2015). I refer throughout with this more recent formulation of wayfaring.

the interpretations of scans, tissue, and interpellations of symptoms. It emerged in the misattributions of symptoms to alternate diagnoses, in the decisions she and Sam made not to call the doctors, in decisions to scan or not scan, and in the other myriad ways in which she and Sam, alongside the clinical team valued and interpreted information. It was not simply a proliferation of cells and the build-up of pressure in her brain.

If we see tumour progression in this way—as unfolding and socially contingent, mutable and disclosed through a progressional ordering of reality—we more faithfully represent how it is *lived*. It is not simply a readily knowable point on the pathway or some other schema, discernible (after the fact) in the identifications of growth or transformation. From here, we are better able to understand how difficult it is to determine the moment when disease is said to have progressed in a way that is *irreversible* and as such, the acute moral ambiguity that accompanies timely planning. Holding in mind this temporal pattern and gradual disclosure, I now consider the last moments of Gabriel and others in finer detail, focusing on the struggles to establish and care with moral certainty.

INTIMACIES

As I outlined earlier in this chapter, discourses of end of life care policy are set around timely planning, providing the best experience possible, and work under a narrative of “every moment counts.” However, as my ethnography reveals, the reality for many patients can be very different. Ambiguity is a stubborn feeling that endures even after disease is recognised as irreversible and care practices shift fully into being palliative. The cases of Gabriel and Cecilia, George and Phoebe, Fay and her sisters are strongly testament to this. In my conversations with Cecilia and Phoebe, the nagging moral uncertainty in how to care appeared full force, brought into relief by the contradictions of institutional routine. I saw how families, struggling with a lack of established cultural script and absence of mapped time, were made to account in their negotiations around how to care well. Phoebe made this point poignantly as we sat alone in the kitchen, my audio recorder running. Closing the door to George who lay in bed so that he would not hear, she told me:

I’ve never ever wanted a timescale until we’ve got to this point. And I just think if this time isn’t going to be very long, I want to make him as comfortable as possible. But if we’re talking about still being here in twelve months or eighteen months’ time, I’d like to try and get him into a routine. Is it possible he’s going to get better? ... I would like to know what I want the carers to do, such as making sure he’s washed his chest. I like the difference between day and night, so he’s got a t-shirt on in the day and he’s got the pyjamas on at night. So you can tell those differences and

what have you—give it as much normality as possible. But then, am I causing him more pain and discomfort by doing that? And should I just be letting him rest whenever he wants? It's hard—it's hard because I suppose even they don't know what is the right thing to do, do they?*

While community teams might be recruited early on in patients' disease, as we saw with Rebecca and Sam, patients and families do not always forge deep practical connections with them until the last moments. Such delays are well documented and, I would argue, due largely to the nature of progression as I have described it above. The consequences of failing to establish these links are significant with choices about place of death, for example, foreclosed. But even in cases when patients and families had made early decisions around place of care and managed to set up more solid structures at the end of life, caring in the right way remained ambiguous and elusive. Given this picture and the impossibility of prediction, caring at the end was lived by a succession of precedents—when everything came anew. It is in this novelty that families struggled to know what was best.

George and Gabriel both died at home according to their wishes and they were mostly provided for in the material terms of hospital beds, clinical waste disposal, care staff and so on. Yet, for Phoebe and Cecilia, an experience that was supposed to ensure stability, familiarity, and support domestic intimacy at the end of life was constantly disrupted by logistics. Both spent hours on the phone chasing people for guidance that never came, arguing with carers about care schedules, negotiating the suddenness with which their homes became public clinical spaces and sites of work, and contending with families about the right way to care. This happened amid what was perceived as an almost ever-present possibility to prolong life. In all this, and the exhaustion as well as confusion of George and Gabriel, Phoebe and Cecilia felt pressured to “make lasting memories”* and “every moment count;”* to make time for domestic intimacy while never knowing which moments might be the last. This ambiguity and embattled politics of care in the home was powerfully evoked by Phoebe as she continued to tell me about her struggles with the care team:

I can't complain because I need them—I feel like I'm between a brick and a hard wall. I've been in touch with the care commission to see if they can help—to see if we can change around the arrangements of the care. But everybody says *they* can't make a decision. My daughter Sally wants to take a career break to look after George—she's a registered nurse. But we've been told you can't employ family. We want to switch the funds from the carers to go to Sally but they say they won't do it. It's crazy—I've heard other people do this. And it's difficult because she has a mortgage and two kids so she can't just quit work and look after him. I seem to spend my life on the phone chasing these things. I really want to sort this out soon because on Wednesday we're supposed to have the meeting about the care plan—the carers won't hoist him and I've said I want him hoisted. Yesterday was a lovely warm day and he asked

to be hoisted so that he could sit outside. Sally and I now have been trained on the hoist—but I can't do it on my own and when she isn't here I need help.

It's harder than I thought it would be—I thought it would be much more relaxed—but I'm rushing around on the phone and getting no rest. We want to be creating moments that last forever not constantly bathing George. I'm tired—I can't go out of the home. The girls are great but the grandkids are back at school. I have to rely on them. They're amazing but it's hard for them—now George is having all these seizures if anything goes wrong then they don't have the confidence—they're scared and nervous about looking after him. *Finally*, I've got Marie Curie coming around for nights, which means I can now hopefully get some sleep. Some nights he's fine but other nights he's fighting, trying to get out of the bed. It's a big thing—I feel like I'm here waiting for him to die.*

Like Cecilia's account given at the outset of this chapter and in the dissertation's introduction, Phoebe's summary of life with George tells us much about how care at the end of life becomes reconfigured in the small decisions around the body: whether or not to lift George; what it means that he should fight to get out of bed. It reveals the minutiae of care at the end of life: the shifting scales of care work and the compromises that must be made in attempts to maintain domestic intimacy. Though she and George had decided not to complete the last cycle of chemotherapy after several major seizures and a hospital readmission, Phoebe never stopped questioning the decision. She read into his small determinations to wrench himself out of bed—what others had called hallucinations—his spirit of fight:

I want to know that we have done everything possible. He didn't finish his last treatment—and you've seen him—he couldn't have any more. But I want to know if there is something out there—I don't care how much it costs or where we have to go. No one is pointing me in that direction so maybe there isn't. I don't know if I'm just clutching at straws but I need to know that I haven't missed anything. It's these night time moods—these *fighting* moods.*

...

Recent policy around end of life care operates from a premise that *how* people die is inevitably bound up with *where* they die; it prioritises patient preference for place of death (Department of Health 2008; Department of Health 2016; The Choice in End of Life Care Programme Board 2015). As part of the commitment to respect patients' preferences for "place of death," end-of-life care in the UK is often centred on supporting dying at home, which is reportedly the most common wish in numerous surveys of end of life care (National End of Life Care Intelligence Network 2012; Office for National Statistics 2016; Macmillan Cancer Support 2017). As such, the NHS directs needs assessments and the import of clinical technologies, such as hospital beds, ventilators, chairlifts, railings, medical

waste bins, as well as all of the equipment and pharmaceuticals needed to manage pain and other symptoms. Community teams comprising especially palliative care specialists and district nurses provide expert coordination of care and support families in the daily management of patients. Private carers are also available to those with the means for pay for them.

Despite these commitments and wishes, discussions around “dying at home” are conspicuously vague about what constitutes “home” and how the physical space of the home becomes transformed as clinical technologies and routines are introduced.

I learned how homes changed with the import of clinical technologies and new professionals who brought professional codes of ethics and institutional logics. They became hybrid—spaces neither wholly home nor clinic, but both; spaces which were fluid and contingent upon multiple sometimes contradictory ideas and assumptions; spaces which were open and continually constructed in negotiations. Gabriel and Cecilia, George and Phoebe attempted to negotiate and maintain a sense of authority, privacy, intimacy and warmth in their interactions with new materials and people who had entered their home.

Thinking back to my description of Gabriel and Cecilia, outlined in the introduction, consider how their home changed. The syringes, ventilator, stockpiles of medications on the chest of drawers, the clinical waste bin that sat upon the armchair. These were the material markers of illness and dying. As well as restructuring the space in a literal sense, they did so figuratively, signifying deterioration and grounding imminence with each addition. Things like the hospital bed, Gabriel and Cecilia had resisted until the point where it was no longer possible to do without. Its metal frame pressed up against the bed which Gabriel and Cecilia had slept in most of their married life. Its handrails, designed to keep Gabriel from falling out, now constituted a physical barrier to their intimacy, as much as the video monitor in the kitchen which became a technology of surveillance as well as satisfying its intended purpose to keep an eye on Gabriel. With these changes, little could be private. This lack of privacy was most concretely set when the bedroom, the most intimate of domestic spaces, became a site of work. The space shrinks to the size of the body.

New people who wore uniforms that signified their role and formality entered and helped with the daily tasks of care. They brought with them professional codes of conduct and their own ways of doing things. Consider the conversation between the district nurse and palliative nurses and how it reminded Cecilia that they have other patients to go to, that they might not have time to see Gabriel, that he was not necessarily a priority. Think of the “constant battle” at the frontline as Cecilia had struggled to manage all the teams—how she

desperately needed professional support but finds their ways of doing things out of step with her own, how she admonished one of the nurses for not remembering the medications or for forgetting to take out the clinical waste.

Yet amid this radical change and import of clinical signifiers, new meanings were being created. This happened in small, improvised acts, for example, in the appropriation of clinical technologies. When Cecilia gave Gabriel some whisky, she reached for a syringe ordinarily intended to administer medication. It was available for her and it afforded her something in a ritual of sharing: to connect, to toast, to be intimate. Even the morphine acquired a certain homeliness, set on a countertop under a cup. Finally, there was Gabriel himself: lying in bed, reduced to the small agentic acts of gripping a syringe between his teeth, hiding bottles, and pretending to be asleep. His way, perhaps, of exercising a boundary and need for privacy.

These kinds of reconfiguration and negotiation happened in a particular temporal frame—one set between the recognition that there was no further cause for treatment and Gabriel's death. In this short time Gabriel's deterioration was rapid and relentless. As such, no pattern was able to emerge, which might have constituted a kind of script or routine to lay rest to some of Cecilia's dilemmas. Each dilemma came anew or was otherwise unresolved, keeping open what Cecilia described as "the frontline."*

CONCLUSION

Patients, families and clinicians live in the peculiar state when death is imminent but unknowable; when the irreversibility of disease is moot and unbalanced by hope and the continued embrace of biotechnology; and when a pervasive avoidance of death-talk seeps into the clinic through idioms of radical treatment and structural deficiencies. While preparation for the end of life is a key tenet of end of life care policy, these stubborn and socially contingent forces often confound timely planning.

I have argued in this chapter that while disease progression is naturalised in the hospital as a biological phenomenon, its constitution is also very much social. It is disclosed to patients and clinicians through a *progressional ordering* of new moments, missed opportunities, positive characterisations of growth, spread, transformation and infiltration given through the interpretations of scans, tissue, and interpellations of symptoms. Progression also includes the misattributions of symptoms to alternate diagnoses, the decisions patients make not to call the doctors, decisions to scan or not scan, and in the

other myriad ways that patients, clinicians and others value and interpret information. It is not simply a proliferation of cells and the build-up of pressure in the brain or a readily knowable point which can be mapped on a pathway: it happens “along the way” (Ingold 2000; Ingold 2007; Ingold 2015:144). This complicates the timely planning advocated in discourses of end of life care policy.

Tim Ingold’s discussion of wayfaring provides insight into the lived experience of tumour progression. While living a timeline with an unknown and unresolved ending it is difficult to establish the certainty of “irreversibility” to confidently shift into palliative care and to make decisions about end of life when it is impossible to know when treatment is futile and death will come.

Even after a moment of disease progression is apprehended and even if decisions are made early on about such things as where to die, there is little surety. Called on to author our own scripts for dying as we do in life (Walter 2003), there is little guidance for a so-called good death. I watched, for example, how Phoebe and Cecilia struggled through multiple negotiations with care teams and their slow acquiescence to bringing in new technology or changing to sheer comfort over routine. Amid the constant chasing of care teams, their own exhaustion and the bodily declines of George and Gabriel, Phoebe and Cecilia sought intimacy. They did so through a choreography of privacy in a home which suddenly became public. Each new shift in the conditions of George and Gabriel complicated these tactical moves and came without precedent, leaving them uncertain with the moral authority and the search for moral approbation. They worked to ensure they did all they could do in what they described in the terms of a moral battleground (Kellehear 2007). And they did so with little guidance.

An approach which considers apparently biological events like disease progression to be intimately entwined with social practices more faithfully captures people’s experiences of disease and their shifts in approaches to care. As Tim Ingold tells us of wayfaring: “[P]eople do not traverse the surface of a world whose layout is fixed in advance—as represented on the cartographic map. Rather, they ‘feel their way’ through a world that is itself in motion, continually coming into being through the combined action of human and non-human agencies” (Ingold 2000:155).

...

I interviewed and spent time with sixteen people with a brain tumour and often members of their families. My relationships with many of these patients continued until they died of their disease. Of those who are still alive, I am in touch with Jamie; my relationships with the others reached a natural close when I left the field or for America.

...

Gabriel died four days after the moments I recount here. Cecilia wrote to me the day after he died:

Gabriel rode off this mortal coil at 5.30 on Tuesday evening. Please raise a glass to HIM. He was running a marathon to the last, awake and looking death in the eye with no fear. His strength and endurance were staggering, and he won. We played his beautiful music, opened the windows wide to the storm and toasted him with whisky. I am happy for his release. Friends are with me, keeping me strong.

...

George died less than four weeks after Phoebe's wonderings about treatment and George's fighting moods. The imperative to treat and its embrace through biotechnical means remained steadfast at the very end of George's life and even beyond. I stayed in touch with Phoebe and went back to see her with George's daughters several months later. They wanted to know if they had done the right things and they thought that I, having accompanied George and others through their journeys, might help them make sense of this. "We had one chance to get it right," they agreed.

...

The seizure which had caused Fay to be admitted to hospital proved catastrophic and she never returned home. Two weeks after I saw her in hospital, she was transferred directly to a hospice. The discharge was rapid—too quick, Maria told me, for her and Fay's other sisters to realise there was another hospice closer to her home; too quick for a home care package to be set up. When I saw Fay, she had nothing but praise for the hospice staff and a constant flow of visitors. She said nothing to me about home, only that Dennis, her cat, could visit her in the hospice if she wanted. I saw her three more times before she died

almost seven weeks after entering the hospice. Each time she would be lying in bed—awake or asleep—and grew progressively weaker.

The last time I saw her, she mostly slept; she was exhausted by opioids and the effects of the disease. When she woke, she could barely see, her eyes made blind by the pressure of tumour growth. But we could talk a little and we could sit silently. No longer did she talk about treatment. Her sisters, who came daily in shifts to be with her, had left for home. We were alone—she in bed and me in the large vinyl chair next to it. Many minutes went by as Fay slept—her breath sometimes deepening to a light snore; her hands moving up and down on top of her chest. Once awake and after a nurse had been in to Fay about lunch, she told me in strung-out words: “I’m just waiting—I get tired waiting around—there’s nothing I can really do. I’m just waiting for my time to pass.”

Maria left a voicemail two weeks later to tell me that Fay had died in the hospice: “Hi Henry, it’s Maria, sorry to have to tell you this in a voice message but Fay’s gone. It happened about half an hour ago. I’ll be in touch, okay? Thank you for caring about her.”

...

Sam and I met up two months after Rebecca died. He was still confused and said he felt lost. He told me the treatment was futile but it gave Rebecca hope. About the doctors, he said: “We gave ourselves completely to them—when it’s like this, you can’t second guess them.”* He told me how much Rebecca had taught him in her attitude to the tumour and treatment and “in her fight:”* “After 27 years of marriage, I found the woman I married in those three and a half years.”*

...

Karen also died during fieldwork. She died in hospice after a long stay at The Warner. Her disease was brief and her treatment complicated by allergies and problems with her liver.

...

Matthew died shortly after I left the field. He was treated with Avastin and made several trips to Germany for another course of treatment shortly before he died. Pam set up a brain tumour fund in his name. She wrote to me after I left for America:

Matthew's final days at home were very peaceful and we were with him to the very last minute. So that has been tremendous solace, as was the huge turnout, touching tributes and celebration that was his funeral. All four children and I are naturally grieving such a huge loss in our lives but living well with it as Matthew implored us to. Your words echo so much about Matthew, intelligent, wise and extremely courageous. He was very loved. I am so happy he contributed to your study as he was determined that others would have different and more favourable outcomes in the future. On that note we have set up a fund in his memory. We have already raised close to 12k for research. Once I have fully regained my energy I intend to run events to raise considerably more.

Pam and I met more recently about collaborating on a future project to trace the social consequences of innovation in brain tumours. Reflecting on how she and Matthew understood and sought places on trials, she spoke of hope and told me how hope is more than just a sentimental thing; it becomes very real. Knowing early on in Matthew's disease what they came to know about trial access and eligibility, and the various databases and patient forums, Pam said they might have "stumbled on" the personalised immunotherapy earlier. This immunotherapy they were excluded from by an earlier set of decisions they were not part of, and it was the treatment they so desperately wanted. Pam's reflections bespeak the timeliness of care and the multiple rhythms one encounters and comes to know "along the way."

...

Sara died not long after I arrived in America. She had finished chemotherapy treatment early while I was still in the field and died six months after, aged 73. Robbie told me he felt lost, apologising on the phone for not being cheerful, for crying, ever conscious of being a burden on others. As Sara had, he trusted in God. More than a year after Sara died, Robbie sent me a load of voice recordings. Messages from Sara to him and from him to Sara. Messages of love, messages of I miss you.

...

Penny, Jim, Chloe and Tony also died after fieldwork, while I was away. I had given them space after leaving the field and heard about her deaths from Suze at the hospital.

...

Jamie, Cath, John, Alice, and Amanda all survived at the time of writing, continuing their navigations of the cycles of treatment and scans, and amid the imminent possibilities of sudden bodily decline, mental absence, death and cure. And yet they continue to live and make life plans. When I last heard from Amanda, she and her husband were talking about having another child. Jamie continues his visits to Turkey. After insisting he would never have another round of chemotherapy, he did in fact acquiesce to the advice of the doctors. The day after taking his first tablet of his third course of chemotherapy, he flew to Turkey, insistent on living his life with the minimal intrusion of disease. We still are still in touch. He tells me of his new visualisations. John moved away from London for another job.

CONCLUSION: NAVIGATING BRAIN TUMOURS

Throughout this dissertation, I have considered the multiple temporalities which characterise the lives of people with a brain tumour and bear on how they attempt to cope and intervene in its course. By presenting a more or less chronological account, from diagnosis to death, I have shown how these lives are not lived along linear paths to an inevitable death, but rather peregrinations—circuitous and punctuated by sudden moments of decline and radical turns. I stood alongside these people and their families and bore witness to their struggles as they unfolded over the course of disease. I listened to their determinations, hopes, fears, doubts and disappointments as they grappled with treatment risk and benefit, weighed evidence, and contemplated the imperative to treat versus notions of a “good death.” By combining this close attention to individual lives with a more “experience-distant” analysis of policy documents and expert opinion, I have tried to situate experiences and navigations of patients and families within the broader backdrops of institutional decision-making and scientific progress.

Analytically, I have argued for a theory of navigation which considers the interactivity between three main vectors—patients’ agencies, the social and structural formations of care and treatment, and the diseased body. For this, I drew inspiration from Henrik Vigh’s social navigation and especially his metaphor of “motion within motion” (Vigh 2009). I argue that these insights offer critical means of understanding how people with a brain tumour imagine and enact trajectories for their lives under conditions of radical embodied and technical change.

...

In chapter 1, I focused primarily on the roles of professionals “behind the scenes”—for example, biomedical scientists, pathologists, radiologists—who produced diagnostic information in tissue processing and image reading—as well as those “front of house”—for example, neurologists and oncologists—who drew clinical pictures by examining symptoms and patient accounts. Their practices and knowledge produced an account of patients and placed them at the beginning of a particular path to be followed. Analytically, I described this work as *fixing the terrain*, emphasising how modern medicine attempts to fix uncertainty and instability in relatively static landscapes over which standardised pathways can be laid out and followed.

Chapter 2 continued with these actors and included a broader international scientific community who are beating a path into a purported new era of treatment—one which attempts to personalise treatment to patients’ tumours on the basis of molecular biomarkers. I showed how amid transition, patients and clinicians are caught in the crosshairs of progress, living and working with new uncertainties and placing their trust in those who appear capable of steering a new course, whether that is pathologist (for oncologist) or oncologist (for patient). The reigning logics of progress and intervention induced decisions that “more treatment is better.” And yet, the on the ground realities were far more complex, with potential for major social fallout. A specific population of treatment-resistant cancer patients, unthinkable before the discovery of predictive biomarkers, is generating extremely difficult ethical dilemmas for communities, which must rationalise opportunity and cost amid futility and hope.

Chapter 3 shifted the lens to place the perspectives of patients at the centre of analysis. Here, I was concerned with patients’ accounts of themselves, making the case for a *subjectivity of negation* in which patients’—mediated by biomedical accounts and the imagery of a mass in the brain and by peculiar symptoms such as auras and seizures—cast themselves as doubtful narrators, not fully capable of making rational decisions about care and treatment. Given the spectre of a mass, patients were terrified of “losing themselves.” Rather than being a state fully realised, and sanctioned by formal clinical measures, such as mental capacity testing, I considered how it was a state anticipated by patients, and in turn how it bore on their self-conceptions. However, such anticipation was not passively received or constructed but also resisted, as patients tried to document or mend what they considered a shared reality.

In chapter 4, I kept patients as the key protagonists, placing their narratives and experiences alongside those of advocates, policymakers, clinicians, scientists and industry representatives, which played out in various documents. Here, I mined regulatory and policy decisions and meetings, industry reports, charity statements and scientific literatures, for the logics that drive the productions and regulation of experimental possibility. I also included first person accounts of clinicians to underscore the importance and contested nature of clinical trials in the daily care of people with a brain tumour. This continued the themes of hope, progress, and the embrace of biotechnology from chapter 2, situating the pursuit of experimental possibility within the scarcity of effective treatment. It also highlighted the despair of those who seek trial places without success and indeed how the failure of promise contributed to what Fay described as a world come crashing down—a world, I suggest,

which was built on the hopes implied in biotechnical obsession. The break with hope foreshadowed the focus on disease progression and care transition in chapter 5.

Chapter 5 argued that disease progression manifests in social relationships among patients, families and clinicians, missed opportunities and micro decisions, for example, about when to scan. By presenting the final months of Rebecca's life as well as descriptions of the last days in the lives of Gabriel and George, I presented how moral dilemmas in care at the ends of life are lived at the nexus of biomedical intervention and its withdrawal. Families—and patients—wanted to know that they had done all they could do to stave off death while establishing comfort and intimacy for when it finally came. Conceptualising disease progression as a social as well as a biological phenomenon, I revealed some of the factors which complicated a simple disease trajectory and confounded efforts to prepare for a “good death.” I drew attention to the enduring and powerful allure of biotechnology in a situation which, though intractable was not perceived as inevitable. I contrasted the on the ground realities of enduring ambivalence and opportunities not taken with policy assumptions about timely planning. These scenarios were in many ways common with other moments along the way of life with disease, though amplified massively in the high stakes of having “once chance to get it right.”

...

My analysis shows that those clinicians that disclosed diagnosis to patients and families and suggested directions for care, were implicated in a web of micro decisions that took place in various sites in the hospital and the broader communities of science and policy. Those behind the scenes, such as radiologists and pathologists, worked to shape the information they produced and contain uncertainty. However much this information appeared neutral, it was rather amalgam of valuations, omissions, and scripted interventions. As clinical members of the multidisciplinary team, those behind the scene did much to direct the courses of patients' lives, though they never met these patients. Outside the hospital walls, scientific communities, policymakers, advocates, pharmaceutical companies, insurance companies, and so on, produced and sanctioned evidence, determined disease categories, and what counts as normal and needed (Jain 2013; Kaufman 2015; Kaufman 2016). Each person or institution I describe in this dissertation was therefore placed somewhere along the way of care and was critical to how the clinical state of affairs was produced and disclosed, and how medical decisions were framed, made, or even brought into being. Decision-making, more

generally, was highly distributed and those decisions which eventually emerged in the lives of patients were highly contingent on the upstream choices of multiple, less visible actors.

Broadening the scope also meant attending to how patients themselves made spaces for choice outside what was immediately given and how they challenged the regulatory constraints configured in standard care. My navigational analysis revealed how understandings developed over the *longue durée* of illness and how unpredictable disease combined with the treatment imperative to motivate the improvisations of those with life-threatening disease. This imperative was firmly rooted in the social imaginaries of care; treatments like immunotherapies circulated widely through forums and the media, and were topics of conversation in hospital waiting rooms. Notably, almost two thirds of those I met received some form of private, non-conventional or experimental treatments in addition to standard care, chose to forego standard treatment in part or total, or were forced to stop because of medical complications. Very few followed standard care pathways without seriously questioning the risks, side effects, efficacy or evidence of treatment, either privately or publicly in clinical consultations. In the spaces they created, these patients attempted to chart their own trajectories based on their ideas about what is tolerable as symptom of disease or treatment side effect and what is acceptable as a goal of care. Standard care became but one among many treatment options.

FUTURES: THE ETHICS OF POSSIBILITY

What happens next in the social formations of care and especially with the integration of molecular techniques and the ever-expanding programmes of research, is uncertain. As we saw in chapter two, the movement towards personalised medicine is expanding and doing so at multiple levels. The publication of the WHO manual and NHS England's personalised medicine strategy in 2016, European and UK guidelines for the treatment of brain tumours in 2017 and 2018, respectively, all signal an increasing consolidation in policy arenas.

However, the details of these programmes remain unformed and controversial. Science, for its part, continues to move at pace, identifying new biological pathways for cancer growth and biomarkers which predict responses to treatments. International experts, like Dr Plank and David Louis, agree that the revolution is just beginning. Cancer services are being reconfigured to accommodate these changes amid a sometimes fraught political, social and ethical backdrop. Alongside all this, an increasing advocacy lobby in brain tumours—in the UK and internationally—is generating and drawing public money to fund high-risk, big

reward biomedical research. Across these arenas, an aspirational discourse towards longer and better lives for people with a brain tumour raises the possibilities of a new way to care. And yet there are major ethical concerns about how these programmes are figured.

While a hoped-for expansion of trials promises to grant more access to cutting edge treatments and locate the experimental in routine care, many remain equivocal about their role in the care of patients. We need only remind ourselves of Dr James, the oncologist in chapter 4, and his proclamation that dozens and dozens and dozens of trials have failed to provide better results than standard care, and of Fay's despair when the vaccine trial failed and her disease progressed against the hope that she could live another ten years. Hope, as Cheryl Mattingly insists, is on intimate terms with despair (Mattingly 2010).

Outside the trials context, a rapid expansion in the development and uptake of crowdfunding platforms is providing patients with greater means to gain access to innovation now—through private means and medical travel (Burtch and Chan 2010; Snyder, Mathers, and Crooks 2016). This received significant media attention in the UK in 2016 following a seven-fold increase in medical crowdfunding (from £530,000 2015 to £4.5 million 2016) by the crowdfunding site Justgiving. Some crowdfunding sites even have immunotherapy as a predetermined category to type campaigns. As such, many of the treatments patients, such as Matthew, look to and fundraise for are the immunotherapies which have drawn major gains from the molecular turn.

Such private funding programmes are highly contentious. Medical communities caution that patients might be at risk of exploitation in a marketplace that is largely unregulated and open to abuse by those advertising unsubstantiated therapies “absent of clinical benefit” (Lancet Oncology 2017). While this might be true of some situations, many patients I met during fieldwork had developed highly sophisticated understandings of disease and scientific literacy while navigating the dizzying array of private, experimental and repurposed treatments. Moreover, as evident in the narratives of crowdfunding pages, these platforms provide a means to get experimental treatments outside the bureaucracies of trials (Llewellyn et al. 2017; Snyder, Mathers, and Crooks 2016). It is a complex problem: dismissing these narratives runs the risk of marginalising discourses of empowerment but privileging them without appropriate safeguards risks endangering those most vulnerable to the promise of treatment.

This is not specific to brain tumours or driven by the molecular turn. What marks the current moment faced by brain tumour communities is the combination of poor funding, scarcity of trial places, sclerotic change in standard care options, which remain

ineffective, and major shifts in the constitution of the brain tumour population, for example, the variation of tumours given in changing diagnostic boundaries and the sudden emergence of new populations of patients for whom standard treatment is increasingly questioned. Moreover, the cases of public figures like Tessa Jowell in the UK, John McCain and Beau Biden in the US, all of whom died from glioblastoma tumours, have done much to place brain tumours in the contemporary public imagination. Their cases highlighted the dearth of effective standard treatments across the world, emphasising the possibilities within experimental programmes and the need for concerted efforts to move quickly on ushering in the new era. These various factors work symbiotically with the embrace of biotechnology and further embed the imperative of “more is better” as an *ordinary way* of managing disease (DelVecchio Good 2001; DelVecchio Good 2007; Kaufman 2015; Koenig 1988). They drive patients to create spaces for treatment choice outside standard models of care (Llewellyn et al. 2017). How will patients draw on the promises of the molecular turn to imagine care options? How will they decide between treatments in the present and the opportunities for future care knowing that trials exclude on their basis of treatment histories? And if excluded from trials, how will they innovate ways around to seek, travel to and finance these treatments?

Aside from these broader concerns about innovation and access, there are other concerns particular to current innovation in brain tumours. What to do with a growing population of people for whom standard treatment is known to be ineffectual? How to promote and maintain a shared approach to medical decision-making, long fought for and in many ways won, amid what appears a challenge to discourses on personalised care which emphasised inclusivity and patient autonomy in decisions over those made by doctors? What about the paradoxical effects of using brain tumour tissue in the production of personalised immunotherapies and its possible effects on recalibrating decisions to operate? And what about its effects on the line between so-called radical treatment and palliative approaches to care, a line already under assault from the ordinary ethics of a technological determinism (Koenig 1988)? Those called on to make decisions now—whether it be for themselves, for their families, or for various designated populations—are, in effect, pioneering ways into a new era of treatment. It is they who pen the first strokes in mandating future approaches to care and establishing the ethical norms which will be embedded for future generations.

What frameworks are appropriate to guide patients as choosers, clinicians as advisors, and policymakers and patient activists as stewards of research and healthcare practice in the responsible integration of these innovations and their further development? Given these

dilemmas are often hard to identify, anticipate and can impose themselves suddenly, these frameworks should be flexible and responsive. As my findings suggest, the affective dimensions of innovation are extremely complex. The key difficulty for the neuro-oncology community at large will be to find an approach to pace which balances expediency while allowing for the identification, acknowledgement, and mitigation of further (potentially negative) social impacts. David Louis and colleagues, who are deeply aware of the potential disruption of revolutionary change, appear cognisant of this balance. Their modes of establishing the field's readiness for diagnostic change and a transitional period, which allows the coordination of knowledge through layered diagnosis, allows for a more inclusive approach to practice.

But what about the other features of change—the thornier issues of treatment prediction and other therapeutic development? Given brain tumours lack effective treatment and technological innovation has been extremely limited, the “responsible stagnation” (Saille and Medvecky 2016) or “judicious slowing” (Kerr, Hill, and Till 2017) advocated in some programmes of responsible innovation will rightly be seen with suspicion by patients, families and clinicians alike. Currently, all brain tumours are potentially deadly, whether malignant or non-malignant, and less than half those diagnosed with malignant tumours will survive a year. But as demonstrated time and again—for example, through the case of Avastin which was sanctioned for use in the US by the FDA under evidence considered spurious by its European regulatory counterparts—evolving technologies faster than the cultural scripts that guide their use runs the risks of catastrophic social fallout.

Social scientists are well-placed to help develop these frameworks. It is urgent that we continue to trace this new moment in neuro-oncology—and cancer more broadly—and further map the complex of patients, scientists, clinicians, industry, policymakers and advocates who are “morally pioneering” a way into this new era. By understanding the diverse hopes, apprehensions and values of these stakeholders and ultimately *what is at stake* for patients in the production of new routines and treatment options, this dissertation makes ground on this aspiration.

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