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Genomic techniques in standard care: gene-expression profiling in early-stage breast cancer

Breast cancer has long been a focus of research and innovation in genomic medicine, from one of the first targeted therapies, Herceptin, as discussed in Chapter 1, to testing for mutations in breast cancer susceptibility genes such as BRCA1 and BRCA2, which developed through the course of the 2000s. Research into the molecular biology and gene expression of breast cancer tumours has spurred the identification of a range of variants or subtypes of breast cancer according to their molecular make-up. In addition to the development of Herceptin for HER2 breast cancers, estrogen receptors were also identified as targets for drugs in women with breast cancer before the menopause who had what is known as hormone-sensitive breast cancer. Cancers were classified into a range of subtypes according to genomic and other tests in the ensuing period. Olopade et al. reported that

> individual cancers could be categorized, based on their gene signature, to at least five distinct subtypes: luminal A, luminal B, normal-like, HER2-like, and basal-like. Normal-like tumors resemble normal breast tissue, HER2-like are characterized by HER2 overexpression, luminal A and B are estrogen receptor positive, and basal-like are triple negative (estrogen receptor negative, progesterone receptor negative, and HER2 negative). (2008: 7991)

These developments were the outcome of considerable research investment by public bodies, charities and commercial companies. Cancer research has been enabled, in part, by strong traditions of community and advocacy among breast cancer patients focused on prevention, research and survivorship in particular (Nahuis and Boon 2011; Gabe et al. 2012). Together, breast cancer research and

activism are considered to have made major inroads into tackling the disease. Many breast cancers are now highly treatable when detected early, and UK survival rates have doubled in the last four decades, bringing ten-year survival rates for women up to 78 per cent across England and Wales for those cancers diagnosed early (Cancer Research UK 2014).

Sequencing and microarray technologies arising from the human genome project have enabled gene-expression profiling within cancer medicine. This technique identifies which genes are being activated in a cell to give a global picture of cellular function.[1] Oncotype DX is a gene-expression test developed by a US-based company, Genomic Health. It aims to provide a personalised prediction for a subset of breast cancer patients for whom the benefit of chemotherapy after surgery is less clear. The test estimates the likelihood of recurrence and can thus aid decisions about chemotherapy (Bourret et al. 2011). As Dowsett and Dunbier note, Oncotype DX was one of several 'multigene expression profiles that aim[ed] to outdo traditional predictive and prognostic factors' in breast cancer diagnosis and treatment, developed to 'quantify the residual risk of … recurrence in patients with lymph node negative, estrogen receptor-positive tumors receiving tamoxifen' (2008: 8022).

Echoing ongoing discourses of optimistic and transformative futures associated with genomic medicine, Oncotype DX has been hailed by some commentators as a key tool to combat the over-treatment of patients via chemotherapy (Joh et al. 2011; Ali-Khan et al. 2015). This has been welcomed because of its potential benefits for individual patients and practitioners in deciding on whether to recommend chemotherapy to prevent the recurrence of cancer, despite its sometimes serious side-effects and the disruption this causes (Bell 2009). Reducing unnecessary chemotherapy could also save resources within the UK NHS (Loncaster et al. 2017), although use of this test is primarily to help define who, from a subset of patients, would benefit from chemotherapy.[2]

As we discussed in Chapter 1, gene-expression profiling tests such as Oncotype DX have also been part of a wider transformation in innovation and regulation. This has involved novel partnerships between commerce and healthcare, with tests utilising proprietary algorithms. It has also involved new regulatory arrangements and pressures, marked by complex negotiations in state-based health

systems such as the UK's, involving multiple stakeholders from healthcare, industry and patient advocacy. As of 2018, the National Institute for Clinical Excellence recommends three such tests: Oncotype DX, EndoPredict and Prosigna, replacing its previous 2013 guidance which included MammaPrint (see below). These tests have been introduced into an already busy diagnostic and treatment nexus in the NHS, which is not only non-linear, but is also already populated with a range of information and expectations, to which additional molecular information adds another layer. This means that, although molecular testing might promise certainty, it brings additional kinds of uncertainties too, all of which have to be navigated by researchers, patients and clinicians in the clinic and beyond.

In this chapter we look at these processes more closely, exploring the ways in which Oncotype DX, as one tumour-profiling test, has been made valuable to the health service, practitioners and patients, including via patients' contributions to processes of regulatory and clinical decision making surrounding the test. We chose to focus on Oncotype DX after discussing our research with senior clinicians in our project advisory group, who pointed out that we ought to include an aspect of genomic medicine already embedded in the clinic alongside the other case studies we were developing on genomic medicine as part of a trial or research. As we discuss further in Chapter 7, we had been finding entry into the clinic to study ordinary care difficult because of the complexities of patient pathways, clinical arrangements and ethical and governance approvals. However, clinicians were keen to understand patient experience of the test and of genomics more broadly, and helpfully assisted in recruitment for this case study, as well as being willing to be interviewed themselves.

This chapter considers transformations in policies and practices surrounding Oncotype DX and what sort of work this involves for patients and practitioners. We draw on research from three settings: the (public) approval process for the 2018 reformulation of UK NICE guidance around tumour-profiling tests; online patient discussions about Oncotype DX (between 2015 and 2017); and interviews with 18 patients who had had the test, interviews with nine healthcare professionals (between 2017 and 2019) and six observations of consultations (2017). To gather the online data, we searched for the term 'Oncotype' on publicly accessible online forums, hosted

by cancer charity websites, and analysed discussion about Oncotype DX among cancer patients therein (Ross et al. 2019).

As we shall see, bringing Oncotype DX into routine practice involved considerable ongoing negotiation around evidence of benefit to the NHS and to patients and practitioners, as its meanings and implications were negotiated across a range of policy, practice and personal contexts. We explore how patients and practitioners worked to give the test value in their practice and experiences across these contexts, and we consider ambivalence about, and at times rejection of, its value. This ambivalence was centred on how the test could amplify, not simply resolve, uncertainty in already unstable treatment pathways regarding the role of adjuvant chemotherapy in this group of patients. Investigating how policymakers and NHS providers framed the test, we also highlight its precarious innovation pathway, exploring how its value had to be renegotiated across policy, community and clinical contexts. Despite the common claim that personalised genomic medicine is mainstream for cancers such as breast cancer because of the long-standing use of targeted treatments facilitated by gene-expression tests, our case study of Oncotype DX suggests a more precarious and contingent story of genomic medicine in the mainstream.

Gene-expression profiling within the UK NHS: crafting genomic futures

Commercial molecular profiling tests for breast cancer have become established since the early 2000s (Bourret et al. 2011; Kohli-Laven et al. 2011). MammaPrint is a 70-gene cancer signature developed and commercialised by the Dutch company Agendia, and Oncotype DX, which analyses 21 genes, was developed by the US company Genomic Health. Oncotype DX remains one of the NICE-approved tests, as noted above.

Oncotype DX is available to early-stage breast cancer patients with estrogen receptor positive (ER+) and human epidermal growth factor receptor 2 negative (HER2–) breast cancer tumour tissue which has not spread to lymph nodes (LN–) where a clinician is unsure about whether they will benefit from chemotherapy to prevent recurrence. It is important to note that this patient group is quite specific – they

are already at low risk of recurrence and Oncotype DX may be used to help determine whether adjuvant chemotherapy might be beneficial. There is variation in the prognoses for these cancers (Nagaraj and Ma 2013), and for some of these patients the risks of chemotherapy, including long-term side-effects, can outweigh any potential utility in reducing the possibility of recurrence. Oncotype DX testing is typically performed when widely adopted risk-assessment calculators which look at markers such as ER and HER2 (e.g. NHS Predict)[3] do not provide a sufficiently definitive recommendation with regard to treatment, placing these patients at what is described as an 'intermediate' or 'moderate' risk of cancer's return in the context of an overall low risk of such recurrence. In these cases, according to NICE guidelines, clinicians can offer Oncotype DX testing (the list price is £2,580 and the discounted cost to the NHS is commercially confidential).[4] This involves sending tumour tissue, taken at surgery, to a Genomic Health licensed laboratory in the United States for molecular profiling of the 21 genes it analyses. The Oncotype DX test generates a personalised prediction for cancer survival with endocrine treatment (such as tamoxifen) alone, and based on this, a quantitative assessment of chemotherapy benefit. This is represented as a numerical 'recurrence score' between 0 and 100, categorised into risk bands. Initially this involved 'low-risk', 'intermediate' and 'high-risk' groups, with those patients at higher and in some cases intermediate risk of recurrence recommended to undergo adjuvant chemotherapy, taking other factors such as age into account. These three categories were represented visually, with the patient's place on the scale and corresponding ten-year survival prognosis, with or without chemotherapy, highlighted on a graph. Recently, following the outcome of the TAILORx trial, results have been presented in two bands – low and high risk.[5]

When NICE first recommended Oncotype DX for NHS use in 2013 (NICE 2013), the announcement was widely welcomed in the UK media, prompting headlines such as 'New Breast Cancer Test Could Spare Women Chemotherapy' (Boseley 2013). Coverage positioned the test as an example of improvements to the health service which could arise from genomic techniques, with the chief executive of a national breast cancer charity declaring that its approval represented a 'step along the road towards personalised treatment' (Smyth 2013), echoing the big future promissory discourses that

commonly accompany developments in cancer science. However, five years later, during a 2018 reformulation of NICE guidance for tumour-profiling tests, initial recommendations suggested that the test ought to be withdrawn because there was a lack of evidence of its benefit. The value of the test for the NHS had to be re-established by the manufacturer, practitioners and patients, as we now go on to discuss.

In January 2018 NICE released a public consultation document following an expert advisory group (EAG) review of available tumour-profiling technologies. Following their diagnostics assessment, including a systematic review of clinical evidence and updated economic analyses (Harnan et al. 2017), NICE's consultation document asserted that:

> There is not enough evidence to recommend the routine adoption of EndoPredict, MammaPrint, Oncotype DX Breast Recurrence Score, Prosigna and IHC4+C to guide adjuvant chemotherapy decisions … In particular, more evidence is needed to prove that these tests have a positive effect on patient outcomes. Their cost effectiveness compared with current practice is highly uncertain. (NICE 2018a)

NICE called for further research on the effect of these techniques on long-term patient outcomes and treatment decision making, when compared with established risk-calculation tools already used by clinicians to predict breast cancer recurrence, such as NHS Predict (NICE 2018a).

Though some stakeholders agreed with the EAG's initial assessment in the consultation document, their recommendation to withdraw Oncotype DX from NHS care was met with considerable criticism. Following a call for stakeholder responses to the public consultation document, NICE received 255 comments from a range of actors including NHS professionals, charities representing patients and manufacturers (NICE 2018c). For these critics, the withdrawal of gene-expression profiling from NHS care was at odds with the transformation of the health service envisaged within wider UK discourses of the genomic revolution; around 170 comments were received from healthcare professionals, the majority of whom reported that the test had transformed their practice. Objecting to the recommendation, they framed it as a retrograde step for the health service, with a minority citing concerns of a return to a one-size-fits-all

approach to breast cancer treatment. For example, one professional wrote:

> Please do not reverse this recommendation which will have the knock on effect to reverse the progress made by NHS in breast cancer treatment in the UK and have a huge negative impact on so many ladies who do not need or deserve the terrible impact they will endure in both short and long-term from having chemotherapy. (NICE 2018c: Comment 78)

Alongside these appeals to the responsibilities of practitioners and the NHS to prevent the harm of unnecessary chemotherapy, others pointed to the certainty and 'relief' offered by the test, as in the excerpt below:

> Being able to request an Oncotype DX test for my breast patients where there is uncertain benefit has revolutionised my practice. It is difficult to put a price on the relief that a patient has when told that they do not need to have chemotherapy which is unlikely to help them. The more we can personalise treatment, the less wastage we shall have and be able to focus treatments on those who are likely to benefit. (NICE 2018c: Comment 1)

The responsibility of professionals and services to reduce waste and target resources at a time when services are already stretched was another common theme:

> In 2018 we cannot ignore the advances technology has given us and go back to the dark ages of giving chemotherapy to everyone 'just in case'. Our day units are too full, lets target our resources wisely and save patients from undergoing unnecessary treatments. (NICE 2018c: Comment 81)

These sentiments were also echoed by the charity Breast Cancer Now, which released a statement following the announcement of these draft recommendations:

> [It is] very disappointing that NICE has been unable to recommend any of these prognostic tools to help guide chemotherapy use on the NHS. In particular, this appears to be a backwards step for some patients … for whom guidance published in 2013 previously recommended the use of Oncotype DX. With studies to assess their long-term impacts ongoing, prognostic tests like these are showing real potential to personalise breast cancer treatment and ensure all patients are

> given the best chance of survival, while reducing overtreatment. (Breast Cancer Now 2018)

Here we see the deployment of a familiar trope of personalisation as future-oriented transformation by both patient advocates and practitioners, who also referenced collective responsibilities to support the NHS and not fall behind the rest of the world. Reducing toxic chemotherapy generates cost savings for the NHS and offers patients better health and emotional relief.

However, very few individual patients submitted comments. Only two out of 255 comments were from patients, both of whom were supportive of approval because it reduced the burden of chemotherapy, including this one:

> I was predicted a 70% survival rating by PREDICT (which you seem to think can take the place of genomic testing) as opposed to 98% by the Oncotype DX genomic test. I would have had to have chemo, the possible long-term drawbacks of which I do not think you have adequately taken into account in your documentation of the site. Not to mention the unquantifiable psychological effects of a relatively poor prognosis. (NICE 2018c: Comment 174)

This forms part of a broader pattern in NICE assessments of novel diagnostics and therapies, where evidence of benefit becomes a key terrain of dispute and epistemological activism (Keating and Cambrosio 2011) on the part of health economists and other policy experts, industry, practitioners and patients. A particular tension arises between the tendency of expert review groups to prioritise the evidence of overall benefit to the health service, while patient representatives and practitioners, sometimes in concert with industry, prioritise individual patient benefit, in this case the avoidance of the psychological and physical burden of unnecessary toxic therapies. Negotiations 'spill over' into the public sphere as part of the co-production of these kinds of NICE decisions (Moreira 2011: 1334), with the entitlements and 'moral worth' of patients forming part of the evidence that stakeholders mobilise alongside practitioners' and regulators' responsibilities to deliver value for money for the health service as a whole (Moreira 2011: 1338).

As Abraham (1995) and Davies and Abraham (2013) have shown, pharmaceutical companies influence regulatory processes affecting their products, including via funding clinical trials and working

with regulators to speed up the approvals process. However, research has also shown that NICE committee members can be particularly sceptical about industry claims and those of patients who are seen as having conflicts of interest (Brown et al. 2016). The gene-profiling industry therefore adopted a muted tone in their submissions to the NICE committee, deploying a range of evidence of benefits and criticising the EAG for insufficient engagement with international study groups and trials.

However, it was the prospect of evidence from one trial that was particularly important in the advocacy work around Oncotype DX. Around thirty responses to the initial NICE report noted that the results of the Trial Assigning Individualised Options for Treatment (TAILORx) trial, a National Cancer Institute (US) sponsored large-scale prospective trial assessing the benefit of chemotherapy for those receiving 'intermediate' Oncotype DX scores, were shortly to be released, stressing the importance of this evidence to the process. In response, the Diagnostics Advisory Committee paused the development of their reformulated guidelines to conduct further analyses incorporating the trial results.

The TAILORx results were widely welcomed because they demonstrated that Oncotype DX offered more precise predictions, identifying the 70 per cent of women who would not benefit from chemotherapy (Sparano et al. 2018). The trial also found no need to use an intermediate score, as women in this category could be considered low risk and avoid chemotherapy. These results were reported with much fanfare in the UK media. When reporting on the technique and the TAILORx study, many news articles adopted terminology including 'life changing', 'ground breaking' (Matthews-King 2018) and a 'breakthrough' (Gallagher 2018). Headlines included 'Most Women with Early Stage Breast Cancer Can Avoid Toxic Chemotherapy' (*The Independent*) and 'Breast Cancer Study Set to Free Women from Chemotherapy' (*Financial Times*). Stories featuring personal testimonies included that of the *Guardian* journalist Joanna Moorhead, who recounted her own experience of Oncotype DX in the wake of the results of the TAILORx study, describing the technique as 'revolutionising' cancer treatment (Moorhead 2018).

These positive trial results, together with the arguments presented by contributors to the consultations, shaped NICE guidance, released

in December 2018. During its final meeting, the NICE Diagnostics Advisory Committee reported scepticism about the applicability of TAILORx results to the UK. Many of those who avoided chemotherapy in this study would not have been routinely offered it in a UK setting, demonstrating that even so called 'gold standard' evidence is not always translatable to other health systems, affording clinicians, patients and regulators flexibility in interpretation and practice (NICE 2018b: section 5.6). Nonetheless, NICE retracted the earlier recommendation to withdraw support for Oncotype DX. The committee also recommended the adoption of Endopredict and Prosigna for use with ER+, HER2– and LN– early breast cancer patients in NHS settings, where certain criteria are met, including whether other validated tools such as NHS Predict had already suggested an intermediate risk, and that information would help patients to choose whether or not to have chemotherapy (NICE 2018b). In Moreira's study of dementia drug regulation, hybrid interactions between practitioners, patients and industry created the conditions for NICE to resolve disputes with pragmatic reasoning, balancing rules with individual cases, rendering the decision 'socially robust' rather than technocratic (Moreira 2011: 1340). We find similar processes in this case, as the regulator navigated a range of different types of evidence and advocacy around the value of the test for the NHS, practitioners and patients, recommending limited use of the test in conditions of uncertainty if the patient, together with their practitioner, would find this helpful.

In these processes of regulatory decision making we can see the articulation of value to patients and to the NHS being asserted and anticipated as an outcome of regulatory approval. The value to patients was articulated in evidence to the regulator, but this was largely second-hand rather than first-hand, via clinicians and patient advocates/representatives. The main form of value being asserted was the avoidance of unnecessary and expensive chemotherapy, something which was presented as mutually beneficial for patients and the NHS. Patients were also framed as deriving personal value from the test, which offered relief and prevented toxic side-effects when they could avoid chemotherapy with more certainty. The NHS was presented as deriving efficiency gains and financial benefits from these outcomes. The value of being 'future-oriented', not being backward or overtaken by other countries, was also asserted through

these processes. Oncotype DX became totemic of the future of personalised medicine, generating a sense of shared commitment to its realisation (Jerolmack and Tavory 2014). Reducing suffering, saving money for the NHS and paving the way for further advances combined national and personal goals and benefits. For patients and practitioners, gene-expression profiling offered certainty and reassurance that they could avoid chemotherapy, resolving lingering uncertainties produced by other algorithms such as NHS Predict. For the NHS, the technology offered greater certainty by reducing wastage, and for policymakers and industry it made the future of personalised medicine less uncertain as the test became an option within standard care pathways.

However, when we turn to practitioners' and patients' accounts of engagement with Oncotype DX, we find it is associated with more complex and contingent value than the three kinds of value (personal value, value to the NHS, totemic value) discussed above. As in Hedgecoe's work on Herceptin (2005), the 'messy realities' of bringing Oncotype DX into treatment decision making meant that its value was contextually negotiated in practice. It was sometimes experienced as particularly valuable and unique, including because it is a novel commercial test, where tissue is processed in a US laboratory rather than an in-house hospital laboratory. On the other hand, it could also be experienced as unremarkable or lacking in special value, as just one of a raft of tests brought into decision making, and sometimes as lacking any additional value where its clinical utility was considered uncertain. All experiences involved patients and practitioners in particular kinds of emotional or articulation work (Star 1985), drawing on social and cultural capital to make meaning from the test in the here and now as well as for service and patient futures. This happened in the clinic and beyond in online breast cancer patient communities, as we now go on to examine.

Integrating genomic tumour profiling in practice

According to NICE guidelines, NHS clinicians are advised to administer gene-expression profiling in HER2+, ER– and LN– early-stage breast cancer where there is uncertainty around whether to recommend adjuvant chemotherapy to prevent recurrence, and where

established tools such as NHS Predict are unable to offer a clear recommendation. This frames the test as a solution to such uncertainty. Yet as with many such tests, practitioners' experiences suggest that Oncotype DX is a means of managing rather than simply resolving uncertainty.

We interviewed nine practitioners involved with Oncotype DX in their practice, including one clinical nurse specialist, seven oncologists and one pathologist. We also carried out six observations of consultations where discussion of the Oncotype DX score took place, and where decisions were made regarding the benefit of adjuvant chemotherapy.

As practitioners in our study frequently pointed out, opting into or out of chemotherapy involves careful consideration of a patient's personal and social circumstances and clinical factors, where non-genomic quantified risk prediction through NHS Predict remains paramount in determining whether to offer gene-expression profiling. As in other fields, clinicians exercised their professional autonomy, non-routine working and tacit knowledge to work flexibly within NICE guidelines (Timmermans 2005; McDonald et al. 2006) when it came to Oncotype DX. Practitioners told us that decisions about Oncotype DX testing were not just based on the patient's cancer but included consideration of co-morbidities and individual patient characteristics, and in the words of one oncologist, their 'scope to benefit'. This flexibility is anticipated in the guidelines which require that 'information provided by the test would help them choose, with their clinician, whether or not to have adjuvant chemotherapy taking into account their preference'.[6]

We can illustrate how clinicians flexibly embed gene profiling in practice in collaboration with their patients through the account of one oncologist who reflected on their experience of treating a patient who had been resistant to undergoing chemotherapy because of the impact on their occupation. The oncologist had already determined that because the cancer was low grade, chemotherapy would not be a good option, and the Oncotype DX test simply confirmed this decision. As they stated, the test played a role in solidifying treatment recommendations that would already have been made: 'we feel really reassured that we're not doing the wrong thing. So that was really helpful for [the patient], but did it change our management? I don't know that it did.' As another oncologist attested, 'Quite frequently,

it gives the result that you fully expected … It's more often that it's simply confirmed the view that we thought was more likely.' Similarly, during an observation of a consultation where the patient was categorised as 'high-risk' following Oncotype DX testing, the clinician confirmed that the patient would benefit from chemotherapy, a decision that they imply they would have reached regardless of the test:

> Speaking to the patient and her husband, the clinician explained that an additional test was required [didn't say why this was the case], which is called Oncotype DX, that tests a number of genes, '21 genes to be precise and based on this score, patients are categorised into 3 groups: "low risk", which is "good cancer", "intermediate' group, and the group with high risk of recurrence in 10 years.' The clinician confirmed that the patient is in the high risk group to which the patient's husband replied, 'yes, because it's 44%.' Based on this, the clinician went on to say 'I would have recommended chemotherapy anyway even without gene testing results.'

According to these accounts the value of the test was as a confirmatory device, reassuring patients and according with decisions reached using other clinical tools and judgements. In other consultations, however, and particularly for patients 'at the margins' with this lower-risk cancer, the Oncotype DX result was a means of providing further, and more precise, information which aided the decision about chemotherapy, as the extract below highlights:

> The consultant explained what the NHS Predict tool is and they went through each section together thoroughly. Because the patient is 'so young' [40 years old] the consultant predicted a good prognosis. They added that without the Oncotype test result [i.e. with just the NHS Predict result], it might have appeared that the patient doesn't need chemotherapy but with this result it shows the benefit – explaining they are 'trying to put different bits of information together'. The husband said 'given the cost of chemo', the benefit seems so small. The consultant said NHS Predict gives you 'a rough average' but because breast cancer is a big group of disease[s], this is 'where Oncotype comes in'.

The test was also used as a means of reassuring the patient's husband that chemotherapy would be beneficial given their concerns regarding efforts to balance the benefit and burden of chemotherapy. We see

consultant, patient and relatives acting together to reach decisions, taking responsibility for obtaining specific information as part of this process.

This is also captured in a further observation with the same consultant:

> And then [consultant oncologist] gave an overview of the patient's cancer that it's common cancer and early grade (Grade 2 she said), 21 mm with clear margin, and ER+ & HER2–. [Consultant oncologist] then explained that breast cancer is a very big family of cancer [exactly same wording she used in the previous consultation I observed]. [Consultant oncologist] explained, by drawing a diagram on a sheet of A4 paper ('it's easier with a picture, isn't it?' the consultant said) – while explaining two subtypes of breast cancer which are estrogen receptor positive and negative, she wrote down ER+ and ER– on the sheet and then each ER+ and ER– is branched out by lymph node status i.e. positive and negative – I couldn't quite see from where I was sitting but I think they wrote down LN+ and LN– on the sheet. 'This is when Oncotype test comes in', [consultant oncologist] said – this looks at LN– within ER+ [categories] … 'on surface this cancer might look good but Oncotype might tell us otherwise' [this explanation is also very similar to what was said to another patient in consultation].

Here we see Oncotype DX being presented as providing certainty to resolve previous doubts around whether to proceed to chemotherapy, or even revealing more harmful cancers that might initially 'look good' on the surface, in the context of such a wide and varied 'family' of diseases. The test was valued by some clinicians because they felt it assisted patients who were finding decision making difficult. This is visible in the following extracts, from a discussion with a consultant following a clinical consultation and a separate interview:

> The consultation finished and the couple left the room to have a blood test done. Before I left, I asked the consultant if Oncotype DX is a useful tool and they said yes, as it helped the patient to change her mind or make up her mind.

> Patients often find it quite useful because it's difficult for them to make these decisions, so in a way having the test to tell you whether you should or shouldn't have chemotherapy takes the difficulty away from you and you just do what the test says. I think that's why a lot of patients quite like them.

In other situations, and for some other clinicians, the test was less useful. A clinical nurse specialist working with the technique noted that the test could not always offer certainty or eliminate the 'grey areas' experienced by patients and clinicians; nevertheless it was valuable because it was 'making them smaller'. After ordering gene-expression profiling many times, one clinician had almost stopped using the tool, now largely reverting to their prior practices of clinical judgement to make personalised decisions about chemotherapy treatment:

> The first year we did about eighty [patients] I think … I don't know how many … so what that showed to me was that almost nobody should get chemo … they were all lower intermediate. So actually using it has been an education, because it reaffirms to me that I think almost nobody who has node negative breast cancer should get chemo. And now I think I've got enough data to feel confident about that, and that's why I think we don't need to get Oncotype to do that. So now I've kind of almost stopped using it … because it's reaffirmed to me the UK backbone that was there all along, which was actually giving cytotoxic therapy to node negative hormone sensitive breast cancer, is almost always the wrong thing to do … now how do you pick out the three or four women out of a hundred? Well maybe you can't, but how much benefit do those people get? In absolute terms not that much. And does Oncotype pick them out? We don't know because in the high risk group it was never randomised. TAILOR X assumed that the low risk group didn't need it, and assumed that the high risk did need it.

The oncologist above began using the test once it was recommended for funding, but found, over time, that their prior clinical experience and the decisions made were reinforced, not challenged, by Oncotype DX results, attenuating its value in practice. Nonetheless, the big future promises of personalised medicine remained, as they went on to say: 'I'm sure one day the computer will beat the human at chess, but I don't think Oncotype's the thing that's going to do it.'

We see, then, in common with other genetic tests as described by Latimer et al. (2006: 621), that Oncotype DX was just one of many resources involved in cancer diagnosis and prognosis, with the relationship between clinical judgement and laboratory testing complex, and by no means unilinear. This could include enacting professional responsibility to make judgements without tests that were perceived to be unnecessary, and questioning whether this test

is an efficient use of limited resources, as the following oncologist describes:

> I suspect it's fulfilling its promise but at the downside of maybe quite a lot of tests are being done, that may not be, you know, for example, in patients that maybe, like you wouldn't really be giving chemotherapy to, but then you do it because they're eligible and it's low and you still don't give them chemo … I just have slight concerns about how many, kind of, how accurately we're using them, you know, by throwing it around a lot. Some of them were hitting the mark, some of them are, are not. And just based on, kind of, how expensive it is and how bankrupt the health service is…

These more equivocal accounts of gene profiling strike a different tone to the optimism and anticipation reported in the UK media about Oncotype DX transforming practice, after the TAILORx trial and NICE consultation of 2018. They form a kind of 'backstage ambivalence' that enabled clinicians to embed the technique in practice, using it as part of a package of support, confirmation of diagnosis and prognosis, and management of patients' circumstances and expectations; yet a moderated frontstage commitment to such technologies can be maintained, as the oncologist quoted above went on to say:

> These sort of technologies are the future, they're not going to go away. Definitely they're going to stay … but there may be a limit to how much predictive information you can get just from the cancer. Because the entirety of what's going to happen in that patient's next ten years is not just encoded in the cancer.

Being flexible also included situations where oncologists chose not to perform the test. For example, one oncologist described how they had chosen not to offer the test to one eligible patient because they did not consider it necessary:

> I had someone recently who was quite a young patient … she had a grade three cancer and it was … only moderately ER positive and so technically we could have done Oncotype on her. But I prejudged it that there was really minimal likelihood that it would come back with a low score and therefore didn't do it, just went ahead and gave chemo. I think doing the test almost certainly would have been a waste of the health service's money, because there's such a minuscule chance of it coming back low.

The potential delay that Oncotype DX testing could introduce to treatment pathways, with results taking around two weeks following shipment of the sample to the US-based laboratory, was also a source of concern.

All of this meant that there was considerable variation in the extent to which the clinicians we interviewed used the test, with some having used it on fewer than ten occasions. As suggested above, cost and patient care may have played a role here, but clinicians were also sceptical about the commercial interests behind the test, and the involvement of the manufacturer in the evidence base that supported its adoption in standard practice, echoing Hedgecoe's (2005) findings about Herceptin use being limited due to cost considerations.

The low usage among some clinicians interviewed was also associated with their high satisfaction with the standard tools and techniques used to estimate recurrence and chemotherapy benefit within the UK. UK pathology practice was framed as more comprehensive than in the US, where Oncotype DX was developed and trialled. Clinicians described feeling confident in the pathology reports used in the UK (these include markers not used in the US), and doubted the additional value provided by gene-expression profiling. One oncologist praised the pathologists they worked with in their practice, noting that they were very 'accurate' and provide a 'good rock' for clinical decisions. This was echoed by another, who contrasted pathology in the UK with the US:

> [Oncotype DX] adds a lot less to UK practice than it might have been expected to add to US practice … and that's important when, in trying to understand the implications and trials like TAILORx which … were predominantly run in the US … which in our opinion probably has been, overtreating people for quite a long time with chemotherapy in, in groups of patients that we would have used existing prognostic parameters to identify.

These accounts differ from the clinical practitioner contributions to the NICE consultation, which emphasised the value of Oncotype DX to the NHS as a means of reducing waste and making cost savings, and instead echo some of the scepticism about over-interpretation of TAILORx trial results as expressed in the committee deliberations that followed. Here, Oncotype DX is framed as an

unnecessary cost in a system that is already able to deliver high levels of prognostic precision, and we see these clinicians rearticulating arguments about value to the NHS as a reason *not* to use the test.

Alongside these multiple rearticulations of value and responsibilities with respect to clinical decision making, guiding patients and being cost-conscious, elsewhere clinicians intimated that Oncotype DX and other gene-expression profiling technologies were part of the future of the NHS, as evidenced in our examples. The promise of genomic medicine reflected in the NICE consultation and responses to TAILORx results was recapitulated in even otherwise ambivalent accounts. This hopeful view for the longer-term future of genomic cancer medicine was also held by one oncologist who had been particularly sceptical about the added value provided by Oncotype DX testing. The fact that this was an 'old' technology impacted their view of genomic profiling in breast cancer; however, they maintained a view that in the future there is the possibility of 'major impacts':

> You see Oncotype DX is old, whereas some of, some of the lung cancer mark[er], receptors are really quite, they are making a difference. So in a way Oncotype is old news, and I think there are other cancers, and it's not my expertise, but there are other cancers where there are markers or things that can be, that do definitely define pathways and outcomes and information regards in prognosis. So I think it will impact actually. I think maybe breast cancer will impact less than some others. But other cancers, definitely there may be some major impacts.

These clinicians did not describe gene-expression profiling for breast cancer – presented in some accounts as a 'poster child' for the movement of genomic techniques from bench to bedside – as revolutionary or transformative to their practice; in fact, many noted instead their satisfaction with long-established procedures. But in other respects, they mirrored public and policy contributions which positioned techniques such as gene-expression profiling as totemic of 'the future' of cancer care, maintaining anticipation while managing uncertainties in present practice.

This representation of the future of genomic medicine as on the cusp, but not quite attained, is a familiar trope that can be found in public discourse since the sequencing of the human genome almost twenty years ago. While this kind of 'genohype' has been a concern

for stakeholders, including policymakers as they attempt to reconcile it with the pressures of a constrained health service, such expectations for genomic medicine have also been recognised as a stimulus and as necessary to drive clinical change (Samuel and Farsides 2017). Ambivalence and flexibility in the use of gene profiling in practice functions alongside anticipation as part of these processes of change. For practitioners, flexibility and ambivalence about the value of the test was part of managing uncertainties in the clinic while maintaining optimism about improved services and prospects for patients in the future. Clinicians' various renderings of the test as totemic of the future, confirmatory, provisional, incremental, and even at times obsolete, do not necessarily diminish but rather repurpose its value as an additional tool and another step along the way in improving cancer care. These accounts and activities are part of the articulation work through which they exercised professional responsibilities to their patients and the service as a whole.

Treatment decision making for early-stage breast cancer: patient accounts of Oncotype DX

In addition to the observations of consultations already discussed above, we also interviewed 19 breast cancer patients with experience of Oncotype DX (the majority of whom had the test as part of NHS care) and analysed 132 discussion threads on Oncotype DX from a total of seven online cancer patient forums. In this case study, patients' narratives had a different form and emphasis than the clinicians' interview accounts or their contributions to public consultations about the test. As with our other case studies, personalised medicine and genomic tests were but one part of patients' stories of cancer diagnosis and treatment, which encompassed a range of experiences of tests, treatments, research and care. This was the case with Oncotype DX too. Patients, on the whole, did not make a detailed case for or against the technology, nor did they articulate an elaborate vision for personalised medicine and its place within the NHS. Instead they narrated intricate stories of managing uncertainty, interpreting information, making choices, coping with feelings of hope and disappointment, pain and frailty and living through cancer with families and friends. Oncotype DX, like other tests,

featured in these accounts sometimes as a key actor (for example, in online forum discussions about what to do after surgery or when detailing its role in decision making), but it was more typically surrounded by a multiplicity of narratives about treatment, care and research.

Within this context, Oncotype DX was loosely framed as an advance by most patients who had experienced the test, for example when they compared their experiences with the care received by friends and relatives, particularly because the test was costly and sometimes because it was performed in the US. Patients faintly echoed some of the promissory discourses of personalisation that we have identified in media and policy accounts. One patient, Bethany, who described the technique as 'state of the art', told us she worked in an environment where any change to her appearance would be noticed and commented upon, so she desperately wanted to avoid chemotherapy, articulating her responsibility to remain active and competent in the workforce despite her cancer. However, because the test was seen by her as authoritative, due to its being more 'advanced' than existing techniques, she conceded that should the result indicate she was at a high risk, the responsible thing to do would be to proceed to chemotherapy: 'I thought if a sort of state-of-the-art test is saying that's what I need then of course, it might be unpleasant but of course I'll go through that, you know, I'll have chemotherapy.' The scientific basis of the test was also a feature of its promise, as described by another patient, Julie: 'I was very pleased when I heard how the test worked because I thought "right, that's fine because that makes it much more specific and that will make me feel I'm not making a hunch decision, I'm making a decision based on actual science, actually related to me"'.

The advanced nature of the test was also referenced in online forums where some participants contrasted Oncotype DX with more widely used tools such as NHS Predict, positioning these as 'low-tech' when compared with gene-expression profiling. One user pointed to a dissatisfaction with established recurrence-risk estimation tools such as NHS Predict, which she noted 'I can access myself' (breast cancer charity forum). For these women Oncotype DX 'is a lot more personal and specific than the original %s' (cancer charity breast cancer forum), because 'generalised tools could be very wrong' (breast cancer charity forum).

For patients such as this, Oncotype DX testing is a way to enact their responsibility to choose wisely, as it was considered to offer more certainty than established tools predicting risk. Patient accounts have much more congruence with the kinds of value articulated in the consultation responses discussed above, particularly in terms of aiding difficult decisions and offering personal relief and reassurance. This was the case for interviewees such as Alice. Like others we spoke to, she described a very 'quick' experience of her breast cancer diagnosis and treatment with a clear set of procedures to engage with, until the possibility of chemotherapy was raised by her clinician. Following Alice's surgery, it was found that one of her lymph nodes was 'slightly affected' by the breast cancer, and the benefit/risk measure in her particular case for proceeding to chemotherapy was unclear. As Alice described, it was 'touch and go' from both her perspective and that of her oncologist, because the spread was 'such a small amount'. Alice wanted to avoid chemotherapy due to her wish to return to 'normal', and an understanding of the treatment as potentially 'worse than the cancer itself'. She described Oncotype DX as a 'perfect fit for what I wanted to understand about … chemo', and positioned the test as providing certainty in the context of complex treatment decisions:

> I need certainty. I said, right, I'll pay for this test if necessary, to make me make the right decision (laughing) … if I needed chemo, then I would just have to knuckle down and get it done … I just needed some certainty, as to whether I needed it or not.

Here Alice articulates her desire for certainty, and assumed responsibility for obtaining the test by paying for it herself if necessary. She was intending to act on the results, accepting chemotherapy if it was recommended, just to 'get it done'. Alice's feelings about Oncotype DX were echoed by Julie, who was very keen to avoid chemotherapy due to her concerns about her immunity being compromised during treatment; but she also felt that the treatment would be unavoidable if the test results predicted a high risk of recurrence. She described the information provided by the test as a 'crystal ball'.

These framings were also observed in online forum discussions. When users asked for information about the test, Oncotype DX was presented positively by some because, in the words of two

respondents, it 'took the guesswork out of whether you should have chemo' and meant the patient would 'know whether you need chemo or not', offering one kind of certainty in an uncertain future. Collectively, patients on these forums encouraged and supported each other to take on the responsibility of accessing and acting upon Oncotype DX results. Oncotype DX was also praised by some as a means to aid chemotherapy decisions because of the way in which results are displayed as a single score representing recurrence risk and potential benefit from chemotherapy. Patients who had until that point experienced uncertain and shifting diagnostic pathways were particularly enthusiastic about this kind of scoring system. Oncotype DX testing was therefore valued by patients who told us they had found the uncertainties and 'false horizons' of diagnosis and treatment difficult. This was especially the case for those patients who had not initially anticipated having to consider chemotherapy, as it was not raised as a possibility until pathology results were obtained following surgery. For these patients, Oncotype DX results offered welcome guidance for an unexpected and unwelcome decision. Lillian, for example, told us of her experience of researching Oncotype DX online after her clinical nurse specialist (CNS) rang her to inform her about the test. Until this point, Lillian, an office worker in her early sixties, thought her cancer was a mucinous breast cancer, which is a rare cancer, but when she found out this wasn't the case, for her, 'it was kind of a sense of relief almost (laughs) … Because I thought, well, they're more used to treating a more common cancer.' Lillian found the CNS and online chatrooms were particularly useful in offering reassurance that the test was valuable for guiding treatment decisions. Of her Oncotype DX result, Lillian explained:

> I think I could see things in black and white a bit more clearly. So you can be told your grade or your stage of your tumour, but to be able to know a bit more about likely recurrence and a bit more about prognosis and things like that, for me … it all came together and made it so much more understandable somehow.

For Lillian, being a 'good patient' involved taking on the mantle of responsibility to research and consider options, to understand and make sense of results and to choose wisely when it came to treatment possibilities. This also encouraged Lillian to take part in the 100,000 Genomes Project (discussed in Chapter 5).

In some cases, where participants were placed in the low recurrence risk category, the test also enabled them confidently to avoid chemotherapy. Susan, whose daughter also had breast cancer at a similar time, explained that the Oncotype DX result 'reinforced' her preference for rejecting chemotherapy. Seeing her daughter struggling with chemotherapy, 'it was only because [of the] Oncotype result' that she could avoid the temptation of 'belt and braces sort of way of doing'. Bethany, meanwhile, described the test as allowing her to feel more 'confident' that it was not irresponsible to forego the treatment. The test results were also welcomed by some patients who were considered to be at a higher risk of recurrence and who might therefore benefit from chemotherapy to reduce that risk. Lois, who had her cancer detected at a three-yearly breast screening, described the meaning of the Oncotype test as 'a second opinion' which allowed her to avoid chemotherapy:

> [They said] 'we could just give you chemo or there is this test available, the Oncotype test' so immediately we said 'yes please, if we could get that'. And fortunately three weeks later it came back to say it was reading 6 so I was clear of needing any chemo so that was a great, a great day.

In other respects, however, certainty was not always provided by a straightforward reading of the test results, even when these were clearly at one or the other end of the spectrum, as the following example illustrates. Zoe, a medical professional, described her sense that there was a 'right' choice to be made about chemotherapy when she told us about her experience of the Oncotype DX. Using NHS Predict her cancer had been designated as at low risk of recurrence, but her oncologist voiced uncertainty about this designation because the cancer was high grade. Oncotype DX testing was recommended and Zoe started reading academic journal articles about the test, including the recent results of the TAILORx study. However, Zoe did not feel secure in rejecting chemotherapy when her Oncotype results came back with a low score of 7, and she deferred to her oncologist following the result, to further confirm that she was making the 'right choice'. Without Oncotype DX testing, she explained, because her cancer was high grade it would have been a 'constant worry' whether not going for chemotherapy was the 'right thing to do'. But it took work on the part of Zoe and her

consultant to interpret the results of the test together in such a way as to achieve her sought-after certainty.

As clinicians emphasised, the interpretation of results was highly contextual. This is illustrated in the extract from fieldnotes below, in which an intermediate result is discussed:

> And then [consultant oncologist] brought up Oncotype test results on the screen saying 'Graph is very useful'. [Consultant oncologist] said 'your score is 30 so it's intermediate risk'. The consultant said, 'hormone therapy will be beneficial but the difficult decision is about chemo'. The consultant asked the patient to guess where they 'belong' – the patient answered 'middle group' with a burst of laughter. The consultant showed the graph on the screen again and compared the risk of recurrence when the patient has hormone therapy (14%) vs. when she has both chemo & hormone therapy (7%). In order to emphasise the difference, the consultant used her fingers to measure the gap. The patient replied by saying, 'noticeable benefit'.
>
> This is when the consultant brought up the patient's heart failure and the patient asked how much chemo will affect her heart condition. [Consultant oncologist] explained that any chemo drugs that might affect the patient's heart won't be allowed to [be] prescribe[d] and also because of the patient's history of pneumonia and kidney stone, alternative chemo drug called taxol will be recommended and the patient will be monitored very carefully. It's 'a diluted form' and will be administrated weekly so it's 'not too bad'. [consultant oncologist] then went on to explain the side effects including hair loss (the patient laughed), infection, and weight gain – the patient laughed again at this and turned to her mother and joked 'it will look really nice mom'. The consultant said they appreciated that the patient's heart condition is 'a significant setback' given that she always has reservation for chemo under any circumstance. The patient said she is 'between a rock and a hard place' but she has always been 'an unlucky person.'
>
> Then the conversation shifted to talk about the patient's care responsibility. The patient's adult son is living with her and her husband and he has severe disability. The patient was concerned about her husband who is in his late 60s, which mean[t] he won't be able to look after their son on his own so she was wondering whether she will be well enough to continue to help out while receiving chemotherapy. The patient said this is the reason why 'this is difficult decision to make'. The consultant said 'I am glad you said this' and it's important to know what kind of 'limited reserve' the patient has. The patient

> said, 'I am a mess'. The consultant said it's possible to suspend chemo depending on the patient's general health and the patient replied 'it's reassuring to know' and suggested that she might 'try and see'. The consultant explained again that they will recommend the chemo that is for frail patients or patients with existing health issues and suggested that the patient can read information leaflet that will be given to her and have a think about it. The patient said she is happy about this arrangement so she could have a discussion with her family. They went on to talk a bit more about other side effects. The patient's mother asked if there is any alternative to chemo. The consultant reiterated the value of Oncotype test – there are some benefits of different treatment options but Oncotype test 'teases out' the benefits.

For this patient and her family, the intermediate test presented a 'difficult decision' given her health and caring responsibilities, and required careful negotiation over the kind of chemotherapy that she could manage. Together with the consultant and her mother, she worked to articulate and balance her various responsibilities to be well and to care for herself and her family, making the Oncotype DX result, and more specifically the intermediate result, a valuable tool for navigating her particular circumstances. The uncertainty of the intermediate result was productive, creating a space for consideration of this patient's unique circumstances, and facilitating her and her family's involvement in treatment decision making (see also Brown and de Graaf 2013; Swallow 2019).

As with the clinicians we interviewed, some patients also took other factors into account when making their decisions, rather than following the recommendations of their test result alone. Supported by her oncologist, one patient 'in the grey area' decided to go ahead with chemotherapy:

> so, my understanding anyway was that it's a low risk cancer but obviously the score on the Oncotype having been fed into that system … I was in the grey area as to, as to whether or not I would need [chemotherapy]. But in my head I'd already decided that it was inevitable.

Another woman with a low risk of recurrence score, writing on a breast cancer forum, noted that because of her young age and her experience of her father's death from bone cancer she would proceed with chemotherapy, despite her Oncotype DX result suggesting a low risk of recurrence. Another patient described receiving a low

Oncotype DX score but proceeded to chemotherapy because of the size of her tumour. For other patients, results could be flexibly interpreted, particularly patients with scores in a 'grey area'; for example, an intermediate result could justify stopping chemotherapy early due to unpleasant side-effects, as was the case with two forum users.

In these situations, the complexities of Oncotype DX did not always resolve uncertainty but raised questions and worries, sometimes making grey areas larger rather than smaller. These included situations where, long after the test had been conducted, patients continued to wonder about their prospects of recurrence. For example, in an interview with Wendy, conducted three years after her diagnosis, she told us she was not sure what the Oncotype DX test was, and 'never really asked', although she described herself as 'somebody who wanted to know as much as I possibly could'. Having gone through treatment and now being back at work full-time, Wendy explained why she never asked about the test:

> I looked it up online later, I did find out quite a lot although it didn't go into detail about exactly what the test was. And it's quite interesting because I never really asked because I could never work out how to find the right words but I never asked whether, if it came back saying you won't benefit from chemotherapy, is that because the tumour is unlikely to spread or is that because it won't respond? Do you see the difference?

Wendy had received a low risk of recurrence score and had accepted the recommendation to forego chemotherapy, but she remained fearful of recurrence, a common feature of living with or beyond cancer, as poignantly discussed by Horlick-Jones (2011). She remained unsure about whether her low score was due to the fact that 'the tumour is unlikely to spread' or 'because it won't respond' to treatment.

The introduction of the test to already complex diagnostic and treatment pathways created additional distress for some women. Several accounts attributed this to the fact that gene-expression profiling exacerbated the 'rollercoaster' experienced during initial diagnostic processes, with all this 'thrown up in the air' by the introduction of Oncotype DX (breast cancer charity forum), especially due to the time required to wait for the results from the US (up to two weeks). Echoing Gillespie's (2012) findings of 'measured

vulnerability', a few participants told us that discussions about the test exacerbated their concerns about their cancer, including Bethany, discussed above, who was diagnosed with breast cancer at the same time as three of her friends. As the only one who was offered Oncotype DX testing, she questioned what this meant about the severity of her cancer as compared with others. Another patient, Chrissy, a woman in her sixties who detected a lump that led to diagnosis, also told us that gene-expression profiling raised a lot of questions for her about why she was being offered this test: 'Who debates whether it, it gets sent off or not? Who … makes that decision? The consultant or … I've got a friend that's got tongue cancer … that's not gone off for any testing. Why … me? (laughs) Why has mine gone off?' When she was told to have chemotherapy, Chrissy said she was 'shocked' as she expected to go back to normal life after the surgery. Chrissy related her anxieties about the test to the fact that the test was 'something new', and processed in a laboratory in the United States:

> So when they said they were sending samples to America, it was like, well, this is something new, something I don't know anything about … you'd tend to think if it's a well-known test they would be doing it in this country as well. So it was a bit of … an alarm bell ringing I suppose as to … what's different that they need to send it away to do this?

Here the 'newness' of the test was a source of concern rather than a sign of its value. For some this was due to their unfamiliarity with the test and its mechanism. Participants were given a variety of levels of explanation about the technology by their clinician, and engaged with further information about the test in varying ways. The way the test might be used as a cost-cutting mechanism, denying patients treatments they might want, also occasionally came up, as in this quote from Ally, whose plans for an active retirement had been blighted by her cancer:

> So then you start to think, knowing the NHS, knowing the state of budgets, whether that [drug] is not going to be [given], because you do hear in the news don't you, that some people could benefit from having a certain type of drug for any particular condition, but because it's expensive, 'oh we can't give that'; that isn't rolled out to everybody just yet.

Other interviewees did not engage with detailed information around the test, including patients who said they did not possess detailed knowledge of the different tests they had received or the implications of their results. Valerie, a young woman in her thirties, experienced her cancer diagnosis and treatment as 'like a conveyor belt'. She had conducted her own research about breast cancer following her diagnosis, and involved her husband in the processes of treatment decision making following her Oncotype DX result. However, she remained unclear about how the result of the Oncotype DX test was achieved, and what this represented. She explained: 'I've found out various bits and pieces in the booklet that, that it goes to California … I think it's difficult 'cause … everyone is clearly different with whether they want to read anything or not. I didn't really want to read anything.'

Here Valerie draws attention to an experience related by many of the patients we interviewed across our wider research, for whom being a responsible patient meant avoiding 'too much' information, limiting their internet searching and the questions they asked, and taking their cancer management 'one step at a time'. In the case of Oncotype DX, this resulted in some women and their loved ones engaging with minimum information about the test, because of the complexity and the amount of information they could take on board at this distressing time. Two patients signalled that they had only engaged with the test because they were required to make a choice, although it would have been, in the words of Alice, 'easier' if her clinician had initially given a clearer recommendation about chemotherapy, rather than offering her a treatment choice. For these patients, a strong sense of trust in their clinician's assessment of the Oncotype DX result, in the context of other information, rather than the score alone was more significant than the intricacies of the test, highlighting the enduring importance of clinical judgement for patients (Latimer et al. 2006; Bourret et al. 2011).

Conclusion

Oncotype DX was totemic of advances and further personalisation of cancer care in the future across policy, practitioner and patient accounts. While there were a range of views about the clinical utility

of the test and its cost-effectiveness, there was nonetheless general support for the role of such technologies in an unspecified future. More pragmatically, the test was commonly associated with greater certainty, and relief for cancer patients from the burden of toxic chemotherapy, or else as providing compelling support for such therapy. Savings and efficiencies in the NHS were highlighted by some as key benefits of the technology being more widely adopted. Practitioners and patients told us the test was valuable as a means of confirming decisions and obtaining reassurance, providing more certainty that enabled them to act responsibly in making wise decisions about the need for treatment to decrease the likelihood of recurrence.

Nevertheless, its promise in practice was muted. There was scepticism, uncertainty and resistance to its wider use, from practitioners choosing not to perform the test as they considered it costly and unnecessary, to patients finding that results did not deliver certainty and reassurance, raising further anxieties and questions (see Ross et al. 2019). At times, patients resisted the impetus to actively research and engage with test results as a means of navigating their illness, and instead sought to limit their engagement with this and other information as a means of maintaining their poise and managing anxiety. The value of the test was thus provisional and in-the-making, as practitioners and patients navigated its implications and experimented with its uptake and interpretation. Being a responsible practitioner or patient could involve a range of orientations towards the test and its results, and choreographing these orientations involved articulation work in the clinic and beyond.

The approvals process was guided by a precautionary logic where uncertainties and scepticism about benefits were given weight, but we found that much of the flexibility and ambivalence we encountered in our study was absent from public discourses about the utility of the test. Although capturing patients' investment in the test and the value it brought to their experiences of treatment, policy and media accounts did not often capture the uncertainties and grey areas that can abound for patients who have been tested, even when certainty is promised or anticipated. Patients' and practitioners' ambivalence was overlaid with more totemic, anticipatory regimes of personalised medical futures, even in processes which purported to question the value of the test and aimed to capture a broad range and variety of experiences to guide policy formulation. The arbitration of

contested and conflicting evidence from trials and patient and clinician testimony resulted in continued valuing of the test within the NHS, thus ensuring both that the commercial imperative and the promise of precision medicine continued apace.

Through these dynamics, our case study of Oncotype DX reveals that the promise of personalised medicine is highly contingent and flexible and enacted through articulation work backstage of policy and public discourses. This promise is nevertheless amplified in frontstage policy, advocacy and media framings which assert benefit at the same time as they tend to mask ambivalence. These processes also frame personalised medicine as mainstream, even as the technologies at its forefront may be rejected or become folded into the complexity of responsibilities and decision making involved in the navigation of cancer diagnostics and treatments by practitioners and patients.

Notes

1 www.nature.com/subjects/gene-expression-profiling (accessed 20 June 2020).
2 www.nice.org.UK/guidance/dg34/chapter/1-Recommendations (accessed 20 June 2020).
3 https://breast.predict.nhs.UK/predict_v1.2.html (accessed 20 June 2020).
4 www.nice.org.UK/guidance/dg34/chapter/4-Evidence (accessed 20 June 2020).
5 www.cancer.gov/news-events/press-releases/2018/TAILORx-breast-cancer-chemotherapy (accessed 8 October 2019).
6 www.nice.org.UK/guidance/dg34/chapter/1-Recommendations, section 1.1 (accessed 1 July 2019).