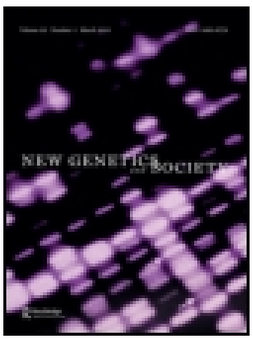

Routledge
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New Genetics and Society

Critical Studies of Contemporary Biosciences

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/cngs20

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To cite this article: Sophie Day , William Viney , Jane Bruton & Helen Ward (2021): Past-futures in experimental care: breast cancer and HIV medicine, New Genetics and Society, DOI: 10.1080/14636778.2020.1861542

To link to this article: https://doi.org/10.1080/14636778.2020.1861542

Published online: 06 Jan 2021.

New Genetics and Society, 2020
https://doi.org/10.1080/14636778.2020.1861542

Past-futures in experimental care: breast cancer and HIV medicine

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(*Received 31 December 2019; final version received 24 November 2020*)

Cambrosio et al. (2018. "Extending Experimentation: Oncology's Fading Boundary Between Research and Care." *New Genetics and Society* 37 (3): 207–226) argue that "experimental care" in contemporary oncology involves the rapid merging of patient research and care, and invite further study into developments across other health conditions. We present a 2018–2019 study of experimental breast cancer care in an urban clinical setting in the light of two other studies in the same hospital group: in the same cancer service (2013–14) and, prompted by these earlier findings, an interview study in HIV services (2014–15). We found that patients and staff anticipated better outcomes by treating sub-types of breast cancer but they also hoped for a better one-size-fits-all approach, akin to the antiretroviral treatments introduced for HIV and explored in our interview study. We conclude that the promise of targeted treatment for sub-types of disease – variously described as experimental care, personalised, precision, stratified and sub-group medicine – is accompanied by hopes for a single, standard, effective approach.

Keywords: Experimental; care; medicine; breast cancer; HIV

Introduction

Developments ranging from genomics to data analytics and the involvement of patients and the public suggest a new dawn in biomedical research. Experimental care, as we gloss these developments, is central to research that aims to improve patient outcomes and it is known by a variety of other terms, including personalised, precision, stratified and sub-group medicine. Rapidly evolving platforms promise to deliver successful treatments based on a more precise classification of disease types and perhaps novel aetiologies. Very often, this success is envisaged through a contrast with a previous one-size-fits-all approach that delivered the same treatment to everyone who had the same broad diagnosis. We argue,

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however, that today's hopes ignore the diversity of previous and contemporary platforms for research and care. These have led to exactly the broad standardised interventions – through vaccination or antiretroviral treatments for HIV for example – that now seem outmoded as well as targeted interventions for subgroups. We hope to show that research and care build on as they supplant previous platforms for experimental care by looking at two different health conditions We ask in conclusion whether experimental care offers a better future of standardised as well as subgroup treatments.

We adopt the term experimental care from Cambrosio, Keating and colleagues (2018). They describe a merging of research and treatment which has involved an unprecedented integration of biological and clinical research as well as data analytics since the 1990s. They suggest that these developments followed a period after World War Two when the figure of the clinical researcher became somewhat less central than previously. Incremental development of networked platforms has since advanced to co-ordinate research practices with the management of data from cancer research and cancer care (Keating and Cambrosio 2011, 2012). Cambrosio et al. (2018) argue that "experimental care" in contemporary oncology is marked by the routine use of trials and the rapid merging of patient treatment and research. It is impossible, they argue, to differentiate research and treatment since patients are invited to participate in research for which they are eligible and since research findings are translated rapidly into new service protocols. Accordingly, they identify a "fading boundary" or "vanishing distinction" between research and treatment (2018, 208) because changes in the content, meaning, and boundaries of one activity result in changes in the other.

In the UK, research and treatment have been variously demarcated and combined. National Health Service (NHS) and private budgets were increasingly distinguished from the 1980s, and budgets for research were increasingly separated as internal – and other – markets were introduced to the health system (Department of Health 1989; Le Grand 1991; Mold 2010). Together with new public management practices (Flynn 2012), marketisation also contributed indirectly to an increasingly firm divide between clinical research, mostly in the form of drug trials, and standard treatment. Currently, clinical staff and research governance in services place boundaries around patients to protect them from formal research (General Medical Council 2010). However, developments in -omics, in data collection and analysis, and policies encouraging collaboration between private and public bodies have led to renewed emphasis on the interplay between research and clinical practice. These developments inform the combination of research and care in contemporary oncology and practices of classifying, identifying and treating cancers. For example, multiple types of breast cancer were described in 2012 (Curtis et al. 2012), confirming a genetic heterogeneity that is associated with increasingly precise therapeutic targeting. These new practices require the wide participation of patients in both clinical trials and routine surveillance of outcomes (NHS 2016; Davies 2017).

Research in both social sciences and oncology agree that it is no longer possible to readily distinguish research and standard treatment. Sacristán and Dilla, for example, comment that "the classical separation between explanatory trials, aimed at understanding, and pragmatic trials, aimed at decision, will become as blurred as the frontier between research and care" (2018, 166). Moreover, the classification of cancers has become uncertain and contested. Heterogeneous combinations of biomarkers, molecular pathways, treatment responses and the evolution of cancers are difficult to align so as to distinguish clearly between diseases that are defined in relation to previous categories such as anatomical site and newer molecular features. This heterogeneity is addressed through varied approaches: basket trials that assess an intervention across what were different diseases; umbrella trials that test combination therapy in a single condition and a variety of n of 1 studies, which include a single patient. Adaptive trial design is a common way of addressing the heterogeneity that may only be defined post facto (Mistry, Dunn, and Marshall 2017; Swallow et al. 2020).[1] It remains an open question how combination therapies can be trialed rationally, and which biomarkers enable reasonable monitoring. Collaborations among scientists, regulatory organisations, patient groups, and industry in the North American context where Cambrosio, Keating and colleagues have conducted much of their research, as well as internationally, are critical to these developments. More generally, this team's work has contributed to social science and humanities research on experimental practices as they are known in specific historical, organisational and epistemic situations (Hacking 1983; Galison 1987; Rheinberger 1997, 2010; Roepstorff and Frith 2012; Callard and Fitzgerald 2015).

We extend Cambrosio and colleagues' concept of experimental care to clinical interactions in a large, research-intensive NHS breast cancer service in London. We reflect on our interview and observational data in the context of contributions from the social sciences, humanities, and clinical medicine that have examined the role that promise, expectation, and potential plays in this combination of research and care (Hedgecoe 2004; Rajan 2017; Tutton 2012, 2014; Feiler et al. 2017; Maughan 2017; Sturdy 2017). In the clinic, staff and patients attached a sense of promise to experimental care, which might help identify types of breast cancer and appropriate treatment. But their hopes were qualified by everyday uncertainties about the evolution of a cancer, response to treatment, and eligibility for particular treatments and inclusion in research studies. Possible therapeutic strategies were a major focus of translational research, in which patients were invited to participate. Although formal experimentation largely takes place in clinical trials, it is difficult in clinical settings to draw firm lines between a platform for experimental care and everyday clinical experimentation. Clinicians and patients routinely adjust and adapt to the effects of therapy and the course of illness. Individuals may be prescribed experimental or "off-label" treatment in the absence of clear evidence of efficacy and safety, particularly when other treatments have failed and for patients with a life-threatening or limiting condition (The Nuffield Council on Bioethics

2018). Evidence-based medicine and treatment protocols are calibrated to particular situations through "tinkering" (Timmermans and Berg 1997; Bowker and Star 1999; Mol 2008). Uncertainties in everyday clinical interactions were expressed in conversations. Could better outcomes be delivered for everyone through differentiating types of breast cancer? Would the apparent antonym of "one-size-fits-all" medicine, which has been realised historically for other health conditions, remain relevant and, if so, how?

These questions led us to interview participants about experimental care in the same hospital group's HIV services in 2014–15 after conducting research from 2013–14 in breast cancer services. We then returned to the hospital group's breast cancer services to study developments from 2018–19. The relatively short history of HIV care in the same setting allows us to ask questions of today's experimental cancer care. Our 2013–14 research in breast cancer services raised questions about varied platforms for experimental care and we selected HIV medicine because of our own backgrounds. Three of us worked in HIV and sexual health during the early response in the 1980s and 1990s: an anthropologist in a sexual health clinic; a clinician and public health researcher in sexual health and HIV; a senior nurse specialist in HIV inpatient and outpatient care. Historically significant developments preclude direct comparison between experimental care in breast cancer and HIV. Changes in translational medicine, health policies and funding as well as the very different aetiologies and populations constituted around these conditions and the different contours of advocacy and collaboration all make direct comparison impossible. Our purpose is to suggest that hopes and uncertainties produced by experimental breast cancer medicine and its markets (Dumit 2012; Gabe et al. 2012; Cohrs et al. 2014) are illuminated by reference to a history of HIV services. We focus on clinical research priorities within paradigms of translational medicine – through which clinicians, researchers, patients, hospitals, bioinformatics and bioengineers, biotechnology companies, and regulators cooperate and compete to shape the "normal" and the "pathological" (Mittra and Milne 2013; Crabu 2018).

We first present research in breast cancer services during 12 months' observation and interviews, 2018–2019 and discuss developments. We then present results from an interview study with patients and staff in HIV services (2014–15) from the same hospital group, but across two different sites. In discussion, we highlight continuities in biomedical approaches amidst otherwise incommensurable dimensions of breast cancer and HIV services. We ask about the implications of exploring experimental cancer care today through an earlier platform in another service area of this hospital group. What questions and possibilities are raised by considering such past futures?

Methods

Previously, we reported our findings from 2013–14 (Day et al. 2016; Mc Grath-Lone et al. 2015; Mc Grath-Lone et al. 2015). Our fieldwork methods

in 2018–2019 mirrored the combination of observation and interview in the earlier study. We observed the main outpatient clinic and accompanied staff or patients to other parts of the clinical pathway, such as chemotherapy services and multidisciplinary team meetings. In 2018–2020 we interviewed 54 staff and patients, including 11 who had participated in the previous study. Three researchers (WV, SD, HW) carried out observation and interviews, and kept field notes. Interviews were recorded and transcribed verbatim, coded and analysed in NVivo12. Key themes were identified and discussed in monthly team meetings before coding, enabling a shared foundation for continuing fieldwork. The integration of these varied data enabled fuller interpretation: interview material was extended by observations across different settings, while fieldwork notes were elaborated in the light of individual and collective views and explanations.

We selected a subset of interviews from a 2014–15 study to include those with experience of HIV services in the later 1990s. We interviewed 11 people with HIV who were diagnosed before effective antiretroviral therapy (ART) became widely available in 1997 and 8 members of staff. These interviews were also recorded and transcribed verbatim, coded and analysed in NVivo12. Key themes were developed through a systematic process of reading, rereading, coding and summarising transcripts and subsequent in-depth analysis of the dataset. Final themes were discussed in the research group, focussing on experiences before and after the introduction of effective ART (Bruton, Rai, Day, and Ward 2018; Rai et al. 2018). Themes relating to combinations of research, care, and treatment outcomes were compared iteratively across the three studies.

Breast cancer services

In our earlier work, staff and patients described problems in receiving and delivering services, which we considered in relation to both government measures and the complexities of translating developments into existing services (Day et al. 2016). We found on our return a continuing emphasis on biomedical research and the promise of genomics, linked to widespread participation of patients in digital platforms to manage both NHS and research data. However, patients and staff rarely referred to "experimental care" or related terms such as "stratified", "personalised" or "precision" medicine.

Despite initiatives to better manage a complex pathway (Day et al. 2016), staff in this London hospital group reported that pressures on the service had increased in the face of growing workloads and more intensive treatments over the past five years. Staff and patients alike credited some constraints, such as shortages of space and staff, to UK government rationing. Other difficulties were attributed to developments in biomedical research and their impact on clinical practice. An oncologist noted, "twenty-five years ago, each type of cancer had two, two or three, types of treatment but now each has got ten types."[2] In interviews, both staff and patients described how treatment kept people with metastatic disease

alive for longer. They also reported that treatment required more monitoring, liaison and intricate adjustments. For example, a doctor explained problems of resistance to a patient as he recommended a new regimen, "We find that adding one [drug] onto another in a version of combination therapy works to turn breast cancer into a chronic disease." Some of the drugs were new; for example, CDK4/6 inhibitors (in combination with aromatase inhibitors) have been introduced since our previous study.[3] They are taken orally, are far less toxic, and do not cause hair loss. Initially available to patients with locally advanced or secondary cancer that is both hormone positive and HER2 (human epidermal growth factor receptor 2) negative, the use of CDK4/6 inhibitors in combination with other treatments and in other types of breast cancer continues to be trialed (e.g. Sobhani et al. 2019). Patients on these treatments were scanned more frequently but there were not enough radiologists to report the additional computerised tomography (CT) scanning. An oncologist complained, "With some of the new drugs like the CDK inhibitors, we used to scan them three monthly and now we see them at least every month … in the past, they would have been on hormone therapy. … If a scan isn't reported and I'm not sure what the result is … we need to scan those patients frequently to make sure they are responding. To make sure that it's best for the patient … " Such judgments also required close liaison among staff, often across service areas. Patients were living longer, often with metastatic disease and other conditions and, as a doctor explained, she now had to work with specialists across the hospital: in neurology, neurosurgery, gynaecology, hepatology, cardiology and so on; "We have spread, we touch everything as patients have multiple appointments with different specialists. They get problems in every system."

The milieu remained challenging. "There are", said an oncologist, "no more averages. I can quote averages from clinical trials, but we don't know." She found it especially difficult when patients asked for advice on tumor sequencing, circulating tumor DNA tests, or the immunotherapy they could buy from Germany for €60,000: "[A test] may come back with lots of mutations that there's no drug for, or there may be several mutations. Which mutation do we go to first? If there's a drug, it's not available, or they may have already had some of that treatment, and there may be heterogeneity within a tumour. If we biopsied a different part of that tumor or a different metastasis, that might throw up different results."

Patients continued to experience significant uncertainties alongside the burden of treatment. NHS-approved algorithms produced scores that were difficult to interpret as well as intermediate groupings where there were no clear guidelines (see Kerr et al. 2019). Moreover, the cancer with which patients were at least provisionally identified was re-evaluated constantly. Proliferating types were rated and ranked and some people were pleased to find they had "HER2 positive breast cancer" in both our earlier and more recent research because they could benefit from targeted therapy. In the mid-1980s, it was found that the HER2 protein receptor affected the growth of some cancer cells. A treatment was developed,

trastuzumab, licensed in the US in 1998 and the EU in 2000 under the brand name Herceptin. Routine screening looks for amplification of the HER2 protein, which is associated with around 20–25% of breast cancers (Arteaga et al. 2012). During a recent (2018) group discussion in a neighbouring non-governmental organisation, a participant asked about her metastatic disease. She praised research developments but remained concerned about her own poor prognosis: "it's all good so long as it doesn't mean that I can't have something like Herceptin [trastuzumab] in a year's time when everything else has run out – if that would give me another six months." Trastuzumab is not a drug used to target her own kind of cancer, which was not HER2 positive in the past. A nurse asked if she would have a repeated biopsy and we wondered whether this might pick up changes suggesting her new tumors were now, perhaps, 20–30% HER2 positive**.** This woman, like others, was aware of the dynamic heterogeneity and mutability of cancers and she navigated multiple classification schemes according to anatomy, histology, genomics and likely evolution.

By contrast, as we reported previously, triple negative breast cancer was considered a bad type. The term, Triple Negative Breast Cancer (TNBC), was first used in 2005 (Brenton et al. 2005) to describe approximately 15–25% of breast cancers in which chemotherapy was the only treatment available, since they cannot be treated with hormonal therapy or anti-HER2 agents (Pareja et al. 2016). TNBC is an umbrella term for an otherwise heterogeneous group of cancers. Discussing the research-intensive nature of the hospital as we were waiting in the outpatients' department in 2013, Tina[4] had said, "the trouble with the research, although it's very good for care here, is I am triple negative and there have been no findings. It's possible there will be developments. Maybe if they keep me alive for them, I will benefit. Who knows?" It was a challenge to identify with a tumor defined in the negative, that is, lacking the three biomarkers which can be targeted. Tina had been a nurse herself and was learning about the new biological landscape, complaining that there was nothing for her cancer and her prognosis was worse than for other types. She concluded that hers was an orphan disease and she saw herself as an orphan in an orphan population that had to wait for improvements in research and care for their kind of cancer (Day et al. 2016). In 2018, we learned, new immunotherapies showed some promise for this type of cancer (Marra, Viale, and Curigliano 2019; see also Schmid et al. 2018).

Surrogate or biomarkers had not changed in routine monitoring and results from measuring CA15–3, a carcinoma antigen that increases in most metastatic cancers, remained an unreliable guide. Meeting a patient we knew from an earlier study, we were greeted with a smile as she said her "marker" was 32. Almost at once, she said this measurement did not really tell you anything but, she emphasised, in the bad old days when she first attended services, it was 200 and, more recently, it was higher than 32. She was therefore encouraged by the trend. In contrast, a young woman was disappointed when she came into the clinic with new liver metastases.

At one point, she asked, "how come the numbers go down and everyone says it looks good – the tumours are shrinking. And then this?" Her doctor responded, "well, it's because it is all good until it's not. With developing resistance, cancer comes back all at once. We can't tell beforehand. … Also, the mechanism is different in every single person so we can't even predict which treatment or course of action will work in which patient. So, we try therapy that might work, like this triple therapy, but we don't know." Outside the clinic, this doctor explained the complexity of dealing with a situation in which every patient could be deemed to have a different cancer.

In sum, we found that the atmosphere in clinical services was more hopeful than five years ago: there were more therapeutic options and many patients thought they would live better for longer, as did their clinicians. Nevertheless, some types of cancer had no new treatment options, and results for most remained provisional. Test results amplified as well as reduced ambiguity; they often led to further tests, further biopsies and further efforts to work out whether your own cancer could (now) fit into a category suggesting a different approach. In this environment, as we elaborate below, women with metastatic disease especially considered that they were treated and studied simultaneously through close monitoring and continual adjustments of regimen. Many were also invited to participate in formal research studies.

Women with breast cancer in this service were and are invited to participate in research. Even with careful screening beforehand, some were found to be ineligible for the available studies but the majority enrolled in formally defined research. Many participants considered that they enjoyed good care as they contributed (Mc Grath-Lone et al. 2015; Mc Grath-Lone et al. 2015). Although consent processes typically limit the formal return of trial results and caution participants against expecting personal benefit, we found that patients were drawn to research for a variety of reasons. They typically anticipated an enhanced form of care, with more frequent contact with clinical and non-clinical staff, appointments in post-treatment follow-up, and the opportunity to contribute to the care of future patients. A single example illustrates the different experiences of Tina and Fiona. As the service protocols for Tina ran out (see above), she continued to hope that she might benefit from experimental cancer care even though she was not eligible at the time to join any of the available studies. We met her in the waiting room when she had come to understand that there was still nothing to help with her condition and she was at "the end of the road". Fiona, in contrast, had been found eligible and was invited to participate in a trial. Towards the end of the study, she wondered if she were a "freak" because she stopped meeting her co-participants on the day that they used to wait together to see the same doctor in the same clinic. It was just her alone. There was no response to her query in an online chat group. What was wrong with her? An oncologist, we learned, responded carefully to this situation and explained that there was nothing wrong. The doctor emphasised to the contrary how special Fiona was. Her cancer was not the same

as others on the trial and it seemed to respond well to the drug, "It works on your individual cancer; theirs was different." To Fiona, experimental care at this point was highly responsive to both her personal well-being and the goal of improving knowledge. Departing the trial, she wondered about the chance of recurrence. Although she was pleased not to come to the hospital so often, she lost the support she had enjoyed from a research technician, who made her visits to the service run smoothly and who facilitated referrals for health issues that were probably unrelated to cancer. The frustrations of discovering where you needed to be when, to do what with whom, returned.

Although Cambrosio and colleagues associate experimental cancer care with a distributed platform for research participation, which rapidly translates research findings into service protocols, we found that staff and patients recognised the benefits of joining formal research studies to obtain "better" care directly. Patients participated in research not only because of their commitment to improving treatment, most likely for future generations, but because they found that they enjoyed continuity, better information and more frequent check-ups. Most patients and staff stressed the additional monitoring that might detect "incidental", that is, unrelated health problems, which could then be addressed. Most participants considered that formal research participation delivered better overall health care (see also Hallowell et al. 2010; Kost et al. 2011).

Amidst these uncertainties, clinical researchers seemed to aspire to therapeutic approaches that worked in the past as well as those that hold promise for the future. One clinician in cancer services drew on historical precursors to situate the present complexity of cancer treatment:

> It would be better if we had one curative treatment. It's a bit like tuberculosis before antibiotics … there were hundreds of different treatments for tuberculosis before antibiotics, very complex surgical and other treatments. But then the moment triple therapy was brought in, there was only one treatment for tuberculosis. So in 20 years' time - it could be that - we have now got an incredible number of treatments for these [breast cancer] patients. But, at the end of the day, in 20 or 30 years' time, we could only have one.

In the absence of established knowledge, it is not clear how to categorise patients with what appear to be common or distinct health conditions. Whether or not this clinician paints a likely future, he hopes for a single effective approach to whatever comes to be described as a single disease. Perhaps too, he is drawing on the principles of equity and access associated with NHS principles of collective provision. Experimental breast cancer care is a dynamic translational platform that affects clinical, research, patient, and corporate partners in different ways. Our interviews and observations suggested that a fading boundary between research and care generates both hopes and uncertainties. These are reflected in the burden of reporting and decision-making associated with the novelty and number of treatments. A mixture of promise and confusion is produced by proliferating categories of

disease that are evaluated by staff and patients against emerging evidence and the changing experiences and expectations of patients participating in research-intensive regimens.

HIV services

Cambrosio et al. (2018) note that care has long been shaped by research but consider contemporary oncology a "forerunner" (2018, 221) in developing a novel integration of care and research practices. They want to historicise the emergence and revival of experimental care, "its repeated re-emergence and re-definition, and the shifting relations between these two components" and they ask, "how generalizable are our findings?" (2018, 213, 221). They look to parallel contemporary developments in cardiology for an answer but we ask about historic developments in HIV services. Periods of experimental care in numerous health conditions have involved scientific research alongside responses to very sick people. Previous collaborations in experimental care may provide insight into the promissory timbre of breast cancer medicine today. HIV research and treatment were tailored to individual responses and preferences as well as formal experimentation in the early years. Subsequently, a far more uniform approach to treatment was developed. Genomic medicine was unknown in early HIV services, but experimental practices spanned laboratories, clinics, government, industry, advocacy and activism in efforts to care for and sort patients according to individual and group responses. More precise measurements developed, populations were stratified and experimental care was tailored along various parameters.

HIV is a retrovirus with a small genome by comparison with cancers, recognised as the cause of AIDS in the 1980s amidst a major public health crisis, great fear and segregation. Discrimination against groups that were already stigmatised compounded the difficulties for those with HIV, most of whom died in the early days. The first UK patient with AIDS was treated in the hospital Trust where we conducted research in breast cancer services towards the end of 1982 and since that time there have always been in-patients with HIV/AIDS in the two hospitals in which we have worked. Between 1982 and 1985, the number of patients increased dramatically and took a fifth of the acute medical beds at one of the two hospitals (Weber 2018). It was inconceivable to treat people in this health crisis without carrying out research. Likewise, it was impossible to carry out research without providing support and care to those affected by HIV. In both hospital sites, early responses were mixed but services attracted staff who wanted to work in the area alongside patients and advocates.

We interviewed 11 people with HIV who were diagnosed before 1997 when ARTs became widely available and 8 members of staff. Some of those living with HIV were diagnosed through their participation in research. Jim had been living with HIV for more than thirty years at the time of interview, and explained how he saw a television show about "this new mysterious illness" whose

mechanism of transmission was unknown. Because he felt that his sexual orientation made him "a prime candidate" he joined a research study that recruited gay men for regular blood tests. He gave samples for about eighteen months without agreeing to receive results. He then asked about his HIV status and a clinical researcher confirmed that he was positive. "There were lots of unknowns," he explained "but those unknowns were unknown to everybody … back in 1985, we were on a learning curve that was changing all the time." Jim found support in the Terence Higgins Trust, Body Positive, and other local groups and charities that developed around clinical services. These relationships were contested, and patients and advocates disputed as they shaped priorities and interpretation (see Shilts 1987; Berridge and Strong 1993; Berridge 2002; Colvin 2014; Padamsee 2020).

Prior to 1997, experimental care had little impact on outcomes; those with HIV participated in research and advocacy and continued to die prematurely – at least one death a day in the services we knew in the 1980s, almost all of them young, gay men. Staff could at best make patients comfortable and experiment with palliative interventions since there was little else to offer. Hospice services expanded and, in hospitals, acute and palliative care introduced more extensive teamwork. HIV provided a unique opportunity to develop nursing roles that worked in practice and not just in theory, as ward teams moved from a task-allocated approach to one of responsibility for individual patients. Accordingly, concepts of "individualised" care were applied from nursing research conducted in the 1970s and 1980s in the USA (Fairbrother, Mary, and Jeffrey 2015). Although this approach reflects longstanding clinical values, it was newly applied and developed in HIV wards during the 1980s and introduced to other service areas subsequently (Jane Bruton in Nicholls and Rosengarten 2019, 43–4). It transformed the environment in which these men lived and died.

Extensive research into the biology of HIV and treatment developed alongside efforts to prevent transmission. HIV trials had unusually high participation rates since many people living with HIV insisted on participating; they were also highly politicised (Elbaz 1995). In the 1980s, an HIV physician recalled, "if you took bloods, you had to tick a box indicating whether it was on an NHS, private or research budget." That said, "everyone wanted to join research studies" (Weber, pers. comms., April 2019). The well-known, largely US organisation, AIDS Coalition to Unleash Power (ACT-UP), pressured for wider availability of experimental treatments and direct action by patients included attempts to identify the active ingredients and therefore detect the placebos. Participants would pool their pills and share them out in "guerrilla clinics" (Institute of Medical Ethics Working Party 1992). Some patients became experts in pharmacology and "evidence-based activism" grew in significance (Epstein 1996). In consequence, treatments were made available through "compassionate release" before they were approved (Merigan 1990). The physician quoted above emphasised, however, "you had to learn from every single patient, and you could not divide patients

into two categories. While only a subset participated in research, data from every patient were used to increase understanding."

The first specific drug, Zidovudine (AZT), had been developed in a US cancer program and was approved for HIV treatment in 1987. However, research showed that it did not prevent progression to AIDS and it was reported that you would likely die at the same time as you would without the drug (Concorde Coordinating Committee 1994). From 1991–1994, two key studies trialed combinations of the three available therapies, AZT and two nucleoside analogues. In Europe, the UK Medical Research Council, with its background in tuberculosis trials, created the infrastructure and protocols for multinational evaluation. By the end of 1994, it was clear that patients survived when AZT and a nucleoside were used in combination. This marks a key transformation in experimental HIV care because these studies suggested that a single, uniform protocol might work for everyone.

The effect for patients was rapid. David, a man in his fifties at the time of interview in 2014, recalled moving onto AZT, lamivudine (3TC) and ritonavir in 1996, as soon as this combination therapy became available. He had followed the Concorde study closely and recalled differences in opinion about when to start treatment. He felt that it was best to "start early" as soon as his CD4 count – measurement of a glycoprotein that helps to track the relative function of a patient's autoimmune response – neared 500. He remembers how difficult the new drugs were to get right – "high-dose ritonavir as an HIV treatment was pretty awful" – and he switched to other combinations. Now, he explained, this is a treatment reserved as a "booster" since it causes upset stomachs and nausea. David felt it was worth it, and still felt after many years living with HIV that he might owe his life to the chance he enjoyed.

As simple and widely tolerated regimens became available, clinical interactions became more streamlined. They were guided by more uniform protocols with minimal monitoring:

> Before effective drugs came in, obviously there was a degree of certainty about how patients would be managed in terms of that holistic approach to care, because it was care and there wasn't that sense of cure. … But when treatment came in all of that got turned upside down (Jane Bruton quoted in Nicholls and Rosengarten 2019, 43).

Simultaneously, relationships between staff and between staff and patients became more hierarchical. David (cited above) described how contemporary services were "a bit more functional"; the doctors told him "'we'll check everything is okay"' whereas "it used to be people would share [tests results] and talk you through them." As staff members corroborated, patients who once saw the same clinician on a regular 2 or 3-monthly basis now had a blood test every six months and an appointment with a clinician once a year.

Sandra remembered the rich network of organisations that supported people affected by HIV in London after her diagnosis in the early 1990s. Her clinician was always available but at the time of interview:

> I'm lucky if I get three or four minutes with him now. All they're interested in is, are you undetectable? That's all they care about […] They just want to check my CD4 count and viral load. They don't actually care for me. They provide me my treatment and take my blood. That's it. There's not any care so to speak. Well they don't. There's not time.

Sandra felt that monitoring had displaced the more expansive form of experimental care she enjoyed in the past. A clinician we spoke to agreed: "We're totally fixated on these sodding [i.e. damn] numbers."

General Practitioners (GPs) play a greater role than they did in the care of those affected by HIV (Matthews et al. 2016; Baylis et al. 2017; Rai et al. 2019). Alan, another man in his fifties who we met in 2015, explained his problems navigating this new division of labor: "I know that, although my GP is very good, their time is limited. They confess to not being terribly knowledgeable on HIV, which is fair enough. They've got thousands of patients with thousands of other conditions to be dealing with, so it's understandable that the GP refers me to the clinic, which is the centre of excellence." The referrals were not a problem, he felt, until he got to the hospital clinic where he might be told, "'well, you need to speak to your GP about that.' I think, 'Hello. I've been referred here, and now you're sending me back,' so, sometimes, it feels that there is a bit of a ping pong, and it's a waste of everybody's time if that happens."

Specialist clinics no longer have the capacity and links to other services that they once enjoyed. Effective antiretroviral therapy (ART) was one factor that promoted the recalibration of tasks across varied health conditions, alongside the need to budget for the cost of therapy for greater numbers within the NHS and wider political priorities to reduce the cost of public services. "Once antiretrovirals came in, then we needed to shrink" (Jane Bruton quoted in Nicholls and Rosengarten 2019, 20); wards shut, and staff lost their jobs. As a healthcare professional observed of her patients, "now that we've got good antiretroviral drugs, we can treat them, but there are a lot more problems with living arrangements, working arrangements, eligibility to be in the country, psychiatric illness, co-infections like tuberculosis or hepatitis." A clinician contrasted the responsiveness of earlier services to a contemporary "medical sense of a cul-de-sac. It's almost completely hopeless coming to see me because whatever it is I diagnose as comorbidity, I am no longer in a position to prescribe for and, hence, manage, which is bizarre and which makes my clinics even more, if you like, from a strictly medical perspective, redundant". The professional quoted above said, "we're having to actually push back patients to their GPs."

Initial HIV treatment today is adapted to individual and host genotyping but subsequent regimens are highly standardised. With simpler regimens, patients are increasingly encouraged to monitor their own health (see Beckmann 2013; Hildebrandt, Bode, and Ng 2019).[5] HIV has become a chronic condition for the majority; services have been streamlined, and – in a UK climate of economic

austerity – reduced. Interviews documented problems that arose as HIV services were aligned with other services in the hospital group, which meant that outpatient clinics needed to be reorganised. They also documented contingent developments. But they did not provide much detail on the benefits of ART since these are now almost taken for granted. For the majority, effective treatment has replaced experimental care with a largely uniform approach that gives people with HIV in the UK a normal life span. Experimental HIV care led to a virtually one-size-fits-all approach, and this uniform approach is strikingly successful, at least as far as treatment of uncomplicated cases is concerned. We therefore suggest avenues for understanding the current promise of translational research from an obvious perspective that asks about the possible consequences of effective treatment.

Discussion

Platforms for experimental care have changed substantially in the space of twenty-five years. Some tools are largely automated, such as digital imaging and risk scoring through standard protocols and a variety of decision support tools. In breast cancer services, gene sequencing is more common, not just for diagnostics but also for tracking the evolution of cancer in individual patients (Coombes et al. 2019). Analysis depends on the processing of large, digitised collections of data (Bourret and Cambrosio 2019), managed through platforms that are increasingly interoperable. Breast and other cancer aetiologies continue to change in response to genomics research (e.g. Rueda et al. 2019), and monitoring of treatment response remains critical to the continuing calibration of biological profiling and treatment options within and across breast cancer types. In HIV services, by contrast, the only routine element of this kind adopted in protocols involved genotyping the virus to check for resistance and the host for a polymorphism that gives adverse reactions to one of the alternative first line drugs, abacavir (Mallal et al. 2008).

Many terms link these and other components of experimental care today. One was coined by Leroy Hood and colleagues under the rubric of P4 cancer medicine (Hood and Friend 2011). It involves widespread Participation in a more Personalised cancer medicine, that is, an approach that tracks response to interventions based on the cancer type that an individual shares with others. This form of stratification is dynamic since individual monitoring and emerging data analytics lead to continuing recalibration, making P4 medicine ideally Preventive and Predictive (see Flores et al. 2013; Pokorska-Bocci et al. 2014; Academy of Medical Sciences 2015). National initiatives have opted for the terms Precision Medicine and Personalised Medicine (Schleidgen et al. 2013; Chadwick 2017; Erikainen and Chan 2019). NHS England, for example, adopted the term "personalised medicine" in 2016. Their webpages link to a National Genomic Medicine Service that was launched in 2018 following Genomics England's 100,000 Genomes Project (Genomics England nd).[6] In the future, NHS England aims to use "cutting edge genomic

technologies to predict and diagnose inherited and acquired disease, and to personalise treatments and interventions" through this new service, particularly for those with rare diseases and cancer, which will pave the way for advances in other (common) conditions (NHS England 2018). NHS England acknowledges that monitoring the course of an illness and applying evidence to different circumstances means that clinicians "have been working to personalise care, tailored to people's individual health needs, throughout the history of medicine" (NHS England 2016; see also Tutton 2012, 2014). They also acknowledge associated terms as with the USA's Precision Medicine Initiative (2015) and, since 2018, its national cohort, "All of Us".

Staff and patients in the London breast cancer and HIV services where we conducted research rarely used any of these terms unless prompted. Since we wanted to explore the hope and promise associated with platforms for experimental care, we did however elicit discussion of terms that could have specific associations, referents, strategic uses and serve as synonyms (see Erikainen and Chan 2019). Staff referred readily to what they perceived as an older synonym, stratified medicine. Some also explained that it was wise to frame bids for research funding in the terms of precision or personalised medicine but showed little interest in their particular inflections. In contrast to academic commentaries and policy documents, it is striking how far staff and patients avoided the contemporary vocabulary of personalisation, precision and allied terms in this research-intensive London hospital group.

Across these different but overlapping terms is a common thread. To take the example of NHS England, their Personalised Medicine Strategy describes "a move away from a 'one-size-fits-all' approach to the treatment and care of patients with a particular condition … " (Keogh 2015; NHS England 2016). Contemporary developments are conceived through a contrast with what is described as a previous, sometimes ineffectual and dangerous one-size-fits-all approach, which failed to differentiate categories of disease in sufficient detail (see Connor 2003).[7]

We do not look to transitions from more experimental to more standardised approaches in HIV as a way of imagining future breast cancer medicine; HIV medicine continues to build on platforms for experimental care in translational studies, basic science, epidemiology and public health, and other fields. To the contrary we suggest that oncology's present, constituted by a fading boundary between research and care, is illuminated by an earlier phase of experimental care in another disease condition. Sociologies of promise, expectation and potentiality have focussed on the constitutive role of promise and expectation in forging biotechnological innovation and the speculation necessary to craft collaborations, resources, and markets that seek to bring futures into the present (Brown 2003; Brown and Michael 2003; Rajan 2006; Martin, Brown, and Turner 2008; Fortun 2008; Adams, Murphy, and Clarke 2009; Tutton 2012; Taussig, Hoeyer, and Helmreich 2013; Haase, Michie, and Skinner 2015). Of special relevance to our research on contemporary oncology is the shift in perspective afforded by looking at the short history of HIV research

and care. As Brown suggests (2003, 10), "expectations of the future change over time. That is, our presents are situated in relation to memories of past futures and future presents." Commentators have identified unrealistic and harmful expectations attached to precision or personalised medicines (see Feiler et al. 2017; Erikainen and Chan 2019). Some note the shortfall between promise and reality, and describe the failure of personalised medicine to achieve personal or public benefits (Prasad 2016; Dickenson 2011; Rushforth and Greenhalgh 2020); others consider that distortions are introduced to clinical consultations, resource and research funding priorities (e.g. Maughan 2017). The deep links between financial economies of promise and pharmacogenomic development are well documented (Hedgecoe and Martin 2003; Tutton 2014; Sturdy 2017), and track the close relationships between corporate lobbying and patient advocacy (Brown 2003; Panofsky 2010). Concerns have been expressed about how these trends may erode solidaristic approaches to healthcare, commodifying "participant-patients" (Prainsack 2017). These contributions have been associated with a range of terms and practices, which we have gathered under the rubric of experimental care.

We have shown that hopes pinned to experimental breast cancer care today are accompanied by doubts and uncertainties: a patient may dispute the apparent stability of her cancer type since it precludes alternative treatment; a clinician may despair of predicting resistance in patients; a clinical researcher may hope for a uniform and effective approach on the model of past advances in tuberculosis care. Initial breast cancer treatment for many people is less enmeshed in experimental practices, like uncomplicated HIV treatment, but overall breast cancer care constitutes an expansive field that includes what are now considered to be many distinct health conditions. Both staff and patients hoped that developments in translational medicine would fulfill their promise (Vecchio et al. 1990) but new biotechnologies, pharmacogenomics or policy had no more purchase than considerations of clinical effectiveness.

We have also shown that interview participants attributed contemporary standards for the management of HIV to a previous epoch of experimentation. Developments in experimental HIV care lasted little more than a decade, from the early-1980s to the mid-1990s when dated to the first effective treatment. It took another decade to resolve difficulties with dosage, toxicity and side effects (WHO 2006), and to register the effects of the 2008 financial crisis on public services, including the UK health system. HIV patients had participated widely in research and advocated for the rapid translation of research findings into treatment protocols. Although most did not benefit from treatment directly in the early days, their participation was critical to clinical and laboratory research and to the eventual effective "universal test and treat" approach taken in the 2010s (Lancet 2015; Hayes et al. 2019). Experimental care led to standard protocols for uncomplicated HIV treatment. In retrospect, some patients and staff regretted the loss of close partnerships that enabled navigation from one appointment to another and between different service areas. But their hopes for better clinical

outcomes were fulfilled. Our interview study confirmed retrospective benefits from experimental care that led, not to the proliferation of ever-smaller disease groupings through targeted treatments, but to a more standardised approach that gave patients a normal life span. Historically, effective biomedical treatments have led to renewed calibration between individual and group – virtually a return to the one-size-fits-all approach for uncomplicated HIV care.

Conclusion

Since care is only king in the absence of cure or prevention – for example, through vaccination – our conclusion is so obvious that the only puzzle is its absence, to our knowledge, from discussions of contemporary experimental care. Proponents of P4 medicine imagine a virtuous circle in which success is forever deferred: more precise and effective treatment will continue to require more knowledge, which will continue to require the participation – and reciprocal care – of those affected and, indirectly, whole populations to which these individuals belong. This variety of future suggests that disease types and biotechnology markets will continue to proliferate. Biomedical idioms of success and failure may indeed change along with concepts of person and population, new molecular and genetic aetiologies, and the increasingly blurred boundaries between health, disease risk and disease. But experiences in HIV and, indeed, TB translational research platforms also suggest important continuities in efforts to improve outcomes. In this context, success and failure may differentiate standard as opposed to experimental care.

Our analysis foregrounds a countervailing hope for a more standardised treatment that can be given to almost everyone, and earlier experiences in HIV continue to provide models for other experimental care platforms, not least SARS-CoV-2. None of the health conditions in this hospital group are directly comparable but research and care build on as they supplant previous platforms for experimental care.

Earlier combinations of treatment and care indicates the appeal that continues to be invested in the apparent antonym of personalised medicine, that is, one-size-fits-all. Examining biomedical criteria for success and failure as they apply to the bundling of research knowledge, treatment outcomes and patient care across diverse services, we ask whether it is plausible to imagine effective and more stable combination therapies for breast cancers?

Even though the hoped-for success of the new is widely constructed through a contrast with a previous one-size-fits-all medicine that has failed, we suggest that this latter paradigm still attracts support in translational research. It is not just an inadequate, harmful and outmoded approach. It remains both a goal and a witness to past futures associated with NHS principles of equal access to appropriate and effective care for all-comers. It is, in short, both companion and limit to the ever-more precise differentiation of people and their health conditions.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

Research in breast cancer services was supported by funding from Imperial College Healthcare Charity, the National Institute for Health Research (NIHR) Biomedical Research Centre based at Imperial College Healthcare NHS Trust and Imperial College London, and our project, supported by the Wellcome Trust (205456/Z/16/Z), "People Like You": Contemporary Figures of Personalisation, 2018–2022. Ethics was approved by North West - Greater Manchester West Research Ethics Committee, 18/NW/0550. Research in HIV/AIDS was funded by grants from Imperial NIHR Biomedical Research Centre, the Imperial College Healthcare Charity, and supported by the St. Stephens AIDS Trust. Ethics was approved by West Midlands - Edgbaston Research Ethics Committee, 14/WM/0147. The authors of this article would like to acknowledge the contributions of patients and staff who participated in this research and collaborated with the team, including Louise McGrath-Lone, Claudia Schoenborn, Tanvi Rai, Jane Rowlands, Christopher Higgs, R. Charles Coombes and Kelly Gleason.

Notes

1. Adaptive trial design has been defined as "a clinical trial design that allows for prospectively planned modifications to one or more aspects of the design based on accumulating data from subjects in the trial" (FDA 2018, 2).
2. While quotations from transcripts are verbatim, signaled in the text using double quotation marks, field note records from informal or group discussions are marked with single quotations.
3. Initially rejected in early 2017 by the National Institute for Health and Care Excellence (NICE) for their high cost in relation to their prospective benefit, the CDK4/6 inhibitors, palbociclib (Ibrance) and ribociclib (Kisqali), were licensed for use in the NHS in November 2017.
4. We use pseudonyms here and throughout this article.
5. We should acknowledge that NHS England have introduced a long-term strategy of Personalised Care (2019) that aims to involve patients in their care. As commentators have noted, this process can involve delegating responsibilities and work to "self-managing" patients.
6. See NHS England, "NHS Genomic Medicine Service", https://www.england.nhs.uk/genomics/nhs-genomic-med-service/ accessed 11th November 2019.
7. Connor notes that Allan Roses, a senior executive at GlaxoSmithKline, suggested that most drugs currently on the market only worked in 30-50% of the population.

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