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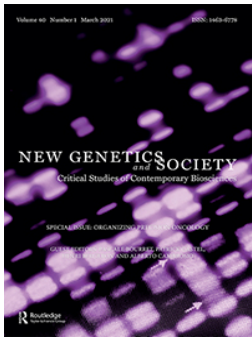
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Local mutations: on the tentative beginnings of molecular oncology in Britain 1980–2000

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Popular and scientific accounts of the molecularisation of cancer typically attribute it to advances in laboratory science, particularly molecular geneticists. However, historical research has indicated that clinical expertise input was often vital for advancing such work. The present paper reinforces that view. Looking in detail at British research into the molecular genetics of familial cancers during the 1980s and 1990s, it shows that that research, too, depended on crucial input from family cancer clinics. Moreover, the development of clinical services for familial cancers was in turn shaped by the demands of contributing to molecular genetic research. The paper concludes that accounts of the molecularisation of cancer that suppose a one-way transfer of knowledge and practice from laboratory to clinic misrepresent the complex interactions that were involved in molecularising familial cancers, and that were informed by the particular local and national circumstances in which they took shape.

Keywords: Molecular oncology; familial cancers; molecularisation; genetic testing; bioclinical collectives

Introduction

Nowadays, cancer is widely understood to be “a genetic disease” caused by changes in genes that govern cell growth and multiplication (Wishart 2015; National Cancer Institute 2017). This understanding is fundamental to what is now often called “precision oncology” – an approach to cancer treatment that targets the molecular characteristics of an individual’s tumor. Popular and scientific accounts of the ascendancy of this molecular genetic approach typically attribute it to advances in laboratory science, in particular the discovery and elucidation of oncogenes by molecular geneticists (e.g. Bishop 1995; Mukherjee 2011). Several important studies in the history and sociology of science have significantly enriched and complicated this narrative, fleshing out the dynamics of discovery, the role of funding and the disciplinary aspirations that led to the establishment

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of the “oncogene paradigm” as one of the devices by which molecular geneticists established their claim to be purveyors of fundamental insights, not just into cancer and its causes, but into human biology more generally (Fujimura 1996; Morange 1997; Scheffler 2019).

Such accounts of the molecularisation of cancer make little reference to clinical knowledge of cancer or to the practice of clinical oncology, focusing solely on the molecular genetics laboratory as the site of knowledge production and medical innovation. However, a growing body of research makes clear that molecularisation involved far more than a one-way flow of oncogenetic discoveries from the laboratory to the clinic. Thus Keating and Cambrosio (2001) have shown that, during the 1980s, clinicians – specifically clinical cytogeneticists – made vital contributions to the development of oncogene theory through their demonstration that certain human cancers could be attributed to the occurrence of observable chromosomal abnormalities. Recent work by de Chadarevian (2020) has situated this work in a much longer cytogenetic tradition, dating back to the atomic anxieties of the 1950s and persisting into present-day diagnostic practice, that associates cancer with visible changes in chromosome structure. Nor was cytogenetics the only clinical source of insight into the molecular genetics of cancer. In a study that parallels many of the findings of the present paper, Necochea (Necochea 2007) has shown how work that led to the identification and cloning, in the early 1990s, of genes that predispose to a specific form of familial colon cancer involved a two-way interaction between innovative research in molecular genetics and an older tradition of clinical genetics based on family pedigrees.

These studies are complemented by research that shows the crucial role that clinical knowledge and practice played in the molecularisation of genetics more generally. Thus Hogan has shown how, even before molecularisation gained momentum in the course of the 1980s, clinically-driven cytogenetic research was crucial in reconfiguring the human genome as a mappable entity, and thereby in shaping the kinds of questions that molecular geneticists would in turn come to ask of it (Hogan 2013, 2016). Navon, meanwhile, casts his explanatory net even more broadly to show how patients and families, too, have brought their own knowledge and experience to bear in shaping cytogenetic and more recently molecular research into a range of disorders (Navon 2019). Their work confirms and adds detail to broader historical narratives which likewise emphasize the centrality of clinical expertise and insight to the development of medical genetic knowledge and practice from the early twentieth century to the present (Lindee 2005; Comfort 2012). Such studies in turn align with historical research on the development of “biomedicine” since the mid-twentieth century, which further underlines the extent to which large areas of medicine, by no means limited to cancer and genetics, have come to be characterized by a similar inseparability of biological research and clinical practice and a similar interdependency of clinical discrimination with biological knowledge production (Gaudillière 2002; Keating and Cambrosio 2003) – a situation that is nowhere better epitomized

than in the “bioclinical collectives” that today constitute so much of the world of molecular oncology (Bourret 2005).

The present paper offers a further contribution to this literature on the development of biomedicine, and specifically on the molecularisation of cancer. It looks in detail at work undertaken in Britain during the 1980s and 1990s that aimed both to isolate genes responsible for a range of familial cancers and to implement medical interventions that would alleviate or prevent those cancers. Similar work took place in a number of other countries at the same time, and social scientists have already argued that, in the case of the Netherlands and France, molecular genetic research and service provision developed in concert with one another, in what Stemerding and Nelis call a “co-evolution” process (Bourret, Koch, and Stemerding 1998; Palladino 2002; Stemerding and Nelis 2006). The present paper examines how similar a process unfolded in Britain. It shows how the search for familial cancer genes and the establishment of family cancer clinical services were deeply entangled from the start. And in particular, it emphasizes the extent to which both developments were shaped on the one hand by the peculiar organizational demands of conducting molecular genetic research into rare familial conditions, and on the other by the particular and contingent institutional circumstances of British oncology and British genetics.

In so doing, this paper adds a further dimension to our understanding of the relationship between clinic and laboratory in the molecularisation of cancer. In the case of familial cancers, at least, molecularisation depended not just on intellectual and practical engagement between clinical and molecular geneticists and oncologists, but on creating the institutional and organizational arrangements that made that engagement possible. Molecularisation thus remained determinedly rooted in local and national circumstances, even as it depended increasingly on the formation of international networks. The following pages document this peculiarly British story, and in the conclusion I draw out some more general implications.

The paper is based on recursive identification and analysis of a range of publicly available primary historical sources documenting the development of familial cancer genetics in the United Kingdom. These included research articles and reports as well as scientists’ own retrospective writings and a number of interviews with key actors conducted by other historians. Particularly valuable was the witness seminar on the history of clinical cancer genetics organized and edited by Tilli Tansey and colleagues (Jones and Tansey 2013). Data collection and analysis followed what was in effect a form of historical snowball sampling. Research began using sources identified in existing secondary accounts of the history of genetics and of cancer. Each source was analyzed for the information it provided on familial cancer genetics in the UK, with particular attention to the kinds of work undertaken, both research and clinical; the sites where that work was conducted; and the collaborations and other relationships that made that work possible. A working narrative was constructed as sources were identified and analyzed, and literature searches were conducted to identify further sources relevant to the places, people and

events that featured in that narrative. New sources frequently indicated additional actors and activities of relevance to the narrative, and sometimes challenged and prompted significant revisions to that narrative. Searching ceased when new sources ceased to yield data that significantly added to or amended the narrative presented in this paper.

The beginnings of cancer family research and practice

It has long been recognized that some families suffer from an unusually high incidence of certain cancers. Despite suspicion on the part of some early twentieth-century eugenicists that cancer might represent a form of hereditary degeneration, however, medical and scientific interest in the genetics of cancer remained sporadic until the 1950s, when a scattering of European and North American geneticists and oncologists began to take a more sustained interest in so-called “cancer families.” Underlying this interest was a growing confidence that early surgical intervention could prevent the onset or progression of cancer in individuals whose family history indicated that they were at elevated risk of developing the disease. This approach was exemplified in the work of geneticist Henry Lynch, one of the pioneers of US cancer family research. From the 1960s Lynch compiled extended pedigrees of families afflicted with hereditary forms of colon, uterine, ovarian and breast cancer, with a view to identifying individuals at particular risk of developing malignancies. For those individuals, Lynch advocated regular clinical examination and surgery where necessary (Cantor 2006; Necochea 2007; Löwy 2010, 171–172).

A parallel development occurred in the UK at St Mark’s Hospital in London, which specialized in surgical treatment of diseases of the colon and rectum. As early as the 1920s, the St Mark’s surgeon Percy Lockhart-Mummery began building a register of patients and pedigrees afflicted with what would eventually come to be known as familial adenomatous polyposis (FAP), initially for the purpose of confirming its hereditary character. From the 1950s onwards, as advances in abdominal surgery made colonectomy safe enough to be used prophylactically, the registry assumed new importance as a means of tracing relatives, with the aim of persuading them to undergo diagnostic screening and surgery where deemed necessary. Now under the care of pathologist Cuthbert Dukes, whom Lockhart-Mummery had engaged in 1924 to assist in his endeavors, the case register developed into a systematic polyposis registry. It also acquired clinical genetics expertise with the appointment in 1960 of New Zealander Arthur Veale to a joint position between St Mark’s and Lionel Penrose’s genetics laboratory at University College London. Through the 1960s and 1970s the St Mark’s Registry would prove to be a valuable resource for research that aimed to distinguish different forms of polyposis, understand the factors influencing behind the incomplete penetrance of the familial polyposis gene, and evaluate the effects of different surgical interventions (Veale 1960; Palladino 2002, 141–148; Jones and Tansey 2013, 19–24, 88–96).

Developments at St Mark's also provided a model for similar initiatives elsewhere. General cancer registries had been set up in a number of countries during the first half of the twentieth century, mainly for epidemiological reasons (Wagner 1991; Terracini and Zanetti 2003; Löwy 2010, 48–50). The St Mark's polyposis registry was distinct in that it focused on a single, strongly familial cancer, and was associated with a concerted program of surveillance and prophylactic intervention. A similar polyposis registry was established in Sweden in 1957 (Björk *et al.* 1999), followed in the 1970s by a growing number of national and regional registries in other Nordic countries, North America and Japan (Bülow 1986). Despite such initiatives, however, research into familial cancers generally remained localized, both geographically and professionally, through the 1970s. Most oncologists were unpersuaded that genetics offered any practical insight into the aetiology of cancer; and insofar as they accepted that some cancers were strongly familial, they saw little to be gained, either medically or professionally, by devoting time and effort to such rare forms of disease. Meanwhile, the field of clinical genetics was largely concerned with calculating the risks and providing reproductive counseling for birth defects such as Down syndrome and early-onset genetic disorders such as phenylketonuria and cystic fibrosis. Late-onset, partially penetrant conditions such as familial cancers therefore offered geneticists little scope either for research or for clinical practice. As a result, into the 1980s, interest in familial cancers remained a matter of individual enthusiasm rather than a common feature of either oncology or clinical genetics departments.

Walter Bodmer, the ICRF, and the introduction of molecular genetics

In 1979 the geneticist Walter Bodmer was appointed director of research at the UK Imperial Cancer Research Fund (ICRF), at that time the UK's largest cancer charity, which supported research in universities and hospitals around the country as well as running its own research laboratory in London. At first sight, Bodmer was a surprising choice for the appointment, never having previously ventured into the field of cancer research. Beneath this apparent mismatch ran a deeper continuity of interest, however. Bodmer's predecessor at the ICRF was Michael Stoker, a virologist who had championed the application of molecular genetic approaches to studying cancer. Under Stoker's direction, the ICRF laboratories had made important contributions to the emerging oncogene theory of cancer etiology (Wyke 2013). Bodmer, for his part, was a distinguished molecular geneticist who, with his wife Julia, had done pioneering work on the genetics of the human immune system, including identifying and mapping genes associated with certain autoimmune conditions. Bodmer was thus well qualified to take forward the ICRF's role as a leading UK champion, not just of cancer research, but of molecular genetics (Bodmer 1988).

Following their arrival at ICRF, Walter and Julia initially continued their earlier research into the genetics of immunity. But Walter also set about familiarizing himself with the world of cancer. His own first steps into cancer research tapped

into the current excitement surrounding human oncogenes, and used somatic cell hybridization – a cytogenetic technique that Bodmer had helped to develop in his previous research – to map the human oncogene *c-abl* to chromosome 9 (Heisterkamp *et al.* 1982). At the same time, in surveying the ICRF's research investments and the state of cancer research beyond the confines of his own laboratory, he became aware that a number of oncologists and geneticists scattered around the country – notably at St Mark's but also elsewhere – were cultivating an interest in familial cancers. This interest presented Bodmer with an opportunity to steer their work in a direction more in line with his own research experience.

As a molecular geneticist with a particular interest in gene mapping, Bodmer was among the first to observe that so-called restriction fragment length polymorphisms (RFLPs) – newly discovered molecular markers scattered across human and other genomes – might provide a powerful new means of mapping genes to their chromosomal locations (Solomon and Bodmer 1979). In 1978 Yuet Wai Kan and Andrée Dozy had identified a RFLP marker closely linked to the sickle cell gene, which they suggested might be used for pre-natal diagnosis (Kan and Dozy 1978). In a commentary he published shortly afterwards with his colleague Ellen Solomon, Bodmer noted that RFLPs had the potential to open up a much wider vista of discovery:

one can envisage finding enough markers to cover systematically the whole human genome ... Such a set of genetic markers could revolutionise our ability to study the genetic determination of complex attributes and to follow the inheritance of traits that are so far difficult or impossible to study at the cellular level ... Association within families between a defined genetic marker and a trait whose inheritance is not clearly defined, provides the best evidence, through genetic linkage, for genetic determination. This powerful approach has so far been limited by the range of genetic markers available, but restriction-enzyme polymorphisms may soon solve this problem. (Solomon and Bodmer 1979)

The following year, a group of American molecular geneticists published a landmark paper, systematically setting out the feasibility of building a comprehensive RFLP linkage map of the human genome and using it to map disease genes (Botstein *et al.* 1980). The methods they outlined were quickly adopted by researchers around the world, and the following decade would see growing number of human genes being mapped with increasing precision.

In referring to the potential of RFLPs to study “the genetic determination of complex attributes,” Solomon and Bodmer suggested that RFLP mapping might be effective for studying not just the kinds of rare monogenic disorders that had so far preoccupied clinical geneticists, but also commoner but more complex disorders. His introduction, shortly afterwards, to the work on familial cancers suggested a way of pursuing that suggestion in the field of cancer. Linkage mapping depends on being able to follow the occurrence of linked traits and markers through sufficiently large, well-documented family pedigrees, in order

to demonstrate non-random segregation from one generation to the next. These were just the kinds of family records held by the St Mark's polyposis registry. For Bodmer, familiar with the techniques of molecular genetics and with the laboratory facilities of the ICRF at his disposal, the St Mark's registry offered an unprecedented opportunity to open up an entirely new line of research into the molecular genetics of cancer.

Building bioclinical research capacity

Up to that point, the St Mark's polyposis registry had been developed primarily to meet the standards set by clinical oncologists. The work of case registration and the construction of cancer family pedigrees had been pursued with enough care to make it possible to trace and identify family members who might be at risk of developing cancer and who could be called in for clinical examination and surgery. It was not clear, however, whether such pedigrees as had so far been collected would be either sufficiently large or sufficiently well characterized to serve in the search for linkage between RFLP markers and the genes responsible for familial polyposis. Consequently, Bodmer set about using ICRF funds to ensure that the St Mark's FAP work met the standards required, not just for clinical surveillance of the hospital's cancer families, but for linkage mapping. In 1984 he funded a new Colorectal Cancer Unit, and recruited clinical geneticist Vicky Murday to work there as an ICRF research fellow. The Unit also took charge of the Polyposis Registry, while the ICRF paid for the appointment of a research nurse, Kay Neale, to help populate and maintain it, and to bring new rigor to the registration of cases and the construction of pedigrees (Jones and Tansey 2013, 24, 28–29).

In case the St Mark's families were still insufficient for his purposes, Bodmer also looked to build additional capacity beyond the hospital, and indeed beyond London. In Manchester, the University had recently appointed the cytogeneticist David Harnden to direct its Paterson Institute for Cancer Research, where a Family History Clinic was already in operation for families with breast and other cancers (Harnden 2004). Harnden quickly teamed up with cancer epidemiologist Ray Cartwright from the University of Leeds to set up a Cancer Family Study Group, which would serve as "a discussion group ... to bring together all the people (doctors, scientists, nurses, statisticians and others) who were involved in the study of families with an increased risk of cancer" (Jones and Tansey 2013, 100). Bodmer too now involved himself in the Study Group, which from early 1984 began to hold meetings at the ICRF laboratories in London as well as in Manchester. As with the St Mark's work, Bodmer also sought to develop the group's activities in ways that would favor his own interests as well as those of its founders. As he put it: "The idea was not that it was a talking shop and a conventional meeting; the idea was mainly that it should stimulate collaborative studies on families aimed at finding linkages." In particular, Bodmer encouraged the Cancer Family Study Group to share not just clinical and epidemiological

knowledge and experience but also tissue samples and pedigrees (Jones and Tansey 2013, 11–12).

These new networks proved fruitful. In the summer of 1987, Bodmer announced in a letter to *Nature* that he and his colleagues had succeeded in demonstrating linkage of FAP to a RFLP marker on chromosome 5 (Bodmer *et al.* 1987). The work of identifying markers and conducting the linkage analysis had been conducted in Bodmer's own laboratory at the ICRF. But he had depended heavily on clinical colleagues to identify suitable families and persuade them to provide tissue samples. The St Mark's team was crucial to this success: Murday and consultant pathologist Dick Bussey were among the paper's authors. But Bodmer had also drawn on the wider cancer family research network he had cultivated beyond London. Bodmer and his colleagues had examined thirteen families, all "well characterized with respect to clinical, pathological and pedigree information," of which six had proved to be "informative" (that is, they possessed an observable form of the linked RFLP). In order to find these families, Bodmer had worked not only with St Mark's but also with Tony Ellis at the Gastroenterology Unit at the Broadgreen Hospital in Liverpool, plus at least one other unspecified source (the paper states only that "Most of the families" came from St Mark's and the Broadgreen) (Bodmer *et al.* 1987, 614–615). Without the extended bioclinical research network he had cultivated – including oncologists as well as clinical geneticists and molecular biologists – it is unlikely that Bodmer would have been able to collect enough pedigrees, patient records and tissue samples to locate the FAP gene so quickly.

Family cancer clinics

Bodmer's efforts to build research capacity around familial cancers were not only fruitful in terms of delivering new biological findings about the genetic basis of FAP. They also created opportunities to provide new kinds of clinical services. In 1986 St Mark's Hospital established a new Family Cancer Clinic with funding from the ICRF. The Clinic was staffed by clinical geneticist Joan Slack and a genetic research nurse, Christina Harocopos, both of whom worked closely with Vicky Murday in the Colorectal Cancer Unit and Polyposis Registry. The work of the new clinic was not confined to FAP, however, covering all kinds of colorectal cancer seen by the Hospital. Epidemiological research conducted there in the early 1970s had shown that relatives of patients with all kinds of colorectal cancer faced some degree of elevated risk of developing the condition, even in the absence of any previous family history of cancer. ICRF now funded a research fellow to re-analyse these findings and devise a method of estimating any individual's risk on the basis of what could be discovered of their family history. Using this method, the staff of the Clinic now began tracing the relatives of all patients presenting with colorectal cancers and, if deemed advisable, counseling them about their risk and offering to screen them for malignancies (Houlston *et al.* 1990;

Jones and Tansey 2015, 50–52, 79–80). Statistics from the first few years of the Clinic's operation indicated that these measures were effective in facilitating early detection of undiagnosed cases of cancer. At the same time, the Clinic identified and described a number of families with what was just coming to be recognized as another strongly familial cancer syndrome – so called Lynch syndrome or hereditary non-polyposis colon cancer (HNPCC) (Itoh *et al.* 1990).

Importantly, the St Mark's Family Cancer Clinic was seen as breaking new ground, not just in the field of oncology, but also in clinical genetics. Shortly after its inception, it officially became part of North East Thames Regional Genetics Service (Houlston *et al.* 1990). Over the previous decade or so, several of the Regional Health Boards that oversaw the delivery of hospital and consultant services under the National Health Service (NHS) had established genetics services run by clinical geneticists and genetic counselors (Coventry and Pickstone 1999; Leeming 2005; Harper 2019). Much of the work of these clinicians was taken up with prenatal diagnosis and counseling for sporadic birth defects such as Down syndrome and neural tube defects, using amniocentesis and either cytogenetic or biochemical tests. But it also included familial risk assessment and reproductive counseling for a growing range of rare monogenic disorders including phenylketonuria, cystic fibrosis and muscular dystrophy. It had not previously included complex, late onset disorders such as cancer, however. The incorporation of the St Mark's clinic into the Regional Genetics Service thus marked a significant expansion in what services clinical geneticists could be expected to provide. At the same time, it represented an important endorsement by the Region's clinical geneticists that the activities of the St Mark's clinic were in line with the expectations of confidentiality, consent and non-directive counseling that were central to the identity and practice of clinical genetics as a specialism (Kingston 1989; cf. Stern 2012).

The St Mark's Family Cancer Clinic also served as a model for developments elsewhere in the UK. Between the mid-1980s and the early 1990s, family cancer clinics were set up in collaboration with regional genetics services in Leeds (whence Vicky Murday moved from St Mark's), Newcastle, Manchester, Cardiff and Oxford. The ICRF actively supported these developments. “[H]aving seen also what could be done at St Mark's,” recalled Bodmer, “in the ICRF we thought there was a case for trying to create places where cancer family studies and genetics would be done in association with oncology units.” The ICRF accordingly provided financial assistance, “generally to fund someone like a nurse, who could be involved in helping with the aspects of the cancer family clinic that went alongside what the genetic consultant would do” (Jones and Tansey 2013, 58–59). In connection with local oncology units, the regional genetics services thus began to take a growing role in providing care and counseling for those affected by familial cancers. They also saw an increasingly wide range of cancers: while the kinds of cases seen at the St Mark's clinic were constrained by the hospital's specialist focus on diseases of the lower bowel, family cancer services based elsewhere took a

wider view, looking beyond FAP and HNPCC to encompass other hereditary cancers including Von Hippel-Lindau disease, Li Fraumeni syndrome, neurofibromatosis, and familial forms of breast cancer (Fraser 1999; Harnden 2004; Jones and Tansey 2013, 26, 55–56, 58–60, 100–101, 108).

Synergy of research and clinical care

Clearly the new family cancer clinics were not set up solely with the aim of delivering clinical services. On the contrary, as one geneticist recalled, they “were largely clinics that were set up for research, to get the families, and to research the families” (Jones and Tansey 2013, 53). But at the same time, efforts to identify families for research purposes also identified new opportunities to expand clinical service provision. In the case of Von Hippel-Landau disease, for instance, clinical geneticist Eamonn Maher recalled that

the initial driver to setting up new clinical services for VHL patients in Cambridge was the fact that we were starting a research study. We were collecting families for linkage studies and we needed to evaluate affected and apparently unaffected members of the family to see whether they were sub-clinically affected. (Jones and Tansey 2013, 63–64)

Using these families, Maher would first confirm the recent mapping of Von Hippel-Lindau disease to chromosome 3p (Maher *et al.* 1990), then make a major contribution to the international collaboration that succeeded in identifying the gene itself three years later (Latif *et al.* 1993). But the search for families also identified needs that the genetic services had not so far met:

As we went round the country collecting VHL families, we found that most were not under surveillance and they needed local follow-up and screening and, more often than not, that was done through a local geneticist. So that was my experience of how VHL clinics developed. (Jones and Tansey 2013, 63–64)

Research stimulated the growth of clinical services, as much as clinical services helped to support research.

Staff from the family cancer clinics also became increasingly involved in the growing number of international research collaborations that were being set up to map familial cancers. Researchers from Iceland and possibly Newfoundland had attended the Cancer Family Study Group from early in its existence (Jones and Tansey 2013, 11–12). But such interactions intensified dramatically from the late 1980s, as efforts to map and clone the genes involved in familial cancers accelerated. UK researchers were drawn into the International Collaborative Group on HNPCC (ICG-HNPCC), for instance, following its establishment by Netherlands-based clinician Hans Vasen in 1990 (Lynch *et al.* 2003). These included geneticists John Burn, who ran the family cancer clinic in Newcastle, and Tim Bishop, who headed the ICRF research laboratory in Leeds. Burn and Bishop also provided pedigrees and samples to American molecular geneticist Richard Kolodner, who

used them in his successful identification of the MSH2 mismatch repair gene in HNPCC (Fishel *et al.* 1993; Jones and Tansey 2013, 56–57). UK researchers also played a pivotal role in the Breast Cancer Linkage Consortium set up in 1989 to coordinate European efforts to map and isolate genes involved in familial breast cancer (Bishop *et al.* 1995; Dalpé *et al.* 2003, 206–208).

Clinical geneticists' familiarity with new molecular genetic research techniques in turn fed back into the clinical services they were able to offer. When the first family cancer clinics were established in 1986, genetic counseling and referral for screening still depended on risk calculations based on family history. Bodmer's identification of a linked RFLP marker for FAP only a year or so later made it possible to determine with a much higher degree of certainty which members of some (though by no means all) FAP families carried a deleterious allele – and to do so, moreover, from an early age, before the onset of the polyps that were previously the principal means of identifying at-risk family members (Houlston, Slack, and Murday 1990; MacDonald *et al.* 1992; Palladino 2002, 149–50). The new molecular test transformed that practice, as John Burn recalled: “the minute we got that marker [i.e. FAP], we then kicked into predictive testing in our dominant families generally” (Jones and Tansey 2013, 57). With the cloning and characterization, from the early 1990s, of genes responsible for FAP, HNPCC, some familial breast cancers and other familial cancers, the use of molecular tests in family cancer clinics expanded rapidly. The publicity surrounding the isolation of the BRCA breast cancer genes, in particular, precipitated a rapid rise in demand for such tests (Jones and Tansey 2013, 53–54).

In effect, the synergy between research and service provision in the work of the family cancer clinics created a positive feedback loop between biomolecular science and clinical practice. The access to cases and families afforded by the clinics greatly facilitated research into the molecular correlates and causes of familial cancers; while involvement in that research facilitated the introduction of new molecular tests into clinical practice. The availability of these new tests in turn brought more cases and families into the clinics, enabling further research into particular mutations and their pathological effects. From their first tentative beginnings in the mid-1980s, the family cancer clinics expanded and spread to become, by the end of the 1990s, a key component both in the NHS's clinical genetics service and in the growth of molecular genetic research around the UK.

Differentiation among family cancers

At the same time, as research and service provision for familial cancers expanded and diversified to include an increasingly wide range of conditions, so differences became increasingly apparent in the collaborations that formed around different cancers. Use of linkage analysis to map family cancer genes depended on being able to determine with a high degree of certainty which members of an affected family carried the pathogenic gene variant and which did not. In many cases,

geneticists had to rely in the first instance on clinical oncologists, who had the diagnostic skills to make such judgements. Hence the efforts of Bodmer and others to ensure that the new family cancer clinics had good connections to local oncology units. As one geneticist recalled: “the evolution of cancer genetics services ... [was] coupled early on to linkage studies where clinical phenotyping was very important” (Jones and Tansey 2013, 65). Just how heavily linkage studies depended on clinical phenotyping varied markedly from one condition to another, however.

Reliance on clinical oncologists’ diagnostic abilities was particularly important in work on HNPCC. The phenotypic expression of this condition varies significantly from one case to another, making it difficult to distinguish individuals and families with HNPCC from sporadic cases of colon and other cancers. Efforts to map and isolate the genes responsible for HNPCC thus involved particularly close collaboration between clinical oncologists and clinical and molecular geneticists. This was evident for instance in the constitution of the ICG-HNPCC, one of the key early achievements of which was the agreement and adoption of a set of diagnostic criteria – the so-called Amsterdam principles – by which oncologists could identify cases with sufficient reliability to permit genetic linkage analysis (Necochea 2007, 272–274). This alliance remained important even after a number of HNPCC genes were mapped then isolated in the early 1990s, and molecular genetic research moved to identifying and characterizing specific variants of those genes. On the one hand, geneticists continued to depend on clinical oncologists to identify cases for molecular testing and further investigation. On the other hand, clinicians were concerned that the tight diagnostic criteria that best served the purposes of genetic research might tend to exclude some cases who would benefit from clinical attention. The ICG-HNPCC therefore continued to provide a forum where geneticists and oncologists could work together to update the Amsterdam principles in line with the changing needs of research and clinical care (Vasen *et al.* 1999; Lynch *et al.* 2003).

In the case of FAP, by contrast, clinical diagnosis was generally much more straightforward, based on the characteristic presence of large numbers of polyps in the colon, with only limited scope for further clinical differentiation thereafter. Consequently, as efforts to map then clone the FAP gene progressed, clinical oncologists found themselves increasingly peripheral to the work of genetic research and testing, as their role was reduced to simply identifying suitable cases for referral to the family cancer clinic. Instead, their own interests came to focus more closely on the practicalities of clinical prevention and treatment. As early as 1985 the St Mark’s surgeons had convened an international meeting at Leeds Castle to consider the clinical implications of the new genetic research for diagnosing and treating FAP (Jones and Tansey 2013, 78–79), and over time, the Leeds Castle Group grew to become the main international forum where clinical oncologists could share their interest and experience with this condition. This focus on clinical management in turn brought the Leeds Castle Group into increasingly close alignment with clinical oncologists in the ICG-HNPCC, and in 2005 the two organizations

joined to form the International Society for Gastrointestinal Hereditary Tumors (InSiGHT).

Finally, in the case of breast cancer, researchers quickly found that there was little clinical difference between familial and sporadic cases of the disease. Familial forms of breast cancer were best distinguished from sporadic cases simply on grounds of family history, and clinical geneticists had little need of input from clinical oncologists beyond the initial diagnosis of a breast tumor. As a result, clinical oncologists were largely absent from both local and international efforts to map and identify the genes responsible. By the later 1990s, however, it was apparent that the genes so identified accounted for only a small proportion of familial cases. Consequently, a separate and more inclusive collaboration had to be established with European Commission funding to draw up guidelines for identifying and following up women at high risk of inherited breast cancer (Møller *et al.* 1999; Jones and Tansey 2013, 79).

If clinical oncologists found themselves aligning in different ways around different kinds of familial cancer research, the geneticists who ran the family cancer clinics were meanwhile confronting new clinical concerns of their own. With the rapid growth in demand for new molecular tests, geneticists faced growing pressure to routinize and quality assure their procedures. The laboratories they had used to map and clone cancer genes had performed well enough for research purposes. But they could not always be relied upon to maintain the strict chains of custody required for routine clinical testing. As one clinical geneticist put it,

I think the problem was the provenance of the blood and the results; you couldn't trust it. Until you could go through an NHS screening laboratory with its set-up, you always had a little degree of uncertainty of what you were getting. (Jones and Tansey 2013, 69–70, 72)

Geneticists' clinical concerns therefore came to focus on aligning cancer genetic tests more closely with the kinds of procedural standards that obtained elsewhere in genetic laboratory services, and with developing "more standardized care package[s] and screening programme[s]" for those individuals found to be at risk (Jones and Tansey 2013, 65). This led to changes in the constitution of the Cancer Family Study Group. Initially a very multi-disciplinary body, reflecting the collaborative nature of efforts to map the genes for FAP and other familial cancers, over the course of the 1990s it became increasingly focused on the concerns of clinical geneticists, while the clinical oncologists redirected their activities around organizations like the ICG-NHPCC. "Gradually through the early 1990s the [Cancer Family Study] group became more and more genetics-oriented," recalled one geneticist (Jones and Tansey 2013, 14–15); and by the end of the decade it was "transforming itself into more of a service type organization" in the words of another (Jones and Tansey 2013, 65). In 2000 the Cancer Family Study Group renamed itself the Cancer Genetics Group and affiliated to the British Society for Human Genetics.

Discussion

From the very beginning, efforts to map and isolate genes associated with familial cancers depended on a two-way exchange of knowledge and expertise between the laboratory and the clinic. Clinical involvement was not confined to providing access to patient records and samples. Molecular geneticists, clinical geneticists, and oncologists all worked together to ensure that recruitment, diagnosis and documentation of patients and families met the standards required for both molecular genetic research and clinical care; and all made essential contributions to the new knowledge that issued from their collaborative efforts. As a result, as new genetic tests become available, they were introduced into clinical settings that were already configured and primed to make sense of and act upon the information those tests provided. The molecularisation of familial cancers in the UK was a process of “co-evolution,” involving “changing configurations of actors, routines, rules, institutions and technologies,” as Stermerding and Nelis have already observed in the case of FAP testing in the Netherlands (Stermerding and Nelis 2006).

Indeed, those configurations changed continuously throughout the process, from Bodmer’s initial efforts to turn the St Mark’s polyposis registry into a viable source of molecular genetic data, to the introduction and routinization of molecular tests not just for FAP but for other familial cancers including HNPCC and familial breast cancer. Moreover, while there were clearly many points of commonality between these different cancers, the precise configurations and dynamics of change also differed between them, depending on the particular clinical and biological questions each cancer posed. This is perhaps one of the key lessons to come out of the present study. It is not just that the molecularisation of familial cancers depended on clinical as well as laboratory knowledge and expertise. More than that, the precise configuration of actors and other resources was different from one cancer to another.

This is worth bearing in mind. We already know that the kinds of bioclinical collectives that formed around the implementation of molecular genetic tests in fields as far apart as cancer and mental illness are significantly different from one another (Rabeharisoa and Bourret 2009). What the present paper shows is that, even with conditions so apparently similar as familial cancers, molecularisation is not uniform and universal, but differentiated and local. We might surmise that this is at least partly a corollary of the pursuit of precision in molecular oncology: to the extent that the molecularisation of familial cancers aimed to discriminate ever more precisely between diseases, between symptomatic patients and asymptomatic carriers, and eventually between the bearers of growing numbers of chromosomal abnormalities and point mutations, so the particular combinations of clinical and biological knowledge and skill needed to achieve such discrimination became ever more specific and more specialized around particular conditions. Precision oncology, in other words, might actually be localized in proportion to the extent to which it achieves precision.

If that much is speculation, it is clear that the co-evolutionary process of molecularising familial cancers did not follow the same path for all cancers. It is also clear that it differed significantly in the UK, especially in its clinical aspects, from other countries that we know about. Thus in the Netherlands, according to Stemerding and Nelis, clinical geneticists did not become involved in the molecularisation of familial cancers until molecular tests for those cancers became available. Up to that point, collaboration around familial cancers was confined to molecular geneticists and oncologists. Consequently, the advent of molecular testing marked an abrupt shift in the way that patients were treated. Up until that point, clinical practice was dominated by oncologists' activist concern with early intervention in the form of surveillance and preventive surgery: what Stemerding and Nelis call a "regime of prevention." Only once clinical geneticists became involved in delivering molecular tests did the less directive forms of counseling and decision-making clinical genetic practice – what Stemerding and Nelis call a "regime of autonomy" – come to prevail (Stemerding and Nelis 2006). A similarly late involvement of clinical geneticists appears to have occurred in France and Denmark (Bourret, Koch, and Stemerding 1998). By contrast, as we have seen, in the UK clinical geneticists were involved in molecular research into familial cancers from very early in the process. Indeed, the clinical aspects of that process quickly became institutionalized within the NHS regional genetics services. As a result, a regime of autonomy – including non-directive counseling for conditions such as familial risk of breast cancer – became the norm for familial cancers in the UK well before molecular tests became available.

Clearly, accounts of the molecularisation of cancer that suppose a one-way transfer of knowledge and practice from laboratory to clinic fall far short of capturing the complex interactions that were involved in molecularising familial cancers, from the production of new molecular genetic knowledge to the implementation of that knowledge in clinical practice. Nor would any single narrative that would apply to all kinds of cancer capture that complexity; molecularisation is a local process – localized around particular medical conditions as well as around particular places – even while it involves circulation and exchange across localities. To understand, molecularisation, we need to grasp the extent to which it is localized. There is clearly room for much more research to comprehend the significance both of locality and of circulation in the molecularisation of cancer and of medicine more generally.

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