Extending experimentation: Oncology's fading boundary between research and care

Alberto Cambrosio[a*], Peter Keating[b], Etienne Vignola-Gagné[a], Sylvain Besle[c], Pascale Bourret[c,d]

[a] Social Studies of Medicine, McGill University, Montreal, Canada

[b] Department of History, Université du Québec à Montréal, Montreal, Canada

[c] UMR SESSTIM, Marseille

[d] Aix-Marseille Université

[*] Corresponding author. Email: alberto.cambrosio@mcgill.ca

Keywords: Clinical research; Clinical care; Total cancer care; Oncology; Genomics; Molecular tumor boards

Abstract: Historians and social scientists view the distinction between research and care as diachronically and synchronically contingent, rather than transcendental, as is often the case in bioethics. Comparing how the notion of total care was used in the 1950s with present-day use of that same term by genomically informed oncology programs, the paper argues that the distinction between research and care needs: to be historicized, by examining its repeated emergence and re-definition, and the shifting relations between these two 'ideal-typical' components; and to be problematized, by paying attention to the entities, practices, and institutions that are constitutive of the successive regimens that have punctuated oncology's development. Shifting to contemporary activities, the paper examines how the recent massive injection of molecular biology and high-throughput genomic technologies in the field of oncology has been accompanied by a reshuffling of the research/care distinction, a process that is leading to new forms of 'experimental care'.

Acknowledgements: A first version of this paper was presented at the Workshop on "Genomics as a health care strategy: Persons, practices, policies" (Institut Curie, Paris, April 14-15, 2016). We would like to thank the organizers of the Workshop, Simone Bateman and Dominique Stoppa-Lyonnet, for their kind invitation, and several participants for their critical remarks. We would also like to thank Jonathan Kimmelman for sharing his views about bioethics, which are not represented in this paper. Research for this paper was made possible by grants from the Canadian Institutes of Health Research (CIHR MOP-133687), the Fonds de recherche du Québec Société et Culture (FRQSC SE-164195), and the French National Cancer Institute (INCa) (SHSESP14-002).

Corresponding author:

Alberto Cambrosio, Ph.D.

Department of Social Studies of Medicine

McGill University

3647 Peel St.

Montreal (QC)

CANADA H3A 1X1

Email: alberto.cambrosio@mcgill.ca

Extending experimentation: Oncology's fading boundary between research and care

Introduction

The distinction between research and care is a topic of interest to both bioethicists and social scientists (not to mention clinicians). While bioethicists tend to treat these notions as transcendental categories that played, and continue to play, a foundational role for their domain, historians and social scientists view them as diachronically and synchronically contingent. It is not simply that 'research' and 'care' embody different meanings and refer to different practices at different times and in different locations; they also entertain a mutual relation, insofar as changes in the content, meaning, and boundaries of one category are associated with changes in the other. In fact, in a domain such as oncology, characterized by a robust tradition of translational research activities (Keating et al. 2016), these two notions have become increasingly intertwined, so that one can speak of a fading boundary or a vanishing distinction. In this paper we would like to explore some of the ways in which 'post-genomic' developments in oncology are erasing the distinction between research and care, while also briefly looking at how 'care' was reformulated in earlier periods in relation to novel research activities. Our goal is not to prescribe what ought to qualify as either research or care, but to historicize these categories. Before doing that, we need to specify our initial claim about bioethicists' and social scientists' differential take on the research and care distinction.

Let us begin by asking why, as empirically minded social scientists, we should examine bioethical prescriptions and debates. We see two main reasons. First of all, a number of

bioethical considerations have now become embedded, for better or worse,[1] in biomedical practices; they are part (albeit not a driving force) of the present reconfiguration of biomedical activities (just think of the debate concerning the 'incidental findings' generated by genomic technologies)[2]. We cannot thus ignore them. We treat them, however, as a topic of investigation, rather than as analytical tools. On a more normative side, one might also want to investigate whether (or at least how) the research/care distinction that has been central to bioethical discussions of medical practices for several decades, still resonates with the recent major transformations affecting clinical research, a question that may also be of interest to a new generation of empirically oriented bioethicists (Borry et al. 2005), as distinct from bioethicists who maintain that the investigation of actual practices "obfuscates" ethical distinctions (e.g., Miller and Brody 2003).

Starting with Beecher's 1966 seminal contribution in the NEJM, the research/care distinction has performed a foundational role for bioethics. In what he perceived as a context of increasing emphasis on experimentation, Beecher drew a bright line between patient care and experimentation on patients, lamenting the growing separation between "the interests of science and the interests of the patient" (p. 1355). The influential 1979 Belmont report (National Commission 1979) devoted a section to the "boundaries between practice and research", consideration of which then informed the rest of the document, and in the 1980s the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, and in particular its Executive Director (Capron 1983) reaffirmed the importance of that same distinction, which has been reproduced, elaborated upon, and policed well into the turn of the new century. For instance, while acknowledging that patients enrolled in clinical trials

received better care compared to general patients, Miller and Brody (2003) claimed that “the ethics of research and of therapy are fundamentally different”.

In the last decade, in parallel with the emergence of a number of innovations (ranging from new experimental drugs to learning healthcare systems), a number of bioethicists began defending a more nuanced or, we might say, ambivalent view. In her 2012 reply to Largent et al. (2011) who had been wondering whether research and care could be “ethically integrated”, King — who had previously co-authored a paper exploring the “many meanings of care” in clinical research (Easter 2006) — while acknowledging that research included care, maintained that it was a kind of care that is “substantively different from that of clinicians”. Commenting on the debate about the ‘therapeutic misconception’, Kimmelman (2007) stated that it “exaggerate[d] the distinction between research and treatment”, but this has not prevented recent authors of continuing to warn against “neglect[ing] a critical difference between clinical care and clinical research” (Churchill et al., 2013). Ambivalence also shades Kimmelman’s (2017) discussion of the 1995 policy declaration by the American Society of Clinical Oncology, amplified in 2014, that emphasizes the therapeutic intent of experimental research, in particular Phase I trials (see also Besle in press). While admitting that such an intent is hard to dispute, he qualifies this claim by listing a number of characteristics that reassert the experimental dimension of clinical cancer research.

To sum up, recent biomedical developments seem to have led some bioethicists to espouse an uneasy mix of the transcendental and the empirical that includes rejecting on empirical grounds the assumption that research and care are two self-contained and mutually exclusive categories, and yet using their polarity as a logical foundation for bioethical reasoning, thus continuing to

embrace a “dogmatic conviction that a bioethical problem persists even if it is shown empirically that it does not” (McKay and Timmermans 2009, p. 1796).

Unsurprisingly, social science accounts of the research/care distinction have adopted a distinctly more analytical tone. In their investigation of the “clinic of mutations”, Rabeharisoa and Bourret (2009, p. 697), expanding on an argument initially presented in Bourret (2005), noted that the dynamics of clinical work now overlaps with research: “both activities are often carried out in the same arenas, or are interconnected, to the extent that the actors concerned find their boundaries difficult to draw”. Drawing on this work, Timmermans et al. (2016) have argued in their study of exome sequencing that the implementation of this technology “blurs the boundary between research and clinical use […] in a distinctly clinical context”. These claims stand in contrast with previous assertions according to which the biomedical world is “divided into two domains, the first a biological realm where research entities are easy to control and manipulate, the second a clinical realm where cure is difficult to achieve and research messy” (Quirke and Gaudillière, 2008, p. 451, paraphrasing Löwy). Similarly, Hedgecoe (2003, p. 63) in his study of cystic fibrosis detected a “tension between clinicians and researchers”. These different interpretations can be ascribed partly to a different unit of analysis: human practitioners with their distinct skills and competences vs. bioclinical collectives mobilizing a number of biomedical platforms. Focusing on platforms, Crabu (2016) recently noted that “the laboratory itself can be re-framed and adjusted to render laboratory facts and scientific phenomena congruent with the processes of care and the clinical management of patients”, and “the clinic itself […] reframed as a research site where patients are enrolled not only for care, but also as

participants in biomedical research activities". Thus, while in his account the clinic and the laboratory maintain distinct institutional identities, they are reconfigured to mimic each other.

While social scientists differ on the degree and extent of the overlap they are willing to concede to research and care, this may be partly due, in addition to the aforementioned attention to distinct units of analysis, to differences in the empirical sites being investigated, and the rapid pace of change. For instance, in comparison to Timmermans et al. (2016), earlier work by Timmermans and Buchbinder (2011) adopted a more traditional approach by focusing on the clinicians' "bridging work" to reconcile laboratory results with clinical activities. Despite these differences, the relevant issue, as far as we are concerned, is that these interpretations direct us to the ongoing attempt to realign the normal and the pathological in both laboratory and clinical settings. This work is both epistemic and organizational. For instance, new institutions are created to frame the epistemic activities of the bioclinical collectives, such as the genetic data boards and the molecular tumor boards analyzed by Timmermans et al. (2016) and Bourret and Cambrosio (2017). As for existing institutions, they experience disruptions in their routines. For instance, as argued by Nelson et al. (2014) clinical trials have taken a distinctively more experimental turn, while simultaneously expanding their therapeutic intent (as noted in the aforementioned 2014 ASCO policy statement). As we will see in this paper, 'care' increasingly displays experimental features.

Historicizing care

In the 1950s, cancer chemotherapy was not only still in its beginnings, it was also a controversial practice. As noted by an American pioneer of this approach, the "greatest underlying controversy" of the early 1960s was whether chemotherapy was an acceptable option for cancer patients since the treatment was often worse than the disease (Emil Frei cited in Keating and Cambrosio 2012, p. 8). A similar backlash occurred in Europe, with its attendant practice — clinical trials — also fiercely criticized for resorting to randomized treatment assignment (ibid.). Reacting to the accusations that they caused unnecessary suffering by experimenting with patients, Harvard medical oncologist Sidney Farber introduced the term 'total care' (Keating and Cambrosio 2012, p. 81-2). Total care framed chemotherapy and invasive ancillary investigations as a subsidiary component of a larger enterprise that shifted the experimental therapeutic strategies out of the realm of human experimentation by combining them with enhanced supportive or palliative care.[3] Total care was nonetheless controversial, since no clear-cut line could be drawn between specific chemotherapeutic effects and supportive therapy. As Farber explained in a publically broadcast lecture:

> There is still no chemical cure for those forms of cancer which cannot be cured by surgical or radiological techniques. Clinical experience of the last few years, however, has shown that chemical agents may, on occasion, cause previously inoperable cancers to become operable, and previously radio insensitive cancers to become sensitive. […] The use of chemical agents as part of *total care* of the patient with cancer has improved greatly the lot of even of those patients with tumors which do not respond to chemical agents because of the *greater amount of care* given to the patient as part of such a program. (Farber 1951, our emphasis)

Nowadays, the website the Dana Farber Cancer Institute has a section on the history of the Institute that includes a link to the presentation, with the following comment:

> In clinical care, one of Farber's innovations sounds as if it could have come out of today's headlines. “He came up with the idea of what is now called ‘total care,’” said former Institute President David G. Nathan, MD, who began working with Farber at Children's Hospital in the early 1960s. “He decided that all services for the patient and family – clinical care, nutrition, social work, counseling – should be provided in one place. All decisions should be made as a team. Everyone involved in care giving should plan the treatment together. (http://www.dana-farber.org/About-Us/History-and-Milestones.aspx)

Nathan’s mention of “what is now called ‘total care’” is somewhat intriguing, given that, as we just saw, Farber already explicitly mentioned ‘total care’ in his 1951 lecture, but he is most likely referring to turn of the century initiatives that have resurrected this term. The Moffitt Cancer Center, one of the leading comprehensive cancer centers in the US (a designation awarded by the NCI) has resorted to the identical term — ‘total cancer care’ — albeit to cover a set of very different practices. In the earlier case, ‘total care’ redefined chemotherapy by factoring into protocols a patient’s psychosocial (as defined back then) and economic needs, in addition to some form of supportive therapy. In the most recent case, total cancer care (a trademarked protocol launched in 2003, and defined on the Moffitt website as a “comprehensive approach to precision treatment”) refers to the possibility for patients to access the new genomic-driven diagnostic, prognostic, and therapeutic tools. In particular, patients donate clinical information

and excess tumor samples to be used for research, and agree to be contacted again when new information becomes available leading to new treatment opportunities, including enrollment in clinical studies. Presented as a "partnership between patients, doctors, and researchers to improve all aspects of cancer prevention and care", total care covers, at least potentially, a patient's entire lifespan.

Rather than shifting the experimental out of the realm of human experimentation, as was the case in the 1950s version of total care, the post-2000 Moffitt program and similar ones in Europe (such as the SPECTA program spearheaded by the European Organisation for Research and Treatment of Cancer; see ESMO 2016), and in Canada (such as the non-profit organization Exactis Innovation and its Personalize My Treatment initiative) promote a new kind of extended experimentation ("everybody is on trial") whose goal is to "*integrate clinical research and care* to enable continuous learning, so that lessons learned from each patient treated can inform clinical decision making for the next patient" (Abernethy et al. 2014, p. 1083; our emphasis). From this perspective, "evidence generation should include the ability to *follow patients throughout their lifetime* for the collection of observational, real-world data after clinical trials have ended". This view also advocates for "policy incentives [to] stimulate the public–private partnerships and coalitions that are needed to create the foundations for implementation, address concerns associated with the *integration of clinical research and clinical care*, and facilitate data liquidity in preparation for such a system" (Abernethy et al. 2014, p. 1083; our emphasis). Concerning this latter point, in 2014 Moffitt, in partnership with other medical institutions and pharmaceutical companies, launched the Oncology Research Information Exchange Network

(ORIEN) that by 2015 had accrued data from 120,000 patients, using Total Cancer Care® as a single protocol (Ong 2015).[4]

We argued that in the initial years of chemotherapy the issue was to legitimize its status as a form of treatment rather than experimentation, while in recent years the issue was to revamp the status of cancer care by interfacing it with experimental activities. Instead, however, of emphasizing differences between the two periods, we can look at commonalities, for instance by "rethinking the connections between events in different time periods", as advocated by Haydu (1998, p. 341). We can thus ask: What was the common problem with which oncologists in the 1950s and the post-2000 period were confronted? The answer is: to find a way of articulating research and care or, in other words, to implement experimental procedures in a context defined by the presence of previous therapeutic routines. Between the 1950s and the 2003 versions of total care, however, oncology underwent dramatic growth by adopting a highly protocolized approach whereby today's experimental protocols quickly become tomorrow's routine treatment protocols. The drugs mobilized by those protocols also underwent a profound transformation, going from cell-killing (cytotoxic) agents to today's targeted therapies, a shift that was coextensive with the emergence of new bioclinical entities (such as actionable genomic alterations and pathways) and technologies (such as microarrays and next-generation sequencing) that coalesced into a new understanding of cancer etiology and development. Thus, following Navon's (2013, p. 97) amendment to Haydu's approach, we need to examine how "the same kind of actant … can give rise to strikingly divergent forms of knowledge and practice across historical contexts and according to the work done by contrasting networks of actors (human and otherwise) over time".

To sum up: it appears that the distinction, or, rather, the relation between research and care needs to be historicized by examining its repeated re-emergence and re-definition, and the shifting relations between these two components. Most importantly, it also needs to be problematized, by paying attention to the entities, practices, and institutions that are constitutive of each of the successive 'regimens' that have punctuated oncology's development (Cambrosio et al. 2014). In what follows, we will examine a few examples of the specific configuration that underlies contemporary claims about the conflation of research and care.

Reconfiguring cancer research and care in 21st century's oncology

Between 2012 and 2014, a network of French investigators led by a team from the Curie Institute in Paris performed a landmark, albeit controversial,[5] trial called SHIVA (Le Tourneau et al. 2015). SHIVA's primary objective was to assess the efficacy of molecularly targeted therapy by comparing it to conventional therapy in patients who had developed resistance to treatment. This 'precision medicine' trial mobilized a number of genomic and sequencing platforms, whose results were processed by a bioinformatics platform, before being interpreted by a molecular tumor board (MTB). Meeting weekly, the MTB's collective task was to issue therapeutic decisions based on the interpretation of the molecular profiling tests. Once the trial ended, instead of dissolving the MTB the Curie Institute decided to render it a permanent institution. Consisting of clinical oncologists, radiologists, geneticists, pathologists, molecular biologists, and bioinformatics specialists, this molecular, multidisciplinary board was entrusted with implementing molecular screening programs by guiding adult and pediatric patients to

appropriate trials "within a time frame compatible with routine clinical practice" (Kamal et al. 2015). In other words, the Institute transitioned the MTB from a research to a care setting, this new institution acting as a translational device for integrating research and care.[6]

Given the availability of effective treatments for early cancer patients, the routine care activities of the MTB only concern the molecular profiling of advanced and rare cancer patients, but it is not unlikely that in a not too distant future, molecular screening, a pre-condition for the use of targeted therapies, will be applied to all comers, as part of a strategy to promote new experimental drugs to first-line treatment protocols. The Memorial Sloan Kettering Cancer Center (MKSCC) in New York has already stepped up its sequencing capacity to more than 10,000 tumor samples per year (Zehir et al 2017). As we will discuss below, MTBs are not a scalable alternative for institutions with such a large tumor profiling activity; as a result, leading U.S. cancer organizations have developed genomic databases and knowledge bases that can be implemented as part of virtual or 'in-silico' MTBs for data interpretation purposes (Cambrosio et al. 2017).

The transition from advanced to first-line patients is reminiscent of the strategy deployed in the 1970s during the early days of chemotherapy, when the primary treatment for solid tumors was surgery and/or radiotherapy, and chemotherapy was confined to advanced stages. In their successful effort to turn chemotherapy into a leading treatment modality, trialists began by testing drugs in late-stage patients, inching the successful ones forward until they reached the therapeutic front line (Keating and Cambrosio 2012, p. 197). In the case of targeted therapies, however, there is an additional rationale for such a strategy (or, rather, for its modification),

insofar as targeted therapies target specific mutations, and their efficacy is likely to be optimal at early stages, before tumors further differentiate and acquire additional driver mutations. For instance, at a recent conference a presenter pleaded for the use of targeted therapies in newly diagnosed disease: “Don’t wait, treat newly diagnosed disease with the new agents” (fieldnotes, WIN 2014 conference). Shortly thereafter, at a 2016 conference (EBCC-10) another team supplied initial evidence supporting this approach by presenting the results of a trial showing the efficacy of a combination of two targeted agents in breast cancer patients with newly diagnosed, operable disease.

The situation can thus be schematically summarized as follows. Traditionally, a primary cancer patient’s trajectory would begin within a care setting with standard-of-care treatments provided by clinical oncologists, with a subsequent transition to a research setting (clinical trials) in the case of therapeutic failure or relapse. An increasing number of clinical trials now feature molecular profiling and other state-of-the-art experimental components, including new institutions (such as MTBs) to operationalize these components. New experimental approaches are increasingly shaping care settings, so that one can envision a situation whereby: (a) research-setting patients are reintegrated, so to speak, into care, and (b) patients at the beginning of their trajectory are able to access experimental treatments in what can be described as an ‘experimental care’ (no longer an oxymoron) environment. Our argument echoes Petty and Heimer’s (2011) claim that research reshapes the clinic (i.e. care), or, in their own words, that clinical trials “shape medical practice by altering the organizations in which both medical treatment and clinical trials take place”. While their analysis is grounded in case studies of HIV clinics largely located in the developing world, ours involves leading Western institutions in the

field of oncology, thus pointing to the fact that their analysis does not merely apply to the modernization of underdeveloped facilities, but also to state-of-the-art organizations. Indeed, major healthcare institutions on both sides of the Atlantic (e.g., Memorial Sloan-Kettering and MD Anderson in the US, Vall d'Hébron in Spain, the Gustave-Roussy Institute in France) have implemented molecular profiling practices coupled with the use of experimental therapies. In a number of cases, a 'molecular triage' is performed to screen patients, dispatching them to a corresponding, genomic-driven trial. No longer part of a trial, molecular screening becomes a mean to redirect patients to ongoing or future trials (as in the Total Cancer Care program discussed in the previous section). For institutions such as MSKCC, the San Diego Moores Cancer Center, or Vall d'Hébron, the management of a large portfolio of clinical studies has become a core component of their care strategies. The PI of a major French tumor profiling clinical trial aptly named ProfilER explained that, after initial publication of trial results (Tredan et al. 2017), they decided to maintain the protocol open on an "ongoing basis, so to speak *sine die*"; the trial could therefore be described as an "infinite protocol that probably foreshadows a new way of performing clinical trials" (Interview, July 2017). We would thus argue, extending Petty and Heimer's (2011) claim, that not only is research shaping care, leading to new forms of 'experimental care', but also that these processes involve transforming research to transform care.

The mutual shaping of research and care is evidenced by a number of developments, some of which are, admittedly, still tentative. Take, for example the issue of MTBs vs. treatment-decision software. We mentioned the role of MTBs as institutions for operationalizing molecular profiling as part of genomic-driven clinical trials, and we also highlighted the wide range of expertise that

they need to mobilize to be “able to discuss the tests and make appropriate recommendations” (Heger 2014). Commenting on this issue, a leading US oncologist involved in the establishment of a pioneering MTB (see Schwaederle et al. 2014) mentioned that “it is unlikely that software [by which she was referring to computerized data analysis and interpretation systems] could provide the same expertise as such boards, at least in the near future” (Dr. Kurzrock cited in Heger 2014). This reference to software points to a crucial issue for the translation of genomic expertise into care: as noted by another US oncologist whose unit, at the time of our interview (November 2014) was sequencing over 100 patients per week, the abundance of samples did not “allow [them] the opportunity to go case by case through each of these things”. As a result, MTBs were mainly used as “an opportunity to educate, and to highlight certain trials or certain classes of alterations or certain genes that we see mutated in a large number of samples”. How, then, should individual clinicians, not necessarily versed in genomics and unable to rely on an MTB, be expected to make sense of genomic data and to adjust treatments accordingly when examining individual patients in a care setting?

To answer this question, one should first note that MTB members in a research setting do not rely solely on their embodied knowledge and skills. Rather, and as is generally the case (Eyal 2013), tools and devices, in particular a number of databases containing information about genes, mutations, variants, related drugs, etc., are constitutive of the collective expertise embodied by the MTB. Given that the bottleneck of precision medicine lies in interpretation, rather than data production, (Good et al. 2014, Jordan 2015), we have witnessed in recent years a proliferation of databases and knowledge bases, each with its own distinctive edge (Dienstmann et al. 2014), not to speak of the birth of an interpretation industry (Curnutte et al. 2014). Resort to databases,

however, is also a skillful activity that needs to be learned, and is more easily found within research settings. Noting that while genomic assays "were initially developed for research or investigational purposes but will eventually become part of cancer care", some researchers are thus promoting the design of structured, standardized reports that make relevant elements more easily accessible to ordinary oncologists "to directly guide patient care" (Diestmann et al. 2014, p. 871). Another way of addressing this problem is to develop a decision-support software infrastructure that will assist "the treatment review team and the clinic team in the development of a treatment plan" (Palmisano et al. 2016). Resort to algorithms has so far mostly taken place within clinical trials, where its promise to replace "subjectivity in a molecular tumor board" with "objective treatment selection" is an attractive feature for regulatory agencies (interview, 19 March 2015), but their use in routine care looms on the horizon. A leader in artificial intelligence, IBM Watson Health, for instance, has established a collaboration with 14 cancer hospitals "to accelerate the translation of genomic information so that clinicians can personalize treatment decisions for their patients" (GenomeWeb 2015). The rise to prominence of genomic databases and algorithms certainly warrants closer attention, in particular given the somewhat disappointing performance, so far, of IBM Watson (Swetlitz and Ross 2017), but for present purposes suffice it to say that it represents a strategic site for the mutual shaping of research and care or, more exactly, for the development of what we call 'experimental care'.

The recent increase in the number of neo-adjuvant studies constitutes another interesting site for examining the interlocking of research and care. Neo-adjuvant chemotherapy refers to the administration of drugs before the surgical removal of the tumor in order to facilitate the intervention by shrinking the cancerous growth. In 1999, 222 studies were indexed with the

MeSH term ‘neo-adjuvant therapy’, a number that grew to 1500 references/year in 2015. Why such an increase in popularity? The rationale and content of neoadjuvant studies changed between these two dates; it now includes the taking of sequential biopsies to assess the effect of drugs on tumors *in vivo*, and in particular on their molecular composition, before tumor removal. As such it offers clinical researchers an opportunity to both progressively adapt treatment to a specific tumor, and to generate unprecedented biological data from individual patients. While neo-adjuvant studies, often combined with new ‘adaptive’ (Bayesian) trial designs — such as the groundbreaking I-SPY 2 breast cancer trial sponsored by the Biomarkers Consortium and taking place at a number of major U.S. medical sites — can be described as research, its promoters explicitly define them as a way to “safely tailor care while accelerating drug development (Yee et al. 2012). Moreover, patient advocates see them as a form of control over their own disease (Perlmutter et al. 2012), although their transition to an ‘experimental care’ setting is difficult to predict. But the important issue, as far as our present argument is concerned, is that in this kind of intervention, the body of the patient becomes simultaneously a locus of experimentation and the subject of hopefully effective care. To put it in a slightly different way, experimentation on an individual patient also qualifies as a form of personalized care.

Finally, although this is not the place for a detailed discussion of regulatory issue (but see Cambrosio et al. 2017), it has not escaped our notice that the processes we discussed in this paper have already had consequences for other key components of the architecture of care, namely the approval of new drugs and the establishment of clinical practice guidelines. There used to be a clear separation between the generation of evidence via clinical research, and the approval of new drugs by regulatory agencies on the basis of that evidence. In recent years,

however, the FDA has become increasingly involved in the design of clinical trials, in particular studies to determine whether matching molecular profiles with targeted treatments leads to differences in outcomes in comparison to traditional chemotherapy or 'un-matched' targeted therapy. Under the Obama administration, the FDA was also contemplating the regulation of genomic tests, medical devices, and even (tentatively) genomic databases, all elements that are implicated in the 'intervention ensemble' (Kimmelman 2012) for the matching of drugs to patients. These developments related to the fact that, as argued by Vignola-Gagné et al. (2017), the new targeted drugs, in addition to their role as therapeutic agents that have found their way into care settings, have become research tools for the exploration of cancer pathways and mechanisms. As such, they encapsulate, at a 'micro-clinical' or even molecular level, the conflation of research and care.

Conclusion

Discussions about the distinction between research and care have mostly taken place within ethical circles, where they have played a foundational role. In this paper we have taken a different approach, by examining research and care not as transcendental categories, but as contingent, relational ones. We would argue, somewhat provocatively, that while, as mentioned in the introduction, some ethicists maintain that the investigation of actual practices obfuscates ethical distinctions, it is instead ethical distinctions that appear to obfuscate the present reconfiguration of biomedical practices. Within the field of oncology, a massive injection of molecular biology and high-throughput genomic technologies has been accompanied by a fading of the research/care distinction. This ongoing process is visible in the emergence of programs,

such as those mentioned in this paper, blending life-long care and experimental interventions. It can also be detected in the reconfiguration of research, whereby the implementation of new trial designs, the increasing role played by molecular boards, bioinformatics, and algorithms, and the focus on new organizational arrangements for assigning patients to treatments, are in turn re-shaping care. The shaping of care by research, of course, is not an entirely new phenomenon, especially in a field like oncology where experimental protocols quickly become treatment protocols, but we can safely argue that this process has been greatly accelerated in recent years, with the emergence of various instances of 'experimental care'. To analyze the different ways in which, at different times, the meaning and content of experimentation and care has been framed as part of a mutually constitutive relation, we need to take into account *both* the organization *and* the content of clinical research and care, and this means being sensitive to the emergence of new kinds of bioclinical entities, the transformation of rules and governance mechanisms, and changes in institutional logics and organizational boundaries.

References

Abernethy, Amy P, Edward Abrahams, Anna Barker, Ken Buetow, Randy Burkholder, William S. Dalton, Margaret Foti, et al. 2014. "Turning the Tide Against Cancer Through Sustained Medical Innovation: The Pathway to Progress." *Clinical Cancer Research* 20: 1081–1086.

Baszanger, Isabelle. 2012. "One More Chemo or One Too Many? Defining the Limits of Treatment and Innovation in Medical Oncology." *Social Science & Medicine* 75: 864-872.

Beecher, Henry K. 1966. "Ethics and Clinical Research." *New England Journal of Medicine* 274: 1354-1360.

Besle, Sylvain. In press. "Évolution des essais cliniques précoces en cancérologie: quels effets sur la frontière entre soins et recherche?" In *La biomédecine et l'expérience du cancer à la lumière des sciences sociales*, eds. Philippe Bataille P. and Norbert Amsellem. Paris: La découverte.

Borry Pascal, Paul Schotsmans, and Kris Dierickx. 2005. "The Birth of the Empirical Turn in Bioethics." *Bioethics* 19: 49-71.

Bourret, Pascale. 2005. "BRCA Patients and Clinical Collectives: New Configurations of Action in Cancer Genetics Practices." *Social Studies of Science* 35: 41–68.

Bourret, Pascale, and Alberto Cambrosio. 2017. “Molecular Tumor Boards as Collective Expertise: Bio-Clinical Decision-Making in Cancer Genomics.” Paper presented at the 4S Annual Meeting, Boston, August 30 - September 2.

Cambrosio, Alberto, Pascale Bourret, Peter Keating, and Nicole Nelson. 2017. “Opening the Regulatory Black Box of Clinical Cancer Research: Transnational Expertise Networks and Disruptive Technologies.” *Minerva* 55 (2): 161-185.

Cambrosio, Alberto, Peter Keating, and Nicole Nelson. 2014. “Régimes thérapeutiques et dispositifs de preuve en oncologie: l’organisation des essais cliniques des groupes coopérateurs aux consortiums de recherche.” *Sciences Sociales & Santé* 32 (3): 13-42.

Cambrosio, Alberto, Peter Keating, Étienne Vignola-Gagné, Jonah Campbell, Bertrand Jordan, and Pascale Bourret. 2017. “Overcoming the bottleneck”: Knowledge architectures for genomic data interpretation in the field of oncology.” Paper presented at the conference on “Varieties of Data Journeys”, University of Exeter, 2-3 November 2017.

Capron, Alexander M. 1983. “Looking Back at the President's Commission.” *Hastings Center Report* 13 (5): 7-10.

Churchill, Larry R., Nancy M R King, and Gail E. Henderson. 2013. “Why We Should Continue to Worry About the Therapeutic Misconception.” *Journal of Clinical Ethics* 24: 381-386.

Crabu, Stefano. 2016. “Translational Biomedicine in Action: Constructing Biomarkers Across Laboratory and Benchside.” *Social Theory & Health* 14: 312–331.

Curnutte, Margaret Ann, Karen L. Frumovitz, Juli M. Bollinger, Amy L. McGuire, and David J. Kaufman. 2014. “Development of the Clinical Next-Generation Sequencing Industry in a Shifting Policy Climate.” *Nature Biotechnology* 32 (10): 980–982.

Dienstmann, Rodrigo, Fei Dong, Darrell Borger, Dora Dias-Santagata, Leif W. Ellisen, Long P. Le, and A. John Iafrate. 2014. “Standardized Decision Support in Next Generation Sequencing Reports of Somatic Cancer Variants.” *Molecular Oncology* 8 (5): 859–873.

Easter, Michele M., Gail E. Henderson, Arlene M. Davis, Larry R. Churchill, andNancy M. P. King. 2006. “The Many Meanings of Care in Clinical Research.” *Sociology of Health & Illness* 28: 695–712.

ESMO. 2016. “Results of the First Cohort of Patients Screened Within the New EORTC Molecular Platform for Patients with Colorectal Cancer.” http://www.esmo.org/Conferences/ESMO-2016-Congress/News-Articles/Results-of-the-First-Cohort-of-Patients-Screened-Within-the-New-EORTC-Molecular-Platform-for-Patients-With-Colorectal-Cancer.

Eyal, Gil. 2013. “For a Sociology of Expertise: The Social Origins of the Autism Epidemic.” *American Journal of Socioogy* 118 (4): 863–907.

Farber, Sidney. 1951. “Newer Agents in the Treatment of Leukemia.” Linsley R. Williams Memorial Lecture, part of the “Lectures to the Laity” series, produced through the New York Academy of Medicine and New York Public Radio. http://www.dana-farber.org/uploadedFiles/Library/about-us/history-and-milestones/sidney-farber-1951-transcript.pdf.

GenomeWeb. 2015. “IBM Collaborates with 14 Cancer Institutes to Decipher Genomic Data.” *GenomeWeb* May 05, https://www.genomeweb.com/informatics/ibm-collaborates-14-cancer-institutes-decipher-genomic-data.

Good, Benjamin M., Benjamin J. Ainscough, Josh F. McMichael, Andrew I. Su, and Obi L. Griffith. 2014. “Organizing Knowledge to Enable Personalization of Medicine in Cancer.” *Genome Biology* 15 (8): 438.

Haydu, Jeffrey. 1998. “Making Use of the Past: Time Periods as Cases to Compare and as Sequences of Problem Solving.” *American Journal of Sociology* 104: 339–371.

Hedgecoe, Adam M. 2003. “Expansion and Uncertainty: Cystic Fibrosis, Classification and Genetics.” *Sociology of Health & Illness* 25: 50-70.

Heger, Monica. 2014. “UCSD Molecular Tumor Board Aids Patient Care Decisions in Age of NGS Tests.” *Genome Web*, May 14. https://www.genomeweb.com/archive/ucsd-molecular-tumor-board-aids-patient-care-decisions-age-ngs-tests.

Jordan, Bertrand. 2015. “Recherche cibles, désespérément.” *Médecine/Sciences (Paris)* 31 (2): 214-217.

Kamal, Maud, Marie Alt, Gaëlle Pierron, Céline Callens, Étienne Rouleau, Samia Melaabi, Odette Mariani, et al. 2015. “La réunion de concertation pluridisciplinaire moléculaire de l’Institut Curie.” *Innovations et Thérapeutiques en Oncologie* 1: 76-83.

Keating, Peter, and Alberto Cambrosio. 2012. *Cancer on Trial: Oncology as a New Style of Practice*. Chicago: The University of Chicago Press.

Keating, Peter, Alberto Cambrosio, and Nicole Nelson. 2016. “’Triple Negative Breast Cancer’: Translational Research and the (Re)Assembling of Diseases in Post-Genomic Medicine.” *Studies in History and Philosophy of Biological and Biomedical Sciences* 59: 20-34.

Kimmelman, Jonathan. 2007. “The Therapeutic Misconception at 25: Treatment, Research, and Confusion.” *Hastings Center Report* 37 (6): 36-42.

Kimmelman, Jonathan. 2012. “A Theoretical Framework for Early Human Studies: Uncertainty, Intervention Ensembles, and Boundaries.” *Trials* 13:173.

Kimmelman, Jonathan. 2017. “Is Participation in Cancer Phase I Trials Really Therapeutic?” *Journal of Clinical Oncology* 35 (2): 135-138.

King, Nancy M.P. 2012. “Research *Is* Care.” *Hastings Center Report* 42 (3): 7.

Largent, Emily A., Steven Joffe, and Franklin G. Miller. 2011. “Can RESEARCH and CARE Be Ethically Integrated?” *Hastings Center Report* 41 (4): 37-36.

Le Tourneau, Christophe, Jean-Pierre Delord, Anthony Goncalves, Céline Gavoille, Coraline Dubot, Nicolas Isambert, Mario Campone, et al. 2015. “Molecularly Targeted Therapy Based on Tumour Molecular Profiling Versus Conventional Therapy for Advanced Cancer (SHIVA): A Multicentre, Open-Label, Proof-of-Concept, Randomised, Controlled Phase 2 Trial.” *Lancet Oncology* 16 (13): 1324-1334.

McKay, Tara, and Stefan Timmermans. 2009. “The Bioethical Misconception: A Response to Lidz.” *Social Science & Medicine* 69: 1793–1796.

Miller Franklin G., and Howard Brody. 2003. “A Critique of Clinical Equipoise: Therapeutic Misconception in the Ethics of Clinical Trials.” *Hastings Center Report* 33 (3): 19-28.

National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. *The Belmont Report: Ethical Principles and Guidelines for the Protections of*

Human Subjects of Research. Washington, DC: US Department of Health, Education and Welfare.

Navon, Daniel. 2013. *Genomic Designation: New Kinds of People at the Intersection of Genetics, Medicine and Social Action*. Ph.D. Thesis (Sociology), Columbia university.

Nelson, Nicole, Peter Keating, Alberto Cambrosio, Adriana Aguilar-Mahecha, and Mark Basik. 2014. "Testing Devices or Experimental Systems? Cancer Clinical Trials Take the Genomic Turn." *Social Science & Medicine* 111: 74-83.

Ong, Matthew Bin Hang. 2015. "Cancer Centers Join to Accelerate Trials, Industry Collaborations, Drug Development." *The Cancer Letter* 41 (10): 1-7.

Palmisano, Alida, Yingdong Zhao, Ming-Chung Li, Eric C. Polley, and Richard M. Simon. 2016. "OpenGeneMed: A Portable, Flexible and Customizable Informatics Hub for the Coordination of Next-Generation Sequencing Studies in Support of Precision Medicine Trials." *Briefings in Bioinformatics* bbw059, https://doi.org/10.1093/bib/bbw059.

Perlmutter, Jane, Susan Axler, Carole Baas, Barbara J Beckwith, Amy Bonoff, Susan Brain, Maryellen Delapine, et al. 2012. "Advocates' Perspective: Neoadjuvant Chemotherapy for Breast Cancer." *Journal of Clinical Oncology* 30 (36): 4586–4588.

Petty, JuLeigh, and Carol A. Heimer. 2011. “Extending the Rails: How Research Reshapes Clinics.” *Social Studies of Science* 41 (3): 337-60.

Quirke, Viviane, and Jean-Paul Gaudillière. 2008. “The Era of Biomedicine: Science, Medicine and Public Health in Britain and France after the Second World War. *Medical History* 52: 441-452.

Rabeharisoa, Vololona, and Pascale Bourret. 2009. “Staging and Weighting Evidence in Biomedicine: Comparing Clinical Practices in Cancer Genetics and Psychiatric Genetics.” *Social Studies of Science* 39: 691–715.

Rabinow, Paul, and Nikolas Rose. 2006. “Biopower Today.” *BioSocieties* 1: 195-217.

Ross, Casey, and Ike Swetlitz. 2017. IBM Pitched its Watson Supercomputer as a Revolution in Cancer Care. It’s Nowhere Close.” *STAT News*, September 5. https://www.statnews.com/2017/09/05/watson-ibm-cancer/

Schwaederle, Maria, Barbara A. Parker, Richard B. Schwab, Paul T. Fanta, Sarah G. Boles, Gregory A. Daniels, Lyudmila A. Bazhenova, et al. 2014. “Molecular Tumor Board: The University of California-San Diego Moores Cancer Center Experience.” *The Oncologist* 19 (6): 631–636.

Timmermans, Stefan, and Mara Buchbinder, M. (2011). "Expanded Newborn Screening: Articulating the Ontology of Diseases with Bridging Work in the Clinic." *Sociology of Health & Illness* 34: 208-220.

Timmermans, Stefan, Caroline Tietbohl, and Eleni Skaperdas. 2017. "Narrating Uncertainty: Variants of Uncertain Significance (VUS) in Clinical Exome Sequencing." *BioSocieties* 12 (3): 439–458.

Tredan, Olivier, Veronique Corset, Qing Wang, Romain Varnier, Camille Pacaud, Alexia Torroja, Nicolas Luppi, et al. 2017. "Routine Molecular Screening of Advanced Refractory Cancer Patients: An Analysis of the First 2490 Patients of the ProfilER Study." *Journal of Clinical Oncology* 35 (suppl; abstr LBA100).

Tsimberidou, Apostolia-Maria, and Razelle Kurzrock. 2015. "Precision Medicine: Lessons Learned From the SHIVA Trial." *The Lancet Oncology* 16 (16): e579–580.

Vater, Laura B., Julie M. Donohue, Seo Young Park, and Yael Schenker. 2016. "Trends in Cancer-Center Spending on Advertising in the United States, 2005 to 2014." *JAMA Internal Medicine* 176: 1214-1216.

Vignola-Gagné, Etienne, Peter Keating, and Alberto Cambrosio. 2017. Informing Materials: Drugs as Tools for Exploring Cancer Mechanisms and Pathways. *History and Philosophy of the Life Sciences.* 39:10.

Wilson, Duncan. 2014. *The Making of British Bioethics*. Manchester: Manchester University Press.

Yee, Douglas, Tufia Haddad, Kathy Albain, Anna Barker, Christopher Benz, Judy Boughey, Meredith Buxton, et al. 2012. "Adaptive Trials in the Neoadjuvant Setting: A Model to Safely Tailor Care While Accelerating Drug Development." *Journal of Clinical Oncology* 30 (36): 4584–4586.

Zehir, Ahmet, Ryma Benayed, Ronak H. Shah, Aijazuddin Syed, Sumit Middha, Hyunjae R. Kim, Preethi Srinivasan, et al. 2017. Mutational Landscape of Metastatic Cancer Revealed from Prospective Clinical Sequencing of 10,000 Patients. *Nature Medicine.* 23(6): 703-713.

ENDNOTES

[1] For a criticism of the "bioethical complex", the" ethics industry", and the "bioethical misconception" see Rabinow and Rose (2016, p. 203), Wilson (2014), and McKay and Timmermans (2009).

[2] A search in PubMed for the MeSH term 'incidental findings' (introduced in 2003), shows that the number of articles indexed by this term went from 196/year in 2003 to 743/year in 2015.

[3] See Baszanger (2012) for a history of the shifting relation between treatment and palliation.

[4] In the largely privatized US healthcare system, the conflation of research and care has even become a marketing strategy in advertisements for the general public (Vater et al. 2016). For instance, the Emory Winship Cancer Institute promotes itself by stating that "since 2005, we've enrolled over 5,000 of our patients in clinical trials" (*Delta Sky Magazine*, November 2015, p. 125), while the tripartite Seattle Cancer Care Alliance (Fred Hutch, Seattle Children's, UW Medicine) advertises itself by stating that "Research and care go hand in hand in hand" (*Delta Sky Magazine*, July 2016, p. 13).

[5] The controversial aspects of the SHIVA trial refer to the fact that its results were negative, thus questioning the value of precision medicine. Several promoters of this approach, however, quickly pointed to flaws in the trial's design as causes of the negative results (e.g. Tsimberidou and Kurzrock 2015).

[6] See Besle (in press) for a discussion of integration of research and care that focuses on early-phase clinical trials.