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On Being "Actionable": Clinical Sequencing and the Emerging Contours of a Regime of Genomic Medicine in Oncology

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This article explores commercial, academic, and national initiatives aimed at using sequencing technologies to generate "actionable" genomic results that can be applied to the clinical management of oncology patients. We argue that the term "actionable" is not merely a buzzword, but signals the emergence of a distinctive sociotechnical regime of genomic medicine in oncology. Unlike other regimes of genomic medicine that are organized around assessing and managing inherited risk for developing cancer (e.g., BRCA testing), actionable regimes aim to generate predictive relationships between genetic information and drug therapies, thereby generating new kinds of clinical actions. We explore how these genomic results are made actionable by articulating them with existing clinical routines, clinical trials, regulatory regimes, and health care systems; and in turn, how clinical sequencing programs have begun to reconfigure knowledge and practices in oncology. Actionability regimes confirm the emergence of bio-clinical decision-making in oncology, whereby the articulation of molecular hypotheses and experimental therapeutics become central to patient care.

Keywords: genetic testing; genomic medicine; oncology; actionability; personalized medicine

Introduction

Linnea Duff is one of several patients featured on the website of the Massachusetts General Hospital (MGH) as an example of the hospital's recent successes with genotyping and "smart" drugs. Diagnosed with lung cancer at the age of 45, Duff underwent multiple surgeries and rounds of chemotherapy that did little to stop the spread of her cancer. At MGH, her tumour was analysed in the translational research laboratory for mutations in several genes known to be involved in cancer, and tests found a mutation in the ALK gene. Based on this information, her oncologist enrolled her in a Phase I clinical trial for a new drug targeting the enzyme encoded by ALK, and within weeks her tumours began shrinking. In a video interview, Duff recalls that she was "absolutely elated" when she found out that she had the mutation, because "it meant that there was something that they could point the medicine at, something that they could go after, something specific."

The applications of sequencing technologies to the treatment of patients have greatly increased in recent years, particularly in oncology. A series of *GenomeWeb* news articles reflecting back on the year 2011 claimed that it would "likely be recognized as the year that genome sequencing broke out of the research realm and moved into the clinic," arguably "[making its] biggest impact in the field of cancer" (Heger 2012a; Heger 2012b). Those involved in recent efforts to apply tumour sequence information to clinical practice in oncology increasingly use the term "actionable" to describe the kind of sequencing results that would, as Duff puts it, give practising oncologists "something that they could point the medicine at." Researchers at the nearby Dana Farber Cancer

Institute, for example, describe their sequencing pilot programme as demonstrating "the clinical feasibility of high-throughput mutation profiling to query a large panel of 'actionable' cancer gene mutations" (MacConaill et al. 2009). A private company offering similar tumour sequencing services, Foundation Medicine, reports that their test has found "actionable genomic alterations" in nearly 80% of the samples tested so far, and advertises its testing service as "more actionable than other molecular assays" (Fieldnotes June 2012; Palmer et al. 2012). The term has continued to gain traction in the medical lexicon: a majority of articles in a May 2013 special issue of the *Journal of Clinical Oncology* on "precision medicine," for instance, explicitly refer to "actionable" molecular alterations as a platform for medical interventions.

What does it mean for sequencing results to be "actionable"? While early instances of the term in the medical literature were confined to its legal sense (i.e., giving cause for legal action), more recent entries use it to describe information that medical practitioners are able (or obliged) to act on and put into practice. This includes, for example, intelligent information systems that flag "clinically actionable" information for nurses or "actionable findings" from organizational studies that can be translated into health policy. The introduction of the term in the cancer genomics domain appears to be quite recent: according to a title and abstract search in PubMed, a first mention of "actionable" appeared in 2005, and almost all of the subsequent articles are from 2009 and later. One widely cited article from 2012 on the detection of actionable genomic alterations proposed a classification system for thinking about the clinical utility of different kinds of genetic alterations (Wagle et al. 2012). The authors term mutations that can be directly linked to a treatment, either an FDA approved drug or an experimental

therapy, “actionable in principle.” These mutations are contrasted with “prognostic and diagnostic” mutations that may contribute to treatment but in a more open-ended way; and mutations “of unclear significance” that may be biologically important but do not currently have therapeutic implications, either for lack of a drug targeting the mutation or for lack of information about the mutation itself.

We argue that “actionable” is more than just a buzzword; it is a term that signals the emergence of a distinctive sociotechnical regime in medical oncology. We describe in this paper the rapid emergence of a host of initiatives designed to apply genomic information to oncology clinical practice, what kinds of actions are enabled by these “actionable” gene panels, and how actionability is accomplished by articulating these new technologies with existing treatment routines, clinical trials, regulation, and health care infrastructures. Although we offer an empirical outline of several different clinical sequencing initiatives, our aim is not to give a comprehensive survey of this field. Indeed, such a project would be nearly futile given the pace of change in this field. Rather, our goal is to delineate the particular features of present strategies for articulating genomics with the clinic, which we believe are distinct from regimes designed around the detection and management of genetic risk in oncology. In our view, “actionability” acts as a *performative classifier* that assigns certain molecular entities to distinct categories that have implications for clinical actions.

Methodology

The paper is based on site visits and interviews with key investigators at eight clinical sequencing project sites in North America and Europe, conducted between November

2011 and June 2013. We interviewed investigators at four translational research and molecular pathology projects based in research hospitals (the Massachusetts General Hospital [MGH] in Boston, the University of Michigan's Center for Translational Pathology in Ann Arbor, the Memorial Sloan-Kettering Cancer Center [MSKCC] in New York, and the Gustave Roussy Institute [IGR] in Villejuif, France), two commercial providers of genetic tumour analysis (Bio-Reference Laboratories, based in New Jersey, and Foundation Medicine, based in Massachusetts), and two national programmes (the Stratified Medicine Programme of Cancer Research U.K. [CRUK] and the French National Cancer Institute's [INCa] genetic testing platforms initiative in France). Additionally, we attended over a dozen international oncology meetings,[1] and we analysed the literature (both the clinical-scientific literature and online newsletters such as *GenomeWeb*) on clinical sequencing programmes in oncology and "actionable" mutations. This research strategy had its own internal control mechanisms: we initially selected fieldwork sites on the basis of their visibility in the field, as inferred from the analysis of published data, and subsequently adjusted our choices by taking into account presentations at meetings and the list of sites consulted by CRUK or INCa when setting up their programmes.

Emergence of clinical sequencing in oncology

According to those in the cancer genomics field, several intertwined developments combined to produce what one researcher described as a "perfect storm" for the recent rise of clinical sequencing initiatives in oncology (Fieldnotes February 2012). One of these factors was a series of transformations in the landscape of genomic technologies.

Some of our respondents spoke of a quick sequence of "technological bubbles": single-gene studies performed by PCR were quickly challenged by multi-gene microarray approaches, which were in turn displaced by "next generation sequencing" (NGS) methods. NGS sequencing platforms in particular have made substantial improvements in terms of the speed, cost, and accuracy of sequencing over traditional Sanger sequencing techniques. Many of these newly available platforms are relatively low-cost and specifically designed for the clinical market, such as the popular "desktop" sequencing machine MiSeq, launched in 2011 by Illumina.

Others noted that these developments were part of a broader trend to promote "translational research" aimed at reducing the perceived gap between basic research and clinical applications (Butler 2008). When asked about the beginnings of its clinical research unit, a leading researcher at IGR explained that the inspiration for the unit came when one of his colleagues returning from a stay at MD Anderson in 2003–2004 reported that translational research had become "the hottest thing in town." As a result, the IGR made the decision to establish a translational research unit that would use molecular analysis technologies to identify patients' mutations and accrue them to targeted clinical trials (André interview).

A final factor was the increasingly large number of "targeted" cancer drugs in development, which, in contrast to traditional chemotherapy agents that kill rapidly dividing cells, function by blocking specific molecules needed for tumour growth. In some cases, the efficacy of these targeted drugs could be linked to particular mutations in the molecules that they target. In one much-discussed case in 2004, researchers showed that patient responses to the epidermal growth factor receptor (EGFR) inhibiting drug

gefitinib correlated with whether they had a mutated EGFR gene in their lung cancer (Lynch et al. 2004; Paez et al. 2004). Retrospective analysis of clinical trials with several EGFR inhibiting drugs showed striking differences in response: as many as 67% EGFR mutant patients responded to those drugs, as compared to 3% of those with normal EGFR genes (Jackman et al. 2009). This trend towards molecular stratification of cancer treatments has intensified, with several newly developed drugs approved only for patients with specific molecular alterations, such as vemurafenib (approved by the FDA in 2011 for melanoma patients with BRAF mutations) and crizotinib (approved by the FDA in 2011 for lung cancer patients with fusions in the ALK gene).

With these developments in mind, many academic medical centres in North America began forming their own in-house molecular analysis programmes. John Iafrate, one of the founders of MGH's cancer molecular diagnostics programme, recalls that the EGFR story in particular encouraged them to set up their own comprehensive testing programme:

> The discovery that patients who responded to EGFR tyrosine kinase inhibitors had EGFR mutations was [made] at Mass General, so we were at the right place at the right time. EGFR testing was set up, and then every few months, we would get asked by a clinician if we could start screening in another gene. … At about the same time multiple people at the institution looked at each other and said, "What are we going to be doing in five years?" They said, "We'll probably be genotyping all of these genes at once rather than one at a time in each tumour." And we all said, "Yeah, so why don't we do it?"

MGH began designing its programme in 2007, starting first with testing lung cancer samples and gradually opening up the programme to all departments in the cancer centre by 2010 (Borger interview). Their test, which when it was first introduced

analysed mutations in approximately a dozen cancer genes that could be linked to particular therapies, is ordered at the request of the oncologist, billed to insurance companies, and filed in patients' medical records (Dias-Santagata et al. 2010). For patients with types of cancer that have many known mutations, such as lung cancer, molecular analysis is now part of the routine assessment at MGH (Shaw et al. 2011).

Many other academic medical centres have followed suit with their own sequencing initiatives. University of Michigan's Oncology Sequencing Project (MI-ONCOSEQ), piloted in 2011, uses a combination of whole genome, exome, and transcriptome sequencing to develop personalized treatment plans for patients with rare or advanced cancers (Roychowdhury et al. 2011). MSKCC, a major US comprehensive cancer centre, has actively recruited leading molecular oncologists and pathologists to strengthen its translational research projects, and now sequences more than 5,000 tumors every year with the eventual goal of routinely sequencing every patient. As the MSKCC physician-in-chief describes it, sequencing has already been incorporated into their routine practice: "The only thing the clinician has to do is to check a box in the chart – click! – and it gets sequenced." (Baselga interview). Another major American centre, the MD Anderson, has established an Institute for Personalized Cancer Therapy that includes a program called T9 (Ten Thousand Tumors, Ten Thousand Tests, Ten Thousand Therapies) that will screen for mutations in approximately 40 cancer genes.

Commercial companies have also begun to offer clinical sequencing services for tumour samples. Bio-Reference Laboratories, one of the largest providers of laboratory services in the United States, collaborated with MGH to develop a commercial version of their mutation panel along with reports providing additional information about the

significance of these mutations, available to clinicians for $995 USD. Foundation Medicine, a Cambridge (Mass.) based start-up company, has developed a cancer genomic test that uses NGS to sequence a relatively limited number of genes at great depth. Foundation Medicine's test was officially launched in 2012 at a cost of $5800 USD, and within the first month the company reported it was already sequencing 40 to 60 samples a week, and announced plans to double their capacity (Karow 2012).

Finally, in Europe there are a number of government-sponsored initiatives to bring sequencing technologies to the oncology clinic. The French National Cancer Institute (INCa) began to develop a national strategy for genetic tumour profiling in 2006, eventually building a network of 28 regional genetic testing platforms designed to ensure equal access to tumour testing for all citizens ("Getting Personal" 2011; Nowak, Soria, and Calvo 2012). Following in INCa's footsteps, the United Kingdom has launched a multi-pronged initiative to develop clinical sequencing capacity. The government's Technology Strategy Board, in collaboration with industry, funded a competition to develop genetic assays that can screen at least 22 known mutations in 9 cancer genes, cost less than £300, and be conducted within a "clinically relevant turnaround time" (Heger 2011). Meanwhile, a demonstrator programme run by Cancer Research UK planned to screen up to 9,000 cancer patients, using a protocol that former program director James Peach says was modeled after MGH's gene panel model and INCa's national service delivery network (Peach, personal communication).

Forms of Genetic Medicine

As already hinted, "actionable" regimes deploy aims and sociotechnical arrangements that differ from many other initial forms of genetic medicine In oncology, the first forays in genetic medicine were largely organized around the idea of assessing and managing inherited genetic risk for cancer, with BRCA gene testing for breast cancer being the most visible and widely studied example of this approach. Diagnosing risk of disease instead of the presence of disease and devising strategies and medical interventions to manage that risk (such as prophylactic mastectomies and chemoprevention for women at high risk of developing breast cancer) are the central projects of this regime of cancer genetics. Social scientists have investigated many aspects of the discourses and practices characterizing BRCA testing and their divergent development in a number of institutional and national settings. In particular, they have examined how these practices, with their focus mutations that run in families, and probabilistic information about the risk of illness and the benefits of prevention, have reshaped the interactions between practitioners from different biomedical specialties, and between new kinds of patients and healthcare providers (e.g., Parthasarathy 2007; Bourret 2005; Rabeharisoa and Bourret 2009; Gibbon, Kampriani, and Nieden 2010).

Thanks to these analyses, we are in a position to compare those early and on-going forms of genetic medicine to more recent forms that are centred on "actionability." Risk-centred genetic analyses in oncology focus primarily on hereditary mutations, often in healthy individuals conceived of as asymptomatic or pre-symptomatic patients, or in individuals who are concerned about the risk to extended (or future) family members. Practices centred on actionable mutations, in contrast, are focused on non-heritable

(sporadic) mutations that arise in the tumour, and they thus involve individual patients who are by definition already symptomatic. Indeed, the majority of the clinical sequencing programs that we analyse in this paper service patients who have advanced (metastatic) cancer and who have often exhausted standard treatment options. Thus, while risk-centred practices are future-looking, actionable regimes are focused on the present, as they concern patients who require immediate medical attention. Risk-centred practices also employ a probabilistic thought-style in relating particular mutations to the future likelihood of developing disease, while actionable genomic tests are predicated upon more mechanistic, causal relationships between genes, diseases, and medical treatment. The relationship between ALK mutations and ALK inhibiting drugs, for example, is not only a statistical association between the mutation and the likelihood that a patient will respond to the drug, it is a molecular hypothesis about how the drug might be able to slow the growth of a cancer by blocking the function of a mutated enzyme. Leaders in the oncology field have called specifically for a "mechanistic understanding of tumour biology, not correlative biomarkers … [as a] starting point for successful clinical translation" (Buettner, Wolf, and Thomas 2013, 1858), and this shift towards mechanism has been instantiated in institutional initiatives such as the establishment of a center for mechanistic-based therapy at the MSKCC (Baselga interview). The differences between these two regimes are of course likely to be much less stark in real world examples, but we resort to this ideal-typical contrast for analytical purposes to point to the important departures of these new regimes of genomic analysis from existing forms of genetic medicine in oncology.

Sequencing programs focused on actionable genomic information often complement future-oriented, risk-centred testing in practice, but yet they are often rhetorically positioned against each other. The very selection of the adjective "actionable" to describe the type of genomic information produced by clinical sequencing programs implies that other types of genomic information are defined by their inability to guide clinical action. The clinical actors we interviewed, for example, often contrasted their efforts with research projects, which might analyse clinical samples without returning information to patients, and with commercial genomic services that provide information to patients with little indication of how it could to be used in the clinic. An MGH respondent gave the example of a patient who had his sequence analysed by a commercial enterprise and brought his results to the clinic:

> And so he proceeded to give me a list of the 25 top genes that he was told were altered in his cancer, zero of which I had ever seen reported being involved in cancer, including olfactory receptors and calcium channel genes, and a variety of things that are most likely passenger mutations or rare variants, but would have no clinical importance at all. (Iafrate interview)

He compared this approach to sequencing cancer samples with the MGH program that focuses on a limited number of mutations that predict responses to presently available therapies. Pitting the promises of genetic medicine with the relative paucity of its present achievements is a familiar trope often found in discussions of genomic medicine beyond the oncology field. A recent editorial in *Science* magazine, for example, argued that routinely sequencing individuals early in life could lead to better detection of rare genetic diseases, inherited susceptibility of cancers, or adverse reactions to particular drugs (Drmanac 2012); while another editorial in the same issue questioned this approach by

arguing that "the vast majority of genomic data is, at this time, not medically actionable" (Brunham and Hayden 2012, 1112). One might interpret the proliferation of discourses in oncology about actionable mutations as a way to counter the recurring criticism about the lack of clinical utility of genomic approaches. And yet, as we will show, actionability is no mere promissory note: it is both a project and a program, embedded in concrete initiatives which, taken together, outline the contours of a novel biomedical regime.

Actionable as a form of prediction

What facilitates the "action" in "actionable" tumour sequencing results is the ability of these results to provide information about whether a patient's tumour is likely to respond to specific therapies—in other words, the ability of these tests to provide *predictive* rather than *diagnostic* (which identifies and characterizes the tumour) or *prognostic* information (which forecasts the natural evolution of the disease in the absence of any intervention).[2] Recent developments in biomedicine, in particular the increasing availability of new technologies produced by a growing medical devices' sector, have led social scientists to call for more attention to be directed to the nature, role and importance of diagnostic practices (Jutel 2011; see also Rosenberg 2002), and to the renewed significance of prognosis (Christakis 1999; Fox 2003). Analysts have described how genomics contributes to and further refines both diagnosis and prognosis, the former by identifying, for instance, molecular subclasses of particular cancers (see Rabeharisoa and Bourret 2009; Navon 2011), and the latter by developing, for instance, "molecular signatures" that differentiate between patients who are at high or low risk of relapse after surgery. Even more significantly, new genomic tools have led to a disjunction between

prognosis and prediction, and to the design of complex clinical trials to test whether separating patients into high- and low-risk groups also predicts benefit from more aggressive treatments (Kohli-Laven et al. 2011; Bourret, Keating, and Cambrosio 2011). For practising oncologists and for companies commercializing genomic tumour signatures, having a test that offers predictive rather than merely prognostic information has clear implications for how that test can be commercialized, marketed, and used in clinical practice.

In the case of clinical sequencing projects, it is tempting to view the information they provide as the foundation of a new diagnostic ontology of cancer. Indeed, the delineation of specific genomic entities in tumours resonates with a broader transformation that has taken place throughout the last two decades and redefined what used to be considered a single disease (e.g., breast cancer) as a collection of different diseases. Treatment in breast cancer today is tailored towards subpopulations of patients whose tumours are characterized by the presence or absence of biomarkers such as hormone receptors that are used to establish whether hormonal therapy is appropriate or not. In their present form, however, clinical sequencing results provide the means for generating quite specific kinds of clinical actions rather than new nosological categories. Foundation Medicine's commercial test, for example, identifies on average three distinct "actionable" mutations per sample, leading to three possible treatments, not three competing diagnoses.

While most definitions of "actionability" focus on the prediction of treatment response, rather than diagnosis or prognosis, some actors have suggested a broader definition that would include "any aberration (germline or somatic) that may impact

cancer management through diagnostic, prognostic, and/or predictive implications," thus confining "druggable" mutations to a subset of all actionable mutations (Tran et al. 2012). Such an encompassing definition, however, does not appear to be dominant. More widely used understandings of "actionable", such as the definition introduced by the aforementioned Wagle and colleagues (2012) article, associate the term with specific drug treatments, differentiating them from prognostic and diagnostic assessments that contribute to clinical decision-making in a more open-ended way.

Clinical sequencing programs have further refined the notion of "actionability" by relating it not to different kinds of diseases, but to the evidentiary status of different treatments and thus to different degrees of clinical certainty. The Michigan MI-ONCOSEQ program, in a way similar to Wagle and colleagues (2012), divides its findings into three main tiers: Tier 1A refers to known mutations linked to an approved drug, while Tier 1B encompasses mutations that are part of the inclusion/exclusion criteria for an experimental drug; Tier 2 mutations do not have a drug that directly targets them but drugs are available that target molecules in the same biological pathway; finally, mutations in Tier 3 have unknown significance. This classification system creates a hierarchy based on the strength of the association between the mutation and the drug. Foundation Medicine similarly defines mutations that are linked to approved or experimental therapies as "highly actionable", and those that have "limited evidence" about their association with a drug as "plausibly actionable", while "biologically significant" mutations provide potentially relevant biological information with as yet no clear clinical implications. These classifications draw bright lines through potentially grey areas of uncertainty about how to act on tumour sequencing results.

As these classifications describing various degrees of actionability suggest, there are numerous pitfalls and problems associated with a strict one-mutation/one-drug understanding of the term "actionable". As explained by a pathologist, mutational data alone are not always enough to decide on how to act:

> I have some examples of genetic aberrations that are drivers, but when I look at the mutation I don't know whether they'd be actionable or not. I'll give an example: BRAF-V600E. Actionable in melanoma, not actionable in colorectal cancer. We know that in one it works, in the other it doesn't. The same mutation, different context. (Reis-Filho interview)

In this example, the link between drug and target is not enough: the mutation needs to be articulated with the histopathological diagnosis in order to form a solid basis for clinical action. Conversely, a narrow understanding of actionable, which could be rephrased as "directly targetable", does not exhaust the repertoire of possible drug treatment strategies. The same pathologist continues:

> Some investigators who are really into functional genomics they would claim that there is no mutation for which there is no drug. You just have not looked at it with the right approach. For instance, if one [uses a technique known as a synthetic lethality screen] it is not uncommon to find one compound that's lethal for a cancer cell harboring a specific mutation for which there is no drug that [directly] targets that particular mutation.

Thus, while actionable is co-substantive with "predictive" (of drug sensitivity or resistance), it goes beyond that category by delimiting an experimental space where a number of different approaches compete to redefine the significance of the prediction and thus its clinical utility.

Articulating actionable findings with sociotechnical architectures

Making a particular genetic mutation actionable depends not only on the relationship between a patient's mutation status and predicted drug effect; it also depends on other factors, such as the regulatory status of those mutations and drugs, the availability of testing and treatments within health care systems, and the geographical location and design of clinical trials for drugs still under development. In creating classification systems of actionability and generating recommendations for treatment, actors address many questions about how clinical sequencing results can or should be embedded in a multi-layered sociotechnical system, such as: How much confidence do practitioners and regulators have in the association between a mutation and a drug? What should be reported to doctors or patients, and how will they act on that information? How safe and effective is the drug being recommended? What are the inclusion criteria of the recommended clinical trials, and where are these trials located? In the remainder of this paper, we examine how tumour sequencing results are made actionable by articulating them with existing clinical routines, the design of clinical trials, the regulation of drugs and diagnostics, and health care systems; and how clinical sequencing programs in turn have begun to reconfigure the "knowledge architectures" of clinical oncology (Amin and Cohendet 2004; see also Parthasarathy 2007).

Actionability and Existing Clinical Routines

Since actionability is intimately concerned with guiding practicing oncologists' prescription of treatment for patients, one obvious place to start is by asking how clinical sequencing results are articulated with oncologists' existing routines. These activities are

focused on creating new avenues for clinical action rather than reorganizing standard-of-care therapy. The patients who are presently most likely to have their tumours sequenced are those who are late stage and have already received and failed multiple rounds of conventional treatment, or those who have rare types of tumours with no available standard treatments. The types of actions generated by clinical sequencing, therefore, are often portrayed as not competing with the standard of care but filling voids in the realm of existing clinical practices, both for patients and oncologists.

Some organizations conceive of their tests for actionable mutations as additions to the existing repertoire of laboratory tests that blend into the background of established laboratory and pathology services. Leif Ellisen, the co-founder of the MGH program, emphasized that in designing their sequencing initiative, their goal was to develop a "clinical assay" that oncologists would use for routine patient management:

> When I say "a clinical assay", I mean a clinical assay. A clinical assay is something that the doctor orders because they needed to make a clinical decision for a patient. … If they don't think it's relevant, then they are not going to order it.

He compared their panel of selected mutations in cancer genes to the chem-20 metabolic panel routinely ordered by general practitioners: a tool that provides an overview of many relevant features of a system (or a tumour) and that they can use to decide how best to treat the patient. The fact that oncologists at MGH have ordered and continue to order the tumour genotyping panel, Ellisen argues, is evidence that it is providing them with information that they find useful.

Unlike tests that characterize only one mutation at a time, (such as "companion diagnostic" tests, see below), programs that test for multiple genes open up new

possibilities for treatment by directing oncologists towards “off-label” uses of existing targeted drugs. Finding a mutation that might be unexpected in a patient’s cancer provides a rationale for attempting treatments that have only been approved for other types of cancer. The ALK inhibitor crizotinib, for example, received FDA approval for use in lung cancer patients, but Foundation Medicine has found that this same mutation is also present in colon cancer patients (Lipson et al. 2012). Since there is often little guidance in terms of treatment standards for advanced patients who have already been through multiple rounds of therapy, making decisions based on genomic technologies is an alternative to the oncologist’s “best guess” about what might be an effective treatment (Baszanger 2012). The French clinical trial SAFIR-01 was designed to test this hypothesis by comparing metastatic breast cancer patients whose treatment is directed by molecular analysis with patients whose treatment is guided by the recommendation the oncologist makes in the absence of such molecular information. The trial was particular concerned with detecting molecular anomalies that, while common in other kinds of cancer, are extremely rare in breast cancer, which means that drugs commonly used in other types of cancer could then be used in these atypical patients (André et al. 2012).

Other organizations position themselves and their clinical sequencing programs as a more radical step towards a truly “personalized” model of cancer therapy. Some programs, such as Michigan’s MI-ONCOSEQ, use a combination of techniques that include gene expression analysis, pathway analysis, and sequencing of the entire tumour instead of selected mutational “hotspots”. These labour intensive programs result in patient-specific clinical plans of action. For example, in one case at Michigan there were no clinical trials that fit sequencing results of a particular rare disease patient, but the

team noted that a drug was available for another molecule in the same pathway harbouring the patient's mutation. This hypothesis led to a specialized treatment plan that involved off-label use of a drug not normally indicated for his type of cancer *or* his mutation.

To the extent that clinical sequencing alters existing treatment practices, it does so by changing how oncologists make decisions in spaces that are already construed as spaces of uncertainty, and are thus prime candidates for the deployment of a technology that generates new hypotheses about treatment response. Maureen Cronin, a former senior vice president at Foundation Medicine, predicted that their technology would be adopted most quickly by practitioners who deal with uncertain cases:

> I think that there are many younger oncologists who are molecularly trained and are really interested in having access to genomic data on their patients. More traditional oncologists go by the NCCN [National Comprehensive Cancer Network] guidelines and that is all they do; so they may never be adopters. Some oncologists are so specialized they get frequent referrals of unusual cases. Because they are so expert in one particular area, they grab opportunities to explore new tests, not for every patient, but for the patients they don't feel they really have a handle on. I think there is going to be an adoption curve and I think genomic testing will get picked up the fastest in the rarer diseases and the non-responding cases.

Similarly, asked why many sequencing projects focused on advanced (metastatic) cancer, a French oncologist answered that "from the point of view of its molecular complexity, of integrated biology, primary tumours [where treatment routines are established] are really less interesting than metastatic tumours, where we're able to do many more things" (André interview). These approaches blur the lines between routine and research by allowing for potential surprises and the subsequent implementation of non-routine

clinical actions.

In the present era of patient activism, the possibility of generating new clinical options has not escaped the attention of patients and has become an important incentive to participate in emerging sequencing programmes. Jessica Everett, a genetic counsellor working in the MI-ONCOSEQ pilot programme, was initially sceptical that patients would consent to do a "non-therapeutic" biopsy of their tumour, but quickly realized they were more than willing to do so:

> I remember [the lead investigator] telling us, "This is the process and people will consent to a biopsy". I thought, "Who's going to do that?" Until I started to meet the patients and realized that the people who are going to do that are people who have run out of options.

For many patients in Michigan's clinical sequencing project having their tumour biopsied and sequenced was a way of getting access to new treatment or clinical trial options when they presently had none. Sameek Roychowdhury, the co-lead investigator for the MI-ONCOSEQ pilot, described one patient who had travelled from across the country to have his tumour tested at Michigan, a patient "who had been through everything plus some", and who "wanted to do everything to treat his cancer."

Actionability is intimately connected to a transformation of the relationships between pathologists and medical oncologists that pre-dates, but is enhanced by, practices centred on actionable genomic abnormalities. Several of our interviews with pathologists revealed shifts in how pathologists think about their work and its connection to the clinic. One told us that while pathologists used to write "pathology for pathologists" reports that contained detailed descriptions of the morphological characteristics of tumours that were of little or no use to clinicians, they are now being

asked to draft shorter reports that include a clear indication of the therapeutic actions that clinicians should take. The use of targeted therapies has further amplified this trend, since pathology reports can now point to specific molecular alterations linked to specific drugs instead of generic categories such a hormonal therapy or chemotherapy. These developments therefore also involve a redefinition of the division of labour in the clinic between pathologists and clinical oncologists.

Actionability and Clinical Trials

While there are a growing number of "targeted" drugs that have received FDA approval, the handful of currently approved drugs is quite small in comparison to the hundreds of targeted anti-cancer agents that are in development or undergoing clinical testing. Linking genetic test results to on-going clinical trials is thus an important part of making those results actionable, and clinical trials become a primary source of therapeutic options for genetically characterized patients. From this point of view, the regime of actionability inverts the typical relationship between clinical trials and clinical utility: while molecular markers are normally considered to be clinically useful only after they have been shown to be so in a clinical trial, in this regime a mutation is considered clinically useful if it generates a molecular hypothesis that can lead a patient to a clinical trial.

The presence of an on-going suite of clinical trials is so important to making clinical sequencing results actionable that MGH sequencing program co-founder John Iafrate argued it makes no sense to build such a program at present unless it is done at a hospital where a portfolio of trials is available:

> If you talk to some clinicians, community oncologists, they'll say, "Why are you giving me this information? There's nothing I can do with this information now." But if you present the results to an academic centre where you have numerous early phase trials, it's simply a different question. For example, we find a lot of genetic alterations in glioblastoma, and zero are standard of care tests. Community oncologists will not do anything with that information. But at MGH, there would be four or five trials with targeted agents to consider.

This can play both ways: as Marc Grodman, CEO of Bio-Reference, pointed out, just getting their tumour genetically profiled is a way for patients to increase their chances of gaining access to a clinical trial:

> There are plenty of trials that are beyond Phase I, and drug companies have a constant need to identify appropriate patients. All of these mutations are relatively rare and the clinical trials desperately need patients that are qualified for the trials. Companies are very possessive of qualifying patients once they are identified.

Indeed, since many mutations are present only in a small percentage of the total population of patients, patients with particular mutations become quite valuable to the clinicians and companies that are trying to recruit for clinical trials.

This entanglement of clinical sequencing with drug development is also connected to in broader changes in the how clinical trials themselves are designed. Historically, early phase trials for new oncology drugs were designed as "all comer" trials (i.e., open to patients with any type of cancer), and their aim was restricted to determining a drug's potential toxicities and appropriate dosage for subsequent trials. The present combination of large numbers of targeted drugs and a large numbers of genetically characterized patients, however, makes it possible to "enrich" early phase studies by recruiting patients who have the mutation that the drug supposedly targets.

Integrating sequencing results into early phase drug development, researchers argue, increases the chances that the patient will benefit from the experimental drug and that the results of the study will be positive, and it also provides an opportunity to test the molecular hypothesis about how the drug works. The MSKCC, which has a large early phase drug testing program, has implemented a "basket trial" design that even further streamlines both ends of this process: MSKCC uses their centralized tumour analysis services to analyse many mutations at once rather than screening for them one at a time, and then directs patients with a specific actionable mutation, regardless of the kind of cancer, to a trial testing an experimental drug targeting that mutation (Baselga interview). In France, the aforementioned SAFIR trial used a similar form of molecular triage to accelerate patient recruitment, where metastatic patients were tested for actionable mutations and, depending on the results, enrolled in specific Phase I/II trials.

This kind of approach raises the question of whether drugs should still be developed and approved for use based on histological categories that classify tumours by their anatomical site of origin. A prominent clinician, for example, has claimed during a conference presentation that histology acts "as a psychological barrier" to designing clinical trials and providing optimal treatment for cancer patients (Fieldnotes June 2011), and the SHIVA and SAFIR 02 clinical trials launched in France will compare standard treatment based on histology with treatment based on the molecular profile of the tumour (Institut Curie 2012; André interview 2013). Meanwhile, participants at the annual College of American Pathologists meeting (Fieldnotes September 2012) and at the IMPAKT 2013 meeting argue that histology still matters not only because mutation patterns are strongly related to tumour type, but because the "same" mutation in a

different cell line behaves differently when acted upon. By testing the "same" actionable mutations in different types of cancers, researchers hope to be able to use the differential results to select the type of cancer where acting on a mutation will be a "game changer" (Reis-Filho interview). This shows, once again, that at issue here is not some sort of diagnostic ontology, but a regime for clinical intervention.

Regulating Actionability

The regulatory status of mutations, drugs, laboratories, and testing instruments is implicated in whether a particular genetic mutation is considered actionable. While there are many regulatory issues raised by the use of NGS in clinical settings (such as how to regulate the accuracy of sequencing information in an environment characterized by the presence of competing, rapidly evolving platforms and software packages), we will focus on the regulatory quandaries raised by the predictive nature of actionability. As prior research on the regulatory issues raised by genomic signatures in oncology has demonstrated, tests that aim to predict treatment response raise serious regulatory questions about whether the locus of clinical decision-making has shifted away from clinicians and become embedded in genomic tests themselves (Bourret, Keating, and Cambrosio 2011). Actionability-focused sequencing, since it explicitly aims to produce information that will change clinical decision-making, raises similar issues. It is often unclear how to regulate clinical actions based on these results in a space of uncertainty at the interface between research and routine.

The strong link between the efficacy of particular drugs and the presence of particular mutations is already modifying drug regulation at the FDA. In the case of anti-

EGFR therapies, retrospective analysis of anti-EGFR therapy showed that patients only benefited from it if they had a wild-type KRAS gene (Karapetis et al. 2008). The American Society for Clinical Oncology released a recommendation in 2009 that all colorectal cancer patients who were candidates for anti-EGFR therapy should have their KRAS gene tested (Allegra et al. 2009), and the FDA responded by revising the labels for two anti-EGFR drugs to include information about KRAS. The regulatory acceptance of the association between specific mutations and targeted drug has resulted in a new co-development strategy whereby a companion test is produced along the new drug to define the relevant patient population (Jørgensen 2012).

The regulatory situation can quickly become more complex, however, as we move past the one-mutation/one-drug model and shift from the realm of state regulation to more informal, endogenous modalities for generating and managing biomedical evidence (Cambrosio et al. 2006). One researcher involved with a clinical sequencing project described how novel results can generate protracted debates about whether to report these findings to clinicians and how to advise them about possible courses of clinical action:

> Honestly, there are some patients where details of how to report a result just gets debated back and forth. In some cases, for example an EML4-ALK with a different translocation breakpoint than has been described before, we might report it with the additional recommendation that the patient should get FISH confirmation and the physician may want to consider the possibility of treating with an ALK inhibitor. Details of individual result reporting can generate some hot debates.

The uncertainty around cases such as these—how to make recommendations based on a novel mutation in a familiar gene—has led to the creation of new venues and

bodies of experts for deliberating on actionability. This can be seen, for instance, at Michigan's clinical sequencing programme, where a new committee, a "sequencing tumour board" (STB) has been formed to deliberate on and form plans of action around sequencing evidence. Roychowdhury describes the problem and its solution:

> The biggest black box is how to interpret the results. … [O]nce you have the results, then you have to figure out what to do with them. That can be a challenge, and so far we've covered that by having a multi-disciplinary STB that brings all of our expertise and we come up with our best expert opinion, because that are no guidelines to tell us what to do. So right now this is an expert opinion based approach and we've brought everybody to the table that we can get to the table that we think is important.

This new body expands and alters existing forms of decision-making in the clinic by replacing the individual clinician's expertise with a new collective form of medical judgement. This was also the case with the introduction of hereditary breast cancer testing; for instance, in France this has resulted in the formation of new "clinical collectives" of practitioners from multiple specialties, as well as hybrid figures such as molecular pathologists or onco-geneticists, who collectively carry out the work of medical decision-making concerning genetic information (Bourret 2005). The structure of STB committee meetings is modelled after traditional tumour board meetings, where clinicians from a particular speciality present the details of difficult cases and discuss a plan of medical action. The STB meetings, however, consist not only of clinicians, but also pathologists, molecular biologists, biostatisticians, bioethicists and genetic counsellors, creating an expert body that is more like a hybrid between "a traditional tumour board and an IRB", as one member put it. The STB draws together expertise from areas of the research hospital that might not normally be in contact, and re-appropriates

some types of expertise for new purposes. Everett, who sits on the STB in her capacity as a genetic counsellor, recalls that initially she was unsure of how her expertise in hereditary cancer would be useful in this new setting, but found that she could play a role in developing a process for patient consent and reporting incidental findings. In addition to regular members "with expertise in different areas of patient management and genetic expertise," an STB can invite individuals with expertise in a specific pathway or gene "to come [and] look at the results of mutational reports and make an informed decision as to what the potential therapeutic approaches for a given patient for which there is no other approved therapy would be" (Reis-Filho interview). Notice the last clause: given the many uncertainties characterizing this domain, decision-making by STBs is for now confined to metastatic patients who, as has been the case for the development of cancer chemotherapies, find themselves on the frontline of biomedical innovation.

These professional venues for deliberating on the actionability of sequencing results can give rise to more formalized routines for recommending treatment that resemble clinical practice guidelines (Knaapen et al. 2010). Caris Life Sciences, another private company offering tumour sequencing services, provides an "actionable report" that contains recommendations for clinical interventions based on their own in-house "evidence integration". They employ a dedicated team of research scientists and external consultants who review of the scientific literature for evidence on predictive biomarkers, grade that evidence, and generate a set of rules for associating sequencing results with actionable therapies. Caris' activities, in this regard, mimic and substitute for the activities of national or professional bodies that aim at implementing and regulating sequencing in the public health care sector.

Health Care infrastructures: Making Actionable Accessible

Finally, many studies of genetic testing in oncology have pointed to the importance of health care infrastructures and national settings in shaping who can access genetic services, how they are offered (e.g., Parthasarathy 2007; Gibbon, Kampriani, and Nieden 2010), and in the present case, how they are made actionable.

Unsurprisingly, third party insurance in the United States substantially impacts access to clinical sequencing and its resulting clinical actions. At Michigan we were told about a case in which making a patient's sequencing data actionable became enormously labour intensive, both in terms of the time and expertise invested in creating a clinical hypothesis and in negotiating with Medicare and pharmaceutical companies to ensure that the patient received the recommended treatment flowing from that hypothesis. Michigan researchers submitted a proposal to Medicare with their rationale for why this patient should receive the drug, but the request was denied. They paid for his initial months of treatment as part of the clinical sequencing project (at a cost of $8000 USD a month), and when we visited their centre they were in the process of trying to secure coverage for the patient's treatment after gathering evidence to show that he was benefitting from the drug (Fieldnotes January 2012).

With the uncertainties around reimbursement both for sequencing results and off-label treatments still unresolved, many clinical sequencing projects portray their efforts as pilot programs aimed at transitioning these techniques from research-only settings into routine care. Arul Chinnaiyan, the lead investigator of the MI-ONCOSEQ project,

reflects that their project provides the opportunity to provide highly personalized care to patients who are enrolled in the research study:

> Here in our centre we do comprehensive sequencing of patients with advanced cancer. Because we're trying to learn about how to better match individual mutations with potential therapies, we're basically studying each patient like a research project. This does give each patient a sort of Cadillac-like treatment that they wouldn't get in a routine setting; but the goal, of course, is to advance this technology so it can be more commonly used in the clinic.

The decision to cast a wide net in examining each patient's tumour genome provides more possibilities for action and more possibilities for highly personalized actions, but at the cost of limiting the number of patients who can be assessed in the research stage.

Conversely, the CEO of Bio-Reference Laboratories, Marc Grodman, describes their strategy for entering the clinical sequencing market as having a democratizing effect on patients' ability to access information about their tumours and ultimately clinical trials:

> So when you look at the number of clinical trials, there is more going on today. The idea of saying to somebody, "I might do EGFR and ALK on your lung cancer and nothing else," it simply isn't good enough; it just isn't what you would want for yourself. You wouldn't want your mother to get the news that she has cancer and I doubt you would say "Okay, that's it." We are really trying to focus on being more cost-effective. So, quite frankly, the reason why we are charging, in essence, less money is because we wanted to, because we believe that in today's clinical environment we must provide more information for lower reimbursement if we want to be effective.

By offering their entire mutation panel at under $1000 USD when mutation testing for a single gene can cost up to $700 USD, Bio-Reference can potentially expand their market to include oncologists and insurance companies who might normally only consider testing one or two genes but can now obtain information on more than a dozen genes for the same cost.

The availability of commercial gene testing services and publicly available information on cancer genomic anomalies also makes actionable results potentially accessible to enterprising patients. The Ingram Cancer Center at Vanderbilt University (Tennessee, USA), for example, launched the My Cancer Genome website in 2011, which allows patients and physicians to search for information on individual genes and variants according to specific cancers (Vanderbilt University Medical Center 2011). More importantly, it allows users to search through more than 37,000 cancer drug trials by mutation (approximately 450 mutations are currently connected to trials; Thomas 2013). This free flow of information may generate new forms of bias within clinical trials. An FDA official recently warned that patients seeking action for their mutations "could cause some headaches for the evaluation of the diagnostic test, and maybe even cause some bias in the estimation of the performance of the therapy" (Ray 2011). In the simplest cases, patients lacking the relevant mutations may simply refuse to be enrolled in clinical trials comparing marker-positive with marker-negative patients.

The situation in Europe is quite different. Providing equitable access to clinical sequencing and targeted therapies is a primary concern of national programs that are aimed at populations rather than markets. The French and UK initiatives, in their different ways, have both defined genetic testing as a public health issue and as a matter

of equal and equitable access to innovative technologies and treatments. The very fact that a mutation is actionable turns it into a public health policy issue:

> It was clear to us [the French INCa] that we needed to develop tests that were linked to treatment, there was no question of testing with the sole purpose of better understanding the disease, it was not a research objective, it was a public health objective. … Given that some laboratories had already started implementing genetic testing, we thought that it was not a good idea to let things develop in such an inequitable way on the national territory and we thus decided to generalize and frame [these local initiatives], and we did this in all of France's regions. (Calvo interview, our translation)

The French initiative, framed as a "public health objective," was originally grounded in a sharp distinction between service and research and was intended to provide testing only for single mutations directly linked to approved therapies. Its developers, however, soon realised that the routine/research distinction was difficult to maintain, and today the platforms also tests for mutations linked with investigational drugs (Calvo interview; André et al. 2012). There already seems to be an emerging consensus in France that lab reports should not only list the presence of mutations but also explicitly mention actionable recommendations, and INCa has recently begun implementing feasibility studies for a national network of advanced sequencing facilities that will be linked to a network of early phase trials (Fieldnotes, June 2013). Unlike the French initiative with its initial focus on service delivery, the CRUK programme was designed from the outset "to cross between service and research" by "wiring research into daily care" (Peach interview); for example, by using a gene panel that deliberately mixes the clinically actionable genes such as EGFR with genes that are not yet clinically actionable and genes that are interesting for scientific research (Peach, personal communication).

Conclusion

This paper has examined an emerging regime of genomic medicine in oncology, one that is focused not on managing future risk but on making predictive connections between mutations and drugs. While it is tempting to see genomic analyses of cancer patients' tumours as a new diagnostic ontology of disease, we have shown in the paper that the focus in this domain is less on sorting out classifications of cancer and more on generating new rationales for patient treatment. The fact that these treatment plans often involve off-label uses of drugs or drugs still under development has intensified increasingly dense connections between genomics research, cancer care, and the clinical trials system; and therefore between routine and experimental spaces. The logic behind this regime of actionability, therefore, is consistent with Callon's (2012) claim that in contemporary technoscience intervention takes precedence over representation: "We intervene in order to know, more than trying to create knowledge in order to intervene." (pp. 9–10; our translation)

Examining actionability provides a window into broader transformations that are taking place in oncology, such as a shift away from thinking in terms of individual biomarkers towards a focus on molecular pathways. While Linnea Duff, the patient described in the introduction, had a remarkable response to the ALK inhibiting drug crizotinib, many patients are not so fortunate. For the majority of the patients who do respond to targeted therapy, the results are short-lived, and the tumours quickly develop resistance to the drug. After nearly three years of successful treatment, Duff's cancer also acquired an additional mutation and relapsed, and she once again returned to a clinical

trial to try a new experimental drug (Duff 2013). The failure of many biomarkers to show clinical utility, and of many targeted drugs to have curative effects beyond a relatively short-lived initial response, has led to the investigation of the molecular pathways that link individual molecules into a complex signalling cascade, reveal the presence of "cross-talk" between various components, and show the emergence of alternative communication pathways following disruption of the main pathway by drug therapy. These developments in turn pull clinical sequencing and notions of actionability even further into experimental spaces and on-going research programs.

Finally, our analysis of the new sociotechnical arrangements emerging around the production of "actionable" genomic findings about tumours also offers evidence of a new form of bio-clinical decision-making emerging in oncology. Rather than moving discussions of clinical utility further into the realm of statistical evidence, as have discussions of the predictive value of risk-oriented genetic signatures, discussions about the potential actionability of sequencing results are centred on molecular hypotheses about drug action. Actionability, therefore, entails not only a shift towards focusing on genomic results that can generate new clinical actions, but also a shift in the types of evidence on which clinicians can act.

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1 Oncology meetings attended include the American Society for Clinical Oncology (ASCO) and the European Cancer Organization (ECCO) annual meetings, the San Antonio Breast Cancer Symposium, the European Breast Cancer Conference, the IMPAKT Breast Cancer

Conference, and the Paris Biopathology Symposium.

2 While the distinction between prognosis and prediction appears clear in the abstract, it is often much less obvious in practice. Countless discussions and publications have been devoted to debating whether these two categories require different kinds of clinical validation and evidence (e.g., clinical trials as opposed to retrospective analyses), and what would be the proper design for studies involving prognostic and predictive biomarkers (Freidlin, McShane, and Korn 2010).