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Opening the regulatory black box of clinical cancer research: transnational expertise networks and "disruptive" technologies

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Introduction

During the last 15-20 years, a number of major innovations grounded in a combination of molecular biology techniques and computer technologies have transformed biomedical research. Commentators disagree as to whether these innovations should be qualified as "disruptive". Many participants, including grant agencies,[1] believe they should, insofar as they appear to have significantly affected diagnostic, prognostic, therapeutic, and organizational activities. Others maintain that they are better understood as part of more gradual changes, having been grafted onto pre-existing clinical activities. Detailed empirical studies show that the situation is best defined in terms of a mixture of the mundane and the disruptive (Keating et al. 2016). They also show that the degree to which innovations take into account existing practices is a major determinant of clinical adoption and commercial success (Kohli-Laven et al. 2011). In this paper, we will resort to scare quotes and refer to genomic innovations as "disruptive", to signify that while caution is needed, they are treated as such by biomedical practitioners. Characterizing a set of innovations as "disruptive" has real consequences, including the design of dedicated programs to sustain and implement them.

Unevenly distributed, the transformations linked to genomics nonetheless affect specialties as diverse as psychiatry, cardiovascular diseases, and clinical genetics. Their most profound effects, however, have undoubtedly been felt in oncology, where they have led to a renewed understanding of cancer as a disease of the genome, the development of novel diagnostic and prognostic tools, and a revamping of the therapeutic toolbox thanks to the emergence of targeted therapies (Keating and Cambrosio 2012). Such therapies deploy new kinds of drugs that, rather than indiscriminately killing cells (hence the toxic side-effects of traditional chemotherapy), target molecular alterations specifically affecting cancer cells, thus pursuing (with so far mixed outcomes) the century-old dream of therapeutic "magic bullets" (e.g. Mann 1999; Vasella 2003). As a result, the traditional, organ and tissue -based classification of tumors is also subject to major revisions, wherein previously homogeneous categories, such as breast cancer, are replaced by a number of diseases whose specificity is based on their reaction to different therapies. These new disease entities are defined by specific molecular features collectively known as *biomarkers.*

Needless to say, this transformation has regulatory consequences. The approval of new drugs by regulatory agencies such as the US Food and Drug Administration (FDA) or its

[1] See, e.g., http://www.genomecanada.ca/en/programs/leading-edge-technologies/past-competitions/2015-disruptive-innovation-genomics-competition.

European equivalent, the European Medicines Agency (EMA), requires the staging of clinical trials to show their safety and efficacy for precisely defined therapeutic purposes, such as the treatment of a particular stage of a given disease. A reordering of disease categories undeniably affects this regulatory process both in terms of the entities regulated through the collapse of the distinction between disease and therapeutic target, and the means used to create those entities (biomarkers) both of which are now subjects of regulatory interventions. As we will see, contemporary biomedicine, and in particular oncology offer a very interesting case study of how regulation does not simply adapt to the development of "disruptive" innovations, but also participates in their shaping and framing.

In addition to standardizing tools, entities, and measurements, the bio-clinical collectives discussed in this paper also reorganize the biomedical domain. Their activities include "not only setting out the conditions that must be respected in order to produce reliable test results (quality control, etc.) but also the conditions that define the relations (within a clinical context) between the different diagnostic elements as well as the consequences of such relations on clinical judgment" (Cambrosio et al., 2006: 195-196). This is why we cannot treat organizational practices, including the regulatory practices that are intimately connected to the very notion of organization, as distinct from the content of bio-clinical activities. We thus contend that (a) a full understanding of the dynamics of regulation in the biomedical domain ought to consider the numerous mediations (as contrasted with mere intermediaries[2]) whose status and function cannot be captured in a taxonomy of state vs. professional regulation, or a dichotomy between formal and informal activities; (b) their analysis necessitates taking into account the content of the practices they regulate; and (c) in addition to examining the interactions between different regulatory modalities, we need to pay attention to their development insofar as regulation, far from being mere routine, participates in the production of novelty by co-producing the entities it regulates. We thus need to investigate the reconfiguration of regulatory networks coincident with the emergence of new techniques and entities such as molecular biomarkers, as they operate via the establishment of transnational networks of expertise.

Rules, regulation, and biomedicine

Before going any further, we must invoke an important distinction. As Brunsson and Jacobsson (2000: 10) tell us, "to regulate is … to create and propagate rules". We note, however, that regulation instantiates two very different kinds of rules, as classically defined by Searle (1995). The first, *regulative rules*, are, so to speak, external to the practices being regulated, insofar as those practices existed and can continue to exist in

[2] On the distinction between intermediaries and mediators see, e.g., Latour (2005: 39): "An *intermediary* … is what transports meaning or force without transformation. … *Mediators*, on the other hand, … transform, translate, distort, and modify the meaning or the elements they are supposed to carry".

the absence of those rules, such as the "rules of the road" when driving. In other words, regulative rules govern an activity, but do not define it, insofar as the activity can be performed independently of these rules. This is the case of the (self) regulation of advertisement discussed in Boddewyn (1991). *Constitutive rules*, differ from these in the sense that they define the activity itself and the entities it engenders, which would not be possible or exist without those rules. Without the regulatory apparatus of clinical trials and the standardization networks we will discuss in this paper, there are no clinical trial data or biomarkers. Thus, while regulation affects a motley of different domains, we argue that unlike a field such as advertisement, the regulation of biomedicine co-produces the entities being regulated in the sense that they do not exist prior to the rules that regulate their production and use. This claim has been formalized by the notion of *regulatory objectivity* (Cambrosio et al. 2006), a notion that built on previous empirical work on inter-laboratory quality assessment, quality control, and external quality evaluation (Keating and Cambrosio 1998). Regulatory objectivity is based on the systematic recourse to the collective production of evidence. It consistently results in the production of conventions most often arrived at through concerted programs of action. As we will see in this paper, practitioners involved in these kinds of regulatory activities take into account the conventional dimension of these activities, thus displaying a high degree of reflexivity. Our present contribution also extends the notion of regulatory objectivity by showing that, in the context of innovation, transnational networks of expertise (more or less loosely linked to other regulatory institutions) that involve leading clinical researchers are a key site for generating new nosological *and* regulatory entities. As a result, the sharp distinction that can be observed in other domains, both in terms of content and actors, between regulatory science and proper research activities (see Demortain 2016) does not seem to apply.

Additional empirical support for this claim comes from a number of sources. Castel and Merle (2002) have argued that regulations should be understood as resources deployed by biomedical practitioners as part of the ongoing transformation of medical work. As part of her investigation of the field of hereditary cancer, Bourret (2005: 43; see also Bourret and Rabeharisoa 2008; Rabeharisoa and Bourret 2009) has shown that contrary to more traditional domains where regulation usually occurs only after clinical and research practices have stabilized, in this research-front specialty, regulation "acts as a condition of possibility for the definition and performance of the activities that it regulates". In other words, the objective of regulation "is not simply the stabilization of the new tools from a technical point of view, but [the definition of] the entities that make up those tools as well as the frameworks for their implementation" (Bourret et al. 2011: 823). This is an open-ended task, due to the emergent nature of bio-clinical knowledge and findings, and one that, far from being confined to routine, leads to the emergence of novelty. As also shown by the case studies collected in Jasanoff (2011), regulation can be said to be constitutive of scientific practice and not merely some downstream activity with no relevance for the production of knowledge.

This claim is relevant for two distinct audiences. For those of us whose primary interest is contemporary biomedicine rather than regulation *per se*, a close examination of the latter becomes a necessary step for understanding the former. For those whose primary interest is regulation (which is presumably the case for most readers of this special issue), our case study provides additional insights into both the diversity of regulatory knowledge and the variety of intermediary regulatory bodies that produce regulatory evidence (Demortain 2016). Indeed, the analysis of how this activity applies to the field of biomedicine can provide a better understanding of the dynamics of regulatory activities and allow analysts to avoid hasty generalizations. For instance, Brunsson and Jacobsson (2000: 35) erroneously conclude that "areas dominated by strongly established professions, such as health care and the legal system, tend to show relatively little standardization". As we will show in this paper, this clearly does not apply to contemporary oncology, a state of affairs that can be generalized to all biomedical domains where platforms (and not solely human professionals) play a decisive role (Keating and Cambrosio 2003).

We do agree with Brunsson and Jacobsson, however, when they observe that standardization, as a form of regulation, facilitates co-operation and co-ordination. More specifically, in the case of biomedicine one of the key tasks for regulators is to create equivalencies between different domains of activity, such as laboratory and clinical activities (e.g. Leonelli 2012). While acknowledging that in the case of controversial standards "a strong element of innovation may also be involved", Brunsson and Jacobsson (2000: 15 and 11) also argue that rule-following is a backward rather than a forward-looking activity, insofar as it is based on adherence to pre-existing rules. As we show in this paper, however, norms are the outcome of normative practices, rather than the opposite, which often act as potential harbingers of novelty. Finally, biomedicine provides additional material with which to examine the transition from one kind of rule into another. Brunsson and Jacobsson (2000: 14) note, for instance, that standards can turn into directives, i.e. mandatory rules issued by organizations that have the authority to enforce them, as when quality standards became incorporated into health care legislation. Our case study provides clear indication of the fluidity of the boundaries between these categories, and of the intimate connections between a state agency such as the FDA and a number of initiatives by often-transnational networks of standardizers. Close examination of the bundle of scientific and regulatory activities that generate and manage the platforms at the core of clinical trials — the "gold standard" of clinical research and evidence-based medicine (Timmermans and Berg 2003) — will provide evidence for this claim.

Other contributions to the analysis of biomedical regulation include Gaudillière's (2009) suggestion, reminiscent of Boltanski and Thévenot's (2006) economies-of-worth framework, that we distinguish between different ways — professional, industrial, state/administrative, and consumerist/activist — of regulating the production and use of therapeutic agents. Each of these ways of regulating mobilizes different forms of evidence, actors, values, and regulatory tools. One can easily imagine that this approach

could be extended by combining it, for instance, with Brunsson and Jacobsson's (2000) focus on norms, directives, and rules. Rather than yielding to this (admittedly tempting) typological lure, however, we prefer to investigate the dynamics of regulation. We do so by taking into account the fact that, as already hinted and as will become abundantly clear in the rest of this paper, biomedical regulation involves the definition of constitutive, rather than merely regulative rules. Thus, a focus on the transnational expert communities (Djelic and Sahlin-Andersson 2006) that produce many of the standards that make biomedical work possible, is a first step in this direction. In keeping, however, with our previous claim that regulation co-produces the entities it regulates, and building on Eyal's (2013) criticism of the inherent limits of a sociology of *experts* narrowly centered on human actors, we will examine regulatory *expertise*, defined as a network associating human agents with devices, concepts, and institutional arrangements (Cambrosio et al. 1992).

It should by now be clear that when we speak of regulatory networks, the term regulation does not refer solely to government regulation but spans a seamless web of activities ranging from explicit initiatives to tacit agreements. This contrasts with discussions of medical regulation that are often confined to state agencies such as the aforementioned FDA in the United States and EMA in Europe, whose stated purpose is to assess the safety and efficacy of new drugs (Marks 1997; Daemmrich 2004; Carpenter 2010). The agencies define and prescribe the means of evaluating these two parameters through clinical trials and their organization according to a sequence of "phases" (from Phase I for an initial toxicity and safety assessment of new experimental compounds, to Phase IV post-marketing studies). Policy analysts have described the activities of individual agencies (e.g., Carpenter 2010), and explored the dynamics of regulatory regimes that, in addition to representing an "amalgam of regulatory and governance structures, values, and varied types of democracy", mobilize "systems of science, evidence and knowledge in support of regulation" (Doern and Phillips 2012). At the opposite end of the regulatory continuum, science and technology studies researchers, while not framing their endeavor as a study of regulation as such, have investigated what may be called the hidden face of medical regulation. They do so by resorting to notions such as "tacit knowledge" (Collins 1985) and "situated action" (Suchman 1987) to examine the informal, embodied arrangements that underlie daily activities in clinical and laboratory settings (Jordan and Lynch 1992; see also Lynch et al. 2008). Some of these arrangements will remain at the level of norms, i.e. internalized rules that describe competent researchers, while others will evolve from norms to standards or even directives, thus formally contributing to the socio-technical framing of newly emergent domains. Deciding what to explicitly regulate and what to leave unregulated is a key aspect of the regulation of biomedicine.

It would be misleading, however, to surmise that the analysis of biomedical regulation has been structured by a dichotomy between the "micro" level of local practices underlying everyday clinical and laboratory activities, and the "macro" level of state regulation and policy decisions. There is a large and diverse literature, albeit often in

domains other than biomedicine, that examines different sets of interconnected regulatory activities, and in particular standards. Combining insights from science & technology studies and political sociology, Lampland and Star (2009) and Busch (2011) focus on different kinds of standards as tools for governing people and things. Within the field of organization studies, in addition to the aforementioned contribution by Brunsson and Jacobsson (2000), Ahrne and Brunsson (2004) have introduced the notion of soft regulation, to examine rule-setting practices often used outside of formal organizations, and in particular by meta-organizations such as those that are at work in the field of clinical practice guidelines (Knaapen 2013a). Indeed, a micro/macro dichotomy, while useful for highlighting the existence of different kinds of regulatory knowledge, glosses over the multiple translations that connect the two domains. In this paper we will explore the seamless web of regulations constituted by a chain of mediations that re-shape the content of regulatory components as they cycle through different "topical contextures" (Lynch 1991). Rather than a metaphorical pipeline that gradually translates one level of activity into another, biomedicine presents us with a complex bundle of overlapping institutions and initiatives.

On drugs and biomarkers

Let us begin with a story:

> In 1994, after joining the Milan-based European Institute of Oncology, Dr. Viale (a leading breast cancer pathologist)[3] became involved in the International Breast Cancer Study Group, an organization that performed multi-center clinical trials in Europe, Australia, and New Zealand. As he explained, at the time "it was all comers within the clinical trials", meaning that any patient with breast cancer was eligible to join a trial. Around 1997-1998, however, as it became clear that breast cancer consisted of a number of distinct diseases characterized by the presence of specific biomarkers that responded differently to therapies, a renewed understanding of the nexus between biology and therapy reorganized clinical trials. To avoid "losing the signal", clinical researchers henceforth tailored their clinical studies towards patient subpopulations, separating for instance those whose tumors expressed a certain kind of receptors[4] from those who did not. At this point, pathologists realized that the accuracy and reproducibility of the biological parameters used to measure and assess these receptors, and thus to

[3] See Crompton (2011) for a biographical sketch of Dr. Viale. Our extensive use in this paper of descriptions of his activities and opinions is justified by his strategic position in the field: routinely characterized by other practitioners as one of the two leading breast cancer pathologists in the world, citations to his articles exceed the 10,000 mark, and he has been involved in the major regulatory initiatives discussed in this paper.

[4] Use of the term "receptor" or "biomarker", even when allegedly referring to the "same" entity, implies a subtle semantic shift from an emphasis on the biological features of the cell itself, to the use of those features as part of a biomedical intervention.

> differentiate disease categories in different centers throughout the world were wanting. This resulted in patients enrolled in tailored clinical trials for a disease that was not theirs: "it was deleterious for the patients, on one side, and again, on the other side, it was jeopardizing the results of the trial".
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> Trialists in the International Breast Cancer Study Group (and of related networks, such as the Breast International Group) thus felt an urgent need to "foster accuracy of the identification of candidate patients for the trials," via the central reassessment of local results. Accordingly, Viale's team set up a Central Pathology Office in Milan. They initially performed the pathology review *a posteriori*, i.e. at the end of the trial, "which was not particularly wise because number one, you couldn't avoid the enrolment of patients that were not good, and number two, you had to spend your time in trying to retrieve the [tumor samples] blocks five years later from [names of countries], which was a mess." It soon became obvious that this activity should be anticipated before randomizing patients for the trial, and that this "was good for the patient and good for clinical research: everyone had to send tissue for central pathology review, otherwise the patient would not be randomized, and this also facilitated the collection of tumor specimens." [Paraphrase and quotes from an interview with Dr. Viale, Milan, 27 January 2012]

This account underscores a key event: the progressive transformation of a single disease (breast cancer) into a number of distinct diseases. As stated succinctly by a team of pathologists, "it is currently accepted that what was once called breast cancer now constitutes multiple diseases affecting the same anatomical site" (Weigelt et al., 2010: 267-268). This process of differentiation continues today, as the relatively small number of nosological entities defined by a combination of the aforementioned biomarkers have given way to a potentially large number of rare diseases defined by individual molecular anomalies. State agencies such as the FDA scrutinize and react to these developments. For instance, trastuzumab (brand-name: Herceptin; see Bazell 1998) — a drug that has been hailed as a "paradigm changer" by personalized medicine proponents (Allison 2010: 117) — was approved for use in breast cancer patients bearing a particular receptor, its manufacturer having submitted results of clinical trials with that patient subpopulation.[5] While the connection between the evolution of clinical oncology research and the regulatory knowledge produced by state agencies such as the FDA is far from novel (e.g., Keating and Cambrosio 2012), we argue that these agencies are now more deeply and directly involved in the clinical research process. The emergence of new scientific-regulatory hybrids (Kohli-Laven et al. 2011) means that FDA officials are now sitting in the room with leading clinicians and scientists as they reshape clinical research via, for instance, the design of "next generation oncology trials".[6] We will

[5] Moreover, drugs are generally approved for a specific disease stage (e.g.: metastatic breast cancer). In actual practice, however, a large number (between one half and three quarters in 2005) of anti-cancer treatments are prescribed off-label (Soares 2005).

[6] See, e.g., the October 2014 FDA Public Workshop on "Innovations in Breast Cancer Drug Development - Next Generation Oncology Trials", http://www.fda.gov/Drugs/NewsEvents/ucm410332.htm.

return to this topic later in the paper, after we examine a second component of Viale's account.

Clinical researchers' critical inquiry

The long excerpt from the Viale interview highlights the fact that in order for the results of tailored clinical trials to be trustworthy, one must first ascertain the reliability of the tailoring (in the present case: the presence or absence of a given biomarker). This task falls within the remit of the team of practitioners, often members of a cooperative medical oncology group, who design the trial's protocol and sponsor the study. Central pathology review is one way of introducing appropriate safeguards, whose existence can subsequently be taken into account by agencies (or guideline developers) when evaluating trial results. For our present purpose, however, the relevant issue is that the introduction of central pathology review was not simply an *ad hoc* remedy with limited consequences. Its implementation led to the realization that "inter-observer variation in pathological examination" of breast cancer specimens resulted in "significant differences" in the assessment of a number of relevant parameters. This could have had potentially dire consequences, including not only the selection of the "wrong" patients for a given clinical trial, but also the production of questionable results, undermining future therapeutic advice (Bueno-de-Mesquita et al. 2010). To borrow an analogy from economics, the initial regulatory intervention resulted in a multiplier effect, whereby the acknowledgment that practices varied, leading to discordant results, and the search for methods for reducing such variation, gradually became the focus of a number of subsequent initiatives involving additional components of clinical research.

The existence of inter-laboratory discrepancies threatening the integrity of biomedicine has been a recurrent theme since the massive deployment of biomedical platforms in the post-WWII era (Keating and Cambrosio 2003), but in this case two related, but distinct events conspired to reframe it as a major problem for which solutions were urgently needed: first, the fact that the presence or absence of biomarkers (rapidly redefined as a quantitative issue rather than a qualitative, binary variable: see below), became a key parameter for the design of clinical trials; and, second, the emergence on the pharmacological front of a new class of drugs – targeted therapies – that turned markers into targets. Thus, for instance, given that the aforementioned trastuzumab targets specific receptors on the surface of cancer cells, access to the treatment is predicated upon the demonstration that the tumor bears those receptors. In other words, no longer merely a diagnostic tool for characterizing the peculiar kind of cancer from which a patient was suffering, or a prognostic tool for ascertaining the probable course of the disease, the receptor could now be used to predict the likelihood of response to a specific treatment. As such, and in order to "facilitate appropriate treatment decisions," it must be measured not only reliably, but also in a "timely manner" (Dixon et al. 2012).

How did pathologists respond to this challenge? Two aspects of that response are immediately relevant. The first concerns reflexivity. We refer here to the fact that practitioners (rather than external agents), as part of their technical practices and within their own specialty settings, investigate the significant features (whatever their nature) of a given situation (Lynch 1982: 501). For instance, as part of his presentation at an oncology meeting, Dr. Viale quoted a number of studies showing the existence of important inter-laboratory variations between centers, cities and countries in the assessment of breast cancer biomarkers. He then proposed a typology of the sources of these variations, based not simply on their immediate technical causes (e.g., methods of tissue processing, equipment calibration, test reagents, and so on), but on their practical management, i.e. on whether they were easy, not easy, or quite difficult to handle.[7] The "easy" category included problems with pre-analytical and analytical variables that could be managed by enforcing compliance with guidelines, implementing standardized protocols, and using automatic instrumentation. The "not easy" category included issues of interpretation that, according to the speaker, were "affected by dogmas and incorrect assumptions". Finally, the "difficult to handle" category referred to practitioners' qualifications and attitudes, in particular a lack of awareness of the clinical implications of test results, and the inclination to dismiss marker measurement as too mundane a task for highly skilled pathologists.

One could object to this action-oriented taxonomy by arguing that pre-analytical practices, in particular the handling of biospecimens, also involve organizational, institutional, and sociotechnical aspects that are not so easily managed.[8] But we believe that the issue is not whether the categorization is sound, but that it is a telling example of how pathologists have increasingly engaged in endogenous regulation via the critical investigation of their own activities. These investigations cover the spectrum from experiential evidence derived from long-term acquaintance with the domain, to more formal methods such as the central review of local testing (e.g. Paik et al. 2002; Viale 2011, Kaufman et al. 2014). The third category of sources of variability (qualifications and attitudes) resonates with some of the tensions arising from the transformation of pathology from a largely descriptive/diagnostic specialty grounded in the highly skilled morphological examination of cancer tissues to an experimental, prognostic and predictive activity centered on risk calculations. This transformation resulted from the incorporation and subsequent reshaping of advanced techniques derived initially from immunohistochemistry and later from molecular biology (Crompton 2011). Finally, Viale's intriguing reference to "dogmas" as sources of variation and controversy, refers to the existence of limits in the understanding of the biology of breast cancer: "controversies … arise because tumors continuously challenge our assumptions and dogmas by showing unexpected outcomes and counterintuitive responses to targeted

[7] Beppe Viale, Strategies for improving inter- and intra-laboratory concordance and reproducibility, IMPAKT Breast Cancer Conference 2012 (Brussels).

[8] For a description of these issues, see Carolyn Compton, Historic Consensus Reached on Biospecimen Standards, http://mendelspod.com/podcast/historic-consensus-reached-biospecimen-standards-carolyn-compton-nbda.

interventions" (Viale 2011: 3). This epistemic void resulted in the setting of arbitrary positivity thresholds (defined as the percentage of cells that overexpress a given marker) and in the use of scoring systems that may or may not reflect the biopathological characteristics of tumors (aggressiveness, response to treatment). As an example, initial recommendations advising that a tumor sample positive for a hormone receptor should contain at least 10% positive cells, were subsequently lowered to 1% when studies showed that patients below the 10% threshold also profited from endocrine therapy (Viale interview, 27 January 2012).

As boundaries, thresholds express the conventional/arbitrary nature of these activities. This has interesting ramifications since different organizations set different thresholds. For instance, in the case of a biomarker for which the FDA had opted for a 10% overexpression threshold, the joint guidelines by the American Society of Clinical Oncology and the College of American Pathologists (ASCO/CAP guidelines) set a 30% threshold. This "rift" between the FDA and ASCO/CAP (Schmidt 2011) lies in the different purposes of the thresholds: while the lower FDA threshold gave greater access to the therapeutic agent targeting that receptor, the higher ASCO/CAP threshold sought to increase consistency between two different ways of measuring it (Viale interview, 27 January 2012). Still, these inconsistencies that compound the different testing methodologies, and the evolving understanding of the biology of tumors, have clearly been a source of confusion and debate among clinical researchers (Allison 2010, Dixon et al., 2012, Perez et al. 2014, Kaufman et al. 2014).[9]

Another interesting ramification underscoring the connection of biomarker regulation, research, and clinical practice concerns another biomarker that acts as an indicator of tumor proliferation and thus has increasingly attracted the attention of clinical researchers. The fact, however, that there is "enormous variation in analytical practice … markedly limits [its] value" (Dowsett et al 2011: 1656). At a recent breast cancer conference, when a leading U.S. medical oncologist was asked why he did not include that biomarker in a list of relevant biomarkers, he snappily replied that even the two best pathologists in the world could not agree on how to measure it (fieldnotes, EBCC-8, Vienna, 2012). This remark highlights the qualitative dimension of quantitative measurements, while reflecting different attitudes vis-à-vis a marker that has found more widespread use in Europe (where it was initially defined) than in the US. In this particular case, the results of the pathologists' endogenous critical inquiry uncovered a number of factors contributing to interlaboratory discordance: "tumor region selection, counting method, and subjective assessment of staining positivity" (Polley et al. 2013: 1897). The first factor is of particular interest: "some investigators have focused in

[9] An additional twist to this debate has been recently added by clinicians who, commenting on yet another study showing high rates of discordance in the interpretation of breast biopsy slides, argued that learning to increase agreement is no replacement for "truth", i.e. robust evidence (Borowsky and Esserman 2016). This, of course, begs the question of how one can establish the robustness of evidence outside of a consensus-building technologies.

particular on the analysis of hot spots [i.e. places within the cell where the marker is concentrated], others have included hot spots in a general assessment of the marker across the [entire tissue sample] section, and yet others have recommended avoiding them altogether" (Dowsett et al. 2011: 1660). In turn, differences in tumor region selection follow differences in the strategic role ascribed to the marker as part of diagnostic procedures: a pathologist wishing to use it for "grading" the aggressiveness of a tumor should arguably opt for an assessment of the marker's distribution across peripheral regions of a tumor rather than focusing on hotspots (Viale interview, 27 January 2012).

Expertise as a transnational network

Confronted with this miscellany of endogenous regulatory activities, and in particular their reflexive dimension, we need to ask how to characterize them. We could content ourselves with categorizing activities (such as the aforementioned ones recommending the use of specific markers or specifying thresholds) as instances of professional regulation. After all, several of the actors cited so far have served on expert panels established by professional organizations such as ASCO and CAP (e.g. Hammond et al. 2010). These and similar organizations have a solid record of proficiency testing spanning the continuum from more traditional molecular testing to the most recent, high-throughput technologies (Check 2015). Within domains characterized by intensive innovation, such as the genomic technologies that are just now entering the clinic, professional societies and regulatory bodies promote overlapping initiatives. In the case of next-generation sequencing, they include, for instance, "the College of American Pathologists (CAP); the Clinical and Laboratory Standards Institute (CLSI); a workgroup convened by the US Centers for Disease Control and Prevention (CDC); the New York State Department of Health; the Association for Molecular Pathology (AMP); and the American College of Medical Genetics (ACMG)" (Hagemann et al. 2014). While there is thus no denying the professional nature of these activities, we concur with Eyal's (2013) criticism of the inherent limits of the sociology of professions approach. Its traditional, narrow focus on jurisdictions and human actors is more fruitfully replaced by the analysis of the networks of expertise that account for the socio-technical dynamics of regulation, broadly defined. We can thus start by asking how the members of professional expert panels were recruited, on the basis of what attributes, qualifications, and expertise. We can subsequently map such expertise to networks associating human agents with epistemic, organizational, and other arrangements.

In the present case, although the results of several of the initiatives so far discussed were published under the aegis of national professional organizations, they clearly exceeded national boundaries, as they recruited a core set of European and North American clinical researchers corresponding to "transnational expert communities" (Djelic and Sahlin-Andersson 2006). While individuals are ostensibly recruited to a professional panel because of their expertise, such recruitment is less an event than a

process that results in the gradual production of that expertise. Current oncology takes place within large research consortia characterized by a gradual blurring of the lines between research and routine (Cambrosio et al. 2014). It is not unusual for oncologists faced with the unsuccessful incorporation of, say, a useful predictive biomarker into clinical practice, to mobilize their collaborative networks to standardize its measurement (e.g. Sartore-Bianchi et al. 2012), a course of action that betrays a direct engagement with "getting things done" rather than top-down initiatives.

When asked how they became implicated in the aforementioned ASCO/CAP guidelines, two interviewees described their progressive involvement in a chain of activities that led to their co-optation as members of the ASCO/CAP expert panels.[10] In the case of a pathologist, the trajectory began with membership in an international network of clinical researchers. Initially a European-based network, the expanding scope of clinical research combined with its molecular turn led to its transformation into a joint North American and European endeavor, which in turn increased awareness of the heterogeneity of pathological practices and of the need to harmonize them. In the case of a clinical biochemist closely involved in cancer research, a pharmaceutical company interested in providing expanded access to their pioneering targeted drug in the UK and in staging biomarker-driven clinical trials created a national advisory committee staffed by oncologists. They soon realized they needed to involve somebody familiar with the clinical-laboratory interface. With little information then available about the best way to measure the biomarker, and with admittedly limited experience in the actual measurement of that biomarker, our biochemist set up a pathology advisory group that led to the creation of national guidelines. He then became chairman of the pharmaceutical company's national advisory board, and subsequently a member of their international advisory board, before being finally approached by ASCO/CAP.

These examples all point to the activities of what sociologists of organizations call "soft actors", i.e. actors (both institutional and individual) who "are embedded and partly structured by other actors but … are also themselves contributing to the structuring of other actors" (Djelic and Sahlin-Andersson 2006: 12). Their activities can similarly be described as being centered on the enactment of soft laws (Mörth 2004.). Yet, to focus only on (soft) human actors is to miss the fact that the strength of networks of expertise is provided by the association of human agents with non-human components, namely the previously discussed markers, and all the other novel biomedical entities that redefined the landscape of clinical trials, and with which individual trajectories intersected and combined. Indeed, the pathologists' endogenous regulatory activities cannot be reduced to quality control or the standardization of measurements. They also involve investigations of the clinical utility of the tests and markers they standardize. Addressing the virtual participants of a 2010 online molecular pathology education module, a pathologist stated: "What I would like to do with you is to address technicalities [the quality assurance, the quality control of biomarker testing], but in the

[10] Interview with Mitch Dowsett (9 January 2012). Interview with Giuseppe Viale (27 January 2012).

light of the clinical implications".[11] In other words, the issue is not simply one of assuring that a given biomarker is correctly measured, but, more generally, that it has clinical validity and utility. Thus, one of the outcomes of an annual conference organized by leading breast cancer researchers — the IMPAKT (IMProving care And Knowledge through Translational research) Breast Cancer Conference — was the establishment of two working groups on the clinical utility of prognostic genomic tests (Azim et al. 2013), and on the biomarker-based methods for defining breast cancer subclasses (Guiu et al. 2012).

Other conferences, with a more explicit regulatory objective, provide additional arenas for debates about the clinical utility of biomarkers, and the best or, alternatively, the most practical way of measuring them. Established in 1978, the St. Gallen International Breast Cancer Conference is one of the key events in breast cancer oncology, known in particular for its respected cancer treatment recommendations, which are often non-consensual. The absence of consensus follows from the fact that not all oncologists necessarily agree with the St. Gallen recommendations, as critical comments in leading journals duly note,[12] and the recommendations themselves are the result of a rarely unanimous vote by members of a consensus panel. The conference organizers explicitly label their recommendations as such, not as guidelines, insofar as the latter are in principle solely evidence-based (but see Knaapen 2013b), whereas the former tackle controversial topics on the basis of a mix of evidence and expert opinion, as provided by panelists (interview with Aron Goldhirsch, 5 March 2012). The St. Gallen recommendations thus occupy a peculiar niche within the broader regulatory domain.

As an example of its proceedings, the consensus panel of the 2011 conference, attended by 4,200 participants, aimed to secure a representative sample of opinions and consisted of 51 clinicians and researchers, largely from Europe and North America, with a few Australian/Asian representatives. On that occasion, the expert panel recommended the use of the genomically defined subtypes of breast cancer to supply therapy indications, "since [they] incorporate many of the risk and predictive factors used in previous consensus recommendations" (Goldhirsch et al., 2011). Recognizing, however, that it was often difficult in a clinical setting to test for subtypes using genomic technologies, they recommended using, as "useful shorthand", a "simplified classification" derived from more traditional clinicopathological techniques. While acknowledging that "subtypes defined by [such] criteria were similar to but not identical to [genomically defined] subtypes", the recommendations stipulated that these surrogates nonetheless represented "a convenient approximation".[13] Although the

[11] http://ecancer.org/education/module/2-molecular-pathology/1.php

[12] See, e.g., the following exchange in *Journal of Clinical Oncology*: Hayes (2012), Coates et al. (2012).

[13] An additional complication, and a further example of clinicians' socio-technical reflexivity, is provided by discussions at the 2013 St. Gallen meeting, when the aforementioned recommendation was reopened for discussion. One panelist stated that she was "scared" of a biomarker, because while she found it useful to test for the biomarker at her research intensive hospital, making a statement on its utility might result in testing being taken up in less equipped hospitals around the world. Another speaker more forcefully

implications of this form of regulation seem at first to mainly concern treatment, given the increasingly close connection between treatment and research in oncology (e.g. Yu et al. 2015), they also have ripple effects on clinical research whose experimental protocols constitute tomorrow's treatment routines.

Blending regulation and research

It is now time to return to a claim we made at the beginning of this paper, namely that the activities of regulatory agencies such as the FDA or the EMA intervene at increasingly earlier stages of the clinical research process. The FDA, for instance, has adopted an "increasingly activist role" as exemplified most recently by the fact that it took "a seat at the table in the running of [a major genomic-driven clinical trial]" (Goldberg 2015). Our point in doing so is not to claim that the state agency is now interfering with previously pristine (regulatory-wise) domains, but that the agency itself has been transformed by the novel entities and technologies emerging from biomedical research, thus further exemplifying the co-production processes that lie at the core of contemporary biomedicine (Jasanoff 2004, 2011). Indeed, the fact that the regulation of biomarkers is not confined to biomarkers per se, but overflows into an attempt to regulate the clinical research process, also means that biomarkers constantly threaten to destabilize established regulatory procedures, acting as epistemic things rather than technical tools.[14] This is largely the result of the fact that new biomedical technologies and the novel entities (such as molecular biomarkers) they generate displace (or at least supplement) the entities and criteria at the core of traditional regulatory frameworks.

One of the most obvious examples of these dynamics concerns the long-established organization of clinical trials according to a sequence of distinct phases. The close association between new, targeted drugs and tumor markers has undermined the distinction between, for instance, phase I and II trials (Cambrosio et al. 2014). When, for example, the initial, phase I testing of targeted therapies exclusively enrolls patients whose tumors express the target marker, the traditional toxicity measuring aims of the trial are subtly shifted. The disease-focus associated with phase II trials becomes immediately relevant for phase I studies, thus drawing together pharmacology-focused investigators (phase I) and disease-focused investigators (phase II) (Moscow 2014). A growing infrastructure is devoted to the analysis and regulation of tumor markers. As repeatedly observed during cancer conferences, clinical oncologists consistently argue that "a bad tumor marker is as harmful as a bad drug" (see Hayes and Lynn 2006), which also means, as a looping effect, that clinical studies, including clinical trials, should be used to establish the biomarkers' validity and utility (Simon et al. 2009). In parallel, new

urged fellow panelists to think about testing results from local pathology labs when voting rather than pretending that all patient samples were "going to be sent out to [a top-notch expert]" (St. Gallen conference fieldnotes, 13 March 2013).

[14] For a discussion of the regulatory need for stability vs. the destabilizing behavior of biomedical innovation, see Niezen et al. (2012), Nelson et al. (2014).

institutional arrangements emerge, such as "early phase" clinical trial units that become the object of "investments in form" (Thévenot 1984) such as the Certified Early Phase Centers (CLIP^2) program established by the French National Cancer Institute in 2010.

Until recently, the *de facto* situation was that medical devices and laboratory tests did not have to undergo the strict regulatory review that applies to drugs. In the post-genomic era, however, laboratory-based results increasingly tend to dictate, rather than merely contribute to clinical decisions. As noted in an article co-authored by a heterogeneous group of "stakeholders" (clinical oncologists, pathologists, regulators, patient advocates),[15] "when patient management is contingent on the results of a biomarker test, that test becomes as critical for patient care as a therapeutic agent," and as a result "the same regulatory requirements that pertain to new therapeutics should apply to tumor-biomarker tests because they are used to direct therapy" (Hayes et al. 2013). Indeed, the fact that clinicians increasingly resort to molecular markers to refine prognosis, predict response to targeted treatments, and make therapeutic decisions, has led a growing number of oncologists and regulators to openly question why clinicians, who refrain from using a drug in the absence of clear evidence of its usefulness and efficacy, should want to use markers lacking similar evidence. Given that drugs and biomarkers are not independent variables, the issue is not simply one of extending regulatory oversight from one category (drugs) to another one (biomarkers). Biomarkers are transforming the very design of clinical trials that are used to regulate drugs, so that, in post-genomic oncology, drugs and markers increasingly entertain a mutually constitutive relation.[16]

The FDA has reacted to this situation in a number of ways. It has, for instance, decided to end its "enforcement discretion" over laboratory developed tests (LDTs), which meant that LDTs for all practical purposes escaped FDA oversight and fell under the regulatory authority of the Centers for Medicare and Medicaid Services through the Clinical Laboratory Improvement Amendments (CLIA), which only verify the analytical, rather than the clinical validity of these tests. The ongoing attempt to reassert control over the safety and effectiveness of LDTs has led to fierce controversy with opponents claiming that it amounts to an effort to regulate clinical judgment, usually off-limits for

[15] The emergence and evolution of the very notion of "stakeholders" as part of new regulatory approaches is a topic in itself. For an initial analysis see Hoffman et al. (2016: 69-70).

[16] Although in this article we focus more directly on biomarkers, other related aspects of clinical trials are equally impacted by post-genomic developments. For instance, trialists must use specific endpoints (such as tumor shrinkage and time to the development of disease progression) to assess whether a drug is working or not, and these criteria must be uniformly defined and applied. To this end, oncologists formed an International Working Party in the mid 1990s that defined a set of criteria known as RECIST (Response Evaluation Criteria in Solid Tumors), published in 2000 and updated in 2009 (see Eisenhauer et al. 2009 for a short history). More recently, however, RECIST came under fire by oncologists calling for new tools "chosen to reflect the biology of the disease in the population being studied", the term "biology" referring to "the biologic heterogeneity of cancer, […] functional imaging studies, biomarkers that have emerged for technologic innovations, and advanced computational methods" (see the exchange between Sharma et al. 2012, and Fojo and Noonan 2012).

the FDA (Bourret et al. 2011). Most importantly, the FDA has become directly involved in a number of joint initiatives to develop innovative clinical trial designs. In 2014 the FDA, the American Association for Cancer Research, the American Society of Clinical Oncology, and the Breast Cancer Research Foundation co-sponsored a workshop sought to "bring together an international group of breast cancer experts, FDA, industry representatives, and patient advocates to discuss the intricacies of developing an international genomically driven trial to test multiple agents in patients with metastatic breast cancer". Entitled "Innovations in Breast Cancer Drug Development: Next Generation Oncology Trials" this forum was designed to "explore means of accelerating the development of highly effective targeted agents for patients" and to "discuss potential biomarkers, testing platforms, study designs, statistical models, and implementation strategies to optimize the path to regulatory approval".[17] Meanwhile, the NCI has launched a series of genomic clinical trials (Ong 2013, 2014) implicating the FDA from the beginning in their design. As explained by the NCI Deputy Director for clinical and translational research, the reason why the FDA had "to be intimately involved in all of these activities" was to help the NCI to "try to understand where the regulatory aspects of how to match drugs to patients come in and how we need to get approvals for those kinds of clinical trials".[18]

To repeat, the emergence of new biomedical entities and techniques has brought together actors previously confined to different stages of the regulatory sequence. I-SPY 2, an innovative clinical trial sponsored by the Biomarkers Consortium, a public-private research partnership that includes the FDA, the Foundation for the NIH, major pharmaceutical companies, and non-profit and advocacy groups, provides another telling example of this new state of affairs. The trial, which uses an innovative statistical design and biomarker analysis to screen drugs in breast cancer patients before surgery, also uses a somewhat controversial criterion (Burki 2014) as trial endpoint[19]. Traditionally, clinical trials have used "overall survival" as their endpoint, but this means waiting for several years before obtaining results. In order to accelerate drug approval, I-SPY 2 resorted to a so-called surrogate endpoint. The FDA defines it as "a laboratory measurement or physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions, or survives and that is expected to predict the effect of the therapy"; most importantly, compared to a traditional clinical endpoint, a surrogate endpoint requires "smaller sample size and a shorter follow-up time" (Zhao 2016). It is no coincidence that in 2014 the FDA published a Guidance on the use of that endpoint. More than an isolated incident, I-SPY 2 has functioned as an exemplar and was featured in the presentation of the new US National Center for Advancing Translational Sciences (Collins 2011), and in a White House document on innovation in drug discovery submitted by the President's Council of Advisors on Science

[17] http://www.fda.gov/Drugs/NewsEvents/ucm410332.htm

[18] Doroshow James H., Genomic clinical trials: NCI initiatives. http://deainfo.nci.nih.gov/advisory/ncab/164_1213/Doroshow.pdf

[19] See Epstein (1997) for a discussion of an early controversy about surrogate markers.

and Technology (PCAST 2012). This temporal and substantive convergence of initiatives is not due to some mysterious resonance between micro and macro actors, but to the rather more mundane fact that the relevant human and non-human actors operate and circulate within a singular (in both senses of the word), seamless collective. The components of this heterogeneous collective, moreover, entertain mutually constitutive relations, insofar as new genetic and genomic tests redefine regulatory arrangements at the same time that regulatory arrangements stabilize these new molecular tools (Bourret et al. 2011).

In a domain characterized by the presence of "disruptive" technologies, new actors play an increasingly important role, namely companies offering genomic services and technologies. Kohli-Laven et al. (2011) have analyzed the role of one such pioneering company, Genomic Health: the commercial success of its flagship product (Onco*type* DX, a breast cancer prognostic test) is largely due to the fact that the test is performed in a central laboratory, thus obviating the need for complex guidelines and recommendations to address the variability problem inherent in using advanced molecular techniques in clinical settings. Similarly, one could argue that the remarkable rise of the next-generation sequencing company Foundation Medicine is at least partly due to the fact that by offering its services to many genomic-driven clinical trials it has become, for the time being, a *de facto* standard in its domain. While waiting for the FDA and bio-clinical networks to regulate sequencing technologies,[20] comparisons between the results of different trials are greatly facilitated by the fact that the same company performs the genomic analyses: even if some practitioners might consider their system for calling mutations and annotating their functional significance idiosyncratic, at least the results are systematically idiosyncratic.

Finally, consider Illumina, the undisputed market-share leader in the field of sequencing equipment and technologies. Together with four world-renowned U.S. cancer centers, and under the leadership of its Senior Vice-President and Chief Medical Officer (and previous director of the NCI), Illumina established the Actionable Genome Consortium to provide standards and recommendations to guide the widespread use of sequencing in clinical oncology.[21] Several authors have analyzed the relations between scientific equipment users and producers, noting, for instance, that in the biomedical domain users play a major role (von Hippel 1976) and, conversely, that standardization effected by providers channels, provokes, and orients innovation and research (e.g., Blind 2012). With regards to the present case, we would like to make a more specific claim, namely that while the role of biomedical equipment producers was traditionally confined to the provision of the tools, and did not include the definition of bio-clinical research programs, we presently witness the beginnings of a conflation between these two roles. It could be objected that this is not an entirely new event, but merely an additional step

[20] FDA workshops on this topic took place in February 2015 and February 2016 (Ray 2016).

[21] http://www.fredhutch.org/en/news/releases/2014/09/actionable-genome-consortium-world-renowned-cancer-institutions.html

along a trajectory that includes, for instance, the promotion of immunological reagents and related laser- and computer-based equipment by a company such as Becton Dickinson (Cambrosio and Keating 2000).[22] We maintain, however, that this process has reached new heights, not merely because the regulation of instruments and reagents is closely embedded in the definition of actual *clinical research* practices, but more importantly because, as discussed in detail in Bourret et al. (2011) issues of *clinical judgment* are increasingly built into biomarker tests and gene panels.

Conclusion

We have advanced a number of overlapping claims. First, regulatory activities do not simply act on pre-existing practices or entities, but contribute to creating the objects they regulate. The condition of possibility for the regulation of new biomedical entities, such as the biomarkers discussed in this text, is their (temporary) stabilization, which is made difficult by the fact the new biomedical entities come in different forms. The "same" biomarker can be detected in different ways that mobilize distinct platforms (e.g., traditional pathology grounded in the visual inspection of stained tissue slides, or a number of more recent molecular technologies such as next-generation sequencing). The robustness and reproducibility of these different technologies, and thus also of the entities they (re)produce, are subject to many vagaries, whose nature and origin, according to the practitioners themselves, range from technical to organizational or attitudinal factors.

State agencies such as the FDA or EMA are but several of the many actors involved in this process of stabilization, which simultaneously mobilizes transnational networks of expertise of varying nature, extent, and composition. Often ridden with controversy, this form of reflexive regulation by practitioners is part and parcel of the overall regulatory process or, more precisely, of a regulatory regime that extends beyond governance to systems of evidence and knowledge production. Indeed, it is often difficult to determine where one form of regulation ends and another begins, as clinicians who are involved in innovative, biomarker-driven trials also participate in new FDA regulatory initiatives and in the creation of policies for the redesign of the national clinical trial system. Using the example of molecular biomarkers, we have thus traced and outlined the activities of a chain of mediators within what one could describe as a seamless regulatory web characterized by the interaction of endogenous and hybrid regulatory activities that are neither hierarchical nor linear. The examples we discussed also show that synchronic analysis must be supplemented with diachronic analysis, as genomic technologies affect the evolving bio-clinical and regulatory landscapes.

An obvious consequence of the interconnections between different types of regulatory interventions is that subdomains of activity are not self-contained. Rather, activities in

[22] Another example is provided by Varian in the field of radiotherapy.

one subdomain impact other subdomains. For instance, the regulation of biomarkers does not concern biomarkers as objects or biomarkers *per se*, but amounts to an attempt to regulate the research process, insofar as biomarkers constantly threaten to destabilize the regulatory process. While medical devices and laboratory tests do not yet undergo the strict regulatory process that applies to drugs, things are rapidly changing, notably in oncology that is at the forefront of post-genomic medicine. Clinical researchers increasingly use molecular markers to design their studies, and practitioners are increasingly adopting molecular markers to refine prognosis and predict response to new drugs. Clinicians now argue that a bad tumor marker is as harmful as a bad drug, and regulators similarly concluded that once diagnostic tests are used to make treatment decisions they should also be required to show safety and efficacy. These claims have been translated into concrete proposals to align drug and biomarker development (Taube et al. 2009).

But the issue goes deeper, as biomarkers are transforming the very design of the clinical trials that regulate drugs. For instance, biomarkers are used to stratify patient populations for clinical trials, and thus target subpopulations of responders to drugs to which other patients with the "same" disease will not respond, thereby replacing traditional disease categories with novel bio-clinical entities. The proliferation of (biomarker-defined) targets also leads to the proliferation of potential targeted drug candidates, straining the clinical trial system and prompting calls for a revision of the canonical components of clinical trials for regulatory purposes. Viewed in this way, biomarkers act as epistemic things. Regulatory initiatives attempt to treat them as technical objects and thus to defuse their "disruptive" potential, an approach that is constantly challenged by the many initiatives designed to incorporate the latest scientific breakthroughs into clinical activities.

Finally, we have argued that official instances of biomedical regulation such as those deployed by state agencies, themselves undergoing major transformations, are increasingly incorporated into the early phases of bio-clinical research, where they contribute to an unprecedented degree to shaping the contours of biomedical innovation. Now, one could argue that, as shown for instance by the history of cancer clinical trials (Keating and Cambrosio 2012), this is nothing new, as the different modalities through which state agencies have regulated drug development have also in the past affected the research process. From such a perspective the "disruptive" power of biomarkers reveals connections between regulation and research that have always been there, but which were less obvious in the case of more stable entities such as traditional chemotherapy agents. While we would tend to agree with such an argument, the fact remains that, compared to the previous situation where the FDA waited for the completion of a given trial before assessing its results, the agency has now become directly involved in the very design of a selected number of clinical trials. As biomarkers realign the relations between the normal and the pathological, more in particular reconfiguring the links between disease biology and clinical trial design, relations between state agencies and transnational networks of expertise have become

increasingly entangled, leading to the agencies' more direct involvement in the clinical research process.

One might ask, in this respect, whether the proactive attitude recently displayed by the FDA is due to the work of an emboldened bureaucracy, after years of regulatory restraint under previous, less regulatory prone administrations, or whether this a reaction to being under siege.[23] There is empirical support for both of these not necessarily mutually exclusive hypotheses. Most certainly, the election of the Obama administration is correlated with an increase of FDA attempts to regulate the field of genomic testing, from the aforementioned LDTs to the most recent forays into the field of genomic sequencing. But one can also point to the activities of advocacy groups such as *Friends of Cancer Research* (http://www.focr.org/), who have aptly managed to mobilize bipartisan support for their initiatives aiming at profoundly reforming the regulatory landscape in oncology (e.g. Fromer 2015), or to the pressures to modernize originating from House and Senate committees and, most recently, the President's Precision Medicine Initiative (Evans et al. 2015). Similar pressures are at work in Europe (Prasad and Beckenridge 2011).

And yet, as should by now be clear to readers, we argue that this is the wrong way to frame the question. In both cases what is at stake is not whether a state agency can or should regulate molecular oncology or, more in general, genomic medicine, but whether it can do it properly, i.e. in such a way that the entities and practices it regulates are fit for purpose (National Academies of Sciences, Engineering, and Medicine 2016). The definition of "fit for purpose" mobilizes such a variety of participants, both human and non-human, that it is very difficult to trace boundaries between them. At a more theoretical level, we plead for a return to empirical reality, while acknowledging that we have only imperfectly done so. This means replacing invented categories, such as bureaucracies or even agencies whose boundaries are increasingly fuzzy, with regulatory networks, of which there are multiple instances, and their complex interplays (see Azarian 2005: 25). What is at stake for somebody like Dr. Viale, the passionate respondent repeatedly mentioned in this paper? Paraphrasing Becker (1986), we suggest that it is the possibility of doing things together with fellow practitioners, a task which requires both common regulations and common cause to constantly rewrite those regulations.

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[23] This was an actual question raised by one of the reviewers of this paper.

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