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Version of Record: https://www.sciencedirect.com/science/article/pii/S0277953619307300
Manuscript_517d64090d63d0f4541ec2a7ce6dabb2

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1 Introduction

Biomarkers are iconic entities of contemporary biomedicine that have gradually spanned from research and experimental settings to numerous routine clinical contexts of uses. Their proliferation is all the more visible that they can alternatively be mobilized for diagnosis, prognosis or therapeutic decision. Breast cancer is one of the medical fields in which this extension of biomarkers is the most impressive. Over the last decades, the continuous process of disease reclassification into different rarer subtypes has incorporated a growing biochemical and molecular information (Bourret 2005, Keating, Cambrosio and Nelson 2016, Löwy 2010).

The political context of techno-optimism has been pivotal in this biomarker's rise. The general tendency to overestimate the practical capabilities of technologies in the short term, despite recurring difficulties to meet the expectations in the longer term (Brown 2003), has create favorable economic and social conditions for their development. Yet, the correlated underestimation of uncertainties in favor of widely shared speculative promises (Hjorleifsson, Arnason and Scheia 2008) has specific consequences in the clinic. The perspective, for clinical judgment, to be improperly removed from the professional jurisdiction and regulation of clinicians and included in laboratory tests is an important one (Bourret, Keating and Cambrosio 2011, Rosenberg 2002). The genomic turn and the corporatization of life sciences (Adele E. Clarke et al. 2003, Sunder Rajan 2006) that characterizes it, has further accentuated the sensitivity of the issue.

The right to prescribe medicine has long been a major component of clinical freedom and a battle group on which the cause of clinical autonomy has been defended (Armstrong 2002, Britten 2001, Freidson 1970). The cause has been invested both at the professional level and at the individual practitioner level, with recurring tensions between these two endeavors. Evidence-based medicine, analyzed as a commitment to high science-based standards of care thereby justifying professional

autonomy, has also been accused to do it at the expense of individual practitioners, expected to only act within the decision rules.

The articulation between collective and individual levels in the management of clinical autonomy enacts differently according to the medical subgroup considered. In the specialized field of cancer, drug prescription has been central to the constitution of oncology as a medical specialty. In this highly organized and hierarchical profession, the collective control on prescription is strong. Guidelines are numerous and enforced through the involvement of collective regulatory bodies (Cambrosio et al. 2006). The true culture of experimentation, historically constitutive of the specialty (Lowy 1996), is further characterized by a commitment to transnational networks, through which knowledge, technologies and clinical practices have circulated (Keating and Cambrosio 2011). This context has been favorable to the development of biomarkers, to their introduction in clinical settings and to their inclusion into the collective control on prescription.

Medical oncology thus appears as an interesting study case to evaluate the ways in which biomarkers are mobilized to guide prescription, the extent to which their diffusion questions the authority and the clinical autonomy of clinicians and the collective and individual solutions deployed by clinicians to cope with them. This paper is a contribution to these questions based on a specific case study, namely the prescription of chemotherapy to women with early stage breast cancer with a good prognosis.

The choice of this case study relies on two complementary aspects. First, this treatment decision is massively and routinely made – 30% to 40% of all incident infiltrating breast cancers are concerned. Its study can thus bring insights from a diversity of cancer care settings, including expert centers and standardized cancer services in general hospitals. Second, the decision to prescribe adjuvant chemotherapy aims at reducing the risk of disease recurrence after removal of the tumor and, consequently, at extending the survival of patients. Yet, for early breast cancer with good prognosis, the expected benefit of the treatment is modest and the decision to prescribe chemotherapy is not

straightforward. In addition to a series of clinical, pathological factors and the preference of the patient, a dozen of biomarkers is available to guide the decision. 25-year old cheap in-house protein level measurements have resisted the introduction of cutting-edge genomic signatures evaluated in clinical trials led by expert cancer centers and marketed by commercially aggressive firms. National professional associations (Harris L. N. et al. 2016), (E. Senkus et al. 2013) do not consider any of these biomarkers as providing a fully reliable information to dictate prescription. Their difficulty to reach an international consensus on the biomarker clinical utility (Azim and al 2013, Delaloge S. et al. 2015) further illustrates the important uncertainty that surrounds them.

Our study further focus on three biomarkers, chosen for their wide usage and/or for the existence of a controversy on their usage: Ki-67, uPA/PAI-1 and genomic signatures. Our idea was that a thorough dissection of a biomarker usage requires a fine understanding of both the clinical decision context in which it is mobilized and of the epistemic, material, organizational, financial and discursive dimensions attached to it.

We show that, none of these biomarkers corresponds to an unanimously acknowledge reference guide to chemotherapy decision for early phase breast cancer with a good prognosis. Yet, all the clinicians use them to help making a decision fraught with uncertainties and largely perceived as uncomfortable. The fact that most actors recognize them as imperfect biomedical entities reinforces the importance of local, culturally situated practices, material, organizational and financial constraints over that of international science, technology and clinical data, in their diffusion. The regulation of the uncertainties associated with these imperfections is organized at the professional level. Through an important work, relying on guidelines and enforced in collective staffs, the series of heterogeneous bioclinical evidences available are articulated. Biomarkers tend to be subordinated to the clinic. While maintaining the professional autonomy, the process also strengthens the internal professional hierarchy. When the most expert clinicians manage to inhabit a space for clinical autonomy, the non-expert are torn between stronger professional rules and patient preferences. In

this alliance between biomarkers and experts, their clinical autonomy tends to be the price for the professional autonomy.

In what follows, after a short theoretical section, we present our material. In the results, we first analyse the conditions of the biomarkers development and diffusion. We then present specific aspects of the chemotherapy decision that help shaping these biomarker usages. Finally, we discuss the ways in which the clinicians manage their clinical and professional autonomy in the presence of these biomarkers.

2 Biomarkers in the clinic

Imaginaries of contemporary biomedecine are filled with brand new machines, cutting-edge facilities, newly built laboratories and future therapeutic promises (Tutton 2014). These "technological visions" (Hedgecoe 2004) are internally consistent discursive constructions that "act as both a means of enrolling support and resources into the emerging sociotechnical network and as a guide to the physical design of artefacts" (Martin 1999). Yet, the work of visions and expectations also helps shaping emerging biomedical practices. They constitute a dominant policy approach that affects clinician perceptions and modifies the context in which their authority is exercised.

Analysts of contemporary biomedicine have described biomarkers as "truly biomedical entities that exists as both normal biological entities and as pathological signs, i.e. as biomedical substances with regard to their origins, their uses and their meanings" (Keating and Cambrosio 2003). Produced by biomedical platforms to which they are constitutive, they stand as key actors to be followed in order to grasp the articulations of biology/medicine, science/technology, innovation/routine, constitutive of biomedicine. This analytical framework has been fruitfully applied to study the transformations of clinical research entailed by the introduction of genomic signatures to guide chemotherapy prescription (Kohli-Laven et al. 2011). While reporting divergent innovation trajectories of the different tests related to scientific options, practical materiality concerns and sociotechnical networks, the authors also highlight new modes of interaction between biotech companies and

academic research, characterizing these genomic biomarkers. Building on the debates over the regulation of genomic signatures by the US Food and Drug Administration, Bourret, Keating and Cambrosio (2011) bring stimulating insights on the question of how oncologists problematize the introduction of molecular diagnostics into clinical settings. They describe a contrasted situation. On the one hand, confident clinicians consider that these new tools could be integrated into their practice without threatening their clinical skills. On the other hand, others dread that the genomic signatures would dictate rather than simply contribute to clinical decisions. For the authors, this potentiality of a shift in the locus of clinical judgment from the clinicians to the molecular test should be viewed as a consequence of the accelerated process of conflation between diagnosis, prognosis and therapeutics categories (Christakis 1999, Rosenberg 2002) that genomic signatures entail.

Our study is an additional contribution to the analysis of biomarker's introduction into clinical settings. Yet, whereas the studies mentioned were conducted in experimental and innovative contexts, we are interested in routine contexts. We aim at dissecting the ways in which clinicians individually and collectively handle and negotiate their clinical and professional autonomies in the presence of biomarkers. Professional autonomy includes the regulation of the profession as a whole by controlling entrance to the field, self-monitoring, developing a body of specialized knowledge, and running professional organizations (Timmermans and Berg 2003). Clinical autonomy refers to the control the individual practitioner has over routine work activities and decisions, and the freedom to be innovative in the work process. Considering that our questions require a fine understanding of the ways in which epistemic, technological and social dimensions of biomarkers are appreciated by the various actors concerned, we adopt an ecology of knowledge perspective. Following Rosenberg's urging to understand both cognitive and practical options (Rosenberg 1988), we try to hold together formal intellectual content, social and institutional organization, systems of economic support and values that sanction and reward the career choices of members of the different biomedical professional subgroups involved (Akera 2007). An additional important aspect of this ecological perspective is its emphasis on the dynamic relationships between knowledge, its material

infrastructure and its supporting organizational and institutional forms. As biomedical entities, biomarkers heavily circulate between research and clinical settings, alternatively mobilized for experimental or routine uses. We therefore believe that the study of their incorporation into clinical practices cannot do without incorporating such a dynamic perspective. In a complementary manner, inspired by social-worlds analyses, we pay a particular attention to the meanings and practical uses of the biomarkers and their impacts on the distribution of power among the different actors committed or implicated by the therapeutic decision (Casper and Clarke 1988). Finally, although biomedicine is fostered through an international political economy of biotechnology and by an international community of medical educators and bioscientists, it is taught, practiced, organized and consumed in local contexts. Drawing upon the cultural studies of biomedicine, we examine the dynamic relationship between local, socially and culturally situated clinical contexts and international worlds of knowledge, technology and practice (Delvecchio Good 1995).

3 Material and methods

The study was conducted in the French setting. France has a universal public health insurance system. More than 95% of the hospital expenditure is paid publicly, but hospital care is provided both by public and private-for-profit hospitals. One third of breast cancer chemotherapy is performed in private-for-profit hospitals, specialized in standardized care services like surgery and oncology. Medical research and innovation are performed mostly in public teaching hospitals and cancer centers.

The main material for the study was interviews carried out with clinicians who must regularly decide whether to prescribe chemotherapy (Table 1) to breast cancer patients. More specifically, our interest lied in the category of early breast tumors with a good prognosis, as defined by clinical and pathological parameters. Far from being marginal, this subtype would represent between 30% and 40% of incident breast cancer cases (Abdoli et al. 2017, Dunnwald, Rossing and Li 2007, Exbrayat et

al. 2012). The treatment regimen normally includes hormonal therapies (Harris N and al 2007) but the indication for adjuvant chemotherapy is more controversial.

The medical oncologists interviewed were initially identified through the hospitals in which they were working. Our intention was to include a diversity of institutional professional contexts: public and private-for-profit hospitals; university hospitals and cancer centers; hospitals located in urban and peripheral areas, spread over the French territory. The selection also included two additional correlated parameters, more specifically directed to the clinician's experience: the number of cases treated per year in the hospital and the existence/absence of specialization in breast cancer. The French National hospital-discharge summaries database (exhaustive recording of hospital stays and chemotherapy sessions in France) was used to build our sample of hospitals/oncologists. Oncologists from cancer centers and public hospitals were keener to participate than oncologists from private-for-profit hospitals. Contributors to the guidelines on the use of biomarkers in adjuvant chemotherapy in early breast cancers from the French national cancer institute were also contacted.

Altogether, 20 medical oncologists, 5 surgeons, 2 biologists and three pathologists, all regularly confronted with or associated to the chemotherapy decision, participated in the study. The majority worked in a cancer center (53% of interviewees when 28% of breast cancer patients with chemotherapy are treated in cancer centers in France according to the French National hospital-discharge summaries database), 20% in private for-profit hospital (vs 39% in France) and 27% in public hospitals (vs 39% in France). Finally, two top managers in firms commercializing biomarkers were also interviewed.

For the three biomarkers we decided to study (Ki-67, uPA/PAI-1 and genomic signatures), our data showed a diversity of biomarkers usage. All centers had access to Ki-67 and eight had implemented a platform for uPA/PAI-1. At the time of our fieldwork, genomic signatures were not covered by the French national health insurance. Only one private-for-profit hospital was routinely using the Oncotype DX® genomic signature to guide decision making. Nine cancer centers included in our

sample were involved in the clinical trial which has evaluated the efficacy of Mammaprint genomic signature.

Face-to-face interviews were conducted at the clinician's office, from June 2013 to January 2015, by the same social scientist (LP). They were semi-structured and explored the interviewees' career path, clinical practice, knowledge of local and national guidelines, knowledge of biomarkers (science, technology, clinical utility, costs), practice of chemotherapy prescription (relation to guidelines, usage of biomarkers). Interviews were audio-recorded and transcribed. The resulting 560-page corpus was analyzed thematically during successive round, with regular meetings of the multidisciplinary research team held to discuss the emerging themes.

Our analyses were further complemented with a review of the scientific literature, of the international, national and local guidelines and of the reports produced by the French National Cancer Institute and the French Society of Senology and Breast Pathology (Bellocq and al 2014, INCA 2009, INCa 2014).

4 Findings

4.1 Impact of material, organizational, financial and discursive aspects in the diffusion of imperfect biomarkers

The two oldest biomarkers considered in our study -Ki-67 and uPA/PAI-1- have been initially developed in biology research settings and later only, evaluated as potential biomarkers for clinical usage. Identified as a monoclonal antibody, able to detect human proliferative cells (Gerdes J et al. 1983), Ki-67 levels were further correlated with recognized measures of cell proliferation used in pathology, such as the histological grade (Gerdes J et al. 1991). Subsequent studies described its capacity to discriminate between good and bad prognostic early breast cancers and consequently, to predict response to chemotherapy prediction. Nonetheless, the most recent international guidelines

discourage its use, considering a lack of reproducibility of its measurements and an "unacceptably poor" analytical validity (Polley and al 2013, Varga and al 2012). uPA/PA-1's history is relatively parallel. Early studies proposed that both proteins - urokinase plasminogen activator (uPA) and the plasminogen inhibitor-1 (PAI-1)- were causally involved in the mediation of cancer progression (Duffy MJ and O'Grady P 1984). Complementary studies in clinical contexts, indicated that the two protein levels were correlated with breast cancer prognosis (Janicke F, Schmitt M and Graeff H 1991). Subsequent clinical trials validated their usage for chemotherapy decision making in early breast cancer with good prognosis (Harbeck N. et al. 2013, Look M.P. et al. 2002), but the recommendations remained controversial. In 2016, the American Society for Clinical Oncology (ASCO) considered that using *"uPA/PAI-1 to guide decisions on adjuvant chemotherapy" is a "high quality recommendation"* but with a "*weak strength of evidence*". The history of genomic signatures is notably different, since they have all been specifically developed to serve as biomarkers for clinical usages. Following the rise of molecular biology and the diffusion of microarrays in both biotech and academic contexts, tests quantifying the molecular expression of selected genes within tumors, were proposed. The capacity to distinguish between patients with a high risk of metastasis and patients with a low risk of metastasis was a central criterion in the building of the tests. OncotypeDx (21-gene signature, Genomic Health, Redwood City, CA) and Mammaprint (70-gene signature, Agendia, Amsterdam, The Netherland) were the first genomic signatures validated in the US and in Europe (Paik and al 2004, van de Vijver 2002). Their capacity to predict response to chemotherapy in early breast cancer was then evaluated through large clinical trials and in its 2016 report the ASCO highly supported the use of OncotypeDX in particular breast cancer subtypes. Yet, in its latest 2019 report, the French Health Authority issued an opinion against the reimbursement of molecular signatures due to "the lack of evidence concerning their clinical utility" (HAS 2019).

None of these biomarkers thus corresponds to an unanimously acknowledge guide to chemotherapy prescription in early phase breast cancer with a good prognosis. **In this sense, they are all *imperfect* biomarkers, recognized as such by the profession and by most clinicians**. Nevertheless, all the

clinicians interviewed in our study declared including at least one of these biomarkers in their decision process. Ki-67 was the most widely used. Virtually all professionals we interviewed recognized having *"a quick look at Ki-67*" before making their decision. The situation was all the more intriguing that the only French National Cancer Institute report on the biomarkers available to help in chemotherapy decision-making for early stage breast cancer with a good prognosis (INCA, 2014), did not include the biomarker. Our study pointed to a series of complementary factors that explain this widespread usage. Technically, Ki-67 measurement is carried out by immunohistochemical staining (IHC) on sections of paraffin-embedded tumor tissue (paraffin block), routinely generated in all pathology laboratories. The cost of the test itself – around 60 euros - and that of the organizational circuit needed to run the test, are both low and fully covered by the French National Health Insurance. Finally, as stated by a biologist interviewee: "*Ki-67 is a proliferation factor, the chemos attack proliferation, so from a mechanistic point of view, we have the notions that well, it will perhaps be a predictive factor of response to chemo*". The widespread and easily understood knowledge on Ki-67 biological functions and its capacity to stand as a quantitative molecular measure of standard qualitative histological states are important factors in its construction as a relevant biomarker for clinical uses. In summary, **this large diffusion of Ki-67 compared to other biomarkers relied, above all, on the technical, organizational and economic facility of its usage, backed by a clear biological rational.**

Conversely, clinical use of uPA/PAI-1 remained restricted to expert centers sharing a common culture in scientific biology, an expertise in medical biology and an integrated infrastructure for patient management. All eight hospitals implementing uPA/PAI-1 included in our sample (five cancer centers and three university hospitals), had either participated in the marker's development, or worked in close contact with participants. Several sociotechnical factors contribute to explain this restricted clinical use. First, contrarily to Ki-67, the biomarker cannot be characterized from paraffin blocks. The unique test available requires freshly frozen tumor samples. The management of such samples was regularly mentioned as a strong impediment to using uPA/PAI-1. "*The same test made available on*

paraffin blocks would certainly be widely used", noted an oncologist from a local hospital. Many professionals outlined that the French National Health Insurance reimbursement of the test was not covering all actual costs of the test. Second, when the test was introduced for clinical uses, the technology was already considered as "*outdated and time-consuming*" to use the words of a pathologist. In his own hospital, when the decision to implement uPA/PAI-1 was made, the biochemistry lab had completely stopped using similar techniques. Another oncologist insisted on restricted research options: "*These are only two biomarkers and there is no perspective for complementary analyses*". In cancer centers where clinical research involvements strongly contribute to professional recognition, the perception that these biomarkers were not on current research agendas constituted a drawback for adopting them. Ironically, a couple of uPA/PAI-1 users analyzed this resistance as a sign of poor knowledge on cancer biology. The prognostic factors commonly used today all relate to the tumor's capacity to proliferate. "*It's as if one were only considering the individual itself",* noted one of them*, "But this individual is in an environment, s/he's interacting with this environment and uPA/PAI-1 precisely reflects this interaction with the environment* […] *This parameter is as important as the tumor's characteristics*". In its way, uPA/PAI-1 illustrate the centrality of technical, organizational and financial aspects in the deployment of such imperfect biomarkers. In the absence of strong statistical evidences, biological rationales only have a relatively marginal impact and can alternatively be mobilized to justify or reject a biomarker.

The restricted usage of genomic signatures in France at the time of our study did not allow us to draw a similar picture of the socio-technical factors contributing to the diffusion/non-dissemination of these tests. Nonetheless, the fact that most genomic tests use paraffin blocks was positively praised as a guarantee of feasibility by many clinicians, in particular those working outside expert centers. This capacity to fit in preexisting sample circuits also influenced their perception of cost. Despite the fact that genomic signatures were costing between 2000 and 3000 euro and without reimbursement from the French National Health Insurance at the time of our enquiry, some clinicians considered them manageable because this nominal price covered all the expenses required for the

test. Scientifically and clinically speaking, for the majority of expert clinicians, genomic signatures did not displace the fundamental limits of Ki-67 or uPA/PA-1. First, for a biologist interviewee: "*We have two things, we have markers that are either prognostic or predictive of treatment response. These markers, uPA/PAI-1, MammaPrint, etc… are so-called prognostic markers, this means that they calculate a risk of relapse. We transpose this by saying that we know that chemotherapy has an effect on the patients with a high risk of relapse. We are using them as if they were predictive factors of chemotherapy response, but it's not quite true* ". The clinical trials supporting the use of all these tests as clinically relevant biomarkers, including genomic signatures, have been design to provide prognosis information. Predicting the response to chemotherapy is only an indirect information, that cannot be considered as rigorously validated, according to evidence-based medicine standards. Second, given the biological heterogeneity of tumorous cells, response to chemotherapy is apprehended as a complex multidimensional phenomenon, that can only by poorly captured by all these unidimensional indicators. Commenting on the difficulty to reproduce Ki-67 measurements, a pathologist argued that the problem mainly concerned tumors with midrange Ki-67 values. These tumors, he pointed, were also the more biologically heterogeneous. Similarly, discussing genomic signatures, a cancer center clinician insisted: "*It is not the techniques [of genomic signatures] that are unstable. You sample, prepare, measure… These are well industrialized processes, quite robust. Yet, what you measure is not always exactly the same thing and since the biology of cancer is complex, you're not getting the same results*". This emphasis on the complexity of tumor biology constitutes, in turn, an acknowledgment of the impossibility, in the current state of knowledge, to design biomarkers with a strong predictive power. Analyzed from these clinician perceptions, the novelty of the genomic signature appeared to lay mainly in the commercial strategies of the firms selling the tests. Professionals reported a sense of discomfort with their aggressive marketing practices. "*It's pretty impressive when you see who sponsors many national and international meetings, the importance of Genomic Health for instance [the company selling Oncotype DX], it's pretty disturbing…the lobbying and the power of communication tend to make us forget that it's just*

another test", confessed a clinician, while another condemned the commercial practices directed at non-specialized clinicians that "*create the illusion that this is science-intensive technology*".

Altogether, the three contrasted configurations of these biomarker development, usage and perception, highlight the decisive impact of material, organizational and financial dimensions on their diffusion. The fact that actors recognize them as imperfect biomedical entities reinforces the importance of local, culturally situated practices, regulations and organization of care over that of international science, technology and clinical data, particularly outside expert centers. In the absence of unanimously validated statistical evidences, biological rationales tend to be mobilized with a certain flexibility to justify or oppose biomarker usages. To further grasp the impacts of these local dimensions, we now discuss **specific aspects of the chemotherapy decision that help shaping the ways in which these biomarkers are used**.

4.2 An uncomfortable clinical decision stimulating the need for biomarkers

"*If there was something ideally, that is safe and certain and 100% reliable, that is able to say whether or not the lady needs chemotherapy, well yes I buy it, okay. But, for now, this still seems a bit utopian […] Opting for a chemotherapy is a decision that requires to think in terms of benefice and risk. So this [the biomarker] helps us to try to estimate whether we're going to bring benefits to the patient, and if the benefits become greater than the risks we're going to put her at.*" As expressed by this oncologist, in the context of chemotherapy prescription for early stage breast cancer with good prognosis, biomarkers able to reduce all the uncertainties around the decision, are sought more than dreaded by clinicians. The fact that such ideal tools are unavailable does not disqualify the need for biomarkers. Rather, they are requalified as additional and useful pieces in a complex decision process.

The process itself is strongly influenced by the professional culture, experience and perception of risks of both clinicians and patients. To describe their relation to chemotherapy, several oncologists mentioned a "*dose culture*". A 40-year-old oncologist estimated that his generation was "*trained to*

believe in chemotherapy, to believe in the importance of the dose". For another, getting rid of this culture required "*an important work on one's previous convictions*". Prescribing chemotherapy used to be relatively systematic. Its recent turn into a more open decision has expanded their autonomy. Yet, clinicians have been forced to reconsider their perception of the benefits associated with chemotherapy. This context is important to appreciate the reported difficulty to favor statistical evidence over striking experiences. "*We are so prone to remember the most rotten case, the case that has traumatized us the most. We're very suggestible*", concluded an oncologist after mentioning a patient to whom no chemotherapy was prescribed and who died, although the initial evaluation of prognosis was good. This acute sense of not having the right to make mistakes in a situation that should be manageable, is particularly relevant for cancers with good prognosis. Such cases tend to reinforce an individual experience-based perception of risk favoring the prescription of chemotherapy and, consequently, to widen the gap with statistical evidences. Finally, several clinicians reported their experience of highly contrasted patient attitudes towards chemotherapy – "*You have people who tell you: "As for me, there is no way that I am going to want this, I do not want to lose my hair"; and others tell you, "I have three kids to raise, so get me out of this situation", and if this means walking all the way to the Mecca, they will go.*", an oncologist reported. This variability of the felt experience of disease and of the perception of risk by affected women (Aronowitz 2007), was described as an important element in their assessment of the risk/benefit ratio.

The decision process is also impacted by clinician's critical assessment of statistical evidences produced by clinical trials conducted in experimental settings insufficiently related to the actual conditions of care. An oncologist worried for instance that "*by de-escalating everything, there is a risk of eventually worsening breast cancer prognosis.*" De-escalation here refers to the reduction in treatment to achieve a better equilibrium between curing and iatrogenic effects. The practice concerns chemotherapy but also other treatments such as surgery and radiation therapy, often associated in treatment regimen. The interrogation here is that these regimen contexts may not be

sufficiently accounted for in the trials that produced the statistical evidence supposed to guide chemotherapy prescriptions.

Today, the decision to prescribe chemotherapy for early phase breast cancer with good prognosis thus relies on an assessment of risk and benefits that is fraught with uncertainties and differential perceptions, highly influenced by local contexts and history. The life of patients is at play. In many ways, it is an uncomfortable decision that creates a need for reinsurance and opens a boulevard for decision making tools, including imperfect biomarkers. We, now, analyse the ways in which the clinicians handle these biomarkers; how they collectively and individually manage their clinical and professional autonomy, in the presence of such imperfect biomarkers.

4.3 Managing clinical autonomy in the presence of imperfect biomarkers

In all the guidelines and recommendations mentioned by our interviewees, biomarkers information only enter the decision process, when the clinical and pathological parameters are not sufficient to justify the treatment decision. The professional regulation of biomarkers thus gives priority to the clinic. When the risk of relapse estimated on the basis of the clinical and pathological parameters is high or, conversely, when it is low, the treatment decision rules do not incorporate additional biomarker information. Our interviewees also claimed this approach. "*We do not feel like completely reversing a decision on the sole basis of uPA/PAI-1*", an oncologist noted. Similar usages were reported for Ki-67.

The unique genomic signature routine users had a different vision of the biomarker's role in his introductory presentation. "*What was really striking with OncoTypewas to realize that in situations where we felt fairly confident about the decision, well, the decision resulting from OncoType turned out to be the complete opposite. In such cases, you begin to understand with humility how classic clinical and histological information can be surpasse*d […] *In a pathologist report, there is a very subjective element, that is the pathologist counting this or appreciating that… and now with genomic*

signatures today or next-generation sequencing tomorrow, well it's machines, computers calculating… so in practice there no longer is a human intervention by a pathologist, or at least there is much less". In this enthusiastic vision of genomic technologies, signatures stands as modern, quantitative and consequently more efficient form of biological characterizations, supposed to replace the old preexisting techniques, first and foremost, histopathology. This techno-enthusiasm did, however, not exactly correspond to the practice of the tests he later developed. The oncologist lamented, in particular, the tendency of his colleagues, to extend their use to patients for whom the decision to prescribe chemotherapy could be made on the sole basis of clinical and pathological parameters. The contextualized usage he praised integrated rather than replaced these preexisting technologies, in a mode very similar to that enforced by our other interviewees, with Ki-67 and uPA/PAI-1.

« *There is always a kind of grey zone where, when we ask the question with the classic prognostic factors, the answer is "maybe yes, maybe no, I'm not very sure she needs it", and so in this population it [the biomarker] helps us to switch between "yes chemo" or "no chemo".*"

This oncologist citation is representative of our interviewees reported usage of Ki-67 and uPA/PAI-1. When the clinic and pathological parameters were not sufficiently informative, patients entered what was referred to as "a grey zone" by many clinicians. The biomarker usage then followed specific rules that depended on the test results. Very high levels of Ki-67 - interpreted as clear signals of tumor aggressiveness– or, conversely, very low levels constituted an information deemed robust enough to decide on the treatment, respectively chemotherapy and no chemotherapy. Similar usages were reported for uPA/PAI-1.

Yet, biomarker's usages were much more cautious when results are midrange. As summarized by a cancer center pathologist, "*We thought that by using Ki-67 measurements, the grey zone would disappear, but it is still irrefutably there*". The variations in the regional recommendations mentioning Ki-67 in their decision tree illustrate the uncertainties. In one set of recommendations,

the only Ki-67 levels considered informative are those below 10% or those above 30%, all others being considered insufficient to guide a decision. In another set, all values are deemed informative and the decision depends on whether the Ki-67 is above or below "15 to 20%". In a third set, only Ki-67 levels above 14% are deemed trustworthy. The situation was different for uPA/PAI-1, since none of the users we interviewed discussed the robustness of the test results or the threshold value. All acknowledged its analytical and statistical validity. However, on a finer scale, clinicians reported a variability of practices among centers. "*uPA is not used at the same time, using the same criteria, and we do not get exactly the same thing out of it*", an oncologist pointed out. The availability of a standardized and trusted technology did neither preclude a certain flexibility in the interpretation of biomarkers nor dictated prescription decisions.

"*In fact everything cannot be solved so easily, especially in the breast. There are so many parameters that come into play, and we do not necessarily have weights to apply to each parameter. There is still some unknown, and we still need to discuss, we are happy to be together to discuss, not all cases of course, but there is still a fringe of the population that is problematic. 20-25 %.*"

As described in many similar contexts, collective bodies have a pivotal role in the regulation of such uncertainties. In these "multidisciplinary team meetings" (MTM), the biomarker information is articulated with clinic and pathological parameters and a collective work is conducted to justify the relative importance given to each parameter in the decision. This relative weighting of highly heterogeneous evidences is a matter of intense negotiations. An oncologist lamented what he called the "*scenario of the worst*": "*I erase everything that is positive and I only consider the negative factor. This leads every week, in staff meeting, to "Oh but she's 38". So because she's 38 we should forget about all the positive information and opt for chemotherapy?*". Interestingly, in this collective space, the exchanges focus on the contextualisation of biomarker results by clinical parameters rather than on their biological or technological dimensions. "*Oh no, we don't discuss this. 13,9 is below 14. But, we'll discuss if there is a comorbidity that really makes the risks still significant*", an oncologist

reported. When a biomarker value is not unanimously recognized as informative, the clinical conversations resume. The collective work thus legitimates the priority given to clinical factors over biomarkers in the making of the decision. It can also legitimate the patient preference.

"*In the staff we say "well, really talk to the patient again because we're borderline", […] What I want from the patient is for her to say "I'll do anything, I'm so scared, do me a chemo", or "it's ridiculous, what's your improvement percentage? " […] we have international recommendations, but when it's borderline like that, that's it, this discussion with the patient is important.*"

This collective ability to subordinate the technology to the clinic and the patient's perception is judged very favourably by the most expert clinicians. These zones of irreducible uncertainty are praised as areas where they can exercise their autonomous clinical judgement. As stated by a cancer center oncologist, "*It is one of the rare professions where the human relationship is more important. After all, we are not technicians, we touch upon a very particular thing which is death, permanently, that's how I live it*". The situation is more complicated for the less expert clinicians. In a context of strong professional regulation, receiving a MTM recommendation that invites them to rely on a discussion with the patient is a major source of discomfort. The complexity of the decision-making process and the difficulty for these clinicians to properly evaluate all the elements that motivate the collective decision, and in particular the relative importance given to biomarkers, strongly constrain their ability to feel entitled to exercise their autonomous clinical judgment in these situations.

This professional control of the remaining uncertainties associated with biomarkers, goes along a reassertion of the internal professional hierarchy, as illustrated by the perception of genomic signatures' future of some expert clinicians. « *The main concern with genomic signatures is the level of discussion at which they will be considered. Will the MTM lose its legitimacy because the data will be considered as sufficient? Or, and this is by far the most likely, will it discuss the weights associated with these new biomarkers in the same way than with the older ones?"* In the words of this oncologist, the key issue is that the aggressive commercial strategies of the firms, combined with a

highly stabilized technology adapted to the technical and organizational constraints even in less integrated and specialized centers, could lead less expert clinicians to miss the imperfections of these biomarkers and to bypass the collective control on prescription. Interestingly, a cancer center included in our sample has set up a protocol according to which the ordering of a genomic signature test can only be made by the MTM, after a collective reviewing of the pathological, biological and clinical parameters. This defence of the professional autonomy goes along a clear reduction of the clinical autonomy extended to the prescription of the test.

5 Conclusion

In many ways, the decision to prescribe chemotherapy for early phase breast cancer with good prognosis is an uncomfortable decision, fraught with uncertainties and differential perceptions, highly influenced by local contexts and history. This situation creates a need for reinsurance and opens a boulevard for decision making tools. Biomarkers able to reduce all the uncertainties are sought more than dreaded by clinicians.

In this study, we show that such ideal tools are unavailable and that this fact is acknowledged by the profession as a whole and by many clinicians. Rather than precluding their usage, the imperfection of existing biomarkers is controlled by the profession, through their integration as additional and locally useful tools in the decision process.

If a certain techno-optimism contributes to their diffusion, our case study highlights the particular importance of local material, organizational and financial dimensions, culturally situated practices and regulations in the trajectory of such imperfects biomarkers. Further, in the absence of unanimously trusted and collectively enforced statistical evidences, biological rationales although central in the legitimacy of *bio*markers regarding others decision making tools, tend to be mobilized with a certain flexibility.

In this French case study, the regulation of uncertainties associated with these imperfections is mainly organized at the professional level. Guidelines and collective multidisciplinary team meetings constitute the two dispositifs through which the important collective work required to articulate the series of heterogeneous bioclinical evidences available, is performed. By replacing the biomarkers in their wider clinic and pathological context, the profession enforces its autonomy.

The identification of individual cases for which uncertainty is collectively tagged as irreducible is diversely appreciated by the individual clinicians. The most expert ones praised them as a space for clinical autonomy where their clinical skills are the only legitimate option to make the treatment decisions. The biomarker imperfection sounds as a new tone in the defense of this "*incommunicable knowledge*", introduced by Christopher Lawrence to describe the relationship between science, technology and clinical art at the turn of the 19th century in Britain (Lawrence 1985).

The situation is less comfortable for non-expert clinicians, torn between professional rules produced by an internal hierarchy, that biomarkers have made stronger, and patient preferences. In this alliance between biomarkers and experts, the clinical autonomy of the most generalists tends to be the price for the professional autonomy.

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Table 1. Demographic and professional characteristics of the participants (N= 32)

Characteristics	N	%
Age:		
<40	3	9
40-50	11	34
50-65	15	47
> 65	3	9
Gender:		
Male	22	69
Female	10	31
Healthcare professional:		
Oncologists	20	63
Surgeons	5	16
Pathologists	3	9
Biologists	2	6
Heads of biotechnological companies	2	6