



Mapping ethical and social aspects of cancer biomarkers

Anne Blanchard^{a,b,*}

^a Centre for the Study of the Sciences and the Humanities, University of Bergen, Allegaten 34, 5020 Bergen, Norway

^b Centre for Cancer Biomarkers, Jonas Lies vei 87, 5021 Bergen, Norway

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ABSTRACT

Cancer biomarkers represent a revolutionary advance toward personalised cancer treatment, promising therapies that are tailored to subgroups of patients sharing similar generic traits. Notwithstanding the optimism driving this development, biomarkers also present an array of social and ethical questions, as witnessed in sporadic debates across different literatures. This review article seeks to consolidate these debates in a mapping of the complex terrain of ethical and social aspects of cancer biomarker research. This mapping was undertaken from the vantage point offered by a working cancer biomarker research centre called the Centre for Cancer Biomarkers (CCBIO) in Norway, according to a dialectic move between the literature and discussions with researchers and practitioners in the laboratory. Starting in the lab, we found that, with the exception of some classical bioethical dilemmas, researchers regarded many issues relative to the *ethos* of the biomarker community; how the complexity and uncertainty characterising biomarker research influence their scientific norms of quality. Such challenges to the *ethos* of cancer research remain largely implicit, outside the scope of formal bioethical enquiry, yet form the basis for other social and ethical issues. Indeed, looking out from the lab we see how questions of complexity, uncertainty and quality contribute to debates around social and global justice; undermining policies for the prioritisation of care, framing the stratification of those patients worthy of treatment, and limiting global access to this highly sophisticated research. We go on to discuss biomarker research within the culturally-constructed ‘war on cancer’ and highlight an important tension between the expectations of ‘magic bullets’ and the complexity and uncertainty faced in the lab. We conclude by arguing, with researchers in the CCBIO, for greater reflexivity and humility in cancer biomarker research and policy.

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1. Introduction

Cancer research has witnessed important developments over the last two decades towards personalised medicine, which aims to tailor cancer treatments to subgroups of patients sharing similar genetic traits. Biomarkers have been an important tool in this transition, and are often presented as a revolutionary new technology used for patient assessment to help determine predispositions to particular types of cancer, to screen and diagnose cancer types and stages, to estimate the disease prognosis, to predict the most effective course of treatment, and to monitor cancer recurrence [1]. There is a noticeable techno-optimism regarding cancer biomarkers, especially in policy reports where they are anticipated to facilitate a higher-quality, safer and

more efficient treatment of cancer while decreasing health care costs [2–4].

However, as for many revolutionary new technologies, biomarkers bring with them a host of ethical and social considerations. This has seen a small but growing body of literature addressing some of these particular issues, ranging across different disciplines including health economics and policy (see e.g. [5,6]), bioethics (see e.g. [7]), and philosophy of medicine (see e.g. [8,9]). Arguably, the cross-disciplinary nature of these issues has led to a fragmented literature, without an overview of this complex ethical and social terrain. We seek to contribute to the literature through a mapping of this terrain, and the interrelatedness of the ethical and social issues in it.

Another contribution of this paper is that it takes its point of departure in the ethical concerns and issues of scientific quality met in the cancer biomarker lab. This anchors the mapping of ethical and social aspects of cancer biomarkers in their laboratory context; while also providing practitioners and researchers working in the field a legitimate guide for their personal reflections on the ethical aspects and scientific norms of their everyday work.

* Corresponding author at: Centre for the Study of the Sciences and the Humanities, Allegaten 34, 5020 Bergen, Norway.

E-mail address: anne.blanchard@uib.no (A. Blanchard).

The mapping presenting in this paper therefore stems both from discussions within a working cancer biomarker research centre called the Centre for Cancer Biomarkers (CCBIO), in Bergen, Norway; and the cross-disciplinary literature. The author has been eliciting reflections among CCBIO researchers on the ethical and social aspects of their work, from the lab looking out; these reflections being triggered by some key themes in the literature. At the same time, the diverse considerations raised by CCBIO researchers have in turn framed the literature review. In this way, the review emerged from a dialectic move between literature and practice.

This paper explores the social and ethical issues that have been formulated through the practice-literature interaction, and highlights the interrelatedness of these issues. Here, we explore social issues both in terms of those faced in wider society, and more specifically those faced by the scientific community exploring biomarkers; what can be considered as the *ethos*, or norms, shaping that community. The exploration will be structured around three clusters. After elements of background and method in Section 2, Section 3 explores issues related to the ethos of science and ethical concerns met in the lab. Beginning from these issues of the ethics and ethos of science, Section 4 explores the ethical aspects of cancer biomarkers in a context of social and global justice, while Section 5 focuses on the social aspects of cancer biomarkers, in particular the cultural meanings of cancer. Finally, Section 6 concludes by arguing that the complexities, uncertainties and questions of scientific quality surrounding biomarker research demand humility and reflexivity, both in the lab and in policy-making.

2. Background and method

2.1. From blockbuster drugs to personalised medicine

In the last two decades, cancer research and care has been undergoing important changes as a result of an increased awareness of the complexity and heterogeneity of cancer (see e.g. Nature's special issue [10]). Traditional forms of cancer therapy associated with 'blockbuster' chemotherapy drugs have been increasingly criticised for leading to under- or over-treatment of patients, with a higher risk of adverse and sometimes lethal side-effects [11]. This 'one-size-fits-all' approach does not account for the heterogeneity within the primary tumour (intratumoural heterogeneity), between the primary tumour and metastases (intertumoural heterogeneity), or between cancer patients (intra-patient heterogeneity) [12]. In response, an expanding body of literature from the biomedical sciences (see e.g. [11,13]) has put forward 'personalised' or 'tailored' medicine as an alternative model for cancer research and care. Personalised medicine aims to adapt cancer treatments to sub-groups of patients who share similar genetic traits and tumour characteristics, and to provide patients with the right drug, at the right time and dose [11].

One clinical way of implementing personalised medicine is through cancer biomarkers. Biomarkers are substances or processes found in patients' tissues, blood or other body fluids, which indicate the presence of cancer in the body. According to Mishra and Verma [14], biomarkers can either be a molecule (like a protein or an antibody) secreted by a tumour, or a specific response of the body to the presence of cancer, such as biochemical changes like gene expressions and mutations. In a metaphorical way, cancer biomarkers are the 'fingerprints' of different tumours, and can help stratify patients according to their genetics and tumour characteristics. Research on cancer biomarkers is in its infancy, and so far only a few biomarkers have entered clinical practice. One successful cancer biomarker is the protein HER-2, which is overexpressed in about 20–25% of women with breast cancer,

indicating that they have higher chances to react well to the drug trastuzumab. Another example is the normal (non-mutated) KRAS gene, present in about 60% of patients with metastatic colorectal cancer, that indicates that only these patients are likely to respond to the drugs cetuximab and panitumumab.

Cancer biomarkers offer the promise of treatments that are both more efficient and safer for the patients, and cheaper than traditional cancer therapies in the long run, considering technological advances and reduced harmful side-effects in the patients. Biomarkers are thus a source of hope for cancer patients and medical practitioners alike, and have increasingly received both considerable political attention and public funding, including in Norway.

2.2. The Centre for Cancer Biomarkers (CCBIO) and integrated ELSA research

The Centre for Cancer Biomarkers (CCBIO) is a research centre based in Bergen, Norway. It aims to improve biological understanding, early diagnosis and treatment of cancer by using novel biomarkers. It was funded in 2013 by the Research Council of Norway for a period up to ten years, and received the status of Norwegian Centre of Excellence. Based at the University of Bergen, with most activities taking place at the Faculty of Medicine and Dentistry, the CCBIO consists of nine principal investigators and gather in total about 140 people including medical researchers, clinicians, bioinformatics researchers, economists and social scientists. Research activities are organised around three core programmes: pre-clinical studies, clinical studies and biomarkers. To integrate the three programmes, specific research projects have been initiated at CCBIO, that look for instance at the tumour-microenvironment interactions or at the discovery and validation of cancer biomarkers.

One particular characteristic of CCBIO is that it has integrated the study of the ethical, legal and social aspects of its research; also known as ELSA research. ELSA research looks at the ethical, legal and social aspects around emerging technologies in the various fields of biotechnology, nanotechnology or biomedicine. 'Integrated ELSA' in particular encourages a dialogue between the ELSA researchers and the researchers developing the new technology under scrutiny. The ethical, legal and social questions are identified in close cooperation, so that they can be reflexively discussed and integrated to the research process at an early stage, thus encouraging reflections about scientific responsibility [15]. Concretely for CCBIO, this means that alongside its three core research programmes, it also has an ELSA team, led by a Professor in philosophy of science, working with a post-doctoral researcher, myself as the author of the paper with a background in Science and Technology Studies, and a part-time research assistant. The ELSA team looks mainly at the ethical and social considerations around cancer biomarkers, and does so in an integrated way with the cancer biomarker researchers. This is why the mapping in this paper takes its point of departure in the ethical and social concerns met in the lab, to then look out to broader, ethical and social aspects of cancer biomarkers.

2.3. Method and purpose for the mapping

Mapping the terrain of the ethical and social aspects of cancer biomarkers was the starting point to the integrated ELSA research in CCBIO. The ELSA team first teased out key ethical and social considerations around cancer biomarkers from the cross-disciplinary literature, and presented these key themes to CCBIO researchers to help trigger their own reflections and discussions. Our interactions mainly took place during bimonthly junior scientist seminars, CCBIO's annual symposia and during a PhD

course organised by our ELSA team. There were also frequent informal discussions between the CCBIO junior researchers and myself.

Second, on the basis of the interest triggered by these interactions, I undertook during the period of June to October 2014, a set of 15 informal one-hour discussions across CCBIO's various research programmes, including biomarker research for melanoma, breast and gynaecologic cancers, and spanning early career scientists (PhDs and post-docs) to senior scientists (researchers and clinicians) (see [Table 1](#)). The discussions were not recorded as they were informal, but extensive notes were taken and the quotes of the CCBIO researchers that figure in this paper were all approved by their authors. These discussions introduced me to the ethical and social concerns met in the lab, with a particular focus on questions of complexity, uncertainty and quality in research on cancer biomarkers. The output of the discussions in turn helped steer and frame the mapping of ethical and social aspects around cancer biomarkers presented in this paper. This integrated ELSA approach has allowed us to achieve a more contextualised and comprehensive mapping, that can be seen as a legitimate guide for researchers and practitioners in the field of cancer biomarkers to further reflect on the social and ethical concerns they meet in their everyday work.

3. Ethics and ethos in the lab

One cluster of issues relates to the conduct of science itself; what could broadly be discussed as the ethics and ethos of scientific research. In the lab, the investigation into the social and ethical issues of cancer biomarkers came to focus on the norms that shape this scientific community, particularly relative to notions of complexity, uncertainty and quality, while not dismissing the ethical character of these norms. As a new field, biomarker research explicitly tries to address cancer as heterogeneous, and therefore highly complex; introducing significant attendant uncertainties. These uncertainties have implications for the norms by which this scientific community judges the quality of their research, and its ethical conduct. As a biomarker researcher, navigating within these uncertainties means to carefully examine the research assumptions, method and objectives. Are the research assumptions not too simplistic with regard to the complex biology of cancer? Is the research method transparent about its limitations in the face of non-linear systems? Are the research objectives feasible, and how will research results contribute to the field and to society at large, knowing that they will be surrounded by significant uncertainties? As we see in this section, it is crucial for researchers and practitioners of the field to be critical and transparent about their ways of working with uncertainties, as this impacts the quality and relevance of research results, and puts into question whether investing in research on cancer biomarkers is a good use of public money. Indeed, the plasticity and heterogeneity of tumour cells make it very difficult for biomarkers to find a clinical application (see e.g. [\[16,17\]](#)). CCBIO

researchers have reflected upon these questions and have raised four concerns related to the quality and ethical conduct of their science, discussed in this section in the light of the literature.

3.1. The problem of reproducibility

Taking the complexity and heterogeneity of cancer and its associated uncertainties as a point of departure, a first family of issues related to the ethics and ethos of science is the difficulty to reproduce scientific experiments and results in cancer biomarker research.

3.1.1. Lack of standardised methods

A first barrier to reproducibility is the fact that research routines, quality standards and technologies available change from a laboratory to another. Informant A states: "In biomarker studies on the same biomarker, there is often a lack of standardised methods for measuring the biomarker under study. The importance of assay development is maybe underestimated in biomarker development." This concern is echoed in the literature, with Mishra and Verma [\[14\]](#) pointing at the non-uniform preparation and storage of cancer samples across laboratories, and Allison [\[18\]](#) arguing that different laboratories may have different quality standards.

3.1.2. Limited quality and availability of tumour samples

A second barrier to reproducibility is the quality and availability of tumour samples used for research. Tumour tissues that are collected as part of diagnostic routines are preserved in formalin before they are embedded in paraffin blocks and stored. Additional tissues are sometimes collected solely for research purposes, and conserved as fresh frozen tissue. But these samples used for research only are sparse as their storage needs to be organised in research biobanks and requires informed consent. Further, there are also practical issues to sampling for research purposes: it has to be organised without disturbing clinical standard procedures and, depending on the localisation of the lesion, it can be challenging to obtain a sufficient amount of tissue. As Informant B explains: "As researcher, I am fully aware of the fact that the clinicians need to ensure that sufficient tissue is available for optimal diagnosis for treatment planning. Therefore, the use of tissue for diagnostic purposes has the highest priority to benefit the patient. Only if feasible and considered completely safe for the patient, can researchers use snap-frozen tumour tissue for molecular and genomic studies. For instance in cervical cancer, some tumours are too small to allow clinicians to collect snap-frozen tissue for research purposes." The problem with paraffin-embedded tissues, however, is that they are manipulated and contaminated by the paraffin and formalin. This concern of limited quality and availability of samples for research is found in the literature, particularly the slow enrolment of patients and hence the lack of fresh tissue samples for cancer research (see e.g. [\[19\]](#)).

Table 1

The CCBIO informants quoted in this paper.

Informant A	Post-doctoral researcher working on breast cancer
Informant B	PhD candidate working on gynaecologic cancer
Informant C	Post-doctoral researcher working on breast cancer
Informant D	Post-doctoral researcher working on transcapillary exchanges
Informant E	PhD candidate working on melanoma
Informant F	Researcher working on gynaecologic cancer
Informant G	Clinician part of the CCBIO network
Informants H and I	Two PhD candidates working on breast and endometrial cancer
Informant J	PhD candidate working on melanoma
Informant K	Post-doctoral researcher working on transcapillary exchanges

3.1.3. Representativity of tumour samples

A third barrier to reproducibility is the representativity of the tumour samples used for biomarker research. It is indeed difficult to collect samples that account for the intratumoural heterogeneity, as recalled by Informant B: “The specimens sampled for molecular and genomic studies are collected based on a macroscopic assessment by the responsible surgeon. These samples are not used before the routine diagnosis has been secured by the team of pathologists and discussed with the clinicians. Even if we aim to study representative tumour areas, heterogeneity may introduce bias. It is after all only a small part of the tumour that may be explored, and this part may not reflect all parts of the entire tumour.” Bearing in mind that tissue samples might not account for intratumoural heterogeneity, and considering as well the heterogeneity of tumours between patients, we quickly realise the difficulty to replicate research results and to validate conclusions for clinical practice.

3.1.4. Environmental sensitivity in pre-clinical models

A fourth barrier to reproducibility raised by CCBIO researchers concerns pre-clinical models, and in particular the environmental sensitivity of the mice's biological traits. Studies by Prinz et al. [20] and Begley and Ellis [21] show that despite careful and systematic approaches to reproduce results from landmark pre-clinical studies, with “the same laboratory, the same people, the same tools and the same assays, with experiments separated by 5 months”, there were important differences in the results. For instance, the Amgen scientists in the study of Begley and Ellis [21] were able to reproduce results of only 6 pre-clinical studies out of the 53 they emulated. This is in part explained by the mice's sensitivity to the environment, which means that different experimental conditions, such as different labs, may lead to different results. Furthermore, as explained by Informant C: “Even in a group of mice born of the same womb from the same pregnancy, and living in the same cage, the results of a particular experiment would vary within that group; potentially because inbred mice are not always identical like the cloned ones.”

3.1.5. Publication bias towards positive results

Finally, a fifth barrier to reproducibility is found in the very competitive climate in the field of cancer research. Many in CCBIO researchers recognise the pressure to publish positive results, as they are more easily accepted into highly ranked journals. In the literature, the bias towards publishing positive results in the medical sciences is also discussed, with for instance, Yaqub [22] revealing that about half of all clinical trials undertaken in the USA are not being published. This is both due to the publication bias towards positive results, as well as to the intense competition in cancer research that can lead to “negligence over the control or reporting of experimental conditions” [20]. In addition to making it very difficult to reproduce results, this creates an illusion that the biology behind the results is less complex and more certain than it actually is. The problem of ‘anchoring’ reinforces this bias; it is indeed relatively difficult to publish “results that contradict data from high-impact journals or the currently established scientific opinion in a given field” [20]. In response to this pressure to publish positive results, scholars argue for more opportunities to present negative data, in articles and at conferences for instance, and state that publication institutions should encourage the sharing of imperfect, complex and non-linear results [21].

3.2. Reducing complexity

Recognising the heterogeneity of cancer, a second family of issues related to the ethos and ethics of science concerns the necessary reduction of complexity when undertaking cancer

biomarker research. This reduction of complexity is especially noticeable in mouse models, but also appears in the concept of biomarker itself.

3.2.1. Mice are not men

Mouse models are used for cancer biomarker research at the pre-clinical level. Mice comprise a simple model in which a scientific hypothesis can be tested under conditions where the known variables of the experiment can be controlled. The mice share the same genetic background and only ones of the same weight, age and gender are employed in a particular experiment. The mice are bred and maintained under the same conditions (temperature, food, etc.). Informant D explains that researchers want the variations of the genome to be minimal in mice, as working with all the variables found in real animals would make it impossible to arrive at, and repeat, certain observations. However, as lab mice are simpler than humans and do not reflect genetic variability, we can wonder whether the results are still valid for higher levels of complexity. Another issue related to the ethics and ethos of science raised by Informant D is the relevance of subcutaneous models, which are the most common pre-clinical models in cancer research. In these models, the tumour is injected under the skin of the mouse, to evaluate the spread of the tumour over time. However, this is different to a tumour that grows in an organ: in patients, the microenvironment influences the way the tumour develops and how it spreads. It is thus difficult to interpret results from subcutaneous models. Concerns around the relevance of mouse models are also raised in the literature, with Strand [23] asking whether it is possible to justify the biological relevance of knowledge obtained under artificial conditions, and a recent study by Seok et al. [24] claiming that the genomic responses in mouse models poorly mimic human inflammatory diseases like cancer. The literature has also plenty of examples showing the non-linearity and emergent properties between pre-clinical and clinical studies. Among them, the striking 2006 case of the antibody TGN1412, tested in phase I trials on six human volunteers at a dose that was 500 times lower than the dose proven safe in several pre-clinical studies. Soon after being given the dose, all six volunteers “faced life-threatening conditions involving multi-organ failure for which they were moved to intensive care units” [25]. This implies that ensuring the reproducibility of results in the lab does not necessarily mean that these results will be successfully translated into clinical studies. To prevent disasters like in the TGN1412 trial, measures like Informant A suggests for trial design could be taken: “Clinical studies should have a more adaptive design, allowing for changes in the course of the trial, as new knowledge comes in or unexpected effects are experienced. As always, patient safety has top priority.”

3.2.2. Evaluation of biomarkers by immunohistochemistry

Evaluating the presence of cancer biomarkers in tissues is often done by immunohistochemistry, which, put very simply, is a process to detect biomarkers in a tissue sample by staining them. It is then possible to evaluate the cancer biomarker's ‘expression’, which is the protein expression in the tissue, on a scale from 0 (negative) to 3+ (strongly positive) (see for instance the scoring guidelines for the HER2 biomarkers [26]). However, it is difficult to rate ambiguous results on this simple scale, and Informant E argues: “The problem is that the grading from 0 to 3 of the protein expression in the light microscope is semi-objective. People may give different numbers for the same sample.” Further, like evaluating the intensity of a colour on a tissue sample, assessing the difference between “a faint/barely perceptible membrane staining” (which is 1+ on the scale) and “a weak membrane staining” (which is the lower end of 2+ on the scale) is also subjective. This discussion would not bear significant importance if

it did not have clinical consequences. But it has: according to the score in the tissue sample, patients will be offered more or less aggressive drugs, or no treatment at all. This ethical concern of where to place the cut-off was first coined by Callahan [27] under the label of ‘ragged edges’, and then taken up by Fleck (see for instance [8]). According to the latter, there is no clear, well-defined line between strong responders and non-responders; rather, there is a continuum of responses, which means that those who are on the ragged edge will ‘fall off’ and not get access to the treatment. We discuss in Section 4 the ethical concerns associated with ragged edges in a context of health care rationing.

3.2.3. Mismatch between simple biomarkers and complex biology

Biomarkers try to indicate whether a patient is likely to develop cancer, will benefit from a particular treatment, or is at risk of relapsing. An iconic biomarker that is frequently referred to is the protein HER2, for breast cancer. From the discovery of HER2 in 1982, to the cloning of the HER2 gene, its testing in Phase I to III trials, the creation of the companion test, and the approval of the drug, Herceptin, in 1998, only 16 years passed [28]. However, such success stories are rare in cancer biomarker history. As Informant A observes: “There is a mismatch between simple, linear biomarkers and the heterogeneity and complexity of tumours. Such ideal biomarkers do not fit the complexity of human biology.” This is confirmed by Informant E: “There is a high complexity in cancer, and probably one biomarker is not likely to give you the perfect prediction because so many processes are involved.” The plasticity of tumour cells explains in great part why even the most efficient targeted drugs fail to act as a long lasting cure, and “why even the best personalised approaches mostly delay disease progression but rarely eradicate it” [29]. Against the complexity and heterogeneity of cancer tumours, what then is a good biomarker? Informant A asks: “Is a reliable biomarker measurement of only one protein or several? The mRNA expression of 10 or 100 genes?” We will see in Section 5 that describing biomarkers as simple may give patients the illusion that their cancer type can be neatly categorised, and that choosing a treatment option can be equally straightforward.

3.3. The problem of validation

With the heterogeneity inherent to cancer biology and the subsequent challenges to work with this complexity and reproduce results, it is very difficult to validate cancer biomarkers and put them into clinical practice. There are further barriers to the validation of new cancer biomarkers, as notes Informant A: “Validating a biomarker demands a lot of efforts but it is maybe not seen as innovative enough to be published. Therefore it is easier to jump to research on a new biomarker.” Scholars also underline the lengthiness of the validation process [30,19] and its costs, with Brodniewicz and Gryniewicz [31] arguing that it takes up to one billion US\$ to launch a new drug in the USA. There is also the risk to engage in a validation process for a cancer biomarker that may be too expensive or inconvenient to use, that may lack clinical utility, or even, that may lead to harm through over-treatment [32].

Another barrier to the validation of cancer biomarkers is the lack of dialogue between clinicians and researchers. As Informant F observes: “My job as a researcher is to discover biomarkers and not to check whether they are implemented or not. But clinicians are in contact with patients, so they understand the context of patient care.” Likewise, in the literature, authors encourage greater dialogue between clinicians, researchers and patients in the context of cancer research and care: “Scientists benefit from learning about clinical reality. Physicians need better knowledge of the challenges and limitations of preclinical studies. Both groups benefit from improved understanding of patients’ concerns” [21].

Because of the difficulty to validate cancer biomarkers, less than 1% make it to clinical practice [32]. As we will discuss in Section 4, this poses a question of social justice, in particular whether allocating public money to cancer biomarker research is a fair and wise choice.

3.4. Informed consent, data privacy and incidental findings

A last concern met in the lab, of a more classical bioethical nature, relates to how informed consent forms are collected from cancer patients, and how the digital datasets generated from their samples are managed and protected. Unlike the three previous subsections, this subsection relates less directly to the ethos of the scientific inquiry, but the ethical concerns discussed here are exacerbated by the questions of complexity, uncertainty and quality.

Cancer research is based on the availability of biological samples, and demands that in addition to the samples collected for diagnostic purposes, supplementary samples are taken for research purposes. To ensure a responsible and ethical collection of samples for research purposes, patients receive an informed consent sheet, including information on the purpose of the research and its potential benefits (making clear that these will likely to go to future patients). But even if patients can withdraw their consent at any time, and even if refusing to give their consent in the first place has no impact on the way they are treated, Informant G wonders: “We are very aware of the fact that patients are vulnerable at the time when we need to collect their informed consent. They are newly diagnosed with cancer, and our experience is that most are willing to contribute to research. It is important that they have easy access to withdraw their consent if they change their opinion.” Indeed, there is a relation of dependence between the researchers and the patients, and one must be careful not to “push informed consent onto the patient”.

Another ethical issue concerns new genome sequencing methods and the large amount of genetic data they generate. As Informants H and I note: “We are about to reach the point where whole genome sequencing is becoming a standard in cancer research.” This first poses the problem of incidental findings: when using new genome sequencing methods, incidental findings are more likely to occur. Incidental findings, discovered during the course of a research study, concern a research participant and have potential health or reproductive importance for him, but are beyond the scope of the study [33]. How then to manage such findings? Should the patient know about them, and if yes, under which conditions: if there is an acute and imminent risk of genetic disease? If there is a risk of passing the disease to the next generations? Should the decision be made according to a risk threshold? Second, new genome sequencing methods also pose the question of data privacy. From a single, physical entity, the tumour itself, which is kept in a biobank at the hospital, new genome sequencing methods derive digitalised files containing large datasets. Informants H and I explain: “This raises the question of storage and protection of the material. A physical tumour sample is stored in one location, and can be easily protected, but once sequencing analysis has been performed, the information lying within the tissue is transformed into a readable DNA sequence.” One risk is that these hackeable digital data fall in the hands of employers or insurance companies, who may act counter to the interests of the patient [34].

3.5. In sum: complexity, uncertainty and quality in biomarker research

In moving between the literature and informal discussions with CCBIO researchers, it emerged that most of the social and ethical issues in the lab centre on the ethos of the scientific community,

while also raising some more classical bioethical concerns, like issues of informed consent, data privacy and incidental findings. Essentially, what do the particular complexities and uncertainties surrounding cancer biomarkers imply for scientific norms of quality? We saw that for reasons ranging from technical aspects (for instance the lack of standardised methods across laboratories) to the intrinsic complexity of the biology of cancer (that leads researchers of the field to use simplifying pre-clinical models), it is difficult to reproduce and validate scientific results, and thus to put them into clinical practice. Such issues of quality in cancer biomarker research tend to remain implicit because they are not 'ethical' in the sense that they are not often dealt with by ethical committees or ethical guidelines. However, these issues do have an ethical component in that they underpin more classical ethical debates around prioritisation of care and social and global justice for instance. They also have a social component to the extent that we consider the biomarker community as guided by these norms. Indeed, they are all the more important, and deserving of attention, in that they do not explicitly enter the everyday decisions in the lab, and it is possible to continue producing papers without too much attention to them.

4. Social and global justice

The issues of complexity, uncertainty and quality that are met in the biomarker lab reach out to contribute to broader social and ethical questions. Cancer biomarkers are very high on political agendas and are often described in the media as 'magic bullets' (see e.g. the cover of *Time Magazine* of May 2001, depicting Imatinib pills as 'ammunition' targeting diseased cells). This hype around cancer biomarkers gives a strong incentive for researchers to work within this field, but as noted by Informant A, it is not propitious to critical thinking: "We all run into the mainstream lane of research on biomarkers, and too rarely are we taking distance, thinking outside the box." Arguably, taking the time to think about the broader social aspects of cancer biomarkers in the light of the ethical and quality concerns met in the lab seems necessary. What are the costs of personalised cancer therapies? Who has access to them? Can we, and should we pay for the health care needs of all cancer patients? What about the access of personalised medicine in third world countries? These ethical and social concerns, clustered around the theme of social and global justice, are discussed by CCBIO researchers as well as the literature.

4.1. Prioritising health care

The rationing and allocation of healthcare resources according to priority criteria (in particular the severity of the disease, the effectiveness and the cost of the drug) is inevitable in a context where health care resources, or rather our willingness, as a society, to pay for all the healthcare needs of every citizen, is limited [35]. It is for instance hard to justify paying for a treatment that will allow one individual to live a few weeks longer, while the same amount of money could be spent on the total healthcare fees of one single person for one year. Utilitarian ideals, whereby a moral choice is one that produces the most 'utility', are strongly built into Western health care decision-making processes. Accordingly, health economists assess how many Quality Adjusted Life Years (QALYs) a patient can get through a particular treatment option, and at which cost. These economic tools allow decision-makers to visualise the opportunity costs of their prioritisation choices: if money is allocated to a particular cancer drug, then X number of vaccines, or X number of heart operations will not be funded. These trade-offs allow maintaining the sustainability of health care systems. The question of prioritisation is particularly stringent for cancer for three main reasons.

First, cancer most commonly affects older patients. According to the latest report from the American Cancer Society [36], 78% of all cancers in the US are diagnosed in people above 55 years old, and figures are similar in Norway [37]. Further, the UK Macmillan Cancer Support [38] shows that only 10% of people aged 25–49 years old and less than 2% of people under 25 years old are diagnosed with cancer. In addition, elderly cancer patients are often more vulnerable than younger patients to the toxicity of cancer drugs [39]. This can translate into serious side-effects that will necessitate additional resources to tackle them. Further, these costs may later multiply where ex-cancer patients develop other age-related diseases, like dementia, requiring specific health resources and care [8].

The second reason why prioritisation questions are particularly stringent for cancer is the high costs of therapies, especially personalised therapies. The targeted cancer therapies that are approved by the American Food and Drug Administration, cost between US\$ 70,000 and US\$ 130,000 for a course of treatment [40]. In Norway, Informant J explains that the new targeted therapy for aggressive melanoma with the drug Vermurafenib "offers a median progression free survival of 6–7 months, for a cost of 21800 NOK [about US\$ 2600] per week." These costs are significant, and examples from the literature emphasise the need to ration the access to personalised therapies in order to keep a sustainable health care system. Fojo and Grady [41] show that keeping a patient with epithelial lung cancer alive for one year costs US\$ 800,000; which, when extrapolated to all the Americans who die from cancer each year, would bring the costs to US\$ 440 billion per year. Jackson and Sood [42] look at how one year of treatment with Bevacizumab, costing around US\$ 50,000, corresponds to the median household income in the US in 2008.

Third, what adds further heat to the questions of prioritisation of care is the fact that several studies show that the expensive cancer therapies only yield a few weeks to a few months of survival (see e.g. [42,43]). Considering the cost of the therapies and the age and vulnerability of the patients, this poses the question whether public money dedicated to targeted cancer therapies could be better allocated to other health care needs, where it would buy more high-quality life years at a lower cost [40].

However, prioritisation of care is not only based on utilitarian criteria, but also on considerations of fairness and compassion. As Informant J argues: "Even if the price for Vermurafenib is high, it is a revolutionary therapy because before that, nothing existed for these patients who wanted and needed a therapy." Justice as fairness is what we turn to in the following section.

4.2. Social justice and fairness

In parallel with debates on how to prioritise health care resources in an efficient way, emerge debates of just and fair access to cancer therapies. Arguably, personalised cancer therapies can lead to the stratification of society along three axes.

Firstly, and related to the debate on prioritisation of health care, personalised therapies are mainly targeted at and benefiting older patients, most of them above 55 years old. This constitutes a powerful group in society, who is vocal in the media, recounting their life with cancer, their struggles, their hopes and despair. Such stories are part of a powerful discourse, what Brekke and Sirnes [44] term the 'sovereignty of suffering', and bear a lot of weight in decision-making processes, as we will see in Section 5. But are elderly cancer patients sometimes over-shadowing less powerful and visible patients? Are their needs prioritised over other, younger patients' needs?

Secondly, personalised cancer therapies can exacerbate gaps between the wealthy or well-insured, and poorer or less well-insured cancer suffers. Targeted cancer therapies could potentially

add billions of dollars per year to the cost of public health care in the USA and in Europe, a burden that will need to be met by increased taxes or privatisation through the insurance sector. As Fleck [8] notes: “The well insured will increasingly resist paying such taxes because they would not see themselves as beneficiaries of those programs.” However, it is not even sure whether private or public insurers will be able to reimburse these costs [45]. Insurers facing these costs in the USA have begun off-loading the expenses onto patients, with an estimated of 62% of all personal bankruptcies attributable to medical costs, principally cancer [42]. This all amounts to personalised cancer therapies being solely accessible to the wealthy.

The third axis relates less to the age or financial status of patients, and more with how patients are technically stratified in the lab. As we saw in Section 3.2, classifying cancer patients with biomarkers into categories of strong, weak or non-responders is not straightforward. Fleck [8] argues that the “clinical reality in metastatic cancer is most often a continuum of responses from weak to strong”. In this case, where do we draw the cut-off line between those who will be granted access to the newest personalised cancer therapy, and those who won't; those along the ragged edge? Callahan [27], who first coined the concept of ragged edge, argues that wherever we draw the line, there will always be people on the other side; and we should try and accept to live with ragged edges: “We can accept [the ragged edge], not because we lack sympathy for those on it, but because we know that, once a ragged edge is defeated, we will then simply move on to still another ragged edge, with new victims – and there will always be new victims.”

Personalised cancer medicine may provoke inequalities of access: mainly for older, richer patients who are lucky enough to be assigned to the ‘safe’ side of the clinical cut-off. It is possible to argue that money invested in other diseases or in younger patients would be a fairer use of healthcare resources. However, cancer patients, whatever their age or social status, are faced with the prospect of a terminal outcome. Targeted therapies often represent their last chance of survival, and arguably they deserve compassion [40]. Balancing compassion and the fair allocation of health resources is difficult, and demands, as we will see in Section 4.4, some human judgement and debates on what it is to be a fair and caring society.

4.3. *Global justice*

The two debates around the prioritisation of health care and the fair access to health care resources take a particular character when they zoom out from focussing on one developed country context to consider questions of global justice.

The utilitarian debates around the distribution of scarce health resources at the global scale have been phrased by some scholars in terms of ‘global availability’, or “the problem of incentivising new medicines for diseases that afflict primarily or exclusively the developing world” [46]. These scholars argue that global health systems are organised such that financial incentives privilege diseases more prevalent in the developed world: “drugs are not developed for the health needs of the poor because incentives for pharmaceutical innovation are built around patients’ ability to pay” [47]. For example, according to Trouiller and Olliaro [48], of the 1223 new drugs that were sold worldwide during 1975–1996, less than 1% tackled tropical diseases. More recent numbers indicate that 100 million dollars per year worldwide are spent on tropical disease research versus over 3 billion dollars per year in the US alone for cancer research [49] (see also [50]).

In a context of global justice, the debate about fair access to personalised medicine is shifted from the access between the well-insured and the others, to the developed and developing countries.

Expensive personalised cancer therapies pose questions of ‘global access’, or “the problem of ensuring that the poor can obtain medicines that already exist” [46]. According to a 2009 report from the United Nations, about two billion people do not have access to essential medicines, and “improving access to medicines could save 10 million lives a year” [51]. As noted by Informant K, most cancer biomarkers are not simple, and they therefore cannot be easily used in clinical practice in the third world, because of their high costs and the sophisticated technologies they require for their implementation.

4.4. *In sum: issues in the lab contributing to global debates*

We can see how issues of complexity, uncertainty and quality in the biomarker lab can contribute to debates around social and global justice for cancer research and care. Looking at the prioritisation of care, framed by policy-makers in terms of the severity of the disease, the effectiveness and the cost of the drug, we see how the complexities and uncertainties in the lab can act to undermine this prioritisation process. The QALY system is based on an instrumental rationale, predicated on clear causation and a certainty of outcomes; it is difficult to weigh up alternative options for medical spending when it is not clear what will come of this spending. Looking to social justice and fairness, we see how some scholars have framed this debate around stratification; elevating the powerful group of older patients exercising their sovereignty of suffering, and driving wedges between those who can afford treatment and those who cannot. Questions of complexity, uncertainty and quality in the lab also act to formalise (and normalise) this stratification relative to how the ‘ragged edge’ is drawn between patients who will or will not respond to treatment. Finally, issues of global justice are often framed relative to global availability and access. Scholars discuss this availability and access as limited by pharmaceutical business models, the powerful voice of the developed country patients, but also by the complexity, uncertainties and issues of quality in the lab. As noted by Informant K, research on cancer biomarkers demands sophisticated equipment and a depth of expertise that cannot be readily set up via a simple technology transfer.

In the light of these social and global justice debates, many CCBIO researchers agree that it is important to question the extent to which their work influences the fairness and sustainability of health systems. Fleck [52] encourages medical students to engage in health policy debates, otherwise “political interests or economic interests will dominate and potentially corrupt the values that are supposed to be central to the practice of medicine”. Issues around social and global justice indeed benefit from the participation of cancer researchers in democratic deliberations. However, one should not consider these deliberations or increased training for medical students as ways to arrive at a clean answer. For complex health justice questions, characterised by ragged edges, there is no one technical ‘formula’ to provide us with clear answers. Callahan [27] believes it is rather a question of human judgement; where the ‘reasonable’, ‘sensible’ and ‘prudent’ standards that society decides to live by, have to be discussed.

5. The cultural meaning of cancer

This section takes a critical perspective on the importance of cancer research in Western societies. The social constructions of cancer, often seen as an invasive and unfair disease that we ought to control, have influenced the development of cancer research, in particular towards personalised therapies. In turn, personalised cancer research has also influenced the social constructions around cancer, giving the illusory hope that it can be understood, predicted and controlled. This critical section is different to the

ethical and social discussions in Sections 3 and 4, as we here focus on the social and cultural constructions of cancer. These constructions and discourses are important, to the extent that they frame the ethical and social concerns in Sections 3 and 4.

5.1. War spending

We have seen in Section 4.3 on global justice that despite a much lower incidence worldwide, more money is spent on cancer than on tropical diseases. We saw as well that this was in part due to a lack of research and innovation incentives when the patients' ability to pay is low. However, how can we explain that spending on personalised cancer drug in developed countries increases every year by 14% [42], especially considering that most of these drugs only give a few more months of survival? How can we explain that the global market for cancer drugs has reached US\$ 100 billion annually in 2014, and that it is expected to reach up to US\$ 147 billion by 2018 [53]? Is it only because patients, or the country they live in, can afford these expensive therapies? Is it because of the huge hope placed on biomedical research? Is it out of fear, despair or guilt of loosing the 'war against cancer'? Arguably, spending on cancer drugs is high because of all of these reasons and probably others. But one powerful reason is the social construct of cancer: how it is depicted in the media, in movies and in the literature; the place and shape it takes in social narratives and imaginaries. In other words, the metaphors that are used to refer to cancer, and the cultural meaning they lend to this disease. As explained by Helman [54], diseases that are difficult to understand, predict and cure "come to symbolise many of the more general anxieties that some people have, such as a fear of the breakdown of ordered society, of invasion or of divine punishment". As a result, war narratives are often used for describing cancer: 'invasion' and 'battle' were metaphors for cancer and its treatment used by President Nixon in his 1971 declaration of 'War on Cancer' [54]. Another telling example from the 1950s, as Cold War America faced the destruction of its social ideals, shows how cancer embodied these fears: "It was the ultimate emergence of the enemy from within – a marauding cell that crawled out of one's own body and occupied it from the inside, an internal alien" [55]. According to this social construct, war can either be lost or won, and patients are left with only two options: surrender or fight it to the bitter-end.

5.2. Medicalisation

The 'war on cancer' is presented as a noble enterprise; someone who defeats cancer is a survivor who has managed to keep the disease at bay, and someone who has cancer should at least put up a good fight. As Informant G explains: "It is my impression that only a decade ago, chemotherapy was discontinued after a few rounds of treatment. Today, many women and their doctors are willing to try additional rounds of chemotherapy, also in the context of little evidence for clinical benefit. Indeed, there is a literature on practices in the USA where chemotherapy is used right up until the last week of life, when there is limited evidence of benefits to the patient [63]. This introduces concerns around effective and fair use of health resources, as well as the impact of aggressive cancer therapies on the quality of life of patients at the end of life.

Pharmaceutical companies have an interest in reinforcing the social construct of cancer as a monster that we ought to control, as there are important profits to be made in selling screening tests and drugs (see Section 5.1). Via marketing and direct-to-consumer advertising, 'big pharma' contributes to a culture of medicalisation, where illnesses and diseases alike are managed through clinical examinations, screening tests and drugs [49]. Screening tests for estimating healthy patients' risk factors for diseases, in particular cancer, have indeed become an important part of the medical

activity [56]. They are generally depicted as a simple, potentially life-saving action, which might augment the feeling of guilt among society: since it is so easy to undergo screening tests and get checked for a particular cancer biomarker, one has a nearly moral obligation to take them (see the discussion of Sharon Kaufman [64]). However, the associated harmful side effects are not often talked about: the stress caused to patients that are waiting for results [57], the change in self-conception and how others relate to someone who is categorised as being sick, and last but not least, "the harms of false alarms, over-diagnosis, and unnecessary treatment" [58], what Fredriksen [59] also calls 'snowballing medicalisation'. In addition, it is easy to think that biomarker screening tests can disclose everything; but these tests are only looking at a small spot, when countless mechanisms actually enter into play in the development of a cancer tumour.

5.3. Hope

The medicalisation of cancer is not only enforced because of big pharma's influence on the social constructs of cancer. It also stems from a trend towards more mathematical models in biomedicine, as asked by policy-makers, which "implies a focus on simple, controllable and predictable objects" [23]. This gives an illusion that human biology is simpler than it actually is, and gives hope that all cancers might be curable in a near future. It is frequent to read that the ultimate goal of personalised cancer medicine is to one day be able to read and manage the billions of data points for each individual in such way that it will predict any transitions into disease [34], or to one day find solutions to the problem of cancer drug resistance such as identifying the full range of resistance mechanisms [60]. This hope and optimism towards biomedical research brings with it the belief that the needs of every cancer patient can be met if health care is delivered in an efficient way.

Patients' hope, important financial support and new promising research on cancer come together to constitute what Brekke and Sirnes [44] call the 'emerging economy of hope'. This in part unrealistic 'agenda of hope' has not been thoroughly scrutinised and questioned in the light of the ethical dilemmas seen in Sections 3 and 4; rather, it is left unleashed, as "dreams and longing command money, not limits and realism" [27]. In this context, new communities appear, gathering patients hoping for a cure tailored to their own type of cancer, pharmaceutical companies seemingly eager to help these patients, and research groups demanding more means and resources in order to develop these personalised cures [44]. These communities are well connected and informed on the latest scientific advances, and have a powerful voice in policy debates. According to these communities, "there are no inherent obstacles or pitfalls of science that could stop the realisation of revolutionary cures" [44]; rather, it is the politicians that refuse to invest the necessary resources into every type of cancer.

However, the hope and belief that biomedical research, if granted with the necessary means, will one day be able to deliver high-quality personalised cures to every cancer patient, is misguided. As Callahan wrote already in 1990: "We cannot pursue a limitless idea of quality and hope to do so efficiently. We cannot achieve both maximum quality and full equity" [27]. Excessive hope and optimism towards biomedical research leads to a low tolerance for uncertainty and a mismatch between what patients expect in terms of possibility of treatments and what doctors can offer them. As Informant G puts it: "In some patient-doctor relations, it may be a challenge to balance evidence for clinical benefit with unrealistic expectations conveyed in the news, sometimes hyping hopes based on small studies. Also, research on the Internet by the patient and their relatives may contribute to unrealistic expectations. Building mutual trust over time is important in this setting." Acknowledging the randomness of

cancer, our relative powerlessness in its face, and the fact that “adults must accept responsibility for their own situation, no matter how much bad luck they have suffered from” [61], might help reintroduce some human judgement – ‘realism’, ‘reason’, ‘sensitivity’ and ‘prudence’ [27] – into the debates of what we, as a society want from cancer research and care.

5.4. *In sum: waging total war*

We saw in Section 5 how the war on cancer is inspiring cancer sufferers to battle the enemy within to the bitter end, and ‘not go gentle into that good night’. Such total war demands our full arsenal of weapons and tactics, legitimising a medicalisation that promotes screening tests and preventive medicine in addition to the normal treatments after diagnosis of cancer. However, medicalisation brings with it potential side-effects, for instance to our self-perception and perception by others, or indeed our conception of what constitutes a healthy person. One major side-effect that has accompanied medicalisation is the hope and expectations foisted on cancer research and therapy. Emerging communities have mobilised to argue for the limitless potential of medical science. This makes clear an important tension between the expectations of ‘magic bullets’ and the complexity and uncertainty faced in the lab. The imaginary of cancer research still outstrips the struggles in the lab and the quality of biomarkers produced.

6. Conclusion

This review set out to explore the particular ethical and social aspects of cancer biomarkers, through a dialectic move between the literature and informal conversations in a working biomarker centre. In doing so, it adopted a unique perspective from inside the lab, looking out. Notwithstanding some more classical bioethical dilemmas, this perspective regarded many of the issues in the lab relative to the ethos of the cancer biomarker community; how the complexity and uncertainty characterising cancer biomarker research influence their norms of quality. Looking out from the lab, we saw how this ethos can influence, or indeed complicate, wider social and ethical debates, nationally and globally. In turn, we saw that socio-cultural constructions of cancer and imaginaries of biomedical science have acted to shape, and sometimes conflict with, the ethos in the lab. By incorporating an ELSA component to its centre, the CCBIO has taken steps to make these implicit issues explicit, in order to discuss them.

This paper joins other scholars in arguing that the complexity, uncertainty and questions of scientific quality in biomarker research demand more humility and reflexivity, both in the lab and in the research policy decisions that promote cancer biomarkers. Reflexivity implies that the biomarker research community is able to reflect on the underlying principles and purposes of their field, and on the potential impacts of their research on society. Humility implies awareness “about both the limits of scientific knowledge and about when to stop turning to science to solve problems” [62]. In recognising the fallibility of science, particularly in such a bold new field as biomarkers, Kern [32] notes: “A greater recognition of biomarker failures is constructive and acknowledges the richness of biologic, technical, and philosophical complexity, the full appreciation of which could improve the management of scarce research resources.” In emphasising that many social and ethical considerations lie outside the realms of science, Fleck [8] argues that even if we were to discover perfect biomarkers, we would be left with the moral and political problems of ragged edges, pricing human life and deciding whether to grant desperate patients their last chance therapies.

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