Introduction

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With the exception of the COVID-19 pandemic, which has triggered an unprecedented mobilisation of resources and political will, no disease (or rather group of diseases) attracts more attention than cancer. This holds true for many different public spheres, and most certainly in the world of scientific research and technology. Indeed, as the panorama of diseases change with human development, cancer has become increasingly prominent as a cause of death and suffering. For this reason, cancer research, its agendas and trajectories, is an important site for understanding modern societies. What cancer researchers, patients and healthcare workers do, think, fear and desire is not only interesting in its own right but an important part of how our future science, technology and society are conceived, imagined and produced.

This book is the result of close collaborations between researchers and members of the extended network of the Centre for Cancer Biomarkers (CCBIO). CCBIO is a Norwegian centre of excellence located at the University of Bergen, funded for a ten-year period over 2013–2023, which does research on "new cancer biomarkers and targeted therapy, […] how cancer cells are affected by the microenvironment in the tumours, and what significance this has for cancer proliferation and poor prognosis".[1] More precisely, the research at CCBIO is articulated around four overlapping research programmes, that respectively look at: (i) the mechanisms of tumour-microenvironment interactions, looking at how tumour cells interact with the surrounding and supporting microenvironment with different types of cells; (ii) the discovery of cancer biomarkers, aiming at validating different types of

[1] On the website of CCBIO: https://www.uib.no/en/ccbio#

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biomarkers in tissue samples from patients; (iii) the clinical applications and trial studies, through performing clinical trials with associated biomarker studies; and (iv) the questions of health ethics, prioritisation of care, economics and other societal issues pertaining to cancer biomarkers and precision oncology. The CCBIO was funded both on the basis of its potential for excellent research in these fields, and the innovative set up of these research teams across seven departments at the University of Bergen. While most of the CCBIO activity is located at the Department of Clinical Medicine, the Department of Clinical Science, and the Department of Biomedicine, there are also ongoing collaborations with the Department of Informatics, the Department of Economics, the Department of Global Public Health and Primary Care, and last but not least, the Centre for the Study of the Sciences and the Humanities.

Of the 18 co-authors in this book, 14 are affiliated with CCBIO and spread across these various departments, as follows: the editors, Anne Bremer and Roger Strand, are researchers in the fields of Science and Technology Studies and philosophy of science at the Centre for the Study of the Sciences and the Humanities. Four more collaborators and authors are affiliated to the same centre: Irmelin W. Nilsen, Caroline Engen, Mille S. Stenmarck and Karen Gissum. With the exception of Nilsen, who is a media scholar, all three are health professionals and early career researchers who have combined biomedical research with building their own research expertise in STS/philosophy, a demanding combination. Several co-authors are biomedical researchers who, in the course of development of CCBIO, have developed if not an additional research track in STS, philosophy etc, then definitely a strong interest and affinity towards such work, including the CCBIO director Lars A. Akslen, Elisabeth Wik, Hanna Dillekås, Maria Lie Lotsberg and Stacey D'mello Peters. In addition, our interdisciplinary team has included the medical ethicist Eirik Tranvåg at the Centre for Ethics and Priority Setting, Department of Global Public Health and Primary Care and the health economists John Cairns and Jiyeon Kang, health economists respectively working economic evaluation in the field of cancer, who are long-distance affiliates of CCBIO from their home institution at the London School of Hygiene and Tropical Medicine. Beyond CCBIO, the network of co-authors extends to the Center for Ethics, College of Human Medicine, Michigan State University (USA), where Len Fleck, philosopher of medicine and medical ethicist, focuses on just health care rationing and democratic deliberation processes supporting those debates; as well as to the Department of Anthropology, University of Copenhagen, and Centre for Medical Science and Technology Studies, Department of Public Health, University of Copenhagen, where Line Hillersdal and Mette N. Svendsen, anthropologists, share research interests on cancer patients in experimental treatment with personalised medicine. Finally, we have Dominique Chu, computer scientist, complex systems theoretician and philosopher at the School of Computing, University of Kent, which has been collaborating with Roger Strand on critically looking at the limits of models in the life sciences.

To further understand the interdisciplinary collaborations at play between the co-authors of this book, we think it is important to specifically look at the role of the

editors within CCBIO. We have been part of the CCBIO research team 'Health ethics, prioritisation and economics' from the beginning. This team, composed of philosophers of science, Science and Technology Studies scholars, health ethicists and health economists, is charged with linking the research on cancer biomarkers that is being done at the centre to the ethical, legal and social aspects and implication of this research; in other words, we have a role as *critical* social science and humanities scholars within CCBIO. Worthy of note, it is through this team 'Health ethics, prioritisation and economics' that we have met and kept ongoing interdisciplinary collaborations with John Cairns, Jiyeon Kang and Eirik Tranvåg, co-authors of this book and part of the team. Particularly, our research interests have converged into exploring how the social, political and economic debates around prioritisation of health care and the medicalisation of society (unfair cut-offs and 'ragged edges', the constitution of new 'bio-communities' of patients, the emerging side-effects of pursuing precision oncology, etc.) are deeply anchored in the complexity of and uncertainties around cancer biomarker research. For the most part, our collaborations were concretely articulated around teaching a common CCBIO PhD course (see below) and the co-supervision by Roger Strand of Eirik Tranvåg's PhD project.

But what is our explicit role and mandate within CCBIO, as formalised in the project proposal? What is our less explicit agenda, that has developed through our experience with working with CCBIO? What are some of the activities we do in CCBIO, and how is all of that received? These considerations form a background from which this anthology was elaborated, and therefore contribute to the reader's apprehension of the book.

The role we take on the CCBIO 'Health ethics, prioritisation and economics' team can be said to be twofold. First, we have the explicit mandate to call attention to the concrete and visible Ethical, Legal and Social Aspects (ELSA) of cancer biomarkers, and look at how these are linked to what happens in the laboratory. For instance, we discuss the challenges of reproducibility and validation in the lab, the complexity of cancer biology and tumour heterogeneity that cannot be grasped even by sophisticated models, and the ethical, legal and social aspects these lead to: questions of how to justly and fairly prioritise health care, nationally and globally, in a context of expensive drugs and limited efficacy, or the complicated alignment between academia, pharmaceutical companies and regulatory agencies, when it comes to getting a scientific discovery to the clinical setting (Blanchard 2016). This part of our role is therefore about making the social and political context of cancer biomarker research more explicit, and integrating awareness of these ELSA-type issues into everyday research practices. This is mainly done through regular informal interaction (even friendship) with cancer researchers at CCBIO over the years, but also laboratory visits, participating in CCBIO meetings and events, ranging from junior researcher meetings, PI meetings and our annual symposia, co-authoring of papers and opinion pieces (for instance between Lars A. Akslen and Roger

Strand[2]), co-supervising students (for instance by Elisabeth Wik and Anne Bremer[3]), as well as a yearly course that we organise for CCBIO PhD candidates (we return to this below).

By way of example, collaborations between CCBIO cancer researchers and the 'health ethics, prioritisation and economics' team led us to a first anthology titled 'Cancer Biomarkers: Ethics, Economics and Society' (Blanchard and Strand 2017). Based on the ongoing collaborations we were having within the 'health ethics' team, and with CCBIO more generally, several co-authors of this book already participated in the first anthology: John Cairns, on the evaluation of targeted cancer therapies, Eirik Tranvåg on the influence of cancer biomarkers on priority settings, Elisabeth Wik, on what is a good biomarker, Caroline Engen, on concepts of good life and health in a context of cancer, and Len Fleck, on ethical ambiguity around cancer biomarkers. That first anthology was rooted in the interdisciplinary collaborations and reflections ongoing at CCBIO, and aimed to provide a map of different ethical, social, political, institutional, economic and existential issues around cancer biomarker research. It began by questioning what a 'good' biomarker might look like in a context of hypes, high hopes and substantial biological complexity, to then explore how the complex terrain of cancer biomarker research is structurally entangled with questions of what a 'good' (just, fair and caring) society is, and what the 'good' life is (with or without cancer). In that sense, this first anthology aimed to *map* the different aspects of this terrain to each other, and to the high levels of complexity and uncertainty that characterise cancer biology; whereas this second anthology is more concerned with *critically scrutinising* the ideal of precision oncology, through actor-centred perspectives – what it really means to pursue ideals of precision oncology for patients, for society at large, for oncology research or for priority-setting institutions, for instance. We come back to the essence and key themes of this anthology below.

The second aspect of our role on the ELSA team in CCBIO is somewhat less explicit, and developed through our experience with working in CCBIO. We quickly realised, by discussing and reflecting with CCBIO researchers, that there was a need to go beyond the immediate issues faced by cancer researchers, to reflect on the underlying endeavour that these researchers are part of. We chose to approach that by a deeper analysis of the sociotechnical imaginaries surrounding cancer biomarker research, notably the imaginary of precision oncology.[4] A sociotechnical imaginary being defined in brief as the "collectively held and performed visions of desirable futures, animated by shared understandings of forms of social life and social order attainable through, and supportive of, advances in science and

[2] See for instance: Strand, R., and Akslen, L. A. 2017. What is responsible cancer research? *Tidsskr Nor Legeforen* 137(4): 292–294.

[3] In 2019, Elisabeth Wik and Anne Bremer co-supervised the research assignment of two students on the topic of uncertainties in the use of biomarkers in breast cancer and monogenic diabetes.

[4] In this book, see the chapter by Bremer, Wik and Akslen: "HER2 revisited - Reflections on the future of cancer biomarker research", and the chapter by Stenmarck and Nilsen: "Precision oncology in the news".

technology" (Jasanoff 2015), we critically call into question and discuss with CCBIO researchers why the sociotechnical imaginary of precision oncology has been deemed a 'desirable' and 'feasible' future in the first place, and explore what is 'co-produced' – what things mutually emerge – in pursuing this imaginary.

A particularly important way we manage to convey these reflections is via a yearly PhD course that we organise, primarily targeted at CCBIO PhD candidates, and titled: 'Cancer research: Ethical, economic and social aspects'. This course introduces the various 'ELSA'-type issues mentioned above, but also allows for what Åm (2019) calls 'moments of dislocation'. These dislocatory moments occur when one realises that there are differences and discrepancies between the practices one claims to follow ('espoused theories'); and the practices one actually adopts and implements (or 'theories-in-use'), that can be made explicit by studying the individual's actions, views, identities or organisational policies (Argyris et al. 1990). Hesjedal et al. (2020) argue that such dislocatory moments "may trigger learning processes that encompass the revision of mental maps, that is, double-loop learning" (p. 6). Double-loop learning (Argyris and Schön 1974, Schön 1983) distinguishes itself from single-loop learning insofar as reflection on the discrepancies between espoused theories and theories-in-use results in a learning process which entails a revision of one's mental maps and models. It is therefore not about 'simply' learning about ways to incrementally adjust our practices around challenges or problems, like introducing new policies to hire more women in research positions for example. Rather, it is about deeply reflecting on institutionalised practices, values and ontologies, so that everyday practices and theories-in-use can be questioned and potentially revised (Hesjedal et al. 2020); rethinking the gendered aspects of oncology, and rationales and approaches for incorporating gender perspectives to use this example.

This is what we aim for in our CCBIO PhD course, to provide opportunity and support for participants who want to, to experience dislocatory moments as a first step to a double-loop learning. We observed that double-loop learning was triggered by discussions around broad themes, such as the lack of ambivalence and the power of goodness (Loga 2004) that characterise discourses and practices around precision medicine, the resulting framing and overflowing dynamics (Callon 1998), or the importance of sustaining an economy of hope (Rose and Novas 2004) in fuelling the imaginary of precision oncology. These themes are central in this anthology as well, and we come back to them later in the introduction.

Unsurprisingly, we have witnessed tensions between espoused theory and theory-in-use among the course participants. Our course runs over two weeks, with one month in-between where participants proceed with their research work, including their duties in the lab. It was frequent that at the beginning of the second week of our course, participants would raise the discomfort they had experienced when trying to apply their new reflections or insights into their everyday practices. Either they felt 'locked-up' in a tightly-designed project with very little room to manoeuvre, or overwhelmed by the duties in the lab that leave little space for reflection, or again met with resistance from the disciplinary or hierarchical structures of their field.

Reflexivity is part of the researcher's practice, and we all engage in some kind of reflections in the course of our work. But as Schön (1983) argues, "[scientists] seldom reflect on their reflection-in-action" (p. 243), or in other words, they do not often engage in double-loop learning (Hesjedal et al. 2020). The lack of reflexive discourse and practices around the context, status and inherently complex nature of cancer biology is a source of naivety in the field (Strand 2000), and arguably contributes to developing blind spots around important concerns that lie to the side of the main trajectory of precision oncology. However, as we saw above, our invitation to a double-loop learning and a reflexive critique of precision oncology within CCBIO was sometimes justly met by resistance and unease: 'are you against cancer biomarkers?' Our answer is a profound "no" but whenever that remained unclear it was evidence of immature reflection or communication on our side. Indeed, we soon came to realise that we were asking (mostly) early career scientists to carry responsibility for the trajectory of current cancer research – which was unfair from our side. This responsibility is too heavy to be carried by single individuals, or even research groups; Åm et al. (2020) have rightly questioned the way in which scientists are being imagined in certain imaginaries of RRI.

We therefore had to readjust the way we wanted to convey double-loop learning, and as such, we became very explicit in our PhD courses that our invitation to critically reflect on cancer biomarkers and precision oncology aimed at mutual learning and the uncovering of blind spots in those fields: Which other research areas receive less attention because of the focus on biomarkers? What are the scientific, structural, organisational limits of biomarker research? What is the political economy of precision oncology? We think that double-loop learning is crucially important when working within the field of biomarkers, as it highlights the fusion of hope and reality around precision oncology, and helps us realise that the current efforts and resources placed in this endeavour are to a large extent justified by optimistic future imaginaries of precision oncology. It is important to note that this course was key in further consolidating collaborations between several of the co-authors of this book: Anne Bremer, Roger Strand and John Cairns being the main instructors, Elisabeth Wik being a recurrent guest lecturer in the course, and Caroline Engen, Mille Stenmarck, Irmelin Nilsen, Hanna Dillekås, Karen Gissum, Maria Lie Lotsberg being first participants in the course, and presenting their work and reflections in subsequent editions of the course. Holding a course together was an important way to meaningfully discuss each other's visions, assumptions and overlapping research interests. Mutual learning and an interdisciplinary approach have been key to our efforts, as they draw on a multitude of knowledge fields, professions and disciplines. Thus, the authors of this book are medical doctors, pathologists, philosophers, nurses, media researchers, molecular biologists, STS scholars, sociologists, computer scientists, economists and ethicists – individuals frequently belonging to more than one of these categories. Long-term collaborations built on mutual trust developed in real time is another key component. Indeed, as noted above, nine of the authors in our first anthology contribute also to the present volume. In our view, we have enjoyed and sustained a high degree of mutual reflexivity and openness between the biomedical perspective on one hand, and the various SSH (social sciences and humanities)

perspectives on the other hand, including the STS tradition that was created with the explicit purpose of providing social critique of science and technology. To us, this is an indication of a growing distance from the polarized past of the "science wars" in which STS scholars and sociologists of science – rightly or unfairly – were accused of relativising scientific knowledge and undermining public trust in science. At least in the Norwegian context, with decades of SSH-STEM collaboration in and around biotechnology and the life sciences, this mostly feels as a distant past while the tensions and conflicts may still be strong in other parts of the world. Our SSH scholars and STEM scientists could all agree with Andrew Pickering's famous claim that high quality scientific knowledge is both objective and relative: It is objective in the sense of being the outcome of well-organized intersubjective practices and processes of experimental work, observation, analysis, peer review and so on. But it is also relative to the problem context where it emerged, in the sense that certain research questions were asked and certain model systems were employed, rather than others. With the science wars well behind us, this insight should not threaten anyone. As explained in the preface, co-authored by CCBIO director Lars Akslen, a pathologist and cancer researcher, and Roger Strand, a professor of philosophy of science, our vision is to employ the critical resources from STS and other SSH disciplines to *improve* cancer research, make it stronger, more relevant and more aligned to the needs and concerns of society. In this way, a conceptual basis can be developed to rigorously identify, describe and discuss the difficult social and *sociotechnical* issues that exist within cancer research and cancer care itself, problems for which biomedicine by itself does not provide theories or concepts. SSH, such as the STS, philosophy, ethics, economics and media studies traditions represented in this volume, provide such theories and concepts as well as methods to identify, observe and analyse these issues within and around biomedicine as *phenomena.* This is the essence of the collaboration between the "two cultures": We are all researchers who create knowledge.

In sum, interdisciplinary exchange in an atmosphere of trust gives the opportunity to enter fearlessly into rigorous critique. As mentioned, revealing and critically discussing "blind spots" is central to our approach within CCBIO. It is also central to this anthology, and we have articulated this attempt around three overarching themes: (i) uncomfortable knowledge and lack of ambivalence in the discourses and practices around precision oncology; (ii) dynamics of framing and overflowing, when trying to control biological, social and ethical complexity; and (iii) the role of the economy of hope in legitimising and sustaining the imaginary of precision oncology, and the starch dichotomy between illness and disease it leads to. We will now go through these themes, and present how the various chapters broadly relate to them.

(i) Uncomfortable knowledge and lack of ambivalence

The first overarching theme in this anthology is the all-encompassing vagueness and lack of ambivalence found in discourses and practices around precision medicine. Is precision oncology already here? Is it working? What is it supposed to achieve? We know, as of today, that less than 1% of published cancer biomarkers

actually enter clinical practice (see Kern 2021; but the trends mapped almost ten years ago are seen to largely hold true). And we know that 'we have done an about face', from a period where molecular and genetic research gave hope that cancer could be understood through simple and reductionist thinking, to now where we struggle to interpret and make sense of the complex data that is being accumulated by sophisticated imaging and sequencing techniques (Weinberg 2014). Kern and Weinberg's observations are in the domain of 'uncomfortable knowledge': they undermine the legitimacy of the imaginary of precision oncology by demonstrating that it faces huge failure rates, and that it is deeply limited by biological complexity. Rayner (2012) defines uncomfortable knowledge as knowledge that contradicts the simplified, predictable and closed models that we use for making sense of our complex world. For those simplified models to 'work', uncomfortable knowledge needs to be excluded, either by denial, dismissal or diversion. In that sense, to exist and survive as an imaginary worthy of interest despite the uncomfortable knowledge conveyed by Kern, Weinberg and others, precision oncology needs to dismiss these claims, notably by constantly being surrounded by vagueness and a lack of ambivalence.

In chapter "Precision Oncology in the News", Stenmarck and Nilsen look at the lack of diversity in how the news media frame issues related to cancer treatment and research. They show how new cancer drugs are framed as future revolutions, and how their efficacy and high cost are left unquestioned. Similarly, precision oncology is depicted as a way to achieve "the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease, and/or to deliver timely and targeted prevention" (EC 2015, p. 3). Uncomfortable knowledge about the significant opportunity costs of precision oncology, the problems relative to prolongment of life for cancer patients, and the reality for already fragile healthcare systems with limited healthcare resources, are being diverted from by rather pointing at the tragic stories of suffering cancer patients. The 'truth' about cancer seems to be owned by the patients and their doctors, and other, outside perspectives are seen as unwelcome and irrelevant, and dismissed as being pessimistic views. This reflects the 'power of goodness' (Loga 2004) that is at play here. According to Loga, an argument that openly represents goodness gains a superior stance that makes it difficult for other arguments to get a foothold as legitimate. It is therefore less controversial for news media and policy debates to speculate on the potential for win-win solutions where there is going to be better health for everyone, and to drive forward these developments as urgently needed by cancer patients.

Critical claims about the feasibility and desirability of precision oncology are also invalidated as having no solid scientific foundation. As Lakatos (1970) argues, we have indeed no means to evaluate whether a 'research programme' is 'degenerating' or 'progressing' before reaching some historical hindsight. But Kern's uncomfortable knowledge about the 99% failure rate in cancer biomarker research is telling. Chapter "HER2 Revisited: Reflections on the Future of Cancer Biomarker Research", by Bremer, Wik and Akslen, relies both on oncology research and perspectives from Science and Technology Studies to show how even successful cancer biomarkers face important limitations, and cannot be seen as the solution to solving

ethical, social and clinical dilemmas. The authors revisit the story of the most successful cancer biomarker: HER2 for breast cancer, and discuss how HER2 has become the standard reference for showcasing the success of precision oncology. However, despite its important applications in the clinic, is not a perfect biomarker. Notably, there are challenges related to inter- and intra-tumoral heterogeneity, which question the reliability and quality of biopsies taken from patients. The determination of HER2 positivity is not straightforward either, which means that treatment options are chosen on the basis of best, but uncertain, knowledge, and that questions of where to place the cut-off between subgroup of patients remain. This uncomfortable knowledge, however, is often overshadowed by the extraordinary success consisting in HER2 finding important applications in the clinic, and therefore being one of the key arguments in validating precision oncology.

The lack of nuances and ambivalence in discourses and practices exacerbates, perhaps ironically so, the ambiguity with regard to whether precision oncology is a reality now, a soon-to-be realised miracle, or a 'mirage of health' (Callahan 2003). It fuels confusion about the temporalities of precision medicine, and results in a fusion of hope and reality. According to Callahan (2003, p. 261): "Medical miracles are expected by those who will be patients, predicted by those seeking research funds, and profitably marketed by those who manufacture them. […] The "mirage of health" – a perfection that never comes – is no longer taken to be a mirage, but solidly out there on the horizon." Not only have hope and reality fused, but the current predicament is justified by the future imaginary of precision oncology. The legitimacy of the current efforts put into precision oncology lies precisely in the future: "targeted drugs will work"; or "every patient will get his/her targeted cancer treatment". In chapter "Introduction to the Imaginary of Precision Oncology", Engen notes that more than two decades have passed since precision medicine was projected to bring significant advances to cancer research, treatment and care. The author reviews several studies that display uncomfortable knowledge by showing how the overwhelming majority of novel oncological agents are approved without clear evidence of clinical benefit and utility. This further contributes to illustrate the increasing gap between hope and reality around precision oncology.

(ii) Framing and overflowing

The second overarching theme in this anthology Callon's notion of *framing and overflowing* (1998). Callon defines framing as "the identification, measuring and containment of […] overflows" (p. 244), and overflows as positive or negative externalities, or in other words emergent products or practices that result, expectedly or not, from the scientific work of framing. Callon further explains that in some cases "framing is either impossible to achieve or is deliberately transgressed by the actors: this produces overflows which cause the barriers to become permeable" (p. 251). Precision oncology is, to a great extent, a project about removing ambivalence and reducing uncertainties by providing an illusion of molecular certainty that would allow us to solve any kind of social, ethical or clinical dilemma. However, the harder we try to domesticate or frame the highly uncertain and complex biology of cancer and associated dilemmas, the more there is a risk of an 'overflow'. Framing and

overflowing dynamics are indeed particularly relevant when discussing the limits of biological and mathematical models in addressing the complexity of cancer biology. Every time a model tries to capture or frame tumour heterogeneity, it overflows in the shape of a reproducibility crisis, as this specific aspect of cancer biology we thought we had control of, dissolves into hundreds of different complexities.

In chapter "The Dynamics of the Labelling Game: An Essay On FLT3 Mutated Acute Myeloid Leukaemia", Engen looks at how the 20 years of trying to 'label' and frame the FLT3 mutated acute myeloid leukaemia through temporal, spatial, multidimensional and high-resolution analyses, resulted in an overflow of vast inter- and intra-individual heterogeneity. This move towards high levels of molecular resolution also means that diagnostics are becoming increasingly refined and precise, with consequences on how cancer is defined, as the categories between cancer as an 'illness' and cancer as a 'disease', seem to dissolve.

Chapter "Crossing the Styx: If Precision Medicine Were to Become Exact Science", by Strand and Chu, also addresses the problems with trying to frame the high complexity of cancer biology in highly sophisticated and exact science. Computational models on which the imaginary of precision oncology relies, promise unachievable levels of numerical precision and conceptual rigour, which would require framing everything from cells to patients as closed and deterministic systems, when they are not. The authors point at the design flaw in precision medicine: it wants to achieve precision and tailoring by relying on exact science, but exact science does not translate into exact technologies that apprehend the complexity of cancer biology. The overflow here, is that the shift to a biology dominated by computational models may reinforce our understanding of life as essentially predictable, understandable and controllable, which in the end supports industrial and economic exploitation. In addition, striving for an unattainable objective will blind us away from what is really at stake here.

Chapters "Assessing the Cost-Effectiveness of Molecular Targeted Therapies and Immune Checkpoint Inhibitors" and "Real-World Data in Health Technology Assessment: Do We Know It Well Enough?", by Cairns and Kang, respectively, direct the analysis towards the details of health technology assessment and specifically, the assessment of the cost-effectiveness of expensive cancer therapies. Their chapters enter into the technical details of such assessments and, by opening these black boxes, show in different ways how what may appear as a "purely" technical frame is, if not necessarily overflowed, co-produced and shaped with social and political concerns. Along such lines, Cairns shows how seemingly parallel innovations, i.e., molecular targeted therapies and immune checkpoint inhibitors, receive subtly but crucially different assessment in terms of the methodologies used. The reader is left with a difficulty to explain these differences except within the more general narratives of the desirability of immune checkpoint inhibitors. Kang offers a similar perspective by discussing how complex and uncertain 'real world data' are incorporated in the relatively rigid frames of health technology assessments, which aim to provide a 'systematic evaluation of short- and long term safety, clinical effects, and cost-effectiveness of health technologies'. The hope with integrating real world data into health technology assessments is more robust clinical and

economic decision-making processes. However, managing and making sense of these overwhelming quantities of real world data produced at a very rapid pace is extremely challenging. As a consequence, this will arguably overflow in a much higher degree of complexity when assessing the cost-effectiveness of treatments in health technology assessments.

In chapter "Publication Bias in Precision Oncology and Cancer Biomarker Research; Challenges and Possible Implications", Lotsberg and D'mello Peters explore another overflow that is central to precision oncology: publication bias, i.e., published results are not a representative selection of all results within a study, and not all studies are published, with an imbalance towards reporting 'positive' results. The authors argue that aiming for 'hyper precision' as a general research direction or frame, results in the overflow of publication bias being more present in the fields of precision oncology and biomarker research. Indeed, as the imaginary of precision oncology relies on removing ambiguity, reducing uncertainty and providing molecular certainty, there is naturally less appetite for 'negative' results.

The issues of framing and overflowing are also very stringent in health care priority setting in a context of very expensive drugs. Indeed, it seems like the more efforts are put into establishing a precise cut-off between subgroups of patients for treatment allocation, the more it overflows as heated controversies; with patient subgroups just below the cut-off wanting the unfair situation reframed. In chapter "Reconstruction of Trouble", Dillekås relates the 2012 campaign of the 'Norwegian Breast Cancer Society', who managed to influence policy agendas in order to prioritise immediate breast reconstruction to breast cancer treated patients. This resulted in the dramatic overflow in terms of a resurgence of cleft lip and palate as a public health issue, as plastic surgeons were instructed to prioritise breast reconstructions over this group of patients. This story of frame and overflow is heightened by the fact that Dillekås and her colleagues published a paper pointing at a peak in early relapses in patients who had reconstructed breasts; peak that was not present in patients with similar tumour characteristics that choose not to reconstruct the breast. Their paper is a direct example of 'uncomfortable knowledge', as it points at how the complexities of cancer biology undermine what we think is 'good' prioritisation of health care.

Framing and overflowing also occur in projected priority setting decisions. Fleck analyses in chapter "Just Caring: Precision Health vs. Ethical Ambiguity: Can we Afford the Ethical and Economic Costs?" the argument developed by the oncologist Dr. Raza to abandon paying for targeted therapies for metastatic cancer, in order to rather invest that money for early cancer detection using liquid biopsies. Fleck explains that the apparently simple and 'framed' transaction from handling metastatic cancer to focusing on early detection would result in sacrificing identified lives (those who have metastatic cancer) for the statistical lives of future cancer patients identified through liquid biopsies. This would result in a significant overflow in terms of controversies and heated debates about fairness, compassion, care, and the unjust and unsustainable use of limited health care resources.

Finally, the dynamics of framing and overflowing are found at the level of priority setting institutions themselves, as Tranvåg and Strand explain in chapter

"Rationing of Personalised Cancer Drugs: Rethinking the Co-production of Evidence and Priority Setting Practices". They describe how the priority setting institution in Norway, among other countries, tries to cope with the scientific development of ever finer stratification and smaller patient groups by increasingly refined principles of priority setting (the umbrella values being neutrality, transparency and equal treatment). However, these attempts overflow in the shape of persistent controversies around drug reimbursement decisions as well as novel ways of providing drugs to patients in spite of priority decisions (as by recruitment into trials). The authors argue that the priority-setting frame itself may be due for fundamental reform that also entail a redressing of its umbrella values.

Both relative to the biological complexity and questions of priority setting, we see how all the efforts to frame, control and domesticate biological, ethical and social complexities are extremely resource-intensive, imperfect and often futile, as they result in overflows. It allows us to realise that optimistic discourses around precision medicine have shaky factual foundations.

(iii) The economy of hope and distinction between illness and disease

The resource-intensive efforts put in dismissing or diverting from uncomfortable knowledge, and in attempts to frame biological complexity lead us to the third overarching theme of the anthology. One aspect that contributes to explain why such efforts are developed to shielding at all costs the imaginary of precision medicine from ambivalence and criticisms, is the economic, political, and social interests for sustaining an 'economy of hope' (Rose and Novas 2004). Within the economy of hope, hope is sustained that targeted therapies work, and that every patient will eventually get her or his tailored drug. The limits to achieving these prospects are seen as not being inherent to science: "there are no inherent obstacles or pitfalls of science that could stop the realisation of revolutionary cures" (Brekke and Sirnes 2011, p. 356). Rather, the limits are seen as being exclusively political. It is the politicians who deny suffering cancer patients their life-saving therapies, by not funding them or by not prioritising them. In this economy of hope, patients, or 'somatic individuals' who understand themselves more in biological terms organise themselves into new constellations of 'biocollectives', or alliances with pharmaceutical companies and research groups, in order to influence agendas to promote research on 'their' disease, or enrol themselves actively as research subjects in trials for instance (Brekke and Sirnes 2011).

In chapter "Cancer Currencies: Making and Marketing Resources in a First-in-Human Drug Trial in Denmark", Hillersdal and Svendsen explore the dynamics of the economy of hope by looking at the collaboration between a public hospital in Denmark and a multi-national pharmaceutical company in setting up and running early cancer drug trials for personalised medicine. Notably, they look at how these public-private partnerships stir the direction of research and shape what precision oncology looks like in early clinical trials. They point to the fact that medical advances have become extremely dependent on industrial sponsors and agendas, which has led to less considerations about the real benefit for patients. In addition, they argue that trial qualities such as fast-tracking trial procedures, high-quality data

and high compliance of research subjects, were highly demanded by the public-private partnerships, are in fact 'currencies' used in transactions on the global market for drug development. In that way, Hillersdal and Svendsen unravel the ambiguities of the economy of hope, where a demand for a particular targeted drug is grounded in public-private partnerships, further facilitated by the danish welfare state, and finally expected by cancer patients (although the authors argue that participating in an early clinical trial was for some patients a way to give meaning to their disease, by considering that they help research and thus future patients for instance). The tragic irony here, is that these drugs are often too expensive to be prioritised by the same welfare states that contribute to their development.

The economy of hope also runs on fear. The fear of not being able to control one's own last moments of life, the fear of dying 'prematurely' from cancer, the fear of not having the strength or courage to try every extraordinary treatment available, as one has seemingly nothing to lose. In chapter "Filled with Desire, Perceive Molecules", Strand and Engen argue that these fears, and underlying strive, desire and passion to provide immediate help to acute myeloid leukaemia patients leads to losing sight of the important biological questions, such as: 'what is the function of cancer?' Curiosity on the biological, rather than medical questions, would arguably bring important learnings to light. Further, the authors argue that the urgent desire to advance science on AML and help the concerned patients also overshadows the variety of ways to help and accompany patients, in particular by having a better understanding of their illness is for them: is AML an enemy to be defeated, a deficiency to be removed, or an illness to accept? Indeed, the urgency to help may become an obstacle on the road that many of these patients will have to walk, from shock through despair to acceptance of their destiny. In this way the need to act can risk adding to the suffering.

Chapter "Lost in Translation" by Gissum further unravels the distinction between illness and disease that is sustained by the economy of hope. The economy of hope indeed needs to frame cancer as a disease that can be addressed, without ambiguities, by sophisticated technologies and targeted therapies. There is little place for illness in this picture. However, cancer patients 'own' their cancer: it is their illness, and their subjective, personal experience is an important (arguably the most important) consideration to take into account in clinical decision making. However, Gissum point at the mismatches between, on one side, the physician's perception of cancer as a disease that can be measured, and on the basis of which a rational treatment regimen can be established, and on the other side, the patient's experiences of her illness: what it does to her body, her mind, her self-perception, her networks, her activities: in other words, her home-world. The author argues that this mismatch is heightened in a context of precision oncology, where both patients and physicians operate within confusing hopes, realities and temporalities, and where the categories of health, illness and disease are being redefined. Arguably, precision oncology and the strive for hyper-precision and sophistication, both in scientific practices and developed therapies would benefit from being accompanied by a much more prominent place given to cancer as an illness.

This anthology looks at the culture and practice of biomarker research, and how it is powered to a significant extent by the sociotechnical imaginary of precision oncology. The issues at stake and matters of concern are approached with a revealing set of lenses, assembled by a team of authors from fields including fields like oncology, philosophy, STS, anthropology, economics, ethics, and media studies. This anthology is particularly relevant for scholars and practitioners in the many fields that are covered by precision oncology and cancer biomarkers, and for those who want to unpack the timely questions around the feasibility and desirability of precision oncology.

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