Rationing of Personalised Cancer Drugs: Rethinking the Co-production of Evidence and Priority Setting Practices

Eirik Joakim Tranvåg and Roger Strand

Introduction

In this chapter we will address the challenge of rising health care costs, how countries have developed systems and institutions for systematic priority setting and how these rationing decisions are taken with increasing uncertainty, fuelling public controversy. While personalised medicine is seen as a potential solution to this, we argue that due to some inherent traits it may also contribute to more uncertainty and controversy. The current system and strategies for priority setting might not be sufficient to address this. First we introduce concepts from science and technology studies and post-normal science in order to analyse the situation with a new perspective, and secondly we offer some new thoughts that might promote a fair and sustainable public priority setting practice in the future.

E. J. Tranvåg
Centre for Cancer Biomarkers CCBIO and Bergen Centre for Ethics and Priority Setting, Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
e-mail: eirik.tranvag@uib.no

R. Strand (✉)
Centre for Cancer Biomarkers, Centre for the Study of the Sciences and the Humanities, University of Bergen, Bergen, Norway
e-mail: roger.strand@uib.no

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Personalised Cancer Care Increases the Health Gap

The sustainability of publicly financed health care systems are challenged by increasing costs. Well-known drivers of this health gap are an increasingly aging and sick population, higher expectations of what the health care system can do, and the development of new diagnostics and treatments. Advances in medical science and technology result in an even larger range of potentially beneficial treatments. Moreover, we live in a world in which medical innovation to a large extent is organised as a rent-seeking activity performed by private enterprise. As a consequence, medical progress also tends to lead to more expensive treatments. This general phenomenon holds very much true for new cancer drugs.

Health care systems across the world struggle to manage the escalating cost of new cancer drugs (Fojo and Grady 2009; Sullivan et al. 2011). Most new drugs for treatment of advanced cancers offer only a modest benefit to patients, while costs are far from modest (Saluja et al. 2018). Yearly treatment costs above 100,000 USD is a rule rather than an exception; some treatments cost far more. Kymriah, a CAR-T therapy for acute lymphoblastic leukaemia in children, was launched by Novartis with a list price of 475,000 USD (Prasad 2018). Anyone can sympathize with the child and the parents for whom this drug might be perceived as the last hope. However, there are opportunity costs, i.e., the costs of foregoing health benefits that could have been obtained if that money was spent elsewhere. The level of potential public spending associated with very costly cancer drugs is likely to cause poorer treatment and more suffering for other patients both within and outside of the sector of cancer care.

In Norway, priority setting in the specialized health care sector is guided by three principles: health benefit, resource use, and severity of disease (Meld. St. 34 (2015–2016) 2016). These criteria were unanimously endorsed by the Norwegian parliament in 2016, after a process that started 3 years earlier when an official committee on priority setting was established (NOU 2014:12 2014). This was the third such committee in Norway, illustrating a decade-long tradition of systematic priority setting discussions. In the white paper it is clearly stated that "equal cases shall be treated equally" (p. 11) and also that "…transparency and user participation will be central values" (p. 11). Another important feature is the distinction between individual and group level decisions, where the latter involve quantifying the criteria using quality adjusted life years and cost-effectiveness estimations.

Many publicly financed health care systems, like Norway, and also the UK, Sweden and in many member states of the European Union, have established governmental policies and institutions for health care priority setting. Within these institutions, procedures for evaluation and appraisal of new drugs have been developed to ensure that public money is spent in accordance with rules or criteria for priority setting. Typically, and in line with the principle of equal treatment, drugs included in the public health care scheme are held against an equal standard, independent of drug type and targeted patient groups. This systematic approach is based on theories and models from medical ethics, distributive justice and health

economics, and is meant to enact basic ethical values by providing health care in a reasoned, reasonable and (tentatively) transparent manner. Impartiality and treating equal patients equally are key ethical considerations that are meant to be universal and uncontroversial (Kieslich et al. 2016).

Controversy is nevertheless common in many countries, and not the least with respect to cancer drug pricing and rationing (Gross and Gluck 2018; Wilson et al. 2008; Aggarwal et al. 2017). In the case of Norway, media studies indicate that public controversies are ubiquitous, to the extent that there have been years with new media stories about cancer patients who have been denied publicly paid access to a new treatment (Stenmarck et al. 2021).

Controversy as such is not a sign that anything is wrong. Health care rationing is an important political issue upon which there is legitimate disagreement. For the actors in the supply chain there is considerable economic interest; for individual patients the stakes may be a question of (prolonged) life or death. Indeed, a certain level of public contestation can be seen as healthy, as a sign of a vital democracy. In our opinion, the real cause of concern is rather the spiralling costs and the increasing unsustainability of public health care systems. The unsustainability seems in some cases to be aggravated by the nature of the surrounding public controversies, which strains the system, lead to ad hoc measures and exceptions from priority setting principles that drive costs up the spiral. Furthermore, the drivers of unsustainability on the public-political side seem to work in synergy with equally important drivers on the side of medical science and technology. We shall take some care to explain what we mean by that claim.

We noted above that medical progress tends to increase rather than decrease health care costs by at least two mechanisms: increase in range and volume of treatments, and the capitalist logic whereby a new product, sometimes medically superior to existing treatments, will be of higher worth and as a rule will be priced higher than its predecessors. A third mechanism, peculiar to the current trend towards personalised medicine, is that a larger share of new treatments are "tailored", aiming to prescribe "the right drug to the right patient at the right time". In other words, there are more new drugs that sell in relatively small volumes and fewer blockbuster drugs that, by economies of scale, may be sold at lower prices (Duffy and Crown 2008). A perverse effect is that very high list prices make negotiations for discounts widespread, which again implies less transparency in priority setting when governments agree to keep discounts confidential (Tranvåg 2019).

More to the core of personalized medicine, however, there is a proliferation of diagnostics schemes that each target smaller groups of patients defined by ever finer diagnostic criteria and biomarker characterisations. From a purely scientific point of view, this development promises higher precision in identifying patients and to better match drugs with their responders, and by avoiding ineffective and costly treatment of non-responders as well as toxicity and side effects. Indeed, the latter years the imaginary of "precision oncology" has gained traction. According to this imaginary, at least in its purest expressions, one may arrive at an exact scientific characterization of the molecular basis of disease in each individual and thereby devise the precise molecular cure or treatment.

It is outside the scope of this study to discuss the eventual realism of the reductionist imaginary of precision oncology. However, in the context of health care priority setting, personalisation has as a matter of fact so far often implied the opposite of precision. Personalised medicine leads to a higher number of treatments to test and finer stratification of patient groups, which both imply that clinical trials are done with fewer patients in each group, faster, and with more surrogate endpoints (Schork 2015; Chen et al. 2019). In this way, the development towards personalized medicine poses risks to methodological validity and a weakening of the evidence base (Moscow et al. 2018). For priority setting institutions the number of new drugs to assess have grown, whilst the evidence base for the assessment has gradually become increasingly thin and provisional (Davis et al. 2017; Naci et al. 2019; Tranvåg et al. Submitted).

At the same time nearly every new drug is met with a claim that the drug is highly beneficial to some small and narrowly defined subgroup of patients, and so science, industry and the public put high pressure on authorities to approve these drugs. And then, if the drug is approved for some small subgroup, there are always "ragged edges" around the definition of that group and always possible to make claims of scientific uncertainties in order to argue that the drug should also be made available to those who now find themselves excluded by the first limited approval (Fleck 2010). Such claims are well suited for news media because they typically concern a small number of individuals and allow for news coverage in terms of storylines about individuals at risk. This is an example of a new type of synergy between personalized medicine and personalized politics that focuses on the tragedy of the individual terminal patient, what Brekke and Sirnes (2011) called "the hypersomatic individual".

In sum, the development towards personalized cancer medicine poses new challenges and increases the pressure on institutions of health care rationing. At one level, more and better business-as-usual could appear to solve these challenges: Clearer and better specified criteria for priority setting; stronger demands on the pharmaceutical industry to present methodologically strong evidence; integrating real world evidence; international collaboration between governments to refuse secret price negotiations with the industry; better education of citizens so that they understand the realities of opportunity costs and the need for rationing. If all of this worked well for priority setting between groups of thousands of patients, it may also work for groups with dozens of patients by increasing the effort on all sides. Let us call this Plan A.

The authors of this chapter are not convinced that Plan A will work. If we were, there would be no need for the chapter; then we might as well leave our governments to continue as before. At least in the case of Norway, there is little sign of anything but Plan A on the side of governmental policy. Still, the level of controversy does not seem to decline, in an age where erosion of public trust in political and governmental institutions has been seen in many sectors. The rest of this chapter is devoted to our reasons for why Plan A might not work, and our suggestions for a possible Plan B.

Why Plan A Might Not Work and Why the Problem Is Connected to Biomarkers

Above, we delineated a Plan A for health care rationing in the age of personalised medicine, namely to strengthen its frameworks and institutions without much need to rethink its practices, or medical and scientific practices for that matter. At the same time, we opened up for the possibility that Plan A might not work. From a sociological perspective one might state, for instance, the quite obvious fact that governmental institutions in modern societies do not operate in isolation from the sectors that they govern and the public on behalf of whom they govern, but that they are in fact in need of some sort of legitimacy vis-à-vis both. Controversy and contestation can be a sign of vitality – but not without limits. There is a question of how much tension an institution can live with and how much power it will be able to gain.

Taking the immanent perspective, it is possible to give a more principled argument for why personalised medicine may create a need to rethink a priority setting strategy based on impartial and equal standards. The argument does not per se go against the rationality or desirability of such standards, but rather shows how the scientific development threatens to undermine the possibility of enacting them.

While the exact content of such standards may vary, some common features may be distinguished of the type of rationing principles that we are discussing here. First, they are not entirely casuistic and pragmatic. It would be entirely possible to organise health care rationing in terms of case-by-case deliberation and decision-making, say, performed by a sovereign committee whose composition secured some sort of legitimacy by its representativity. Such entities exist in health care systems; clinical ethics committees and internal review boards may resemble this extreme type of procedural legitimacy. However, this is not how health care rationing at the governmental level tends to be organized. Instead, it is designed to ensure some degree of distributive justice by making decisions with regard to groups rather than individuals, and by aiming to treat the groups fairly so that they receive whatever proportion of the health budget that is considered to be fair.

For a priority setting approach based on impartial assessments of different patient groups to work, a number of assumptions have to be made. One needs some form of generic accounting of resource use (e.g. monetary costs) and of health benefits (e.g. quality-adjusted life years (QALYs)) in order to make comparisons across patient groups. These measures of cost and benefit can be adjusted with some form of distributional aspects, typically by some estimate of need (in Norway, including severity of disease). The overall framework does not have to be utilitarian – it could be based on needs or capacities rather than utilities in the strict sense, and it could be adjusted with deontological principles about the duty to provide life-saving emergency treatments (as the end of life-criterium in the UK) – but it will have to be similar to utilitarianism in the sense that the right decision will be one that maximises some balance between overall health benefit and a fair distribution of health benefit.

Moreover, it will have to satisfy the requirement often alluded to by John Rawls' concept of "the veil of ignorance": fair principles for a just society can be agreed if no one know which status and interests they will have, thereby making decisions neutral and separated from self-interests (Rawls 1999). As a consequence, priority setting decisions should expressly *not* be based on nepotistic interest or undue discrimination. Examples of what is meant by the latter, are easy to give: For instance, it would be undue discrimination if the procedures or outcomes of the rationing process result in a systematic favouring of men rather than women; of Caucasians rather than Asians; of rich rather than poor people; of young rather than old persons, and so on. Along the lines of the sociological perspective we mentioned earlier we may note that such health care rationing systems *de facto* are at odds with social reality, in which the interests of, say, Caucasian rich men often are favoured over most other groups. In this sense the principles are ideals of a modernist, human rights- and Enlightenment-based type, trying to improve the social world by institutionalizing and enacting moral principles.

A crucial working assumption for such priority setting strategies to work is that it is possible to distinguish between legitimate and illegitimate discrimination of patient groups. Central in the priority setting frameworks in Norway and the UK is the principle of equal treatment. This states that persons that are equal in all ethically relevant characteristics must be treated equally, and that persons that are unequal in some ethically relevant characteristic can be treated unequally. Most people see gender, political views, religious convictions and sexual orientation as ethically irrelevant, and therefore as illegitimate grounds for unequal treatment. Need, severity of disease and benefit of treatment are by most seen as ethically relevant characteristics in priority setting decisions and may give reasons for a legitimate discrimination of patient groups. An example of such legitimate discrimination is to provide targeted treatment to patients with an EGFR (epidermal growth factor receptor) mutation and not to an otherwise similar group of patients who lacks the mutation.

But for this working assumption to hold, two conditions must be in place: First, the methods we use to estimate or predict benefit, need or some other ethical relevant characteristic must be of good enough quality, and second; the classification of groups should be independent from and uncorrelated with the classification of social groups.

In previous studies (Tranvåg et al. 2018, 2021) we have shown how this former condition can break down in clinical practice, in ways that are relevant to priority setting. Patient age is a well-suited example: On one hand, age discrimination is by most seen as *prima facie* morally unacceptable. On the other, patient age can be a highly informative and useful piece of information in clinical decision-making and may provide relevant information about risk and potential benefit. Therefore, age is used in multiple ways in which it is not easy to separate the descriptive, "objective" function from the normative function. For instance, clinical knowledge about how tough it typically is for an 85-year-old person to recover from surgery or live well with the side effects of a highly toxic cancer drug, may blend into the overall

question of whether it is medically worthwhile to give the treatment – also in the absence of a scientific evidence based on the question.

In Tranvåg et al. (2021) clinicians were presented with hypothetical priority setting decisions. A high chronological age was found to be the single most important patient characteristic that influenced the doctors' priority setting decision for a new cancer drug. In the same survey the patients' smoking status was considered as an irrelevant characteristic for priority setting, despite it being a piece of information that may be relevant to patient-centred clinical decisions. It may very well be that whether a patient smokes or not would have had clear prognostic and predictive value of high relevance to many priority setting decisions. However, in real life this could often lead to allegations of undue discrimination.

A problem posed by personalised cancer medicine, and even more so by the imaginary of precision oncology, is that the information being used to stratify the patients is becoming massive and comprehensive. The working assumption that patient groups are uncorrelated with social groups is likely to fail more often. Moreover, as patient stratifications are being used in the arguably social system of health care priority setting, they take on social meaning and can become social groups. In a hyper-connected world with social media, one can easily envisage that patient subgroups can form their own communities, say, a community for those who score slightly below the threshold for being regarded as PD-L1 positive with respect to a certain treatment. Now, if their PD-L1 status is not only a negative predictive biomarker but also a negative prognostic biomarker for their condition, they could make the claim that they as a group are faring worse than the PD-L1 positive and accordingly are being unduly discriminated against if PD-L1 status is the unique criterion for denying them access to treatment. Adding the endless possibilities of combining biomarkers into batteries, there are equally endless possibilities of forming such imagined communities around claims of illegitimate discrimination.

A central challenge for the current priority setting strategy when faced with personalised medicine at a full scale, is that new ways of organizing clinical trials, with small groups of patients, surrogate endpoints and short follow-up time makes the evidence used for decisions uncertain. At some point it will no longer be meaningful nor ethically acceptable to classify patients into different groups and give them unequal treatment based on biomarkers for which the quality of prediction is very uncertain. If precision diagnostics are not precise enough to stratify patients into smaller groups in an ethically acceptable way, priority setting based on such stratification cannot be ethically acceptable either.

While the scenario laid out above is not full reality as of yet, it is the case that the public controversies witnessed especially since the entrance of costly immunotherapies against cancer indeed already do contain claims of undue discrimination. The typical proponents are not necessarily arguing against any form of rationing or cost control. Rather, they make a claim of being equivalent with those who got the drug or being different from those who should not get it. What we are arguing, is that the presence of such arguments is related to scientific progress and scientific literacy, and that there is reason to believe that the trend towards personalised medicine will make such arguments ever more frequent.

In order to sum up and characterize our argument, Plan A will work if the pressures against health care priority setting can be resolved by shifting the power balance, strengthening the priority setting institutions, reducing the power of big pharma and educating the public. This may very well be enough. But we, both as scientists and as a society in general, are obliged to think further. Plan B will be needed if the problem runs deeper and undermines the very assumptions upon which priority setting is built. What we believe is undermining these assumptions, is a blind spot of ethics and economics, namely the trajectory of the scientific development. To borrow a pair of concepts from the French sociologist Michel Callon (1998), the *frame* provided by priority setting principles is being *overflowed*, and this is the deep cause of contestation and controversy.

The Co-production Perspective as an Analytic Tool

> Increasingly, the realities of human experience emerge as the joint achievements of scientific, technical and social enterprise: science and society, in a word, are co-produced, each underwriting the other's existence. (Jasanoff 2004, 17)

During the final decades of the twentieth century, scholarship on science, technology and society advanced the understanding of how scientific, technological and societal development processes are "co-produced", how they are causally entangled into each other. This insight did not come easy; most philosophy of science used to emphasize the autonomy of science from society, and most modern institutions were built upon the assumption of that autonomy. Indeed, Bruno Latour (1993) argued that the efforts to conceptually demarcate between science and politics (and by implication, between nature and culture) are not only key to modern societies but constitute a type of work (of purification) that is necessary to enable and justify the massive production of linkages between science and politics (and nature and culture) that is characteristic of these societies. "Being modern" is to believe in the fiction that science and politics are independent; this belief is what allows us to create the reality that science and politics, and nature and culture, become ever more entangled, to the extent that cancer patients may be enrolled into the forefront of international research as well as becoming the subject of headline news and parliamentary debate. Part of that fiction is also to believe that facts and values are wholly independent and can be assessed independently from each other.

In reality however, value choices are embedded into scientific methodologies, such as when clinical endpoints are chosen, and conversely. Furthermore, factual matters influence value choices, for instance by changing the (actual or potential) option space (Hofmann et al. 2018). As long as these dependencies between science and technology and its interactions are not noted and pointed out, the assumption of their non-existence may be upheld and the modern institutions that are built upon this assumption may continue to appear functional. The moment they are noted and pointed out, however, disturbance arises: uncertainties, controversies, contestation and loss of legitimacy. These are expressions of the modern frame being overflowed.

While this may sound terrible to a Cartesian mind, the achievement of scholars such as Callon, Jasanoff and Latour has been to show how overflowing is the rule rather than the exception, and how all institutional arrangements will have to be seen as dynamic and situated, that is, contingent to their context in time and space.

To our knowledge, this co-production perspective has not been overly prominent in scholarly debates on health care priority-setting. A notable exception is Tiago Moreira (2011), who analysed cases of controversies surrounding the UK National Health Service and its advice authority NICE (National Institute of Health and Clinical Excellence). The main analytical concept in Moreira's study is that of *uncertainty,* defined as "the non-determinate or unsettled quality of a statement or a knowledge claim" (p. 1335). Along the lines with our description above, uncertainty is seen as a key expression of overflow of the frame: Controversy and contestation can be analysed in terms of claims of uncertainty, and such claims, if successful, can lead to a change in principles and practices of priority setting. Moreira presents two dimensions with regard to which such uncertainty claims were made in the case studies investigated: standards and disease-specific knowledge. For instance, both with respect to cancer drugs and dementia, the standards themselves were subject to problematisation. It was argued that the standardised metric of QALYs was inappropriate to deal fairly with the particular suffering and needs of cancer and dementia patients. What Moreira finds, is that in such cases an *exception* from priority setting rules is a likely outcome. Indeed, in the UK such exceptions have been introduced both for dementia and cancer. In other cases, the target of the claims of uncertainty are disease-specific knowledge, for instance whether a particular drug works well, and for whom. In such cases, an *impersonal rule* may be the likely outcome (for instance a threshold for allowable expenses per QALY gained). Finally, Moreira finds cases where uncertainty claims are successfully made in both the general and the disease-specific dimensions, and where a deliberative, pragmatic approach may be sought to provide justification in procedural fairness in the relative absence of authority based in scientific certainty.

We noted earlier that a possible blind spot of ethics is its tendency to take for granted the description of matters of fact as provided by science, or rather, to take for granted the possibility and desirability of science providing such descriptions. Within such working assumptions, the mechanics of priority-setting can work to calculate what it the just and fair solution given the matters of fact. The advantage of the co-production perspective as provided by science and technology studies (STS) is that it offers a more nuanced and complex analysis in which scientific descriptions are also seen as dynamic, as provided by actors in contestation with other actors, and as something that can be deconstructed as well as reconstructed in the course of action. Equipped with this analysis, nobody ought to be surprised by the presence of controversies.

Hofmann et al. summarised the Scylla of what they called "the traditional positivist account" with the Charybdis of "the social constructivist account" as the choice between simplistically "evaluating facts" and an equally simplistic approach of "facting values" (Hofmann et al. 2018). The Charybdis can be sensed in Moreira's quasi-normative conclusions in which the pragmatic, deliberative approach is seen

as a solution that contributes to social robustness of the priority setting process. Effectively, the argument can be seen as going from "is" to "ought" as much as in a positivist account: Because various actors as a matter of fact challenged expert knowledge and hence created uncertainty about them, the decision process ought to take into account that uncertainty by taking a broad participatory, inclusive and deliberative approach in hybrid expert-lay fora whereby one may aim for a pragmatic balance between the various claims of matters of fact and value.

An important critique of this approach of "facting values" is that some claims may be truly unreasonable, uninformed or even not put forth in good faith. Sometimes a governmental body will dismiss such protests as unreasonable or unfair, and proceed notwithstanding the controversy. And sometimes they may be right in doing so, as when citizens want a new facility for waste management but Not In My Back Yard ("NIMBY") or when they want health care rationing but not for their own disease. And in that case, what we called Plan A above is warranted.

The positions of Scylla and Charybdis juxtaposed by Hofmann et al. (2018) are not entirely men of straw. Historically, there was some degree of political resonance between the science critique conveyed in the social constructivist heydays of STS (see e.g. Collins and Pinch 1993) and the agenda of citizen empowerment through public participation. Both movements grew out of the same political sources in the late 1960s (Sardar 2015). In this sense, a genealogical line can be drawn to Moreira's conclusion that pragmatic balance through hybrid fora is a way forward for health care priority setting and all the way back to Sherry Arnstein (1969) and the *ladder of participation*, where citizen control reigned highest in the hierarchy of public participation and where consultation and providing information were considered inferior and symbolic forms. It would not do Moreira's analysis justice, however, to ascribe to it the somewhat romantic views on citizen control of the 1960s. Rather, when discussing the possible Plans B for health care priority setting, we should enter into finer detail of the purpose of the participation.

Andy Stirling distinguished between instrumental, substantive and normative rationales for public engagement (Stirling 2008). The instrumental rationale is to use public engagement as a vehicle for apparent legitimacy, as when a lay person is included in an ethics committee more or less as a hostage, without much opportunity to influence the processes and outcomes. This rationale seems to be close to how lay persons are acting in the New methods system in Norway, as observers without any influence on the actual decision making. What Stirling calls the normative rationale, is the one of deliberative democracy: That certain processes and institutions may suffer from democratic deficit, and that public engagement may correct that deficit and the power imbalance that comes with it.

Somewhat in between, the substantive rationale is the idea that decision outcomes may be substantively *better* by opening up the processes to broader participation. At its core, the substantive rationale is consistent with Jürgen Habermas' ideas of discourse ethics and universal pragmatics: decisions get better if every argument is listened to and considered. In practice, however, the argument of the substantive rationale is often more specific and involves a critique of technocracy, how expert knowledge entails a risk of tunnel vision and that broader participation can improve

decision-making by including experiential knowledge and a broader range of values and perspectives.

The Achillean heal of this substantive rationale is the notion of "better" – in what sense is the decision imagined to become "better" by changing the process? If "better" simply means more desirable from a certain actor's point of view, the substantive rationale is undistinguishable from the instrumental one, and the participation was actually non-participation in Sherry Arnstein's definition. Similarly, if "better" simply means more democratic, this would be equal to the normative rationale.

The discourse ethics tradition, with philosophers such as Habermas and Karl-Otto Apel, would translate "better" into some notion of validity or criterion of truthfulness, consistency or objectivity, connecting it to the ideal, "herrschaftsfreie Diskurs" that by respectful listening and talking moves towards consensus. In real life, however, instead of consensus, it appears that modern societies are moving into a phase in which ever more classes of decision problems are plagued by persistent controversies. Appraisals and priority setting of expensive cancer drugs seems to be such a class of problems (Strand 2017).

Silvio Funtowicz and Jerome Ravetz (1985) offered an analysis of such problems, an analysis that later was to be associated with the concept of "post-normal science". In their analysis, these types of controversies are typically not resolved by scientific and technical attempts to reduce uncertainty; rather these attempts are themselves politicised and may as well end up increasing the controversy. The normative suggestions by Funtowicz and Ravetz were similar to those of Moreira: Broadening the perspective with respect to who can bring relevant knowledge and values to the table – "extending the peer community" in their terms – and preparing for processes of sustained and inclusive deliberation. However, their rationale was not an idealist belief in the herrschaftsfreie Diskurs or a true democracy. Rather, it was based in the more pragmatic solution that otherwise the controversy will simply not go away by itself.

Central to the idea of post-normal science is to let go of unrealistic hopes of attaining certainty and truth about the issue at stake and rather aim for a set of knowledge and value claims of mutually acceptable quality for the involved parties. In this framework, "quality" is to be understood as fitness for purpose; and part of the deliberation process is to decide on the acceptable purposes. While being formulated within a type co-production perspective, the idea of quality as fitness for purpose actually gives more guidance than the usual "broaden the participation" and offers one possible middle route between the Scylla and Charybdis mentioned above – it guides us towards what "better" decisions could look like.

Let us recall the problem set out in the first two sections of this chapter: Not only the increasing health gap due to scientific and technological advances in a particular political economy, but also a concomitant deterioration of the evidence base for priority setting decisions, as clinical trials get smaller and faster. And even worse, as patient stratification becomes ever more fine-grained, it will be increasingly difficult to distinguish between due and undue discrimination.

In line with Moreira we can conclude that the problem is likely to imply persistent controversy. It will continue to be possible to raise uncertainty claims both with

respect to standards and disease-specific knowledge; it is likely to become ever easier. The isolation between governmental priority-setting bodies and the political and public spheres that contest these bodies, is likely not to work much longer. Some new forms of broader deliberation are needed, and some kind of "pragmatic balance" is called for. But how?

The post-normal answer would be that the deliberation should aim at clarifying the purposes and revisit the knowledge base with respect to its fitness for purpose. It is not enough to make an uncertainty claim; in principle everything in this world can be questioned and called into uncertainty. What is needed, is to deliberate in good faith whether the uncertainty prohibits a decision, or whether the decision problem can be revisited and reframed. In this sense, fitness and purpose come together, in what we earlier called a *frame*. Part of these deliberations would deal with the question of standards, which means that the production of such standards – currently the work of health care ethicists, health economists and other experts –will have to be discussed. Also, how disease-specific knowledge is produced must be addressed. This means that trial design, how research and development of new drugs are organized and also how the whole political economy of drug development is set up, ought to be deliberated.

Sustainable Future Imaginaries for Cancer Drug Priority Setting

The post-normal question to rationing of cancer drugs is accordingly how the problem could, might and ought to be reframed (Stenmarck et al. 2021; Strand 2017). To ask such questions is to engage in socio-technical imagination (Jasanoff and Kim 2009), that is, to explore visions of future desirable scientific, technical and societal orders. In line with Jasanoff's co-production perspective, we insist that such orders, real or imagined, are scientific, technical and societal *at the same time;* they are co-produced in the sense of being produced together. Accordingly, if Plan A is merely to adjust and strengthen the institutions and practices of health care priority setting, the co-production perspective suggests that Plans B may reimagine the whole constellation of medical research, technology and practice together with the institutions and practices of priority setting. Plans B allow us to refuse to take for granted the current political economy of science and technology and the currently dominating reductionist imaginaries of personalised cancer medicine and precision oncology. The future *may be otherwise,* and we are entitled to imagine and strive for different futures.

We find it useful to distinguish between co-production (different things being produced together) and co-creation (different actors producing the same things). This distinction is in line with Jasanoff's perspective, although individual authors have defined these terms differently. At the same time, the co-production perspective lends itself naturally to the idea of co-creation and that the involvement of a

wider range of actors may lead to more democratic, more socially robust and ultimately *better* sociotechnical imaginaries and realities by extending the peer community. There are, in other words, two fronts that would have to be opened up in parallel in order to reimagine future cancer care, research and priority setting. The post-normal co-creation perspective suggests a front in terms of procedure, while the co-production perspective would also suggest a front in terms of substantive matter.

The procedural dimension of more sustainable imaginaries is not too difficult to envisage. For example, there will be no co-creation of knowledge in the Norwegian system which Moreira labels as "the public education model" (p. 1334) where expert assessments are the only valid source of knowledge and public engagement is close to what Stirling describes as an instrumental rationale for public engagement. Further, as decisions are to be neutral and rational, this effectively excludes patients, relatives, many health care workers and others who have their own skin in the game or the skin of those they care for. Currently, their opinions and viewpoints are dismissed within the frame of priority-setting institutions as "emotional" and accordingly biased. No wonder, then, that the frame is regularly overflowed:

> From the perspective of the suffering patient, the arguments about bias effectively imply that those who are most affected by the decisions are excluded from taking part in them. Even worse: It is exactly the fact of being directly and severely affected by the decision that disqualifies them from taking part in it. […] Modern society empowers them to create their own careers, families, households and living conditions and democratically influence the development of their own communities and societies. However, when they arrive at the critical point in their lives – perceived as a life and death decision over a certain immunotherapy – they no longer have a say as citizens at the general level of priority setting because they are affected and therefore not impartial and rational. (Strand 2017, 136–7)

If one rethinks how the role of patients in priority setting decisions could be, we could imagine that very ill, perhaps terminally ill cancer patients were invited to deliberative processes that would decide if their treatment could be prioritized. If the deliberation was real and not just what Arnstein called manipulation or placation, one would have to meet their demands with real counterarguments. Those included in the deliberation would have to accept that valid arguments against giving priority to their potential life-saving drugs was articulated. Essentially, one truth that would have to be put on the table is that no man is an island and that someone's suffering and death is in fact no tragedy for society. Humans are mortal and death is part of life, an insight that modern society is trying to neglect, hide and forget.

Indeed, the current ecosystem of rationing decisions in publicly financed healthcare systems is remarkably poor. Those who are directly affected are represented by proxies – patient organizations and of course also the pharmaceutical industry, that presents itself as patient guardians while at the same time have their own legal obligations to maximize profit for their owners. Those who are indirectly affected – citizens who pay taxes and may have other and competing welfare needs – are also represented by proxies in the form of governmental actors and institutions. Indeed, the latter may be seen to try to represent everybody's interest and well-being. On the top of all this, there are confidential drug prices, censoring of published documents

and unavailability of public justifications for decisions. This is the frame the overflowing of which still surprises some. From the co-creation perspective, bearing Stirling's normative rationale in mind, one would suggest to open up these processes to become inclusive and transparent.

When arguing as we do above for procedural reform and with a normative rationale, we should be careful not to be too directive in terms of the substantive issues. Indeed, what counts as *better,* is something for the deliberative processes in extended peer communities, and ultimately, society at large, to decide. Still, as we insisted above, the co-production perspective offers the view of scientific, technical and societal matters as entangled into each other and dependent on one another. Rather than "facting values" one can and, we believe, ought to open up the many value-laden assumptions underlying how personalised cancer medicine is imagined, practiced and governed.

A question that was already indicated above, is why at all society should devote so much public spending to cancer medicines or to health in the first place. Another question is why treatment innovations have to be so expensive. The answer may be found in the political economy of the research and innovation system of the health sector, which is characterized by the choice to allow private companies to seek high profits in return for the promise of fast innovation. Without going into a sweeping critique of capitalism, one could very well imagine that priority setting policies and research and innovation policies were coordinated to obtain policy coherence around the goal of reducing cost and finding a sustainable path for personalised medicine. Currently, public money subsidizes research that produces modestly beneficial drugs that the public health care system later has to buy for what many would say are perversely high prices.

A different trajectory could even be included under the increasingly important research policy concept of "openness", as in open access and open science. One could imagine policies by which public research funding was provided to develop biomarkers that predict toxicity and poor effect, and that could discover new indications for old drugs that no longer was under patent protection. By ceasing to accept the discourse of urgency and the imperatives argued for by industry, sometimes in coalition with patient organizations, other innovation trajectories could be sought – for effective prevention, for repurposing, for biomarkers to reduce ineffective or harmful treatment, for adaptive treatment regimes and other innovations that resist commodification and accordingly could be more affordable.

We present such imaginations while stating that we do not wish to be overly directive. This may seem strange to the reader: How can one deliver a proposal that, if implemented, would be likely to cause multinational pharmaceutical companies to go bankrupt, and still pretend to be careful and cautious? Our reply is to be found in the post-normal perspective: We are not experts who are speaking truth to power. First of all, we do not know better than everybody else. As combined citizens and researchers, we express our position for others to engage in and discuss. Secondly, even if we were under the illusion of being omniscient, we would not consider such changes, concomitantly in the political economy of research and the governance of the health sector, as nowhere viable if they were to be enforced by a technocratic

process. Co-production is de facto political; this is why there is overflow in the first place. This means, however, that neither a Plan A nor a Plan B will work as a technical quick fix. As personalized medicine evolve, priority setting problems and public controversies will continue to erupt; if we are right, they can only be resolved by rethinking and remaking science, technology and society.

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