Cancer Medicine and Precision Oncology

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Abstract

Cancer has garnered increasing interest among philosophers. This chapter focuses on cancer medicine and precision oncology, an influential approach to cancer which seeks to individualize treatment on the basis of genetic or molecular features of disease. It reviews a range of ontological, epistemic, and ethical questions raised by precision oncology, relating developments in cancer medicine to broader issues in the philosophy of science and medicine.

Introduction

Why should philosophers care about cancer? Cancer, to be sure, cuts across a range of topics covered in this *Handbook*, from issues of disease definition, classification, and causation to concepts of genetic disease and personalized medicine.

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Philosophers frequently cite cancer as a case study in natural kinds (e.g., Khalidi 2013), causation (e.g., Broadbent 2009), complexity (e.g., Plutynski 2021a), and inductive risk (e.g., Biddle 2016; Plutynski 2017). Over the past decade, however, there has been growing interest in philosophical study of cancer in its own right, not merely to inform pre-existing philosophical debates, but also as a source of new questions and puzzles for philosophers. Plutynski's *Explaining Cancer* (2018) is a standout example, who joined and was joined by a handful of others (e.g., Malaterre 2007; Germain 2012; Bertolaso 2016; Laplane 2018) who use cancer to open novel avenues of inquiry in the philosophy of science and medicine. Some hope that philosophy will also contribute to progress in the scientific understanding of cancer (Pradeu et al. 2023).

With some notable exceptions, existing philosophical literature has largely focused on the basic biology of cancer. Cancer *medicine*, however, has received relatively less philosophical attention. As Plutynski (2018, p. 216) recently remarked, few philosophers studying cancer have traced the trajectory from bench to bedside, which offers a potential trove of interesting philosophical questions. This chapter aims to survey this philosophical lacuna, focusing in particular on an influential idea that increasingly shapes this trajectory: the idea of precision oncology. As this chapter shows, the idea of precision oncology intersects with longer-standing ontological, epistemic, and ethical issues in cancer medicine, while also raising new questions, bringing new problems to the fore.

The chapter is structured as follows. "What is Precision Oncology?" introduces the idea of precision oncology, proposing a definition based on a review of recent literature. "Ontological Implications" examines how precision oncology informs ontological questions about cancer causation and classification. It highlights two possible implications for thinking about cancer classification, one modest and one radical, arguing in favor of the former. "Epistemic Implications" examines how precision oncology weighs on epistemic questions regarding how best to study cancer. It focuses on implications for clinical research, specifically the design of clinical trials, arguing that while precision oncology introduces certain methodological novelties, it largely relies on established approaches in clinical epidemiology. "Ethical Implications" concludes by reflecting on ethical questions raised by precision oncology, examining whether it represents a fair and equitable use of public resources in cancer research and patient care.

What Is Precision Oncology?

Definitions of precision oncology are notoriously imprecise. Precision oncology has been variously referred to as a "concept," "approach," "strategy," "initiative," "hypothesis"—even "era." So, which is it? Above, I used the vague term "idea" to describe precision oncology. In this section, I try to add further precision, proposing a definition of precision oncology.

Any attempt to define precision oncology must begin with its overarching idea: precision medicine. In 2015, the Obama White House announced the "Precision Medicine Initiative," which promised a "new era of medicine through research, technology, and policies that empower patients, researchers, and providers to work together toward development of individualized care" (Collins and Varmus 2015). Later rebranded as the "All of Us Research Program," the initiative seemed to promote a capacious notion of "individualized care," which considered not only genetics, but also factors such as environment, lifestyle, and family history for both disease prevention and treatment (NIH 2023a). However, as Tabery (2023) argues, this capaciousness is largely illusory—genetics always was and remains precision medicine's primary focus. Perhaps, then, a more accurate and straightforward definition is offered by a recent pamphlet from the US Food and Drug Administration (FDA): "Precision medicine is about matching the right drugs or treatments to the right people, based on a genetic or molecular understanding of their disease" (FDA 2019).

Precision oncology, in many ways, exemplifies this narrower scope of precision medicine. Simply replacing "disease" with "cancer" in the preceding sentence gives a reasonable first attempt at a definition. Early commentators (e.g., Garraway et al. 2013; Collins and Varmus 2015) situated oncology at the vanguard of precision medicine owing to the dominant understanding of cancer as a genetic disease. Targeted cancer drugs, such as imatinib (Gleevec) and trastuzumab (Herceptin), were (and still are) routinely cited as examples of the movement's unequivocal success.

But definitions of precision oncology have also evolved over time (see Tran et al. 2020). As Prasad and Gale (2017) observe, whereas early on precision oncology largely referred to a handful of targeted cancer drugs, it later focused on selecting treatments using biomarkers, especially genomic biomarkers generated by advances in sequencing technologies. According to these authors, however, the most "paradigm-shifting" definition of precision oncology not only advocates for treatment selection on the basis of genomic biomarkers, but more boldly argues for the priority of genomic-based cancer classification and treatment over more conventional approaches based on tumor site or tissue type (e.g., breast or prostate). I evaluate this argument further in "Ontological Implications" and "Epistemic Implications." Table 1 highlights some recent definitions of precision oncology from the medical literature.

Philosophers have tried to make sense of this evolving mash-up of definitions. Some sidestep definitions altogether. Lemoine (2017), for example, argues that precision medicine's vagueness creates insurmountable challenges for traditional conceptual analysis. This leads him to characterize precision medicine in terms of its specific therapeutic achievements, namely monoclonal antibody drugs ("mabs"). Mabs, he argues, are the "archetype" for precision medicine, more aptly termed "*mab*-medicine," according to Lemoine. Mabs work by binding specific proteins on the surface of cells, allowing their effects to be directed at specific cells implicated in a disease process, with minimal effects on surrounding tissues. This contrasts with

Table 1 Definitions of precision oncology from the medical literature

Definition	Type	References
"Exciting era in cancer research . . . in which doctors are choosing treatments based on the DNA signature of an individual patient's tumour."	"Era"	NIH (2023b)
"To develop treatments that target the molecular characteristics of an individual's tumour . . . [some] eschew the question of where in the body the tumour originated, and instead focus on particular genetic mutations."	"Premise"	Hodson (2020)
"Molecular profiling of tumors to identify targetable mutations."	"Approach"	Schwartzberg et al. (2017)
"All patients with cancer would undergo germline and tumour sequencing to identify a unique mutational profile that will guide a highly effective therapy with few side effects."	"Hypothesis"	Prasad et al. (2016)

other drugs, such as conventional cancer chemotherapies, which have a wider array of "off-target" effects.

However, while mabs do instantiate a certain sense of precision in their mechanism of action, whether they serve as an archetype against which precision medicine should be understood is less clear. Most oncologists, for example, would find it strange to call rituximab (a mab against the cell surface protein CD20) the "archetype" of precision medicine given its widespread use in nearly all patients with a broad category of cancers that express CD20 (namely, B-cell lymphomas), where it serves as a marker of a type of cell (namely, B-lymphocytes, both normal and malignant) rather than an "individualized" molecular feature of disease. A focus on mabs—indeed, on any therapeutic technology in isolation—does not fully capture what is seen as innovative about precision medicine. Thus, while exemplars remain indispensable, precision medicine and oncology can and should be defined beyond resemblance to a particular therapeutic archetype.

Focusing on precision oncology, Plutynski's (2022, p. 7) offers a more inclusive definition, defining it in terms of its aim "to identify and deploy genetic and molecular features of cancer in service of diagnosis, prognosis, and treatment." Crucially, according to Plutynski, this includes identifying molecular features of disease "in each cancer patient" in order to tailor treatment "to each patient." Here, "precision" does not simply refer to a treatment's "precise" mechanism of action in relation to a type of tumor (as is the case for most mabs) but rather in relation to a token tumor, i.e., a particular tumor, in a particular patient. Plutynski's definition does seem to better capture the sense of precision expressed in the literature to use "the right drug, for the right patient" (e.g., FDA 2019), and is very close to the definition proposed here.

One worry, however, is that this definition is overinclusive. Just because a treatment is tailored to the molecular features of an individual's disease does not make it precise. For example, faced with the finding of *IGHV* mutated status in a patient with chronic lymphocytic leukemia (CLL, a cancer of B-lymphocytes), the oncologist may tailor treatment, say, opting for multiagent chemotherapy given that

IGHV mutated status predicts good response to this conventional treatment. Few, however, would call this an example of precision oncology. At best, this approach might be called "stratified" medicine. Examples of stratified treatment of cancer are common. On the other hand, when the same oncologist uses the BCR-ABL kinase inhibitor imatinib in her patient with chronic myeloid leukemia (CML, a cancer of myeloid cells) harboring a *BCR-ABL1* translocation, celebrations over the success of precision oncology seem to follow. The difference between these cases lies in what is being tailored: precision oncology does not simply involve tailoring any old treatment, but rather using a *targeted treatment* that bears a specific relation to the molecular feature in question.

What I propose, then, is a revised definition to better account for this distinction:

> Precision oncology is an approach to cancer that involves applying and expanding the use of *predictive biomarkers*, specifically molecular or genomic biomarkers, and paired *targeted treatments* to improve clinical outcomes of patients with cancer.

This definition aims to capture how precision oncology is at once an approach to cancer medicine and to cancer research, seeking not only to apply existing predictive biomarkers and targeted treatments in practice, but also to expand the set of biomarker-treatment pairs through translational research. The term *predictive biomarker* here refers to molecular or genomic data used to identify individuals expected to have a favorable response to a particular intervention (FDA-NIH 2016). In this definition, the intervention takes the form of a *targeted treatment*, where "targeted" refers to a specific relation to the biomarker in question. Roughly speaking, this targeting relation consists in a treatment intervening in some capacity on the disease part or process measured by the biomarker. This helps distinguish precision oncology from mere stratified cancer treatment. *IGHV* mutated status might predict a favorable response to chemotherapy in CLL, but chemotherapy does not have a targeting relation to this biomarker. By contrast, not only does the presence of the *BCR-ABL1* translocation in CML predict response to imatinib but imatinib *qua* BCR-ABL kinase inhibitor *targets* this genomic alteration—it intervenes on the aberrant protein produced by the translocation to abrogate its function.

This definition is more stringent and demanding. It also leaves out precision oncology's putative diagnostic and prognostic aims (c.f., Plutynski 2022). This isn't a problem: while diagnosis and prognosis are crucial aspects of cancer medicine, "precise" prediction without effective treatment overlooks precision oncology's fundamental aim. Precision oncology seeks novel ways to intervene in cancer to improve patient outcomes. This proposed definition, therefore, more accurately captures what is touted as new and distinct about precision oncology. Recent therapeutic advances in cancer, such as certain monoclonal antibodies, immune checkpoint inhibitors, and small molecule inhibitors, fit this definition. Some examples are listed in Table 2.

While this definition helps clear up conceptual ambiguities, one consequence is that it is not possible to determine a priori whether a given biomarker-treatment pair counts as a successful example of precision oncology. Research into biomarker-treatment pairs might be pursued under the banner of precision oncology without

Table 2 Examples of targeted treatments and corresponding biomarkers

Targeted treatment	Biomarker	Drug class	Cancer	FDA approval
Trastuzumab	HER2 expression	Monoclonal antibody	Breast cancer	1998
Imatinib	*BCR-ABL1* translocation	Small molecule inhibitor	Chronic myeloid leukemia	2001
Gefitinib	*EGFR* mutations	Small molecule inhibitor	Lung cancer	2003
Crizotinib	*ALK* rearrangement	Small molecule inhibitor	Lung cancer	2011
Vemurafenib	*BRAF* mutation	Small molecule inhibitor	Melanoma	2011
Pembrolizumab	PD-L1 expression	Immune checkpoint inhibitor	Melanoma, lung cancer, lymphoma, and others	2014
Midostaurin	*FLT3* mutations	Small molecule inhibitor	Acute myeloid leukemia	2017
Enasidenib	*IDH2* mutations	Small molecule inhibitor	Acute myeloid leukemia	2017
Ivosidenib	*IDH1* mutations	Small molecule inhibitor	Acute myeloid leukemia	2018

yielding success in particular cases. Moreover, the development of predictive biomarkers and targeted treatments may not happen in concert. Discovery of a predictive biomarker might precede the development of a targeted treatment. Conversely, therapeutic innovation might outstrip biomarker development to identify patients who differentially benefit from the novel therapy. On their own, these might represent important advances in cancer medicine, but only when paired together, and shown to improve clinical outcomes, are they considered successful examples of precision oncology. This point bears emphasizing—as an *approach* to cancer, precision oncology can encourage certain forms of research and clinical practice. We might call these practices attempts to implement precision oncology. Such attempts might (often do) fail. Precision oncology's success ultimately rests on generating cases where predictive biomarkers and paired targeted therapies do in fact improve patient outcomes. Only these are considered successful instances of precision oncology. It is in this way, *pace* Lemoine (2017), that therapeutic exemplars play a central role in precision oncology. With this definition in mind, I now turn to precision oncology's implications for thinking about cancer causation and classification.

Ontological Implications

Prima facie the above definition of precision oncology does not seem to say much about the nature of cancer, its causes, and how it is best classified. But as an approach to cancer medicine and research, precision oncology does weigh on these ontological

questions. In this section, I explore how precision oncology is often taken to promote a reductionist view of cancer which can engender rather radical conclusions about cancer causation and classification. I reject these conclusions, arguing that precision oncology's ontological implications are in fact more modest—still potentially revisionary, but not radically so.

Precision oncology is seen as promoting genetic reductionism, privileging genetic causes in its approach to cancer. As we have seen, precision oncology (and precision medicine more generally) explicitly seeks to base treatment on "genetic or molecular understanding" of disease (FDA 2019), at once reflecting and bolstering the dominant view of cancer as a genetic disease. This view of cancer is often associated with "somatic mutation theory," according to which cancer is caused by acquired genetic mutations (or other genomic alterations) in somatic cells (Marcum 2005; Malaterre 2007). In CML, for example, a myeloid cell in the bone marrow acquires a specific genomic alteration, the *BCR-ABL1* translocation, which drives cell proliferation and results in cancer. Somatic mutation theory has had explanatory successes across a range of cancers. But it has also faced push-back from anti-reductionists who argue that somatic mutation theory fails to explain salient phenomena in cancer better accounted for by factors at the tissue, organism, or systems level (see Bertolaso 2016). Such phenomena include, for example, spontaneous regression or induction of cancer resulting from changes in tissue architecture (Soto and Sonnenschein 2011). Other rival views include cancer stem cell theory, which holds that cancer initiation and progression is caused by a distinct subpopulation of self-renewing cancer stem cells (Laplane 2016). These arguments will not be reviewed in detail here. Ultimately, these apparently competing theories may not be as incompatible as their proponents suggest (see, for discussion, Plutynski 2019). Although one might still raise questions about relative emphasis or research funding allocation (see "Ethical Implications"), cancer research today likely benefits from the co-existence of multiple perspectives in its efforts to explain and intervene in cancer.

On the whole, contemporary cancer research may adopt different perspectives; however, it is harder for precision oncology to shake accusations of genetic reductionism. As the above definitions make clear, precision oncology is expressly committed to the belief that genomic biomarkers serve as the best guide to treating cancer. How deep does this commitment go? On the one hand, precision oncology's reductionism might simply be a pragmatic bet. The pragmatist might acknowledge that cancer is caused by a range of factors across different levels of organization, while also believing that targeting molecular or genomic alterations is the most expedient strategy for treating cancer in light of the successes of this approach. On the other hand, precision oncology's reductionism might run deeper. In contrast to the pragmatist, the radical reductionist might see the discovery of effective biomarker-treatment pairs within existing cancers as an intermediate step toward a more radical end of redefining cancer in wholly genomic terms, which they take to capture cancer's "true" causes. Both pragmatist and radical reductionist proponents of precision oncology are found in the literature. A closer look at current approaches to cancer classification (and disease classification more generally), however, reveals the radical reductionist to be misguided and argues in favor of the pragmatist view.

Problems in cancer classification relate to broader philosophical discussions of disease nosology (see Part "► VI Nosology" of this *Handbook*), as well as debates over diseases as natural kinds. To be clear, debates over cancer's status as a natural kind are somewhat adjacent to debates over genetic reductionism, and affirming the former does not entail the latter. The intention here is not to adjudicate whether cancer is a natural kind, which, as Plutynski (2018) shows, depends rather heavily on one's view of natural kinds. This debate, however, does provide a useful entry point for Plutynski's (2018, pp. 18–60) illuminating analysis of cancer classification, whose broadly pragmatist outlook lends support to a pragmatist reading of precision oncology.

As Plutynski discusses, certain defenders of cancer as a natural kind seek a universal system of cancer classification in terms of its genetic mechanisms or causes. More generally, some see this as the basic aim of precision medicine: to re-orient disease categories toward natural kinds, identifying the genetic mechanisms that "carve nature at its joints" in service of effective interventions. Likewise, the abovementioned radical reductionist takes this to be the mission of precision oncology. But as Plutynski points out, attempting to classify cancer in terms of mechanisms or causes creates problems of causal selection. How do we choose between competing classifications to identify the one that best reflects "the causal structure of the world"? Such choices are underdetermined. A brief look at disease models in modern medicine makes this point clear and shows why, *contra* the radical reductionist, knowledge of genetic causes alone will not produce a wholesale re-classification of cancer.

Progress in modern medicine is often attributed to approaching disease from "the etiological standpoint," that is using causes as a guide to explaining, defining, classifying, and ultimately controlling disease (Carter 2003). The most celebrated examples come from infectious diseases, where conditions like tuberculosis or anthrax were re-defined and re-classified according to specific causes, namely microorganisms such as *Mycobacterium tuberculosis* or *Bacillus anthracis*, which paved the way to effective interventions. Philosophers call these examples the "monocausal model" of disease, which seeks to define and classify diseases in terms of universal necessary causes (Broadbent 2014; Fuller 2018). The monocausal model of disease, emerging in the nineteenth century, represented a shift from what Fuller (2018) terms the "constitutive model," where diseases were defined in terms of what the condition is, that is to say state descriptions, rather than in terms of a specific cause. Such state descriptions might range from constellations of signs or symptoms to evidence of physiologic or tissue dysfunction. In the twentieth century, the rise of non-communicable diseases, including cancer, led to the development of a "multifactorial model" which tried to account for the fact that these diseases were not explained by a single, specific cause but rather a range of causes, or rather "risk factors," such as smoking, environmental exposures, diet, and genetics. But while a multifactorial model here is surely correct, unlike the monocausal model, it does not provide a straightforward means for defining and classifying disease. Instead, Fuller argues that the multifactorial model is better understood as the product of the longer-standing approach to disease definition and classification present all along—the constitutive model.

Whether disease is best understood according to constitutive or causal models is debated by philosophers. For cancer, however, the constitutive model seems most apt. Take the example of CLL, the cancer of B-lymphocytes mentioned above. The World Health Organization defines CLL as "a neoplasm composed of monomorphic small mature B cells that co-express CD5 and CD23 [cell surface proteins]" (Campo et al. 2017). Like most cancers, CLL has a multifactorial etiology which includes factors such as aging, environmental exposures, and genetics. But it is not defined in terms of any one of these causes, or even in terms of a confluence of causes. Rather, it is a state description: CLL is defined by the presence of a certain number of cancer cells in the blood "with characteristic morphology and phenotype." CLL is not unique in this respect. Fuller (2018) shows how one can, in principle, attempt to re-classify multifactorial diseases according to the monocausal model if one is willing to tolerate some shifting of disease categories. We could, for example, choose to define CLL in terms of putative genetic causes, such as disruption of the tumor suppressor gene *TP53*, found in up to 15% of cases of CLL. But in cases of multifactorial causation, an etiological classification leads to the problem of causal selection mentioned above. Why should a classification privilege this genetic cause over other potential factors, say carcinogens or viral infections, which may also be important causes of CLL? Causal specificity is not the answer here: *TP53* mutations are found in nearly all types of human cancers with rates approaching 50%.

Does this situation simply reflect our relative ignorance about "the causal structure of the world" as it pertains to CLL? Should we hold out for more research into cancer genetics to yield a truly "mechanism-based" nomenclature on the model of infectious diseases, as some researchers predicted at the turn of the century (e.g., Bell 2003)? Many anticipated that large-scale sequencing initiatives like The Cancer Genome Atlas Project (TCGA) would produce such insights into genetic causes of cancer, leading to an etiological classification. The TCGA did yield valuable knowledge of cancer genomics, helping to refine classifications and, in some cases, leading to genetically defined cancer subtypes. But it did not engender a wholesale re-classification of cancer in terms of genetic causes. Rather, TCGA's take-home message was that genetic causes of cancer are complex, diverse, overlapping, and multifarious. (All this leaving aside conceptual and methodological problems defining what counts as a genetic cause or "driver" in the first place; see Plutynski 2021b.) Recent advances in cancer genomics, therefore, show a genetic-based monocausal model, inspired by the micro-organism-based model of infectious diseases, to be the exception rather than the rule in cancer.

This should not be cause for surprise, nor necessarily for pessimism. While knowledge of causes can lead to effective intervention, contrary to some beliefs, this does not require a fully etiological classification. These two aims, while seemingly coterminous, are in fact distinct. As Fuller (2018) argues, even diseases for which we have in-depth causal knowledge continue to be defined constitutionally. He makes this point with examples from infectious diseases, but his arguments easily extend to cancer. In cancer, the *BCR-ABL1* translocation in CML is as close as one gets to a universal necessary cause. Indeed, the discovery of this genomic alteration in CML served as initial inspiration that universal genetic causes might be found across all cancers. But to this day even CML continues to be defined constitutionally.

Yes, the presence of the *BCR-ABL1* translocation is a necessary criterion for this diagnosis. But crucially this must occur in "the appropriate clinical and laboratory settings," i.e., in a patient with clinical features of CML, such as symptoms or blood test abnormalities (Campo et al. 2017). It is highly contentious whether asymptomatic patients with normal blood counts who are incidentally found to have *BCR-ABL1* translocations (not all of whom invariably develop overt disease) should count as having CML. Just as a yeast infection (candidiasis) is not defined simply by the presence of its specific cause, the *Candida* yeast, but rather as a state description of pathological overgrowth (Fuller 2018, p. 14), CML remains constitutionally, not etiologically defined. The same applies to other cancers with well-described genetic causes.

What does this all mean for precision oncology's ontological implications, specifically for thinking about cancer causation and classification? Precision oncology, to be sure, entails a certain degree of reductionism in its focus on genomic biomarkers and targeted treatments. But it need not be committed to the radical reductionist position, which holds that the success of this approach will ultimately rest on a wholesale re-classification of cancer in genomic terms. Precision oncology's commitment to genomic-based treatment need not be premised on a view of cancer classification as a hunt for the one "true" causal structure of cancer. As Plutynski (2018) makes clear, such a hunt is likely to be fruitless. Most cancers don't have universal necessary causes, and even if they did, diseases are not defined in solely etiological terms.

Instead, precision oncology should embrace the pragmatist outlook, recognizing that what we count as causes and how we classify cancer is interest relative. Precision oncology brings particular interests to the table: it argues that prioritizing genomic causes confers practical benefits, enabling interventions that improve outcomes for patients with cancer. This argument might extend to classification as well: revising diagnostic categories in light of genetic causes might have epistemic and practical benefits. This was certainly the case with diseases like CML. Distinguishing *BCR-ABL1*-positive CML from other cancers previously regarded as similar, now classified as distinct myeloproliferative neoplasms, enabled more effective diagnosis, prognosis, and treatment. But as recent updates to blood cancer classification make clear (e.g., Khoury et al. 2022; Arber et al. 2022), these revisions are piecemeal and provisional, and categories are never defined solely etiologically. Thus, the radical reductionist quest—at least when it comes to cancer classification—is misguided.

Next, I turn to precision oncology's epistemic implications, focusing on how it answers the question of how best to study cancer in a clinical setting.

Epistemic Implications

Ontological issues in cancer causation and classification discussed above weigh on epistemic questions of how best to study cancer. Different views of cancer causation, for example, suggest different approaches to cancer research. As we have seen, somatic mutation theory encourages a hunt for genetic causes of cancer. Historically,

this involved techniques of molecular biology applied in model systems such as cell culture or transgenic mice to study mechanisms of cancer initiation and progression. Increasingly, however, the hunt for genetic causes applies "big data" approaches, exemplified by large-scale sequencing projects such as TCGA, which analyzed over 11,000 individual tumors in an attempt to uncover unique genetic signatures across a range of cancers. These approaches dovetail with precision oncology's goal of individualized, genomic-based treatment, and indeed many characterize such initiatives as directly servicing the aims of precision medicine (Plutynski 2022). The promise of precision oncology thus inspires some of the most influential initiatives in cancer research during the past few decades. This section, however, will focus on precision oncology's more downstream implications for cancer research, examining how precision oncology influences approaches to studying cancer in clinical settings, specifically the evaluation of predictive biomarkers and paired targeted treatments.

On the one hand, it might seem that precision oncology carries rather radical implications for clinical research, suggesting a need to overhaul approaches to clinical trial design and therapeutic decision-making. Tonelli and Shirts (2017), for example, argue that precision medicine will necessitate revisiting the evidence hierarchy set out by the Evidence-Based Medicine movement (see chapter "► Evidence-Based Medicine in Theory and Practice: Epistemological and Normative Issues"), elevating the role of mechanistic knowledge, including data from in vitro and in silico functional studies, vis-à-vis population-level data.

Precision oncology aims to match predictive biomarkers with targeted treatments for individual patients. As we have seen, some go further to argue that precision oncology's "paradigm-shifting" impact lies in its advocacy for treatment selection based on genomic biomarkers rather than tumor site or tissue type (Prasad and Gale 2017). This raises potential challenges for clinical research. Unlike conventional anatomic or histologic categories, a given genomic biomarker is usually only found in a smaller number of patients. Attempting to evaluate the "precision" approach biomarker by biomarker, drug by drug, using traditional clinical trial designs, many argue, would be underpowered, time-consuming, costly, and ultimately infeasible.

As a result, several novel trial designs have emerged with precision oncology (see, for discussion, Janiaud et al. 2019). One often emphasized is the so-called "basket trial," which includes a mixed "basket" of cancer types and assigns treatment based on genomic biomarkers rather than tissue type. For example, whereas a conventional clinical trial might enroll only patients with breast cancer and assign treatment in a randomized fashion, a basket trial enrolls patients with any cancer type (e.g., breast, prostate, lung, etc.) and assigns treatment according to genomic biomarkers. Basket trials are often cited as a key methodological innovation of precision oncology. Some go further to claim that they provide a true test of the "precision" approach. Prasad (2020, p. 107) in particular argues that the success of the precision oncology "hypothesis" hinges on demonstrating three things in a basket-type trial: (1) "matches between patient tumors and drugs (ideally, a considerable number of matches);" (2) "tumor shrinkage in matched patients (ideally, total tumor shrinkage);" and (3) "longer survival in [matched] patients compared to patients who had

not undergone sequencing but instead had a doctor prescribe drugs the old-fashioned way." Prasad contends that evidence from existing basket trials fails to establish (1–3); he is skeptical that these will be achieved but proposes further randomized trials to evaluate this.

In reality, however, basket trials face numerous methodological limitations, especially in determining which "actionable" mutations should be used to assign treatment, given the considerable heterogeneity in responses within biomarker-treatment pairs across cancers (Mandrekar et al. 2015; see also Chin-Yee and Plutynski 2023). Their use, therefore, is generally limited to early-phase, discovery trials, typically enrolling patients with advanced cancers for whom standard treatments have already been exhausted. Basket trials may suggest the efficacy of particular biomarker-treatment pairs, potentially identifying "exceptional responders," but are better seen as stage-setting for more rigorous, later-phase clinical evaluation.

Therefore, while basket trials may represent a methodological novelty in clinical research brought about by precision oncology, it is not clear that precision oncology's success hinges on this approach. Given their exploratory nature, such trials are unlikely to represent a fair test of precision oncology. Moreover, as discussed in "Ontological Implications," precision oncology is not clearly committed to eschewing conventional disease categories altogether, but is often satisfied with more iterative, piecemeal identification of effective biomarker-treatment pairs within existing cancer types. "Umbrella trials," for example, provide a less radical alternative to the basket trial, which respect conventional disease categories, assigning treatments based on biomarkers within a particular cancer type. Rather than a crucial test of precision oncology, basket trials should instead be understood as one tool in precision oncology's broader methodological armamentarium, which encompasses a range of trial designs spanning various phases of clinical research.

In fact, although more traditional clinical trial designs are often construed as infeasible for advancing precision oncology, they still form the basis for approval of most successful targeted treatments. Consider midostaurin (Table 2), for example, a drug which targets the FLT3 kinase, known to be mutated in up to one-third of patients with acute myeloid leukemia where it drives uncontrolled cell proliferation and survival. Approval of midostaurin was based on a more traditional randomized trial comparing the use of midostaurin to standard chemotherapy in patients with *FLT3*-mutation-positive acute myeloid leukemia (Stone et al. 2017). Such trials represent a more modest modification to conventional trial designs in cancer, simply including the presence of the biomarker of interest among eligibility criteria for enrolment. In the case of the midostaurin trial, over 3000 patients with acute leukemia were screened; nearly 900 had *FLT3* mutations making them eligible for enrolment. While this approach, referred to as biomarker "enrichment," is sometimes cited as a novelty of precision oncology, it is in reality no different than the longstanding approach in clinical research to stratify patient populations and focus interventions on particular subgroups that might stand to benefit. What is unique to the "precision" approach, then, is not the clinical trial design and patient

stratification, but rather the specific relation between the biomarker and targeted treatment, as discussed in "What is Precision Oncology?"

Another modification to traditional clinical trials often seen in precision oncology is the use of surrogate endpoints (Del Paggio et al. 2021). Surrogate endpoints are meant to substitute for clinically meaningful endpoints that attest to the efficacy of interventions, namely survival or quality of life. At best, surrogate endpoints are chosen to address important practical and ethical demands, such as limited trial enrollment or duration. These can be important considerations in precision oncology where, as we have seen, designing trials adequately powered for survival in small biomarker-defined subgroups can present challenges. At worst, however, surrogate endpoints are selected simply to expedite approval of drugs with marginal clinical benefit. Indeed, the use of surrogate endpoints is not unique to precision oncology and has long been a point of contention in cancer research (Booth and Eisenhauer 2012). In some ways, targeted treatments in particular might lend themselves to evaluation by surrogate endpoints. One example is the growing use of minimal residual disease, a measure of residual cancer cells, as a surrogate endpoint in cancer clinical trials (Chin-Yee 2024). Minimal residual disease can be used to infer the efficacy of a targeted drug in eliminating its specific target, indicated by eradication of a particular cell type or molecular biomarker. But aside from such examples, precision oncology does not have any special reliance on surrogate endpoints, nor does it provide any special justification for their use. Rather than any sound epistemic rationale, the trend toward increasing use of surrogate endpoints in precision oncology more likely reflects a rise in industry-funded trials aimed at expedited drug approval in an era of lax regulatory practices (Del Paggio et al. 2021; see also Prasad 2020). Against such trends, precision oncology's targeted drugs should be evaluated just like all other cancer treatments: in terms of their ability to help patients live longer and better.

Therefore, just as precision oncology's ontological implications are rather modest, so are its epistemic implications for clinical research in cancer. Fuller (forthcoming) also makes this point, arguing that precision medicine is largely an extension of traditional approaches to clinical research. According to Fuller, precision medicine closely resembles "epidemiological medicine," his term for the dominant approach to medicine during the twentieth and twenty-first centuries which studies disease and its treatment using methods of epidemiology, including clinical epidemiology, the science of clinical trials. Fuller likewise acknowledges that precision medicine does include some tweaks to traditional clinical trials and may open the door to more interdisciplinary research that elevates the role of biological rationale and mechanistic knowledge compared to Evidence-Based Medicine's rigid epistemology.

By and large, however, precision oncology's implications for clinical research are unlikely to be "revolutionary" or "paradigm shifting" in the way that proponents sometimes suggest. Proponents might reply that these are early days; pointing to a future where "precision" drugs with sound mechanistic rationale produce effect sizes so large that they obviate the need for population-level studies. This future, however, seems improbable. Even the most successful of "precision" drugs, such as imatinib

for CML, still require evaluation by clinical trials for approval and acceptance. The fact that medicine still (rightfully) demands clinical trials reflects the fact that so-called "magic bullets" are, unfortunately, few and far between (see Stegenga 2018, pp. 54–67). Precision oncology's track record to date fails to provide a compelling reason to anticipate relaxing these epistemic standards.

To recap, while precision oncology might at first seem to require radical reform to clinical research, it will likely leave existing approaches to clinical research in cancer largely intact. This is not to say it won't have any impact. Biomarker-guided basket- or umbrella-type trials may serve an exploratory, hypothesis-generating role in the early phases of clinical research. In some cases, they may help uncover new effective biomarker-treatment pairs. However, on their own they are unlikely to provide sufficient evidence to shape routine clinical practice, not to mention, *pace* Prasad (2020), sufficient evidence to accept or reject precision oncology as an approach to cancer treatment *tout court*. Later-phase trials of targeted treatments may utilize biomarker enrichment in their designs. However, these techniques are better understood as continuous with longer-standing approaches to patient selection in clinical epidemiology. Lastly, precision oncology may suggest the use of novel surrogate endpoints in clinical trials. However, it does not provide any special justification for their growing use, which should remain under close scrutiny in cancer research.

Ethical Implications

While precision oncology's epistemic implications for downstream clinical research in cancer may be modest, as noted at the beginning of "Epistemic Implications," the approach may be more influential in upstream cancer research, inspiring major genomic research initiatives such as TCGA. With respect to precision medicine, the "All of Us Research Program" (formerly "Precision Medicine Initiative") mentioned in "What is Precision Oncology?," is essentially a large-scale observational cohort study built on genomic data, which aims to enroll and sequence the genomes of one million participants in the United States. Since 2015, the program has received over $2 billion in federal funding (All of Us 2019). Despite claiming to investigate a broad range of determinants of health, Tabery (2023, p. 197) details how the All of Us initiative remains "skewed scientifically, financially, organizationally, and educationally towards DNA." Thus, he argues, precision medicine's focus on genetics occurs at the expense of research focused on environmental and social determinants of health. Although substantial investment in precision medicine comes from the private sector, there is no question that research in precision medicine and oncology consumes a large amount of public resources, especially in the United States but also in Europe and Canada (Gyawali et al. 2018). This raises an ethical question for precision oncology: is allocating funding to research programs primarily focused on genetic causes of cancer a fair and equitable use of public resources? Do such programs really stand to benefit "All of Us"?

If recent history is any indication, the answer to the latter question is most likely no. Consider, for example, trastuzumab (Herceptin). Despite being among the first and most celebrated examples of precision oncology, which gained FDA approval in HER2-positive breast cancer in 1998 (Table 2), significant disparities in access to this targeted treatment have persisted for decades. In the United States, for instance, Black women were 25% less likely to receive this drug than white women with the same indication (Reeder-Hayes et al. 2016). These disparities are even more pronounced on a global scale (Li et al. 2017; Ades et al. 2017). Although the majority of new cancer cases and cancer deaths occur in low- and middle-income countries—70% according to recent estimates (Gopal and Loehrer 2019)—as things currently stand few patients in these countries are likely to benefit from advances in precision oncology. Despite its universalist rhetoric, the benefits of precision oncology are likely to remain narrowly and unequally distributed.

This section focuses on two distinct yet related ethical concerns raised by precision oncology. The first is the opportunity cost argument, which claims that funding precision oncology detracts from investment in programs that generate more substantial and widespread improvements in cancer outcomes. The second is the solidarity argument, which worries that an individualized approach promoted by precision medicine and oncology undermines commitment to universal healthcare.

The opportunity cost argument is fairly clear-cut: public dollars spent on initiatives in precision oncology are dollars that could otherwise have been spent on programs that better improve clinical and population health outcomes in cancer. (Here, the focus is on cancer outcomes, although the argument is sometimes extended to health outcomes in general.) Two dimensions of this missed opportunity for health benefit are emphasized: magnitude and distribution. In terms of magnitude, programs focused on prevention and early detection of cancer are known to confer the greatest aggregate benefit on a population level. The over 30% decline in cancer mortality in the United States since 1991, for example, is primarily explained by preventive measures, such as tobacco control and human papillomavirus vaccination (Siegel et al. 2023). That such population health initiatives—the ostensible opposite of a "precision" approach (see Chin-Yee et al. 2018)—confer the greatest magnitude of benefit is not surprising. As highlighted by Rose's (1992) so-called "prevention paradox," strategies targeting large segments of the population at low risk confer larger aggregate benefit than strategies targeting smaller segments at high risk (or, indeed, those with overt disease). Although genomics may itself help define risk, and in turn inform approaches to prevention and early detection (see, however, John 2013), in its current form precision oncology remains an ultra-high-risk strategy.

Precision oncology faces further criticisms in terms of how it distributes health benefits relative to population health initiatives. Strategies in the prevention and early detection of cancer are certainly not immune to distributional challenges, which primarily arise from lack of access to programs among marginalized groups (Berland et al. 2019). Disparities in access and funding giving rise to disparities in cancer prevention and screening are only amplified when it comes to cancer treatment. However, concern about precision oncology's unequal distribution of health

benefits runs deeper. Evidence shows that knowledge produced by research in precision oncology may favor specific groups over others. TCGA, for example, has been criticized for its bias toward patients of European ancestry, who made up 83% of patients studied, compared to only 6% of patients with African ancestry and 6% with East Asian ancestry (Rajagopal and Olopade 2020). Such disparities in representation in upstream genomic research have downstream consequences. Studies show that Black and Asian patients with cancer are more likely to have ambiguous genetic test results (e.g., Kurian et al. 2021), potentially limiting the ability to base effective treatment on genomic data for members of these groups, the central aim of precision oncology. Ambiguous genetic test results, so-called "variants of uncertain significance," also pose additional harms to patients (see, for discussion, Reynolds 2020). This racial and ethnic gap in the interpretability of genomic data may only be widening over time with the increasing use of genetic testing in oncology practice. As discussed in "Epistemic Implications," genomic data are increasingly used in clinical trials as eligibility criteria or to assign treatment based on "actionability," raising further worries that upstream disparities will be reinforced downstream. Indeed, recent evidence shows that underrepresentation of racial and ethnic minorities extends to clinical trials of precision oncology drugs (Aldrighetti et al. 2021), potentially hindering their generalizability to members of these groups. Together, these trends raise concerns that large segments of the population are systematically left out of precision oncology's goal of individualized cancer care.

Precision oncology's distributional inequities link to concerns over solidarity. Roughly speaking, solidarity in healthcare refers to a shared commitment to "equal access to *effective* healthcare for all" (Fleck 2022, p. 194; see also Prainsack and Buyx 2017). Fleck (2022) argues that precision medicine threatens healthcare solidarity primarily due to its exorbitant costs and narrow distribution of marginal benefits, namely for patients with advanced cancer. These are important concerns. As the prior discussion makes clear, distribution of precision oncology's benefits may be narrow indeed. Provided limited resources, precision oncology thus often conflicts with the goal of effective healthcare for all in polities committed to universal healthcare. To say this is just to restate the opportunity cost argument, or rather, to show that a commitment to solidarity is a premise of that argument. But these concerns are not unique to precision oncology. They equally apply to other high-cost interventions that benefit small segments of the population, from advanced fertility treatments to gene therapy for rare diseases. For this very reason, publicly funded healthcare systems have mechanisms in place to determine which such interventions to fund, ideally reflecting universalist principles in the interest of solidarity. These mechanisms are no doubt imperfect—many criticisms, for example, are raised against disproportionate and ineffective public schemes for funding cancer drugs (e.g., Aggarwal et al. 2017). But precision oncology per se does not provide any unique challenge to solidarity on this basis.

What may have unique consequences for solidarity is precision oncology's goal of individualized care based on genomic data. John (2020, p. 23) raises the worry that genetic risk prediction offered by precision medicine might threaten solidarity by

undermining the "equal risk" assumption that motivates citizens to contribute to socialized healthcare through taxation. Simply put, individuals whom genetic testing identifies as having low risk of cancer might lose motivation to fund universal cancer care, knowing they stand to benefit less than high-risk individuals.[1] A closer look at this argument, however, should again lead us to question to what extent these concerns are unique to precision medicine and oncology. Differential perceptions of individual risk are no doubt an important challenge to solidarity. But there are many ways that these perceptions are formed. Your non-smoking status (*n.b.,* a stronger negative predictor than any current polygenic risk score) makes you less likely to develop lung cancer, which may weaken your commitment to publicly funded lung cancer screening or other programs that benefit high-risk individuals. Likewise, a white family may have little concern of having a child with sickle cell disease and may prefer their federal tax dollars go toward programs targeting other genetic diseases instead, such as cystic fibrosis (see Farooq et al. 2020). Differential risk-based challenges to solidarity are clearly not limited to precision medicine. Individual interest motivated by the perception of equal risk, therefore, provides a rather fragile basis for healthcare solidarity, and is "unveiled" by more factors than genetics alone.

To summarize, then, among the most compelling ethical challenges to precision oncology is the opportunity cost argument: precision oncology's high-tech, high-cost focus on genomic biomarkers and targeted therapies may detract from other more effective and equitable approaches to cancer care. Insofar as precision oncology reappropriates public resources to benefit narrow segments of the population it may undermine healthcare solidarity, but whether precision medicine more directly or uniquely undermines solidarity is doubtful. Recognition of these opportunity costs in part motivates recent calls for a cancer "groundshot" (contrasting a high-tech cancer "moonshot"), which prioritizes investment in low-tech, proven solutions to address disparities in cancer outcomes on a global scale (Gyawali et al. 2018; Mutebi et al. 2022; see also Gyawali and Booth 2022).

Conclusion

This chapter has reviewed a set of ontological, epistemic, and ethical questions for cancer medicine raised by precision oncology. It proposed a definition of precision oncology and highlighted some implications for cancer classification, clinical research, and health equity. The ideas and arguments put forward in this introductory chapter only sketch the contours of this rapidly evolving field. The preceding discussion is primarily intended to promote clarity on the meaning of precision oncology and its relation to core problems in the philosophy of cancer. This, in turn, can serve as a stimulus and guide to further scholarship. Enthusiasm for precision oncology is

[1] Strictly speaking, this ethical worry about genetic risk prediction does not directly apply to precision oncology, at least according to my definition "What is Precision Oncology?" which concerns itself with targeted treatment.

unlikely to be slowed by philosophical argument alone; nevertheless, philosophers can still play a role in ensuring that purported advances in cancer medicine face healthy scrutiny to help improve how we study and treat cancer.

Definition of Key Terms

Precision oncology: an approach to cancer that involves applying and expanding the use of *predictive biomarkers*, specifically molecular or genomic biomarkers, and paired *targeted treatments* to improve clinical outcomes of patients with cancer.

Predictive biomarker: biological data used to identify individuals expected to have a favorable response to a particular intervention. In the case of *genomic biomarkers*, these data are genomic, usually derived from DNA sequencing.

Targeted treatment: a treatment that bears a targeting relation to a biomarker of interest, intervening in some capacity on the part or process measured by the biomarker.

Genetic reductionism: the view that biological phenomena are primarily explained by genes. In cancer, it manifests as the view that cancer is primarily explained by genetic causes.

Somatic mutation theory: the view of cancer according to which cancer is caused by acquired genetic mutations (or other genomic alterations) in somatic cells.

Constitutive model of disease: model according to which diseases are defined in terms of state descriptions, such as signs/symptoms or evidence of physiologic/tissue dysfunction, rather than in terms of a specific cause.

Basket trial: type of clinical trial which includes patients with different cancer types, regardless of tumor site, and assigns treatment based on genomic biomarkers rather than tissue type.

Surrogate endpoint: a substitute measure used in clinical trials that is not itself a direct measure of clinical benefit but intended to predict a clinically meaningful endpoint, such as survival. In oncology, common surrogate endpoints include progression-free survival, overall response rate, and minimal residual disease response rate.

Summary Points

- Precision oncology is an influential approach to cancer medicine, yet it remains poorly defined. It can be defined as an approach that involves applying and expanding the use of *predictive biomarkers*, specifically molecular or genomic biomarkers, and paired *targeted treatments* to improve clinical outcomes of patients with cancer.
- Precision oncology is sometimes seen as promoting genetic reductionism, privileging genetic causes in its approach to cancer. However, while precision oncology argues that cancer treatment should be based on genomic biomarkers, it

can do so from a pragmatist perspective, rather than a commitment to genetic reductionism.

- Cancer can be understood according to a *constitutive model of disease*, according to which diseases are defined in terms of state descriptions, e.g., based on evidence of tissue dysfunction such as abnormal growth of cells, rather than in terms of a specific cause.
- Precision oncology's implications for clinical research may be rather modest. While it introduces certain methodological novelties, such as basket trials and novel surrogate endpoints, it largely relies on established approaches in clinical epidemiology.
- Precision oncology raises ethical concerns over whether allocating funding to research programs primarily focused on genetic causes of cancer is a fair and equitable use of public resources. Precision oncology's high-tech, high-cost focus on genomic biomarkers and targeted therapies may detract from other more effective and equitable approaches to cancer care.

References

Ades F, Senterre C, Zardavas D, Azambuja E, Popescu R, Piccart M (2017) Are life-saving anticancer drugs reaching all patients? Patterns and discrepancies of trastuzumab use in the European Union and the USA. PLoS One 12(3):e0172351

Aggarwal A, Fojo T, Chamberlain C, Davis C, Sullivan R (2017) Do patient access schemes for high-cost cancer drugs deliver value to society? Lessons from the NHS cancer drugs fund. Ann Oncol 28(8):1738–1750

Aldrighetti CM, Niemierko A, Van Allen E, Willers H, Kamran SC (2021) Racial and ethnic disparities among participants in precision oncology clinical studies. JAMA Netw Open 4(11): e2133205

All of Us Research Program Investigators (2019) The "All of Us" Research Program. N Engl J Med 381(7):668–676

Arber DA, Orazi A, Hasserjian RP, Borowitz MJ, Calvo KR, Kvasnicka H-M, Wang SA, Bagg A, Barbui T, Branford S (2022) International consensus classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. Blood 140(11): 1200–1228

Bell JI (2003) The double helix in clinical practice. Nature 421(6921):414–416

Berland LL, Monticciolo DL, Flores EJ, Malak SF, Yee J, Dyer DS (2019) Relationships between health care disparities and coverage policies for breast, colon, and lung cancer screening. J Am Coll Radiol 16(4 Pt B):580–585

Bertolaso M (2016) Philosophy of cancer. Springer, Dordrecht

Biddle JB (2016) Inductive risk, epistemic risk, and overdiagnosis of disease. Perspect Sci 24(2): 192–205

Booth CM, Eisenhauer EA (2012) Progression-free survival: meaningful or simply measurable. J Clin Oncol 30(10):1030–1033

Broadbent A (2009) Causation and models of disease in epidemiology. Stud Hist Phil Biol Biomed Sci 40(4):302–311

Broadbent A (2014) Disease as a theoretical concept: the case of "HPV-Itis". Stud Hist Phil Biol Biomed Sci 48:250–257

Campo E, Harris NL, Pileri SA, Jaffe ES, Stein H, Thiele J (2017) WHO classification of tumours of haematopoietic and lymphoid tissues. IARC, Lyon

Carter KC (2003) The rise of causal concepts of disease: case histories. Routledge, London

Chin-Yee B, Subramanian SV, Verma AA, Laupacis A, Razak F (2018) Emerging trends in clinical research with implications for population health and health policy. Milbank Q 96(2):369–401
Chin-Yee B, Plutynski A (2023) Concepts of actionability in precision oncology. Philos Sci 2023:1–12. https://doi.org/10.1017/psa.2023.115
Chin-Yee (2024) Minimal residual disease: premises before promises. Biol Philos 39(17):1–12. https://doi.org/10.1007/s10539-024-09958-w
Collins FS, Varmus H (2015) A new initiative on precision medicine. New Engl J Med 372(9): 793–795
Del Paggio JC, Berry JS, Hopman WM, Eisenhauer EA, Prasad V, Gyawali B, Booth CM (2021) Evolution of the randomized clinical trial in the era of precision oncology. JAMA Oncol 7(5): 728–734
Farooq F, Mogayzel PJ, Lanzkron S, Haywood C, Strouse JJ (2020) Comparison of us federal and foundation funding of research for sickle cell disease and cystic fibrosis and factors associated with research productivity. JAMA Netw Open 3(3):e201737
Food and Drug Administration (FDA) (2019) Understanding precision medicine. http://www.fda.gov/media/138005/download
Food and Drug Administration-National Institutes of Health (FDA-NIH) Biomarker Working (2016) Best (biomarkers, endpoints, and other tools) resource. http://www.ncbi.nlm.nih.gov/books/NBK326791/
Fleck LM (2022) Precision medicine and the fragmentation of solidarity (and justice). Med Health Care Philos 25(2):191–206
Fuller J (2018) Universal etiology, multifactorial diseases and the constitutive model of disease classification. Stud Hist Phil Biol Biomed Sci 67:8–15
Garraway LA, Verweij J, Ballman KV (2013) Precision oncology: an overview. J Clin Oncol 31(15):1803–1805
Germain P-L (2012) Cancer cells and adaptive explanations. Biol Philos 27(6):785–810
Gopal S, Loehrer PJ (2019) Global oncology. JAMA 322(5):397–398
Gyawali B, Booth CM (2022) Cancer treatments should benefit patients: a common-sense revolution in oncology. Nat Med 28(4):617–620
Gyawali B, Sullivan R, Booth CM (2018) Cancer groundshot: going global before going to the moon. Lancet Oncol 19(3):288–290
Hodson R (2020) Precision oncology. Nature 585(7826):S1
Janiaud P, Serghiou S, Ioannidis JPA (2019) New clinical trial designs in the era of precision medicine: an overview of definitions, strengths, weaknesses, and current use in oncology. Cancer Treat Rev 73:20–30
John SD (2013) Cancer screening, risk stratification and the ethics of apt categorisation: a case study. In: Strech D, Hirschberg I, Marckmann G (eds) Ethics in public health and health policy: public health ethics analysis. Springer Netherlands, Dordrecht
John SD (2020) Artificial ignorance, epistemic paternalism and epistemic obligations. In: Axtell G, Bernal A (eds) Epistemic paternalism: conceptions, justifications and implications. Rowman and Littlefield, Lanham
Khalidi MA (2013) Natural categories and human kinds: classification in the natural and social sciences. Cambridge University Press, Cambridge, UK
Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, Bejar R, Berti E, Busque L, Chan JKC, Chen W, Chen X, Chng WJ, Choi JK, Colmenero I, Coupland SE, Cross NCP, De Jong D, Elghetany MT, Takahashi E, Emile JF, Ferry J, Fogelstrand L, Fontenay M, Germing U, Gujral S, Haferlach T, Harrison C, Hodge JC, Hu S, Jansen JH, Kanagal-Shamanna R, Kantarjian HM, Kratz CP, Li XQ, Lim MS, Loeb K, Loghavi S, Marcogliese A, Meshinchi S, Michaels P, Naresh KN, Natkunam Y, Nejati R, Ott G, Padron E, Patel KP, Patkar N, Picarsic J, Platzbecker U, Roberts I, Schuh A, Sewell W, Siebert R, Tembhare P, Tyner J, Verstovsek S, Wang W, Wood B, Xiao W, Yeung C, Hochhaus A (2022) The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia 36(7):1703–1719

Kurian AW, Ward KC, Abrahamse P, Bondarenko I, Hamilton AS, Deapen D, Morrow M, Berek JS, Hofer TP, Katz SJ (2021) Time trends in receipt of germline genetic testing and results for women diagnosed with breast cancer or ovarian cancer, 2012–2019. J Clin Oncol 39(15): 1631–1640

Laplane L (2016) Cancer stem cells. Harvard University Press, Cambridge, MA

Laplane L (2018) Cancer stem cells modulate patterns and processes of evolution in cancers. Biol Philos 33:18

Lemoine M (2017) Neither from words, nor from visions: understanding P-medicine from innovative treatments. Lato Sensu 4(2):12–23

Li J, Wang S, Wang Y, Wang X, Wang H, Feng J, Zhang Q, Sun T, Ouyang Q, Yin Y, Liu Y, Geng C, Yan M, Jiang Z (2017) Disparities of trastuzumab use in resource-limited or resource-abundant regions and its survival benefit on Her2 positive breast cancer: a real-world study from China. Oncologist 22(11):1333–1338

Malaterre C (2007) Organicism and reductionism in cancer research: towards a systemic approach. Int Stud Philos Sci 21(1):57–73

Mandrekar SJ, Dahlberg SE, Simon R (2015) Improving clinical trial efficiency: thinking outside the box. Am Soc Clin Oncol Educ 35(1):e141–e147

Marcum JA (2005) Metaphysical presuppositions and scientific practices: reductionism and organicism in cancer research. Int Stud Philos Sci 19(1):31–45

Mutebi M, Dehar N, Nogueira LM, Shi K, Yabroff KR, Gyawali B (2022) Cancer groundshot: building a robust cancer control platform in addition to launching the cancer moonshot. Am Soc Clin Oncol Educ 42:100–115

National Institutes of Health (NIH) (2023a) All of us research program. http://www.allofus.nih.gov/about/program-overview

National Institutes of Health (NIH) (2023b) Precision oncology. http://www.nih.gov/about-nih/what-we-do/nih-turning-discovery-into-health/precision-oncology

Plutynski A (2017) Safe or sorry? Cancer screening and inductive risk. In: Elliot K, Richards T (eds) Exploring inductive risk: case studies of values in science. Oxford University Press, New York

Plutynski A (2018) Explaining cancer. Oxford University Press, Oxford

Plutynski A (2019) Cancer modeling: the advantages and limitations of multiple perspectives. In: Massimi M, McCoy CD (eds) Understanding perspectivism: scientific challenges and methodological prospects. Routledge, New York

Plutynski A (2021a) How is cancer complex. Eur J Philos Sci 11:55

Plutynski A (2021b) The cancer genome atlas project: data-driven, hypothesis-driven or something in-between. In: Donahue C, Love A (eds) Perspectives on the human genome project and genomics. Minnesota studies in the philosophy of science. University of Minnesota Press, Minneapolis

Plutynski A (2022) Why precision oncology is not very precise (and why this should not surprise us). In: Beneduce C, Bertolaso M (eds) Philosophical issues in precision medicine. Springer, Cham

Pradeu T, Daignan-Fornier B, Ewald A, Germain PL, Okasha S, Plutynski A, Benzekry S, Bertolaso M, Bissell M, Brown JS, Chin-Yee B, Chin-Yee I, Clevers H, Cognet L, Darrason M, Farge E, Feunteun J, Galon J, Giroux E, Green S, Gross F, Jaulin F, Knight R, Laconi E, Larmonier N, Maley C, Mantovani A, Moreau V, Nassoy P, Rondeau E, Santamaria D, Sawai CM, Seluanov A, Sepich-Poore GD, Sisirak V, Solary E, Yvonnet S, Laplane L (2023) Reuniting philosophy and science to advance cancer research. Biol Rev Camb Philos Soc 98:1668–1686

Prainsack B, Buyx A (2017) Solidarity in biomedicine and beyond. Cambridge University Press, Cambridge, UK

Prasad V, Gale RP (2017) What precisely is precision oncology – and will it work? The ASCO Post. http://www.ascopost.com/issues/january-25-2017/what-precisely-is-precision-oncology-and-will-it-work

Prasad V, Fojo T, Brada M (2016) Precision oncology: origins, optimism, and potential. Lancet Oncol 17(2):e81–e86

Prasad V (2020) Malignant: how bad policy and bad evidence harm people with cancer. Johns Hopkins University Press, Baltimore

Rajagopal PS, Olopade OI (2020) Black lives matter worldwide: retooling precision oncology for true equity of cancer care. Cell Rep Med 1(5):100079

Reeder-Hayes K, Peacock Hinton S, Meng K, Carey LA, Dusetzina SB (2016) Disparities in use of human epidermal growth hormone receptor 2-targeted therapy for early-stage breast cancer. J Clin Oncol 34(17):2003–2009

Reynolds JM (2020) What if there's something wrong with her? How biomedical technologies contribute to epistemic injustice in healthcare. South J Philos 58(1):161–185

Rose GA (1992) The strategy of preventive medicine. Oxford University Press, Oxford

Schwartzberg L, Kim ES, Liu D, Schrag D (2017) Precision oncology: who, how, what, when, and when not. Am Soc Clin Oncol Educ 37:160–169

Siegel RL, Miller KD, Wagle NS, Jemal A (2023) Cancer statistics, 2023. CA Cancer J Clin 73(1): 17–48

Soto AM, Sonnenschein C (2011) The tissue organization field theory of cancer: a testable replacement for the somatic mutation theory. BioEssays 33(5):332–340

Stegenga J (2018) Medical nihilism. Oxford University Press, Oxford

Stone RM, Mandrekar SJ, Sanford BL, Laumann K, Geyer S, Bloomfield CD, Thiede C, Prior TW, Döhner K, Marcucci G, Lo-Coco F, Klisovic RB, Wei A, Sierra J, Sanz MA, Brandwein JM, de Witte T, Niederwieser D, Appelbaum FR, Medeiros BC, Tallman MS, Krauter J, Schlenk RF, Ganser A, Serve H, Ehninger G, Amadori S, Larson RA, Döhner H (2017) Midostaurin plus chemotherapy for acute myeloid leukemia with a Flt3 mutation. N Engl J Med 377(5):454–464

Tabery J (2023) Tyranny of the gene: personalized medicine and its threat to public health. Alfred A Knopf, New York

Tonelli MR, Shirts BH (2017) Knowledge for precision medicine. JAMA 318(17):1649–1642

Tran A, Klossner Q, Crain T, Prasad V (2020) Shifting, overlapping and expanding use of "precision oncology" terminology: a retrospective literature analysis. BMJ Open 10(6):e036357