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The prospects of precision psychiatry

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Abstract
Since the turn of the twenty-first century, biomedical psychiatry around the globe has embraced the so-called precision medicine paradigm, a model for medical research that uses innovative techniques for data collection and analysis to reevaluate traditional theories of disease. The goal of precision medicine is to improve diagnostics by restratifying the patient population on the basis of a deeper understanding of disease processes. This paper argues that precision is ill-fitting for psychiatry for two reasons. First, in psychiatry, unlike in fields like oncology, precision medicine has been understood as an attempt to improve medicine by casting out, rather than merely revising, traditional taxonomic tools. Second, in psychiatry the term "biomarker" is often used in reference to signs or symptoms that allow patients to be classified and then matched with treatments; however, in oncology "biomarker" usually refers to a disease mechanism that is useful not only for diagnostics, but also for discovering causal pathways that drug therapies can target. Given these differences between how the precision medicine paradigm operates in psychiatry and in other medical fields like oncology, while precision psychiatry may offer successful rhetoric, it is not a promising paradigm.

Keywords Philosophy of medicine · Precision medicine · Precision psychiatry · Biomarkers

Introduction

Precision medicine is often characterized as a revolution in clinical care, a revolution brought about through the novel application of scientific knowledge and technologies to "ensure the delivery of the right treatment to the right patient at the right

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time" [1, p. 1]. In fact, *precision medicine* is an umbrella term for a number of major funding initiatives, both public and private, that were introduced around the globe toward the beginning of the twenty-first century. Most of the funding distributed under precision medicine initiatives has gone toward ambitious new programs of data collection and analysis, such as the All of Us initiative in the United States, which aims to recruit a million-person cohort of participants whose genomes, health records, and physiological measurements are collected into a broadly accessible data resource [2]. The success stories of precision medicine reflect not only the transformation of diagnostics and clinical care by big data, but also breakthrough discoveries of underlying disease mechanisms. Most of these successes have occurred within areas of medicine where knowledge about causal pathways is proceeding by leaps and bounds. For example, the majority of research papers published in the last decade that contain the phrases "personalized" or "precision" medicine are in the field of oncology [3]. Many focus on pharmacogenomics, tailoring treatments to particular genetic blueprints, or investigate monoclonal antibodies, a specific type of medication characterized by a complex, macromolecular structure and a very high specificity for certain targets in the body, as well as a higher sensitivity to individual genetic variations.

In this paper, we argue that there has been a sleight of hand whereby the success of precision medicine in oncology and other fields, such as immunology, has led to its presentation as a revolutionary transformation of medicine writ large—with unfortunate consequences for psychiatry. Precision has come to be thought of as a universally appropriate and desirable paradigm for twenty-first century medicine, when in fact its successes are contingent and dependent on circumstance. We argue that the successes of the precision medicine paradigm in certain fields can be attributed to relatively specific aspects of those fields, which may not be present—at least not to the same degree—in other areas of medicine. Psychiatry has been described as undergoing a precision revolution [4]; yet while there is a robust foundation of oncological research informing agreement about the molecular mechanisms implicated in cancers, psychiatry lacks this kind of consensus with respect mental disorder. Given the amorphous role of the concept of precision, either precision medicine must be understood to mean different things in different fields or, if its usage in oncology is taken to be paradigmatic, psychiatry (and likely other fields as well) must be admitted to be imprecise.

We begin in the next section by introducing precision medicine, highlighting the lofty rhetoric that has been used to justify its expansion across the medical specialties. We then open our critique of this broad championing of precision in the third section by analyzing the term "biomarker," which has played a crucial, but slippery, role in articulating precision medicine's aims and methods. We propose a definition of *mechanistic biomarkers* that is based on the notion of "locus of control" [5]—namely, a mechanism where the system can be intervened upon—and distinguish mechanistic biomarkers from *statistical biomarkers*, whose presence merely correlates with the presence of a condition but whose role in the disease process is unknown. We also observe that in precision medicine, biomarkers are used theranostically to stratify the patient population on the basis of predicted treatment outcomes. The fourth section demonstrates how precision medicine's success in oncology has

relied on the discovery of mechanistic biomarkers that perform this kind of theranostic function.

In the fifth section, we turn to psychiatry and show that psychiatric biomarkers for the most part function quite differently. While some statistical biomarkers have been discovered in psychiatry, they lack a mechanistic basis, and so far have displayed little theranostic utility. Mechanistic biomarkers have already played an important role in oncology and other fields like immunology, where they exemplify the evidence-based ideal for medicine and, in some cases, have provided a step toward the discovery of new treatments. Leading figures writing in journals like *Nature* and *Molecular Psychiatry* are hopeful that mechanistic causes for psychopathology will be discovered and that mechanistic biomarkers will ultimately transform clinical care in analogous ways. We argue, however, that psychiatry differs from oncology in ways that make the integration of statistical and mechanistic information more challenging, such that theranostic biomarkers will be harder to discover and implement. We therefore conclude that the comprehensive methodological transformation signified by the "precision" label is only aspirational for psychiatry. Other fields of medicine likely fall somewhere between these two extreme examples, and we discuss the significance of such discrepancies for recent enthusiasm about precision in our sixth section. We conclude that, given the diversity and complexity of the explanatory challenges that biomedicine faces, the prevalent optimism about precision medicine is far more warranted in some areas than in others. Accordingly, talk of precision as a paradigm shift for medicine is, generally, misleading.

Precision medicine

While the language of precision has come to prominence in the United States, diverse terms are used in English to refer to the concept, including "personalized medicine," "stratified medicine," and "P4 medicine."[1] These terms are often understood to signify the tailoring of treatments to patients; an early description of personalized medicine defines it by the practice of "targeting drugs for each unique genetic profile" [14]. An article in *Science* in 2000 describes the vision of personalized medicine as the use of "prognostic genotyping and diagnostic molecular profiling … in routine medical practice" [15]. The United States National Research Council, in turn, defines precision medicine as follows:

> "Precision medicine" refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology and/or prognosis of those diseases they may develop, or in their response to a specific treatment. [16, p. 125]

[1] For a description and analysis of these terms, see [3, 6–13].

Three features commonly characterize research programs that are hailed as "precise": (1) an *-omics* approach that reduces traditional disease categories to lower levels of description, (2) an algorithmic approach to diseases and their treatments [17], and (3) a revisionist approach to nosology [18]. With respect to the first feature, precision medicine often incorporates pharmacogenetics, the science of assessing treatment choices on the basis of genetic profiles [19]. Precision medicine claims to expand on pharmacogenetics by analyzing *all* available information, in theory including the psychological and the social, but most often focuses on the biological. Relevant *-omic* information is envisioned as including not only genomic information but also transcriptomic, proteomic, and metabolomic information. Precision medicine generally works on the premise that molecular characteristics of either the person or the treatment offer the key to matching patients with the right treatments.

The second feature of precision medicine, an algorithmic approach, becomes necessary in the face of the complexity that a broad *-omics* focus introduces. In the discovery phase of precision medicine, new statistical methods are crucial for processing the vast amounts of data required to home in on mechanisms that may be causally significant only in a small set of patients sharing a diagnosis. Algorithms are also required to make sense of the results of this research in relation to the development and distribution of new therapies. In other words, algorithms can help establish useful correlations between states and treatments. A typical example of this practice is the connectivity map (CMAP) project, a database of treatment signatures—levels of transcription of all genes from cells exposed to the treatment—and an algorithm that calculates whether transcription levels from cells taken from a population, or even an individual patient, are anticorrelated to all available treatment signatures [20]. The goal is to match states to treatments based on transcription levels.

The generic term for this approach is *theranostics*. A portmanteau of therapeutics and diagnostics or prognostics, theranostics can be understood as the prediction of a response to a treatment, generally based on a so-called companion test for the presence or level of a biological sign or symptom specifically associated with the treatment in question. Theranostics involves a targeted therapy and a personalized (or at least stratified) treatment. Although it is most often used as a refinement of a diagnosis, it can also describe a prescription that is not based on the diagnosis of a traditional disease entity. The CMAP project is an example of a systematic theranostic approach.

It is in this sense that precision medicine aims to exhibit the third feature mentioned, the revision of traditional diagnostic categories. Instead using clinical expertise or instruments that categorize patients into disease classifications, precision medicine uses biomarkers to match patients to treatment protocols. The diagnosis here becomes discretionary; while it may be useful as a proxy to refer to strata of patient responses, it is the relationship between the biomarker and the treatment that constitutes the central relation of precision medicine.

We turn in the following section to the question of what the term "biomarker" refers to. An analysis of this concept brings into view the complex relationship between the different features of precision medicine and the pursuit of mechanistic knowledge. Although the hunt for mechanisms at the different *-omic* levels can, in

theory, turn up discoveries relevant for improving treatments, mechanistic knowledge is not needed for the second or third features of precision—namely, the reliance on big data and the ongoing project of taxonomic revision [18]. While programs emphasizing the first feature are more in line with mechanistic understandings of medicine, programs emphasizing the second and third are more congruent with evidence-based medicine approaches. We shall show that the latter programs, therefore, often employ a distinct concept of biomarker that deemphasizes causal explanation.

Biomarkers

In a nutshell, then, precision medicine can be understood as the project of prescribing treatments on the basis of biomarkers that are predictive of treatment response, rather than on the basis of traditional diagnostic systems that rely on signs and symptoms. Yet the term "biomarker" has functioned differently across the precision medicine literature. The Biomarkers Definitions Working Group of the US National Institutes of Health defines a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [21]. In representing biomarkers as "objectively measured and evaluated," it seems the authors intend to set them in opposition to the signs and symptoms used in clinical examination, most of which need subjective interpretation. The emphasis on process (as opposed to results) suggests that a biomarker should reflect the fundamental pathophysiology of a disease, and not just the symptoms [22]. Yet the use of "indicator" implies that the main function of a biomarker is to reliably inform the clinician as to the presence, level, or activity of a process that cannot be directly observed, even if the biomarker is neither perfectly specific nor perfectly sensitive to the presence of the disease, and even if it does not represent a significant underlying mechanism. The term "biomarker" thus has some ambiguity to it, functioning to refer either to causal mechanisms or to signs of pathology. It is worth noting that neither use represents a new mode of medical explanation: laboratory tests, diagnostic imaging, and other techniques for discovering clinical signs (representing fundamental pathologies or otherwise) are the traditional business of medicine. What is taken as revolutionary in precision medicine is the discovery of markers beyond those that are easily observable in the clinic, using cutting-edge technologies and big data.

In order to reduce this ambiguity, we will use the term *mechanistic biomarker* to refer to biomarkers whose causal role in the disease process in question is understood, and we will use the term *statistical biomarker* to refer to those whose involvement is established but whose role is not. All biomarkers that have an unknown causal status—that is, which are utilized even though their causal role cannot be established—are statistical. An example is amyloid plaques in Alzheimer's disease. While these plaques are diagnostically useful, it is not yet understood why they are found in the brains of those displaying the signs and symptoms of Alzheimer's disease. Statistical biomarkers have value not because they shed light on a mechanistic process, but because they have theranostic properties: they can allow for predictions about therapeutic response. They also suggest where to look in the quest for

causal understanding. Yet insofar as they may only be caused indirectly by a disease process, they can sometimes, in this respect, be misleading—consider the example of the doomed hunt for dopamine's causal role in schizophrenia [23]. The difference between mechanistic and statistical biomarkers is epistemological rather than metaphysical.

There is an additional important distinction to be made, one that does have to do with the underlying entities being referred to and not just medical theories about them. In some cases, mechanistic biomarkers represent key components of the disease process, as when high levels of phenylalanine are directly due to a genetic deficiency in the enzyme phenylalanine hydroxylase in phenylketonuria. In cases like this, where intervention on the mechanistic biomarker alters the course of the disease (in our example, through a diet), we refer to the biomarker as a *direct* mechanistic biomarker. In other cases, while not causally mysterious, biomarkers are just byproducts of the process in question, as when high levels of creatinine in the blood indicate renal failure, but are not a cause of it. We will refer to these as *indirect* mechanistic biomarkers, recognizing that, while they are implicated in a disease process, they do not in and of themselves constitute a key component of the disease pathway. If creatinine were removed from the blood, in this example, the condition of the kidneys would not be affected. The difference between direct and indirect biomarkers is thus ontological; it comes down to the importance of the biomarker's role in the disease process, regardless of what is known about it.

Now in precision medicine, the quest for biomarkers follows a reverse path as compared to traditional practices in biomedical research. Instead of elucidating mechanisms and then assessing whether one of their components might function as a biomarker, precision medicine looks for biomarkers before mechanisms are elucidated. In the traditional approach, candidate biomarkers are always mechanistic. Experimental intervention generally establishes whether they are direct or indirect. In precision medicine, biomarkers are statistical first: correlation with a disease is established, and a potential mechanism is investigated only after the correlation has been found. A "merely statistical" biomarker, then, is one whose significance is established but whose status as direct or indirect is not.

One reason why the traditional approach in medicine often fails has to do with the challenges of translating knowledge of direct biomarkers into treatment modalities for real populations. One way to understand the challenge is to consider when the specific mechanism identified as a necessary condition for a disease counts as a locus of control. According to William Bechtel and Robert Richardson, the identification of a locus of control consists in the identification of "a component within the system as itself responsible for the phenomenon, without yet inquiring how that component produces the effect" [5, p. 36]. A necessary condition for the success of the traditional approach is this sort of localization of disease. For instance, Cushing's disease, which produces a depressive-like state among other manifestations, is a disease of the brain. It also is hyperactivity of the hypothalamic pituitary adrenal axis due to an adenoma in the pituitary gland. However, the discovery of a direct biomarker does not automatically afford any therapeutic leverage—in the scientific literature, what are referred to as "targets" that are "actionable" or even "druggable" [24]. It is possible that even if a mechanism is identified, it does not allow for any

new sort of control over the system, and there is no immediate impact on clinical care.

Precision medicine is an attempt to circumvent the difficulties of localization by focusing on the mechanisms of treatments rather than on the mechanisms of disease. Indeed, whether they are statistical or mechanistic, direct or indirect, the goals of precision medicine (as outlined in the first section above) require that biomarkers be theranostic—that is, that they provide a stratification of the patient population via correlation with different observed responses to the treatment. There is widespread endorsement of the idea that mechanistic biomarkers are more likely to be theranostic because they can shed light on the disease process and thus aid the discovery of new therapies. But there is also growing recognition that direct mechanistic biomarkers may be localized in a mechanism with poor leverage on the therapeutic outcome. Moreover, even statistical biomarkers can help tell whether different strata of patient responses can be matched to effective therapies.

A very important final note is that even in precision medicine, where (as will be discussed below) one starts with a statistical approach, a locus of control is assumed, although it is conceived of in a way that is only loosely connected to potential treatments. The more restrictively localized and the more therapeutically promising a locus of control is, the higher the chance that a statistical biomarker will be found. For example, it is easier to find biomarkers in a tumor than in the brain of someone with a mental disorder. The reason is not that a tumor is smaller than the brain, but that it is more distinguishable from the rest of the healthy tissue than is a dysfunctional part of the brain where there is no lesion. Histology is sufficient to already localize the disease precisely enough in the case of cancer, while it falls far short in the case of functional diseases of the brain.

Precision oncology

The emblematic techniques of precision medicine—mainly genomics and transcriptomics (the systematic study of RNA transcripts produced by the genome that can reveal differences in gene expression)—have led to significant discoveries in oncology. These discoveries have been conceptualized in the framework of a paradigmatic treatment that predates them: trastuzumab (Herceptin). Trastuzumab has proven significantly more efficient than standard chemotherapies in treating some breast (and stomach) cancers. While tumors overexpressing a receptor called HER2/neu are sensitive to the drug, it has no benefit at all to people whose tumor does not overexpress this receptor beyond a certain point [25]. The population which uniquely benefits from trastuzumab did not, before this discovery, represent any preexisting classification in oncological nosology, suggesting the overexpression of HER2/neu could act as not only a mechanistic biomarker but also as a theranostic one [26]. Other treatments with the same characteristics have since appeared on the market, such as nivolumab, pembrolizumab, and ipilimumab (immune checkpoint inhibitors), with many more coming.

But in the main, precision oncology has been about designing and calibrating treatments first and understanding disease later [27]. The sort of instruments used

to assess HER2/neu overexpression are not testing patients for natural subtypes of the disease, but rather for their predicted responses to available treatments. In other words, the emphasis is not primarily on the mechanisms of the disease—that is, on its etiology, functional pathways, or natural history (what is generally called tumor progression and cancer development) [28]—but rather on the mechanisms of the treatment: how the intervention disrupts the pathological process, what it latches onto, and, consequently, who can benefit from it. The aim of all this is to transform treatment: whereas standard chemotherapy is like an aggressive and indiscriminate carpet bombing, exposing patients to toxicity regardless of the treatment's efficacy for their particular cancer, new treatments can be targeted like precision missiles—just like Herceptin. Rather than being broadly applied in the hope of doing some good, precision therapies can be deployed narrowly against those tumors that they can effectively fight. They thus exemplify precision medicine's goal of finding better matches between patients and available (to clinical practice) or potential (through medical research) treatments via mechanistic discovery.

In other words, to succeed in its aims with respect to nosology, precision medicine need not make much contribution to classical explanatory models of diseases, which trace processes from genes up to symptoms. What matters is that it shows success in identifying theranostic biomarkers, whether they be mechanical or statistical. In this way, traditional classifications based on organ of origin are giving way to taxonomies that differentiate types of cancer on the basis of drug response. For unknown reasons, stomach tumors overexpressing HER2/neu have been revealed to be as sensitive to trastuzumab as breast cancers of this type, while bladder or lung cancers which show similar overexpression are not. In the face of this new classificatory information, traditional disease entities have been abandoned, or maintained only as shorthand heuristics to coordinate research efforts—what have been called "epistemic hubs" [29]. For treatment purposes, a new category of cancers—such as those characterized by tumors that overexpress HER2/neu and respond to trastuzumab—is employed de facto. The same is true of many other biomarkers of cancer.

Mostly during the phase of research, and increasingly, but not universally, during the phase of treatment, precision medicine draws on big data to find new matches between the various predicates of the biomarker relation: between treatments and diseases, or between diagnostic tests and treatment responses. Large data sets are gathered in pursuit of theranostic biomarkers. The hypothesis is that molecular precision offers a better chance of matching the right cases with the right treatments through the identification of blood products, genetic variants, or other markers. This approach abstracts away developmental, environmental, and behavioral characteristics of both the patient and the disease in order to offer a better chance of finding possibly interesting correlations.

Importantly, the search for theranostic biomarkers is made possible by previous knowledge of a circumscribed subpart of the system that is relevant to the disease—in our example of cancer, tumoral cells—which can already be spotted among a population of normal cells. This direct localization is crucial to the success of any big data approach in oncology, as it dramatically decreases the amount of information to be scanned. In other words, while researchers do not need to understand the mechanisms causing the disease in order to identify theranostic biomarkers using

big data, they must have established a relevant and sufficiently circumscribed target for their inquiry. Even if indirect, mechanistic biomarkers can contribute to the process of localization that makes the discovery of theranostic biomarkers more likely. Statistical biomarkers cannot.

Precision psychiatry?

With respect to mechanistic biomarkers, psychiatry has had only middling success, in part because, to a degree unlike oncology, psychiatry has struggled with direct localization. Indeed, there is still enormous debate over whether psychiatric disorders are best conceived of as brain diseases (that is, problems of neural circuits) or mental illnesses (that is, psychopathological syndromes) or some combination of the two. Psychiatric diagnostics also rely on behavioral criteria that are accessible only through patient self-report. While in some diseases treating the target of diagnostic criteria directly is curative—for example, bacteria in the blood that are both a direct mechanistic biomarker and the target of antibacterial medication—behavioral criteria have traditionally been adopted as targets of psychiatric intervention even when it is acknowledged that they are only manifestations of an unknown underlying pathology.

Precision psychiatry hopes to overcome these challenges by discovering mechanistic biomarkers that show the value of pathophysiology for psychiatric medicine, even without a complete revolution in causal understanding. But so far, only statistical biomarkers have been discovered—for example, common genetic variants that increase risk, physiological shifts in chemicals like cortisol and neurotransmitters like serotonin, and behavioral signs like eye movement.[2] None of these biomarkers maps cleanly onto specific treatment protocols, so none of them is used for theranostic purposes, although some are included in the appendices of the most recent edition of the dominant diagnostic manual for psychiatry, the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) [31]. Similarly, environmental and developmental causes such as childhood abuse, marital stress, poverty, and so forth, while implicated strongly by empirical studies, are merely statistical and nonspecific. The same goes for many behavioral characteristics, such as change in affect or deterioration of social functioning. Accordingly, psychiatry has had no success so far in precisifying treatments using biomarkers. Indeed, the heterogeneity of patient populations sharing a given diagnosis has been a continuing factor contributing to the disappointing performance of psychopharmacology [32, 33].

In the 2000s, Thomas Insel and others at the National Institute of Mental Health (NIMH) developed the Research Domain Criteria (RDoC) initiative, a taxonomic protocol for grant-seekers intended to provide a new way for researchers to classify their research without using *DSM* categories [34]. The initiative grew out of a worry that psychiatric research targeting the mechanisms underlying diagnostic categories would ultimately be unsuccessful, given that the *DSM*'s classifications

[2] For a review of these and other biomarkers of depression, see [30].

were drawn up in response to treatment needs rather than pathophysiological theory [35]. The concern was that the *DSM*'s diagnostic criteria therefore might not discriminate between patients whose conditions, while superficially similar, are caused by diverse underlying mechanisms. Better than trying to validate faulty constructs, these critics argued, new classifications should be drawn up on the basis of scientific discoveries about the mechanisms underlying the signs and symptoms of psychopathology. The first step, therefore, should be discovering pathways to disorder using approaches from the basic sciences, such as genetics, neuroscience, and molecular biology. "While we can improve psychiatric diagnostics by more precise clustering of symptoms," Insel writes, "diagnosis based only on symptoms may never yield the kind of specificity that we have begun to expect in the rest of medicine. Behavioral symptoms are multidetermined, so diagnoses based only on presenting complaints are unavoidably heterogeneous in terms of pathophysiology" [4].

Insel has described RDoC as precision medicine because it ultimately aspires to a diagnostic system based on causal mechanisms; however, he also acknowledges that "RDoC is not a diagnostic system, it's merely a framework for organizing research. It begins with the humble realization that we do not know enough to develop a precision medicine approach to mental disorders. We need a decade of intense scientific work—from molecular factors to social determinants—to understand normal and abnormal behavior, based on a deep understanding of mechanisms" [4]. The NIMH aims to promote the discovery of direct biomarkers by advancing psychiatric research on basic domains of functioning, rather than syndromes, and by supporting new methodologies, such as compiling an information commons, which will enable researchers to share data and provide for data-mining across disciplines. The hope is that through collaboration, the discovery of mechanisms at different levels of description and translational work will link explanatory models across levels to give a clear picture of psychopathology that allows for the discovery of new theranostic biomarkers. Diagnoses, understood as constructs that mediate between whole persons and treatment modalities (including the option of no treatment at all), have no place in this picture, just as diagnosis is dispensable in a theranostic approach in somatic medicine.

Writing in 2005 with Remi Quirion, Insel suggests that after what the authors call the "decade of discovery" will come a "decade of translation," in which new understandings of psychopathology generate new treatment protocols or improve on existing ones [36]. In that paper, Insel suggests that the decade of translation may begin as early as 2015; later, writing in 2014, he suggests that the decade of discovery is only just beginning [4]. What is clear today is that the best theories about psychopathology have generated few novel treatment protocols as of yet. This of course does not mean that they will not generate successful protocols in the future—it just means that the "precision" label is, at this point, only aspirational for psychiatry [18]. As an increasing amount of the NIMH's budget is invested in precision medicine approaches, it becomes important to ask when, and how, these aspirations might be fulfilled. Will the discovery of direct biomarkers for psychopathology emerge from vigorous basic science research on the brain? If so, will these discoveries translate into theranostic biomarkers that can better match patients with (potentially new) treatments?

We think there are reasons to be pessimistic about the possibility of psychiatry's following in oncology's footsteps. We argued in the previous section that in oncology, the theranostic biomarkers that allow treatments to be applied with precision to stratified patient populations are often discovered on the basis of previous efforts at direct localization. The failure to localize explanations in psychiatry can explain some of the distance between precision psychiatry and precision oncology: whereas the latter is typically looking for tests predicting the response of individual tumors to potential treatments, the former has interventions that are aimed at a wide range of targets. As touched on above, there is a long-standing and fierce debate about whether psychiatric disorders can be localized within the organism (at the level of the gene or neural circuit), within the mind (at the level of the mental module or phenomenological state), or even outside the person (at the societal or environmental level). Psychopharmacological and behavioral therapies—such as psychotherapy, cognitive behavioral therapy, and social services—are taken to be successful when they alleviate the behavioral signs and symptoms of the disorder. There is no consensus in the field, however, about whether these signs and symptoms are direct or statistical biomarkers of disease. While both psychopharmacological and behavioral therapies surely act on underlying causal pathways, because these pathways are not known, calling them direct biomarkers would be merely wishful thinking [37]. To claim that these interventions work mechanistically is to obscure profound differences between what goes on epistemically in psychiatric medicine and what goes on in areas of somatic medicine, where treatment efficacy can often be assessed via direct and indirect mechanistic biomarkers.

To claim as such is also to obfuscate the methods used in psychiatric care, in which doctors use a trial-and-error procedure to try to match patients with the right medicines given their general symptom profile, rather than on the basis of clinicians' knowledge about the action of the psychopharmaceuticals at their disposal. Because behavioral genetics has only implicated genes of very small effect in psychopathology, genetic characterizations are based around hereditary traits rather than analyses of the genome. Due to the haziness of the current understanding of risk factors behind mental disorder, as well as a lack of clarity about if and how signs and symptoms correlate to underlying causal mechanisms, matches between patients' clinical profiles and treatments are necessarily imperfect. Behavioral, environmental, and developmental characteristics may guide intervention, but they do so discretely, rather than by contributing to a unified understanding of the pathophysiology underlying the condition.

Furthermore, in comparison to oncology, psychiatry for the most part lacks knowledge of loci of control—namely, as described above, those parts of a system whose functions contribute to the effect of interest, and which can be manipulated to ultimately allow for the discovery of "precise" targets for intervention within the parts themselves [5]. A specific mechanistic biomarker involved in psychiatric disorder should provide potential molecular targets for precisely designed medications, analogous to monoclonal antibodies like trastuzumab. However, precision psychiatry cannot yet investigate loci of control for treatment, let alone exploit such mechanisms, because it has not found where exactly mental dysfunction is located in the body. For example, the discovery of a complex mutation of *C4* that increases the

risk of schizophrenia was hailed as a significant breakthrough in molecular psychiatry [38], exemplifying the sort of result one might hope for from the RDoC initiative, but researchers are still very far from the development of a treatment protocol based on a precise causal pathway. The contribution of the genetic dysfunction to the disease is only weakly established, and the mechanistic pathway from the genetic pathology to the signs and symptoms of the disorder is still unknown.

The lack of loci of control and therefore of mechanistic biomarkers is in large part due to the molecular complexity of psychiatric disorders, resulting from the involvement of many alternative causal pathways leading to the same or similar outcomes. It has been claimed that although most diseases are known to be complex in this sense, psychiatric disorders are substantially more complex than others [39]. An illustration of this point can be seen in what has been referred to as the "missing heritability" problem, which is particularly acute in psychiatry [40]. For certain psychiatric disorders, heritability has been found to be high to very high, meaning that genomic factors are in principle predictive of the risk. But genome-wide association studies have shown that it is very difficult to find genetic biomarkers for psychiatric disorders—not because there are none, but because they are many [41]. A potentially therapeutic target might be found in only a small fraction of people sharing a diagnosis, and due to the small effect of individual genes, fixing the problem caused by any one gene might be akin to changing the tire of a totaled car.

Additionally, the statistical biomarkers that psychiatric genetics has investigated so far are mainly biomarkers of susceptibility to disease, not biomarkers of disease. Although advances in the understanding of biomarkers might have a profound impact on the management of risk through genetic counseling about prophylactic care, precision medicine in oncology is not for the most part about treating risk (e.g., treating women with high-risk BRCA variants), but about treating extant tumors. As opposed to precision oncology, precision psychiatry is at this stage entirely concerned with locating molecular tags for susceptibility to disease. The discovery of a *C4* mutation that plays a role in schizophrenia, described above, explains an increase in relative risk from 1 to 1.27 percent [38]. These statistical biomarkers are not easily translatable into clinically relevant findings.

A further consequence of the complexity of mental disorders is that psychiatry calls for the gathering of a richer and more varied set of data than is needed in oncology, leading to additional taxonomic headaches. Whereas oncology draws on big data that are primarily molecular, psychiatry requires the manipulation of heterogeneous psychosocial variables—unless one is to neglect many markers that, while stubbornly qualitative, are much more sensitive and specific than molecular ones. As of now, very few papers in psychiatry approach these aspects of mental disorders using big data methods (compare [33, 42, 43] with [44, 45]). Nonetheless, psychosocial factors like early childhood abuse and adverse life events, as well as demographic factors like gender and socioeconomic status, are more predictive of mental disorder than any known biomarkers [46].

A final problem lies in the status of disease entities in precision psychiatry. As promising as RDoC may be, it is understood as a new starting point for psychiatry qua clinical neuroscience, a new framework for diagnosing the targets of psychiatric research which would replace current diagnostic entities. Whereas in precision

oncology a reshuffling of disease entities is a potential but not inevitable outcome of the discovery of new medications directly targeting types of tumors, in precision psychiatry this reshuffling is taken as a necessary prerequisite for progress [18]. One of us has argued that apologists for this reshuffling may be justified—it may be the case that the *DSM*'s diagnostic categories are not conducive to basic science research on the causes underlying the signs and symptoms of mental disorder [35]. However, given the powerful problems of translation from small insights about the causal pathways of psychiatric disorders to more powerful theories concerning the loci of control for psychopathology, it is clear that the road to discovery from direct to theranostic biomarkers will be much less smooth in psychiatry than in oncology.

Problems with precision

We have argued that the rhetoric around "precision" is laced with ambiguities which mask fundamental differences in the methods and aspirations of different research programs sharing the label. In particular, the term "biomarker" is used to refer to causal mechanisms implicated in diseases, to byproducts of disease processes of interest, and to physiological signatures that shed light on treatment outcomes. In this brief penultimate section, we will suggest some reasons that differentiating these distinct senses of the term "biomarker" is important—and why, therefore, the umbrella term of "precision" should be used with caution.

Theranostic biomarkers are appealing because they can lead to the refinement or replacement of current disease categories with new stratifications of the patient population on the basis of treatment response. When theranostic biomarkers are also directly mechanistic, they may contribute to the development of new therapies by pointing the way toward loci of control. However, if the distinction between mechanistic and statistical biomarkers is not kept in view, medical research can fall into a vicious circle where statistical biomarkers that correlate with drug response are confused for mechanistic biomarkers capable of revealing something important about etiology. For example, the relation between neuroleptic drug treatments and outcomes among patients with schizophrenia led to a decades-long, feverish pursuit of the mechanism by which dopamine regulation impacts on neuropathology—one which ultimately ended in disappointment [23]. Statistical biomarkers do, of course, offer tantalizing suggestions about where one might begin the search for loci of control. But insofar as they may, with further investigation, be revealed to stand in anywhere from direct to highly *in*direct causal relation to the disease process, they should be treated as merely a possible starting place for the hard work of direct localization. The wild popularity of the dopamine hypothesis of schizophrenia shows how researchers' attention, and funding bodies' resources, can be driven by quixotic faith that a statistical biomarker will, with sufficient ingenuity, be revealed to be directly mechanistic.

Indeed, the history of medicine shows that theories about diseases are often revised to conform to treatment response, in a process Jennifer Radden has referred to as "drug cartography" [47]. While psychopharmacological discoveries have provided more clinical advances than neurobiological or genetic research on mental disorder, they have

also resulted in a narrowing of the focus of research to mechanisms that can explain, for example, the efficacy of selective serotonin reuptake inhibitors for treating depression or of neuroleptics in battling schizophrenia [48, 49]; and the same can happen in somatic medicine. Researchers may focus on hypertension, hypercholesterolemia, hyperglycemia, or amyloid plaques, even though treatments able to affect these targets are not always the best way to change clinical outcomes, such as vascular disease or dementia. Clinical signs can be poorly specific and/or sensitive markers of diseases, as advocates of RDoC emphasize. But at the same time, clinical outcomes are the only variable patients and health practitioners are ultimately interested in. Biomarkers are intended to replace clinical signs, and as such it is crucial that their complex role as a sign which is *indicative* of an outcome, with *possible* mediation by a mechanism, remains in view.

In the specific case of oncology, the theranostic approach typical of precision medicine is sometimes justifiably hailed as a breakthrough, and sometimes leads to the kind of vicious circle just described. The emergence of concepts like "stage 0 cancers" and "precancerous lesions" and the use of biomarkers such as prostate-specific antigens for prostate cancer and breast cancer susceptibility proteins for breast cancers have raised worries about the risk of overmedicalization [50, 51]. In the case of stage 0 cancers, the discovery of a pathological mechanism does not necessarily indicate the discovery of a theranostic biomarker; it may be that the abnormal tissue growth referred to as "stage 0" is not a clinically relevant category, in the sense that treating it may not improve patient outcomes. On the other hand, it may be that the relationship between the BRCA mutation and the development of breast cancer needs to be thought of as statistical rather than mechanistic, because the presence of the gene variant does not give direct evidence of the presence of a known causal pathway, only of its likelihood. But insofar as most claims about biomarkers in oncology are based on previous work establishing direct localization, these problems seem less dramatic than in psychiatry.

Generally speaking, to the extent that biomedical research is, financially speaking, a zero-sum game [52], there are ethical reasons to resist the seductive language of precision. In psychiatry, for example, clinicians, sociologists, and researchers critical of the biomedical paradigm have expressed growing concern that non-reductive approaches to psychiatric research are being abandoned as "not precise enough" [53, 54]. More broadly, it is worth asking whether the precision paradigm, which is often narrowly focused on genetics, is the most appropriate response to twenty-first-century crises in public health brought on by climate change, increased inequality, systemic prejudice, and, alarmingly, the arrival of new epidemic threats due to increased globalization and migration [52, 55]. Our hope is that the present discussion of how the term is used, and what it truly can promise, will allow for more clear-eyed assessments of these concerns.

Conclusion

We conclude that even if the precision paradigm is, despite these worries, deemed to be a success in oncology, this success cannot justify the wholehearted adoption of the approach in other fields, like psychiatry. In fields that have lagged behind

in the search for direct localization, new methods for discovering theranostic biomarkers will not be as readily applicable. We considered the example of the NIMH, which has advocated pouring research dollars into basic science research on cognitive neuroscience to discover the loci of control for psychiatric illnesses. Given the complex nature of psychopathology, it is doubtful that this process of discovery will be an easy one. This does not, of course, mean that it should not be undertaken, but rather that "precision medicine," in the sense of discovering theranostic biomarkers that can revolutionize taxonomy and clinical practice, is still a long way off for psychiatry.

Disciplines in a similar position to psychiatry could more realistically adopt modest, yet still ambitious, research programs that might deserve the title of "stratified medicine"—for example, programs analogous to those investigating the mechanisms of resistance to standard antidepressant or antipsychotic treatments, or investigating statistical biomarkers of response to available treatments. Such projects could avoid genomic complexity by focusing on the resulting neurobiological pathways, doing what one might call old-fashioned neurophysiology. Other research programs might expand on work done on the social determinants of mental disorder to discover which specific symptom profiles best benefit from proven interventions such as poverty relief, employment assistance, and behavioral therapies. Such approaches would consider a nosological revolution not as a starting point, but rather as a possible consequence of potential findings about strata of patients that respond, or fail to respond, to available therapies.

Psychiatry may well follow the NIMH in attempting to reestablish its foundation on the basic sciences. In this case, however, to call psychiatry a branch of precision medicine would be to make a misleading category mistake. We have given arguments above for why it should not be considered precise; we wish to close by noting that it would also no longer be obviously medical. It is possible to remain profoundly committed to the exploration of psychopathology through the methods of the basic sciences while still acknowledging that it is misleading to refer to such efforts as precision *medicine*, insofar as the theranostic piece is missing. While this may seem like a conceptual quibble, the ramifications of this language are in fact important. As long as precision psychiatry is not generating novel treatments or improving existing treatments, it is not doing clinical work. To the extent that psychiatry is both a science and a practice, it is responsible for improving the quality of care for the 450 million people thought to suffer from mental or neurological disorders globally each year [56]. While critics may be right that the etiological understanding of psychopathology is being held hostage by current diagnostic categories, they have not demonstrated that the search for mechanistic biomarkers will ultimately pay the dividends they claim. The point can be generalized away from psychiatry. In every different field—and every different health context—the value of a precision approach should be argued for, rather than assumed.

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