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Theoretical and clinical disease and the biostatistical theory

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ABSTRACT

Although concepts of disease have received much scrutiny, the benefits of distinguishing between theoretical and clinical disease—and what is meant by those terms—may not be as readily apparent. One way of characterizing the distinction between theoretical and clinical conceptions of disease is by relying on Boorse's biostatistical theory (BST) for a conception of theoretical disease. Clinical disease could then be defined as theoretical disease that is diagnosed. Explicating this distinction provides a useful extension of the BST. The benefits of this approach are clearly and non-normatively demarcating disease from non-disease, while allowing for values and purpose to determine what criteria are used in clinical practice to represent a disease's underlying dysfunction. Through discussion of a variety of medical conditions, including polycystic ovary syndrome and type 2 diabetes mellitus, I explore how the relationship between BST-based theoretical and clinical disease could make sense of various features of clinical practice and medical theory. It could do this by lending focus to a nuanced understanding of the pathophysiological defects present in disease and the means by which they are assessed. This could contribute to making sense of revised nosologies and diagnostic criteria.

1. Introduction

Christopher Boorse's biostatistical theory (BST) is a naturalist account of disease that describes a value-free conception of disease in terms of biological dysfunction (Boorse, 1977; 1987; 1997; 2002; 2011; 2012; 2014). Boorse avowedly provides a theoretical account, stating that "the judgment that something is a disease is a theoretical judgment" (Boorse, 1977, p. 544). However, what it means for an account of disease to be theoretical or clinical/practical may be unclear. Indeed, in the philosophy of medicine the distinction between theoretical and clinical disease has not been fully explicated (with the notable exception of Schramme [2014]) or used consistently among authors. Moreover, the BST has failed to convince many that it is a tenable account of disease, leading some philosophers to recently declare that, "In the eyes of many, the refutation of the biostatistical account of Christopher Boorse has shown the naturalistic approach to understanding the concept of disease to be unworkable" (Simon, Carel, & Bird, 2017, p. 240). This pronouncement may be too hasty, however. My goals in this article are therefore three-fold: (1) to argue that the BST is best seen as a theoretical account of disease which, if extended, provides a unified conceptual framework that explains one possible relationship between theoretical and clinical disease and that explains these terms, (2) to articulate how extending the BST—a value-free theoretical conception of disease—could be applicable to particular diseases and value-laden issues in medicine, and (3) to defend the validity of my framework and its applicability to medicine. I do this in part by supplying a detailed discussion of a wide variety of medical examples to demonstrate how a naturalist conception of disease can be directly relevant to practical matters in medicine.

The article is structured as follows: First, I briefly review concepts of disease and what it might mean for some of these to be theoretical or practical. Next I situate the BST as an example of a theoretical account of disease, and introduce the clinical disease conception (which I define as diagnosed theoretical disease) specifically as it relates to the BST (bearing in mind that clinical disease could mean different things depending on one's philosophical outlook or conception of disease). Then I elaborate on potential benefits of BST-defined theoretical and clinical disease and how they are related to each other. My project is partly animated by the drive to show how this non-normativist conception of disease can deal with many of the issues and concerns normativists talk about. The rest of the article is devoted to responding to potential objections and issues (such as the BST's ability to demarcate disease from non-disease), and exploring implications for specific diseases, including a detailed discussion of polycystic ovary syndrome (PCOS) and a response to Doust et al.'s (2017) treatment of it. Finally, I discuss some alternative views of BST-based clinical disease and potential shortcomings of drawing a BST-based distinction between theoretical and clinical disease.

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2. Concepts of disease and theoreticity

Over the past forty years a variety of concepts of disease have been advanced to demarcate disease from non-disease. These accounts range from non-normative (sometimes called naturalist) positions (e.g., Boorse, 1977; Sulmasy, 2005), to normative or value-based accounts (e.g., Clouser, Culver, & Gert, 1997; Cooper, 2002; Engelhardt, 1976; Reznek, 1987), to hybrid accounts that comprise value-based and non–value-based components (e.g., Wakefield, 1992a; b). The accounts on offer could be harm-based (e.g., Clouser et al., 1997; Wakefield, 1992a; b) and/or dysfunction-requiring (e.g., Boorse, 1977; Schwartz, 2007, p. 366). Some accounts relativize disease to environment (e.g., Nordenfelt, 1987/1995, p. 107; Reznek, 1987, p. 85; Canguilhem, 1943, pp. 88, 142, 228), while others (or the same ones) relativize disease to individuals (e.g., Sholl & De Block, 2015, pp. 2, 17). The types of normative accounts are in fact considerably more diverse than has traditionally been thought (Simon, 2007). For example, George Khushf (2007, p. 24) offers a taxonomy of the debate that further distinguishes weak normativists as those who see values as integral to health concepts, but are still able to disentangle values from facts, whereas strong normativists are unconvinced of the possibility of disentangling evaluative and factual judgments. The concepts of disease debate has thus been heavily invested in the role of values in defining disease. However, less attention has been paid to the role of theoreticity and what it means with respect to a practical concept of disease.

What makes any of the accounts of disease just mentioned theoretical, as opposed to clinical or practical, may not be clear at first blush. To moot one possibility, Boorse drew the distinction between theoretical and practical conceptions of disease as resting on whether the conception is value laden or not (Boorse, 1997, p. 11). This view indicates how the distinction between theoretical and clinical disease could map onto the opposition between naturalist (i.e., value free) and normativist (i.e., value laden) conceptions of disease. However, this is possibly not the only mapping, and even this mapping fails when it comes to what could plausibly be seen as theoretical accounts of disease, such as Reznek's (1987) or Cooper's (2002), that are value laden. One feature that distinguishes the BST from these accounts is the requirement for biological dysfunction to be present for a condition to be a disease.[2] The mapping also fails when the simplistic dichotomy between value-laden and value-free concepts of disease is called into question, such as by Kingma (2014, p. 591) and Simon (2007). There may therefore be better reasons for calling an account of disease theoretical than whether or not it is value laden.

Nonetheless, the question could arise why a theoretical conception of disease is needed in the first place. De Vreese (2017, p. 432), for example, on her way to presenting a "pragmatist" conception of disease, argues that disease is not a theoretical concept at all. It is possible that the distinction between theoretical and clinical disease may only be present, or at least is most fully developed, within naturalist accounts of disease.[3] This is especially true if theoretical disease is equated with a value-free conception of disease. The distinction between theoretical and clinical disease may thus not even arise on most, if not all, normativist conceptions of disease.

Assuming that the BST provides clear criteria for demarcating whether a condition is a disease or not,[4] there may be didactic benefits to having a separate conception of clinical disease that relies on theoretical disease (assuming the BST is taken to be an example of a theoretical account of disease, and I do not rule out the possibility that other accounts of disease, even strongly normativist ones such as Cooper's [2002], could do the same). In part this is motivated by the breadth and complexity of the BST and the lack in the published literature of explanations of how it applies to clinical practice. For example, as I will argue later, an early stage of a disease, which is not clinically detectable (by current technology), would still count as a (BST-based) theoretical disease. If encapsulated by diagnostic criteria and detected, then the early stage would be (BST-based) clinical disease. Many clinical conditions go undiagnosed, and one reason for using "theoretical" could be to draw a distinction between a disease that could be diagnosed given appropriate resources and disease as it could be used clinically—meaning already diagnosed based on the purposes to which the diagnostic criteria aimed. This would then highlight that there is not always a one-to-one correspondence between theoretical and clinical disease, or that the currently used diagnostic criteria for a condition might not reflect a disease but might reflect something else, such as risk for disease. The importance of the mismatch between theoretical and clinical disease (i.e., diagnosed theoretical disease) is particularly pronounced for some conditions, such as Alzheimer disease (AD), that have recently undergone a renaissance in redefinition (Shermer & Richard, 2018). By redefining AD (via its diagnostic criteria) from a clinico-pathologic construct to solely a pathologic construct—able to be diagnosed via laboratory tests even in the absence of symptoms—AD's redefinition not only creates a tension between research and clinical purposes but introduces thorny ethical issues for persons positive for the diagnosis but who never go on to develop dementia. This is because such persons could still be viewed as if they are diseased (with the consequent risk of being harmed, such as by engaging in unnecessary worry, losing driving privileges, and even being pressured into receiving treatment). By contrast, drawing the distinction between theoretical and clinical disease can help highlight situations where diagnostic criteria do not capture any (BST-based) theoretical disease (e.g., many psychiatric conditions and some cases of hypertension, hypercholesterolemia, and other risk-based diseases). The clinical implications of this are potentially profound, considering that such persons could still receive diagnoses as if they had genuine diseases. Drawing the distinction between theoretical and clinical disease can help bring attention to these cases.

In short, the theoretical portion could provide a value-free way to demarcate disease from non-disease, while the clinical portion could allow for values and purpose in determining what it is that answers to the disease label in a clinical encounter. These considerations underlie the current account and are discussed more fully later. Possible practical benefits of this approach are that it offers a typology of clinical conditions (Tresker, 2020) and a conceptual framework that can possibly guide nosology and the setting of diagnostic criteria. The conceptual scheme inherent in the theoretical/clinical distinction is illustrated in Fig. 1. This shows the relationships between theoretical disease, clinical disease, and other clinical conditions. The figure illustrates the fact that clinicians[5] deal with a lot more than just disease. The present article, however, focuses solely on the relationship between theoretical and clinical disease. In fact, Boorse (1975) outlined a conceptual framework for the distinction between theoretical and clinical disease. He also advanced a theory of disability that explains what theoretical disease does, and does not, imply for practical notions of disease (Boorse, 2010). Despite this there is no comprehensive

[2] To be sure, the BST is not the only possible dysfunction-requiring, putatively theoretical, account of disease. Wakefield's (1992a; b) harmful dysfunction analysis, for example, could also be seen as offering a theoretical approach to the demarcation of disease from non-disease, at least insofar as Wakefield analyzes the *concept* of disorder, thus ostensibly advancing a theoretical account. Yet Wakefield's account involves the presence of a normative component—harm—which entails the use of value judgments in deciding whether something is a disease. If theoretical and clinical disease are mapped to value-free and value-laden conceptions of disease, respectively, then Wakefield's account would not be a theoretical account, because of this value component.

[3] I thank Mary Jean Walker for this point.

[4] I acknowledge that this is an assumption that may trouble some readers.

[5] Instead of "physicians" or "doctors" I use the term "clinicians" to refer to health care practitioners, because more than physicians diagnose and treat disease, such as nurses, physician assistants, dentists, and osteopaths.

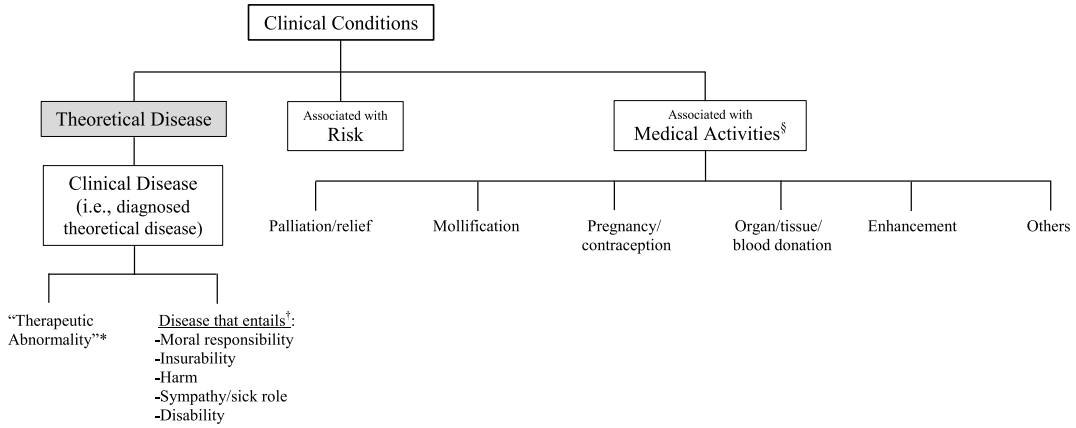

Fig. 1. Categorization of Clinical Conditions. *This is Boorse's term (2014, p. 685) for what could also be described as disease "worthy of treatment". Therefore, it could alternatively fall under the "Disease that entails" heading given that "meriting treatment" is an aspect of clinical disease. †Items (with the exception of 'Sympathy/sick role') are based on (Boorse, 1997, p. 100). These features can also apply to other clinical conditions besides clinical disease. §The defining feature, or feature in common, of medical activities seems to be that they are done by medical professionals, or in a medical capacity of some sort (for example, a midwife). Boorse lists various activities related to conception, adjustments to the sleep-wake cycle; relief of discomfort related to normal conditions such as teething; cosmetic surgery; anesthesia; organ, tissue, and blood donation; treating typical dysfunctions of old age, such as presbyopia; and reassuring the worried well as being ways clinicians treat patients without specifically treating theoretical disease (Boorse, 2016, pp. 150–151).

framework in the literature describing the conceptual benefits of distinguishing between theoretical and clinical disease, particularly with respect to the BST. Moreover, the relevance of this distinction for any particular disease has not been fruitfully explored. It is unsettled in the literature just how useful a theoretical conception of disease is on a practical, clinical level. Indeed, because the BST is so avowedly value-free (at least according to Boorse), it may also be unclear how the BST can be used in the service of value-laden pursuits—clinical medicine to be exact. The remainder of this article is meant to show how.

3. The biostatistical theory as a theoretical account of disease

According to Boorse (2014, p. 688), "[The BST] aims to analyze a theoretical concept of disease in the sense of 'pathological condition'." The BST is meant to provide a set of necessary and sufficient conditions of disease, and Boorse notes that other conceptions of disease, such as "treatment by physicians, statistical normality, pain and suffering, disability, adaptation, and homeostasis" are unable to do this (Boorse, 1997, p. 7). The BST is presented by Boorse as follows (2014, p. 684, italics and brackets in original):

1. The *reference class* is a natural class of organisms of uniform functional design; specifically, an age group of a sex of a species.
2. A *normal function* of a part or process within members of the reference class is a statistically typical contribution by it to their individual survival [or] reproduction.
3. *Health* in a member of the reference class is *normal functional ability*: the readiness of each internal part to perform all its normal functions on typical occasions with at least typical efficiency.
4. A *disease* [later, *pathological condition*] is a type of internal state which impairs health, i.e., reduces one or more functional abilities below typical efficiency.

A key aspect of the BST is that in defining pathology, the BST rests on an account of normal physiology. Because of the goals of this article and the BST's aim of describing a theoretical conception of disease, I henceforth use "theoretical disease" to be disease as defined by the BST. Some conditions that are considered diseases on some normativist views are not diseases on the BST (e.g., pregnancy, as in Clouser, Culver, and Gert's view of malady [1997, pp. 205–207]), and conversely, some conditions considered by the BST to be diseases (e.g., sickle-cell trait) are not diseases on some normativist views (e.g., [Reznek, 1987, p. 86]). My account of theoretical disease, accordingly, is only relevant to diseases recognized by the BST.

What good is theoretical disease conceived of on the BST? Boorse (1977; 1997; 2014), over the past forty years and in response to his many critics, has discussed its strengths, usefulness, and advantages over other conceptions of disease. Therefore, I will largely not repeat these. Readers unsympathetic to the BST may find the focus on the BST and distinction between BST-based theoretical and clinical disease to be otiose. Nonetheless, for the previously mentioned reasons and based on the assumption that the BST provides clear criteria for demarcating whether a clinical condition is a disease or not, the BST's relationship to a clinical conception of disease can be gainfully explored.

4. What is BST-based clinical disease?

Some authors do not see the need for theoretical disease, or they view disease as an intrinsically value-laden concept (De Vreese, 2017, pp. 425, 428–429). "Clinical" disease may therefore be pleonastic. In practice, once it is established that a person has a disease, adding "clinical" to "disease" would seem to only signify a degree of recognition and/or severity from a clinician. In theory, the "clinical" modifier may seem to do nothing.

By contrast with these views, appreciating the utility of being able to demarcate disease along naturalistic, non-individual- and/or non–environment-relative terms, the clinical disease conception can support the BST-based theoretical disease conception by showing how values determine how a disease is *recognized* in clinical practice. BST-based clinical disease I thus define as theoretical disease that is diagnosed. An equivalent way to state this is that BST-based clinical disease is theoretical disease that is detected, either through symptoms or signs or both, depending on the diagnostic criteria of the disease. Signs (i.e., objective findings, such as abnormal gait, serum creatinine concentrations, and height) and symptoms (i.e., subjective findings, such as fatigue and pain) are necessary for diagnosis because they constitute diagnostic criteria.

BST-based clinical disease bears some resemblance to Boorse's (1987) diagnostic abnormality concept. The chart he offers (Boorse, 1987, p. 365) is meant to show what he calls grades of health, not features of clinical disease, and represents that there is a core, value-free notion of theoretical disease (i.e., the "Pathological" rectangle; Fig. 2, inverted top-to-bottom to better show the relationship between diagnostic abnormalities and disease). Other, value-based

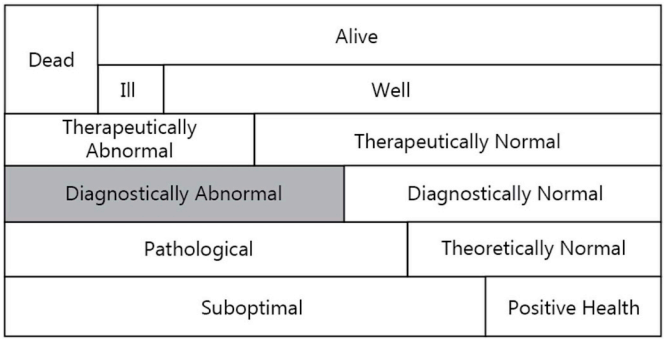

Fig. 2. Diagnostic abnormalities and grades of health (based on Boorse, 1987).

notions can be constructed from this core notion. For example, a therapeutic abnormality is the presence of a diagnostic abnormality worthy of treatment (Boorse, 2014, p. 685). The chart shows that a person can have theoretical disease (the "Pathological" rectangle) but be diagnostically normal. This could occur in cases of undiagnosed disease, or as Boorse (1987, p. 365) suggests for pathological conditions "such as minor liver cirrhosis, tiny pancreatic cysts, transient cardiac arrhythmias, and early atherosclerosis." However, according to Boorse's chart a person could not be theoretically normal and have a diagnostic abnormality at the same time; if a person has a diagnostic abnormality they must have pathology. In the terms of my distinction between theoretical and clinical disease, this could lead to some confusion, however. This is because patients often receive diagnoses despite the absence of pathology. This could include simple cases of misdiagnosis, or cases where the diagnostic criteria are correctly applied but do not pick out any pathology, as in some cases of depression. The flip side of the coin also applies—a person could have pathology and be diagnostically normal, again as a result of misdiagnosis, or perhaps less commonly when a theoretical disease exists but diagnostic criteria for that disease do not, such as with the acquired immunodeficiency syndrome before it was characterized and diagnostic criteria created to aid its identification in clinical practice.

Because of the dysfunction-requiring "block" provided by theoretical disease, diagnosed theoretical disease (i.e., clinical disease) makes it automatically clear whether a condition involves biological dysfunction, such as that reflected by pathology. With the BST there is also an intrinsic bulwark against boundary inflation, such as the creep many conditions (e.g., type 2 diabetes mellitus [T2DM], hypertension) have undergone in recent years, whereby the boundaries marking positive cases of these conditions have become more lenient, making many more people "diseased". This is because the BST presents a core minimum for a condition to even be considered a disease.[6] Whether the boundary is considered too permissive depends on where the statistical cut-off for a reduction from typical functional efficiency is set.

Conceptions of disease other than the BST, such as normative conceptions, or implicit conceptions used in clinical practice, could also serve important clinical ends in medicine. Similarly, the ways in which values affect diagnosis can be fruitfully explored without any philosophically inspired conception of disease. I revisit these issues in §10.

Does what is counted for clinical purposes as disease simply reflect *general* evaluative considerations related to diagnosis and treatment, or does clinical disease have the resources to provide *individual* evaluative notions? Thomas Schramme (2016, p. 67), for example, points out that different people with the same disease (i.e., pathological condition) merit different evaluations based on individual goals, interests, and circumstances. He believes that a practical notion of disease is required in addition to the theoretical notion. He is skeptical though whether Boorse's therapeutic abnormality concept (and one would assume diagnostic abnormality concept as well) can capture this.

These concerns can be mitigated by recognizing that all normative concerns surrounding various uses of the concept "disease" relate to it as a clinical concept as I have defined it, rather than as a theoretical one. As Kingma (2014, p. 592) writes, "all naturalists adhere to a 'two-layer' account of health and disease: a core naturalist concept—usually function/dysfunction—which they claim is value-free, but which gets overlaid or augmented with values as soon as it is to be applied to any particular question or used in a practical setting." Because of this, BST-based clinical disease can be reconciled with some of the concerns expressed by Canguilhem (1943) and leveled against the BST as being unable to accommodate, such as adaptation and relativity to local environments, as well as an individual's goals and values. The next section starts by examining the role of diagnostic criteria in clinical disease and their normative importance.

5. Diagnostic criteria and clinical disease

What is meant by diagnostic criteria and why are they important? Diagnostic criteria are the signs and/or symptoms by which a clinical condition is identified. By reflecting not only clinical norms but also societal norms, diagnostic criteria are one place where values come into the picture for any given clinical disease (i.e., diagnosed theoretical disease). Diagnostic criteria can be enshrined in clinical practice guidelines, or be tacit knowledge that points to the presence of a disease. But even in the latter case criteria are being used if a patient is deemed to have a disease, whatever manner that diagnosis is meted out. Diagnostic criteria are not immutable and could even subtly change from patient to patient, such as when a clinician is not clear as to how a condition should be diagnosed or when a patient applies slightly different criteria from that used by a clinician. Misapplication of diagnostic criteria could result in under- or overdiagnosis. Official diagnostic criteria also change, but typically over longer time periods, such as when an expert group convenes to discuss practice guidelines. In all cases, criteria are implicitly or explicitly, consciously or unconsciously, deliberately or inadvertently being used to ascertain the presence of a disease. Moreover, as Jutel (2011, p. 197) observes, "While the diagnostic process might not employ a unique standardized classification system, the post-diagnosis process often includes classification," pointing out that such classification (i.e., diagnostic criteria) also serves to legitimize various authority relations and aspects of medicine. Diagnostic criteria are also important because they provide a basis by which outcomes in clinical studies can be chosen to evaluate the effectiveness of medical interventions. This is because a reduction in or elimination of a diagnostic criterion (e.g., lowering of fasting plasma glucose [FPG] levels or no longer having difficulty falling asleep) could indicate effectiveness of an intervention. Finally, although medicine relies on diagnoses by clinicians, not all diagnoses are made by clinicians; consider self-diagnosis of eczema or acne, or anytime a parent diagnoses their child with a cold.

Diagnosis can reflect a patient's or clinician's values because some tests (say, a prostate-specific antigen test) will not be ordered for a patient for whom the benefit–risk ratio is not favorable. Similarly, diagnostic criteria for some diseases may not include a certain test if that test is too expensive, not sensitive enough, or for any number of other reasons. Thus values determine whether a person has a BST-based clinical disease because they inform whether a diagnostic test should be performed, as well as influencing or determining the criteria constituting the diagnosis itself.

BST-based clinical disease, via the diagnostic criteria that serve to define it, is one way theoretical disease is identified in clinical practice. Because some diseases are subclinical, this distinction between clinical

[6] However, not all scholars share this view. For example, Doust et al. (2017) argue that the BST can lead to disease category inflation as diagnostic tests become more sensitive to very minor abnormalities, thereby enabling dysfunction to be identified at very low levels. I thank an anonymous reviewer for this journal for this point.

detection (i.e., via symptoms) and presence of disease can lead to much terminological confusion (Boorse, 2015). Boorse (2015, p. 8) offers three examples of diseases—emphysema, type 1 diabetes mellitus (type-1 DM), and coronary artery atherosclerosis (CAA)—where the underlying disease process can be present for years before being clinically detectable. He states (Boorse, 2015, p. 12):

> Medicine offers innumerable such examples of chronic, local, subclinical disease processes, pathologically defined, which progress over many years before signs and symptoms appear. In some cases, the common disease name covers all phases of the process (emphysema, CAA); in others, the common disease name is reserved for the clinical stage (type-1 DM). Even when the name covers all stages, it is also sometimes used in a narrower clinical sense (emphysema, CAA). But at all stages the process is called a disease.

It is thus very possible that symptoms and/or signs indicate the likely presence of theoretical disease but are not sufficient to meet the diagnostic criteria for a BST-based clinical disease. These cases represent suspected or presumed disease, which could result in a presumptive or provisional diagnosis (which is quite common in clinical practice). For example, a person could have sign 1, sign 2, and symptom 3, but if the diagnostic criteria for a BST-based clinical disease require sign 1, sign 2, symptom 3, and symptom 4, then they do not have the BST-based clinical disease. However, based on the signs and symptoms they do have, it might be likely that they have a theoretical disease. If it is important that such patients' theoretical disease be recognized by medicine as a clinical disease, for example, then this would indicate the importance of revising the diagnostic criteria to coincide with the signs and symptoms such patients do have.

A high rate of medically unexplained symptoms in clinical practice (Nimnuan, Hotopf, & Wessely, 2000; Reid, Wessely, Crayford, & Hotopf, 2001) means a patient could emerge from a clinical encounter without a diagnosis—such as no BST-based clinical disease—yet still possibly have a theoretical disease. This disease could be undiagnosed because no diagnostic criteria exist for it that could capture it on the basis of the symptoms and signs the patient has, or the patient could simply not meet the current diagnostic criteria for an already-characterized disease. In fact, because many diseases are self-limiting a patient's theoretical disease could go undiagnosed and resolve itself even before reaching the clinician's door. A precise diagnosis might not even be needed or desired by some clinicians or patients, especially when the focus is the patient's symptoms and not their underlying pathophysiology (discussed in [Armstrong, 2011]). The unacceptably high rate of diagnostic errors in clinical practice (e.g., missed, delayed, or incorrect diagnoses; Graber, 2013) means it could be rather likely that a patient's theoretical disease could go unrecognized. This does not necessarily mean that diagnostic criteria should be changed to capture more people with the theoretical disease. This is because the presence of a theoretical disease does not necessarily determine how it should be managed. This is especially the case for poorly understood theoretical diseases. The Undiagnosed Diseases Network (UDN), for example, is a National Institutes of Health–funded consortium of medical research centers aimed at diagnosing rare and unrecognized diseases (Ramoni et al., 2017). The UDN illustrates the likelihood of a person having a theoretical disease without a BST-based clinical disease, such as when that disease is rare or never before characterized by medicine. Besides the often great suffering such patients endure from the symptoms, the uncertainty of their condition not having a definitive diagnosis results in enormous emotional distress, in addition to futile treatments (Spillmann et al., 2017). The UDN also illustrates the importance of objective findings versus subjective findings in determining whether a patient with a medically unexplained illness will eventually receive a diagnosis by the UDN (Walley et al., 2018). The importance of this with respect to the distinction between BST-based theoretical and clinical disease is that the presence of symptoms does not always indicate the presence of biological dysfunction. Clinical medicine, however, is not solely invested with the diagnosis and treatment of conditions involving biological dysfunction. It is important to recognize that an "essential continuity [exists] between persons who have symptoms that have been given a name and disease-like status and persons whose suffering remains unnamed and unrecognized" (Aronowitz, 2001, p. 808). The ways in which medicine parses these groups are influenced by social factors and not just a strict focus on biological aspects of medical conditions. The BST-based clinical disease conception recognizes these social factors while at the same time providing a well-elaborated naturalist rationale by which conditions can be labeled as disease or not, regardless of the prominence of symptoms in the conditions' presentations.

In addition to the possibility of there being theoretical disease without BST-based clinical disease, there are also many clinical conditions that do not involve theoretical disease. Medicine may still recognize these conditions as "diseases", however, especially when accompanied by "official" diagnostic criteria. The disruptive, impulse-control, and conduct disorders listed in the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5; APA, 2013), for example, might not involve any pathology or internal part or process dysfunction at all and therefore would not be theoretical diseases on the BST. Yet there are still diagnostic criteria for these conditions. For a patient with a medically unexplained symptom who visits a clinician, an eventual diagnosis, if not reflective of the patient's theoretical disease, could not be a BST-based clinical disease on my usage. It would count as a clinical condition, however (Tresker, 2020; Fig. 1), and could still merit treatment. Whether a condition merits treatment or not has no necessary relationship with whether it is a theoretical disease, clinical disease, or other clinical condition. After all, treatment can be empirically based ("see what works") and guided by symptoms or considerations having nothing to do with a conception of disease.

If no diagnostic criteria for any disease are met there is no BST-based clinical disease, but if diagnostic criteria for a "disease" are met this does not necessarily mean there is BST-based clinical disease. The presence of theoretical disease would have to be ascertained. These possibilities also illustrate that there is a panoply of factors besides pathophysiology, such as patient advocacy groups, pharmaceutical companies, intra- and inter–medical-specialty dynamics, and political and economic forces (Horwitz, 2011), that influence a condition's diagnostic criteria. Yet in all cases, because of the value-free nature of the BST, none of these factors affects whether a condition is a theoretical disease.

To summarize this section, a distinct advantage of distinguishing between BST-based theoretical and clinical disease is that it provides a rational basis for the setting of diagnostic criteria for diseases (i.e., deciding what criteria should be used by which a person can be diagnosed as having a specific disease) and the practice of disease research. BST-based clinical disease thus serves a number of practical ends in medicine, such as those related to diagnosis. There is a difference, though, between ascertaining the likely presence of theoretical disease and identifying a condition in clinical practice through the use of diagnostic criteria. The next section discusses how to distinguish between BST-based theoretical and clinical disease.

6. Clinical evidence of disease

For any given clinical condition, how is it known that statistically subnormal function is present (i.e., there is a BST-based theoretical disease) and how can it be identified? Boorse explains the capacity to distinguish between theoretical disease and disease recognized in clinical practice as resting on the ability of tests to accurately measure the underlying dysfunction(s) of a disease: "[There is a] gulf between (i) statistical abnormality of most clinically observable variables and (ii) true medical abnormality (= statistical subnormality of internal physiological function)" (Boorse, 2012). This is consistent with the distinction between BST-based theoretical and clinical disease I have

drawn; as explained, BST-based clinical disease is theoretical disease that has been determined to be present based on symptoms and/or the results of clinical/laboratory tests, because that is what diagnostic criteria comprise.

However, theoretical diseases are not defined on the basis of diagnostic criteria (although signs and symptoms are the only way to indicate if a theoretical disease might be present). Rather, the presence of theoretical disease can be ascertained by, for example, looking at a clinical condition and seeing whether it fulfills the BST's definition of disease (outlined in §3). These points have been explicated at length by Boorse and others and applied to many clinical conditions to discern whether or not disease is present. Admittedly, this is not always a straightforward matter in the way that marking off a checklist of signs and/or symptoms is to determine whether diagnostic criteria are fulfilled.

A key criterion of the BST's definition of disease is the presence of dysfunction. Tests can be used to detect dysfunction and in some cases these will be the same tests (i.e., diagnostic tests) used to identify clinical diseases (or other clinical conditions), but sometimes (such as with biopsy) a test result will not be part of the diagnostic criteria of a condition because the test is too dangerous, expensive, inconvenient, or lacks the sensitivity or specificity to be of much use. This implies that there might be theoretical diseases that are unknown (as exemplified by the UDN) or not of enough importance to be of concern in clinical practice.

Because internal physiological function is difficult to directly observe, inferring the presence of dysfunction from clinical and/or laboratory tests is not as straightforward as it may seem (Boorse, 2012). Many clinical tests, such as those measuring cholesterol levels or blood glucose concentrations, offer only a limited view into whether there is statistical subnormality of internal physiological function; i.e., theoretical disease. Moreover, the reference range on a laboratory test merely reflects a statistical normality that may coexist with theoretical disease, and therefore does not necessarily reflect the absence of theoretical disease. This is because some people falling inside the range might still have the disease in question and some people falling outside the range might not have the disease. If they meet diagnostic criteria that reflect an underlying theoretical disease, then they also have clinical disease. How clinically evident a disease is depends on multiple factors, such as the availability and accuracy of diagnostic tests that measure aspects of the disease's pathology, whether the disease produces readily detectable signs and symptoms (and what they are), and the organ(s) the disease affects. Some organs, for example, offer a clearer view into their pathology than others, the skin being a prime example, where pathology is typically visible to the naked eye. However, there is no relationship between how clinically evident a disease is and its severity. Some diseases, such as many skin diseases, are clinically evident but trivial, even harmless, whereas symptomatic coronary atherosclerosis is always important (Christopher Boorse, personal communication). In fact, there is often a disparity between the diagnostic criteria used to ascertain the presence of disease and the underlying disease-defining dysfunction, acute kidney injury, T2DM, and amyotrophic lateral sclerosis being prime examples. In T2DM, for example, no fewer than eight physiological functions can be affected (DeFronzo, 2009) yet typically only a single or dual indicator (i.e., glycated hemoglobin [HbA1c] and/or FPG levels) is used to ascertain T2DM's presence. Hucklenbroich (2014, p. 618) also recognizes that diseases' diagnostic criteria differ from diseases' defining conditions, and that diagnostic criteria are used because ascertaining the presence of the defining conditions may be too time-consuming, expensive, difficult, or burdensome to the patient.

Defining disease in terms of dysfunction raises a potential objection related to the inability to directly measure dysfunction, and thus whether a theoretical disease is even present. Because clinicians cannot usually directly test whether dysfunction is present, they use mechanistic (i.e., underlying the disease) biomarkers or, less optimally, descriptive (i.e., byproducts of the disease process) biomarkers, to ascertain its presence (Robinson, Lindstrom, Cheung, & Sokolove, 2013). In other cases still, when biomarkers are not available, exclusively symptom-based diagnostic criteria are used. But even in cases in which quantitative biomarkers are available, such as levels of triiodothyronine (T3), thyroxine (T4) and thyroid stimulating hormone (TSH), only a proxy of the dysfunction present can be provided, and therefore not a 100% correspondence with the putative theoretical disease. Although it may be tempting to consider a reference standard as a perfect measure of the dysfunction present in theoretical disease, a reference standard is helpful insofar as it provides a measure of the accuracy of a diagnostic test (Knottnerus & Muris, 2003). However, a reference standard is still a test. Thus, it can never assess what is a statistically typical contribution of a body part or process to an individual's survival or reproduction. This rests on the BST's notion of functional efficiency, discussed next.

7. Identifying theoretical disease based on functional efficiency

Élodie Giroux (2015) rightly points out that normality should be defined relative to functional efficiency, not the level of some variable that may not track a functional process. Hausman (2012, pp. 532, 534; 2014), who provides useful amendments to the BST with his theory of functional efficiency, clearly holds a place for multiple quantitative variables as being reflective of functional capacities, the environment in determining how well a part is functioning, and the goals of the organism as a whole or by its systems. However, Giroux (2015, p. 188) goes a step further by claiming that by relying on statistical normality, the BST cannot practically demarcate the normal from the pathological. Her point of contention appears to be that because of the near impossibility of demarcating between disease and non-disease in clinical practice (i.e., based on laboratory and clinical tests), the gap between the BST's practical and theoretical conceptions of disease becomes too wide to bridge. She thinks that even if the level of functional efficiency of blood pressure or any other physiological parameter could be defined this still would not be sufficient to demarcate the boundary between disease and health (Giroux, 2015, p. 188). Epidemiology, by contrast, could help to clarify the levels of functional efficiency of traits or parts by "providing a measure of the physiological contribution of a trait (or process) to individual survival" as revealed by case-control and cohort studies (Giroux, 2015, p. 192). Such an approach, Giroux (2015, p. 192) writes, offers "a better estimate of the functional efficiency of a trait than the population distribution of [biological/physiological] variables."

It is not clear how epidemiology could do this, however. Case-control and cohort studies already include patients with the disease as defined by some set of diagnostic criteria—criteria which already reflect a level of functional efficiency of some part(s) or trait(s). The most a case-control or cohort study could do then would be to assess the effect of such a level of functional efficiency on survival, but not to define it itself. Moreover, it could only do this with respect to a reference class in a contemporary environment. It would neither reflect a time-slice of the species nor typical environments, only a local, clinical study protocol–defined environment. The benefit of a theoretical notion of disease and functional efficiency resting on physiology is that disease is not defined relative to local vagaries of time, place, or individual.

Nonetheless, if it is not possible to precisely identify a theoretical disease based on functional efficiency, this would seem to present an insurmountable obstacle to ascertaining the presence of BST-based clinical disease based on theoretical disease. Indeed, the boundaries between health and theoretical disease are vague (Boorse, 1997; Rogers & Walker, 2017; Schwartz, 2007). This only presents a potential obstacle for identifying a theoretical disease. Recognizing the presence of vagueness does not have to prevent the possibility of identifying theoretical disease, however (Boorse, 1997, p. 19). Moreover, when it comes to matching a clinical state with a set of dysfunctions, medicine accepts a variety of different approaches. For example,

> The clinician may regard heart failure as a clinical syndrome associated with certain symptoms and signs. … In contrast, the physiologist may consider it a disease state, in which one or several functional parameters indicate reduced cardiac function. No clearcut [sic] relationship can be expected to exist between two so entirely different approaches to characterize the functional state of the heart. Therefore, the discrepancy between clinical examination and quantitative methods of assessing ventricular function should not be used to discredit either of them. (Gadsbøll et al., 1989, p. 1027)

The functional state of the heart admits of multiple characterizations at different levels of analysis. Which one is focused on determines which theoretical disease may be present. BST-based theoretical disease looks to dysfunction, and there could be many types of dysfunction affecting the heart in heart failure, just as there could be many types of dysfunction present in other "diseases", such as T2DM (discussed later). Which dysfunctions are focused on inform what ends up getting called a disease by researchers, clinicians, and patients, and what become the diagnostic criteria set for that disease. Consumption and infection of the lungs with *Mycobacterium tuberculosis*, for example, turned out to involve the same dysfunction, and thereafter became known as tuberculosis (Boorse, 1987, p. 364). There was always just one theoretical disease, but it took in this case identification of the causal pathogen to create better diagnostic criteria for the disease, in the process subsuming what were previously multiple clinical diseases.

The next section examines an example of a clinical condition involving multiple types of dysfunction, and shows how the BST-based theoretical and clinical disease conceptions offer nosological insights into what theoretical disease(s), and, by extension, clinical disease(s), may be involved.

8. Diagnostic criteria and identifying diseases' dysfunction

Diseases can be defined by a single gene or group of genes, or by a particular phenotypic feature, such as a radiologic finding (Bonafe et al., 2015). Nosological systems—the methods and sets of criteria by which diseases are classified—may change because of consolidation of diseases into single ones, such as when no or not enough phenotypic difference exists, or new causative genes are discovered. Nosology can be phenotypically based in terms of symptoms, molecularly based, genetically based, or a combination. In the case of the aforementioned tuberculosis, classification is currently based on etiology and pathogenesis, although it wasn't always so. Nosology also depends on the disease and body system(s) involved, because some nosological systems may make more sense than others for diseases affecting certain organs.

There are some diseases, such as some autosomal dominant genetic diseases, where the dysfunction is readily apparent, diagnostic criteria readily match up with the dysfunction, and diagnosing any given patient is relatively easy or straightforward. Most diseases, however, do not have definitive features; e.g., many neurological diseases are diagnosed via sets of criteria (criterial diseases). These criteria can and do change with new information or approaches. In continuous-variable diseases, such as T2DM, hypertension, and hyperthyroidism, some quantitative value on a diagnostic test is meant to represent a threshold beyond which disease is said to exist. There may be multiple dysfunctions underlying the disease. To speak of the thyroid's functioning, for example, solely as a reflection of altered T3, T4, and TSH levels, is a simplification; if this was not true then there would be no basis for the distinction between thyrotoxicosis (i.e., the state of thyroid hormone excess) and hyperthyroidism (i.e., the state of excessive thyroid function; Fauci et al., 2009). Hybrid cases, such as urinary tract infections, involve a set of criteria at least one of which involves a continuous variable (in this case, the amount of bacteria in urine). For these and other diseases rational formulation of diagnostic criteria can be difficult if it is not clear what the dysfunction is and/or how best to assess it.

For example, Jenny Doust, Mary Jean Walker, and Wendy A. Rogers (2017) raise PCOS as an example of a disease the BST cannot sufficiently handle. The crux of their argument is that the BST cannot adequately define the boundary between normality and pathology because it is not clear according to them which function is "pathognomonic" of PCOS (Doust, Walker, & Rogers, 2017, p. 355). More specifically, they argue that depending on which dysfunction is the focus, the boundary between normality and pathology shifts (Doust et al., 2017, p. 355). They acknowledge that this is only a problem for the BST insofar as it regards nosology, not demarcating health from disease. However, they also argue that the changing, multiple criteria for PCOS reflect lack of agreement as to the underlying disease (and by extension, function).

PCOS is a criterial disease, and, as the name states, a syndrome. It is thus incorrect to speak of there being a pathognomonic feature for PCOS (i.e., having 100% specificity and 100% sensitivity[7]); at best there are necessary features, although some of the features (such as polycystic ovaries [PCO]) occur in other diseases or in non-diseased women as well (Goodarzi, Dumesic, Chazenbalk, & Azziz, 2011). As with most syndromes, there may not be a well-defined etiology. The problem with PCOS's changing diagnostic criteria, as Doust et al. (2017) see it, is that it is not clear which function(s) (and on what level(s)—cell, tissue, organ) constitute the underlying disease PCOS. Moreover, it is not clear how these should be assessed. Here is where the distinction between BST-based theoretical and clinical disease can shed some light.

As shown in Table 1, multiple phenotypes are possible based on the four key features (hyperandrogenemia, hirsutism, oligoanovulation, and PCO) constituting the various sets of PCOS's diagnostic criteria. Where among these is the true PCOS? This question is a non sequitur because there is no true PCOS—there are simply different combinations of signs and symptoms. Which combinations are focused on—and therefore which diagnostic criteria are used to define the condition—depend on the purposes for which the diagnostic criteria are set (Kushner et al. (2003) provide excellent examples of this for Kawasaki disease). Diagnostic criteria, unlike theoretical disease, are chosen for evaluative reasons; any expert group report promulgating new diagnostic criteria for a disease is testament to this. Necessarily, such criteria rely on diagnostic tests, even if as simple as gross observation in the case of skin diseases. Evaluation of the value of diagnostic tests involves more factors than simply how well they measure the disease's underlying dysfunction. This is especially true for diseases involving multiple dysfunctions. Other factors of importance for diagnostic tests include capabilities under laboratory conditions, the test's place in the clinical pathway, diagnostic accuracy, the impact on the patient, cost-effectiveness (Van den Bruel, Cleemput, Aertgeerts, Ramaekers, & Buntinx, 2007), the effect of the diagnostic test on patient outcomes (Sonke, Verbeek, & Kiemeney, 2009), the risks of over- and under-diagnosis, whether patients could benefit from therapy if diagnosed, and the prevalence of the disease (Björk, Grubb, & Nyman, 2009).

Coming back to PCOS, deciding on what dysfunctions are definitive of the condition is not a question the BST can directly answer. It is a clinical, sociological, economic, and practical question. The diagnostic criteria that are eventually set, however, can point to what the dysfunction is, and therefore what the theoretical disease(s) might be, if any.

For example, Khadilkar (2016) proposed renaming PCOS as the Hyperandrogenic Persistent Ovulatory Dysfunction Syndrome to better reflect the putative dysfunction. This definition is at odds with the Rotterdam criteria, which allow for a phenotype not involving hyperandrogenism. The National Institutes of Health criteria, by contrast, do

[7] It could be said that a set of diagnostic criteria are pathognomonic for a disease, since only people who meet those criteria have that disease and not another disease. Pathognomonic signs in medicine (like Koplik's spots for measles) unambiguously signify the presence of a disease but are not necessarily causal features of the dysfunction present.

Table 1
PCOS's possible phenotypes (adapted from Azziz et al., 2009).

Potential phenotype	Polycystic ovaries	Hyperandrogenemia	Oligoanovulation	Hirsutism	National Institutes of Health 1990 criteria	Rotterdam 2003 criteria	Androgen Excess and PCOS Society 2006 criteria
A	x	x	x	x	x	x	x
B	–	x	x	x	x	x	x
C	x	x	x	–	x	x	x
D	–	x	x	–	x	x	x
E	x	–	x	x	x	x	x
F	–	–	x	x	x	x	x
G	x	x	–	x	–	x	x
H	x	–	–	x	–	x	x
I	x	x	–	–	–	x	x
J	x	–	x	–	–	x	–
K	–	x	–	x	–	–	–
L	x	–	–	–	–	–	–
M	–	–	x	–	–	–	–
N	–	–	–	x	–	–	–
O	–	x	–	–	–	–	–
P	–	–	–	–	–	–	–

PCOS, polycystic ovary syndrome.

not even include PCO among the diagnostic criteria. By the BST this makes sense given that 20–30% of women of reproductive age have PCO and PCO is present in women with ovulatory disorders other than PCOS (Azziz, 2006, p. 783). Asymptomatic women with PCO might constitute a heterogeneous class of women with preclinical PCOS, mild PCOS, or more likely, healthy ovulatory women (Dewailly et al., 2014). Further, not all women with PCOS are entirely infertile. This subfertility, along with increased muscle mass and bone density from hyperandrogenism and hyperinsulinism, and the increased energy storage from being overweight, may even have been evolutionary adaptations (Goodarzi et al., 2011, p. 224). Although the BST does not use an etiological account of function, on a goal-based account it is not clear which functions are more important (Autzen, 2019). Thus, some of the phenotypes listed in the table may not involve any dysfunction at all and thus not be theoretical diseases, whereas other phenotypes may.

Moreover, the increased risk for T2DM, cardiovascular disease, obstetrical morbidity, and cancer found in women with PCOS (Goodarzi et al., 2011, pp. 223–224) raises suspicion that PCOS—at least on definitions that include women without any dysfunction—may be a risk-based disease, in the sense used by Schwartz (2008). To avoid overdiagnosis, this may be a reason for more conservative diagnostic criteria. As mentioned, Doust et al. (2017) argue that the BST's identification of dysfunction with disease can actually expand the boundaries of disease, which could lead to negative forms of medicalization and overdiagnosis (Walker & Rogers, 2017a). However, the dysfunction requirement can also contract disease boundaries. This depends upon how diagnostic criteria are set for a disease and the purposes for which they are set.

In sum, the clinical disease conception instantly shows whether a condition involves dysfunction. For syndromes like PCOS in which some phenotypes do not involve dysfunction, theoretical disease and therefore clinical disease may be absent, with something like a risk state being present instead. Yet with the typical features and manifestations of PCOS it is also possible that multiple theoretical diseases exist. This does not mean, however (for PCOS or any other syndrome), that there need be multiple clinical diseases. After all, medicine does not need to recognize every disease that exists. But for those theoretical diseases deemed important enough, diagnostic criteria (subject to myriad evaluative concerns) can be created to identify instances of such diseases in clinical practice.

9. Endotypes and the proliferation of diseases

To elaborate on the distinction between BST-based theoretical and clinical disease the notion of an endotype may be useful. Many diseases, some of which occur together as comorbidities, have common underlying pathophysiological mechanisms (Klimek, Aichberger, & Thurner, 2016; Ko, Cho, Lee, & Kim, 2016). Conversely, some diseases involve widely divergent pathophysiological mechanisms yet produce similar signs and symptoms. An endotype is “a subtype of a condition, which is defined by a distinct functional or pathophysiological mechanism” (Lötvall et al., 2011, p. 356). Although the concept of an endotype has traditionally found purchase in the field of asthma, it can be applied to many diseases. The endotype concept, if extended, allows identification of medical conditions (such as asthma) that involve multiple underlying diseases (i.e., endotypes) and assessment of how well diagnostic criteria reflect a specific endotype or collection of endotypes.

In some cases there may be value in having nonspecific, symptom-based, or functional diagnoses (Aronowitz, 2001), even if an endotype is unknown. In other cases greater endotype–diagnostic-criteria concordance may be desired. This depends on clinical or population-based health goals. If the goal is to capture a wide group of people suffering from a constellation of symptoms, even if the cause is unknown, but for which treatment is available, then ignorance of endotypes may be acceptable. There may also be benefits for diagnoses for conditions in which the pathology is not well defined or the clinical picture does not line up neatly with the pathology (Bedson, McCarney, & Croft, 2004).

PCOS is one of many diseases, including asthma, T2DM, rheumatoid arthritis, and AD, which are best seen as umbrella terms encompassing multiple sets of endotypes that lead to symptoms indicative of the conditions. T2DM, for example, is diagnosed by HbA1c or FPG levels. This can present a disparity between how clinically evident the disease is (i.e., as measured by HbA1c or FPG levels) and the underlying severity of pathology, be it in adipocytes, beta cells, alpha cells of the pancreas, the kidney, the incretin system, etc. There is thus not only a problem in localizing which pathophysiological defects (i.e., dysfunctions) constitute the theoretical disease(s), but also in capturing putative diabetics who actually have the dysfunction(s) definitive of T2DM. This is because HbA1c or FPG levels constitute only a proxy or biomarker of glucose homeostasis, not direct measures of physiological function in the systems that contribute to such homeostasis. Given the multiple pathophysiological defects in T2DM (DeFronzo, 2009) and the multiple pathways leading to beta-cell loss or dysfunction (Skyler et al., 2017), T2DM likely represents multiple theoretical diseases.

As an improvement over current T2DM nosology, different T2DM endotypes could each contain their own diagnostic criteria. This is because each endotype necessarily involves a different set of dysfunctions (if endotypes involved the same dysfunction they would be the same disease). There are practical benefits to this approach. For example, subtyping by etiology (e.g., as with maturity-onset diabetes of

the young) can lead to more rational treatments (Skyler et al., 2017). Diagnostic/clinical inertia, lack of knowledge or ascertainability of the pathophysiological defects, practical considerations, and questions of cost-effectiveness related to dividing T2DM into multiple diseases, each of which could have their own diagnostic criteria, may be why T2DM is currently considered a single disease. Yet as medical science advances the gap between BST-based theoretical and clinical disease may diminish as diseases are better subtyped and as more tests are able to identify their underlying pathology. However, this is not necessarily always a good thing. There may be compelling reasons, for some diseases, to keep a large gap between BST-based theoretical and clinical disease. This depends upon the purposes to which the diagnostic criteria are set. For example, to define AD solely on the basis of biomarkers (reflecting the putative underlying dysfunction of the disease) may hold certain research benefits but be of less importance to patients, and indeed could cause them harm (McCleery, Flicker, Richard, & Quinn, 2018). Further discussion of these points appears in Tresker (2020) but is beyond the scope of the present article.

10. Limitations and alternative accounts of BST-based clinical disease

Although I have attempted to make a case for the usefulness of the BST—at least when supplemented with a clinical disease account—there is no shortage of views disclaiming the ability of the BST to address many of the issues discussed in this article (Azevedo, 2015; Demazeux, 2015, p. 76; Doust et al., 2017; Hucklenbroich, 2014; Krueger, 2015; Stempsey, 2000, p. 329). At the very least, it is clear that though various authors have tried to clarify or improve the BST (e.g., Hausman [2012; 2014] and Schwartz [2007; 2014]), it is still controversial.

Indeed, once the layers of BST-based clinical disease are peeled back is all that remains a sterile view of disease beset with forty years of criticism? Although I do not believe this, consistent with Hesslow (1993) I do believe that moral or social issues do not necessarily hinge on any conception of disease. To be clear, Hesslow does not think that the concept of disease cannot be explicated. He in fact thinks the BST is likely the best explication (Hesslow, 1993, pp. 3, 8, 13). Hesslow (1993, p. 3) also admits that the disease concept can be useful in everyday affairs. But treatment decisions and attribution of moral responsibility should not depend on whether someone has a disease or not but rather should depend on other criteria. A medical ethics restricted to disease ignores a vast variety of other activities and conditions, some of which are shown in Fig. 1. Which activities/conditions should be privileged from an ethical standpoint, or proscribed completely, would require detailed argumentation, but the figure at least makes conceivable the notion that such argumentation could proceed along lines independent of whether something is a clinical disease or not, and focus instead on more ethically salient features (which would have to be identified and argued for independently). The rejection of disease prioritarianism (that whether a health care system should address a condition depends on the condition's disease status) is a well-argued position (Jebari, 2016). Nonetheless, conceptions of disease might still bear important implications for medicine and society. Deciding matters of health insurance and social health benefits, attributing responsibility or the sick role, or serving a rhetorical role by making negative evaluative judgments can benefit in some sense from having a condition classified as a disease as opposed to some other type of clinical condition. Such purposes could be fulfilled other ways (such as based on folk concepts of disease), but that does not mean theoretical and clinical accounts of disease cannot help, at least if only to bring to the fore important considerations.

Nonetheless, it would be rare to meet a clinician or medical professional who has ever applied the BST's four criteria (see §3) to a condition to determine whether it is a disease, or who has relied on the BST in any way for the diagnosis, treatment, or prognosis of a patient. But that is not what the BST was ever meant to do. For that, knowledge of a medical condition's etiology, pathophysiology, typical presentation, etc., is more suitable. BST-based theoretical and clinical disease, however, can make sense of, respectively: Is it a disease? And: How can clinicians tell?

One potential limitation of the BST-based clinical disease conception I have advanced, however, is that it is not clear what exactly "diagnosis" means. Is diagnosis a clinician entering a code into a computer, a performative act constituted by a clinician conveying a disease name to a patient and the patient then acting in accordance with the meanings the patient attaches to that name, and/or an unspoken apperception (by clinician or lay diagnostician) of determining that the patient's signs and symptoms are consistent with a specific disease and not any others? Although I cannot settle on a definitive account here, of these possibilities (and there may be more), only the third escapes difficulties encountered by the first two. For example, as to the first it is not clear why the billing or administrative aspects of diagnosis should be so important as to entirely comprise diagnosis. A comatose patient being diagnosed addresses obvious limitations of the second example. By contrast, the third possibility—a diagnostician concluding that a patient has a specific disease—is consistent with that diagnosis also being conveyed to the patient, and similarly can entail that diagnosis taking on meaning from an insurance and social perspective by being entered into "the system".

The account of BST-based clinical disease I have presented is not the only possible account. Some alternative views of BST-based clinical disease are worth mentioning. These alternative views include: (1) theoretical disease that is (or is not) encountered in a clinical setting, and (2) theoretical disease characterized as a type according to clinically recognizable signs and/or symptoms. Although the first view is compatible with the view I have advanced, the vagueness and ambiguity of "encountered" and "clinical setting" do more to cloud the clinical disease concept than elucidate it. Are clinical settings to be limited to physicians' offices? Do shamanic consultations count? Even settling professional boundaries does not completely help. Would house calls qualify the home as a clinical setting? Since lay diagnosis is possible could any place be a clinical setting assuming a disease is diagnosed there? If so, would this not then qualify what "encountered" means, and simply collapse the key feature of BST-based clinical disease as being centered on diagnosis? Indeed, I have argued that diagnosis should be seen as a necessary feature of BST-based clinical disease.

To explore the second alternative view, BST-based clinical disease considered as a type instead of a token could perhaps be thought of as theoretical disease that is diagnosable in principle. For example, when clinicians talk of multiple sclerosis (MS), typically it is the type that is discussed—the signs and symptoms that comprise MS *sub specie aeternitatis*. A specific case of MS could then be a (token) patient with the signs and symptoms that exemplifies the type. A major issue with viewing clinical disease as a type defined by diagnostic criteria, however, is that it seems to remove diagnosis itself from the equation. This makes it unclear when a person has a disease. A type is general and abstract, whereas a person with a diagnosis has a concrete problem. If "diagnosable in principle" were to become the arbiter of BST-based clinical disease, there would have to be a means by which such an in-principle diagnosis could be reached. In some cases a presumptive diagnosis might be enough to guide empiric treatment—itself a method of diagnosis if the condition improves and other explanations (like the natural course of a disease) are considered unlikely. But if the diagnostic criteria for a disease rely on a certain test result, failure to meet the criteria, despite all other signs pointing to the presence of the disease, does not mean the patient really has the clinical disease even if they likely do have the theoretical disease. Failure to meet the diagnostic criteria in such cases instead signifies that perhaps the criteria should be revised (if reaching such diagnoses is considered important, such as for reimbursement or disease management). Indeed, one of the main points of this article, and a key virtue of BST-based clinical

disease, is that it underscores the importance of diagnosis, nosology, and the myriad normative considerations that shape diagnostic criteria and their application. The utility of BST-based clinical disease conceived as a token is that it highlights the need for diagnostic criteria that can best accomplish the goals for which those criteria are set.

Could though the BST-based clinical disease conception be ameliorated by defining clinical disease to be theoretical disease that could be diagnosed *under ideal conditions*? This, however, seems very much the same as "diagnosable in principle". In addition to not knowing what ideal conditions are (unlimited diagnostic equipment?) this change would render BST-based clinical disease impractical for clinical use and opposed to one of the motivations driving the BST-based clinical disease conception in the first place (i.e., practicality). Clinicians never encounter ideal conditions of diagnosis, but are always faced with limitations of time, money, potential for harm, and patient preference, and the benefit–risk ratio derived from these factors.

The BST was not designed to be used in clinical settings. Whereas theoretical disease can be identified on the basis of the BST, there is no way of recognizing a clinical disease without diagnostic criteria. Importantly, clinicians deal with medical conditions (some of which have diagnostic criteria), yet only some of these conditions are diseases; the BST only deals with diseases (not all of which have diagnostic criteria).

> [T]he BST offers the best of both analytic worlds. It provides a theoretical, value-free concept of disease or pathological condition. But on this foundation one can build value-laden disease concepts, by adding evaluative criteria, to taste. Starting from the basic disease concept, one can define clinically evident disease, or harmful disease, or serious disease, or treatable disease, or disabling disease, or disease that should be covered by insurance, or disease that should remove civil or criminal responsibility, and so on. Best of all, one can use different "disease-plus" concepts for different purposes. Yet the value-free scientific disease concept remains as a bedrock requirement to block the subversion of medicine by political rhetoric or normative eccentricity. (Boorse, 1997, p. 100)

11. Conclusions

Through exposition of a conception of clinical disease, I have argued that the BST's theoretical disease conception can be practical on a clinical level. Moreover, I have offered an explication of the distinction between theoretical and clinical disease and what could be gainfully meant by these terms. By applying a wide variety of medical examples and couching my rebuttal of Doust et al.'s (2017) charge against the BST within an overarching theory (i.e., the distinction between BST-based theoretical and clinical disease), I aimed to support the utility of this distinction and to extend the BST in a way that explicitly accepts the influence of values on disease definitions. BST-based clinical disease requires that dysfunction be present because of its dependence on theoretical disease as defined by the BST. Its additional requirement—that it be diagnosed—highlights the importance of diagnosis. Diagnosis is suffused with meaning for patients, clinicians, family members, and society (Davis, 2010; Jutel & Nettleton, 2011), often serving to justify and enable benefits (e.g., insurance) and duties (e.g., for a clinician to treat if appropriate). Although I have argued that there can be benefits to a person being diagnosed with an asymptomatic disease, there can also be downsides (Walker & Rogers, 2017b). Further work can clarify the relationship between BST-based clinical disease and over/under-diagnosis, as well as ethical and conceptual implications related to clinical disease and medical treatment.

For any condition, clinicians (or anyone for that matter) only know a disease is present because of signs and/or symptoms. Whether there is really a disease involved and not just a clinical condition (such as pregnancy) depends on whether there is a BST-based theoretical disease present. The BST and BST-based clinical disease in no way put any restrictions on which conditions medicine can or should deal with, be it medical interventions for aging, pregnancy, or to enhance one's function. To determine the proper place of diagnosis or treatment for these and other types of clinical conditions a different type of theory is needed, and that theory is assuredly a normative one, the particular features of which other work is best positioned to clarify.

BST-based clinical disease is a value-laden conception to the extent that diagnosis is; thus, all the purposes and considerations relevant to the setting of diagnostic criteria apply to BST-based clinical disease. But to what extent is BST-based clinical disease practical? It is practical to the extent that diagnosis of theoretical disease is practical. In most cases BST-based clinical disease is likely to be a very practical concept, because diagnosis usually is.[8] What the BST-based clinical disease conception highlights is that diagnostic criteria—especially current diagnostic criteria for a range of diseases—do not always reflect underlying diseases, or they reflect multiple underlying diseases, or simply risk for disease.

In conclusion, I have extended the BST to show how the distinction between theoretical and clinical disease could be explicated. Whether this is a useful explication may depend in part on how convincing the BST itself is. Other conceptions of disease might also do a good job of explicating the distinction, or eliminating it in the first place. What I have hoped to show, at least, is that any explication should be consistent with medical usage and serve conceptual functions to make sense of pressing issues in medicine, such as diagnosis and nosology.

Declaration of competing interest

None.

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[8] Whether a particular diagnosis is justified is a different story, but it seems uncontroversial that the diagnosis concept itself is a practical concept. Some cases could be envisioned, however, where this is not true. For example, a sailor treating scurvy on a desert island by eating limes would likely get no practical benefit by being diagnosed with scurvy (whether through self-diagnosis or by others), assuming limes are his or her principal source of food that would be eaten anyway, coincidentally serving as treatment for the scurvy. In this case it is not just the application of the diagnosis concept that serves no practical effect but the very concept itself. This also illustrates the fact that diagnosis is an evaluative notion. Other examples are cases where there are benefits to diagnosis that do not necessarily or predominantly redound to the diagnosed, such as with respect to asymptomatic carriers of certain infectious diseases.

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