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Précising definitions as a way to combat overdiagnosis

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Abstract

Roughly, overdiagnosis (ODx) occurs when people are harmed by receiving diagnoses (often accompanied by interventions) that do not benefit them, usually because the diagnosed conditions do not pose a threat to their health. ODx is a theoretical as well as a practical problem as it relates to definitions of disease. Elsewhere it has been argued that disease is a vague concept, and that this vagueness may contribute to ODx. In response, we develop a stipulative or précising definition of disease, for the specific purpose of decreasing or preventing ODx. We call this disease\textsubscript{ODx}, aimed at distinguishing cases where it would be beneficial to identify (and treat the condition) from those where diagnosis is more likely to harm than benefit. A preliminary definition of disease\textsubscript{ODx} is that X is a disease\textsubscript{ODx} iff there is dysfunction that has a significant risk of causing severe harm.

This paper examines the three concepts in this definition, using a naturalistic account of function, a Feinbergian account of comparative harm, and a probabilistic understanding of risk. We then test the utility of this approach using examples of clinical conditions that are currently overdiagnosed.
Introduction

Overdiagnosis (ODx) is a serious problem as it leads to harms to patients who receive diagnoses (often accompanied by interventions) that do not benefit them. ODx arises when individuals are diagnosed with a condition commonly thought to harm those afflicted (e.g., increased morbidity, mortality), but in that particular patient, the condition would not have followed the anticipated disease trajectory. Thus, overdiagnosed patients are not benefited by their diagnosis and any subsequent interventions may constitute net harms [1-4]. Commonly overdiagnosed conditions include cancers (e.g. screening-detected breast cancer); lesions found incidentally in the investigation of other conditions (e.g., small thyroid cancers discovered during neck imaging); and conditions that fall within accepted diagnostic boundaries but are not harmful disease (e.g. kidney function that falls below the threshold for chronic kidney disease but does not progress to renal failure) [1]. In all of these examples, if the person had not been diagnosed, they would have remained unaware of their occult abnormality and suffered no adverse health consequences. However, once diagnosed, individuals are labelled with having diseases, and may receive interventions of no benefit.

These practical problems of ODx raise theoretical questions about the definition of and diagnostic criteria for specific diseases. Further, ODx challenges the concept of disease itself, raising questions about the conceptual links between disease and features commonly taken to be typical of disease, such as dysfunction, harm, and risk. One response to the challenge of ODx proposes re-labelling or re-sorting current disease and risk categories to reduce the risk of ODx [5. In this paper, we argue that a précising definition may provide the conceptual framework for this kind of re-labelling aimed at combatting ODx [6].
Section 1 summarises the problem of ODx. We focus on a narrow conception of ODx [7], and currently exclude ODx of mental illness in order to test our definition on physical disease before attempting to broaden its scope to the more challenging area of mental illness. In section 2 we outline reasons for using a précising definition (“diseaseODx”) to combat ODx. Our definition stipulates that diseaseODx involves dysfunction that poses a significant risk of causing severe harm. Section 3 explains what we mean by the key terms of dysfunction, harm, and risk and how they function in the definition. In section 4 we apply the definition to examples of overdiagnosed diseases, showing that a précising definition may be a conceptually defensible way to counter ODx.

1: Overdiagnosis as a theoretical and a practical problem

ODx is defined counterfactually: “the condition would not have” caused harm [2], making identification difficult. In the absence of diagnostic intervention, many individuals have conditions of which they are unaware, as the abnormality remains occult. Once diagnosed however, there is no way of distinguishing whether or not a particular lesion or condition is a typically harmful instance of disease, or whether it is a case of ODx. Current diagnostics cannot, for example, distinguish between screening-detected breast cancers on a malignant trajectory, and those that are indolent or regressive [8]. ODx is indistinguishable from beneficial diagnosis of progressive disease at the individual level. At a population level, ODx is identified through comparing changes in the incidences of disease over time, in the context of changes to diagnostic criteria or the introduction of new interventions that detect the disease in question. The typical epidemiological pattern for ODx is of rising rates of diagnosis of a specific disease, with little or no change in disease-specific mortality or
numbers of advanced cases, which would drop if the rise in cases were due to earlier diagnosis. Instead, the increased rates are apparently due to the detection of an occult reservoir of abnormalities, which meet diagnostic criteria, but do not follow a typical progressive disease trajectory [1,2,6].

Known antecedents to ODx include changes in diagnostic thresholds [9], introduction of screening programs, and uptake of new diagnostic technologies coupled with strong beliefs in the value of early detection of disease or disease-precursors, and medico-legal fears [10]. These events lead to more people being diagnosed with the relevant conditions, but with no corresponding changes in advanced cases or disease-specific mortality.

Overdiagnosis is a serious ethical and practical problem, because it results in many people being diagnosed (and usually treated) for otherwise harmless conditions. The attendant harms may be considerable, ranging from individual distress at disease labelling through to diversion of healthcare resources away from those with established harmful disease towards those who do not benefit from intervention [3,4]. Further, ODx raises questions about the precision and utility of definitions of specific diseases, since ODx demonstrates that current diagnostic criteria (the clinical or medical definition of those particular diseases, and what we take as evidence that the criteria are met) include non-harmful instances. Overdiagnosis may reflect not only problems in the current definitions of specific diseases, but also ambiguity or lack of precision in the concept of disease itself. ODx involves biological dysfunctions of kinds that current medical science leads us to expect will result in harm, but which do not do so in overdiagnosed cases, challenging conceptual links between disease and several of its usual analysans, such as dysfunction, harm/risk of harm, and the warrant for treatment.
Disease is notoriously difficult to define. One contributing factor to this difficulty may be because the concept is vague. By this we mean that there are borderline cases, which do not clearly either meet, or fail to meet, the criteria for inclusion under the concept [6]. Just as a woman of a certain height may or may not count as being tall, there are conditions that seem to evade classification as either ‘disease’ or ‘not-disease’. While the general concept of disease sorts many conditions into clear cases of health or disease, for borderline cases, it may be neither wholly true nor wholly false, or it may be indeterminate, whether a particular instance is a case of disease [11]. It is this pool of borderline cases, secondary to a lack of precision in the concept of disease, from which ODx may arise.

2: Vague concepts and précising definitions

The vagueness of disease involves two kinds of borderline case. The first relate to threshold problems. Disease typically involves features such as dysfunction, undesirability, statistical abnormality, harm, warrant for medical treatment, and so on. Many of these features are matters of degree, leading to the ‘line-drawing problem’: it is difficult and seemingly arbitrary to specify any particular point on the spectrum of, for example, dysfunction, where the concept disease necessarily applies [11,12]. We call this ‘threshold vagueness’.

Other cases may be borderline because they have some, but not all, of the typical features of disease (dysfunction, harm etc.). There are states that involve some of these features but not others in ways that make us hesitant to consider them diseases. For instance, welcome infertility may be a borderline disease because it has some typical disease features (dysfunction, statistical abnormality) but not others (harm, undesirability). We call this ‘criterial vagueness’. Both threshold and criterial
Vagueness may apply simultaneously, where a condition involves some but not all of the usual features of disease, and also raises threshold problems. Vagueness is a general problem with the concept of disease itself, and it has been argued to underlie some of the difficulties of defining the concept [11]. In the context of specific diseases, cases of ODx are borderline cases of the disease in question, and may be vague in either (or sometimes, both) of these senses. Instances of ODx linked to changes in diagnostic thresholds on measures of dysfunction, such as blood sugar levels, involve threshold vagueness. The overdiagnosed cases involve some degree of abnormality, but it is not clear at what level these abnormalities are (or should be) sufficient to count as disease. Any choice of diagnostic threshold will be stipulative, but where the current threshold routinely includes harmless cases, ODx occurs. Other cases of ODx involve criterial vagueness. This occurs, for instance, with overdiagnosed cancers. These cases do involve a relevant dysfunction (such as histopathological signs of malignancy), but do not have the expected malignant trajectory. The dysfunction, identified by current ‘gold standard’ diagnostic tests (and hence distinguished from false positives) does not predict harm, may not be undesirable and requires no treatment.

Conceptually then, overdiagnosed cases are borderline cases that are not clearly disease or non-disease. When at least some of these borderline cases are nonetheless classified as disease, ODx occurs. This suggests that a more precise notion of disease could provide a principled way to respond to ODx. Despite vagueness in the concept of disease, more precise notions (précising definitions) for specific purposes can be developed [13]. Précising definitions have limited aspirations: they do not seek to resolve longstanding challenges in defining the concept of disease, and do not preclude other potential ways of sorting borderline cases. Previously we proposed a
preliminary definition with the specific purpose of combatting ODx (“disease\textsubscript{ODx}”), which draws on established criteria from existing analyses of disease. We stipulated that:

\[ X \text{ is a disease}_{\text{ODx}} \text{ iff there is dysfunction that has a significant risk of causing severe harm } [6]. \]

Disease\textsubscript{ODx} may combat the occurrence of ODx because only conditions that meet these criteria (which we specify in detail in the following section) are classified as diseases for the purposes of diagnosis, investigation and intervention. On this account, conditions that do not meet these criteria are not disease\textsubscript{ODx}, although they may be classed as some other kind of condition (for example, risk factor, or “harmless lump”). While our definition is specifically for the purposes of limiting ODx, the criteria of harm and dysfunction occur in more general accounts of disease (see e.g. [14,15]).

The aim of the précising definition is to create more exact definitions of specific diseases that will reduce the incidence of ODx and thereby decrease the associated harms. If diseases can be defined such that only conditions involving identifiable dysfunction with significant risk of causing severe harm are classified (and treated) as disease, then the overall balance of harms and benefits associated with making diagnoses will become more favourable.

3: Dysfunction, risk and harm in disease\textsubscript{ODx}

This initial précising definition of disease\textsubscript{ODx} requires further specification, since its key terms, ‘dysfunction’, ‘significant risk’ and ‘severe harm’ can be variously theorised, and all admit of degrees. In the following discussion, we illustrate the definition using the example of well differentiated micro-papillary thyroid cancer
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(mPTC). On our account, mPTC is a disease$_{ODx}$ iff it involves a dysfunction with a significant risk of causing severe harm. If it meets these criteria, it warrants diagnosis and intervention, if the affected individual so desires.

*Dysfunction*

Dysfunction in the précising definition refers to a naturalistically describable failure to conform to normal or proper functioning. For many areas of medical practice, the functions of parts, processes and organs are taken to be largely self-evident. Each system of the body is ascribed an overall function (the cardiovascular system to circulate oxygenated blood; the immune system to overcome infectious and other threats). These system labels are necessarily simplistic as each system has multiple and interconnected functions (e.g., the cardiovascular system contributes to temperature regulation). Despite this complexity, for many organs and bodily processes, there is an underlying medical view of the normal or proper function of that organ or process. We take ‘dysfunction’ in the précising definition as the failure of this function.

Despite ongoing philosophical controversy about whether dysfunction is necessary for disease, even if there are diseases that do not involve dysfunction, overdiagnosed conditions do typically involve an identified dysfunction (e.g. neoplastic changes in a breast lump; raised eGFR). It is this dysfunction that leads them to be identified as diseases. Therefore all cases of disease$_{ODx}$ will involve some identified dysfunction based on current diagnostic criteria [6].

Dysfunction cannot serve as the sole criterion for defining disease$_{ODx}$ because of the line drawing problem [11,12]: biological dysfunction frequently occurs on a spectrum with no clear dividing line between levels of dysfunction that count as disease, and those that are normal variations. Further, taking any identified dysfunction to indicate
disease is a main driver of ODx [16]. Thus for disease_{ODx} to be able to discriminate between overdiagnoses and conditions that warrant treatment we need additional criteria to do with risk and harm.

Regarding mPTC, the relevant dysfunction is disordered cell growth with malignant changes. The presence of dysfunction alone does not warrant disease_{ODx} status as autopsy studies show that there are high levels of occult mPTC that have not caused harm to affected individuals [17]. Whether or not this constitutes disease_{ODx} will depend upon the risk of severe harm.

**Harm**

Harm is our second criterion for disease_{ODx}. Dysfunctions that are now causing, or will progress to cause harm, should be counted as disease_{ODx}, while currently harmless dysfunctions with low risk of future harm should be excluded. The précising definition refers to significant risk of (severe) harm. We clarify our notion of risk in the following section; here we explain what we intend by ‘harm’ and what makes a harm ‘severe’. We adopt this separation of risk and harm for the purposes of explication, recognising that it is the combination of the likelihood and severity of harm which is central to the definition of disease_{ODx}.

Harm is frequently invoked in the disease literature but rarely analysed in detail [18]. Harm is, in this literature, typically regarded as a value term related to social norms. However, other areas of philosophy have developed non-relativistic accounts of harm. One of the most influential is from Feinberg, which has a counterfactual structure and mechanisms for grading the seriousness of harms, making it useful for thinking about ODx [19]. Feinberg claims that someone is in a harmed state when they are worse off than they would have been, had some particular event not occurred. More specifically, for Feinberg, a harm is “the thwarting, setting back, or defeating of an interest” [19,
To have an interest in something is to have a stake in its wellbeing, or to stand to gain or lose depending on its nature or condition. One’s interests are thus aspects of one’s wellbeing, upon which one’s flourishing depends [19, p.33-4].

On this account, diseases are harmful when they set back interests. Many diseases will set back near-universal interests, such as freedom from pain, capacity to pursue activities of daily living, and so on. Others set back more specific interests such as having children, or pursuing an athletic career. And some diseases may not be not harmful or cause only minor or trivial harms, such as self-limiting conditions that have minimal impact on a person’s interests. Following Feinberg, for the purpose of defining disease_{ODx}, we consider a dysfunction to be harmful when it sets back (or will in the future set back) an individual’s interests. This criterion narrows the range of conditions counted as diseases for the purposes of combatting ODx.

The précising definition stipulates severe harm, thereby excluding conditions that do not warrant intervention; that is, dysfunctions leading to minor or trivial harms. Therefore we need to discriminate between degrees of harm. Additionally, the notion of harms as setbacks to interests means that the same condition could be a harm for one individual, but not for another, given different interests. But to combat ODx, we need a sense of harm that is similar enough between individuals to justify population-level generalisations about severity. To address these issues, we follow Feinberg’s grading of the severity of harms.

Feinberg evaluates a harm’s seriousness with reference to the importance of the interests it sets back. He distinguishes between ‘welfare’ and ‘ulterior’ interests, either of which might be considered the most important, in different ways. Ulterior interests include “a person’s most ultimate goals” such as writing their novel, or advancing a social cause [19, p.37]. These interests are important because they are final goals, to
which other, smaller goals contribute. Welfare interests include aspects of well-being such as health, bodily integrity, lack of overwhelming pain, opportunities for social intercourse, and some measure of liberty [19, p.37]. These interests are important because they are necessary for the pursuit of any goals. Feinberg argues that the objects of welfare interests function as a network, such that curtailing one welfare interest will affect others. For example, chronic pain (which sets back the interest in lack of overwhelming pain) jeopardises opportunities to pursue friendships, an infringement of liberty might be detrimental to interests in health, and so on. Since harms that set back welfare interests are likely to set back both other welfare interests, and ulterior interests, Feinberg concludes that setbacks to welfare interests will typically be more serious than setbacks to ulterior interests [19, p.37].

Feinberg’s analysis indicates potential approaches to grading the severity of harm associated with different diseases. Some diseases typically cause only transient and/or minor inconvenience, such as a self-limiting skin disease whose only symptom is slight itching. Such a disease does not set back any important interests, so is not harmful. Other diseases set back health-related welfare interests in the short term, but have little impact on other welfare or ulterior interests, such as a short-lived bout of flu which affects the interest in being able to undertake everyday activities. As no other interests are affected and the impact on health-related welfare interests is transient, the harm from such a condition is relatively minor. Yet other diseases set back both health-related and additional welfare interests, such as a heart condition which limits an individual’s capacity for employment and social interactions, generating more serious harm. Feinberg’s account thus provides general guidelines for evaluating the seriousness of harms in terms of the importance of the full set of interests which are set back.
For the purposes of disease\textsubscript{ODx}, we propose that harms count as ‘severe’ when they set back welfare interests. Such harms are likely to be more serious than set backs to ulterior interests. Further, for commonly overdiagnosed conditions, the relevant interests will typically be welfare interests. Regarding mPTC, the dysfunction can lead to metastatic disease and premature death, which are serious setbacks to welfare interests. For other overdiagnosed conditions, the harms may be less serious than premature death, while still being severe. Osteoporosis, for example, is linked to the risk of hip fractures, which generally set back welfare interests. Thus the harms of disease occur on a spectrum of severity. We propose that assessing harm in terms of set-backs to welfare interests provides a useful threshold for identifying ‘severe harm’ in the précising definition.

Defining severe harm in terms of setbacks to welfare interests allows generalisation between individuals, since welfare interests are at least near-universal. However, there may be cases where individual differences in ulterior interests will impact on the seriousness of a harm. For instance, losing a little finger might be relatively innocuous for many people, but be a serious harm to someone with an ulterior interest in becoming a pianist. Such harms are not encompassed in the précising definition of disease\textsubscript{ODx}, which aims to provide a critical framework for examining specific disease definitions.

mPTC involves (potentially) severe harm as well as dysfunction, meeting two out of the three criteria for disease\textsubscript{ODx}. Therefore we must ascertain the likelihood of the severe harm eventuating: if the risk is significant, then all three criteria for disease\textsubscript{ODx} are met.

\textit{Risk}

Risk has multiple meanings [20]. At its simplest, ‘risk’ refers to an unwanted event
that may or may not occur, such as the risk of rain spoiling tomorrow’s picnic. A second meaning takes risk to be the cause of the unwanted event, such that the impending low pressure weather system is the risk threatening the picnic. Third, risk may refer to the probability of the unwanted event occurring. Thus the weather forecaster might predict a 70% risk of rain during the picnic.

In disease\textsubscript{ODx}, “significant risk” refers to the probability of the unwanted event (severe harm caused by dysfunction) occurring. Thus the definition must be amended:

\[
X \text{ is a disease}\textsubscript{ODx} \iff \text{there is dysfunction that has a significant probability of causing severe harm.}
\]

Probability values may be subjective or objective. Subjective assessments of probability rely upon agents’ own views about the likelihood of the outcome in question [21]. Despite the Bureau of Meteorology’s prediction of a 70% chance of rain during tomorrow’s picnic, an individual may believe that it will stay dry, putting the subjective probability at zero. In contrast, objective interpretations of probability use evidence about the world to determine a frequency that is taken to be independent of individual beliefs [20]. The weather forecaster’s prediction of a 70% probability of rain is based upon information about pressure systems, wind speeds and other objectively measured variables rather than her personal views.

Objective probabilities about harmful disease outcomes are derived from population level epidemiological data. For example, a person’s five year risk of heart attack can be calculated using variables (risk factors) including age, gender, smoking status, level of systolic blood pressure etc [22]. The calculation is based upon epidemiological evidence about the frequency of heart attacks in people who have various combinations of the risk factors. Using this data, an individual can calculate their objective five year risk level for heart attack. However, this assessment may
differ from that person’s subjective view about her own likelihood of having a heart attack, which may be based on family experiences or a view about her own state of health unrelated to the risk factors in the calculator.

For many conditions that are overdiagnosed, but certainly not all (e.g. DCIS), there is epidemiological data that provides an objective probability value for harmful events associated with that dysfunction. For example, less than 1% of people with eGFR < 60 mL/min/1.73 (stage 3A chronic kidney disease) go on to develop end stage renal disease [23]. Likewise, there are various well-validated risk assessment tools, such as MACIS (Metastases-Age-Completeness of Excision-Invasion-Sex), for assessing the prognosis of well-differentiated mPTCs. MACIS attributes risk based upon criteria including presence or absence of metastases, sex, age and tumour features. A MACIS score of less than 6 predicts a twenty year cancer-specific survival rate of 99% [24]. That is, patients with MACIS < 6 have a 1% probability of dying from their thyroid cancer in the twenty years following diagnosis.

In contrast, a subjectivist approach would generate widely varying probabilities for similar levels of dysfunction, depending upon individuals’ views. A risk-averse individual with a MACIS score < 6 might nonetheless believe that her own personal probability of dying from thyroid cancer is much greater than 1%; an optimistic person might think that her probability is much lower. Thus a subjectivist approach to probability would lead to multiple individual definitions of mPTCs, which would jeopardise the précising approach to ODx. If individuals are taken to have a diseaseODx based upon their individual risk tolerance, ODx might well continue or even multiply. Empirical research has shown that many people prefer to be “safe rather than sorry”, choosing diagnostic interventions for conditions known to have high levels of ODx [25]. Thus we propose using an objectivist approach to probability
in our précising definition, based on epidemiological data.

Next we need to determine what level of risk should count as significant and thus meet the stipulated conditions for disease\textsubscript{ODx}. If the threshold for significance is very high, then we will certainly avoid the problem of ODx. For example, if we stipulate that breast cancer is a disease\textsubscript{ODx} iff there are cancerous changes that have a 100% chance of causing severe harm we will avoid ODx. But this comes at the cost of excluding cases of breast cancer in which there remains a high likelihood of serious harm (e.g., 85%, or 60%). If the threshold for significant probability is set very low, the opposite problem arises. For example, defining breast cancer as a disease\textsubscript{ODx} iff there are cancerous changes with a 0.1% chance of causing severe harm includes everyone at some probability of serious harm, but will increase ODx as many women covered by this definition will have non-harmful disease.

We therefore need a nuanced approach to determining what level of probability should count as significant for disease\textsubscript{ODx}. At the theoretical level, it is not possible to specify a single figure (e.g., 10%) as the ‘significant probability’. Rather, this will need to be determined on a case by case basis for each overdiagnosed condition, taking into account relevant contextual factors. These might include: the vagueness of the condition; the nature, safety and effectiveness of interventions triggered by diagnosis; the harms of ODx for that condition; and the relationship between overdiagnoses and potentially avoidable missed diagnoses at different levels of probability.

This kind of contextual approach is evident in another area of medicine that uses probabilistic thresholds. The “number needed to treat” (NNT) to prevent one additional harmful outcome is a probability measure that specifies the chances of benefitting from a treatment. An NNT of 5 means that if 5 people with similar levels
of risk are treated with that drug over some specified timeframe, on average one less bad outcome occurs [26]. NNTs are one measure to evaluate therapies: in general, the lower the NNT, the more beneficial the treatment. For example, the NNT is 22 for captopril used in post heart attack patients with left ventricular failure. This is described as very beneficial: if 22 patients are treated, one death is avoided by 42 months. In contrast, the NNT is 1451 if all heart attack patients are treated with captopril, indicating very little clinical benefit [27].

Assessments of the ‘right’ value of NNTs vary by condition. In psychiatry, for example, scholars claim that the NNT should be less than 10 [28]. In contrast, much higher NNTs are accepted in the treatment of hypertension to avoid outcomes such as heart attacks, stroke or heart failure. The Australian Heart Foundation guidelines on hypertension advocate intensive treatment for patients at high risk (defined as > 15% chance of cardiovascular event over 5 years). In this cohort, the NNT to avoid 1 additional cardiovascular event over 3 years is 61 [29]. Thus despite having a single objective measure, the threshold NNT for any specific condition seems to reflect differences in contextual factors relevant to that condition.

Despite some controversy over their utility [26], NNTs can inform our thinking about significant probability in disease, regarding both the lack of a single ‘correct’ value, and potentially relevant contextual factors. First, we can expect that a lower probability will be deemed significant where the relevant potential harms are imminent without intervention, or particularly grave; and a higher probability where the potential harms, although meeting the threshold for ‘severe’, are less serious.

Second, we should expect relevant contextual factors – including the potential harms of missed diagnoses, and the nature, safety and effectiveness of the available interventions for the condition – to impact on judgements about what counts as
‘significant’ probability. We are thus effectively including such contextual factors in our understanding of ‘significant probability’. The following examples show how this might work in practice.

4: The précising definition in practice

Regarding the example of mPTC, we suggest that it does not meet all three criteria of the précising definition therefore, on this account, is not a diseaseODx (Insert Table 1 around here).

This conclusion turns primarily on the question of significant probability. We flagged above that contextual factors are relevant in determining ‘significant probability’. In the case of mPTC, these include: harms of thyroid cancer ODx for individuals (thyroid removal, surgical complications, ongoing medical surveillance, potential for lifelong thyroid replacement therapy); and societal burdens such as costs to health care systems [31]. In contrast, the risk of harm from a delayed diagnosis is low. The combination of low probability of serious harm coupled with severe harms from ODx can plausibly result in the judgement that the probability is not sufficiently significant to meet the definition of diseaseODx. This preliminary conclusion is for demonstration purposes, to show how the précising definition could work. To put this into practice, a fair and transparent process would be required for making decisions about condition-specific levels of significant probability, discussion of which is beyond the scope of this paper.

Our second example is osteoporosis in women. Since 1994, this has been defined as hip bone mineral density (BMD – known as T-score) of 2.5 standard deviations (SD) or more below the young adult female mean. Prior to 1994 osteoporosis was diagnosed only after fracture; now dual energy absorptiometry permits measurement
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of bone density and diagnosis of osteoporosis in the absence of fracture [32]. Bone density decreases with age. Using a T-score of -2.5, the prevalence of osteoporosis in women aged >65 is 22%, rising to 47% at age > 80 years [32-33].

The most severe harm associated with osteoporosis is hip fracture. As noted above, this can set back welfare interests (e.g. in pursuing activities of daily living), and may affect other welfare and ulterior interests, thus counts as a severe harm according to the précising definition. The probability of hip fracture in a woman with osteoporosis rises with age, from 2.6% at ages 50-64, to 18.6% at ages 65+ [34]. But most of this increase is due to ageing rather than to osteoporosis per se: the effect of ageing is eleven times that of decreased bone density, and less than one third of hip fractures are associated with low T-scores [32].

Given the lack of close correlation between bone density and the probability of harm, we conclude that osteoporosis is prima facie not a diseaseODx, although we leave open the possibility that it may be a disease in younger women. Relevant contextual features include the limited evidence for effectiveness of treatments to increase bone mineral density on fracture rates and corresponding high NNT; the cost of treatment; and the effect of diagnosis on women [35].

*(Insert Table 2 around here)*

The aim of these examples is to demonstrate how the précising definition might operate in practice and thereby provide conceptual foundations for initiatives such as the recently published guidance for modifying the definition of diseases [36]. For each condition in which ODx is known to be of concern, detailed examination is required of the probabilities and harms of existing diagnostic definitions, including psychological effects (e.g., of disease labelling) and social effects (e.g., costs for healthcare systems), and age stratification where relevant. Finally, a democratic
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process would be necessary to agree and validate new diagnostic definitions that meet the conditions for disease\(_{\text{ODx}}\).

**Conclusion**

The précising definition, disease\(_{\text{ODx}}\), is an attempt to clarify the boundaries of diseases, with the aim of combatting ODx. Our approach is based on the claim that the concept of disease is vague. Of course, there are alternative ways of trying to combat ODx. It is possible that an overall harm/benefit analysis may lead to similar conclusions about particular overdiagnosed conditions in practice. However, such an approach makes disease status overly dependent on the harms and benefits of available treatments, and potentially leads to the conclusion that if less harmful treatments are developed, more conditions become diseases [37]. Our formulation of disease\(_{\text{ODx}}\) retains the possibility that a condition might be a disease without being harmful, a concept we take to be central in understanding how the problem of overdiagnosis differs from false positives, iatrogenic harms, overtreatment, and medicalisation.

The aim of the précising definition is to provide a clearer boundary than currently exists, in conditions that are commonly overdiagnosed. The examples, mPTC and osteoporosis, illustrate how to use the précising definition to assess whether particular conditions are disease\(_{\text{ODx}}\). Where conditions do not qualify as disease\(_{\text{ODx}}\), this suggests the need to reassess the disease status of particular conditions or revise the diagnostic criteria to meet the disease\(_{\text{ODx}}\) standard. More work is required to refine the contextual features, and to develop ethically justifiable ways of determining the cut-off values for probability in different conditions. Nonetheless, we have proposed a philosophical solution to address the practical problem of overdiagnosis.
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Table 1: Disease\textsubscript{ODx} status of micro-papillary thyroid cancer

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Micro-papillary thyroid cancer</th>
<th>Meets criteria for disease\textsubscript{ODx}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysfunction</td>
<td>Disordered cell growth</td>
<td>Yes</td>
</tr>
<tr>
<td>Serious Harm</td>
<td>Disseminated disease, premature death</td>
<td>Yes</td>
</tr>
<tr>
<td>Significant Probability</td>
<td>5 year probability of metastases of 1.4%; &lt;1% probability of death [24,30]</td>
<td>No: probability not significant</td>
</tr>
</tbody>
</table>
Table 2: Disease\textsubscript{ODx} status of osteoporosis in women

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Osteoporosis (OP)</th>
<th>Meets criteria for disease\textsubscript{ODx}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysfunction</td>
<td>Low bone mineral density (T-score &lt;2.5)</td>
<td>Yes at younger ages</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No at older ages</td>
</tr>
<tr>
<td>Harm</td>
<td>Hip fracture</td>
<td>Yes</td>
</tr>
<tr>
<td>Probability</td>
<td>10 year probability of hip fracture in women with OP aged:</td>
<td>No: the probability of fracture is related more strongly (11-fold)</td>
</tr>
<tr>
<td></td>
<td>50-64: 2.6%</td>
<td>to ageing compared</td>
</tr>
<tr>
<td></td>
<td>65+:18.6 [34]</td>
<td>with low bone density [32]</td>
</tr>
</tbody>
</table>