Potential Consequences of Changing Disease Classifications

Jenny A Doust[1,2], Katy JL Bell[3], Paul P Glasziou[2]

[1]Centre for Longitudinal and Life Course Research, School of Public Health, University of Queensland
[2]Institute for Evidence-Based Healthcare, Faculty of Health Sciences & Medicine, Bond University
[3]Sydney School of Public Health, Sydney Medical School Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia;

Corresponding author: Professor Jenny Doust, Centre for Longitudinal and Life Course Research, School of Public Health, University of Queensland, Level 3 Public Health Building, 288 Herston Rd, Herston QLD 4006, Australia
Email: j.doust@uq.edu.au
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Clinicians tend to think of diseases as being immutable, existing in nature like elements of the periodic table or the planets. The medical literature reinforces this myth, implying that changes are a result of increasing scientific knowledge moving medicine towards better and more accurate descriptions of these natural kind concepts. In fact, diseases are not fixed, and even with common diseases – such as diabetes, depression and anemia – their definitions have changed considerably over time, with significant, but often unrecognized harmful potential consequences for patients. What constitutes a disease may change in one of three ways: (i) a change in the formal definition, (ii) a change of tests, or (iii) a shift of the implicit threshold.

First, a professional society or guideline committee may change the criteria for a disease. These changes frequently widen the definition of the disease to include patients with milder or earlier disease[1]. In the 50 years since the first trial showing the benefits of treating patients with high blood pressure was published in JAMA[2], 'hypertension' has expanded from a narrow definition (diastolic blood pressure greater than 115 mmHg) that included only a small proportion of the population to a broader definition (blood pressure greater than 130/80 mm Hg) that now includes an estimated 46% of US adults[3]. The expansion of hypertension occurred by lowering the blood pressure threshold. Allowing more criteria (such as symptoms, signs, blood tests and imaging tests) to be included in the definition can also change the definition. For example, adding ultrasound as a third criteria for polycystic ovarian syndrome (along with oligo- or anovulation, and symptoms or signs of hyperandrogenism), and requiring any 2 of the 3 criteria, approximately doubled the prevalence of this syndrome in young women, from 1 in 12 to 1 in 6[4].

Second, disease classifications can also change when a test is altered, with more "sensitive" tests increasing prevalence. For example, the use of functional cardiac magnetic resonance imaging rather than two-dimensional transthoracic echocardiogram was associated with an increase in the estimated prevalence of left ventricular non-compaction cardiomyopathy (LNVC) in the population from 1% to 15% [5]. Expanded screening criteria and increased case finding also may contribute to increased disease prevalence. With these activities, tests are used in patients with fewer or no symptoms, leading to identification of a greater proportion of patients with milder and earlier cases of disease.

Third, there can be a shift in the implicit threshold clinicians use to diagnose a disease. This appears to have occurred with the diagnosis of autism. Studies examining differences in psychological and

neurologic measures between individuals diagnosed with autism and those not diagnosed have shown a decreasing gap in these measures over the last 20 years[6]. This trend commenced prior to the definition changes of the DSM-5, so factors such as increased disease awareness and incentives for clinicians to make the diagnosis so patients can access funding and educational assistance are thought to be involved.

Changes in disease definitions distort perceptions of what is happening to the incidence and prevalence of disease, and also result in artefactual "improvements" in outcomes. Reports in both the medical and the mainstream media frequently discuss the growing "epidemic" of diabetes, but it is difficult to disentangle the effect of the 1997 redefinition of diabetes (lowering the fasting glucose threshold from 140 to 126 mg/dL) from any true underlying change in disease prevalence. A 2009 population survey from China [AU:correct? - yes] showed that lowering the threshold for diabetes [AU: diabetes ? - yes] would result in a doubling of prevalence in this population[7]. Much of the apparent increase in the incidence and prevalence of disease seen in the years following the change in the definition can be attributed to the detection of patients defined as having diabetes with the new lower threshold.

Changes to disease classifications also distort the.perception of how successful clinicians are at treating disease. When the definition of a disease is modified to include milder or earlier disease, individuals with milder cases are less likely to have severe consequences from their disease, but are still included in the total number of cases of disease diagnosed. Health outcomes, measured as disease outcomes/cases diagnosed, will therefore appear to improve, even when there is no true effect. This effect is common in screening programs. Measures such as 5-year survival for a disease (or any other measure of complication/case diagnosed) are unreliable for detecting improvements in treatment effectiveness over time (for example in cohort studies or studies examining health outcomes before and after the introduction of new diagnostic test), or to compare differences in health outcomes between countries with different rates of screening.

Much of the rationale for widening disease classifications is based on false assumptions about the benefits of earlier detection of disease. Frequently, the same, or even greater, benefits from treatments tested in clinical trials using the older definition of disease are assumed to apply to patients with earlier and milder disease. Evidence from clinical trials that stratify patients based on stage of disease or baseline risk show that the reverse is generally true. Patients with earlier and milder disease are less likely to benefit in absolute terms, but are just as likely to experience harm

from medical interventions as those with more severe disease, making it more likely overall that a patient will experience harm. The SPRINT trial was used to support the lower threshold of hypertension in the 2017 definition, even though this trial enrolled patients with a systolic blood pressure of 130 mm Hg or higher *and* an increased risk of cardiovascular disease. Trials of treatment of patients with blood pressure at the same level but lower baseline cardiovascular disease risk have shown no benefit from medical treatment[3]. Using the 2017 definition of hypertension, approximately 25% of the patients labelled as having hypertension are at low risk of cardiovascular disease[8] and therefore unlikely to benefit from medical treatment.

Earlier diagnosis is also justified by claims that making patients aware of their increased risk of disease will allow for greater lifestyle intervention. This impression is likely not true since multiple trials have shown that even highly personalised risk information does not change health-related behaviors[9].

To date, professional societies and guideline committees have shown little awareness of the consequences of their changes to disease definitions or recommendations to introduce more sensitive testing for disease. A review of changes to disease definitions in guidelines for 14 common conditions showed that none rigorously assessed the potential harms of the changes for patients[1]. Harms from changes to disease classifications can be related to the medical complications and adverse effects of interventions, the psychological harms and anxiety caused by the disease label, and financial harms, such as costs related to additional testing and treatments. [AU:correct? - yes] There are also significant implications for health systems. The diversion of health care resources and attention to treat those with mild disease is threatening the viability of health care systems worldwide. One estimate suggests that the drug costs alone of treating the *additional* patients that would have been [AU:correct? - yes] affected by the changes to the definitions of diabetes, hypertension, and hypercholesterolemia around 2000 would have consumed 56% of the Chinese government's total health expenditure in 2010[7].

Widening disease classifications is not always harmful. The use of anti-hypertensive medications to treat patients with increasingly lower levels of blood pressure has been a significant factor in the decline in cardiovascular deaths seen in high-income countries since the 1960s. Earlier detection and treatment of some diseases, for example rheumatoid arthritis, does seem to modify the natural history, leading to significant clinical benefits. What is missing is a balanced

and systematic evaluation of the benefits and harms before the implementation of such changes.

What can be done to reverse this? Each of the three processes of changing disease classifications needs to be addressed. First, changes to disease classifications need to be evaluated and challenged as rigorously as any other healthcare intervention. A checklist provides suggestions that could be used by groups modifying definitions of disease[10]. . The current methods, which often rely on opinion rather than evidence and may be influenced by academic and financial conflicts of interest, are not sustainable. Second, health technology assessment processes for tests need to consider both accuracy and potential changes in the spectrum of patients classified as diseased. Third, professional societies and organized medicine need to monitor and modify the incentives that might induce implicit changes in clinicians' implicit threshold. All of these will require considerable effort, but are vital for both patient safety and managing the increasing costs of healthcare.

References [AU: as you revise, please limit to no more than 10 referneces [ith no in-text URLs]

1. Moynihan RN, Cooke GP, Doust JA, Bero L, Hill S, Glasziou PP. Expanding disease definitions in guidelines and expert panel ties to industry: a cross-sectional study of common conditions in the United States. PLoS Med. 2013 Aug;10(8) :e1001500. doi: 10.1371/journal.pmed.1001500. Epub 2013 Aug 13. PubMed PMID: 23966841; PubMed Central PMCID: PMC3742441.
2. Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effects of Treatment on Morbidity and Hypertension: Results in patients with diastolic pressures averaging 115 through 129 millimeters of mercury. JAMA 1967;202:1028–34.
3. Bell KJL, Doust J, Glasziou P. Incremental Benefits and Harms of the 2017 American College of Cardiology/American Heart Association High Blood Pressure Guideline. JAMA Intern Med. 2018 Jun 1;178(6):755-757. doi: 10.1001/jamainternmed.2018.0310. PubMed PMID: 29710197.
4. Copp T, Jansen J, Doust J, Mol BW, Dokras A, McCaffery K. Are expanding disease definitions unnecessarily labelling women with polycystic ovary syndrome? BMJ. 2017 Aug 16;358:j3694. doi: 10.1136/bmj.j3694.
5. Ross SB, Jones K, Blanch B, Puranik R, McGeechan K, Barratt A, Semsarian C. A systematic review and meta-analysis of the prevalence of left ventricular non-compaction in adults. Eur Heart J. 2019 May 29. pii: ehz317. doi: 10.1093/eurheartj/ehz317. [Epub ahead of print] PubMed PMID: 31143950.
6. Rødgaard EM, Jensen K, Vergnes JN, Soulières I, Mottron L. Temporal Changes in Effect Sizes of Studies Comparing Individuals With and Without Autism: A Meta-analysis. JAMA Psychiatry. 2019 Aug 21. doi: 10.1001/jamapsychiatry.2019.1956. [Epub ahead of print] PubMed PMID: 31433441; PubMed Central PMCID: PMC6704749.
7. Yang ZY, Fan H, Tang JL. Considerations Concerning Disease Redefinition. JAMA Intern Med. 2017 Dec 1;177(12):1872-1873. doi: 10.1001/jamainternmed.2017.6139. PubMed PMID: 29204632.
8. Muntner P, Carey RM, Gidding S, Jones DW, Taler SJ, Wright JT Jr, Whelton PK. Potential US Population Impact of the 2017 ACC/AHA High Blood Pressure Guideline. Circulation. 2018 Jan

9;137(2):109-118. doi: 10.1161/CIRCULATIONAHA.117.032582. Epub 2017 Nov 13. PubMed PMID: 29133599; PubMed Central PMCID: PMC5873602

9. French DP, Cameron E, Benton JS, Deaton C, Harvie M. Can Communicating Personalised Disease Risk Promote Healthy Behaviour Change? A Systematic Review of Systematic Reviews. Ann Behav Med. 2017 Oct;51(5):718-729. doi: 10.1007/s12160-017-9895-z. Review. PubMed PMID: 28290066; PubMed Central PMCID: PMC5602036.
10. Doust J, Vandvik PO, Qaseem A, Mustafa RA, Horvath AR, Frances A, Al-Ansary L, Bossuyt P, Ward RL, Kopp I, Gollogly L, Schunemann H, Glasziou P; Guidelines International Network (G-I-N) Preventing Overdiagnosis Working Group. Guidance for Modifying the Definition of Diseases: A Checklist. JAMA Intern Med. 2017 Jul 1;177(7):1020-1025. doi: 10.1001/jamainternmed.2017.1302. PubMed PMID: 28505266.

[Zeidler H. The need to better classify and diagnose early and very early rheumatoid arthritis. J Rheumatol. 2012 Feb;39(2):212-7. doi: 10.3899/jrheum.110967. Epub 2011 Dec 15. Review. PubMed PMID: 22174195.]