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# Guidance for Modifying the Definition of Diseases
## A Checklist

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**IMPORTANCE** No guidelines exist currently for guideline panels and others considering changes to disease definitions. Panels frequently widen disease definitions, increasing the proportion of the population labeled as unwell and potentially causing harm to patients. We set out to develop a checklist of issues, with guidance, for panels to consider prior to modifying a disease definition.

**OBSERVATIONS** We assembled a multidisciplinary, multicontinent working group of 13 members, including members from the Guidelines International Network, Grading of Recommendations Assessment, Development and Evaluation working group, and the World Health Organisation. We used a 5-step process to develop the checklist: (1) a literature review of issues, (2) a draft outline document, (3) a Delphi process of feedback on the list of issues, (4) a 1-day face-to-face meeting, and (5) further refinement of the checklist. The literature review identified 12 potential issues. From these, the group developed an 8-item checklist that consisted of definition changes, number of people affected, trigger, prognostic ability, disease definition precision and accuracy, potential benefits, potential harms, and the balance between potential harms and benefits. The checklist is accompanied by an explanation of each item and the types of evidence to assess each one. We used a panel's recent consideration of a proposed change in the definition of gestational diabetes mellitus (GDM) to illustrate use of the checklist.

**CONCLUSIONS AND RELEVANCE** We propose that the checklist be piloted and validated by groups developing new guidelines. We anticipate that the use of the checklist will be a first step to guidance and better documentation of definition changes prior to introducing modified disease definitions.

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Supplemental content

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Globally, concern is increasing about the effect of overdiagnosis, that is diagnoses where harms outweigh benefits.[1] A major driver of overdiagnosis is the widening of disease definitions.[2] Changes in disease definitions can benefit patients, principally by providing access to beneficial treatments, but also increases the risk of overdiagnosis. The risk of overdiagnosis is particularly great when definitions are widened to include earlier or milder disease. The absolute magnitude of treatment benefits commonly increases with severity of disease or baseline risk,[3] a relationship shown empirically for elevated cholesterol[4] and blood pressure.[5] The probability of harms are generally constant regardless of baseline risk because they are less related to the patient's baseline risk and more a fixed effect of the proposed intervention itself. Therefore, patients diagnosed with earlier or milder disease are more likely to be harmed than to benefit (**Figure 1**).

A recent study[6] highlighted the tendency of panels to widen disease definitions. None of the 16 guidelines included a rigorous assessment of potential harms from proposed changes. Such changes can have major effects on the prevalence of a disease (**Table 1**). Reports in the Less Is More Series in *JAMA Internal Medicine* [http://jamanetwork.com/collections/6017/less-is-more] and the Too Much Medicine series in the *BMJ* [http://www.bmj.com/too-much-medicine] show that the widening of disease definitions is occurring across all medical disciplines, and that current processes are not sufficient to prevent inappropriate modification of disease definitions.

Despite the widespread effect of changes in disease definitions, we have been unable to identify any currently accepted criteria for modifying disease definitions. Diseases do not generally have discrete boundaries and judgment is required to determine the thresholds for diagnoses, but at present there is little to guide panels in making these decisions. This is in contrast to standards for producing trustworthy and transparent clinical practice guidelines more generally.[12,13] The Guidelines International Network (G-I-N)—which includes 107 organisations and that aims to lead, strengthen, and support collaboration in guideline development, adaptation and implementation—recognizes the need to address this challenge.[13] We created a G-I-N working group with

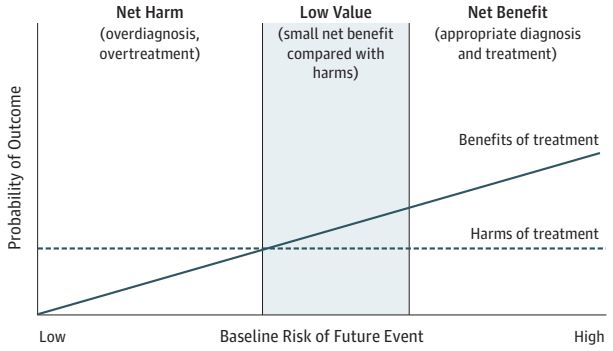
the aim of developing guidance for modifying disease definitions, including a checklist of issues to be considered.

## Methods

We assembled a multidisciplinary, multicontinent working group of 13 members to develop the document. We included members with specific expertise and experience in taxonomy, epidemiology, pathology, genetics, and guideline development and with a range of clinical backgrounds, including members from the GRADE working group and the World Health Organization. Development of the checklist was guided by the methodological framework for developing reporting guidelines suggested by the Enhancing the Quality and Transparency of Health Research (EQUATOR) Network.[14] It consisted of (1) a literature review of issues to be considered, (2) a draft outline document, (3) a Delphi process of feedback on issues, (4) a 1-day face-to-face meeting, and (5) further modification of the checklist.

For the search, we used an iterative snowball technique of forward and backward searching in the Scopus database, beginning with 4 key articles.[15-18] We circulated an outline of the issues identified to the working group and conducted a survey of 36 randomly selected members from the G-I-N network and 40 members of the GRADE working group using a structured, open ended questionnaire, asking participants to judge the relevance of each suggested issue on a 4 point Likert scale and for further comments.

Figure 1. Relationship Between Baseline Risk of a Future Health Event and Treatment Benefit




We held a 1-day face-to-face meeting, where the working group discussed the issues raised by the literature search and reviewed feedback from the survey to determine the order, structure, and wording of the checklist. The group selected an example to illustrate the use of the checklist: the consideration of the definition of gestational diabetes mellitus (GDM) by a recent Norwegian guideline committee.

Finally, the checklist was circulated to the working group for further clarification and refinement. The final checklist, the rationale for each item's inclusion, and the types of evidence needed to address each item are outlined below.

## Results

### A Checklist to Guide Modification of Disease Definitions

The initial search found 99 relevant citations. We found surprisingly little advice on how the definition of diseases should be modified, with most of the literature outlining potential or actual problems resulting from changes to definitions. Issues identified were clarity of the definition, potential for misuse, consistency, effect on incidence, changes to the natural history of disease, the effect of treatment in patients, adverse effects including psychological and financial consequences, and the utility of the disease definition to individuals and society.

From these items and the feedback of the survey, the working group developed a 7-item checklist. This was later expanded to 8 items, including a final question on the overall balance of potential benefits and harms. The checklist is shown in **Table 2**, with the rationale for inclusion of each item. We describe these below, with explanations of how a guideline panel would consider evidence in each case.

#### Differences in Previous and New Definitions

The panel needs to clearly describe the new and previous definitions of disease and how they differ. Previous definitions may not have been standardised, and if so, versions of the previous definition in widespread use should be outlined.

#### Changes in the Incidence and Prevalence of the Disease

The panel should describe the expected effect of proposed changes on incidence and/or prevalence of disease. Seemingly minor changes in disease definitions can result in large changes in prevalence, as

Table 1. Changes in Disease Definitions and Prevalence of a Condition

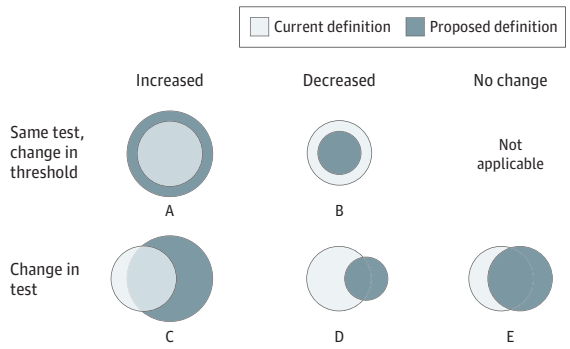
| Condition | Population | Previous Definition | Old Definition Prevalence, % | New Definition | New Definition Prevalence, % |
|---|---|---|---|---|---|
| Osteoporosis | Community sample of US women aged >65 years[7] | Femoral neck BMD T-score of −2.5 or less | 21 | NOF 2008 guideline | 72 |
| Myocardial infarction | Patients presenting to hospital with a troponin level measure ≥30 ng/L[8] | WHO criteria using MB fraction of creatine kinase | 18 | ESC/ACC 2000 criteria using troponin | 29 |
| Polycystic ovary syndrome | Sample of women aged 12-44 years in China[9] | NIH criteria | 7 | Rotterdam criteria | 11 |
| Prediabetes | Survey of adults aged >18 years in China[10] | Impaired fasting glucose | 26 | ADA 2010 criteria | 50 |
| | NHANES survey of adults ≥18 years in the United States[11] | Impaired fasting glucose | 26 | ADA 2010 criteria | 31 |

Abbreviations: ACC, American College of Cardiology; ADA American Diabetes Association; BMD, bone mineral density; ESC, European Society of Cardiology; NHANES, National Health and Nutrition Examination Survey; NOF, National Osteoporosis Foundation; WHO, World Health Organisation.

Table 2. Checklist of Items to Consider When Modifying a Disease Definition

| Checklist Item | Rationale |
|---|---|
| 1. Definition: What are the differences between the previous and the new definition? | It is important to delineate the proposed change precisely. |
| 2. Number of people affected: How will the new disease definition change the incidence and prevalence of the disease? | The number of people affected is important in understanding benefits, harms, and resources needed. |
| 3. Trigger: What is the trigger for considering the modification of the disease definition? | Stating the trigger for considering modification helps understand the necessity for modifying the disease definition. |
| 4. Prognostic ability: How well does the new definition of disease predict clinically important outcomes compared with the previous definition? | The most important feature of a disease definition is its ability to accurately predict clinically meaningful outcomes. |
| 5. Disease definition precision and accuracy: What is the repeatability, reproducibility, and accuracy (when estimations are possible) of the new disease definition? | Disease definitions that are repeatable and reproducible improve the consistency of clinical decision making. Accuracy is often not able to be estimated owing to the lack of a reference standard. |
| 6. Benefit: What is the incremental benefit for patients classified by the new definition vs the previous definition? | Benefits of the disease definition can be outlined, using methods such as GRADE. It is particularly important to estimate benefits in conditions where the new definition will be used to determine treatment thresholds. |
| 7. Harm: What is the incremental harm for patients classified by the new definition vs the previous definition? | Harms may also be outlined using methods such as GRADE. It is often more difficult to quantify harms, and particularly the psychosocial harms and harms on the societal level, including resource related harms. |
| 8. Net benefit and harms: What is the net benefit and harm for patients classified by the new definition vs the previous definition? | A panel should consider all of the above, and the balance of net benefits and harms prior to modifying a disease definition. |

Figure 2. How a New Disease Definition May Impact Disease Prevalence




shown in Table 1. Lowering a disease threshold will include all patients previously diagnosed with disease in the new definition (**Figure 2**A). Less commonly, raising a disease threshold will reduce the number of patients diagnosed (Figure 2B). Where there is a change in the method of defining disease and not just a change in threshold, studies of prevalence need to cross-classify patients, showing where the definitions agree or are discordant. A change in testing methods can cause changes in the type of patients being diagnosed with a decrease or no change in incidence (Figure 2D and E) but most commonly will increase the incidence of disease (Figure 2C). For example, the change in the definition of myocardial infarction in 2000 increased the incidence by about 61%, and also changed the mix of patients, with 9% of those previously diagnosed using MB fraction of creatine kinase no longer diagnosed using troponin levels.[8] Similarly, there is poor overlap in who is diagnosed and not diagnosed with prediabetes when using the different measures of glycaemia (glycated hemoglobin, impaired fasting glucose, and impaired glucose tolerance), with considerable variation between ethnic groups in the degree of overlap.[11]

Studies estimating changes in incidence or prevalence should be conducted in their respective clinical contexts using the methods of measurement that will be used in clinical practice. Field testing of the revision of the definition of attention-deficit/hyperactivity disorder in *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) in academic research centers estimated a 15% increase in the prevalence of the disorder,[19] considerably underestimating the increase observed when the new definition was used in wider clinical practice.[20]

### Trigger for Considering Modification of a Disease Definition

Outlining the trigger for the modification allows greater understanding for the need of a new disease definition. A panel might have 1 or several reasons for considering modifying a disease definition. Examples include the emergence of new treatments with clear benefits for patients identified by a new definition of disease, the development of a new test, new evidence on prognosis, a need to standardise definitions across clinical settings or for research purposes, or to improve the clarity or precision of a disease definition.

### Modification of Prognostic Ability

Being diagnosed with a disease only benefits a patient if the diagnosis assists in understanding current symptoms or the risk of future clinically important events, or if the patient can benefit from specific treatment. To appreciate potential harms and benefits of the change in definition, it is necessary to understand the natural history for those patients labeled by the new definition but not by the previous definition (the lighter shaded areas of Figure 2). The event rates in all patients diagnosed is not sufficient to understand the natural history of disease in these additional patients, and may conceal important differences. Where the prognosis of the additional patients is better than those classified with the previous definition, the average prognosis of all patients classified with the new definition will improve. Guidelines and recommendations based on the old definition cannot then be unconditionally applied to those identified with the new definition.

Information on natural history comes ideally from well-designed cohorts.[21] Careful consideration needs to be given to potential confounding by treatment, because the treatment of patients currently labeled with the condition can reduce the event rate and cause spurious associations.[22] Randomized trials that include a no-treatment or standard treatment arm can give information about both the ability of disease definitions to predict clinically important events (prognostic ability) and response to treatment decisions (predictive ability).[23] However, one has to be cautious about

the generalizability of the results given the frequently stringent inclusion criteria in trials.

Many definitions of disease are based on measures of pathological dysfunction. Measures derived from pathological models of disease do not always improve prognostic ability. For example, prediabetes, using measures of impaired glycaemia, was not a strong predictor of development of diabetes in a review of diabetes risk models.[24,25]

### Repeatability, Reproducibility, and Accuracy

The criteria used to classify patients in a new disease definition can be thought of as a form of diagnostic test. However, an appropriate gold standard will rarely be available and therefore, traditional measures of diagnostic test accuracy, such as sensitivity and specificity, will generally not be appropriate.

Although accuracy cannot necessarily be estimated, the precision of the new disease definition should be considered. Disease definitions with poor precision result in inconsistent diagnoses in patients and have poor clinical utility. Measures of precision include repeatability (agreement in identical conditions) and reproducibility (agreement across comparable conditions). The variation observed around the threshold for the disease is of the most relevance.

The performance of a disease definition cannot be easily separated from the proposed method of measurement. Limited precision may be owing to biological variation (eg, how blood pressure varies throughout and between days) or analytical variation (eg, how well a sphygmomanometer measures the "true" blood pressure). It may be possible to improve precision by taking the mean of repeat measures or by standardising the testing procedure. For example, standardising the parathyroid hormone assay could reduce misclassification of patients with secondary hyperparathyroidism.[26] Precision is ideally tested in the clinical context using the measurement methods that will be used in clinical practice.

### Incremental Benefits for Patients

Wherever changes in disease definitions will alter which patients receive treatment, it is essential to assess treatment benefits and harms, focusing on the balance of benefits and harms for those diagnosed by the new definition and not diagnosed by the previous definition (the lighter shaded areas of Figure 2). Changes to disease definitions can provide benefits to patients, mostly by providing access to treatments with beneficial effects. For example, the 2010 revision of the definition of rheumatoid arthritis allows earlier diagnosis and treatment, which may reduce the risk of later joint erosions.[27] Even in this case, however, the working group acknowledged that evidence from previous treatment trials in patients with later or more severe disease cannot be extrapolated to patients with milder or less severe disease, and concerns remain regarding misclassification.[28]

Diagnostic criteria that provide improvements in prognostic ability are useful, but not sufficient to ensure improvements in health outcomes, because prognostic markers may not adequately classify patients for treatment decisions.[29] For example, molecular profiling of tumors shows promise as a method of determining treatment in breast cancer, but the net benefits of using such markers to guide clinical decisions are still uncertain.[30]

Guideline panels may need to consider a wide variety of benefits, including nonhealth outcomes. For example, a diagnosis may provide validation of symptoms, and access to social and other benefits.

### Incremental Harm

The potential harms from diagnosis include the physical harms of diagnosis and treatment; psychological effects, such as anxiety; social effects, such as stigma and discrimination; and financial consequences, such as effects on employment. In the case of genetic diseases, harms may extend to family members. Harms are often poorly measured in clinical trials, and the harms observed in trial populations may not reflect the harms seen in the wider population.[31] Potential harms also include the misapplication and misinterpretation of the disease definition when taken from a confined research application to more widespread clinical use.

Changes in resource usage can result in harm by reducing access to care for some patients and by diversion and distraction of clinical care. This can happen at both the societal level, with resources taken from areas more important to health, and at the individual level, by distracting individuals from activities more important to their well-being. Modifications of disease definitions can have considerable impacts on costs, including the costs of testing, and the resources needed for treatment and follow-up for those diagnosed using the new criteria. There may also be resources needed for training and implementation regarding the change, and to minimise misdiagnosis. Costs are particularly important in low- and middle-income countries where inappropriate disease definitions can result in considerable diversion of limited health care resources.

### Balancing Incremental Benefits and Harms

Modifying a disease definition should be guided by a balanced assessment of the anticipated benefits and harms, using the best evidence available. The definition should reflect the values and preferences of patients and the wider community and include the impact on resource usage. We recommend a transparent and explicit process, such as the approach developed by GRADE, using structured evidence summaries to tabulate anticipated absolute effects across important patient outcomes.[32]

Decision analytic methods may be a pragmatic first step to model potential benefits and harms of the proposed changes in disease definitions. Models can use data from existing trials where suitable adjustment is made for differences in baseline risks. For example, an analysis stratified by baseline risk using the individual patient data in a meta-analysis of trials of blood pressure lowering therapy demonstrates that the proportional risk reduction is consistent across the subgroups, and therefore could be used to estimate treatment benefit in patients at lower baseline risk (eFigure in the Supplement).[5]

If the new definition of disease will be used solely for research purposes, the assessment of treatment benefits and harms may not be necessary. Different definitions may be required for research purposes, for example more stringent standardization, than for clinical purposes where more stringent definitions may deny access to care for patients who would benefit.

In general, we recommend that panels consider both an individual and societal approach to assessing the overall benefits and harms of changing disease definitions. We recommend introducing a new disease definition where there is an expected positive balance of harms and benefit for individuals, and in aggregate at the societal level.

With the assistance of members of a recent Norwegian guideline committee considering GDM, we illustrate the use of the check-

list showing a brief summary of some of the evidence considered relevant to this decision (eTable in the Supplement).[33]

## Discussion

Currently, there is little to guide those who wish to modify disease definitions. Our 8-item checklist provides a conceptual framework to assist such decisions and to encourage transparency in the decision-making process regarding the uncertainties and trade-offs involved. It follows a similar approach to that used by the GRADE working groups in the assessment of other health care interventions, but seeks to explicitly consider the needs for modifications of disease definitions. We suggest that guideline committees and other groups use the checklist as a reminder of the issues that need to be considered and to communicate the why and how of the new disease definition.

Modifying disease definitions can have benefits for both clinicians and patients—there can be greater consistency of decision making, a standardisation of processes to improve communication and research, and improved access to effective treatments for patients. However, the potential for overdiagnosis and overtreatment of patients demands caution. At a minimum, we need to ensure that patients are not harmed. Disease definitions should be modified only when there is strong evidence of benefit.

A recent review illustrated how guideline panels widen disease definitions without rigorous consideration of the issues now compiled in this checklist. Concerns about overdiagnosis and the potential harms of treating patients with the new definitions of disease have been raised for several of the conditions included in the 2013 review, such as ADHD and hypertension[34,35] and remain for many other conditions, such as chronic kidney disease, osteoporosis and prediabetes.

### Limitations

Changes in disease definitions may occur with no implications for treatment, as has occurred with the definition of a preclinical phase of Alzheimer.[36] In many cases, however, the widening of disease definitions is a driver of widened treatment recommendations. Considerable financial conflicts of interest can occur within committees considering disease definitions.[6] Intellectual and emotional conflicts of interest are also important and may be just as difficult to manage.

The checklist does not try to resolve the current conflation of risk factors and symptomatic disease entities that has become widespread in modern medicine.[37,38] This distinction may need to be considered and further refined in future iterations of the checklist.

We developed the current checklist through a consultative process with experts from a range of backgrounds. However, the checklist has not yet been trialled or validated. Piloting and feedback by groups considering modifying disease definitions is desirable.

## Conclusions

The proposed checklist is a first step to guidance and better documentation of definition changes. Further work is needed to clarify the methods and to help guide judgement about the adequacy of evidence and the balancing of benefits and harms. A G-I-N working group will be continuing to support work in this area.

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