Beware of overdiagnosis harms from screening, lower diagnostic thresholds, and incidentalomas

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Clinical practice guidelines should support clinicians in delivering preventive health services. Unfortunately, they often do not provide the information we need to have meaningful discussions with patients. When offering a screening test, we require information on both the potential benefits and harms of screening. These include the harm of overdiagnosis.

For many people, the concept of overdiagnosis remains elusive. One possible reason is that the term is employed in different circumstances, which may lead to confusion. Another Prevention in Practice article addressed the causes and consequences of overdiagnosis with examples linked to screening for overt disease.[1] In this article we provide examples of overdiagnosis in other situations to clarify this concept and help clinicians provide useful information to patients. We give examples of overdiagnosis arising when the output of screening is the risk of a future outcome. We also discuss incidentalomas and identification of pre-disease, which may also lead to overdiagnosis. Information about overdiagnosis in different contexts is needed to inform shared decision making and minimize the harms of screening interventions.

Case description

Marc is 68 years old. Because of his age, you decide to screen Marc for diabetes, osteoporosis, and abdominal aortic aneurysm (AAA). You order the tests without having calculated his risk of diabetes or fragility fracture and without having engaged in shared decision making about whether to screen for AAA. His glycated hemoglobin A_{1c} (HbA_{1c}) result is 6.1%, his bone mineral density (BMD) is normal, and the ultrasound scan reveals a normal aorta, but a 1-cm lesion is present on his left adrenal gland.

The radiologist recommends a repeat ultrasound scan in 6 months and a repeat BMD test in 2 years. You are not sure what to tell Marc about the newly discovered prediabetes. You will encourage him to be active and to eat well, but you wonder if a label of prediabetes will negatively affect his quality of life or help him avoid complications down the road.

A nurse hears you talking about Marc with a colleague and offers to see him for his prediabetes. She is convinced that early intervention can only be beneficial. As for the follow-up ultrasound scan, you believe you have no choice but to order it. When you explain this to Marc, he becomes worried that he is now "at risk" (ie, something is wrong). After he leaves, you wonder whether Marc, with these new diagnoses, is a victim of overdiagnosis.

What is overdiagnosis?

Overdiagnosis is the diagnosis of a condition that, if unrecognized, would not result in symptoms or cause a patient harm during their lifetime.[2] Unlike false positives, overdiagnosed individuals have the condition (ie, the result is a true positive). As they cannot benefit from this diagnosis, these people can only be harmed, whether physically (as a result of investigation and treatment) or psychologically (from being labeled *unwell*).

In the literature, overdiagnosis has mostly been discussed in the context of cancer screening; however, overdiagnosis can also arise from interventions that identify nondisease conditions such as osteoporosis, which is a proxy for the risk of fragility fractures. To make the issue even more complex, overdiagnosis is not limited to the screening context, but can also arise when following diagnostic pathways (eg, finding incidentalomas in imaging) (**Box 1**).[3] Clinicians need practical ways to think about overdiagnosis in different circumstances to help them incorporate information about this harm in shared decision-making discussions.

Overdiagnosis and expansion of disease definitions

Over time the definitions of diseases can change. For example, lowering fasting blood glucose threshold values

Key points

- Overdiagnosis has most often been discussed in the context of cancer screening, but this harm also arises in other forms of screening and in diagnostic testing. For shared decision making to happen in practice, we need to understand the implications of this harm.
- Lowering diagnostic thresholds for diseases raises the potential for overdiagnosis.
- Disease labeling can negatively affect patients.

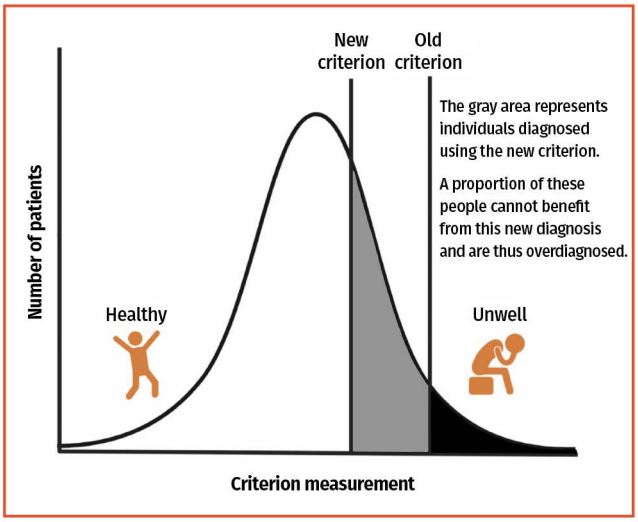
Box 1. Overdiagnosis: what leads to it, and what it is not

Factors that can contribute to overdiagnosis
- Lowering thresholds for diagnosing a disease (individuals at lower risk become labeled—not all will benefit)
- Overdetection (more sensitive tests) can increase overdiagnosis
- Overuse of tests can lead to the discovery of incidentalomas (many represent overdiagnosis)
- Screening (overdiagnosis is an inevitable consequence of screening—its magnitude varies depending on the type of screening test)

What overdiagnosis is not
- Overdiagnosis is not misdiagnosis (overdiagnosis is a real diagnosis)
- Overdiagnosis is not a false-positive result (a false positive will eventually be proven to not be a disease)
- Overdiagnosis is not overtreatment (overtreatment can occur without overdiagnosis)
- Overdiagnosis is not overuse or overtesting (overdiagnosis can occur because of overtesting, but it is not the only consequence of overtesting)

Data from Brodersen et al.[3]

Figure 1. Lowered diagnostic thresholds raise the potential for overdiagnosis



increased the number of patients diagnosed with diabetes mellitus.[4] However, not all who are newly diagnosed with diabetes can expect to benefit from being diagnosed. Although some may benefit, others will be harmed by being labeled as having a disease. Changing diagnostic thresholds usually results in more people being labeled with a condition, with all that this entails, including adverse psychosocial and financial consequences, as well as possible overtreatment. When thresholds are lowered, many people with newly recognized disease are in fact overdiagnosed (**Figure 1**). Unfortunately, much of the time no assessment of potential harms is included in the process of redefining a disease.[5]

There are numerous other examples of individuals being overdiagnosed following expansion of criteria for defining a disease (eg, hypertension).[6] In chronic kidney disease, the decision to use the same estimated glomerular filtration rate cutoff for all adults (instead of age-adjusted cutoffs) inflated diagnosis rates among older adults and recommendations for subsequent interventions without clear benefit.[7] It seems obvious that prior to accepting a new definition of disease we should be confident this change will lead to more good than harm.

Some guidelines have gone further and created new disease categories, such as prediabetes. Estimating the prevalence of prediabetes is difficult because variable criteria are used to define it. In a systematic review of the efficacy of screening, 5 studies provided information on the prevalence of prediabetes using different diagnostic criteria.[8] Only 1, a cohort study from England,[9] used World Health Organization prediabetes criteria (ie, fasting plasma glucose of 6.0 to 6.9 mmol/L, impaired glucose tolerance of 7.0 to 11.1 mmol/L, or HbA_{1c} of 6.0% to 6.4%), which are similar to criteria suggested by Diabetes Canada.[10] The other studies used American Diabetes Association criteria, which are too different to give relevant approximations for the Canadian situation. The systematic review noted that 27% of the adult populations included in the English cohort study (40 to 75 years of age) had prediabetes (with nearly half diagnosed based on HbA_{1c} alone).[8,9] This proportion in itself raises many questions.

Approximately 3.5% of individuals with prediabetes (defined as HbA_{1c} of 6.0% to 6.4%) will progress to diabetes over a 1-year period.[11] Lifestyle interventions could prevent diabetes for some of those who would progress. In trials where lifestyle interventions lasted 6 months to 2 years, approximately 7% of individuals with prediabetes in lifestyle intervention groups developed diabetes compared with 10% in nonintervention arms.[8] For lifestyle interventions lasting between 3 and 6 years, the respective numbers were 17% and 24%.[8] One or 2 sessions with a nurse or dietitian might not be enough to produce similar results. Given the prevalence of prediabetes, it would take many hours of clinical time to achieve this potential benefit.

Should you have screened Marc for diabetes? Only 2 trials have looked at diabetes screening,[12] and neither showed any beneficial impact on mortality, cardiovascular events, nephropathy, or retinopathy. Yet, considering information from modeling studies, the Canadian Task Force on Preventive Health Care[13] does recommend screening for diabetes, but only for individuals at high or very high risk of diabetes based on scores determined with a validated risk calculator (such as the Finnish Diabetes Risk Score [FINDRISC][14]). This implies not screening everyone and instead screening only those at risk based on a tool such as FINDRISC. If you had calculated Marc's risk of diabetes, he would have had a

FINDRISC score of 10 (indicating a risk of developing diabetes within 10 years ranging from 1% to 17%).[14] This low level of risk means you should not have screened him.[13]

While lifestyle interventions are known to confer health benefits, no pharmacologic or lifestyle intervention offered to patients with prediabetes has been shown to affect patient-important outcomes such as mortality or cardiovascular disease outcomes[15] (except in 1 trial—out of 38 in an evidence review[12]—that unfortunately did not have similar groups at baseline). The importance of identifying prediabetes thus remains an open question, and we should reflect on the problem of labeling patients as prediabetic.

Discovery of a risk of an outcome

Some screening tests identify risk of a disease. Similar to elevated serum cholesterol levels, low bone mass is not a disease but is a risk factor for a disease or condition. As such, screening to prevent fragility fractures involves risk calculation to inform patients of their probabilities of sustaining fragility fractures. For the outcome of preventing fragility fractures in men, only 1 nonrandomized trial of screening has been published,[16] and it showed no benefit. Screening men to prevent a fragility fracture who are not at high risk should probably wait for better evidence.

Among women, the most recent trials used some form of risk identification before participants were offered BMD testing.[17,18] For example, you could screen a woman who is the same age as Marc using the Fracture Risk Assessment Tool (FRAX)[19] and find she has a certain level of fracture risk in the next 10 years. Even if a high risk is identified, not all women will benefit from preventive treatment. Some will fracture a bone, regardless; others would not sustain a fracture even if untreated. Only a subset will not have a fracture because they were screened and then treated. In that context, overdiagnosis describes individuals classified (labeled) as high risk and likely exposed to further assessments or preventive treatments, but who, had they not been screened, would never have known they were at high risk, nor would they have experienced a fracture.[20] One could debate whether the term *overdiagnosis* applies to risk of a future event, but the label of being at increased risk has its own consequences.

Screening a man like Marc, unless he has a comorbid metabolic disease or takes medication that puts him at high risk of low-bone density, is not warranted. For women 65 years and older, trials showed limited benefits from screening,[17,18] but shared decision making is important to help women decide if they want further investigations (eg, BMD testing) that could lead to preventive treatment.

Incidentalomas

Imaging test modalities are changing rapidly. As tests become more sensitive, we can detect previously unrecognized abnormalities. An example of creating overdiagnosis with a more sensitive test is the use of chest computed tomography to diagnose pulmonary embolism, resulting in increased prevalence of pulmonary embolism.[21] The problem is that a non-negligible proportion of these newly diagnosed individuals do not benefit from this discovery.[21]

As with changing diagnostic criteria, when we implement new diagnostic or screening tests without first investigating their impact, or when we rely on surrogate outcomes for efficacy (eg, counting the number of diagnoses), we are left with an incomplete idea of the balance of benefit and harm for those newly diagnosed.[5]

Incidental findings on imaging are frequent and will happen whether the test was needed or not (eg, thyroid nodules identified on a chest computed tomography scan). The prevalence of incidental findings is quite variable but common enough to be a concern.[22] They could be benign or malignant. Even if these findings are malignant, it is far from clear that we can improve patient outcomes with their discovery. Hence, many incidentalomas (benign or not) are in fact overdiagnosed. If these diagnoses are made following a test that was not needed or a screening intervention that was not appropriately discussed, we are truly creating harm.

Case resolution

Marc is back for a follow-up appointment. He had an hour-long discussion with the nurse. He has not changed his lifestyle much, as he was already active and eating well. His follow-up ultrasound scan has shown a stable lesion and no follow-up is warranted at this stage. You discuss his BMD test result and decide to postpone any further testing. As there is no specific recommendation as to when he should be rescreened for diabetes, you decide to check his HbA_{1c} level in 2 to 3 years.

You have decided that from now on you will not order a screening test for AAA without engaging in shared decision making with the patient. You will also make sure not to label your patient as having prediabetes but will offer him lifestyle advice and organize follow-up. As for the incidentaloma, you realize this is somewhat inevitable but also that you can decrease this risk by ensuring you order only those screening tests that have more benefit than harm based on evidence from randomized controlled trials.

Conclusion

As patient preferences for screening interventions vary, it is important to provide accurate information about the possibility, as well as the burden, of overdiagnosis. This is particularly true when benefits and harms for an intervention are in equipoise. Clinicians should not assume their patients understand the possible outcomes associated with screening interventions.

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Competing interests

None declared

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Suggested reading

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