Too much of a good thing? Overdiagnosis, or overestimating risk in preventive genomic screening

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“Harris and colleagues propose replacing categorical thinking such as ‘disease’ and ‘predisease’ with a broader concept they dub ‘predictor of poor health’ (PPH) that is meant to capture probabilistic understanding of an adverse health event that offers a candidate for prevention”

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Forward

Preventive screening for rare, actionable monogenic disorders is among the armamentarium of tools that might be useful for personalized patient care. Currently, genetic testing is clinically indicated for patients with a strong personal or family history of heritable disease, or related symptoms [1]. However, these tests (even genome-scale sequencing) are increasingly being offered to asymptomatic patients without clinical indications – and consequently the list of potential results from these tests is expanding dramatically. As such efforts scale up, they can begin to approximate proposals for genomic screening in the general population [2]. Although typically articulated in terms of personalized benefits to individual patients, the underlying approach to early detection also permits precision initiatives to target interventions to high-risk groups. Thus, the programmatic success of preventive genomic screening (PGS) can be evaluated in terms of both personalized and population health outcomes. However, overdiagnosis, a complex phenomenon that represents a downside of any population screening endeavor, requires increased scrutiny in this new context.

A cautionary tale

Conceptually, there is no settled definition of overdiagnosis, a matter complicated by related concepts such as misdiagnosis, false positives and overtreatment [3,4]. Overdiagnosis has been defined as diagnosis ‘that would otherwise not go on to cause symptoms or death’ (p. 605) [5] or as giving a diagnosis that does not yield a net benefit [6]. Moreover, the notion of overdiagnosis is conceptually mismatched to preventive genomics, which is not always considered diagnostic per se, but rather detects genetic variants that confer greater risk of morbidity or mortality [7]. We therefore sought to explore the concept of overdiagnosis in the setting of preventive genomic screening.

The history of other screening efforts suggests that concerns about overdiagnosis should be heeded before adopting widespread PGS programs. For example, some estimates indicate that 23–42% of prostate cancer cases detected through prostate-specific antigen screening in the USA are overdiagnoses [8], because they would never have been detected clinically or symptomatically in the absence of screening. In some cases, cancers grow so slowly that the patient would never have experienced symptoms, while in other cases the patient is already ill or becomes sick from a different condition and dies as a result [8]. In these cases, screening simply does not clinically benefit such patients. Worse yet, screening can be detrimental when it leads to downstream interventions, such as biopsies or aggressive treatments. As a result, some patients may shoulder significant burdens of both screening and subsequent interventions, without experiencing health benefits to offset these harms.

Genomic screening, predisease & drivers of overdiagnosis in genetic disorders

Hofmann notes that concerns about overdiagnosis often reflect a bundle of related problems for screening programs that need unpacking [4]. For example, consider how such worries have been posed as an important ethical consideration in testing for autosomal dominant polycystic kidney disease (ADPKD) among children at risk due to family history [9]. Previously considered an adult-onset condition, evidence suggests that symptoms can be detected at an earlier age among those with deleterious ADPKD variants. However, detecting at-risk children might come at the cost of labeling and potentially subjecting healthy children to increased scrutiny, given the wide variability in the progression of the condition [9]. Importantly, the ADPKD case demonstrates that overdiagnosis is a concern in preventive clinical care within at-risk families, a worry that could be heightened by moving to the general population.

What are the sources of overdiagnosis in PGS? Pathirana and colleagues performed a scoping review to identify general drivers of overdiagnosis and suggested five domains: culture; the health system; industry; professionals; and patients and the public [10]. A full discussion of each of these domains is beyond the scope of this commentary. Nevertheless, implementing PGS in a responsible fashion should involve careful consideration of the evidence, promoting societal benefit and minimizing individual harms [11]. Shared decision-making in light of patient attitudes is also relevant, as screening decisions can be highly preference-sensitive, reflecting patients' underlying values [12].

We will set aside for now the concern about 'false positive' results, which can be the result of technical errors (sample swaps or sequencing artifacts) or interpretive errors (such as incorrectly asserting pathogenicity when in fact a variant is not causal for a monogenic condition). These false positives clearly constitute a serious constraint on positive predictive value in genomic screening, where the prior probability that an individual has a given genetic disorder is very low and our ability to properly interpret variants remains substantially suboptimal [13,14]. Even assuming that these concerns were minimal, we are still faced with two fundamental and intertwined facets of every monogenic condition: penetrance and expressivity. Penetrance is a measure of the proportion of patients with a pathogenic variant who will develop symptoms of the condition, while expressivity represents the range of manifestations seen among individuals with a given condition (age of onset, severity of disease, presence or absence of specific subphenotypes, etc.). We propose that incomplete penetrance and variable expressivity, both of which are likely underestimated in the current literature, comprise two specific sources of overdiagnosis in PGS. These facets of underlying genetic disease etiology reflect complex interactions with social determinants of health, age, sex and comorbid medical conditions that govern how many of those who screen positive will ultimately benefit from early detection.

A scaled up PGS program would situate these facets in a societal context that leads to medicalization of predisease stages. 'Predisease' labels often arise as a result of screening, capturing instances in which there is no sharp line demarcating the healthy from the sick [15] – such as precancerous lesions or borderline elevations in blood pressure or glucose levels [15,16]. Similarly, PGS positive findings will prompt a cascade of downstream evaluations, including detailed family history gathering, further diagnostic tests, surveillance, behavior modification recommendations or even invasive preventive interventions. A clinical diagnosis may be established in some who receive follow-up evaluations in the wake of genomic screening, but for many such findings there may not be a gold-standard confirmatory test or a means of determining who is more likely to develop symptoms, or when. The rise of prediseases reflects the convergence of experiences of patients who are at-risk with the experiences of patients with the condition itself [17]. The prospect of viewing deleterious genetic variants as prediseases is not farfetched: the hereditary breast and ovarian cancer genetic advocacy group *FORCE* has self-described their own members as 'previvors' [18].

Furthering evidence-based PGS

As described here, overdiagnosis underscores the potential for PGS to fall flat due to the identification of genetic predispositions that do not reliably track current or future harms to health. Harris and colleagues propose replacing categorical thinking such as 'disease' and 'predisease' with a broader concept they dub 'predictor of poor health' (PPH) that is meant to capture probabilistic understanding of an adverse health event that offers a candidate for prevention [19,20]. Using this framework, overdiagnosis can be viewed as inappropriately approaching treatment or monitoring for a person with a weak PPH the same way we would treat a person with a strong PPH [19,20]. Screening should aim for detection of those with strong PPH [20] while the recommended strategy for those with weak PPHs should exclude invasive interventions and potentially even eschew increased surveillance. In PGS, calculating PPH

would include not only the degree of certainty on the part of the variant interpretation but also the penetrance and expressivity of the condition, each of which serve as variables in predicting manifestations for any given condition.

PGS offers the tantalizing prospect of forestalling disease progression by stratifying patients into precise risk groups. Yet the combined confusion resulting from incomplete penetrance and variable expressivity in a context prone to medicalization demands serious consideration of the question: how many people will have a genetic ‘predisease’ that never leads to symptoms, for every person that is considered to be saved from disease or death? [4]. The population health consequences of detecting genetic risks are likely to be understood in hindsight, when health outcomes for cohorts who do and do not receive PGS are retrospectively compared. As a result, at the advent of genomic screening, clinicians will encounter situations of uncertainty in which an intervention’s individual risk–benefit profile for an asymptomatic patient is unknown. Moreover, the future is likely to hold more of the same challenges that prostate-specific antigen screening currently encounters, where determining the wisdom of screening for an individual patient involves a nuanced reconciling of population screening guidelines with clinical judgment and patient attitudes.

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