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Review

Avoiding the Technological Imperative: Criteria for Genetic Screening Programs

Anne-Marie Laberge [1,*], Wylie Burke [2]

1. Department of Pediatrics, Université de Montréal; Medical Genetics and Research Center, CHU Sainte-Justine, 3175 Côte-Ste-Catherine, Montréal, Qc, Canada; E-Mail: anne-marie.laberge.hsj@ssss.gouv.qc.ca
2. Department of Bioethics and Humanities, University of Washington, Box 357120, Seattle WA 98195, USA; E-Mail: wburke@uw.edu

* **Correspondence:** Anne-Marie Laberge: anne-marie.laberge.hsj@ssss.gouv.qc.ca.

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Abstract

Genetic screening is the process of systematically evaluating a defined population for genetic conditions or predispositions, in the hope of providing benefit to those with a positive result. With advances in sequencing technology, genetic screening is moving from phenotype-based to genotype-based testing. Although sequencing technology offers expanded opportunities for early identification of disease, the availability of a suitable and acceptable test is not a sufficient justification to proceed: established criteria for screening apply to genetic screening efforts as to other screening programs. We review here criteria for screening developed in public health practice, applications of screening in genetics, and particular challenges posed by genetic screening. These challenges include the potential for overdiagnosis of rare conditions, the special case of reproductive genetic screening, the pitfalls of opportunistic screening, and the implications of genotype-based population screening for individuals and health care systems. Promising opportunities in genetic screening underscore the need for evidence to evaluate proposed genetic screening programs to determine whether they can meet the established criteria for screening. Some

contested issues, such as indications for prenatal screening and opportunistic screening, cannot be resolved by research but also require judgements about values and priorities, ideally involving input from all stakeholders (clinicians, healthcare payers, and the public). If technology capacity is allowed to drive genetic screening activities in the absence of evidence for benefit, a growing number of asymptomatic individuals will receive a genetic diagnosis yet will remain uncertain about whether their test results represent a legitimate diagnosis, overdiagnosis, or a false positive finding. This will in turn drive additional medical work-up and treatment, resulting in costs to the healthcare system and the risk of iatrogenic harm. Criteria for screening were developed to minimize these potential harms and apply to genetic screening as much as to other types of screening.

Keywords:
Genetic screening; screening criteria; newborn screening; prenatal screening; screening for adult-onset disease; opportunistic screening; next-generation sequencing

Introduction

Genetic screening is the process of systematically evaluating a defined population for genetic conditions or predispositions, in the hope of providing benefit to those with a positive result. The first screening programs to target genetic conditions were newborn screening programs, starting in the 1960s with screening for phenylketonuria. Since then, newborn screening has expanded and other opportunities for genetic screening have emerged [1].

With advances in sequencing technology, screening for genetic conditions is moving from mostly phenotype-based tests – that is, tests to measure biological or physiological effects of a genetic condition, such as phenylalanine level to identify phenylketonuria - to genotype-based tests, in which the identification of DNA sequence variants indicates a genetic condition or predisposition. Genotype-based screening tests have many advantages: They provide an opportunity to identify an affected person before any effects of the disease have occurred; in addition, DNA samples are stable and can be transported easily, and genotyping can be performed for many conditions for which no phenotype-based test is available. However, such tests may over-estimate disease when the genotypes in question have low penetrance. Phenotype-based testing, on the other hand, is more likely to be informative about disease severity and can often be accomplished in an early, latent phase of disease, but sample handling, preparation and analysis are often more sensitive to external factors.

Advances in sequencing technology have led to the identification of growing numbers of genes associated with disease. This growing knowledge of the genetic basis of diseases, coupled with the availability of next-generation sequencing, has driven the expansion of genetic testing, and enabled concurrent testing for multiple genes. Tests can assess either multiple genes associated with a given condition (e.g., inherited cancer), or multiple conditions at the same time, or both. This growing technological capacity drives interest in new opportunities for genetic screening. Genetic screening tests are now offered by private companies directly to the consumer. Interest in commercially available tests by patients and prospective parents drives the use of these tests,

which in turn may influence professional practice. Evidence of adequate test performance is often available for genetic tests used in screening, but evidence establishing a health benefit is typically lacking.

Although sequencing technology is innovative and offers expanded opportunities for early identification of disease, genetic screening has the same purpose as other types of screening: to identify individuals at risk early enough to perform preventive measures or early intervention, with the intent to prevent the disease or its complications. Established criteria for screening, used in public health practice, are relevant to genetic screening efforts as to other screening programs. The availability of a suitable and acceptable test meets only a subset of screening criteria.

We will review here criteria for screening developed in public health practice, applications of screening in genetics, and the particular challenges posed by genetic screening.

Criteria for population screening

Screening has long been recognized as a strategy to prevent disease or disease complications by identifying individuals at risk of disease early enough to intervene and prevent the development of the disease or its complications.

Criteria for screening were first articulated by Wilson and Jungner for the WHO in 1968 [2] (Table). They include characteristics of the disease, the available screening test, available interventions and treatments, and the health care system. The disease must be an important health problem, have a known natural history and a latent or asymptomatic phase during which the disease can be recognized, allowing for early treatment. The available screening test must be suitable and acceptable to the population. Successful screening requires an accepted treatment for individuals with recognized disease, and an agreed policy on whom to treat. Finally, facilities for diagnosis and treatment should be available, cost of case-finding should be economically balanced, and case-finding should be an ongoing process.

These criteria for screening have been reaffirmed by others. In 2008, the WHO revisited Wilson and Jungner's screening criteria for the genomic age [3]. A synthesis of emerging screening criteria applicable to genetics were proposed, in addition to the classic criteria for screening, to explicitly address topics like program structure and evaluation, evidence-based policy, and ethics (Table). For example, they proposed the need for informed consent, equity of access and evidence of benefits outweighing the harms be explicit criteria for screening.

Applications of screening in genetics

One of the first applications of genetic screening was the development of newborn screening for inborn errors of metabolism in the late 1960s and early 1970s. Phenylketonuria (PKU) was the first target of newborn screening, thanks to technical advances that allowed for testing of phenylalanine levels on filter paper, i.e. a sample that was easy to collect, easy to ship, and stable over time. An effective treatment was available, in the form of dietary management, which, if started in the first weeks of life, changed the outcome in individuals with PKU from severe intellectual disability to normal development. Newborn screening for PKU was widely implemented in developed countries by the end of the 1970s [4]. The success of newborn screening for PKU motivated expansion of newborn screening to other inborn errors of metabolism, but it was another technical advance, tandem mass spectrometry, in the early 2000s,

that enabled newborn screening to expand rapidly from a handful of inborn errors of metabolism to close to thirty [5].

Table Screening criteria. (One line: middle; more lines: justified, right and left=1 cm)

Wilson and Jungner classic screening criteria [2]
1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a “once and for all” project.
Emerging screening criteria [3]
1. The screening program should respond to a recognized need.
2. The objectives of screening should be defined at the outset.
3. There should be a defined target population.
4. There should be scientific evidence of screening program effectiveness.
5. The program should integrate education, testing, clinical services and program management.
6. There should be quality assurance, with mechanisms to minimize potential risks of screening.
7. The program should ensure informed choice, confidentiality and respect for autonomy.
8. The program should promote equity and access to screening for the entire target population.
9. Program evaluation should be planned from the outset.
10. The overall benefits of screening should outweigh the harm.

Newborn screening for inborn errors of metabolism, for all its successes, has faced and continues to face challenges. First, new evidence emerges about a disease once screening is initiated. In many cases, PKU being a prime example, newborn screening detects individuals with mild or even asymptomatic forms of the condition that had previously been unknown. Screening test thresholds and treatment guidelines need to be adapted as more is learned about the natural history and range of severity of the condition. Second, by screening for one condition, we may end up identifying individuals with different but related conditions for which natural history is not as well-known and/or there is no clear agreement on whom to treat. Newborn screening for 3-methylcrotonyl CoA deficiency is an example of this challenge [6]. Evidence from newborn screening programs shows that the vast majority of individuals with this condition remain asymptomatic over time. Since it is not possible at the time of screening to determine who will become symptomatic, most cases are followed and likely to be treated, thereby medicalizing individuals who will remain asymptomatic. Third, since the purpose of newborn screening is to prevent disease complications, individuals with inborn errors of metabolism identified through newborn screening then need lifelong care. Access issues, both in childhood and as more and more of these individuals reach adulthood are becoming increasingly apparent [7].

As technology for molecular testing – in particular next generation sequencing - becomes faster and cheaper, the ability to test multiple genes or much more extensive DNA sequence in a single test, this technology becomes more attractive for newborn and other forms of genetic screening. Molecular testing is used as part of the newborn screening algorithm for cystic fibrosis [8] and investigation of broader use of genetic screening is underway [9].

There is also interest in population screening for genetic predispositions for adult-onset diseases. For example, some argue for population screening for hereditary predisposition to breast cancer (mutations in BRCA1 and BRCA2) [10]. For the time being, most efforts with adult patients are directed toward screening clinically defined groups instead of geographically or age-defined groups. For example, screening individuals with colorectal cancer for Lynch syndrome is recommended [11] and is more cost-effective than population screening [12]. However, the use of next generation sequencing to enable broad screening of adults for genetic conditions has been proposed [13].

Next-generation sequencing has also opened the door to expansion of reproductive genetic screening, which includes carrier screening to identify individuals who may be at risk of having a child with a genetic disorder and prenatal screening to identify risk of that the fetus has a genetic condition. As discussed below, genetic screening in this context differs from usual screening, in that the goal is to inform reproductive decisions rather than to improve health outcome. Both expanded carrier screening [14] and new forms of prenatal screening, such as cell-free fetal DNA testing for chromosomal disorders during pregnancy [15] are made possible by advances in genetic testing.

Challenges in genetic screening

Certain aspects of genetic screening call for special consideration and have implications for the criteria to be applied. Challenges in genetic screening include the potential for overdiagnosis of rare conditions, the special case of reproductive genetic screening, the pitfalls of opportunistic screening, and the implications of genotype-based population screening for individuals and health care systems.

Screening for rare conditions leads to a potential for overdiagnosis

Most of the time, genetic screening is done to look for rare conditions like those identified in newborn screening. The initial screening test often identifies more positive cases than the observed incidence of the disease in the population [16]. If an effective test is available to confirm the diagnosis, false positives results can easily be identified and those receiving them can be reassured. Unfortunately, confirmatory testing is not always available; in these circumstances, all individuals with a positive genetic screen will need to be followed despite the likelihood that some represent false positive findings. In some cases a positive result represents overdiagnosis, a term used to describe individuals who, although accurately identified, will not develop the disease in question. In genetic terms, overdiagnosis reflects incomplete penetrance or variable expressivity, that is, the observation that some individuals will have mutations associated with low penetrance or mild forms of the conditions, and may never actually develop the manifestations of the disease for which screening is justified. When using phenotypic tests, individuals with borderline or intermediate results may have mild forms of the condition. This is especially true if screening

asymptomatic individuals with no family history of disease: it is well established that disease penetrance in the general population cannot be extrapolated from disease penetrance in individuals with a family history. Recent research on incidental findings from genomic testing has shown that penetrance of variants classified as disease-causing based on studies of affected individuals is much lower when found in unselected individuals [13, 17].

Because of this risk of misclassifying individuals as being affected or at high risk of disease, a strong rationale for screening is needed to justify the follow-up and management of all individuals with positive screen results. Also, an important goal of the screening program should be to minimize the identification of individuals who are unlikely to benefit from follow-up and management. This means favoring targeted approaches at many levels: restricting screening to an appropriate target group and choosing a targeted screening test or a screening algorithm that helps minimize the identification of false positives, or mild, late or low-penetrance forms of the disease.

The special case of reproductive genetic screening: who benefits and how do we measure outcomes?

Genetic screening in the context of reproduction, i.e. carrier screening and prenatal screening, is an atypical form of screening on many levels. First, the risk identified has no impact on the health of the person being screened: it is a risk of disease for the person's or couple's future child. Second, the purpose of screening is most often not to prevent disease or complications of the disease, but to provide prospective parents with information they can use to make decisions about their reproduction, including in some cases, the decision to terminate a pregnancy. Reproductive screening therefore is a departure from classic screening criteria, with the end goal not of improved health outcome for the person screened but rather informed reproductive decisions.

Although early carrier screening programs reported reduction in incidence of disease as a marker of success, emphasizing the goal of preventing affected births, there has been a shift in the stated purpose of carrier screening over the last two decades: disease incidence is no longer considered the primary outcome of interest of carrier screening programs and instead, programs focus on delivering information of value to prospective parents [18]. Furthermore, in the last few years, commercial labs have started offering "expanded carrier screening". Traditionally, carrier screening has been offered to individuals with a family history of a particular genetic condition or individuals from a population with a high carrier rate of one or more specific autosomal recessive disorders (e.g. Tay-Sachs disease in Ashkenazi Jews). Carrier screening based on family history or ethnic origin is still recommended, but expanded carrier screening is now available commercially to all individuals considering a pregnancy or in early pregnancy, regardless of their family history or ethnic background [14]. The list of conditions that are included in commercially available carrier screening panels often cover over 100 conditions, including some that are much rarer or milder than those targeted by long-standing carrier screening programs and recommendations. Responsible implementation of expanded carrier screening raises technical, ethical, legal and social questions [19]. Carrier couples identified through carrier screening have an increased risk of having an affected child. Potential reproductive options include access to prenatal diagnostic testing, preimplantation genetic diagnosis (for those able to afford the significant out of pocket

costs involved and willing to go through in vitro fertilization, despite its limits and potential health risks), or other approaches such as the use of donor semen or adoption.

The advent of non-invasive prenatal testing or cell-free fetal DNA testing has changed the discussion around genetic screening. Until recently, prenatal genetic screening was focused primarily on Down syndrome. In this approach, an integrated screening process is offered for Down syndrome, with serum and ultrasound markers used to estimate risk. For those with a positive screen result, invasive prenatal genetic diagnostic testing (of fetal cells obtained from amniotic fluid) is offered. Because obtaining fetal cells from amniotic fluid via amniocentesis is an invasive test, it involves a risk of miscarriage. It detects Down syndrome more accurately than integrated screening and is increasingly used for other chromosomal disorders despite lower accuracy for rarer conditions [20]. It is now recommended as a screening test for aneuploidies [15]. In some instances, it is used as a second-tier screening test after a high-risk result from integrated screening. Since cell-free fetal DNA testing is considered a screening test, its results must be confirmed by diagnostic testing, i.e. invasive prenatal diagnosis procedures, such as amniocentesis. Because of its higher accuracy, use of NIPT has reduced the number of false positive screening results, the number of amniocentesis performed for diagnostic testing, and therefore the number of miscarriages due to invasive testing.

Discussions about prenatal genetic screening using amniocentesis were set around a balance of risks: the risk of the fetus being affected vs the risk of miscarriage. NIPT changes the discussion to one about the woman and couple's desire to know, which can be rooted in the risk that the fetus is affected, but without the counterbalance of the risk of miscarriage. In that setting, the threshold for what is worth screening may become personal to each woman and couple. As the technology used for NIPT is being developed to detect other types of genetic conditions (microdeletions, monogenic disorders) and even provide whole genome sequencing, the use of screening criteria to put boundaries around such screening becomes increasingly relevant.

With advances in both technology and identification of new genes associated with disease, more and more reproductive genetic screening options are available, raising the challenge of how we should measure screening outcomes. Since the purpose of screening is for women and couples to make informed reproductive decisions, there is no preferred clinical outcome, and decisions are based on personal values. To ensure that women and couples get accurate and useful information, reproductive screening must apply stringent criteria in selecting the screening process to be offered, an in particular to ensure that highly accurate test with high predictive value is available to confirm initial positive screening tests. Some argue that genetic screening for reproductive purposes should be limited to severe conditions, but there is no consensus amongst professionals about what constitutes a severe or serious condition [21] and prospective parents may have different perspectives on what types of conditions they are worried about. It is therefore difficult to set a threshold to determine which conditions should be part of a screening panel.

The pitfalls of opportunistic screening

Advances in genomic technology – specifically, in the technical capacity to evaluate a large amount of DNA sequence at relatively low cost -– have created a potential for opportunistic screening. The term refers to a screening process that is added on to an unrelated clinical evaluation. For example, current evidence supports the use of a comprehensive exome test

(evaluation of DNA from the protein-coding regions of the genome) and potentially a full genomic analysis in the work-up of children with neurodevelopmental disorders, as an efficient approach to identify a genetic cause for the disorder [22-24]. The testing process occurs in multiple steps: DNA sequence is generated; specific regions of the sequence – filtered to focus on genes implicated in neurodevelopmental disorders – are evaluated for any variations from reference sequence; and analysis of variants is undertaken to determine their likelihood of being pathogenic. The analysis relies on available evidence about particular variants, evaluation of the structural characteristics of the variant (nature of variant, potential impact on gene function, frequency in the general population, etc.), and may sometimes include testing of both affected child and parents to determine whether or not a variant is inherited. The same analytic steps could be applied to other parts of the exome sequence that are not relevant to the clinical question. This additional analysis allows for opportunistic screening to be undertaken.

As an example, the American College of Medical Genetics and Genomics (ACMG) has recommended that a set of 59 genes be evaluated whenever exome or whole genome testing is done, even if the genes are unrelated to the clinical question that prompted testing [25, 26]. The justification for this approach is two-fold. The genes selected for additional analysis are all associated with serious diseases for which medical intervention is available; that is, pathogenic variants found in these genes are "medically actionable." This rationale speaks to the fundamental goal of screening, that is, to identify individuals who can benefit from early medical intervention, at a time when they are still asymptomatic. The second rationale is practical: once the DNA sequence has been generated, further analysis can be readily accomplished; in essence the testing process is already partially completed. However, the resources involved in completing the additional analysis are not trivial, because variant interpretation often involves review of databases and medical literature to determine the pathogenicity of a particular finding; many findings cannot be definitively characterized. Furthermore, as new knowledge emerges from genomic sequencing, variants previously thought to be highly penetrant pathogenic variants, based on limited evidence, have been found to be either benign or of uncertain clinical significance. Individuals labelled opportunistically as having one of these 59 conditions may thus have a lower likelihood of actually developing the disease than initially thought.

The second rationale raise questions about the threshold for screening, specifically, whether less stringent evidence of health outcome benefit should be required when screening is opportunistic. The ACMG recommendations imply a less stringent threshold, noting that evidence to establish clinical utility is not yet available for all the genes proposed for opportunistic screening [25]. Rather, the screening recommendation is based on an argument for likely benefits, and the identification of secondary findings in these genes is seen as a matter of prudence when patient care has already generated the DNA sequence. The recommendation emphasizes that only known pathogenic and likely pathogenic secondary findings should be reported, that is, variants of uncertain clinical significance are not considered suitable for return in this context. This approach assumes that the benefits of early treatment seen in families with a genetic disorder – for example, reduced incidence of colorectal cancer from colonoscopy screening in unaffected family members with Lynch syndrome – will also occur for unselected individuals diagnosed on the basis of secondary findings. It also assumes that the test characteristics and health outcome benefits in individuals without clinical indications for testing will be the same as for those with indications.

Emerging data pose concerns about this approach. To start with, variant interpretation is not only time-consuming but also often unable to provide a clear characterization of the clinical significance of the variant. Two sources of data are available for addressing this task: accumulated data on the clinical outcome of people with the variant and laboratory or computational analyses that predict the functional effects of the variant. Recent papers document inconsistency for both approaches [17, 27-30]. Because findings for most genome and exome studies include novel or rare variants, these analytic limitations mean that many variants of unknown significance will be found in any screening effort. This problem is compounded by the lack of population-based data on the clinical implications of most variants. Evaluation has generally occurred in families where a genetic disorder has been found. In some cases, a clear segregation of the variant with disease allows for confidence in predicting the pathogenicity of the variant; in others, accumulated evidence from several unrelated families provides confidence about pathogenicity. However, a number of findings suggest that penetrance, even of a known pathogenic mutation; will be lower in the general population than in families ascertained by their genetic disorder. These include reports documenting genomic results consistent with disease in adults without phenotypic manifestations and population-based studies suggesting lower penetrance in unselected populations than in high risk families [13, 17, 31, 32]. Reduced penetrance in unselected populations is consistent with a body of data documenting substantial variability in clinical outcome for many genetic disorders [33, 34]; this observation suggests that modifiers of disease outcome are common even among single gene disorders. Taken together, these concerns suggest that opportunistic screening should be undertaken cautiously if at all.

The implications of genotype-based population screening

Cautions about variant interpretation and penetrance become even more important in considering proposals for using exome sequencing, genome sequencing or large gene panels to screen for genetic conditions in unselected/low risk populations, that is, not just as an add-on to a clinical test. The documented difficulties with variant interpretation suggest that this testing approach has unknown sensitivity and specificity and thus does not represent a suitable test for screening. False positive results are likely, due to the reduction in a test's positive predictive value when a condition is rare in the population being tested, and overdiagnosis is also a concern. A recent report of genomic testing in 50 "ostensibly healthy" adults found pathogenic or likely pathogenic results for single gene diseases in 22% of individuals [13]. Yet only 2 individuals (4%) had symptoms and in both cases symptoms were mild and the utility of clinical identification was unclear. One likely pathogenic finding was subsequently re-classified as a variant of unknown significance, underscoring current challenges in variant interpretation. A prevalence of single gene findings of 22% is an order of magnitude higher than would expected from the population prevalence of single gene disorders; whether the problem is solely one of variant interpretation or also reflects reduced penetrance of many variants in unselected populations is unknown. While there are good reasons to expect lower penetrance than has been seen in clinically ascertained families, the lack of data mean that penetrance for individuals identified in population screening is also uncertain and difficult to estimate. In addition to the risks posed of overdiagnosis and false positive results, evidence on appropriate treatment to improve outcome is often lacking for a low-risk population.

Technology driven expansion of genetic screening

Much of what is discussed above illustrates the potential for technology-driven expansions of genetic screening. Next-generation sequencing allows for faster, cheaper and more comprehensive genetic tests and has led to interest in its use for screening in unselected populations, be it for carrier screening in prospective parents, NIPT in pregnant women, or ACMG 59-gene panels in healthy adults. Much of this drive to broaden the number of diseases screened and the target population for screening has been pushed by commercial interests and justified by the availability of the technology and a presumption of benefit. These screening efforts are not part of comprehensive screening programs, with pre-test education components or clear referral and management pathways for those with positive results. Individuals either order tests directly from companies or through their provider, and the private laboratory offering the test will not ensure that those with positive results get appropriate care. The provider often hasn't been trained to use these new tests and isn't comfortable explaining the test or interpreting its results. Misunderstanding of test characteristics, test limitations and test results by health professionals and patients can have dire consequences: unnecessary tests and interventions in a patient wrongly thought to be at risk of disease, or insufficient follow-up and treatment in those wrongly thought not to be at risk of disease.

Furthermore, this focus on what the technology can detect to justify expansion of genetic screening has taken the attention away from classic screening criteria (Table) [2, 3]. The availability of a suitable test is only one criterion (and arguably a multi-gene panel or exome will not be a suitable screening test until variant interpretation becomes more reliable): screening should only be put in place if all screening criteria are met.

A related issue is the expansion of the definition of benefit to include benefits not related to health outcomes, such as ability to use information for life choices, including reproductive planning. The use of genetic information related to rare highly penetrant conditions is well established in this context, with medical genetics practice emphasizing the importance of personal values in determining whether or not to be tested as well as the actions to be undertaken when test results are positive. This approach assumes access to detailed information and counseling related to the genetic condition in question, neither of which can be readily offered when testing expands to hundreds of conditions of varying severity and clinical manifestations.

Conclusion

As successful newborn screening programs attest, the criteria for screening originally articulated by Wilson and Jungner can be appropriately applied to genetic screening [2]. These criteria require rigor in both identification of appropriate conditions for screening and construction of well-designed and sustainable screening programs. They require that a disease condition be sufficiently understood that early detection and treatment can be confidently predicted to lead to improved health outcomes in the population screened; that the testing process has sufficient predictive value to minimize the harms of false positive findings; and that a program of screening and follow-up be cost-effective and on-going. The emerging screening criteria proposed by the WHO emphasize the need for evidence to support genetic screening policies, and the importance of evaluation of screening outcomes [3]. Several adult genetic

screening opportunities have emerged that arguably can meet these criteria. For example, considerable evidence is now available to support screening for hereditary hemochromatosis [35, 36] although there remains uncertainty about the relative merits of the use of phenotypic versus genotypic screening and the appropriate candidates for screening. Similarly, strong arguments can be made for screening Ashkenazi women for the three BRCA mutations prevalent in that population [37], although the benefits and harms of sequence-based BRCA screening in the general population are still open to debate. It is also likely that a targeted gene panel, possibly including *BRCA* and *BRCA2*, could prove beneficial in population screening, if issues of variant interpretation can be resolved. Other issues that would then need to be addressed are the definition of the target age group for screening, and the most appropriate management protocol for unselected women with a positive result.

These promising opportunities underscore the need for more evidence to evaluate proposed adult genetic screening programs, in order to determine whether they can, in fact, meet the criteria generally accepted for screening programs. Such evidence could potentially be obtained by practical clinical trials or comparative effectiveness studies, in which genetic screening is introduced in one of two comparable clinical settings, with rigorous measurement of clinical, personal and economic outcomes. As these options are considered, established screening criteria should be applied to either single condition or multiple condition genetic screening, as there is no reason to question their relevance to this screening approach.

However, it is important to acknowledge that reproductive genetic screening has a different goal from other genetic screening and from the screening programs for which Wilson and Jungner articulated criteria: reproductive screening seeks to inform reproductive decisions rather than to improve health outcome. This subset of genetic screening cannot therefore be evaluated in terms of health outcomes. Among the classical screening criteria, the relevant ones have to do with the nature of the condition, the predictive value of the screening test, and program features that establish equitable access. It is also important to consider how the community or population perceives the proposed screening. We have found that screening is more likely to be adopted and successful if community members, patients and their families, patient representatives and advocacy groups support screening for this condition [18].

Some contested issues related to genetic screening cannot be resolved by research on screening outcomes, and need careful policy attention, ideally involving input from all stakeholders, including clinicians, health care payers, and the public. One of these is the threshold of disease severity to be applied to reproductive screening, in particular in the use of prenatal tests where the primary decision options available to prospective parents in the event of a positive test results during pregnancy is termination vs continuation of pregnancy. Should prenatal testing be available for relatively mild conditions, or when testing has limited predictive value – e.g., for genetic variants that confer a susceptibility to conditions such as autism spectrum disorder? This policy question must be determined by judgments and values related to the role of patient choice and appropriate use of health care services.

Another controversial issue is the appropriate threshold for opportunistic screening with exome or other genomic sequencing tests. Given the uncertainties about penetrance and challenges with variant interpretation, an argument can be made that opportunistic screening should not occur unless all screening criteria are met (Table). This approach would effectively limit opportunistic screening until substantially more is known about the implications of genetic

findings in unselected populations. Experts convened by the ACMG take issue with this approach and argue by contrast that a prospect of benefit is sufficient, if sequence data have already been obtained [25, 26, 38]. As with the threshold for reproductive screening, stakeholder input is needed to define appropriate policy. Although patient preferences are important to consider, the impact of opportunistic screening on the use of resources also needs to be considered.

The decision process for genetic screening programs or policies varies based on the context and type of screening activity. In some instances, there is a specific decision-making process. In the U.S., newborn screening policies are driven by the recommendations of the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. For other types of genetic screening, there is no one source of policy, and practice is influenced by the positions of professional societies on the issue. For example, the American Congress of Obstetricians and Gynecologists and the American College of Medical Genetics and Genomics have both issued recommendations about NIPT. The role of stakeholder input in the process of developing recommendations varies.

In addressing these policy questions, it is important to consider the consequences of the technological imperative. If technology capacity is allowed to drive genetic screening activities, allowing for ever expanding efforts in the absence of evidence for benefit, several harms can be predicted. These include a growing number of asymptomatic people with a genetic diagnosis yet with uncertainty about whether their test results represent a legitimate diagnosis, overdiagnosis, or a false positive finding. These diagnoses will in turn drive additional medical work-up and treatment, resulting in costs to the healthcare system and the risk of iatrogenic harm. Criteria for screening were developed to minimize these potential harms and apply to genetic screening as much as to other screening technologies.

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Author Contributions

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Competing Interests

The authors declare that no competing interests exist.

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