

# Population Screening for Genetic Disorders in the 21st Century: Evidence, Economics, and Ethics

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## Key Words

Clinical utility • Cost-effectiveness • ELSI • Genetic testing • Newborn screening

## Abstract

**Background:** Proposals for population screening for genetic diseases require careful scrutiny by decision makers because of the potential for harms and the need to demonstrate benefits commensurate with the opportunity cost of resources expended. **Methods:** We review current evidence-based processes used in the United States, the United Kingdom, and the Netherlands to assess genetic screening programs, including newborn screening programs, carrier screening, and organized cascade testing of relatives of patients with genetic syndromes. In particular, we address critical evidentiary, economic, and ethical issues that arise in the appraisal of screening tests offered to the population. Specific case studies include newborn screening for congenital adrenal hyperplasia and cystic fibrosis and adult screening for hereditary hemochromatosis. **Results:** Organizations and countries often reach different conclusions about the

suitability of screening tests for implementation on a population basis. Deciding when and how to introduce pilot screening programs is challenging. In certain cases, e.g., hereditary hemochromatosis, a consensus does not support general screening although cascade screening may be cost-effective. **Conclusion:** Genetic screening policies have often been determined by technological capability, advocacy, and medical opinion rather than through a rigorous evidence-based review process. Decision making should take into account principles of ethics and opportunity costs.

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Given the growing number of genetic tests, it is timely to examine approaches to evaluating population screening for genetic diseases. For the most part, the same evidentiary, economic, and ethical criteria that are used to assess screening for common complex diseases such as breast, cervical, or colorectal cancer also apply to screening for disorders that are associated with specific genotypes [1–3]. However, screening for genetic disorders typically lacks high-quality evidence from randomized tri-

**Table 1.** Principles of population screening as applied to genetic susceptibility to disease (reproduced from Khoury et al. [3])

Public health assessment	<p>The disease or condition should be an important public health burden to the target population in terms of illness, disability, and death.</p> <p>The prevalence of the genetic trait in the target population and the burden of disease attributable to it should be known.</p> <p>The natural history of the condition, from susceptibility to latent disease to overt disease, should be adequately understood.</p>
Evaluation of tests and interventions	<p>Data should be available on the positive and negative predictive values of the test with respect to a disease or condition in the target population.</p> <p>The safety and effectiveness of the test and accompanying interventions should be established.</p>
Policy development and screening implementation	<p>Consensus regarding the appropriateness of screening and interventions for people with positive and negative test results should be based on scientific evidence.</p> <p>Screening should be acceptable to the target population.</p> <p>Facilities should be available for adequate surveillance, prevention, treatment, education, counseling, and social support.</p> <p>Screening should be a continual process, including pilot programs, evaluation of laboratory quality and health services, evaluation of the effect of screening, and provisions for changes on the basis of new evidence.</p> <p>The cost effectiveness of screening should be established.</p> <p>Screening and interventions should be accessible to the target population.</p> <p>There should be safeguards to ensure that informed consent is obtained and the privacy of those tested is respected, that there is no coercion or manipulation, and that those tested are protected against stigmatization and discrimination.</p>

als. Also, concerns about the implications of genetic information for privacy and autonomy have highlighted the importance of ethical, legal, and social issues (ELSI) in genetic screening [4, 5].

Screening involves the clinical and laboratory examination of individuals who exhibit no health problems with the aim of detecting disease, predisposition to disease, or risk factors that can increase the risk of disease [2]. Genetic screening of asymptomatic individuals can be done using a combination of molecular and biochemical testing strategies. Population screening offers testing to all individuals in a particular demographic group and does not require individuals to request testing. Cascade

screening of close relatives of patients with diagnosed genetic syndromes can be done on request or an organized population cascade screening program can be established. For instance, a population cascade screening program for familial hypercholesterolemia has been in operation in the Netherlands since 1994 [6]. A similar program has been recommended for the National Health Service in England and Wales [7].

The most common settings for genetic screening are the newborn period (1st month after birth) and the reproductive setting (preconception and prenatal screening), although screening occurs at other life stages as well. Almost all high-income countries have programs that screen newborns for phenylketonuria (PKU), congenital hypothyroidism, and other diseases [8, 9]. Prenatal carrier screening for cystic fibrosis (CF) or hemoglobinopathies has been implemented in a few countries, including France, the United States, and the United Kingdom. Although this may result in savings to health care payers [10], many ethicists argue that projected economic benefits from the termination of affected fetuses should not play a role in decisions to offer testing [11]. Finally, adults can be screened for mutations associated with late-onset diseases such as hereditary hemochromatosis, familial hypercholesterolemia, or familial cancers, including cascade screening of relatives [12]. Within each life stage, screening can be either universal, with equal access to testing mandated by legal authority, or as a standard of care, or targeted to at-risk groups.

### Criteria for Population Screening for Genetic Disorders

Since the 1968 publication of the Wilson and Jungner criteria for population screening by the World Health Organization, dozens of lists of criteria have been developed [1–3]. Commonly cited criteria include the magnitude of the health problem, the availability of effective therapies that substantially alter the course of disease, the expected benefits and harms from early detection and treatment during a latent period, and the perceived validity and acceptability of tests. Cost is also typically mentioned, although no consensus exists that one must demonstrate a particular balance of economic costs and health benefits. Additional criteria that have received attention in recent years focus on the need for the quality of the overall screening program to be monitored and assured, informed choice and equity in access, and the acceptability of screening (table 1) [3]. Such criteria were anticipated in

a 1975 report from the U.S. National Academy of Sciences on population genetic screening [13], but the report's recommendations were not instituted [14].

The National Screening Committee in the United Kingdom uses a set of criteria that 'are based on the classic criteria first promulgated in a WHO Report in 1966 but take into account both the more rigorous standards of evidence required to improve effectiveness and the greater concern about the adverse effects of healthcare' [15]. Specifically, the NSC sets a high evidence bar, with one criterion being the availability of randomized trial data demonstrating effectiveness in terms of improved health outcomes. Also, the NSC requires that an infrastructure of diagnostic and clinical services be in place throughout the country prior to the introduction of screening.

The most basic criteria relate to the existence of a safe, accurate, and acceptable test that can reliably detect risk of disease in healthy individuals. Rather than addressing technical issues of analytic and clinical validity [16], we focus on clinical utility and ethical issues. Specifically, we review 3 broad classes of criteria for screening programs, related to (1) scientific evidence regarding improvement in health outcomes, including both medical benefits and harms, (2) the balance of economic costs and health outcomes, and (3) ethical issues, including risks of psychosocial harms, adequacy of communication about risks, informed choice, and perceived acceptability and fairness in access. These criteria are interrelated. For example, assessing aggregate health outcomes requires balancing health benefits and harms that may occur to different groups of individuals, and cost-effectiveness analyses require evidence of effectiveness and involve questions of values and ethics [17].

### **Evidence-Based Practice in Genetic Screening**

Countries have adopted diverse policies regarding genetic screening. This reflects differences in the availability of resources as well as willingness to invest in costly new health technologies and differences in screening criteria and standards of evidence. This is particularly apparent in the case of newborn genetic screening. In recent years, a new technology, tandem mass spectrometry, has been introduced that can be used to screen for dozens of inborn errors of metabolism [18]. High-quality observational evidence is lacking for most disorders [19]. Consequently, there is little agreement among countries as to which specific disorders should be included in screening

panels [20]. Differences in disease frequency can play a role in decisions on screening for specific disorders, but countries with similar disease prevalence often reach different decisions about the appropriateness of screening.

Multiple mechanisms and processes for systematically assessing the utility of genetic tests are available [16, 21–23]. In the United States, the U.S. Preventive Services Task Force follows a rigorous approach to reviewing scientific evidence and has addressed the offering of *BRCA* mutation testing, suggesting that offering genetic counseling and voluntary testing for mutations be restricted to women with a strong family history [22]. A similar evidence-based initiative specific to genetic testing has been established by the U.S. Centers for Disease Control and Prevention (CDC), the Evaluation of Genomic Applications for Practice and Prevention (EGAPP) initiative [23]. An independent, non-federal, multidisciplinary EGAPP Working Group selects topics to review, oversees the systematic review of evidence, including data not yet included in peer-reviewed publications, and makes recommendations based on that evidence. The most recent EGAPP recommendation statement relates to testing for Lynch syndrome [24].

In the United States, decisions on which disorders to include in newborn screening panels until recently were made on a state-by-state basis with few national-level recommendations [25]. One exception was a CDC-sponsored evidence review conducted by a multidisciplinary team that included epidemiologists, ethicists, and an economist, who in 2004 concluded that screening for CF was justified by evidence of moderate benefit as long as ethical and practical concerns were satisfied [26]. After the publication of a task force report [25], the Maternal and Child Health Bureau of the Health Resources Services Administration (HRSA/MCHB) commissioned the American College of Medical Genetics (ACMG) to develop criteria and a core screening panel to be recommended to the states [27]. An expert panel convened by ACMG developed criteria and obtained input from interested parties as to whether each of 84 disorders satisfied those criteria. In addition, clinical experts were commissioned to produce brief disorder-specific reviews. The panel did not include experts in evidence-based practice, economics, or ethics and has been criticized by ethicists and advocates of evidence-based medicine [28–31]. The ACMG core panel of 29 disorders was endorsed in 2005 by the U.S. Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. At the end of 2008, 21 of the 29 disorders had been incorporated by all 50 states although 2 states had not yet implemented expand-

ed screening [32]. Subsequently, an evidence-based review process was established by the Committee to evaluate new candidate conditions for screening [33].

The Health Council of the Netherlands provides recommendations for the National Screening Program as well as advice as to which screening tests are suitable, either for coverage by health payers or paid for by consumers [34]. In 2008 the Health Council issued a report which called for new approaches to evaluate new tests to avoid coverage of unsound screening tests while promoting research into worthwhile screening approaches [2]. The National Screening Program includes cascade screening of relatives for familial hypercholesterolemia (FH), which has been publicly funded since 1994 [6], and newborn screening, which until recently was restricted to PKU, congenital adrenal hyperplasia (CAH), and congenital hypothyroidism. A 2005 Health Council report on newborn screening [35] endorsed 13 additional metabolic disorders and sickle cell disease for which an acceptable screening test was available and for which early treatment could prevent irreparable damage. On January 1st, 2007 the National Screening Program was extended to include these disorders. Cystic fibrosis was advised conditional on a suitably specific test, and a large scale pilot screening study for CF started in 2007 in 4 of the 12 provinces of the Netherlands.

Newborn screening for CF and CAH illustrate the challenges in making evidence-based assessments for genetic screening. In North America most jurisdictions that screen for 1 of the 2 disorders screen for both [9], but in Europe a 2004 survey [8] reported that just 2 countries screened for both CF and CAH, Austria and France. Italy and the United Kingdom screened universally for CF but not CAH. Countries that screened all infants for CAH but not CF included Belgium, the Czech Republic, Germany, the Netherlands, Slovakia, Sweden, and Switzerland. The number of deaths prevented through screening for either disorder is difficult to quantify [36–39]. Conclusive evidence of the magnitude of the preventable burden of early childhood mortality from genetic disorders such as CF or CAH that can result in death without a clinical diagnosis requires case-control studies of stored residual dried blood spot specimens [38].

The one adult-onset genetic disorder for which universal screening has been seriously discussed is type 1 hereditary hemochromatosis (HH), the autosomal recessive disorder with the highest frequency of homozygosity among individuals of European ancestry [40]. HH is associated with elevated iron stores in the majority of homozygous adult males, which can be prevented or re-

duced through regular phlebotomy [40]. However, despite high biochemical penetrance in terms of iron overload, the degree of clinical penetrance or expressivity is limited [41]. The vast majority of cases of type 1 HH are due to the C282Y mutation of the *HFE* gene. Two large population-based studies indicate that only about 3.5% of men who are homozygous for the C282Y mutation develop liver cirrhosis [42, 43]. No country has yet endorsed screening of adults for HH, and evidence-based recommendations have discouraged population-wide screening for *HFE* mutations [44]. Certain specialists call for targeted screening of adult males of Northern European ancestry for HH [40, 45] but without an apparent effect on practice.

### Economic Criteria for Screening Programs

Economic evaluation methods include partial analyses that focus on cost per case or mutation detected and full evaluations that assess health effects as well as costs [46]. The cost of a screening intervention includes the costs of induced diagnostic tests and treatments. The net cost is the total cost of the intervention minus averted costs of care resulting from improved health outcomes. The dominant economic evaluation method that has been used to assess genetic tests is cost-effectiveness analysis, which calculates the ratio of net costs and health outcomes, such as cases of disease or death prevented or life-years gained [47–49]. A cost-utility analysis is a variant in which a preference-based measure of health, usually the quality-adjusted life-year (QALY), is used to combine information on mortality and morbidity [46]. QALYs do not include non-health outcomes such as the perceived value or harm of knowledge of genetic information per se, which may be important aspects of personal and social utility [50]. Because cost-effectiveness and cost-utility analyses are limited in the ability to inform policy decisions, alternative methods of economic valuation of genetic technologies need to be explored [50, 51].

If the averted costs of care exceed the intervention cost, a strategy is said to be dominant or cost saving, and no cost-effectiveness ratio is calculated. Relatively few preventive services, however, are cost saving [52]. Deciding whether a given cost-effectiveness ratio is considered to demonstrate good value for money for an intervention is a challenge [53–58]. In the United Kingdom the National Institute for Health and Clinical Excellence (NICE) generally discourages interventions costing more than

GBP 30,000 per QALY to be funded by the National Health Service [53]. In the United States a comparable figure of USD 50,000 per QALY has long been cited as a threshold for cost-effectiveness, but that lacks empirical or theoretical support [54]. The WHO has endorsed use of a figure of 3 times the gross domestic product per capita as a threshold for cost-effectiveness of health interventions [55], equivalent to roughly USD 133,000 in 2006 [54]. On that basis, a threshold for acceptability of health care costs of EUR 80,000 per QALY has been proposed in the Netherlands [56]. In most countries, including the United States, no body equivalent to NICE makes decisions about screening programs taking cost-effectiveness explicitly into account. For example, interventions that are recommended by the U.S. Preventive Services Task Force are highly variable in terms of cost-effectiveness ratios, with one-fifth estimated to cost more than USD 165,000 per QALY gained [57]. An even wider range of estimated cost-effectiveness ratios are associated with public health programs and policies [58].

Cost-effectiveness considerations appear to have played a little role in influencing the adoption of genetic screening tests. In the United States none of the national groups that have made recommendations relating to genetic or newborn screening have used cost-effectiveness as a criterion [59], as is also the case for the Health Council of the Netherlands [35]. The handful of U.S. states that have set cost-benefit or cost-effectiveness as a criterion have made it sufficiently loose for it to not be restrictive in practice [59]. In the United Kingdom, although cost-effectiveness is a stated criterion for the National Screening Committee [15], it does not appear to have played a determining role in newborn screening decisions. Indeed, a number of disorders for which cost-effectiveness calculations of screening using tandem mass spectrometry appeared promising [18] were not recommended by the National Screening Committee because of concerns about the lack of robust epidemiologic evidence [19, 59]. Although screening policy decisions should be evidence-based, the evidence process is occasionally bypassed for certain policy decisions, such as for cystic fibrosis and hemoglobinopathy newborn screening in England and Wales [59, 60].

Evidence for the cost-effectiveness of expanded newborn screening is mixed. Almost all analyses of screening for medium chain acyl-CoA dehydrogenase (MCAD) deficiency using tandem mass spectrometry conclude that screening is either cost-saving or cost-effective [59, 61, 62]. Because of the lack of robust outcomes data, the cost-effectiveness of screening for CF and CAH is uncertain

[59]. Two U.S. cost-effectiveness analyses of screening for CAH reached conflicting conclusions, in large part because of differences in assumptions about the numbers of deaths averted [61, 63]. Although information on the effectiveness of screening in preventing CF-related deaths will likely remain inconclusive, newborn screening for CF appears cost-effective [64] and may even be cost saving [64, 65].

Because of the small number of cases of clinical disease prevented, population screening for HH using either a DNA test or a biochemical screening test does not appear cost-effective, although cascade testing of first degree relatives might be cost-effective [66]. Biochemical screening of adult males of German ancestry for iron overload, followed by molecular testing for confirmation, appears to display lower cost per life-year gained than molecular screening [66]. However, it is unclear to what extent either approach is likely to be effective in preventing mortality, and the evidence of long-term adherence to preventive phlebotomy is very weak.

### **Ethical Issues in Population Screening for Genetic Disorders**

A first ethical challenge in population screening is how to deal with the requirement of informed consent, particularly in the context of newborn screening. Different positions in this debate have been taken in the United States and in Europe. Almost all U.S. programs mandate that infants be screened and do not require parental consent or even ensure parental awareness [67, 68]. Newborn screening was originally promoted as a mandatory program to ensure universal access, and this model persists in most U.S. states. The majority of U.S. states allow parents to opt out of newborn screening in certain circumstances, particularly for religious reasons, but this fact is not generally made known [69]. Many ethicists have questioned the justification for mandatory screening, even for disorders such as PKU, and have instead called for promotion of informed participation by parents in newborn screening or genetic testing in children [70, 71].

Few non-U.S. programs mandate screening of newborns for genetic diseases, although the majority of programs do not require written consent. In the Netherlands, for example, screening has always been voluntary, but prior to the recent expansion of screening, parents were provided with limited information about the tests and were not informed of the option to decline screening

[35, 72]. In France, bioethics legislation requires written consent before a specimen is collected for DNA analysis, and when IRT (immunoreactive trypsinogen)/DNA screening for CF was introduced in 2002, a new written consent protocol had to be introduced [73]. When asked to consent on behalf of their child's best interests, most parents do; by the end of the first year of screening for CF in France, 99.8% of parents gave written consent.

Obtaining truly informed consent during the perinatal period is not feasible due to stress and the multiplicity of tests and procedures. Information about screening disorders and tests must be provided during prenatal care if parents are to be aware of screening and their options [33, 69]. Whether explicit written consent should be required or implicit opt-out consent is sufficient is a matter of debate. For disorders for which early identification can prevent irreversible harm, parents and experts generally appear to support opt-out consent [72]. One issue on which experts and parents are agreed is the need to improve parental education about newborn screening prior to labor and delivery in order to allow for informed parental understanding, decision making, and participation [31, 35, 72].

A burning policy question in newborn screening, particularly in the United States, is whether and how to provide voluntary screening for disorders for which the evidence of benefit to the child is less compelling, either because of lack of direct evidence or because the primary motivation for screening is to provide information to parents [69, 74, 75]. The President's Council on Bioethics [31] has suggested a two-tiered approach similar to the approach implemented in Massachusetts in 1999, in which verbal consent is obtained for screening for disorders included on an optional panel [76]. The Council proposed an approach that would involve mandatory screening for conditions that fulfill the traditional public health criteria, including high-quality evidence of benefit, and a voluntary pilot screening program for selected conditions that do not yet meet these criteria. Whether it would be suitable to include disorders for which efficacious treatment is not currently available or conditions in which the natural history is not well-understood in voluntary pilot screening panels is unresolved.

Not all disorders are necessarily suitable for population-based pilot screening studies, even if a screening test is available and there are advocates of screening. Pilots can generate further evidence before a final decision about extending the scope of a screening program, but they should only be undertaken if there is good reason to believe that the benefits will outweigh the harms [77]. Pi-

lot screening studies require substantial preparation in order to be conducted responsibly, including activities to inform parents, train health professionals, and devise protocols for the entire system from laboratory to treatment. For other disorders it may be advisable to conduct additional observational studies or small-scale pilot studies with strong clinical research protocols rather than pilots within the newborn screening program.

Another critical ethical challenge facing any population screening program is to strike the right balance between the expected benefits for certain individuals and the potential harms that might accrue to others [4, 5, 16, 31, 74]. In particular, false-positive screening results can cause unnecessary anxiety, require additional diagnostic tests, and lead to unnecessary treatments that are not necessarily benign; also, the misunderstanding of genetic risk information can influence life planning decisions in unintended ways [31, 75, 78–80]. If the benefits resulting from early identification are dramatic and well-established, they can more easily outweigh such concerns than if the expected benefits are more modest or not rigorously documented [26, 31]. Such concerns provide the justification for evidence-based groups such as the U.S. Preventive Services Task Force, the U.K. National Screening Committee, and the Health Council of the Netherlands.

The appropriate balance between sensitivity and specificity depends on the expected benefit of detection [26]. For screening tests which are literally a matter of life and death, it is reasonable to minimize false negatives regardless of the number of false positive screening results [74]. Despite concerns by some observers that screening using tandem mass spectrometry might result in large numbers of false positives that could overwhelm systems of care [78], only a modest increase in positive screening results has been reported in U.S. programs employing this technology [81].

For screening tests for which the expected benefit is relatively moderate, efforts should be made to keep the number of false positive screens to a minimum [26, 74]. For example, CF newborn screening strategies that refer children for further testing based on elevated immunoreactive trypsinogen (IRT) from a single specimen face the trade-off of either very high false positives or numerous missed cases. The primary alternative strategy, which involves testing a DNA mutation panel on the same specimen following an elevated IRT, reduces the number of children who need further testing for a given IRT cutoff but raises challenges associated with carrier identification and the communication of genetic information [79].

In order to detect infants with CF who do not have one of the common mutations included in the mutation panel, certain U.S. screening programs refer infants with very high IRT values for sweat testing even if no mutation is detected, but the positive predictive value of such testing is extremely low [82, 83].

Carrier screening poses additional ethical challenges [5, 11, 31]. The Health Council of the Netherlands proposed that the National Screening Program incorporates preconception carrier screening for CF and hemoglobin diseases [84]. Challenges include whether risk differentiation in offering of screening by population of origin would be considered acceptable and whether other disorders (e.g., Tay-Sachs disease, fragile X syndrome) should also be included in preconception counseling and screening [2]. Pilot studies need to be undertaken to demonstrate low risks of persistent anxiety and misunderstanding of test results and to assess the acceptability of testing to the public [85].

Ethnically-targeted screening also raises ethical issues. Offering screening to individuals on the basis of perceived ancestry faces challenges in deciding how ethnicity is determined and the potential for discrimination caused by labeling. Ethnic targeting may be particularly problematic if public funds are used. Prenatal hemoglobinopathy screening in the National Health Service in England and Wales is offered selectively to women based on their perceived ethnicity [86]. The same is true in the United States, where prenatal screening is conducted privately. Problems in accurately identifying ethnicity and ancestry and the potential for stigmatization have led some to call for the universal offering of testing [82] and others to propose self assessment of ancestry-based risk [87].

Targeting of newborn screening for sickle cell disease in the United States and United Kingdom was calculated to cost less per case detected than universal screening in areas with a low prevalence of the disorder [60]. However, practical difficulties in accurately assessing risk based on ancestry and in separating neonatal dried blood spot specimens for high-throughput laboratory analysis offset such potential advantages. The ethical and political difficulties in restricting access to a public screening program also appear to have played a crucial role in policy decisions in both countries to recommend universal screening for hemoglobin disorders in newborns [59, 60].

The practical and ethical implications of molecular screening strategies include the fact that certain individuals are identified as carriers of an autosomal recessive

disorder. Indeed, this is the primary rationale for reproductive testing strategies [88]. For newborn screening, carrier identification is an incidental by-product of screening to detect individuals at risk of developing clinical disease [79]. For example, in the United States, approximately 50 children are identified as carriers for each child diagnosed with sickle cell disease [89]. A smaller proportion of carriers are identified through CF newborn screening using DNA as a second-tier test because most carriers have normal IRT values [82]. Although relatively few carriers are detected, CF carrier detection is controversial because it is not an inevitable by-product of screening [79].

Policies vary regarding the reporting of carrier status. The Health Council of the Netherlands argues that the interest of the family should serve as the ethical ground for disclosure of carrier status as an incidental finding [2, 84]. In the United States, newborn screening programs routinely disclose carrier information to either physicians or families but without consistency in the reporting of information or the provision of genetic counseling [70, 89–92]. Not surprisingly, the implications of carrier status are often not adequately communicated or understood by families [93–95]. Furthermore, it is uncertain how often the information is retained for future use or whether the child ever receives genetic counseling. Programs in other countries sometimes choose not to disclose carrier status on the grounds of lack of immediate medical relevance and the view that testing violates the rights of privacy, confidentiality, and autonomous decision-making of the individual [96].

Another fairness issue is that mutation panels have differential sensitivities in different ethnic groups. This issue has arisen in particular with regard to molecular screening for hereditary hemochromatosis and cystic fibrosis [95]. Mutations incorporated in screening for both diseases are most commonly found in individuals of European origin. Individuals with cystic fibrosis or iron overload disease of other origins are less likely to be detected by molecular screening. In contrast, biochemical screening strategies for the same disorders do not discriminate on the basis of ancestry [79, 97].

## Conclusion

Genetic screening policies have typically been determined by technological capability, advocacy, and medical opinion rather than through a rigorous, objective, evidence-based review process. Decision making should ex-

PLICITLY take into account the principles of ethics and opportunity costs [26, 30]. Costs have an ethical dimension because of the opportunity cost in terms of foregone health improvements if funding for other services is displaced [2, 30]. In particular, screening programs may induce further diagnostic tests and treatments that are not necessarily benign but nevertheless costly. Nonetheless, policy makers and clinicians are often reluctant to consider cost-effectiveness in health care prioritization [59, 98, 99].

We do not imply that there is a single ethical perspective or that economic analysis will determine which tests should or should not be conducted. Rather, decision makers should address ethical and economic issues alongside scientific evidence and involve ethicists and economists alongside other types of experts and representatives of health care payers, providers, and the public. It is imperative that policy development in public health genomics is transparent and open to stakeholder engagement [100] and that full consideration is given to scientific evidence, ethics, and economics.

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