

# Genetic screening

## A primer for primary care

Anne Andermann MD DPhil CCFP FRCPC Ingeborg Blancquaert MD PhD

**G**enetic screening is often touted as an important vehicle for translating genetic and genomic advances into population health gains.<sup>1,2</sup> This has contributed to increasing pressures from various sources to introduce or expand population-based genetic screening programs.<sup>3,4</sup> However, the availability of new tests for genetic screening is outpacing our ability to adequately integrate these into services, as the epidemiologic data, regulatory frameworks, infrastructure, clinical capacity, and public debate often lag far behind.<sup>5-9</sup>

Deciding whether or not to introduce or expand population-based screening programs is complex and involves systematic analysis and synthesis of different kinds of evidence to evaluate the risks, benefits, and costs of screening from various viewpoints.<sup>10</sup> Because the introduction of new screening tests involves more than scientific judgment alone, there has been a call for greater public engagement with and debate about the moral issues and societal values at stake. Far-reaching implications have indeed been described, ranging from the psychological effects of living with risk and the potential for discrimination, to being denied insurance or suffering loss of employment. The technological imperative and the increasingly broadening conception of benefit are rapidly increasing the number of screening tests being offered,<sup>11</sup> in spite of the fact that each has its own distinct implications and needs to be considered on a case-by-case basis. This primer was therefore developed to assist primary care professionals in the complex task of discussing the growing number of genetic screening services with their patients and with the communities that they serve, thereby facilitating informed choices.<sup>12</sup> In particular, the primer begins by clarifying the nature of a *genetic screening program*, then explores the implications

### Abstract

**OBJECTIVE** To provide a primer for primary care professionals who are increasingly called upon to discuss the growing number of genetic screening services available and to help patients make informed decisions about whether to participate in genetic screening, how to interpret results, and which interventions are most appropriate.

**QUALITY OF EVIDENCE** As part of a larger research program, a wide literature relating to genetic screening was reviewed. PubMed and Internet searches were conducted using broad search terms. Effort was also made to identify the gray literature.

**MAIN MESSAGE** Genetic screening is a type of public health program that is systematically offered to a specified population of asymptomatic individuals with the aim of providing those identified as high risk with prevention, early treatment, or reproductive options. Ensuring an added benefit from screening, as compared with standard clinical care, and preventing unintended harms, such as undue anxiety or stigmatization, depends on the design and implementation of screening programs, including the recruitment methods, education and counseling provided, timing of screening, predictive value of tests, interventions available, and presence of oversight mechanisms and safeguards. There is therefore growing apprehension that economic interests might lead to a market-driven approach to introducing and expanding screening before program effectiveness, acceptability, and feasibility have been demonstrated. As with any medical intervention, there is a moral imperative for genetic screening to do more good than harm, not only from the perspective of individuals and families, but also for the target population and society as a whole.

**CONCLUSION** Primary care professionals have an important role to play in helping their patients navigate the rapidly changing terrain of genetic screening services by informing them about the benefits and risks of new genetic and genomic technologies and empowering them to make more informed choices.

### Résumé

**OBJECTIF** Fournir un guide original aux professionnels des soins primaires qui sont de plus en plus appelés à discuter avec leurs patients des tests génétiques de plus en plus nombreux désormais disponibles, et de les aider à prendre des décisions éclairées sur l'intérêt de participer à ce genre de dépistage, sur la façon d'interpréter les résultats et sur le choix des interventions les plus appropriées.

**QUALITÉ DES PREUVES** Dans le cadre d'un programme de recherche plus large, on a effectué une revue minutieuse de la littérature sur le dépistage génétique. On a consulté PubMed et Internet à l'aide d'un vaste éventail de termes de recherche. On s'est aussi efforcé d'identifier la documentation parallèle.

**PRINCIPAL MESSAGE** Le dépistage génétique est un programme de santé publique qui est systématiquement offert à une population spécifique de personnes asymptomatiques, dans le but d'offrir aux personnes à risque élevé des mesures préventives, un traitement précoce ou des choix concernant la reproduction. Pour profiter des avantages supplémentaires du dépistage comparativement aux soins cliniques courants, et prévenir des préjudices involontaires tels que de l'anxiété ou une stigmatisation inutiles, il faut bien concevoir et exécuter les programmes de dépistage, notamment les méthodes de recrutement, les services d'information et de counseling, le moment du dépistage, la valeur prédictive des tests, les interventions disponibles, et la présence de mécanismes d'encadrement et de sauvegardes. On craint donc de plus en plus que des intérêts économiques puissent mener à une démarche axée sur le marché visant à adopter et élargir les programmes de dépistage avant que ne soient démontrés leur efficacité, leur acceptabilité et leur faisabilité. Comme pour toute intervention médicale, il est moralement impératif que le dépistage génétique comporte plus d'avantages que de risques, du point de vue non seulement des individus et des familles, mais aussi de la population ciblée et de la société dans son ensemble.

**CONCLUSION** Les professionnels des soins primaires ont un rôle important à jouer pour aider leurs patients à comprendre le domaine en rapide évolution des services de dépistage génétique, en les informant des avantages et des risques des nouvelles technologies génétiques et génomiques, et en les rendant aptes à faire des choix plus éclairés.

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of genetic screening for different types of genetic conditions using different screening tests at different phases of the life cycle, and finally highlights key features of the decision-making process.

### Quality of evidence

As part of a larger research program, a wide literature relating to multiple aspects of genetic screening policy-making was reviewed. PubMed and Internet searches were conducted using broad search terms such as *genetic screening*, *prenatal screening*, *newborn screening*, and *population-based screening*. Identified abstracts were scanned for relevance. Reference lists of retrieved documents were used to identify further sources. A special effort was also made to identify the gray literature through attendance at genetics conferences and discussions with key informants in the field.

### Genetic diseases and hereditary diseases

Diseases caused by alterations in the genetic makeup of an individual (eg, single-gene mutations, chromosomal aberrations) are considered *genetic diseases*.<sup>13</sup> For instance, cancer is a genetic disease resulting from an accumulation of genetic mutations over time. However, not all genetic diseases are hereditary. Only diseases passed down from parents to offspring, according to laws first described by Gregor Mendel in the 19th century, are *hereditary diseases*.<sup>14</sup> Thus, although cancers are genetic diseases, less than 10% or 20% are due to inherited predispositions that can be transmitted from one generation to the next.<sup>15</sup>

Traditionally, the discourse on genetic diseases referred to rare single-gene Mendelian conditions, which are both genetic and hereditary, often causing severe disability and death at an early age.<sup>16</sup> However, discussion of genetic diseases is becoming increasingly complex as a growing number of genetic alterations are being discovered for several common late-onset diseases with complex, multifactorial inheritance, such as the nonfamilial forms of cancer, type 2 diabetes, heart disease, and many psychiatric conditions.<sup>17</sup>

### Single-gene diseases and complex genetic diseases

Most diseases result from a combination of genetic and environmental factors.<sup>18</sup> There is, however, an etiologic spectrum on which diseases at one end are mostly due to genetic factors and diseases at the other end are mostly due to environmental factors.

At the “genetic” end of the spectrum, there are more than a thousand *single-gene diseases* (eg, Huntington disease, cystic fibrosis, and hemochromatosis),<sup>19</sup> which share certain features: they tend to be rare conditions; they are inherited in a Mendelian fashion; and genetic factors are strong determinants of the disease.<sup>16</sup>

At the “environmental” end of the spectrum, *multifactorial* or *complex genetic diseases* (eg, heart disease, psychiatric conditions, and cancers) are caused by the interplay of multiple low-penetrance genes with various behavioural and environmental factors.<sup>17,20</sup>

Although there are high expectations that *personalized medicine* could be used to screen individuals for multiple low-penetrance disease genes associated with common late-onset conditions, this remains highly controversial.<sup>21-23</sup> For now, genetic screening might be most promising for rare diseases, as more than 80% are single-gene diseases, each with a strong genetic basis, inherited in a more predictable fashion.

### Rare diseases and orphan diseases

*Rare diseases* have been defined as having a low prevalence of less than 1 in 2000.<sup>24</sup> There exist between 5000 and 7000 distinct rare diseases that together affect between 6% and 8% of the world's population, including an estimated 54 million people in Europe and North America combined. Thus, taken together, rare diseases are in fact not so rare.<sup>25</sup>

Owing to the low prevalence of each disease in isolation, however, rare diseases have not traditionally been considered a public health concern. Some progress has been made,<sup>26</sup> but it remains difficult to get rare diseases onto the agendas of policy makers and pharmaceutical companies.<sup>27,28</sup> Many rare diseases are therefore also *orphan diseases*, which receive little attention in terms of research focus, market interest, and public health policies.<sup>27,29</sup> Special efforts are needed to reduce morbidity and mortality related to orphan diseases.<sup>30</sup>

### Screening as a strategy to improve health outcomes

Screening forms part of a continuum of approaches for improving population health, ranging from health promotion and disease prevention to treatment and rehabilitation.<sup>31</sup> *Screening* has been defined as a health service in which members of a specified population, who do not necessarily perceive themselves to be at risk of a disease or its complications, are asked a question or offered a test with the aim of identifying those individuals who are more likely to be helped than harmed by further tests or treatments.<sup>32</sup>

Screening is known in public health terms as a *secondary prevention strategy*,<sup>33</sup> which identifies disease before symptoms develop, as early intervention might lead to improved health outcomes. Such benefits do not always occur, however, and screening can also have disadvantages.<sup>34-36</sup> Many factors must be considered, often through the use of established criteria,<sup>37</sup> to determine whether or not to introduce or expand screening programs.

### Genetic screening

*Genetic screening* refers to screening for genetic diseases;

however, the term is not used in a consistent manner.<sup>38</sup> Depending on how genetic screening programs are organized, the recruitment strategies used, the timing of screening, the predictive value of the screening tests, and the interventions available for those with positive results, there can be very different activities involved with a range of implications.

*Genetic screening* is broadly defined here as a systematic program offered to a specified population of asymptomatic individuals whereby a variety of test methods can be used to make a risk estimate regarding an inherited predisposition to disease, to detect an inherited disease at an early stage, or to make a risk estimate regarding the possibility of transmitting a disease to offspring, for the purpose of disease prevention, early treatment, or family planning.

### Genetic screening programs

*Genetic screening programs* are a type of public health program.<sup>39</sup> Public health programs are systematically offered to most or all members of a specified population, with the aim of delivering a net benefit to the population, as well as benefits to individuals.<sup>40</sup>

Genetic screening involves more than just tests, but rather encompasses a complex and systematic program of services offered to a defined population who are informed of the potential risks and benefits through extensive education and counseling. Genetic screening programs thus require coordination among the testing, the clinical services, and the program management levels to enable the overall objectives of the program to be achieved and to ensure accountability.<sup>41</sup>

### Genetic screening recruitment strategies

In *mass screening* (Figure 1), a test is offered to all individuals within a defined target population who are recruited through systematic outreach efforts; in *opportunistic screening*, individuals are recruited when they consult the health system for unrelated medical services.<sup>42</sup> Genetic screening should not be confused with *genetic testing*,<sup>43</sup> which is part of a diagnostic workup within a clinical setting for individuals who present with health-related

concerns. *Cascade screening*, however, which involves the systematic identification and testing of asymptomatic relatives of those affected by a genetic disorder or previously identified as a carrier,<sup>13</sup> constitutes a gray zone between population-based genetic screening and genetic testing in a clinical setting.

### Genetic screening tests

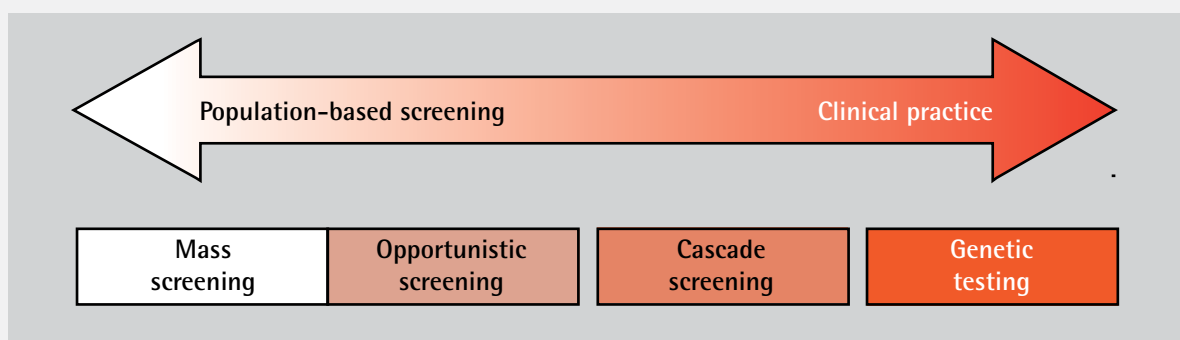
Genetic screening tests can involve molecular,<sup>33</sup> biochemical,<sup>38</sup> and other types of analyses, or even the use of family history questionnaires,<sup>44</sup> to predict which individuals are at risk of developing or transmitting (or both) a genetic condition.<sup>45</sup> Some tests are strong predictors of disease occurrence,<sup>46</sup> but many have a high degree of uncertainty. It can be difficult for those who have positive screening results to decide how best to proceed, as the proposed interventions vary greatly depending on the disease in question, they are not always highly effective, and might also involve certain risks.<sup>47</sup>

### Predictive value of genetic tests

Not all genetic tests have the same predictive value. This largely depends on whether the disease is caused by a single gene or chromosomal abnormality, as opposed to complex gene-gene and gene-environment interactions. *Penetrance* is a way of quantifying to what extent a given genetic alteration will be expressed as signs and symptoms of disease.<sup>48</sup> The greater the penetrance, the more likely an individual carrying a genetic alteration will develop the disease and become symptomatic. Genetic tests can thus be classified into *presymptomatic*, *predisposition*, and *susceptibility tests*.

**Presymptomatic tests.** Presymptomatic tests (eg, for Huntington disease)<sup>49</sup> test for rare conditions caused by single genes with autosomal dominant inheritance and very high penetrance (eg, more than 90% of those with the genetic alteration will develop the disease during their lifetimes). Nonetheless, the severity of the disease and the age at onset of symptoms can vary (ie, as a result of genotype-phenotype heterogeneity).

**Figure 1. Genetic screening continuum**



**Predisposition tests.** Predisposition tests (eg, for hereditary breast or ovarian cancer)<sup>50</sup> test for rare forms of otherwise common conditions that in a small subset of cases (usually less than 5% or 10%) are each caused by a single gene with autosomal dominant inheritance and an intermediate level of penetrance (eg, approximately 20% to 80% of those with the genetic alteration will develop the disease).

**Susceptibility tests.** Susceptibility tests (eg, for heart disease)<sup>51</sup> test for common conditions caused by complex gene-gene and gene-environment interactions, in which each individual gene has a low penetrance (eg, 5% or 10% of those with the gene will develop the disease). The overall risk profile for a set of markers might have a higher predictive value, although it still remains to be demonstrated whether genetic information provides any added value to more traditional environmental and behavioural risk factors of common chronic diseases (eg, advancing age, sedentary habits, obesity, smoking) and whether it will be useful in promoting preventive behaviours.

### Carrier screening

In autosomal recessive conditions, offspring are only at risk of becoming ill if they receive 2 copies of a mutant gene, 1 from each parent.<sup>13</sup> Generally, however, the birth of an affected child comes as a surprise, as parents are often healthy carriers, with 1 normal copy of a gene and 1 mutated copy.<sup>52</sup> If both parents are carriers, there is a 1 in 4 risk that the child will be affected by the disease (depending on the disease penetrance and environmental factors) and a 1 in 2 risk that the child will be a carrier. In *carrier screening*, a test is used to identify couples who might be at risk of transmitting a genetic condition to their offspring.

### Timing of genetic screening

The rationale underlying why certain conditions are screened for at specific times during the life course is generally linked to the optimal time for intervening that maximizes benefit and minimizes harm. Thus, the timing of screening is often used to divide genetic screening programs into 3 main types: *preconception screening* (ie, before having children), *prenatal screening* (ie, during pregnancy), and *newborn screening* (ie, after birth).

Preconception, prenatal, and newborn screening programs have long existed. More recently, screening for adult-onset conditions has been envisioned. However, whether such programs (eg, screening for early-onset Alzheimer disease or hereditary hemochromatosis) should be developed at all is highly controversial, largely owing to uncertainty about the predictive value of tests, the lack of preventive and early treatment options, and the fact that there is as yet no proven added benefit compared with standard care. For now,

population-based genetic screening programs for adult-onset conditions are limited to the research context. However, with advances in knowledge and technology, this area might evolve rapidly.

**Preconception screening.** Preconception screening occurs before having children, and generally involves screening for carriers or identifying couples in which both individuals are asymptomatic carriers of a recessive condition (eg, cystic fibrosis),<sup>53</sup> to better predict whether their future offspring could be affected and to offer reproductive choices. Carrier screening is generally recommended in the preconception period, as it offers the widest range of reproductive options. In practice, however, carrier screening also occurs during pregnancy, when individuals are more conscious of reproductive issues. It would even be possible to determine carrier status in the newborn period; however, there are many ethical issues involved, and the general consensus is that screening newborns should only be carried out if it is directly relevant to their health and well-being during infancy and childhood.<sup>54,55</sup> Carrier screening programs are generally limited to specific high-risk groups, such as Tay-Sachs screening in Ashkenazi Jewish<sup>56</sup> and French Canadian populations. However, the primary care team can also identify couples planning to start families who have family histories of hereditary disease (particularly for diseases in which the gene is known) and who would be interested in referral to genetic counseling services for more detailed information and nondirective counseling tailored to their specific situations.

**Prenatal screening.** Prenatal screening, also known as *antenatal screening*, is carried out during pregnancy and generally identifies whether an unborn fetus has or is at risk of having a congenital condition (eg, chromosomal anomalies, such as Down syndrome, and structural anomalies, such as neural tube disorders or cardiac malformations).<sup>57</sup> The parents generally do not have identifiable genetic risk factors for these conditions; rather these conditions are associated with certain environmental influences (eg, advanced maternal age for Down syndrome, insufficient maternal intake of folic acid for neural tube disorders). Prenatal screening often involves a number of preliminary screening tests, followed by a confirmatory diagnostic test for those identified as high risk. The primary care team plays a key role in informing pregnant couples of the availability of such screening tests, which are generally time-sensitive. Prenatal screening offered to the general population should not be confused with clinical testing or cascade screening offered during pregnancy to a parent who might be at increased risk on account of having an affected relative with a single-gene disorder, for instance. Although here again, the primary care team can identify candidates who warrant referral

to genetic counseling services by eliciting detailed family histories with respect to hereditary disease.

**Newborn screening.** Newborn screening, also known as *neonatal screening*, is usually carried out shortly after a baby is born and identifies whether the newborn is at risk of developing a disease in childhood for which prevention or early treatment exists (eg, a low-phenylalanine diet for phenylketonuria or hormone-replacement medication for congenital hypothyroidism).<sup>58</sup> Blood-spot screening has existed in many countries around the world for several decades. The most common form of newborn screening occurs a few days after birth, when a drop of blood from the heel of the baby is placed on a piece of absorbent paper (known as a *Guthrie card*) to be analyzed using traditional biochemical techniques or newer tandem mass spectrometry methods.<sup>59</sup> In some countries, newborn screening is mandatory by law, and in other jurisdictions it is universal with implicit consent (with the option to opt out). Originally, diseases being screened for had very severe consequences (ie, profound mental retardation or death), which could be easily prevented if detected early with minimal or no risk to the child. However, over the years, the list of conditions being screened for has expanded from the initial 2 mentioned above to 29 conditions or more in certain jurisdictions,<sup>60</sup> making the estimation of risks and benefits even more complex.<sup>61</sup> This rapid expansion also poses a challenge for primary care teams who will be increasingly called upon to participate in the process of informing pregnant couples of what to expect after the birth and, at the very least, to make them aware of the existence of screening programs. Many new parents are not even aware that their newborns are being screened, as historically the benefits so greatly outweighed the risks that consent was considered to be implicit. As programs and times change, keeping up to date and informing parents will be increasingly important.

## Decision making

As with any medical intervention, there is a moral imperative for genetic screening to do more good than harm. Introducing new genetic tests into clinical practice for diagnostic purposes when patients present with clinical indications (eg, symptoms of disease or high risk owing to family history) entails complex consideration of the analytical validity, clinical validity, and clinical utility of the tests.<sup>62,63</sup> However, the moral imperative is even more pronounced in the case of screening, which involves offering unsolicited services to asymptomatic individuals at baseline risk of developing the disease.

Population-based genetic screening has both individual and collective implications, thus the balance of risks and benefits has to be considered not only from the perspective of individuals and families, but also from that of the target population and of society as a whole. Even when there is scientific evidence that screening

provides an added benefit to individuals and families, implementing a population-based screening program requires evaluation of the potential for the realization of these benefits and the minimization of risks in a given context, as well as consideration of the opportunity cost of funding the screening program.

## Conclusion

The benefits of genetic screening programs stem from providing high-risk individuals with prevention, early treatment, or reproductive options. As science advances, making it possible to screen for a growing number of genetic conditions, it is important to consider the added value of genetic screening, as compared, for instance, to addressing the social, behavioural, and environmental determinants of health.<sup>64,65</sup>

Critics are concerned that the “geneticization” of health and “routinization” of genetic information are being used to justify the introduction of new technologies before their potential effects are fully understood.<sup>66-68</sup> There are concerns that this might fail to improve health at a population level, that it could draw attention away from interventions with greater potential for disease prevention, and that it might exacerbate health inequities.<sup>69</sup>

There is also growing apprehension that economic interests, with additional pressures from consumer groups,<sup>70</sup> might lead to a market-driven approach to genetic screening policy development<sup>71</sup> before the value of screening has been demonstrated. Governments must therefore balance the many different perspectives and needs of society, while promoting greater equity and supporting vulnerable groups,<sup>72</sup> such as individuals and families bearing the burden of rare and orphan diseases.

Even in genetic screening for rare diseases, there are many complex considerations to take into account. Risk information pertaining to genetic conditions, especially those caused by highly penetrant single genes, can have important implications for family members who might also be at risk.<sup>73-75</sup> In some instances, entire communities have been subjected to discrimination or stigmatization, particularly when there was insufficient community involvement or education when developing screening programs. Therefore, to avoid the premature introduction of new technologies and to ensure that concerns about genetic screening are adequately addressed, there needs to be a more “balanced and informed approach to the development of genetic policies and regulations”<sup>76</sup> through greater consultation, transparency, and public participation.<sup>77</sup> Primary care professionals have an important role to play in helping their patients navigate the rapidly changing terrain of genetic screening services, by informing and empowering them on how to maximize the benefits of new genetic and genomic technologies, where appropriate, while minimizing the risks.<sup>78</sup>



**Dr Andermann** is a Visiting Lecturer and Research Scholar at the Woodrow Wilson School of Public and International Affairs at Princeton University in Princeton, New Jersey, and an Assistant Professor in the departments of family medicine and epidemiology, biostatistics and occupational health at McGill University in Montreal, Que. **Dr Blancquaert** is Scientific Director of APOGEE-Net in Montreal and Adjunct Clinical Professor in the Department of Social and Preventive Medicine at the University of Montreal.

## Contributors

**Drs Andermann and Blancquaert** contributed to the literature search and the preparation of the article.

## Competing interests

None declared

## Correspondence

**Dr Anne Andermann**, Family Medicine Centre, St Mary's Hospital, McGill University, 3830 Lacombe Ave, Montreal, QC H3T 1M5; telephone 514 734-2677; e-mail [anne.andermann@mcgill.ca](mailto:anne.andermann@mcgill.ca)

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## EDITOR'S KEY POINTS

- The growing number of genetic tests now available are rapidly being incorporated into genetic screening services—both public and private—often before the far-reaching implications of such tests can be fully determined.
- Patients are faced with an increasing number of complex decisions about whether to participate in genetic screening, how to interpret their test results, and what action to take in the event of positive or indeterminate result. Primary care professionals will increasingly be called upon to help their patients assess whether there is an added benefit from screening that outweighs the risks, as well as to better navigate the screening process.
- To promote informed and balanced decision making, this primer explains key terms and concepts related to genetic screening and highlights the often complex implications of the type of condition screened, the timing of screening, the recruitment strategy used, the predictive value of the screening tests, and the effectiveness of interventions offered to those with positive test results.

## POINTS DE REPÈRE DU RÉDACTEUR

- Les multiples tests génétiques désormais disponibles sont rapidement incorporés aux services de dépistage génétique – tant publics que privés – souvent avant même qu'on en connaisse toutes les implications.
- Les patients sont appelés à prendre de plus en plus de décisions complexes concernant une éventuelle participation au dépistage génétique, la façon d'interpréter les résultats des tests et le choix des mesures à adopter en cas de résultat positif ou incertain. Les professionnels des soins primaires seront de plus en plus appelés à aider leurs patients à bien comprendre le processus de dépistage et à décider s'il comporte plus d'avantages que de risques.
- Dans le but de favoriser une décision équilibrée et bien informée, ce premier guide explique les termes et concepts-clés du dépistage génétique, et rappelle les implications souvent complexes spécifiques à chaque type de condition dépistée, le moment opportun pour le dépistage, la stratégie de recrutement utilisée, la valeur prédictive des tests génétiques et l'efficacité des interventions offertes en cas de résultats positifs.

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