The Quality of Genetic Screening: An Integral Approach

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Key Points

- Genetic screening, as opposed to diagnosis, is offered to persons not known to have an indication for testing based on symptoms or increased risk.
- Several frameworks of criteria are available to evaluate whether the benefits of genetic screening outweigh the drawbacks that it always also entails.
- A reliable and valid screening method has a high analytic and clinical validity, implying a high sensitivity and specificity; the clinical utility of a screening method reflects whether screening helps to prevent or reduce the burden of disease, and whether the benefits to participants outweigh the drawbacks.
- Advantages to participants may go beyond treatment and prevention; especially when genetic screening is applied for reproductive reasons and for untreatable conditions.
- Ethical and economical aspects have to be integrated in a comprehensive approach to the evaluation of the quality of genetic screening programmes.

Keywords Genetic screening · Screening criteria · Clinical utility · Autonomy · Cost-effectiveness

Introduction

Many chapters in this book concern genetic testing for diagnostic purposes. Genetic diagnosis is offered to patients who have symptoms of disease, to family members of patients already diagnosed, or (in prenatal or pre-implantation genetic diagnosis) to prospective parents with a known elevated risk of having a child with a

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particular disease. Genetic screening, by contrast, is offered to persons not known to have an indication for testing based on either symptoms, family history or the outcome of prior pregnancies. This chapter concerns the quality of genetic screening programmes. We propose an integral approach in which quality refers not only to test characteristics and laboratory standards, but also to organisational issues and to the ethical, legal, and social (ELSI) aspects of genetic screening (De Wert and Dondorp 2006; Health Council of the Netherlands 2008).

Genetic screening can be either reproductive (aiming at enlarging reproductive choice for would be parents) or non-reproductive (aiming at providing opportunities for treatment or prevention). Reproductive genetic screening can be performed either prior to pregnancy (preconceptional screening for carrier status of autosomal recessive disease) or during pregnancy (such as prenatal aneuploidy screening). Genetic screening of IVF-embryos has until now mainly been done in view of deselecting embryos with chromosomal defects that would limit their chances of succesful implantation. However, the current approach to this is not evidence based (Fritz 2008).

Neonatal screening aims at reducing the burden of metabolic and other usually autosomal recessive childhood diseases by providing opportunities for timely treatment (e.g. dietary measures). However, the recurrence risk of 1:4 entails that parents of an affected child may also have a reproductive interest in neonatal screening that is not limited to finding treatable disease. Genetic screening later in life usually takes the form of screening within families affected by dominant disorders or monogenic subtypes of common disorders, such as familial hypercholesterolemia or colon cancer ("cascade screening"). Whereas neonatal screening is offered as population screening to all newborns, cascade screening is a systematic offer to family members at risk of a dominant disorder (sometimes with reduced penetrance) or a recessive disorder (hemochromatosis in brothers/sisters; fragile X carriership in female relatives). Finally in families with chromosomal translocations a systematic offer of karyotyping is often made.

A future development is genetic profiling of a person's risk of a larger or smaller range of multifactorial diseases. Although genetic susceptability tests for this purpose are already on sale, the scientific foundation of most of these tests is still inadequate (Janssens et al. 2008). Although the commercial provision of such tests to the general public falls under the definition of screening as understood in this chapter, readers are referred to chapter "US Oversight and Regulation of Genetic Testing" for a more detailed discussion of direct-to-consumer testing. Nor will we deal with genetic screening for non-health related purposes (e.g. forensic screening), as that field is outside the scope of this book.

Integral Approach to Quality

Contrary to popular belief, screening is not always beneficial. Whether the benefits that screening may have (in terms of health gains or the provision of reproductive choice) outweigh the drawbacks it always also entails (impact of false-positive or

negative outcomes, overdiagnosis, burdening of the health care system, stigmatization of vulnerable groups), very much depends on the quality of the whole chain of elements that together make up a screening programme. This approach fits in with a tradition of evaluating screening programmes using a framework of criteria the first version of which was drawn up by Wilson and Jungner for the World Health Organisation in 1968, but which has been continuously refined and adapted to new developments ever since. Important contributions to this tradition were made by the Council of Europe, the European Society for Human Genetics and, on a national level, by advisory bodies such as the British National Screening Committee, the French National Agency for Accreditation and Evaluation in Health Care (ANAES) or the Health Council of the Netherlands. A notable contribution to enhancing the implemention of this framework with respect to the evaluation of new genetic tests was made by the international ACCE project (Analytical validity, Clinical validity, Clinical utility and ELSI aspects) at the initiative of the American Centers for Disease Control and Prevention (CDC). In this chapter, we will present some crucial elements of this widely supported normative framework as discussed in a recent report from the Health Council of the Netherlands (2008). We were involved in drawing up this report.

Methods of Genetic Screening

Screening has to be simple, fast and cheap. Initial tests usually give information about an increased risk, but no certainty. A positive (or unfavourable) screening result will often be followed by a diagnostic test. The initial tests used in genetic screening programmes often measure proteins or metabolites and only rarely involve DNA technology. In prenatal screening for Down syndrome in the first trimester free beta human chorionic gonadotropin and pregnancy-associated plasma protein-A are assessed in maternal serum. In neonatal screening analysis of the metabolite octanoylcarnitine on newborn screening blood spot cards by tandem mass spectrometry is used to identify medium chain acyl Co-A dehydrogenase deficiency. A combination of two metabolites is used in phenylketonuria screening (phenylalanine and tyrosine). The combination of a metabolite and an enzyme are assessed in galactosemia screening (total galactose and galactose-1-phosphate uridyltransferase). Also imaging techniques can be used in screening programmes. In Down syndrome screening fetal nuchal translucency thickness can be assessed by ultrasound. Finally questionnaires are sometimes used. In colon cancer screening programmes the question whether first degree relatives had colon cancer at a young age can identify persons that should be advised to undergo colonoscopy instead of fecal occult blood testing. DNA technology is nowadays used as a second step in some neonatal cystic fibrosis screening programmes after an increased immunoreactive trypsinogen was found. For many screening purposes DNA technology is still too expensive and may lead to a high proportion of false positives (mild or unknown mutations).

Quality of Method

Test-methods used for screening must be reliable and valid. The former means that repetition of the test gives the same outcome (reproducibility). The latter means that the test measures what it is supposed to measure.

Analytical validity refers to how a test performs in a laboratory setting, for example how often it produces a positive (or negative) result in the presence (or absence) of the targeted mutation (genotype). Clinical (or diagnostic) validity goes a step further: how often does the test give a positive result for individuals who have or develop the condition in question (phenotype) and how often does it produce a negative result for people without that phenotype? A test can accurately indicate the presence or absence of a genetic mutation, for example, but if people with that mutation hardly ever develop the disease (the penetrance is low), the test serves no purpose.

The validity of a test is determined by its sensitivity and specificity. The (clinical or diagnostic) sensitivity of a test is its ability to identify all individuals with the disease in question; its (clinical or diagnostic) specificity is the ability to identify those who do not have the disease in question. A highly sensitive test produces few false-negative outcomes; a highly specific test few false-positives. The sensitivity and specificity also depend on the clinical spectrum of the disease among the individuals being tested. As compared to patients who are referred to a hospital, it is much harder to distinguish between those who do and those who do not have the disease in question in people with an earlier stage of the disease in the general population. Finally, the most important factor in deciding whether a particular screening method is useful in practice, is the predictive value of the test result. This depends not just on the validity of the test but also on the disease prevalence. A test that performs well in a group with many cases of disease may be unsuitable for use in the general population.

Clinical Utility

It is not enough for screening to lead to early detection of disease or to information about carrier status or risk factors. The purpose of screening is not the outcome of the test, but the ensuing health gain or other benefit to the person being tested. This is often referred to as "clinical utility" (Grosse and Khoury 2006). In a more limited sense, clinical utility is the extent to which the use of a screening method can help prevent or reduce the burden of disease in terms of mortality, morbidity or quality of life. In a broader sense, it refers to whether, all things considered, the benefits that screening can offer to participants outweigh the drawbacks that always exist as well.

In the orginal account of the criteria by Wilson and Junger (1968), the benefits of screening were framed in terms of the availability of "acceptable treatment" leading to a better prognosis than would have existed without early intervention. Without

this, Wilson and Jungner argued, "there can be no advantage to the patient and, in fact, (....) actual harm may be done". The subsequent introduction of genetic screening has not only led to a rephrasing of these conditions so as to include the preventive benefits that timely genetic information may sometimes have, but also to questioning the categorical rejection of screening for diseases not amenable to treatment or prevention.

This latter development was driven by the acknowledgement that prenatal screening for foetal conditions such as Down's syndrome and neural tube defects could not without moral problems be accounted for in the prevention paradigm underlying the original Wilson and Jungner framework. If reducing the birth prevalence of specific disorders is seen as the reason for offering this screening, the danger is indeed that expectant parents are put under pressure to regard selective abortion as an obvious and socially desirable choice. It might also be thought as implicit in presenting them with this choice that people with those conditions have no place in society. In order to steer clear from these moral pitfalls, there is a broad international consensus that prenatal screening for fetal abnormalities has the different aim of providing pregnant women and their partners with an opportunity for reproductive choice and should be presented, conducted and evaluated accordingly. Not only is informed decision making the central quality concern for this type of screening, it also means that its yield should be perceived in terms of choices provided rather than births prevented. However, measures to evaluate informed decision making have rarely been used in the assessment of prenatal screening programmes (Michie et al. 2002).

The break that screening for other purposes than early identification of treatable conditions signifies with Wilson and Jungner's initial criteria need not necessarily be limited to reproductive screening. It could be argued also in other contexts that screening may have benefits beyond treatment or prevention. The findings of the REVEAL study (a study into the psychosocial aspects of screening for genetic sensitivity to Alzheimer's disease) suggest that one might think here of the potential significance of benefits like being given the time to settle personal affairs, achieving certain life plans when one still can do so, or emotional preparation (Hurley et al. 2005). Of course, this does not settle the acceptability of screening for (genetic sensitivity to) serious late onset diseases that are not amenable to treatment or prevention. Potential benefits must be weighed against the obvious risks involved in offering screening for such diseases.

Pros and cons of screening do not only relate to the goal of the screening, also non-intentional findings should be considered. In neonatal screening for sickle cell disease, carriers of hemoglobinopathies will be identified for instance. Whether this is a pro or con depends on the perspective. Parents may consider it an advantage to be aware of their positive carrierstatus in view of future reproductive choices. Others, however, may find this additional information burdening. Moreover, if the child is found to be a carrier, this information will only be useful to him or her at a much later stage of life.

Among the potential drawbacks of genetic screening are furthermore the psychosocial implications of a positive test-result, including the (mis)use of information

by third parties (insurers or employers) and straining of family relations. These concerns would appear in the first instance to arise mainly in the context of screening for a hereditary predisposition to a monogenic disease (including the "Mendelian variants of common diseases") and less so in the case of screening for genetic "sensitivity" to common diseases ("susceptibility testing"). The predictive value of the results of this type of screening is generally low, and the likelihood that relatives will have exactly the same genetic profile is very small (Janssens and Khoury 2006). However, this type of testing may still have the potential of confronting some individuals with high risks of serious conditions with the potential risk of stigmatization or discrimination. If integrated risk profiling would be performed, testing for a number of genetic and non-genetic conditions and risk factors at the same time, it is conceivable that people will not be sufficiently prepared for such an outcome.

Recently, there is much debate about the scope of neonatal screening. Should this, following the classical account of the aim of neonatal screening, be limited to conditions the early detection of which is clearly in the health interest of the children screened? Or is it acceptable to use the same method to also screen for conditions where this would not be the case, given the interest of the parents to be able to also take the recurrence risk of non-treatable recessive diseases into account when making further reproductive plans? First of all, this conflict will in practice be mitigated by the fact that screening for non-treatable disease may still confer benefits to the child (eg. avoid the diagnostic long-haul through the health-care system and enable optimum care to be given as soon as the first symptoms appear). From an ethical point of view, the bottom line should be that screening of neonates in the interest of the parents or the family as a whole is unacceptable if the child would suffer disadvantages as a result. The recent draft additional protocol to the Convention on Human Rights and Biomedicine concerning genetic testing for health purposes drawn up by the Council of Europe does leave somewhat more space for this: the expected benefit to the parents must "significantly outweigh" the risk to the child associated with collecting, processing or sharing the information.

Respect for Autonomy

Participation in screening must be voluntary, and provision must be accompanied by balanced, adequate information that can be understood by the target group. This information must relate to all aspects that are of importance in allowing individuals to reach a well-considered decision on whether or not to take part. It must always include: information about the condition for which the screening would be performed, the nature and design of the screening test, the reliability of the test and the predictive value of a normal or abnormal result, possible implications for relatives and other (different) advantages and disadvantages of participation for those concerned.

In the case of escalated screening, providers and counsellors should be aware that the often "innocent" nature of the first step can conceal the sometimes risky or otherwise invasive nature of follow-up testing or of the options available if a definitive diagnosis is established. Moreover, little if any empirical research has been done into the feasibility of actual informed consent for multiplex screening including the use of imaging techniques such as prenatal ultrasound or body scans using CT or MRI. It has been argued, by the European Society of Human Genetics among other groups, that "screening packages" should be available only for conditions that are sufficiently similar in terms of their nature, severity and implications. In the context of neonatal screening, this would mean for example that screening for treatable conditions would be clearly separated from screening for untreatable conditions.

A related observation is that the notion of respect for autonomy has divergent implications where different forms of screening are concerned. As the aim of prenatal screening is the provision of reproductive choice, this means that in this context non-directive counseling must be the norm. On the other hand, to the extent that neonatal screening is offered in the clear interest of the child, directive counseling of parents reluctant to give their consent is not only acceptable but morally desirable. Respecting parental autonomy does not entail that parents may not be reminded of their responsibilities.

Approriate Use of Resources

Contrary to what many people think, screening does not usually save on the healthcare budget. Therefore, screening that is funded from public or collective resources must address a significant health problem. That does not mean that the condition in question must always have a high prevalence. Wilson and Jungner (1968) already mentioned that phenylketonuria (PKU) is "extremely uncommon but warrants screening on account of the very serious consequences if not discovered and treated very early in life".

The so-called "opportunity costs" must also be taken into consideration: introducing an expensive screening programme might mean that other forms of screening cannot be carried out, or that health care services will have to be cut. In this context, it is important that the balance between the proceeds of a screening programme, in terms of health gain or other benefits for participants, and the costs incurred comes down on the positive side. These must also cover the net costs of follow-up tests and ensuing interventions, ie. after deducting any savings made. A screening method that produces a high proportion of false-positive results soon generates considerable unnecessary cost down the line, and therefore the cost-effectiveness profile of the entire screening process becomes unfavourable.

It is incorrect to think that these considerations are irrelevant to screening offered in the private sector because people pay for it themselves. After all, what they pay for themselves is only the initial screening test and not the subsequent steps of diagnosis and intervention.

An Integral Approach

Quality is determined by the weakest link in a chain. An effective screening programme needs to be properly planned in terms of design, implementation and evaluation. Key components in this are a centralised system for inviting target groups for screening, providing clear, standardised information and reports, quality monitoring and assessment. Systematic investigation of the functioning of screening programmes shows that there is much room for improvement in this area (Antilla et al. 2004). The evaluation of genetic screening programmes has often focussed on laboratory quality and public health impact. A broader assessment integrating all elements of screening is needed.

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