Measuring the effects of genetic testing: studies on thrombophilia, sickle cell trait, recurrent miscarriage and male subfertility
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Chapter 11

General discussion
Genetic testing: the gap

In recent years the field of genetics has changed dramatically. The rapid evolution of research in molecular genetics has paved the way to a proliferation of novel diagnostics and predictive tests.

The first genetic tests were for monogenetic disorders with high penetrance, such as Huntington's disease or Duchenne muscular dystrophy. These tests confirmed a clinical diagnosis of a disease suspected to be genetic in origin. Genetic testing for these conditions was a new task for clinical geneticists. After identification of the genetic cause, the first pre-symptomatic genetic tests could be performed. This led to a debate about the use of genetic testing in predictive medicine and the identification of possible negative psychological effects of receiving a positive test result (indicating that the disease causing mutation was present). Because of these concerns, extensive genetic counseling was offered before a genetic test was performed.

Genetic counseling is defined as the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This complex process integrates:

- interpretation of family and medical histories to assess the chance of disease occurrence or recurrence;
- education about inheritance, testing, management, prevention, resources and research;
- counseling to promote informed choices and adaptation to the risk or condition.

Comprehensive research projects were started to evaluate any negative effects of genetic testing. Overall, the presumed negative effects seemed to be minimal. Extensive genetic counseling might lead to a (self-) selection in pre-symptomatic subjects where individuals who feel that they may not be able to cope with the genetic test result do not proceed with the testing procedure. These self-selection mechanisms could lead to more favourable psychological outcomes in pre-symptomatic subjects after testing.

More recently, the whole genome was sequenced in the Human Genome Project in 2003. Large genome-wide association studies have now identified genetic variants or mutations that contribute in small proportions to risks for multifactorial diseases, such as cardiovascular disease or diabetes. These genetic variants or mutations were often immediately introduced in daily clinical practice and affected patients were tested, and subsequently relatives without the disease.

In most cases, there was no extensive debate about the clinical utility of the genetic test in affected patients, or about the possible negative psychological effects. We hypothesized that genetic testing in a clinic based population, in patients diagnosed with a specific condition and without proper genetic counseling, might have very different - and potentially worse - psychological effects, compared to testing in pre-symptomatic individuals who received proper genetic counseling. The studies in this thesis were performed to investigate these effects. In addition, we evaluated the effects of a population based genetic screening program, also performed without extensive genetic counseling. The work reported in this thesis examined the effect of genetic testing from different dimensions, for the following conditions.

Thrombophilia

Thrombophilia refers to the endogenous risk factors for venous thromboembolism. A growing number of common abnormalities in venous thromboembolism were discovered in the 1990s, such as factor V Leiden (FVL) and the prothrombin gene mutation. Since the discovery of these more prevalent thrombophilias, at least one thrombophilic defect can now be demonstrated in approximately 50 to 60 percent of patients with venous thromboembolism. The discovery of genetic risk factors for venous thromboembolism and widespread clinical application of genetic testing for this condition have engendered a debate regarding the pros and cons of thrombophilia testing.

Sickle cell trait

Sickle cell disease is an autosomal recessive genetic blood disorder characterized by red blood cells that assume an abnormal rigid sickle cell shape. This leads to substantial morbidity and a shortened life expectancy. Heterozygous carrier status of sickle cell disease is called sickle cell trait. Because early identification of sickle cell disease leads to a decrease in morbidity and mortality, testing for sickle cell disease was added to the neonatal screening program in the Netherlands in 2007. Within this program it was decided to disclose newborns with sickle cell trait as well, to subsequently identify couples at risk and to help them in deciding on future reproductive options.
Recurrent miscarriage and male subfertility

A balanced structural chromosome abnormality is a risk factor for recurrent miscarriage. Unbalanced offspring can lead to miscarriage, stillbirth or even the birth of a child with major congenital malformations. Parental karyotyping has therefore become part of the diagnostic work-up of couples with recurrent miscarriage.

Genetic testing in men with poor semen quality (karyotyping and evaluation for deletions on the Y-chromosome) is generally performed if the total sperm count is < 1 million spermatozoa per ejaculate. A genetic defect associated with poor semen quality is found in 10% to 15% of cases. Men with a chromosomal abnormality have a higher risk of aneuploid offspring after Intra Cytoplasmatic Sperm Injection (ICSI). In case of Y-deletions, all sons conceived by ICSI will inherit the same deletion with possible consequences for their reproductive chances.

The utility of genetic testing

Before an identified genetic mutation or variant can be used in clinical care the utility of such a test must be proven. The utility of genetic testing has different dimensions: public health, clinical, and social.

The public health dimension implies that the genetic test needs to improve health outcomes, such as mortality or morbidity, on a population level. The expected health benefits must outweigh any expected negative consequences and testing has to be cost-effective. If we consider the genetic tests assessed in this thesis one can question whether there is any utility from a public health perspective. In thrombophilia testing there seems to be no benefit in terms of morbidity or mortality. In recurrent miscarriage previous studies have shown that parental chromosome analysis is not cost-effective, nor does it lead to a decrease in morbidity or mortality for offspring. From a public health perspective there does not seem to exist an evidence-based rationale for disclosure of sickle cell trait in newborn screening.

A genetic test has clinical utility if it is able to alter clinical management, influences decisions on therapeutic options, or leads to better prediction models. The studies on thrombophilia show there are no extra therapeutic options for patients with thrombophilia compared to patients without. There is no evidence that patients with thrombophilia need a longer duration of anticoagulant treatment to prevent recurrence of venous thromboembolism. In recurrent miscarriage carriers of a balanced structural chromosome abnormality have similar chances of having a live born child compared to noncarriers. Carrier couples have a higher risk of miscarriage compared to noncarrier couples, but identifying these carrier couples by a genetic test does not prevent those miscarriages. Carrier couples are offered invasive prenatal diagnostics in subsequent pregnancies, to identify fetuses with unbalanced chromosomal abnormalities, which is an example of its clinical utility. Our study showed however that only a small proportion of carrier couples opted for invasive prenatal diagnostics in subsequent pregnancies, indicating that the clinical utility seemed low from patients' perspectives. So, in these cases, one can question the utility from a clinical perspective.

The last dimension in defining utility is the social utility. Here psychosocial, ethical, legal and social issues are assessed, the benefits and burdens or harms of genetic information, often referred to as ELSI. Potential benefits can be the choice for prenatal diagnosis or to avoid the conception of an affected child, family planning, reassurance or reduction of uncertainty. Potential harms include, for example, an increase of anxiety or fear of discrimination.

Social utility is generally considered an essential dimension in the assessment of the utility of the genetic test. If a certain genetic test has no proven utility from a public health or clinical perspective, it could still be an useful test if it has strong advantages from the social perspective. An example which illustrates this is presymptomatic genetic testing for Huntington's disease. Testing healthy at-risk relatives for this disease has no advantages from a public health or clinical perspective, since Huntington's disease cannot be prevented, treated or cured, but testing for it is still performed because of its social utility. The reduction of uncertainty and the possibilities for family planning are, for some individuals, legitimate motivations to undergo genetic testing.

When assessing the social dimension both potential benefits and potential harms must be taken into account. Social utility is only demonstrated if the potential benefits outweigh the potential harms. If there are more harms than benefits from a social perspective we must be careful about using that specific genetic test in routine care. It is possible that the potential benefits from a public health or clinical perspective outweigh the harms from the social perspective. If so, the genetic test can be used, but individuals tested must be carefully informed about these harms and supported after receiving the test result. If the harms outweigh the benefits...
on the social perspective and the utility is not demonstrated from a public health or clinical perspective, this must be a strong indicator to abandon the genetic test.

The rationale for introducing the disclosure of sickle cell trait in newborn screening was to guide reproductive choices of parents in future pregnancies. There is no research, however, that demonstrated unambiguously that this is a decision parents actually will make when offered testing. So the benefit from a social perspective is far from established. We showed that disclosure of carrier status of a balanced structural chromosome abnormality leads to an increase in distress in carriers and their partners, which persists over a longer time. This potential harm must be carefully balanced against potential benefits when assessing the utility of genetic testing in recurrent miscarriage and male subfertility.

Clinical implications

Our research showed that there is no evidence of clinical utility for genetic testing for thrombophilia in patients with venous thromboembolism. Genetic testing for thrombophilia may have negative psychological effects, although this could not be concluded directly based on our systematic review. If we adhere to one of the most important ethical principles in medicine – primum non nocere (first do no harm) – we can conclude that genetic testing for thrombophilia should be abandoned. In recent years, more and more hospitals have stopped testing for thrombophilia in patients with venous thromboembolism. In the literature, a debate has started about the necessity of thrombophilia testing on a routine base.

We showed that the implementation of disclosure of sickle cell trait in newborn screening in the Netherlands has been far from ideal. The limited level of knowledge among general practitioners is reason for concern and could lead to unnecessary anxiety in parents of newborns with sickle cell trait, if they receive unclear or incomplete information. The Dutch Center for Population Studies (RIVM) did take notice of publications on this subject and efforts have been made to provide better information to general practitioners and parents, in the form of new information leaflets for general practitioners and parents and DVD’s with information for general practitioners. An expert panel has been formed recently to advise on further improvements and to make recommendations for the future. In our opinion, it would be better if sickle cell trait is no longer disclosed to parents of newborns, until more research has been done on the expectations of parents and on the best ways to communicate the test results. More effort is needed to inform general practitioners and help them in defining their task in newborn screening.

Genetic testing in couples with recurrent miscarriage and male subfertility has been a part of daily clinical practice without much debate for a long time. Several clinical guidelines advised karyotyping in couples with recurrent miscarriage without solid evidence to back up these recommendations. In 2005 and 2006 two studies were published that showed that the prevalence of carrier status of a balanced structural chromosome abnormality among these couples was low, and that the chances of having at least one healthy child were as good for carrier couples as for noncarrier couples. The risk for carrier couples of having a severely handicapped child, due to a chromosomal abnormality, was shown to be very small. We found that even though couples knew they were a carrier couple and were advised to opt for invasive prenatal diagnosis, a substantial proportion discarded this advice. We also showed that receiving an abnormal genetic test result can lead to an increase in distress. The combination of these findings leads us to recommend refraining from ordering karyotyping in couples with recurrent miscarriage on a routine basis. The updated clinical guideline on recurrent miscarriage by the Royal College of Obstetricians and Gynaecologists, published in April 2011, no longer advises parental karyotyping in couples with recurrent miscarriage.

Recommendations for future research

In an era of evidence-based decision making in health care, the principle has become firmly ingrained that we require a systematic assessment of the effects of genetic testing before making any recommendations about their use. As the availability of genetic tests expands, it is important to evaluate the outcomes that matter not only to patients, but also to society and clinicians. If there is no clear benefit, the genetic test should not be implemented in clinical care. Although the principle has been accepted, research in this area leaves a lot to be desired. In the coming years we should critically appraise all information collected from research in the genetic field. The utility of testing must be documented before tests are introduced in routine clinical practice.

More research is needed regarding disclosure of sickle cell trait in newborn screening. Research in this area should focus on two main aspects. First there is a need for studies that involve the populations at risk for children with sickle cell trait. We need to study their views...
and expectations. How they perceive sickle cell disease and sickle cell trait? Do they want to have prenatal diagnosis in subsequent pregnancies? Will they have prenatal diagnosis? How do cultural, religious and social aspects influence this? Non Caucasian populations are underrepresented in research in general and it will not be easy to involve them in clinical research projects. Second we need studies on the best ways to communicate these results to parents in general, and the populations involved specifically. How do we inform them and what do we tell them taking into account low literacy and cultural beliefs? What would be the best time to offer this test to parents? Immediately after the birth of their child, during pregnancy or even before pregnancy? Whom would be best to discuss this with parents, the midwife, the general practitioner or maybe even a genetic counselor? These topics are both actual and necessary to study since there is debate about adding more autosomal recessive diseases to the newborn screening and maybe disclosing other carriers, such as in cystic fibrosis.

Requiring verified utility before clinical use does not mean that we should stop testing for genetic mutations or variants altogether. Gathering information on the prevalence of mutations or genetic variants will help to identify and clarify relations between genotypes and disease. This will improve our understanding of the origins of diseases and conditions, which may lead to better prediction of disease and help in selecting treatment options. Yet these genetic tests should initially be performed in a research setting only, and results obtained in such a research setting cannot unconditionally be used for management decisions, and should not always be disclosed to patients.

Not only must we critically appraise all genetic tests before implementing them in clinical care, we also need to evaluate all genetic tests that are currently used in clinical practice, and abandon those that fail to show any real utility for patients and society.

REFERENCES
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