Measuring the effects of genetic testing: studies on thrombophilia, sickle cell trait, recurrent miscarriage and male subfertility
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Chapter 1

Introduction and outline of the thesis
In 1953 the structure of DNA was presented by Watson and Crick. Since then the field of genetics gained an enormous momentum and genetic testing has shown considerable growth in the last few years. In 2003 the Human Genome Project completed sequencing of the whole human genome (www.genomics.energy.gov). Nowadays genome-wide association studies can be performed to find genetic variants associated with a specific disease.

Advances in genetics and a growing understanding of the genetic origins of disease have resulted in the expanding use of genetic tests, to identify genetic factors in patients affected by specific diseases or conditions. Once a mutation in a gene is identified in a patient, it is possible to test family members. If these family members are found to have the same mutation they are at risk of developing the disease themselves. Genetic testing of individuals who are at high risk but still unaffected is called predictive or pre-symptomatic genetic testing. A benefit of pre-symptomatic genetic testing is that high-risk persons can act upon the risk and, in some cases, take measures to prevent disease or attend screening programs to detect disease early, such as regular colonoscopies in Lynch syndrome (prevention) or regular mammography in hereditary breast cancer (early detection/screening).

Genetic information can help predict a person’s medical future, it discloses information about family members, and is immutable throughout life. Because of these features, disclosing genetic information may result in serious psychological morbidity, especially in genetic tests concerning untreatable or unavoidable conditions such as Huntington’s disease. In testing pre-symptomatic persons normally extensive genetic counselling takes place, where benefits, limitations, risks of testing and coping strategies can be discussed. Pre-test genetic counselling and testing is usually performed by a clinical geneticist.

Yet more and more genetic tests are used in daily clinical practice, ordered by medical specialists, not only clinical geneticists. There is a difference between patients and pre-symptomatic subjects in the way they are confronted with genetic testing. Patients are often tested within a diagnostic work-up, without receiving pre-test genetic counselling, sometimes even unaware of the fact that a genetic test is performed. Conclusions about the psychological effects of genetic testing based on research in pre-symptomatic subjects can therefore not automatically be generalized to patients.

The studies in this thesis were performed to improve our understanding of the psychosocial impact and implications of genetic testing in patients tested in a clinic-based setting, already diagnosed with a condition, or tested as healthy individuals in screening programs. Although the participants described in this thesis have different diseases or conditions, they all have one thing in common: a genetic test was performed without pre-test genetic counselling by a clinical geneticist. We explored the effects of genetic testing for a number of conditions and from different perspectives. This thesis is divided into three parts, each addressing a different condition or set of conditions.

**Thrombophilia**

Thrombophilia refers to the endogenous risk factors for venous thromboembolism. It has gained interest after a growing number of common abnormalities had been 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 have engendered a debate regarding the pros and cons of thrombophilia testing. We conducted systematic reviews to document the psychosocial effects of genetic testing for thrombophilia and to summarize the research done to substantiate the main goal for thrombophilia testing, which is to prevent recurrent venous thromboembolism by means of prolonged antithrombotic medication.

**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, it was added to the neonatal screening program in the Netherlands in 2007. Within this program it was decided to report newborns with sickle cell trait as well, to subsequently identify couples at risk and help guiding their future reproductive options. We conducted studies to evaluate the first year of disclosure of sickle cell trait, to report the incidence and distribution...
of newborns with sickle cell trait, and to explore potential barriers from general practitioners in reporting sickle cell trait to parents.

**Recurrent miscarriage and male subfertility**

Carriership of a balanced structural chromosome abnormality in one of the partners of a couple 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.

In 2000, a study was conducted in the Netherlands to investigate the efficiency of karyotyping couples with recurrent miscarriage. By then the annual number of parental chromosome analyses had grown from 1,298 couples in 1992 to 2,362 couples in 2000, while the proportion of carrier couples in those tested decreased from 6.8% to 3.8%. The study showed that a more selective chromosome analysis in couples with recurrent miscarriage, inviting only those at high a priori risk of carriership, would be a safe and more efficient alternative system.

The group also showed that reproductive outcome, defined as the birth of at least one healthy child, was as good for carrier couples as for noncarrier couples and that the risk of viable offspring with an unbalanced structural chromosome abnormality was very small. These studies led to questions about the additional value of parental karyotyping in couples with recurrent miscarriage.

In 2005 we initiated a study to evaluate parental karyotyping in recurrent miscarriage from patients’ perspective. In this CONGENO-study (CONsequences of GENOtyping in reproductive medicine), we also included couples with male subfertility, in which the male partner had poor semen quality. 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.

Our aim was to evaluate the impact of receiving an abnormal genetic test result in couples with recurrent miscarriage and in couples with male subfertility. Is knowing the likely genetic explanation for the recurrent miscarriage or subfertility a relief for couples, or is carriership of a chromosome abnormality perceived as a burden? What are the consequences of carrier status from couples’ perspectives? Will carriers make other choices regarding reproductive options?

**Outline of this thesis**

Chapter 2 reviews studies that have previously evaluated psychological effects of genetic testing in symptomatic patients. We included 16 studies with, in total, 2,868 participants and summarized the study designs used, methods and the reported patients outcomes.

Part I contains studies in patients undergoing genetic testing for thrombophilia.

Chapter 3 reviews the studies that have been performed to evaluate the psychological impact of thrombophilia testing in patients, both pre-symptomatic individuals and patients already affected. In total 6 studies were found that measured to some extent the impact of testing for thrombophilia.

Chapter 4 presents a systematic review of studies to support thrombophilia testing, the rationale of which is to prevent recurrent venous thromboembolism by means of prolonged antithrombotic medication. No studies to support that aim were found.

Part II reports on testing for sickle cell trait in the neonatal screening.

Chapter 5 describes the first year of the introduction of reporting sickle cell trait in the neonatal screening in 2007. In total 806 newborns with sickle cell trait were identified. We report the number of carriers of sickle cell per province and the subsequent follow-up.

In Chapter 6 results are shown of a questionnaire sent to 285 general practitioners who received notice of a child with sickle cell trait in their practice in 2007 or 2008, identified through neonatal screening. We evaluated general practitioners’ knowledge, ideas and actions after reporting these sickle cell carriers and explored and analyzed potential barriers experienced by general practitioners in counseling parents about sickle cell trait in their newborn.
Part III describes genetic testing in couples with recurrent miscarriage and male subfertility.

Chapter 7 reports on a study among couples in which one of the partners is carrier of a structural chromosome abnormality. In 239 carrier couples, we evaluated the uptake of invasive prenatal diagnosis in subsequent pregnancies and compared this with the uptake in noncarrier couples aged 36 or older.

Chapter 8 contains a study in which the knowledge about the genetic test and the perceived risks before disclosure of the genetic test result in couples with recurrent miscarriage or male subfertility were evaluated.

Chapter 9 describes the impact of receiving the genetic test result in terms of anxiety, depression and stress in couples with a genetic abnormality compared to couples without a genetic abnormality three and 12 months after disclosure.

In Chapter 10 we describe the effect of disclosure of a genetic abnormality on reproductive choices of carriers, taking into account perceived risk on different outcomes, such as the risk of another miscarriage and having a child with major congenital malformations.

In Chapter 11 we provide a general discussion of the results of the studies presented in this thesis, with their clinical implications and offer suggestions for future research.

The thesis closes with Chapter 12, which summarizes the findings presented in this thesis.

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REFERENCES

3. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007;447:661-78.