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Publication of the Leopoldina Round Table Discussion

"En route to the complete rationalization of reproduction? German perspectives on the latest developments in genetic diagnostics"

In 2013, the German National Academy Leopoldina initiated an interdisciplinary round table discussion of perspectives on the latest developments in genetic diagnostics within the context of family planning. The availability of recently developed methods, and their future improvement, may have a profound influence on human reproduction and even the ethical credos of society. The topic is of particular importance in Germany, where fear of "a slippery slope" is widespread. The round table panel comprised leading German experts in prenatal diagnostics, human genetics, law, ethics, sociology, and the history of medicine. The edited transcript of the meeting, which was held on 16-17 February 2013, is now available in print (www.leopoldina.org/de). The aim of the meeting was not to formulate recommendations, but rather to hold an open discussion on all aspects of the topic.

The possibility of avoiding the birth of children with genetic disease has been revolutionized by two recent technical developments: non-invasive prenatal testing (NIPT) to diagnose chromosomal imbalances in the fetus; and preconceptional genetic diagnostics to uncover heterozygosity for recessive diseases. Both approaches are based on "next generation sequencing". Ultimately, these methods may prevent the birth of children with genetic disease. This would undoubtedly represent an entirely novel and uncharted dimension for mankind.

In determining the title of the present publication, the editors Peter Propping and Heinz Schott selected a term coined by the Austrian economist Julius Wolf (1862-1937). In 1912, Wolf published a book in which he interpreted the declining birth rate in the second half of the 19th century as the consequence of the "rationalization" of sexual life. Wolf regarded this as a justified moral decision of the individual.

The round table meeting was structured into the following sections: non-invasive prenatal testing; preconceptual genetic testing; regulations concerning prenatal diagnostics under German Gene Diagnostic Law; historical aspects of the "medicalization" of the fetus; and ethical and social aspects of preconceptual genetic diagnostics. Each section began with an invited introductory paper. To ensure emphasis on interdisciplinary discussion, more time was allocated to discussion than to the introductory presentation. In a separate session, a 16 year project to evaluate the opinions and attitudes of a group of adults with Down's syndrome was presented.

Over the course of the interdisciplinary discussions, it became apparent that these new genetic diagnostic methods represent a revolution for mankind and will therefore require ongoing debate. The panel viewed both NIPT and preconceptual genetic testing as new options to promote the autonomous decision of the individual. However, many aspects of genetic diagnostics within the context of family planning proved contentious and were discussed in depth by the panel. Each generation must confront the issues raised by novel technology in order to achieve consensus on their use. However, as Bettina Schöne-Seifert, a member of the panel, stressed at the end of the meeting, answers to three questions will always be necessary: "How can the voluntary decisions of couples, and the rights of those who make use of genetic tests, be protected? How can children born with diseases that could have been diagnosed through prenatal genetic testing be protected? How can society be protected from erroneous changes in attitude?"

Introductory presentations and subsequent discussions:

Non-invasive prenatal testing.

In his introductory presentation, Wolfgang Holzgreve pointed out that invasive methods of prenatal diagnosis, such as amniocentesis, are associated with a pregnancy loss of around 1%, whereas NIPT can be performed without risk to the fetus. In Germany, LifeCodexx, a subsidiary company of the US-based company Sequenom, has obtained an exclusive licence for non-invasive prenatal chromosome diagnostics. Thus, for fetal chromosome analysis, German gynecologists are required to send all maternal blood samples to LifeCodexx. At the time of writing, the national health insurance system in Germany does not cover the costs of NIPT, in contrast to the situation for amniocentesis and chorionic villous biopsy.

Although NIPT is indicated in women with an increased risk of a child with a chromosomal disorder, gynecologists are receiving an increasing number of requests for this approach from women with lower risk status. Claims for NIPT would certainly increase if the health system opted to cover the costs.

The complete fetal genome can now be sequenced through NIPT. It can therefore be assumed that in the future, virtually all genetic diseases in the fetus will become diagnosable on a non-invasive basis.

Interdisciplinary Discussion. The panel agreed that a definite advantage of NIPT over invasive prenatal diagnostics is the absence of a miscarriage risk, since the procedure only requires blood sampling. Subsequently two major points were discussed. Firstly, during the laboratory development phase, LifeCodexx performed a study on the validity of NIPT and made the results available to the public. In the long run, however, the consensus view of the panel was that private companies will not be willing to share their diagnostic experiences with research institutions. The case of Myriad Genetics has shown that whereas private companies access genetic data available in scientific publications and public data banks, they do not contribute to this knowledge. In the opinion of the panel, companies will prefer to use their accumulated genetic data bank in order to maintain or achieve market leadership. From a legal point of view, however, the obligatory publication of relevant genetic data would represent a feasible future approach in Germany.

The second point of discussion concerned the issue of the so-called “pregnancy on probation”. For parents who wish to avoid the birth of a child with a severe genetic disease, selective abortion of an affected fetus is frequently the preferred option. In cases where the couple is aware that their common children have an increased risk for a severe genetic disease, the option of a pregnancy on probation is available. If a fetus is proven to carry the disease-relevant genotype, the woman or the couple might opt for termination of the pregnancy in order to try again. Catholic representatives have characterized this option as cynical. In the round table discussion, this view was regarded as unrealistic. The concept of ‘pregnancy on probation’ was already in use when only invasive prenatal diagnostics were available. Through the advent of high throughput genetic analysis, the number of couples with identified high-risk status will certainly increase.

Preconceptual genetic testing. Christian Kubisch reminded the panel that this type of genetic testing has been used for decades in populations with a high incidence of particular recessive diseases. These diseases include Tay-Sachs disease in Ashkenazi Jews or beta-thalassemia in Mediterranean populations. The concept can now be applied to any gene in any population. When hundreds of diseases are being considered, informed consent in the traditional sense is impossible. Instead, only a generic consent can be obtained. Heterozygosity testing for recessive alleles may have unexpected implications. For example, research has shown that individuals who are heterozygous for a mutation in the gene responsible for Gaucher’s disease have a 30% risk for Parkinson’s disease.

The future will show whether genetic panel diagnostics or whole exome sequencing will be the preferred method of testing.

Discussion. There was consensus among the panel that widespread use of preconceptual testing will occur in the future. However, no danger of a slippery slope towards unethical attitudes was foreseen. For several decades in Germany, a woman has had the legal option to terminate a pregnancy when the fetus carries a genotype leading to a severe disease. No evidence is available to suggest an abuse of legal regulations concerning pregnancy termination.

Semen donation in reproductive medicine may be the gateway for the systematic application of preconceptual genetic testing.

The panel engaged in a detailed discussion of the advantages and disadvantages of compiling a "positive list" of genes for evaluation in preconceptual screening. In different countries, different lists might be indicated, depending on the allele frequencies for recessive disease. However, the compilation of any list would involve the problem of defining the severity of diseases or even of genotypes. There was agreement among the panel that the only solution would be the provision of competent interdisciplinary information. Even in developed countries, however, medical systems would not be able to provide adequate expertise in terms of providing information or counselling when the number of screening tests increases. Panel members stressed the need to commence education on genetics in school in order to ensure that the population gains genetic literacy. Furthermore, society must differentiate between the societal, normative, and legal aspects of reproductive decisions and their consequences for handicapped individuals.

Regulations concerning prenatal diagnostics under German Gene Diagnostic Law. German law regulates both pre- and postnatal genetic testing. Jochen Taupitz pointed out that the legislator aims to preclude the unfair discrimination of persons on the basis of inherited characteristics. Under German law, no method of prenatal risk evaluation is, in principle, curtailed. Thus, NIPT is not forbidden by law. However, prenatal diagnostics is confined to medical purposes. Before the 12th week of pregnancy, the sex of the fetus should not be disclosed.

Discussion. German gene diagnostics law restricts a pregnant woman's right to self-determination. However, the legislator must always provide valid reasons for any restriction. The panel discussed the degree to which restriction on the right to self-determination under German Gene Diagnostic Law is justified. The panel members agreed that legislation reflects the moral values of a society. However, each generation has the right to reconsider, and eventually redefine, moral values.

Historical aspects of the "medicalization" of the fetus. In her introductory presentation, Susanne Michl cited Friedrich Schlegel, who said that the historian is a "backward oriented prophet". The hope prevails that analysis of history may teach us something of value for the future. This also applies to family planning and reproductive decisions. In the 19th century and up until 1945, the eugenic movement forwarded the concept that the state should rationalize family planning through the controlling of reproductive decisions. Today, the individual is able to shape his or her own future. This has led to the development of personal autonomy. In the context of reproductive decisions, this is particularly important for women. However, the degree to which personal decisions are genuinely free is open to question. Most individuals assume that medicine as a whole, and human genetics in particular, can in some way contribute to an improvement of the personal life plan ('Lebensentwurf'). Despite technical advances, these expectations might lead to uncertainty concerning the normative borders of technical feasibility ('Machbarkeit'). On the other hand, the defining of unintended childlessness as a "disease" for which the health system must bear the costs has also had a positive effect. In Germany at least, this development has contributed to the success of reproductive medicine.

Discussion. The panel raised the question of whether eugenic ideas still exist. A recent publication was used as an example. In his book on the future of Germany, the economist and politician Thilo Sarrazin made use of eugenic arguments in expressing his opinion on recent immigration from Turkey to Germany. The book was published in 2010 and had enormous success, with more than one and a half million of copies being sold. This may be an indication that at least nebulous eugenic thinking is still prevalent in Germany.

The 'Ohrenkuss' ('Ear Kiss') project –16 years experience with a group of adults with Down's Syndrome. For the past 16 years, Katja de Bragança, a trained cytogeneticist and recipient of the German Federal Cross of Merit, has worked with a group of adults with Down's Syndrome in order to gauge their opinions and attitudes towards living with a disability. The topic of Down's syndrome was chosen for the round table meeting, as trisomy 21 has been the major target of global prenatal diagnostics since its inception 40 years ago. Katja de Bragança commented on four preconceptions of the phenotype. Firstly, it is widely assumed that the appearance of affected individuals resembles that of Mongolians. To investigate this, the Down's Syndrome group actually visited Mongolia. They concluded that while they are aware that their appearance is different to that of non-trisomy 21 Western individuals, they did not agree that their appearance is similar to that of Mongolians. Furthermore, persons with Down's Syndrome feel humiliated when labelled as 'Downies'. Secondly, it is widely assumed that individuals with trisomy 21 'suffer' from the fact that they are different. In her experience, Katja de Bragança has found that this is untrue, and that in contrast, many individuals with Down's Syndrome feel happy. Thirdly, it is widely assumed that individuals with trisomy 21 cannot read or write. In fact, if instructed appropriately, many Down's syndrome individuals do learn to read and write. This is illustrated by the fact

that all articles in the journal 'Ohrenkuss' are written by authors with Down's Syndrome. Finally, it is widely assumed that individuals with trisomy 21 cannot appraise their status within society. In her experience. Katja de Bragança has found that whereas many individuals with Down's syndrome know that they are different from the majority of people and can identify others with the same chromosomal disorder, they wish to be respected by other members of society.

Discussion. This presentation was followed by intensive discussion. The consensus view was that at best, the decision to abort a fetus with trisomy 21 can only be justified by a lack of competence in affected persons; the decision cannot be based on the assumption that affected individuals suffer as a result of their disorder. The opposite is in fact true: many affected individuals are content.

Katja de Bragança described the case of a married woman with trisomy 21 who became pregnant. She opted for prenatal diagnosis and subsequent abortion. When asked by a journalist to explain her reasons for undergoing prenatal diagnosis, the woman answered: 'You all opt for prenatal diagnosis, but I know better than you why you do it. I was frequently mistreated. I did not want my child to be treated in the same way.'

Ethical and social aspects of preconceptual genetic diagnostics. Silke Schicktanz referred to the 2011 report of the British Human Genetic Commission. The report concludes that preconceptual genetic testing is recommendable. Silke Schicktanz questioned what the prerequisites for such a recommendation should be. On one hand, the report regards "informed choice" as a central condition. On the other hand, the report states that the individual should have the moral duty to inform his/her relatives of the test result, since relatives may carry disease-relevant mutations. In this context, the report refers to the concept of "genetic solidarity". For Silke Schicktanz, however, the meaning of this phrase is unclear: does this refer to solidarity with relatives or responsibility for the gene pool?

Positive lists for preconceptual screening should not be drawn up according to pragmatic or economic criteria. Rather, they should be based on disease-severity and unavailability of treatment. Silke Schicktanz reminded the panel that all improvements in preconceptual diagnostics will render 'orphanization' of rare diseases even stronger, thus reducing motivation for the development of treatment still further. On the other hand, she regards the concept of the widespread use of preconceptual genetic testing as positive, since people would then be reminded that everyone carries multiple disease-relevant variants, thus limiting the stigmatization of mutation carriers.

Discussion. With respect to the issue of genetic solidarity, the panel was reminded that informing relatives about genetic data is problematic. The experience of panel members has shown that it might be associated with multiple areas of conflict, including the assignment of guilt to family members.

Some members of the panel considered the view that preconceptual testing should consider the availability/unavailability of therapy problematic. People have different reasons for deciding to refrain from having children. Furthermore, the panel agreed that the distinction between "health" and "disease" should not be abandoned. The issues of stigmatization and guilt refer to very different - and non biological - concepts.

The panel agreed that abstaining from preconceptual screening for rare diseases on the grounds that this might reduce motivation for the development of treatment does not represent an ethical dilemma. Although the potential for the further orphanization of a disease must be taken into account, allowing the birth of children with a disease in order to promote research into novel therapies is ethically unsound.

Final discussion. Among panel members, the opinion prevailed that exome sequencing will be the future method of choice in this field, at least in the case of preconceptual testing.

In countries where new developments in genetics are encouraged, public debate commences earlier and is more informed. Panel members again emphasized the importance of promoting genetic literacy in the general population, particularly among young people.

Summary written by Peter Propping and Heinz Schott