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Some historical and general considerations on NIPT – great progress achieved, but we have to proceed with caution

Wolfgang Holzgreve

Editorial

Some historical and general considerations on NIPT – great progress achieved, but we have to proceed with caution

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Background

Ever since we have recordings in history of human thoughts and emotions there is evidence for concern of expectant parents regarding the health of their unborn child. In the past, however, the ability to find out whether the growing fetus had problems in its development was very limited. Especially in the 70s this changed with the introduction of diagnostic ultrasound which allowed to visualize the features of the unborn child without harm, and around the same time biochemical marker screening approaches were developed for the prediction of neural tube defects or chromosomal anomalies in the fetus.

The improvements of the ultrasound technology quickly allowed amniocentesis to be performed around 16 weeks of pregnancy and since the middle of the 80s chorionic villus biopsy at around 10 weeks of gestation [1]. Ultrasound will most likely never be fully replaced in pregnancy surveillance by genetic techniques, because the majority of the structural defects to be detected prenatally which constitute the majority of the 2–4% congenital anomalies, are multifactorial (e.g. cardiac or neural tube defects) but the new powerful screening tests have to be combined in a logical and affordable way [2].

Development

Cultures from amniotic fluid or chorionic villus cells enabled cytogenetic analysis, and prenatal diagnosis of trisomy 21 was offered to women with an age of 35 years and older because of their increased risk for fetal aneuploidies so regularly that unfortunately and wrongly this offer almost became for many synonymous with “Prenatal Diagnosis” in general. From the beginning, however, the ability to have a legal termination of pregnancy based on a prenatal diagnosis raised the serious conflict between the fundamental prohibition of actively ending any human life based on the concept of dignity of every (born and unborn) human being on the one side and the autonomy of the pregnant woman on the other. This basic conflict ultimately cannot be solved in any absolutely satisfactory way, and different countries found various solutions (Cathy Bilardo [3] in this issue). For a majority in many populations a way to deal with this dilemma is to institute knowledgeable and empathetic counselling about the facts of prenatal diagnosis and its consequences so that women can make their own informed choices within the legal limits of their society. This important issue is one of the cores of this special edition of the Journal of Perinatal Medicine for which I am very thankful to the publisher thus allowing the presentations to be printed from a well-attended and positively received Symposium, which was conducted together with the Foundation for the Handicapped Child in Bonn, Germany in December 2020. The ethical aspects of NIPT are elegantly discussed in this issue by Annette Dufner [4], Bert Heinrichs [5], Christoph Rehmann-Sutter [6], Bettina Schoene-Seifert and Chiara Junker [7], Peter Miny et al. [8] and Klaus Zerres et al. [9], and the legal ones by Stephan Huster [10]. Since dealing with dilemma and complicated alternatives for decision can cause significant stress during pregnancy, the awareness of maternal stress, the consequences for the offspring and the need for intervention to decrease stress resilience is discussed in a comprehensive way by Birgit Arabin et al. [11] in this issue. It is my point of view that the ethical considerations on significant new developments in medicine such as NIPT should not follow their introduction into clinical practice but they should proceed them [12].

A well-known problem of prenatal medicine from the beginning was the fact that in the majority of cases the

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prenatally diagnosed chromosomal and metabolic diseases could not be treated, and therefore Sir William Liley, one of the pioneers in this field, even spoke about a “search and destroy” mission. He was, however, at the same time “the father” of prenatal therapy, because following the ability to assess by amniocentesis and blood sampling in utero the severity of a Rhesus blood group incompatibility, he developed techniques for treating the affected babies prenatally by intrauterine blood transfusion with the delicate technique of fetoscopy. Therefore obtaining just a precise diagnosis mutated into effective though risky prenatal therapy and followed this way in the general principle in medicine that accurate diagnosis should not be considered as the ultimate goal, but as the necessary prerequisite for an appropriate prenatal therapy. In order to highlight this positive development already in 1987 I gave a book about these newly developing techniques the title “Prenatal Medicine” rather than just “Prenatal diagnosis” [13].

In the meantime fetal Rhesus D antigen genotyping in D-negative mothers is one of the many positive examples of applying Non-invasive Prenatal Testing in clinical practice [14]. The traditional approach of administering anti D immunoglobulin to all D-negative mothers is needless in the 40% of pregnancies with a D-negative fetus. Non-invasive fetal D antigen genotyping not only avoids an unnecessary discomfort and exposure to blood products but is also cost saving and has been successfully introduced in a number of countries including Germany [15] thus illustrating the significant and consequential progress achieved by NIPT.

Although prenatal diagnosis was looked at sceptically in some parts of the general population from the beginning, it was soon confirmed that it has saved many lives of unborn children, because less often than before by these technological advances women with anxieties could be calmed based on the proper prenatal diagnosis, e.g. in cases of an in utero rubella virus infection or when they became pregnant with advanced maternal age. Regarding genetic diseases with Mendelian patterns of inheritance Bernadette Modell showed that in populations with increased risk for Beta-thalassemia in the UK after the proper counseling about the 25% recurrence risk, the pregnancy rates went down dramatically, whereas it increased to normal again after the possibility of prenatal diagnosis even by the invasive method of fetoscopic blood sampling [16].

Another burden on prenatal diagnosis by amniocentesis or CVS always was the low, but definitely existing risk of harming the pregnancy by the prenatal invasive sampling procedure [17]. Therefore since the 70s there was an intense search for a non-invasive method of prenatal diagnosis, and in a collective effort of international research first the isolation of fetal cells from the blood of pregnant women was tried whereas later this method became successful and clinically mature by looking at cell-free DNA in the maternal blood. Because progress in medicine through publications, lectures and media travels fast these days, now more than 10 million cases have been investigated noninvasively by the NIPT methodology.

**Ethical and legal concern**

In ethical terms, Non-invasive Prenatal Testing (NIPT) is a major breakthrough and progress for the women concerned and even helps to understand better pregnancy-related diseases such as preclampsia and autoimmune diseases [18], but not surprisingly the general discussion about the justification for prenatal diagnosis of untreatable conditions started immediately again when this progress on non-invasive testing became available. To a great extent the important discussion about the general justification for prenatal diagnosis was, from my point of view, sometimes mixed up with the progress of the non-invasive over the invasive techniques, and these considerations are presented thoughtfully and elegantly in the manuscripts of this special issue of the JPM.

If we look into the fascinating history of prenatal diagnosis in more detail we recognize remarkable progress in prenatal screening and diagnosis within a relatively short time e.g. that after maternal age was for a long time the only parameter used to define a population at risk in pregnancy, the observation of lower maternal serum alphafetoprotein (AFP) levels being associated with trisomy 21 in populations screened for neural tube defects initiated a systematic search for other biochemical markers in the maternal blood suitable to assess the risk for common trisomies. Using AFP, free β-human chorion gonadotropin (hCG), and unconjugated estriol (“triple test”; sometimes complemented by other markers) in the second trimester of pregnancy multi-parameter maternal serum testing became the recommended and widely used approach to assess an individual risk for fetal trisomies. A further significant increase in sensitivity was achieved by including the extension of the skin in the fetal neck (nuchal translucency) as determined by ultrasound in the first trimester of pregnancy and the simultaneous measurement of hCG and the pregnancy associated plasma protein A (PAPP-A), known as the first trimester or combined test. Various additional serum and ultrasound markers as well as testing approaches were proposed [19], but the major step forward
in screening was the development of NIPT which is now by far the best screening method together with applying ultrasound.

The introduction of NIPT is a positive example for how a new technology should be introduced into clinical practice, that is after the research and development after careful planning [20] the proper trials were performed [21–23]. So that the public was prevented from an immature technical approach spreading into clinical use without rigorous evaluation.

Apart from the prenatal diagnosis of trisomies [24, 25] the detection of fetal sequence variants in cfDNA not present in the mother is now reliably feasible by a variety of techniques such as RTQ-PCR, digital PCR and more recently HTS and applicable for a number indications such as paternally inherited dominant conditions or autosomal recessive conditions with different mutations in both parents as well as new mutations [26]. Testing for example of FGFR3 (achondroplasia, thanatophoric dysplasia) or FGFR2 (Apert syndrome) is a non-invasive diagnostic option with suspicious ultrasound findings when the parents are phenotypically normal [27]. The diagnostic approach of course is more challenging in recessive conditions when both parents carry the same mutation as well as for maternal dominant disorders or X-linked conditions when the mother is a carrier. Two approaches have been applied to address these situations: The relative mutation dosage as assessed by droplet digital PCR (ddPCR) reflects slight differences in the ratio of mutant and wildtype alleles in the cfDNA depending on the presence of absence of mutant alleles in the cfDNA. The second strategy is HTS-based genome-wide SNP-genotyping and the assessment of relative haplotype dosage in theory permitting the testing of virtually any monogenic condition [28]. This indirect testing approach uses SNP haplotypes linked to a specific loci of interest and is reliable due to the abundancy of available SNPs. For prenatal diagnosis the paternal haplotype in the cfDNA is detected by the analysis of SNPs homozygous in the mother (AA) and heterozygous in the father (AC). The statistical significance of any allelic imbalance is calculated by a sequential probability ratio test (SPRT). Obviously, the parental coupling phase (i.e. the haplotype linked to the mutation) has to be known e.g. by testing family members in one or both. The genome-wide approach can by customized by recent targeted capture sequencing technologies to restrict sequencing to genomic regions of interest [29]. An alternative approach was proposed by Dan et al. [30] by searching for known or denovo variants following HTS based non-invasive targeted capture sequencing of cfDNA and both parents. This was identified e.g. causative mutations in three affected families following the sonographic suspicion of a skeletal dysplasia analysing a panel of 16 genes of interest. The most recent progress of NIPT for chromosomal anomalies and single gene anomalies is presented elegantly in this issue by Alexander Scharf and Samantha Leonhard [31], respectively.

**Conclusions**

So NIPT in addition to being a reliable method for the prenatal detection of chromosomal anomalies, microdeletions is becoming a valid option for a growing number of monogenic conditions. Some of the approaches are rather complex, however, and it remains to be seen what parents and health care systems with an insurance based solidarity principle are ready to invest in order to avoid the risk of an invasive procedure allowing simple and accurate testing. These medico-legal questions are also addressed in this special issue of the Journal of Perinatal Medicine where we want to be updated on the most recent developments in NIPT on the one side, and to raise the ethical and legal considerations about its justifications, risks and potential side effects in an open and knowledgeable way on the other side without claiming to have the perfect answers to all the serious questions.

Since fortunately the progress in prenatal diagnosis, which for a long time was moving way ahead of the possibilities in prenatal therapy, now is bridging the gap with significant achievements in prenatal therapy such an intrauterine surgery or gene therapy [32].

Our genetic counselling, which has the aim of allowing women to make their own decision based on proper and up to date information, constantly has to be updated based on the progress in this dynamic field of medicine [33]. The so-called “Information consent” has to be thrieved for, but it is always a challenge for counsellors to make sure that counselees can understand the complex information and statistics and can ultimately make decisions in accordance with their own beliefs and judgement [34]. For example, the new option of gene therapy has to be taken into account in those genetic conditions of the fetus, which now can be treated much better such as haemophilia by factor substitution, innovative medicines or gene therapy. This example of progress in gene therapy is therefore also covered in this special edition on NIPT by Johannes Oldenburg.

Overall, since the number of invasive procedures has greatly been reduced by NIPT, this technique has saved many fetal losses caused by invasive procedures, although there risk of amniocentesis and CVS is probably low now in experienced hands. The fascinating development of NIPT
is an example that significant progress in the laboratory after rigorous testing in the general population can enter clinical routine and in this way NIPT has improved the choices significantly for women and couples in a sensitive area of medicine - but we always have to proceed with caution.

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References

The implementation of non-invasive prenatal testing (NIPT) in the Netherlands

Abstract: In the Netherlands prenatal screening is offered as a mean to increase reproductive choices of couples. All women are counseled on the existing options by trained midwives. The government puts a great emphasis on informed choice and on women’s opinions and reactions to screenings options. Since 2017 non-invasive prenatal testing (NIPT, cf-DNA) is offered as first tier screening for aneuploidies in the genome-wide (GW) variant at the cost of 175 Euro’s. Uptake is around 50%. This screenings offer is perceived as unconventional for the traditionally cautious Dutch system.

Keywords: ethical concerns; genome-wide; non-invasive prenatal testing (NIPT); prenatal screening.

In the Netherlands (NL) a unique law, the Population Screening Act, regulates screening for untreatable diseases [1]. The law aims at protecting citizens against the potential negative effects of screening. As a consequence, every time a new screening for these conditions is proposed a governmental license is required before the screening can be implemented [2].

This background explains why implementation of prenatal screening (PS) in the Netherlands has always been careful and thoughtfully weighed, with special attention for its potential side-effects [2, 3]. The foundation on which Prenatal Screening has been endorsed in the NL is that the offer should enhance reproductive choices and it is essential that it rests on informed choice of women/couples [4]. This cautious policy explains why the NL was the last country in Europe to embrace PS for congenital conditions. The national screening program was implemented in 2007 [5, 6]. All pregnant women were from the outset counseled regarding the following screening options:

1. the combined testing (CT) as screening for trisomy 21 (Down syndrome) and
2. a structural ultrasound examination at around 20 weeks as screening for structural anomalies. In 2011, screening for trisomies was extended to trisomies 13 (Patau syndrome) and 18 (Edwards syndrome). Whereas mid-trimester US screening is free, women have to pay 165 Euro’s for aneuploidies screening. This fact may have contributed to the low uptake of screening for trisomies [7]. Uptake increased from 25% in 2013 to 34% in 2016. In 2014, the Dutch non invasive prenatal test (NIPT) Consortium, a collaborative partnership including all sort of stakeholders involved in PS, was granted a governmental license to introduce NIPT in the Netherlands by means of the implementation study Trial by Dutch Laboratories for Evaluation of non-invasive prenatal testing (TRIDENT) [2]. In TRIDENT-1, women at increased risk for common trisomies (risk 1/200) based on the CT or medical history and not on advanced maternal age alone, could choose between NIPT or invasive diagnostic testing. This study confirmed a remarkable reduction in the number of invasive procedures performed to confirm a high-risk result [8]. In April 2017, a second governmental license was granted to evaluate the implementation of NIPT as a first tier screening test for trisomies 21, 18, and 13 within the government-supported national prenatal screening program (TRIDENT-2 study) [6]. All women in the general obstetric population are counseled by midwives and can elect either NIPT (TRIDENT-2) or FCT as a first-tier test at the cost of 175 euro [9]. Tridents-2 is a study focusing on test performance and characteristics, as well as on women’s perspectives. Women with an increased a-priori risk, based on the criteria described above, are excluded from TRIDENT-2 but are still eligible to have NIPT under the TRIDENT-1 study, or choose directly for invasive testing. A unique feature of TRIDENT-2 is that women who elect NIPT can choose to be tested for trisomy 21, 18, and 13 either with or without extra chromosomal aberrations of the other autosomes (size resolution of 10–20 Mb). Sex chromosomes are excluded from the analysis.

Together with Belgium, NL is the only other country in Europe where NIPT is offered as first tier screening test and in the genome-wide option [10].
laboratories analyze the samples and provide the results by using Illumina platforms with the method WISECONDOR [11] first and more recently by using the VeriSeq 2.0 solution.

Previous studies have demonstrated the high sensitivity and specificity of NIPT for the common trisomies in both high- and general-risk populations [12]. However, studies dealing with the nature and clinical relevance of additional findings from whole-genome sequencing-based NIPT are limited. The same applies to studies on preferences of patients for this form of NIPT. Another characteristic of the Trident study is that a large unselected population is tested and a lot of effort is put on follow-up in order to clarify the clinical implications of the so-called ‘additional findings’ and on women experience with these results. It is known that counseling over NIPT is challenging. In the Dutch system counseling is performed by the primary care-givers, i.e. midwives or gynaecologists who had to follow a dedicated training in order to be qualified for it [13, 14]. Post-test counseling in case of abnormal results involving additional findings is carried out by geneticists. The TRIDENT-1 study, conducted in a high-risk obstetric population, highlighted the potential clinical utility of genome-wide NIPT by showing that 80% of the additional findings originated from the fetus or the placenta (the rest being maternal or unresolved, due to lack of follow-up material), and the majority were of clinical relevance for pregnancy management [8]. Other research groups have reported similar results [12]. In contrast, expanding NIPT beyond trisomies 21, 18, and 13 by including rare autosomal trisomies (RAT’s) or segmental chromosomal aberrations (SA) is a new area of investigation, almost exclusive to the TRIDENT-2 study [15]. Extension of NIPT to sex chromosomes and microdeletion syndromes has been shown to be far less sensitive and specific than NIPT for trisomy 21 only and lead to unnecessary invasive diagnostic testing and potentially to pregnancy terminations for relatively mild or uncertain phenotypic conditions [16].

Exclusion criteria for NIPT are a vanishing twin and the finding of a structural anomaly in the fetus, including a thickened nuchal translucency of 3.5 mm or more. In the latter cases a more detailed genetic investigation is needed, such as arrays CGH or whole exome sequencing, capable of detecting sub-microscopic genetic aberrations [17]. One of the limitation of the current NIPT offer is that a scan is offered for dating of pregnancy and confirmation of viability and exclusion of twins at about 10 weeks ‘gestation. The scan is performed by midwife not trained to specifically look for anomalies and at a stage where anomalies or a NT>3.5 mm may not yet be visible. This means that the exclusion criteria are in practice poorly applicable. This results in double costs whenever anomalies are detected at a later stage and women are still offered the option of an advanced genetic investigation faster a normal NIPT result.

The results of TRIDENT-1 have been promising and have shown a good DR for trisomies with a high positive predictive value (PPV) of a positive test and a dramatic reduction in the invasive procedures in comparison with the CT [8]. The cut-off for offering NIPT was set at a CT risk of 1:200. The sensitivity of NIPT for Down syndrome was 97%, 90% for Edwards syndrome, and 90% for Patau syndrome, while the CT had in the NL sensitivities of 85, 77 and 65% (RIVM, 2019), respectively.

Following TRIDENT-1, in spite of the advice of the Dutch Health council to offer NIPT as a first-tier test to all women only as test for trisomies, the NIPT offer was changed to the genome-wide variant (TRIDENT-2).

The study will continue until the end of 2023, after which the Health Council will deliberate on the future standard offer of NIPT in the NL.

In the mean time preliminary results of TRIDENT-2 have been published, reporting the result on 73,239 women who underwent NIPT [10]. Uptake of NIPT was 42%. Sensitivity and PPV for Down, Edwards and Patau syndromes were 98, 91, 100, 98, 53%, respectively. For the additional findings (AF) the overall PPV is 36%, with great variation among the type of AF: from 6% for RATs to 32% for SAs. The PPV of a positive test for abnormal maternal profiles suggestive of an increased risk of malignancy was 64%, although this concerned 11 cases of positive result, the majority of which were uterine fibroids. AF accounted for 35% of the screen-positive results, meaning that more than 1/3 of the invasive procedures were done for this reason. The extremely low PPV for RATs, is mainly attributable to false positive results due to confined placental mosaicism (CPM). Especially in case of trisomy 7, 8 and 20 a positive test was invariably attributable to a CPM [10]. Trisomy 16 seems to be the only RAT with possible clinical consequences, in view of an increased risk of growth restriction and/or premature birth. It is known that in true fetal mosaicsisms for trisomy 16 structural anomalies can occur, but infrequently and intellectual development can vary, but is mostly favorable. The counseling of women after a positive NIPT for AF is particularly challenging. In fact clinical advices and actions are taken in the setting of a research study whose aim is exactly to clarify the clinical outcome of the fetuses affected by these rare aberrations.
The question has also arisen as to how is it possible to obtain an informed consent in a study set-up where to obtain the information necessary for a good counseling is the exact aim of the study. Clinical outcomes for the majority of the additional findings are in fact still largely unknown [19].

A Dutch journalist has expressed in an article the unpleasant emotional roller-coaster his wife went through after a positive NIPT for trisomy 7 [20].

The introduction of NIPT has given rise to ethical and societal concerns about informed consent, felt pressure to undergo screening, and possible inequality in access due to the financial burden of NIPT [14]. The fee women have to pay may create a threshold and discrimination in access. Moreover, another voiced concern is that offering NIPT as a first-tier screening test may lead to routinization [21]. This concept refers to the fact that women may embark on prenatal screening more superficially as there is less risk of having to undergo an invasive procedure implying a (small) risk of miscarriage [22]. This may also lead to societal pressures to participate in prenatal screening and to stigmatization of women, families who do not do it [23]. Moreover, it has also been suggested that it may be easier to decide for termination of pregnancy of an affected fetus at an earlier stage in pregnancy, as compared to after an amniocentesis performed at 16 weeks [24]. However, all these concerns still lack empirical evidence and may not be founded [21].

Expanding the scope of NIPT to the genome wide option would seem to benefit pregnant couples, as more subtle genetic aberrations can be detected in the fetus [25]. However, concerns on expansion of NIPT to include microdeletions and other genetic aberrations have been voiced [17, 18]. It has been suggested that expanding the scope of NIPT may undermine informed decision-making because of the increased quantity and complexity of pre-test information counselors have to give [26]. Moreover, this may be the beginning of a ‘slippery-slope’ that may lead in the future to screening for minor abnormalities and even cosmetic variants. Different studies have shown that both professionals and pregnant women find it difficult to grasp the concept of an expanded NIPT [23]. In the mean time, the offer of an expanded NIPT has already started in many developed countries, including the United States besides Belgium and the Netherlands [27]. More care providers offer their patients commercially available expanded NIPT including, besides the three trisomies, also submicroscopical chromosomal aberrations and microdeletions.

A comment on the first TRIDENT-2 article was recently published in Ultrasound in Obstetrics and Gynecology. The authors express several concerns arising from GW-cfDNA testing [18].

1. Increase in the screen-positive rate of a test that was initially meant to reduce it, and increase in the rate of invasive testing for conditions of unknown clinical significance that remain of unknown significance even after an invasive procedure.
2. There is uncertainty as to the clinical significance of a heterogeneous set of chromosomal abnormalities and how best to manage a positive result. Consequently, no professional society currently recommends this test.
3. There is heterogeneity of home-brew massively parallel shotgun sequencing protocols.
4. There are ethical and legal challenges to overcome regarding how best to counsel parents before they give their informed consent, since accurate information is lacking. In fact, women are already undergoing GW-cfDNA screening without clear information about its limitations and drawbacks, and clinical decisions are already being made based on results of uncertain clinical significance.

There are also ethical concerns regarding increased voluntary termination of pregnancy due to positive RAT results even after a normal karyotype and normal ultrasound scan.

5. The test violates World Health Organization screening principles.

The conclusion of the opinion is that, although research should always be encouraged, the benefits vs. harms of implementation of GW-cfDNA screening must be weighed carefully. Healthcare providers and grant-awarding bodies have a responsibility to ensure that more robust data and management strategies are available before endorsing studies or strategies incorporating GW-cfDNA testing into nationally reimbursed screening programs.

In spite of these concerns the Dutch Health Council, traditionally extremely thoughtful and sensitive to ethical considerations related to PS, has recently released a new report, allowing the TRIDENT-2 study to continue until completion, with the only exception of not communicating anymore results of RATs almost invariably related to CPM [28].

To conclude, there is an urgent need for global ethical guidance to determine an appropriate scope of NIPT. In this context, knowledge of women’s preferences with regard to the scope of NIPT is of pivotal importance.

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Opinion Paper

Annette Dufner*

Non-invasive prenatal testing (NIPT): does the practice discriminate against persons with disabilities?

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Abstract: The most well-known goal of non-invasive prenatal testing (NIPT) is still to determine whether or not a fetus has trisomy 21. Since women often terminate the pregnancy upon a positive result, there is concern that the use of NIPT contributes to discrimination against persons with disabilities. If this concern is justified, it could have an impact on the wider social acceptability of existing testing practices and their potential further expansion. This paper demonstrates four different versions of the discrimination worry, indicates how international policy papers have reacted to them, and identifies the ethically most relevant feature of the concern.

Keywords: Down syndrome; non-invasive prenatal testing (NIPT) discrimination; trisomy 21.

Introduction

The results of non-invasive prenatal testing (NIPT) can create difficult decision situations for prospective parents. The most well-known scenario of this kind is still the case of a test result indicating that the fetus has trisomy 21. While some prospective parents ultimately use such a result to prepare themselves for the arrival of a child with special needs, others decide to terminate the pregnancy. Since the non-invasive character of the newer test methods reduces the risk of health impacts for mother and child, there is a perception that the use of such tests will continue to increase and bring along with it a corresponding increase of pregnancy terminations. As a result, there have been a number of ethical concerns raised against the use of NIPT. One concern — which shall be the focus of this paper — says that terminations due to prenatal test results will contribute to the stigmatization of and discrimination against persons with trisomy 21 and other disabilities. In addition to individual medical ethicists, this worry has been addressed by a number of national ethics councils [1–5], as well as a report for the World Health Organization [6], a report by the UNESCO International Bioethics Committee [7], and a joint position document by the European and the American Societies for Human Genetics [8]. This paper distinguishes between a number of different versions of the discrimination charge, introduces possible responses, and identifies the ethically most relevant feature of the concern.

The various facets of the discrimination charge

The discrimination charge can take on a number of different forms. These forms should be clearly differentiated, since ethical analysis and preventive measures might have to take on different forms depending on the exact aim of the criticism. There is a claim (i) that such decisions will lead to discrimination against persons with disabilities, and (ii) that the parents of children with disabilities will face increased stigmatization and discrimination (the common use of the term ‘disability’ is not intended to suggest that the controversy on whether there is a coherent individual or social account on what constitutes a disability has been resolved [9], or even just that there is a consensus on the assumption that a disability is a negative or undesirable trait [10, 11]).

There are also concerns about (iii) the decision to end/prevent the existence of a fetus with a disability, and (iv) the psychological effects of such decisions on individual members of society with a disability. In the following, I will provide a description and subsequent discussion of these four claims.

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(i) The first version of the argument says that persons with disabilities might face increased discrimination as a result of NIPT. While such discrimination could in principle take the form of intentionally hostile behavior, there seems to be a stronger concern about indirect discrimination in the literature. In particular, there is a worry that it might become harder for persons with disabilities to find specialized health care experts [4]. If fewer patients with particular needs exist in the future, this might lead to fewer medical experts in the field and subsequently to lower-quality healthcare. This would be a form of indirect discrimination: no one would willingly try to worsen the quality of healthcare for persons with trisomy 21, but it would be an indirect effect of the lower demand. Arguably, similar negative effects could also occur in other social domains that have an impact on the lives of persons with disabilities, for example in the realm of education. The most common reaction to this worry consists of arguing that the quality of healthcare for patients with disabilities has actually improved. Their life expectancy has increased and there has been progress in the treatment of some related health problems [12]. In addition, their social rights have been continually expanded [1]. Nonetheless, policy papers tend to emphasize that such developments should remain under surveillance [2–4], and some of them see the need to stress that society has a general responsibility to ameliorate the living conditions of persons with disabilities [3–5, 13].

(ii) The most commonly voiced concern regarding the parents of children with disabilities is that they might be blamed for having a child with a disability [4], that they might be faced with attitudes that the social responsibility for their children should primarily lie with them, or that their children should live more or less separately from the rest of society [1]. There is a consensus in the medical ethics literature that such reactions and attitudes are entirely inappropriate. Even though this may still occur occasionally, it is often argued that there is no empirical evidence that there is now more discrimination of this kind than before the introduction of NIPT. Quite to the contrary, there is reason to believe that the social acceptance of children with disabilities has actually increased [1].

(iii) Another version of the discrimination charge says that a termination of a wanted pregnancy on the mere ground that the fetus has a particular genetic trait implies illegitimate discrimination [14]. Obviously, there are comparatively few things that prospective parents can already know about their child. If they base a termination decision on the information that there is a disability, this seems to be a paradigm case of negative treatment due to disability.

The most common objection to this worry says that such a termination is not discriminatory if it occurs on the ground that the parents want to make use of their reproductive choices or because the mother believes that she would not be able to take care of the special needs of a child with a disability. In other words, the reason or the intention behind the action can be a self-regarding one. Such a reason is different from a negative assessment of persons with disabilities in and of themselves, and it is often emphasized that it should not be taken to imply such an assessment [2, 3, 5, 8]. This view is a central point in statements supporting the use of NIPT.

(iv) A further version of the discrimination charge concerns the fact that terminations of pregnancies after NIPD will have a negative effect on the mindset of children and adults with such disabilities. This concern has been to some extent confirmed by empirical findings. According to a small study by the Nuffield Council, for example, persons with trisomy 21 often feel sad about the fact that some people do not want to have a baby if it has Down syndrome, even though many of them also believe that a woman should have a choice about this. More generally, they report experiences with negative discourses about disability as well as a lack of knowledge about and fear of Down syndrome [15]. The concern about mindsets comes in at least two different versions. One of them is the so-called expressivist argument according to which – irrespective of the actual intentions of the prospective parents – these decisions send the message that lives with disabilities are not worth living [11]. The meaning of such terminations can be taken to include the conviction that it would be better if these disabilities – and the persons who have them – would not exist. A common reaction to this version of the argument consists of referring, once more, to the different possible motivations, intentions or reasons for termination. Arguably, the reason for termination can be the mother’s anticipated lack of her own abilities and not a concern she might have about persons with the particular disability [11].

The mindset of children and adults with disabilities might also be affected in a further way, however. The mere thought that some women decide that a child with a disability like their own would be such a burden on them that they prefer for the child not to exist could be hurtful to persons with disabilities. This version of the charge does not imply that types of actions can carry meanings, and it is independent of whether or not the hurtful feeling is viewed
as justified or not. Reactions to this concern tend to vary. While even some liberal authors concede that this is the most serious problem that NIPT can give rise to [14], others have argued that wanting a world without disabilities does not imply the hurtful claim that certain people should not exist, but that it would be better if they did not have a disability [16]. Policy papers tend to react similarly to these worries than to version (iii) of the argument. They tend to suggest that efforts should be made to emphasize that the permissibility of NIPT and subsequent pregnancy terminations is not geared at producing a lack of appreciation for the existence of persons with disabilities [2, 3, 8].

Discussion

With regard to versions (i) and (ii) of the discrimination charge, there does in fact seem to be an ethical consensus that such forms of discrimination are illegitimate, that the situation should be monitored, and that measures should be taken in the case the situation turns out to be problematic. It should be added that there sometimes seems to be a tendency not to distinguish between discrimination as directed against persons with disabilities and discrimination against their parents. Targeted measurements against particular forms of discrimination always depend on a careful and differentiated analysis of their exact character. While parents of course tend to share the interests of their children, they are bound to be more involved in organizing a social support system, while the children might be more directly affected by the behavior of their individual teachers, neighbors or physicians.

Nonetheless, if the empirical findings are correct, the situation has improved rather than worsened during the more widespread use of NIPT. A plausible reason for this could be that it has become known that the birth of children with trisomy 21 is now more likely to be the result of a fully informed welcoming attitude by their parents. At the same time, they are more likely to be born to well-prepared parents who have had a chance to look for additional support before their birth. If the empirical findings are correct, then further versions of the discrimination argument currently have to be viewed as more important regarding the ethics of NIPT.

Version (iii) of the argument is ethically more controversial. As mentioned before, the most common reaction to the worry that the termination of a pregnancy due to a disability of the child might be discriminatory is the distinction between a self-regarding judgment of the mother and a judgment about the disability of the unborn child. Critics of NIPT might be weary of this distinction. Human motivations, intentions and reasons can be diffuse, and it might be difficult for prospective parents to determine whether the intention behind a termination might be a thought such as “it will be too difficult for me to take care of a child with this trait” rather than “these traits of the child are a problem”. At the same time, though, it is by no means easier to guess at the exact character of an intention from the outside, and putting couples under general suspicion appears problematic as well. Arguing that the parents are unaware of their real intentions is a possible line to take, but since most parents are thoughtful individuals, and the ambiguity of intentions is a general problem including contexts outside of pregnancy, this line of argument can appear morally arrogant.

Perhaps one could still ask how the situation should be assessed if a woman claimed explicitly that she wants to terminate her pregnancy because she believes, “the disability of the child is a problem in and of itself”. This would appear to be a paradigmatic case of discrimination. The discrimination feature would indeed seem to make such a decision worse than a termination on other grounds. Moreover, in contrast to terminations on other grounds, here a couple wants to have a child. The decision does not occur on the ground that no child at all is wanted, but on the ground that a child with this trait is unwanted.

However, it should be kept in mind that the permissibility of pregnancy terminations implies that the fetus has a lower moral status than a child or adult. This lower status implies that the fetus does not yet have an equally strong right to life. This lower status, if one accepts it, also implies that fetuses do not yet have an equally strong right to non-discrimination as children or adults. In other words, there is a dependency relationship between one’s view about the permissibility of abortions in general and the permissibility of prenatal discrimination. If one takes the former to be permissible, it would not be convincing to treat the latter as a decisive argument against abortion. The thought that the potentially discriminatory character of the decision to terminate a pregnancy makes the decision worse seems to be contingent on the premise that fetuses have a rather high moral status. Under this condition, it can be argued that the decision is morally objectionable in two ways rather than just one. This dialectic demonstrates that some of the objections that are voiced against NIPT actually turn on a view about the moral status of the fetus and the
permissibility of abortions in general rather than of NIPT in particular [16].

Lastly, version (iv) of the argument concerns the effects on the mindset of those living with disabilities. The claim that pregnancy terminations after NIPT can be hurtful to persons with disabilities seems to be related to a reaction that any person can experience when finding out that their parents were considering an abortion. It is likely that parents generally hesitate to tell their (adult or minor) children about any such past deliberations. The hesitation seems to be due to the hurtful feelings potentially created when thinking that one’s very existence was once called into question. The realization that, at the time, one was in many essential ways “not there yet” might simply not be compelling to one’s offspring at all times. A life-shaping genetic disability as the only known feature of a fetus might increase the temptation to identify that fetus in some fundamental way with a potentially existing later adult with that disability, and might thereby make the case even less compelling. Even though the question of identity cannot and should not be reduced to any disability, the strange appeal of this conflation might make the concern about a hurtful message towards persons with a disability particularly difficult to engage with.

To summarize, there are a number of different versions of the charge that NIPT could have discriminatory effects. The worry that it might make the lives of those living disabilities or their parents more difficult seems empirically false. Their living conditions seem to have generally improved rather than worsened during the time period during which NIPT has become available. The further concern that the termination of a pregnancy upon NIPT is a paradigmatic case of discriminatory decision seems to depend on the moral status of the fetus. This leaves potentially hurtful effects on those living with disabilities as the most difficult to assess. The plausibility of this version of the charge depends on the plausibility of distinguishing between various possible reasons or intentions of those making use of NIPT, on intricate philosophical views about the relationship between existing (or non-existing) living humans and fetuses, and on psychological coping mechanisms among the members of a vulnerable group.

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References

Opinion Paper

Bert Heinrichs*

Moral ambivalence. A comment on non-invasive prenatal testing from an ethical perspective

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Abstract

**Background:** Non-invasive prenatal testing (NIPT) has been available for almost 10 years. In many countries the test attracted considerable criticism from the start. While most critical comments in this context deal with the (alleged) problem of eugenic selection, I will concentrate on a somewhat broader issue.

**Content:** I will argue that NIPT clearly has the potential to increase reproductive autonomy and benefit expectant parents. However, NIPT can also put people in a situation that is morally overwhelming for them and from which there is no easy way out. In this sense, such tests can have a dilemma-generating effect.

**Summary and Outlook:** I will conclude that this can be adequately described by the term “moral ambivalence”.

**Keywords:** genetic counseling; moral ambivalence; moral dilemma; non-invasive prenatal genetic testing.

Background

Introduction

Since the mid-19th and consistently throughout the 20th century, we have been witnessing an incredible progress in medicine (for a quick and nice-to-read overview see [1]). While life expectancy has increased significantly in most countries (from an average of 47.0 years in 1950 to 73.2 years in 2020, see [2]), the quality of life has also been improved for many people, not least for the severely and chronically ill (for the changes of the Human Development Index over the past 30 years see [3]). Among other things, this is the result of medical research and technological development. Although there is still a deplorable global discrepancy in living conditions, the result of this development benefits many people worldwide today. At the same time, medical progress has made it possible for many people to live a more self-determined life than ever before, again especially chronically ill and disabled persons. In short, medical research and technological development is a success story. But there is hardly a success story without a catch. This holds true also for the field of medicine.

In this paper, I want to examine the moral ambivalence that goes along with some medical technologies. In particular, I will focus on non-invasive prenatal testing (NIPT) as a rather recent development in the field of prenatal testing and diagnosis (PD). While most critical comments in this context deal with the (alleged) problem of eugenic selection, I will concentrate on a somewhat broader issue. I will argue that NIPT clearly has the potential to increase reproductive autonomy and benefit expectant parents. However, NIPT – and PD in general – can also put people in a situation that is morally overwhelming for them and from which there is no easy way out. In fact, the mere availability of PD means that people have to take a stance on it – even if they do not feel prepared for such a decision. Because of its low risk profile NIPT can aggravate this problem. I will conclude that this can be adequately described by the term “moral ambivalence”. Moral ambivalence is associated with some modern technologies and is, apparently, the price we have to pay for the great benefits they bring.

The introduction of non-invasive prenatal testing

The identification of cell-free fetal DNA in maternal plasma by Lo et al. in 1997 paved the way for the development of NIPT [4]. In 2011, the US-American company Sequenom introduced the first non-invasive prenatal test (“MaterniT21”) for trisomy 21 to the market [5]. Only one year
later, the German company Lifecodexx brought the test (“Praenatest”) to some European countries, including Germany. The test attracted considerable criticism from the start. In a way, this criticism was surprising because amniocentesis was already widely available as a prenatal testing method for trisomy 21. The new non-invasive test was initially less accurate, but also less risky than amniocentesis in terms of miscarriage. The harsh criticism therefore appeared to be unfounded. However, a number of authors claimed that the lower risk would make eugenic selection a common practice and, at the same time, decrease societal acceptance of people with Down’s syndrome [6]. This type of criticism proved to be quite persistent and was brought forward again in Germany when a decision was pending about whether the test should be included in the catalog of services of the statutory health insurance [7]. I join those who oppose this line of argumentation. There are, in fact, a number of compelling arguments against it: The notion of selection is inappropriate in this context, expectant parents should not be used as a means for societal goals and, finally, if people oppose liberal abortion rules, they should do so openly and directly [8].

Having said this, I want to admit that I feel a vague sympathy for the criticism raised against NIPT. But how can one reject the common arguments against NIPT and still feel somewhat uneasy about this new prenatal testing method? Is there any rational ground for this discomfort? I think so.

Content

Reasons for using NIPT

In order to see more clearly here, it is helpful to take a closer look at the reasons that speak in favor of using NIPT first. For some parents-to-be, it is clear that they will be unwilling to have a child with trisomy 21. (From the beginning on, the test covered more conditions. For the sake of simplicity, I shall concentrate on trisomy 21 as the most controversial condition.) They take the test in order to have an abortion if the result is positive (for numbers of termination rates after a positive trisomy 21 test see [9]). On the other side, for some parents-to-be, abortion is no option at all. Nevertheless, they take the test for being prepared if their child is affected. In both cases, the test is a useful tool for living an autonomous life. From the perspective of such couples, there is no room for any feeling of discomfort caused by the test. On the contrary, the test turns out to be a welcomed advancement in medical technology.

Not all parents-to-be fall neatly into one of the two groups just mentioned. A recent study by Birko et al. on preferences of Canadian pregnant women, their partners, and health professionals regarding NIPT use and access, for example, shows that there are parents-to-be who initially do not have a clear and unambiguous position on what to do in case of a positive test result [10]. The authors report that 14.3% of the women and 15.2% of partners were “unsure” how they would use a positive test result for Down’s syndrome. Apparently, those parents-to-be neither have an irrevocable attitude towards abortion, nor have they seriously considered the possibility of living a life with a disabled child before. It seems as if they choose to perform prenatal testing simply because it is available. Maybe not taking it would mean not having done ‘everything possible’ in the course of pregnancy – and this may feel like a neglect to them. It is a fact that is hard to deny that the mere accessibility of technologies can create pressures to use them. I understand that counseling services are widely available and that these services are intended to help expectant parents to consider whether and why they would like to take advantage of prenatal testing. Still, it is hard to resist the appeal of an existing technology and not just take it for granted, especially if this technology has the prospect of proving that the unborn child is doing well. After all, this is what all parents wish to hear.

To be sure, even if expectant parents do not initially have a clear idea of what to do in the event of a positive test result, a test can be very helpful. It offers them the opportunity to deal with alternative courses of action and to carefully weigh up which one is the most appropriate for them. A test, then, helps the parents to lead a self-determined life. Again, the test proves to be a beneficial medical technology and there is hardly room for any feeling of discomfort. In sum, it seems as if prenatal testing including NIPT should definitely be welcomed as a useful medical advancement.

Life and death decisions

From the beginning on, prenatal testing has made decisions about life and death necessary. For many fetal disorders and defects there were – and still are – no therapeutic approaches. Of course, parents-to-be always have the option to continue pregnancy despite a positive test result. However, the termination of a pregnancy was – and still is – an option, too. It would, therefore, be naive to deny
the life-and-death character of prenatal testing. To be sure, this is not an argument against prenatal testing. Sometimes we have to make tough decisions in life. But it is also true that we are sometimes not prepared to make such decisions. The only way to avoid decision-making in such situations is to circumvent getting into them in the first place. This is, of course, not always possible. Think, for example, about life-sustaining treatments in hopeless situations. In the absence of a patient will, relatives sometimes have to make the difficult decision as to whether or not to continue treatment. Once the situation is there, they cannot reject making a decision.

With prenatal predictive testing and diagnosis, the situation is slightly different. Expectant parents do have a choice. After counseling, they can decide against taking a test. However, such a decision comes at a price. Parents-to-be have to maintain that not using advanced medical technologies was the right thing to do. As mentioned above, technologies often create pressures and not using them becomes a matter that demands justification – to yourself and to others. However, using them throws parents-to-be into a situation in which a difficult decision suddenly becomes unavoidable.

Imagine the case of a couple that already has a child. This couple may fear that having a second child with Down’s syndrome will inevitably mean that they will not have enough time for their first child. Regardless of whether this fear is justified, they may think that they have a moral obligation to their firstborn child that they will no longer be able to live up to once the second child is born. On the other side, they may equally feel obligated towards their unborn child. An abortion may seem morally wrong to them, especially if the reason for it is a positive test result for trisomy 21. This is the typical form of classical dilemma: a situation in which two (or more) courses of action seem equally morally wrong.

I am not concerned here with the question of whether the situation just described is really a moral dilemma. Some will argue that the life of the unborn child undoubtedly matters morally more than any restrictions that may be placed on the child already born. Others will disagree and refer to the net sum of expected happiness or some other measure they deem morally relevant. The truth is that either point of view or variant thereof can refer to an elaborate ethical theory and can legitimately claim that it is an accepted position in our pluralistic society. So, if the parents do not consider either point of view convincing, it cannot be denied that the decision they face does have the structure of a dilemma. Still, one could argue that it is not the test that leads to the dilemma, but rather the fact that the unborn child is affected by trisomy 21. Of course, this is true in a way. However, it is the test that forces the expectant parents to make a decision. If they hadn’t known about the finding, they would not have had any need to act. It would just have happened. For them, the test does have a dilemma-generating effect.

Of course, everyone is free not to take the test. As already mentioned, counseling services are widely available, and these services are intended to help expectant parents to consider whether and why they would like to take advantage of prenatal testing. However, as also mentioned, it can be hard to resist the appeal of an existing technology. The more widespread a technology is and the easier it is to access it, the more difficult it is to reject it, and the faster one gets into a decision-making situation that is morally overwhelming. And even the preliminary question of whether one wants to take the test or not can present itself as a dilemma: On the one hand there is the moral obligation to do everything possible for an undisturbed course of pregnancy, on the other hand there is the possibility of excessive moral demands. The increasingly easy availability of PD – notably NIPT – thus leads to a kind of second-order dilemma. I think this latter fact can adequately be described by the term “moral ambivalence”.

Summary and outlook: dealing with moral ambivalence

What does all this mean in terms of the discomfort some feel at the introduction of ever better methods of prenatal testing, including NIPT? First, it means that for many people, NIPT is a beneficial medical technology for it can help to live a more self-determined life. Second, it means that counselling is paramount and should empower expectant parents to decide whether they want to use prenatal testing. In particular, not using prenatal tests should not be viewed as requiring special justification (unless therapeutic means are available). Third, we should recognize that easy availability can undermine this decision-making process and throw people into a moral dilemma. Fourth, we must acknowledge both the benefits and the burdens of modern technologies, as well as the moral ambivalence they inevitably create: They sometimes force us to make decisions that we do not want to make. Finally, policy regulations need to find ways for dealing with this moral ambivalence and, at the same time, respect the individual choices of expectant parents. This is especially difficult.

With regard to the recent decision of the German G-BA on whether NIPT should be included in the catalog of services of the statutory health insurance, Christoph
Rehmann-Sutter and Christina Schües maintained that the regulation is both paradoxical and flexible. They continue to argue that “the model of the G-BA could be a socio-politically and ultimately also ethically defensible pragmatic solution, exactly because of its paradoxes and its inherent flexibility.” [11, 386]. This, in turn, can be interpreted as an attempt to come to terms with moral ambivalence.

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References
Opinion Paper

Christoph Rehmann-Sutter*

Should prenatal screening be seen as ‘selective reproduction’? Four reasons to reframe the ethical debate

Abstract: There are a number of problems with the classification of prenatal screening as a form of ‘selective reproduction’ that has become an increasingly dominant classification scheme in the last decade. (1) Since the term ‘selection’ implies choosing one out of several (at least two), it misdescribes the decision to terminate a pregnancy. (2) Deciding whether to have this child is a decision taken within the relationships that constitute the pregnancy. (3) ‘Selection’ is a loaded term, connecting prenatal diagnosis to negative eugenics or to population genetics. (4) Deciding against the birth of a child who would suffer or would not be able to flourish is a decision taken within a negotiation of personal responsibilities and social constraints. The characterization of prenatal screening as selective reproduction is, in a very narrow way, defensible to reconstruct why prenatal screening is permissible in a liberal state and should not be banned, but it needs to be rejected as a general frame for understanding the substance of the ethical issues around prenatal diagnosis and screening. Ethics should rather attempt to create a respectful space of mutual understandings and reflect how women and couples, who are ultimately responsible for these decisions, perceive their responsibilities in care.

Keywords: ethics; genetic counselling; non-invasive prenatal testing (NIPT); prenatal diagnosis; prenatal screening.

Introduction

Triggered by Stephen Wilkinson’s seminal work of 2010, the liberal bioethics literature within the past decade has adopted the label of ‘selective reproduction’ for classifying the choices occasioned by technologies such as prenatal diagnosis (PD) or prenatal screening (PS) – with or without non-invasive genetic tests (non-invasive prenatal testing; NIPT), and, hypothetically, also germline genome editing (GGE). What these choices have in common, so it is claimed, is that people attempt “to create one possible future child rather than a different possible future child” because one is “in some way, more desirable than the alternatives” [1, p. 2]. Health is seen as the most uncontested criterion of desirability. (Who would not wish their child to be healthy?) This characterizes the special type of choices that are essential for PD, PS and GGE and preimplantation genetic diagnosis (PGD), sperm or egg banks. This classificatory scheme has become what Simon Reader called the “orthodox liberal eugenic view of selective reproduction in philosophical bioethics” [2, p. 25].

For people who decide about actions the words matter, which they use to describe and understand the practice in question. In ethics, the categories we use to classify and characterize the meaning of an action or a decision make a difference. It is not technology alone that determines the purpose of its use. A ‘social practice’ is created as a shared meaningful behaviour that ‘one does’ in a society and for which one deserves justification or praise. In the sociology of practices a ‘social practice’ can, according to Schatzki, be broadly described as “a nexus of doings and sayings” [3, p. 25]. A practice is not only an established way of doing things but also an established way of understanding and explaining the meanings of what one usually does in certain situations [4]. Words define how we understand what we do; shared words are part of our mutually communicative ascertainment. Therefore, inherent in a social practice is also a hermeneutics operating within a shared social world. The words used are part of that practice. A label such as ‘selective reproduction’ therefore itself needs to be scrutinized from an...
ethical perspective; sensitive categories such as ‘selection’ come with narratives attached. Their meanings (i) frame the ethical discussion in a particular way, and also (ii) shape the moral understandings in individual decision-making.

Advocates of prenatal diagnosis since the 1970s have categorically rejected the accusation of a ‘eugenic’ drift, and have instead positioned PD and PS as grounded in women’s rights to freely choose whether they wish to give birth to a disabled child [5, p. 71]. Language that connects the practice of PD/PS to the frequency of ‘defective’ genes in a population and to a practice of selection has been carefully avoided. In 2001 Sheldon and Wilkinson used the description “selective termination of disabled foetuses on the grounds of their disability” in a paper that defends the legality of free choice about all abortions, “regardless of any foetal disability” [6]. Wilkinson later generalized the idea and formally introduced “selective reproduction” as a category of practices that covers PD, PS, NIPT, GGE and more. The appeal of this term is that utterly divergent technologies and actions share one common denominator: they allow for selective choices about future children based on genetic characteristics. The broad definition allows for argumentative economy. If we answer the question ‘Is selective reproduction permissible?’ we will at least have the principle of an answer for all the particular technologies so classified.

However, this approach, I will argue, does not convincingly characterize the ethical gist of the situation and the moral point of view of a woman or a couple confronted with the decision about termination after PD/PS. Used as a general framing of the morally complex ethical issues of PD/PS, ‘selective reproduction’ is a rather troubling concept.

Acts of selection

In ordinary English, the word ‘selection’ is used to name an act or a process of selecting. ‘To select’ (lat. *seligere*) is the basic verb. It means to choose from a number or group [7, p. 2058]. A number or a group is more than one. Based on this definition, it would be simply wrong to call the decision to terminate a pregnancy on the grounds of a prenatally diagnosed disability a selection, since there is not more than one future child from which the woman or the couple could choose. At the time of decision-making after a prenatal diagnosis, there is only this one future child to decide about. The woman in this situation has two options to choose from – to terminate the pregnancy or to continue it and to give birth – but she does not have two children to choose from.

She might indeed wish to get pregnant with another child afterwards and the couple might hope that the new pregnancy will lead to a child without the disability. But she cannot decide at that moment about this, since it is a matter of wishing and planning. In the temporal mode of *futurum passatum*, anticipating a future in which she could look back from a point in time after the birth of another healthy child, she could describe her conduct in the long run as selection: as a result of a sequence of actions going through two (or more) pregnancies, she has had an able-bodied child rather than one with a disability, and in this sense she has selected. But it is inaccurate to describe the decision she makes at this point in time as a selective practice.

This analysis of the concept of selection is notably not based in a criticism of PD/PS as ‘eugenic’. It only focuses on the options available in a situation. Using the description ‘selective reproduction’ despite its inaccuracy falsely attributes an overarching selective plan to a woman/couple who may make a decision while feeling deeply troubled and conflicted.

This can be illustrated by one woman from a comparative interview study we conducted in Germany and Israel with women and their partners who had either used or refused to use NIPT [8, 9]. Ute, a German woman who had used NIPT, explained it by referring to her husband’s sister who was 38 and had a severe form of Down syndrome:

“…I have known her for 5 years already, and (.) well, this has … a big influence on me, so that I just see a life I wouldn’t want for me, wouldn’t want for my child.” (#40 Germany, lines 215–218)

The narrative that she gave about her decision was not built around any selective purpose whatsoever, and she did not express any rejection of her sister-in-law.

“Well, I believe my sister-in-law is quite happy in her world, but her world is not connected to our world.” (line 216 f.)

She and her partner had instead thought about what they were capable of and they felt, as she said, that she just could not wish *this* life on herself and her child.

In the process of PGD, however, there is indeed a choice to be taken from a number of embryos created previously in *vitro*. The term ‘selection’ can indeed be used correctly to characterize the decision that must inevitably be taken during PGD: after each embryo in the laboratory is tested, one or more are selected to be implanted. But the term ‘selection’ may still be alien to the motives and intentions of the couple who, like Ute with PD, use IVF plus PGD in order to avoid their child having a genetic disease, because they have reasons to fear having a child with a severe genetic disorder and do not want *their* child after this pregnancy to...
be affected by it. If this is so, fearing this disease in their child, they are not practising ‘selection’ either. They are not deciding to use PGD during an existing pregnancy, as is the case in PD/PS, but before establishing a new pregnancy, often after the experience of one or more miscarriages. They can be motivated by similar considerations in regard to their one future child as they would be using PD/PS.

A reconstruction of Wilkinson’s argument

In the bioethical literature on reproductive genetics, ‘selection’ has appeared mostly with a negative overtone – as a name for a problematic development. Asch and Barley, for instance, begin their encyclopaedic formulation of the ‘disability critique’ of prenatal testing with this statement: “Selecting against embryos or foetuses on the basis of predicted disability reinforces the belief that disability is inimical to a worthwhile life.” [10, p. 1] They use ‘selection’ as a key descriptor, emphasizing its ambivalence: one future child is selected to be born, while another is selected out. This, according to their main argument, reinforces the belief that a life with disability is not a worthwhile life. The essence of the disability critique is that PD/PS itself is discriminatory, nor, as has frequently been claimed, it consists in the ‘expressivist argument’: sending a negative message to those living with disability. Rather, it is “the mistaken belief that disability itself, not the social discrimination against people with disabilities, is the problem to be solved.” (p. 2). Ilana Löwy, writing from the perspective of a historian, also sees selection as problematic, as she considers public debates on PD to be “frequently centred on the risks of a gradual and imperceptible sliding into increasingly selective reproduction.” [5, p. 186] Selective reproduction, in her take, characterizes an undesirable state of societies where the “backdoor to eugenics” is opened by the individualized “parental dream of a perfect child” (ibid.). This problematic state could emerge unintentionally: societies could gradually and imperceptibly “slide” into it.

It is therefore surprising that Wilkinson starts his discussion with a formal definition of selective reproduction, using the term without reservation:

“By ‘selective reproduction’ I mean the attempt to create one possible future child rather than a different possible future child. The reason for wanting to practise selective reproduction is normally that one possible future child is, in some way, more desirable than the alternatives.” [1, p. 2]

Instead of dismissing Wilkinson’s argument on the grounds that it misrepresents PD/PS from the perspective of the woman or the couple, I acknowledge that it argues on a different level. He does not focus on individual decision-making at all but on the laws that regulate them. Unlike Glover for instance, who has treated the question of whether using “genetic and reproductive techniques to have a healthy child rather than one with a disability” is “justifiable” [11, p. 5], Wilkinson asks whether laws should allow or ban this practice, regardless of the motives individuals may have for using PD techniques, and without judging whether it is justifiable for them. “Permissibility” is therefore the term of choice. While justification works on the level of the actors involved, permissibility works on the level of regulation, which needs to tackle this question: are there sufficient reasons to forbid the action regardless of the actor’s motives?

Within a Millian liberal approach to legal philosophy, an action is “permissible (neither wrong, nor obligatory, nor supererogatory) until an argument can be found that shows it to be otherwise.” [1, p. 13] This is what Wilkinson calls the ‘presumption of permissibility’. The task of an ethical analysis on this basis is then rather negative: to search for arguments that might overturn this presumption. As long as none can be found, the action should be permitted. If this method is to produce a reliable result, it of course needs to examine counterarguments (i) comprehensively and (ii) each in their strongest possible form. To do so, Wilkinson could argue (iii) it should not assume that the actors all have ethically justifiable motives. They just may do what they prefer to do for whatever reason. Applied to reproductive genetics, we may assume that with the routine use of NIPT, social expectations are changing and societies may indeed “slide into” selective reproduction on the basis of predictions of disease and disability; parents indeed intend to ‘replace’ a terminated pregnancy with a new one and perform sequential selection (the term ‘replace’ has been suggested by Tarkian [12] to interpret Wilkinson’s definition). Therefore, we may concede that the use of the term selection, even though inappropriate for many parents who have no selective intentions whatsoever, may therefore be warranted as a realistic description of the practice.

I would therefore reconstruct Wilkinson’s argument about PD/PS in the following way:

- Premise A: PD/PS is a form of selective reproduction.
- Premise B. Selection to avoid disease or disability is mostly uncontentious.
- Result of a comprehensive vetting of objections: There are no concerns strong enough to oppose permissibility of selective reproduction.
- Conclusion: PD/PS to avoid disease and disability should be allowed.
Beyond liberalist individualism: responsibility and inclusion

The same argument could be made about PD/PS directly, without using Premise A. Permissibility of PD/PS then does not depend on its classification as selective reproduction. Wilkinson obviously wanted to achieve more than justify the legality of PD/PS alone – to argue for the legality of any form of liberal eugenics, in the widest possible meaning of the term, as long as it does not harm children or other people, or exploit or instrumentalize them. The argumentative thinness of his liberalist approach however reduces the scope of ethics. It reduces the sensitivity to the changes in intergenerational relationships both in families and in societies. Not all that is ethically relevant, that affects justice and a good life, can be captured by harm, instrumentalization or exploitation. As I have argued elsewhere [13], GGE needs to be analysed in the light of the shifts in the moral constitution of intergenerational relationships that it would effectuate, if widely used. Previous generations would assume responsibility for the genetic constitution of their offspring, and also for those parts of the genome that are not altered, for all the good and bad that is in a genome. This could possibly create new forms of injustice and intergenerational guilt.

There is also much more to say about autonomy than the liberal individualist approach allows for. Autonomy in the context of abortion is essentially an embodied and relational concept [14]. As Mianna Meskus has demonstrated in a qualitative study [15], the expectation that they will make autonomous decisions about pregnancies and be responsible for a ‘personalized ethics’ can be perceived as a heavy burden by women who have to make these decisions. They are vulnerable in many ways: to social pressures, demands from their families, or expectations of their healthcare providers. If they have a test mainly for reasons of conformity, perhaps without thinking twice, and subsequently find themselves inadvertently in a difficult situation where they have to decide about termination, they are arguably harmed. If society started to treat women as producers of only healthy progeny to fulfil a social demand, counting on their ‘autonomy’, it would come close to instrumentalization. On the other hand, PD/PS would also harm people with disabilities if societies used it as an excuse for making less effort towards support and inclusion. If the routinized use of PS (triggered by the perceived easiness of NIPT) leads to an even more black-and-white social idea of disability, without seeing the good of variant forms of embodiment [16], one can argue that a social practice of PD/PS is at least strongly ambivalent. This in turn would reduce the well-being of children with disabilities and put more pressure on women to avoid giving birth to a child with a disability. The two factors are therefore related: (1) freedom of decision-making (which presumes adequate information, communication and support, and (2) social inclusion of those who live with the conditions PD is testing for [17–19]. If both criteria are satisfied, it would be difficult to argue for banning or restricting access to PD. The other side of the coin is however that, if PD is practiced and improved, societies create two mutually related social obligations: (1) to respect and support women’s free decision-making, while improving the conditions of decision-making wherever needed, and (2) to improve inclusion of and support for people with disabilities, in order not to create moral pressure to spare a child with a disability suffering because of insufficient support and inclusion. Without satisfying these social obligations, reproductive autonomy slides into a cold ideology of individualism: instead of caring for each other, societies would place this unpleasant responsibility onto pregnant women who then have to carry the burden of taking what Rothman has aptly called “impossible decisions” [20].

Problems with the ‘selective reproduction ’frame

In order to discuss permissibility in a liberal framework, it might be necessary to a certain extent to disregard the motives people might have and to focus exclusively on the evaluation of possible reasons to restrict individual choices. This way of clarifying permissibility however cannot help to understand the moral questions and conflicts in the actors’ perspectives, which constitute the situation of women who undergo PS/PD and their partners.
They will ask themselves how to justify their decisions. To discuss this requires considering not just the legal and moral rules, but also the meanings that are connected to the practice on which they are reflecting. It is here that I see the main problem with the framing of this practice as ‘selective reproduction’.

First, the decision about a pregnancy is inaccurately described by the term ‘selection’. It is not a situation where a choice is made between multiple pregnancies or several possible children, but primarily about one ongoing pregnancy, on the basis of available information about the future living conditions of the child. Termination of a pregnancy is not ‘replacing’ one possible child by another but terminating one foetal life. One can hope to have a next pregnancy, but this will be another pregnancy. Therefore, ‘replacement’ and a fortiori ‘selection’ are terms that do not work from the actors’ perspectives.

Second, this is not only a terminological issue; the description is also an obstacle for the woman or the couple that distracts them from seeing what is at stake in their situation. The assumptions underlying ‘selective reproduction’ are ethically problematic, since they shift the attention away from the special character of the very relationship that makes up a pregnancy. Pregnancy is not an abstract relation to plural future children, among which one could choose, but a genuinely particular and irreplaceable relationship (for a similar argument contra Tarkian, see Mitscherlich-Schönherr [21]; on relationality of pregnancy and birth, see Schües [22]). For the woman and the couple, an answer that can convince them morally must include this existential situation of pregnancy. If a woman imaginatively positions herself as performing ‘selection’ in her dealing with her pregnancy, she is adopting a point of view outside of her pregnancy, looking at herself from an abstract population point of view, or at herself choosing in some sort of ‘free market’. If she, or the couple, bases their thinking on this constructed ‘gaze’, they risk making a decision that disregards their existential involvement and might not convince them in retrospect.

Third, ‘selection’ is a loaded word. It explicitly connects decision-making about PS/PD either to (negative) eugenics, which is exactly what the professional ethics of human genetics constantly argues against ever since the introduction of amniocentesis (for the specific cultural context of German bioethical discourses, see [23]). It would support reductionist thinking of disability as a person’s main feature. Or it would connect the situation of decision-making in a pregnancy to problematic social Darwinist theories.

Finally, the ethical difficulties in the decision against the birth of a child who would suffer and not flourish are rooted in the conflict between responsibilities to the child to be born, and responsibilities to oneself and one’s family. To understand and resolve this difficult conflict as carefully as possible, the selective reproduction frame is not helpful. It is rather an obstacle to addressing this conflict of responsibility adequately – both practically and theoretically.

Conclusion: reasons to reframe the debate

In the emerging social practices of PD/PS, both doings and sayings matter. ‘Selective reproduction’ is a problematic conceptual offer to people who decide about or practice PS/PD. While ‘selective reproduction’ can well be used as the name for a field of comparative anthropology investigating the emerging social practices of reproductive genetics [24], there are more ethically relevant questions than the one about the permissibility of a practice. Bioethics needs to deal with all levels of social practices of technology use: the regulatory and the individual, the social and the intergenerational, its place in history and the comparison with other traditions. It needs to address and acknowledge all perspectives involved: the professionalism of physicians and experts involved in reproductive genetics, the concerns of women and their partners, the perspectives of families and their generations, and of course the regulators’ arguments that raise controversy in different cultural contexts. Such an ethics creates a respectful space of mutual understandings and public deliberation that helps to make ‘personalized ethics’ [15] a less solitary enterprise.

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References

Review

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Making use of non-invasive prenatal testing (NIPT): rethinking issues of routinization and pressure

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Abstract: First mapping the main ethical issues surrounding prenatal testing, we then analyze which concerns are specific to non-invasive methods. Presupposing the privatization premise for reproductive autonomy in fundamentally liberal societies, we go on to specify common concerns about non-invasive prenatal testing (NIPT) covered by the term ‘routinization’, and conceptually unravel the frequently expressed worry of increasing ‘pressure’ to test and/or terminate affected pregnancies. We argue that mindful decision-making should be a key educational goal (not only) of NIPT counseling which could be achieved through stepwise disclosure. In addition, we identify indirect social pressure as the most plausible threat to reproductive freedom. While continuous efforts need to be made to prevent such pressure – not least by ensuring balanced availability of options –, restricting testing options, and thus freedom of choice, cannot be the answer to this concern. Lastly, we suggest abandoning the vague term ‘routinization’ and instead focusing on specified concerns to enable a fruitful debate.

Keywords: freedom of choice; non-invasive prenatal testing (NIPT); prenatal testing; reproductive autonomy; routinization; social pressure.

Introduction

Non-invasive prenatal testing (NIPT) is a recently introduced method that allows to identify certain genetic characteristics of a fetus. Currently, these include but are not limited to chromosomal aberrations. It is to be expected that sooner rather than later medical-technological progress will render a variety of other uses possible [cf. 1].

Undeniably, in terms of medical benefit and safety NIPT is entirely advantageous over other available prenatal diagnostic tests (PND) such as amnio- or chorionicentesis: while these invasive interventions involve a small risk of procedure-induced miscarriage, NIPT requires nothing but a blood sample from the pregnant woman and therefore poses no risk to her pregnancy. Due to its non-invasive nature, it is physically and mentally much less burdensome. Moreover, it can be conducted earlier in pregnancy and more discretely. It is, however, just NIPT’s procedural harmlessness or triviality that in the eyes of critics gives rise to some specific ethical concerns of which the fears of ‘routinization’ and ‘pressure’ seem the most prominent rhetoric coatings.

Mapping ethical concerns regarding NIPT

Objections to the provision and the use of NIPT are usually not directed against the test itself, but against its role as a promoter of selective abortions. Notwithstanding some uneasiness with the term ‘selection’ especially in German contexts [cf. 2], it has become the internationally established label for abortions motivated by certain characteristics of the potential off-spring – e.g. by genetic abnormalities. Selective abortions, much as abortions in general, are viewed as ethically illegitimate by those who ascribe a right to life to human embryos. In addition, ending pregnancies in order to avoid giving birth to a disabled child is often criticized because of these acts’ (alleged) discriminatory implications or consequences for living people with disabilities. And finally, ethical concerns are raised, that selective reproduction might on a general scale deteriorate parent–child-relations or de-humanize society. In the absence of empirical data...
that would give evidence to such undesired social developments in the wake of PND and lacking a consensus on the moral status of early embryos, secular societies tend to be more or less liberal towards selective abortions and thus to respect private autonomous decision-making by individual women and couples on these very personal and moral matters. Let us call this the *privatization premise*, which in this paper we will take for granted and, moreover, for appropriate and legitimate.

Against this background, any plausible objection against NIPT would have to question the *autonomy* of its usage. Thus, the two ethical objections that *specifically* address consequences of NIPT’s procedural triviality, have to be looked at from this perspective. Critics claim or worry that NIPT might:
- turn into a *routine* test;
- go along with some external *pressure* on women to actually make use of this easy-going test. Both physicians and women’s social environment, so the concern, might more and more *expect* the use of NIPT, slowly turning it into a *de facto* screening tool.

Both concerns somehow allude to violations of the autonomy requirement for valid informed consent. But do these concerns survive scrutiny?

In their perennially influential monography *Principles of Biomedical Ethics*, Beauchamp and Childress develop a model of decision autonomy with three necessary preconditions, i.e. patient ‘competence’, sufficient ‘understanding’ and the absence of ‘controlling influence’ by others – influence that would render consent in-voluntary. Thus, to count as valid, any patient authorization of a medical intervention has to meet these three requirements [3, chap. 4]. Issues of defective or questionable competence are typically related to consent in the context of psychiatric or pediatric care or else with regard to patients suffering from compromised cognitive, emotional, or volitive capacities. For the clientele of pregnant women and their partners, this aspect seems of marginal importance for single cases only. Obviously then, the above two concerns against NIPT would, if justified, regard the understanding – or the voluntariness-requirement of NIPT consent.

**Specifying ‘routinization’**

As reported above, NIPT’s benefits are often accused of contributing to its ‘routinization’. Indeed, this concern has been at the center of the debate from its very beginning (see for example [4, 5]). Although not normative in itself, in the context of NIPT this term is mostly used with a decidedly negative connotation. But a clear-cut definition is often missing.

This lack of conceptual clarity has only recently received more attention: ‘routinization’ has been identified as an ‘umbrella term’ [6] or a ‘container concept’ [7] that encompasses a number of underlying concerns. Profiting from those insights, we want to add to the picture by starting from a more general definition.

According to the Oxford English Dictionary (OED), ‘routinization’ means ‘the fact of being or becoming routine in character or operation’ [8]. With an eye to this entry, we will concentrate on ‘routine in character’, since operative excellence cannot as such reasonably be criticized in any (medical) context. In turn, the OED defines ‘routine’ as

> [...] a regularly followed procedure; an established or prescribed way of doing something; a more or less mechanical or unvarying way of performing certain actions or duties [9].

Following the OED, we suggest differentiating between four meanings of NIPT becoming ‘routine in character’, each of which we want to evaluate from the perspective of liberal ethics, i. e. presupposing the privatization premise, as spelt out in the first section:

(i) NIPT will quite likely be used with increasing frequency and – by not only substituting, but amending PND – lead to a rise in overall prenatal testing. But, as has been stated before, an increasing usage *as such* need not be problematic, as long as it does not occur for problematic reasons [cf. 6]. Assuming that women opt for NIPT in the very informed and thoughtful manner that is striving for in all prenatal testing, nothing could and should be criticized – in accord with the privatization premise (see above). Hence, one must take a closer look at the decision-making processes that might lead to women’s increased utilization of NIPT. In short, it is not the pure quantity, but the quality of choosing NIPT that might turn out ethically problematic and might even occur unnoticed. Again following the above OED definition, three such qualitative transformations seem conceivable:

(ii) The decision for NIPT following a ‘routine’ could mean to take an ‘established’ course of action. ‘Established’ is a neutral term but can be interpreted in different ways. It could mean, for instance, that NIPT becomes more widely accepted (as expressed by individual autonomous decisions). This in turn could have an alleviating impact on women who would want to use prenatal testing, but whose social environment is currently intolerant of this decision. These women might be more confident in daring to choose NIPT in
accordance with their personal liberal convictions if their decision is an ‘established’ one. To illustrate this by an innocent (and less ethics-laden) example: some mothers might have wanted to take their young children to kindergarten but could not do this against conservative familial convictions. Routinization of early onset external child-care might make it easier for them to follow their own preferences.

(iii) Critics of NIPT view it as a subtly ‘prescribed way of doing something’, as included in the OED definition. More often, such suspected ‘prescription’ is called ‘social pressure’ by which NIPT would slowly become the social default – so that women might no longer dare to decline the test. We will look at this frequently expressed worry further down. In any case, pressure could potentially impair the voluntariness condition of women’s decisions about NIPT.

(iv) Finally, women might decide in favor of NIPT in ‘a more or less mechanical or unvarying way’. This could be interpreted as a lack of mindfulness or of deliberative diligence regarding the potential personal and moral consequences of a positive test result. Opting for ‘just another blood test’ [10, 11] without realizing its specific meaning for potential future decisional burdens, might indeed violate the understanding condition of autonomous decision making. We will come to this right away.

Understanding

According to the standard view of informed consent, its validity requires quite diverse categories of knowledge on the side of the consenting person. Above all, she must understand that she individually has the unlimited right to authorize or veto any intervention at stake. In addition, she ought to be informed about the intervention’s nature, its comparative risks and benefits, and its potential consequences in any relevant regard. The relevance in question should ultimately be judged from a personal perspective.

In the context of prenatal genetic testing – invasive or non-invasive – ‘pathological’ outcomes (for example a detected chromosomal aberration) inescapably confront pregnant women with the option of deciding for or against continuing a thus affected pregnancy. While some women would not want to receive any genetic information about their future child, others are interested in knowing about their future child’s potential disabilities in order to prepare for a life together. So far however, a majority of women or couples opt for testing because they intend or would consider terminating their pregnancies in case of an abnormal test result. And in case of such a result most of them do decide in favor of an abortion [cf. 12].

As has been emphasized by various authors, autonomous decision-making both before testing and afterwards, requires complex knowledge about testing, its possible results, its safety and reliability, and about the effects that genetic risks of disease or disability could have on the future child and its family. Moreover, women should be informed about potential decisional burdens and the non-medical nature of selective decisions: despite prenatal genetic testing taking place in a clinical setting, the decision to terminate or to continue an affected pregnancy is (outside rare vital problems on the side of the woman or the fetus) not primarily medical in nature, but deeply impregnated by personal interests and moral views. When confronted with a deviant test result, women should get detailed information about financial, social, and medical support in caring for a child born with the genetic deviation at hand. They should be enabled to connect with parents who are or have been in similar situations.

All of this being true for prenatal genetic testing in general, what is specific about NIPT? Some authors fear that autonomous decision-making about NIPT might require an ‘information overload’ [13]; others are concerned that the procedure’s very triviality might reduce the attention given to careful and broad pre-test disclosure on the side of physicians as well as of test-using women [cf. 14]. Seeing the risk of disclosure overload as a general rather than an NIPT-specific issue, we do, however, embrace the second concern. Thus, in agreement with many other authors, not the least a number of Dutch colleagues, we find it very convincing to frame NIPT by a well-structured setting of stepwise disclosure [cf. 15]. For example, this could include a general information offer and, in case of a positive reaction, an exploration of which genetic characteristics of the fetus the pregnant woman would be interested in. Only after this personal scope is set, the desired concrete information would be conveyed. This approach could prevent inattentive or insufficient counseling as well as issues of information overload. It would therefore be useful not only in the context of NIPT, but for prenatal testing in general. Even if empirical data on informational deficits in NIPT might still be inconclusive, there is much to say in favor of preventing any such deficits to occur or aggravate. In particular, counseling experts should neither assume sufficient ex-ante knowledge on the side of their patients nor completely postpone any discussion on the potential termination of the pregnancy until the occurrence of a deviant test result.
Conceptualizing pressure

Increasing ‘pressure’ upon women is a predominant issue of critical concern related to offering and using NIPT. As analyzed above, it is one of the core suspicions framed as ‘routinization’. Once again, however, the term ‘pressure’ is often used without sufficient definition or characterization. While some authors in their analyses presuppose a common understanding of ‘undue pressure’ [14], others apply it to a variety of situations, ranging from ‘explicit coercion on the part of healthcare providers to subtle influences of prevailing social norm’ [16]. In what follows, we want to shed some conceptual light on this key term and draw some normative conclusions.

According to the standard view in medical ethics stipulated above, decisional autonomy requires, among others, ‘freedom from controlling conditions’ [3, chap. 4]. They conceptualize this ‘voluntariness’ condition mainly as the absence of coercion and undue manipulation by other persons or institutions on the decision at stake. Outright coercion being obviously irrelevant for the context of NIPT in a fundamentally liberal society, manipulation seems to be the phenomenon to look at for further orientation. Here, Beauchamp/Childress focus on ‘informational manipulation’ as ‘a deliberate act of managing information that alters a person’s understanding of a situation and motivates him or her to do what the agent of influence intends’ [3, p. 137]. Unsurprisingly, they consider many forms of such informational manipulation as ‘incompatible with autonomous decision making. For example, lying, withholding information, and exaggeration with the intent to lead persons to believe what is false’ [3, p. 137]. On the other hand, they caution against an inflated diagnosis of control by manipulation in health care:

We often make decisions in a context of competing influences, such as personal desires, familial constraints, legal obligations, and institutional pressures, but these influences usually do not control decisions to a morally worrisome degree [3, p. 138].

Where does this leave us with regard to NIPT decision making? First of all, it can never be completely ruled out that individual counselors or caretakers intentionally exercise informational manipulation in order to nudge or even direct women into undergoing/not undergoing a prenatal test or a subsequent abortion [cf. 17]. But on the whole and in a transparent society like ours, it is very unlikely for such unprofessional behavior to occur on a larger scale and to remain undetected and uncriticized. Nevertheless, binding professionals to the standard of non-directive counselling during their training and continued education seems both advisable and feasible.

Yet another form of pressure that critics are afraid of is the slow conversion of NIPT as an option for single cases into a screening tool whose use is widely regarded as part of a responsible and reasonable reproductive care regime. On the other hand, not using NIPT could then gradually be seen as careless, irresponsible, and even objectionable. To be sure, raising and supporting disabled children often require additional financial, emotional, or organizational efforts not only by families but also by society in terms of educational or health care support. The wish to circumvent such perceived ‘burdens’ might, so a common worry, slowly invite subtle pressure towards NIPT and subsequent selective abortions. By no means does this seem a totally ungrounded speculation.

In theory, three varieties of such a potential development could be distinguished. In the first scenario pressure towards NIPT and selective abortions might result from society’s gradual direct or indirect reduction of support and inclusion of disabled children. In a liberal and non-discriminatory society this would be a constitutional, ethical, and political no-go, which would have to be banned in any respect. As a social prognosis it cannot be precluded in principle but does not deserve serious concern in today’s modern societies. Moreover, empirical data prove a significant increase in positive attitudes towards the inclusion of disabled children [cf. 18].

In the second scenario pregnant women might not adequately realize the complex personal and moral issues at stake. Or they might not adequately perceive their unconditional rights to both reproductive autonomy and social support in raising a disabled child. The underlying mechanism would thus start with poor knowledge leading into a spiral of slowly shifting the default line in prenatal testing habits. Quite obviously, this coincides with the already discussed violation of the understanding condition. As a result, future pregnant women might unwillingly adapt to ‘what everybody does’. We emphasize once more that such deficits in understanding should by all means be prevented.

In a third scenario, women would well know about their rights to reproductive autonomy, including the use of NIPT. But despite being thus well-informed, they might feel under pressure to adapt to an increased use of NIPT resulting from autonomous decisions by other women. This possibility touches some deeper issues of freedom in pluralistic societies, which we now want to address. According to social philosopher Philipp Pettit, freedom of choice presupposes the availability of options (‘open doors’) regardless of one’s own preferences and regardless of what others prefer the agent to choose [19]. Again, like doors, options can be more or less easily accessed. Thus,
intentionally rendering options difficult to take, is yet another way to limit someone’s freedom.

Basically, NIPT issues involve option-freedom. Women should thus be well informed about the availability of the test and about their freedom to use it or not to use it – without having to justify their decision to authorities and without having to overcome obstacles that are meant to remind them of the socially unwanted character of either option. Trivially, having more options available for one’s reproductive behavior might entail decisional burdens, but that is the price to be paid for freedom – here as elsewhere. Protecting women from choice-overload by restricting the availability of options would surely be a paternalistic no-go.

All that having been said, how should one assess the reverse concern of the third scenario above – i.e. the concern that women might feel pushed to use the seemingly comfortable option-door of NIPT? It has indeed been a long-standing argument in the pressure debate that the increasingly comfortable option-door of NIPT? It has indeed been a long-standing argument in the pressure debate that the invasiveness and riskiness of PID so far has functioned as a firewall welcomed by some women who repudiate prenatal testing and selecting for moral or principled personal reasons [cf. 20]. With NIPT they would now lose their defensive ‘pretext’ against society’s potentially increasing pro-test expectations [13].

Surely, withholding medically advantageous options from women to protect them from having to explain their decision-leading moral or personal reasons cannot be an adequate solution for preventing potentially contested or heteronomous decisions. Such a solution must rather focus on the way NIPT is framed and portrayed. Procedural aspects must be adjusted to empower and encourage women to make autonomous, individual decisions independent from perceived expectations.

On the other hand, not-testing and thus, if the situation occurs, accepting and raising a disabled child must become a still easier option (a ‘wide open door’) than it often is in reality. Social pressure consisting in unintended, but nevertheless effective neglect of the various needs of affected women, children, and families must be confronted and combated. Such invisible indirect social pressure seems to be the greatest danger for reproductive freedom – much as in other contexts where options are asymmetric in terms of societal costs and efforts. An analogous example might be seen in end-of-life decisional options: critics of liberal regulations of assisted suicide regularly express worries that over time society might diminish its efforts in making life satisfying even under conditions of terminal disease, frailty, or advanced dementia. The required antidot is sometimes called ‘equally valuable options’ [21] or turning available options into ‘real’ ones [22]. We prefer subsuming these ideas under the expression ‘balanced availability of options’ as this might even better illustrate the need for symmetrically open doors.

Once more then, our answer to this problem points to the preconditions of autonomous decision-making: without some stamina, some maturity, some willingness to take final responsibility for how to lead one’s life, the whole idea of autonomy collapses. Literacy in reproductive medicine and reproductive ethics has to be among the educative goals that should to some extent be realized even before women and couples come to procreate. Utmost emphasis should be put on the privatization premise (see above) implying that neither societal disapproval nor social approval should significantly alter reproductive options and decisions.

Talking of ‘societal’ influences somewhat vaguely refers to impacts by health care institutions, counselors, or public climate. In contrast, personalized influences, for example, ‘perspectives of partners, family members and friends’ are not commonly believed to fall into the category of ‘pressure’ but are rather seen as unproblematic ‘social context[s]’ [23]. Needless to say that here, too, repressive or irresistible influences can violate reproductive autonomy – yet another issue that needs mentioning in attentive reproductive education and counseling.

**Practical and normative conclusions**

Throughout this paper we have presupposed the procreative privatization premise, according to which women and couples should be free to decide upon contraception, abortion, and prenatal testing according to their own personal and moral convictions. For NIPT policies, five consequences would in our eyes have to be drawn from this premise.

Firstly, NIPT should in principle be available for every pregnant woman (at most at a small fee – a topic that we cannot address here).

Secondly, stepwise professional counseling [see, i.e., 7, 15] should be standard practice to prevent understanding deficits as one potential reason for non-autonomous decision making. Mindful deliberation must be seen as a common goal of councel and counselor.

Thirdly, society must very carefully monitor the balanced and easy availability of options for couples facing the risk or the certainty of giving birth to a disabled child. Indirect unintended social pressure towards the less challenging and costly option of selective abortions...
should be seen as a real danger to both the autonomy of women and the human liberalism of society.

Fourthly, reproductive literacy vis-à-vis complex option-sets has to rank high on the agenda of public education – already before people’s actual procreation.

Fifthly, the vague worry of ‘routinization’ should be abandoned in favor of the more specified concerns above. Routinization rhetoric has become a common framing for ethical uneasiness with liberal positions in bioethics. It should neither be inflated nor obscure those issues that deserve serious debate and action.

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References


Abstract: By implementation of non-invasive prenatal testing (NIPT) for the diagnosis of Down syndrome (DS) in maternity care, an ethical debate is newly inflamed how to deal with this information. Fears of the consequences of an increased use of NIPT are justified with the same arguments when amniocentesis and preimplantation genetic diagnosis (PGD) were introduced decades ago. It can be expected that the prevalence of people with DS would significantly increase in Western societies as a result of the increasing age of pregnant women and the improved medical care for people with DS. The net effect as to whether an increasing uptake of NIPT will result in more abortions of fetuses with trisomy 21 cannot be reliably estimated. This holds true since more and more couples will use results of NIPT for information only, but will not opt for termination of pregnancy. Although parents love their children with DS, in a society where reproductive autonomy is seen as an achievement, access to NIPT cannot be limited. On this background, comprehensive and qualified pretest counseling is vital, also to avoid possible stigmatization of people with DS and as the resulting consequence to avoid feared deterioration in their living conditions, for which, however, there is no evidence to date. The personal view of a mother of a child with DS illustrates the complexity in dealing with NIPT, which does not allow simple answers and must be understood as a challenge for society as a whole.

Keywords: discrimination; Down syndrome; genetic counseling; non-invasive prenatal testing; reproductive autonomy.

Introduction

In 2001, long before non-invasive prenatal testing (NIPT) was available, the German Parliament discussed about “Law and Ethics of Modern Medicine and Biotechnology”. Andrea Fischer (Member of Parliament) made a statement which is 20 years later still valid and should also apply in the current discussion about the ethical implications of NIPT: “None of us should arrogantly place our own morals above others. Each of us should let ourselves be unsettled by the arguments of the other in this discussion.” [1] This statement sheds light on the complexity of the ethical debate which was initiated with the introduction of amniocentesis more than 50 years ago. In this manuscript, new and old aspects are summarized for a better understanding of an ongoing discussion.

The age of mothers giving birth to their children and the number of nonselective pregnancies with trisomy 21 is increasing

Mother’s age at birth in western societies is steadily increasing. The average age of birth of the first child in Germany increased from about 24 years in 1970 to more than 30 years in 2015, while the average number of children per woman decreased in this period from more than two to about 1.5. Fewer children are born at more advanced maternal age. The single pregnancy moves more into the center of life. Due to increasing age of pregnant women the
expected number of pregnancies with Down syndrome (DS) in Western societies is steadily increasing from 12.5 in 1981–1985 to 21.7 per 10,000 (73.6%) in 2011–2015 in Europe and from 11.6 to 19.2 per 10,000 (65.5%) in the US [2].

More and more parents who refuse abortion use NIPT for information only

Hill et al. [3] showed in their literature review of 14 studies that termination rates following NIPT were unchanged or decreased when compared with the termination rates after invasive prenatal chromosome analysis prior to the introduction of NIPT. The studies included many women who would like to receive additional information about the health of their baby that will not necessarily be used for decision-making about termination of pregnancy. This is most likely due to the fact that NIPT is not associated with a risk of miscarriage as this is the case after invasive prenatal diagnosis (PND). The authors concluded that, where termination rates fall, NIPT may have a minimal impact on live birth rates for DS. Comparison of reported termination rates prior and after the introduction of NIPT suggest that in many settings the implementation of NIPT may not alter the overall number of children born with DS. The often stated figure of termination rates of more than 90% after PND of DS should no longer be anticipated for pregnancies with a NIPT disclosing trisomy 21 (=positive NIPT).

Will there soon be no more children with DS – false alarm?

De Graaf et al. [2] estimated for Europe 8,031 annual live births of children with DS in 2011–2015, which would have been more than doubled without selective terminations (around 17,331 births annually). The estimated reduction of live birth prevalence was on average 54%, ranging from 0% in Malta to 83% in Spain. Improvement of medical care dramatically increased life expectancy of people with DS and as a consequence their prevalence in the population. The mean age of death of people with DS in the USA increased from below 10 years in 1960 up to nearly 50 years in 2000 [4]. As of 2015, De Graaf et al. [2] estimated 417,000 people with DS are living in Europe and without elective terminations about 572,000, which corresponds to a population reduction rate of 27%. The authors, however, assume that with the introduction of NIPT higher termination rates will follow. The effect on the prevalence of DS with increasing maternal age and a possible decrease of termination rates cannot be predicted, which also applies to the fact that neither all pregnant women will demand for NIPT nor will all women with a positive NIPT decide to terminate pregnancies. Since there is strong evidence that termination rates can be influenced by counseling and improvement of the framework, much will depend on these parameters.

Pregnant women’s views on prenatal diagnosis

In a systematic study of the German Federal Centre for Health Education, women who underwent PND were asked on their views on PND in 2007. Eighty-two percent of women stated: “PND leads to relief because it can take away the worry of illness in the child” and 74%: “PND makes pregnancy safer for women” [5]. These statements can be interpreted in such a way that pregnant women want to experience an undisturbed pregnancy above all. The aim of PND was not explicitly mentioned in order to prevent disabled living. Since a negative result of NIPT nearly excludes DS in early pregnancy, the increasing utilization of NIPT can be understood in this sense.

Lack of knowledge about prenatal risks

In a survey performed until 2005 we asked more than 2,000 persons and later in addition medical students in their first year of studies the following question: “What is the risk for a 40 year old pregnant women to give birth to a child with Down syndrome?” The results indicate a severe deficit of knowledge with a serious overestimation of risks, which was even more pronounced in the student’s group [6] (Figure 1) Similar observations have been made by Strauss et al. with 67% of 237 women who overestimated their specific risk more than twofold [7]. The overestimation of fetal risks leads to increased fear and, as a result, to an increasing demand for prenatal testing.

Who should be offered prenatal diagnosis?

In their paper entitled “Who should be offered prenatal diagnosis? The 35-year-old question” Kuppermann et al. [8]
discussed an old question which is still actual. While the risk of a miscarriage after invasive diagnosis has been an argument for limiting invasive prenatal tests to women older than 35 years, the authors believed that it was time to eliminate strict age- or risk-based cutpoints. Instead the authors argued in favor of the preferences of the well-informed individual and summarized: “Strong consideration should be given to adapting policies to permit assess to prenatal diagnostic services for all women whose preferences indicate that such testing would be appropriate.” Carroll et al. [9] came to similar conclusions in their survey about the attitudes of woman and health care providers toward changes about maternal age-based prenatal screening for chromosomal disorders. Limiting prenatal screening to women with high genetic risk is in their view no longer justified. Several recommendations have no rational basis for restricting NIPT to a specific age group or to women with an increased genetic risk. The German Ethics Council, for example, stated in “The future of genetic diagnostics – from research to clinical application” (2013): “The majority of the members are of the opinion that a non-invasive prenatal genetic diagnosis … should only be carried out if there is an increased risk of a genetic disease or malformation.” [10] Recently, the Federal Joint Committee in Germany made the decision that NIPT should only be covered by the general health insurance, if the pregnant woman has special genetic risks or to clarify abnormalities in individual cases. It is suggested that “… a NIPT can be used at the expense of the health insurance if the question arises as part of the medical care for pregnant women whether a fetal trisomy could be present and this represents an unreasonable burden for the pregnant woman.” [11] An exclusively statistically justified risk of a trisomy – for example due to the age of the pregnant woman – is therefore not sufficient to have NIPT reimbursed by the general health insurance. Due to lack of clear in or exclusion criteria these statements are difficult if at all to understand.

What do relatives of family members with DS think about DS and NIPT?

All parents of children with DS love their children as do their siblings. They express the joy the child with DS has brought to the family, as do all parents of handicapped children including the most severely affected children. There are many studies of family members evaluating the family perspective of DS. The overwhelming majority of parents of different studies report that they are happy with their decision to have a child with DS. They universally indicate that their sons and daughters are great sources of love and pride for their families. In a recent publication How et al. [12] express the message in the title of their paper: “We would have missed out so much, had we terminated: What fathers of a child think about current non-invasive prenatal testing for Down syndrome”. Van Schendel et al. [13] explored the attitudes of Dutch parents of children with DS towards NIPT. Although safety, accuracy and earlier testing were seen as advantages of NIPT, some participants were critical about the routine implementation in maternity care. The participants acknowledged that NIPT enables people to know whether the fetus is affected and to prepare for the condition without risking miscarriage. Many parents fear uncritical use of NIPT and more abortions for DS including the consequences for the acceptance of and facilities for children with DS. Kellogg et al. [14] studied the attitudes of 73 mothers of children with DS. 67% of mothers felt that NIPT should be made
available to all pregnant women. In their view NIPT is a good instrument because it allows people to prepare themselves for a child with DS but expected NIPT to cause an increased pressure to test and a social stigma for having a child with DS. In a study of Bryant et al. [15] including 78 women who had a sibling with DS, about one-third of participants would still consider PND and termination if they were expecting a child with DS. Although they overall had a positive experience with DS, about one third expressed a negative impact on their own well-being and that of their families by the fact that they had a sibling with DS. One weakness of many of these studies is a possible ascertainment bias since the majority of families have been contacted through self-support groups with different response rates, which therefore might not be representative.

The effect of routinization and its implication for people with DS

Kater-Kuipes et al. [16] conducted a literature search regarding the different interpretations of routinization in prenatal screening. With regard to NIPT, routinization could have major negative consequences for people with a disability. It is obvious that this might depend on the number of children born with DS in the future, which, however, cannot be predicted today. Although the fear of negative consequences of PND for living people with DS has been expressed already with the introduction of amniocentesis more than 50 years ago, the living conditions of people with DS have improved since that to a great extent. There is so far little supporting empirical evidence for an increase in social pressure to take part in screening or to terminate affected pregnancies. No studies exist indicating possible negative effects of stigmatization with the consequence of worsening the living conditions of people with DS. Rubeis and Steger [17] analyzed the so-called burden assumption which claims that children with disabilities are necessarily a burden to others, especially to their parents and other family members. If this were the case, this would exert pressure on women to decide against the birth of children with disabilities, thus undermining women’s autonomy. The authors claim that such an attitude, which they feel is wrong, can be avoided without restraining reproductive autonomy. They argued that such an attitude is mostly based on misinformation and a false understanding of disability and can be challenged through an advanced genetic counseling as a combination of empirical evidence with narratives from a first-person perspective.

Counseling is essential and a major key for responsible use of NIPT

In the 1980s the Dutch Patient Alliance for Rare and Genetic Diseases (VSOP) imposed with advertisement for genetic counseling in newspapers with headlines like “Life begins before birth. Medical care before conception” resulting in the message GENETIC COUNSELLING MAKE SURE YOUR WAY. By contrast, the relationship between geneticists and representatives of self-support groups in Germany remains difficult [18]. Informing about the real life of people with hereditary diseases in genetic counseling is challenging. In Rubeis’ and Steger’s [17] opinion advanced genetic counseling can address the burden assumption. They emphasize that sound and evidence-based information on the quality of life with disabilities is necessary. In order to achieve the goal, more empirical research about the quality of life of children with disabilities and their family members is needed. In addition, information material should be offered to pregnant women that includes the views of people with disabilities and their family members. V. Schendel et al. [13] report that nearly all participants in their study found that improving information provision is important for informed decision-making in order to avoid routinization. Many other statements emphasize the importance of qualified counseling before performing NIPT as well as after receiving the diagnosis of DS and mention the value of information material. Criteria for written information have been defined [19].

Information about DS should be realistic

Although nearly all parents of children with DS love their children, many thought there was lack of good counseling and up-to-date balanced information about DS, which is portrayed as being either too negative or too optimistic. A statement in a flyer of a DS self-support organization about the message GENETIC COUNSELLING MAKE SURE YOUR WAY. By contrast, the relationship between geneticists and representatives of self-support groups in Germany remains difficult [18]. Informing about the real life of people with hereditary diseases in genetic counseling is challenging. In Rubeis’ and Steger’s [17] opinion advanced genetic counseling can address the burden assumption. They emphasize that sound and evidence-based information on the quality of life with disabilities is necessary. In order to achieve the goal, more empirical research about the quality of life of children with disabilities and their family members is needed. In addition, information material should be offered to pregnant women that includes the views of people with disabilities and their family members. V. Schendel et al. [13] report that nearly all participants in their study found that improving information provision is important for informed decision-making in order to avoid routinization. Many other statements emphasize the importance of qualified counseling before performing NIPT as well as after receiving the diagnosis of DS and mention the value of information material. Criteria for written information have been defined [19].

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Reproductive autonomy vs. right to live – no solution

The German Ethics Council (Ethik-Rat) (2013) [10] stated in their minority statement: “The ethical analysis should be based on the reality of people’s lives.” One major aspect is that reproductive autonomy has long becoming reality in Western societies. In Germany, there were 100.893 legal abortions in 2019, while only 3.875 (3.8%) were performed according to a medical indication [20]. Access to abortion in the Republic of Ireland is possible now due to legislation followed from the 66.4% “Yes” vote in the referendum in May 2018 (Figure 2). Argentina legalized abortions not until 2020. In Poland huge protest against restrictive regulation of abortion law is evident. A very similar ethical discussion took place with regard to preimplantation genetic diagnosis (PGD). The Ethics Committee of the Giordano-Bruno Foundation voted for approval of PGD within extended limits in 2011: “Choosing a healthy embryo with PGD is by no means linked to a downgrading of the disabled. The assumption that the destruction of fertilized egg cells with genetic defects leads to discrimination against the disabled is just as absurd as the demand for the abolition of vaccination against polio could result in discrimination against people with polio. Anyone who takes a rational, humanistic point of view should be aware that the disabled and the sick deserve our full support, but disability and illness do not.” [21] Do these arguments also apply to NIPT?

Letter from a mother of a child with DS as a touchstone for our own opinion on NIPT

We did not use (non-invasive) PND for DS abortion … we wanted to rule out severe organ damage … and I wanted to know which gender the child has. I wanted to know if it has DS in order to prepare myself for it and to welcome my child that was already in the belly … The advice in the hospital … was excellent … and first thing the doctors said was “we don’t see ourselves as a DS prevention center”, which I thought was great. Dealing with the questions of PND was an important part of my late journey to being pregnant and becoming a mom … They helped me cope with the demands of giving birth.

I do not want to go into details as regards the long medical history of my son. But I want to share with you my thoughts which are based on my experiences as a DS mother and in the DS self-support group here on site: I don’t think it helps to create and hold a place for DS people by hiding the different sides of the coin. The distorted image of DS is wrong in both directions: It suppresses the positive aspects (apart from the usual “Mongo romanticism” – “they are always so nice and happy” etc.), but it also underexposes that some DS children die in the first few years (especially those with heart defects), and how much time, energy or money it “costs” to create “flagship downies”. I know wonderful mothers with DS children of considerable handicap who suffer a lot from the silent insinuation that they do less right than those mothers whose DS children already walk with two and speak well with four.

What we need to avoid is a “it-is-not-so-bad” rhetoric, but a positive acceptance of the unavoidable fate, let it be good or bad. This not only relevant for DS, but for everything sick, dying, disabled, restricted … This also means that I would not blame mothers, who decide to opt for the extreme step of abortion, across the board of egoism. … I cannot accuse them, even if I would not have an abortion for the reason of DS myself. BUT !!!! I find it terrible that advances in PND are likely to lead to increased abortions in sick and DS people UNLESS we make significant changes on two major “fronts” …:

First, we need better and comprehensive advice in maternity care which specifically addresses the greatest fears and worries of the pregnant woman and her family.

Second, we need individually adapted help, e.g., trained therapists or midwives who can talk to the mother’s parents about what they need to process the diagnosis and assist the DS mom. There should be support programs for employers of DS parents including a partial assumption of salaries. Caring parents could receive preferential doctor’s appointments taking care of the special health needs and the limited schedule. The fight for school places should end and the unspeakable ongoing discussion about inclusion needs to change. The injurious and restrictive practice of many health insurance companies with regard to care levels should be changed and aids approved more easily. Generally speaking,
there is specific support required in the first year of life of a child with DS (or other disability). Restructuring everything in the midst of all the chaos is not good for the whole family; there is always something going down the drain (either the external facts or the health of the parents; you can rarely keep the two together).

Since my son was born, I have observed two opposing tendencies in my environment: Based on the experience with my extremely popular son, everyone around me has received a much more positive image of DS people and life with DS. However, the same people say that they are more likely to have an abortion because of DS today than they were before my son was born. After seeing what all this has done to me and my life, my friends rather believe they would not cope to have a child with DS.

TO CONCLUDE: THE BEST “ADVERTISING” AGAINST ABORTION OF DS PEOPLE LIES IN SUPPORTING DS PEOPLE AND THEIR FAMILIES! – SOCIALLY VISIBLE! IT IS NOT THE TEST THAT LEADS TO ABORTION – BUT THE LACK OF SPACE IN SOCIETY EXPECTED BY FUTURE DS PARENTS!

In this context, we should handle the prenatal blood test very differently. All mothers over 18 years should make the test; then all parents would deal with the question – instead of repressing it and see it as the problem of somebody else. Then the subject would be in the middle of everyone planning to have children. Everyone would think about what life, a successful life, being human is all about and what is important of having children. Maybe that would be a different perspective in life for everyone .............. I consider the question of how to deal with the blood test to be a litmus test. And I think a defense strategy is doomed to fail. So I think other ways have to be found to keep the place for DS socially – for DS people, and for parents who choose (or are surprised by) DS children ... [Content slightly shortened respectively summarized].

What should be done?

We have to ask about the relation between the cultural appreciation of disabled people and the demand for PND. NIPT is a serious challenge of society as a whole [6].

Five statements on the challenges of receiving genetic information which are also valid for NIPT

- We cannot prevent access to genetic information.
- We (rather) have to advocate responsible use of it.
- Our population knows too little about hereditary diseases and disabilities and their origin.
- We need to increase our knowledge about genetic information and improve “neutral” counseling competence.
- As a society we have to be asked again and again, whether we can offer families affected by a hereditary disease the help that enables them to lead a dignified life.

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Non-invasive prenatal diagnostics (NIPD) in the system of medical care. Ethical and legal issues

In many cases, however, widespread use is not likely until the public health care system, i.e. in Germany the statutory health insurance (GKV), assumes the costs of prenatal diagnostic procedures. In this situation, one can now come up with the idea of solving a – real or supposed – social problem “in a cold way” by preventing exactly this financing. The temptation here is to shift the problem onto the SHI system and its players. This was also observed with regard to the new procedures of non-invasive prenatal diagnostics (NIPD) (cf. section II). Such attempts should be rejected (sections III–V).

II The NIPD in medical device and constitutional law

The introduction of the so-called PraenaTest, a non-invasive method for determining fetal trisomy 21 and possibly other trisomies from the blood of the pregnant woman, has attracted considerable attention [7]. The great advantage of this test and other methods of NIPD is that they allow the determination of genetic defects on the one hand – unlike the invasive procedures of amniocentesis (amniocentesis) and chorionic villus sampling (placental puncture) – without major impairment for the pregnant woman and in particular without the risk of triggering a miscarriage and, on the other hand, this determination can be made relatively early (in principle from the ninth week of pregnancy). This means that – should the pregnant woman decide to terminate the pregnancy due to a detected defect – an abortion is less stressful (and many would say also less morally problematic) than at a later point in time. However, the low access barriers of the test have also attracted critics: Does this not open the door to a “selection” that overburdens parents and puts them under pressure to justify their decision to have a child with a disability in the first place [8]?

This criticism has not changed the fact that the PraenaTest has been available in Germany since 2012. As a medical device – and specifically as a method for
detecting disabilities within the meaning of § 3 no. 1b) MPG – it does not require approval, but only certification (CE marking, cf. § 6 MPG). The responsible state authorities saw no reason or no means to take action against the test, although they were requested to do so by a legal opinion [10]. In fact, the regulation of § 4 I MPG, according to which the placing on the market of medical devices is prohibited if there is a “reasonable suspicion that they directly or indirectly endanger the safety and health of patients, users or third parties when properly used, maintained and used for their intended purpose beyond a reasonable level according to the knowledge of medical science”, is not relevant here: The test does not endanger anyone; this occurs at most through the subsequent decision of the pregnant woman to terminate the pregnancy. Conceivable indirect consequences of a social practice – namely the frequent decision to terminate a pregnancy in the event of a positive test result – for the life situation of people who have already been born and future parents and pregnant women can hardly be subsumed under this standard, even if the test promotes this practice.

Thus, there is no legal basis for a general ban. Whether this could or even should be created is at least uncertain [9–13]. It will hardly be possible to say that the state’s duty to protect human dignity, life and equality of disabled people from Art. 1 para. 1, 2 para. 2 p. 1 and especially 3 para. 3 p. 2 GG is violated if the test is not banned: The state does not discriminate against anyone by its inaction, but merely allows the pregnant woman to obtain information about the genetic constitution of the embryo more easily and earlier than before and to draw consequences from this, which may not infrequently consist in the decision to terminate the pregnancy, but also in the choice of a hospital with a children’s clinic or a planned Caesarean section instead of a natural birth. An obligation to prevent this will not be able to be derived from constitutional law, if only in view of the legislative leeway. This applies in particular to the argument that the social practice promoted by the test jeopardizes the claim to inclusion of persons with disabilities who have already been born: empirical studies in fact tend to indicate that their legal and social situation has improved significantly in recent years despite all the progress made in prenatal diagnostics [14, 15]. Of course, here and there may be the frequently quoted contemporary who reacts to the sight of a child with a disability with the unspeakable remark that “such a thing is not necessary nowadays after all”. The prenatal diagnostic possibilities, however, do not seem to have obscured the majority and politically the view that one can respect the assessment of a pregnant woman not to be able to carry and raise a child with a disability and at the same time advocate that the inclusion claim of people with disabilities is fulfilled. That NIPD will change something in this neither contradictory nor otherwise criticizable but thoroughly humane attitude is not very likely and in any case does not have to be assumed by the legislator.

On the contrary, a legal ban on NIPD procedures would even meet with considerable constitutional concerns. For a “high-risk pregnant woman”, this would mean that she would have to be referred to an invasive examination option and, if necessary, to a later abortion. The argument that this would protect her self-determination because she would then not be subject to “social pressure” to undergo an easily accessible and risk-free test cannot really be taken seriously either (on the applicability of the GenDG, § 15 of which regulates prenatal genetic counseling, to the PraenaTest: [16–18]): Since when is it best to guarantee self-determination in a difficult decision-making situation – despite all the need for education and counseling that undoubtedly exists here – by a total ban that simply takes away a decision-making alternative [19, 20]? Finally, one will have to consider that NIPD prevents miscarriages and in this sense saves lives: The number of abortions of embryos with a genetic defect may increase, but this is probably overcompensated by the avoidance of miscarriages, to which the invasive methods of prenatal diagnostics lead in a certain, in detail not uncontroversial percentage of cases. Especially representatives of a strict protection of life should think about this; this effect of NIPD can only be avoided if all methods of prenatal diagnostics are banned.

III NIPD and the SHI system

Neither simple law nor constitutional law therefore provide a comfortable basis for a ban on NIPD. However, it is now a completely different question whether SHI will cover the costs of these procedures. On the parallel question in state aid law, see [21]. Even if the tests are becoming cheaper and cheaper (according to the manufacturer, offers for the Praena test currently start at around 130 euros [22]), this question is likely to be of central importance for their widespread use for the foreseeable future. And so the discussion has shifted to this aspect [23].

1. The procedure at the G-BA

The Federal Joint Committee (G-BA) is initially responsible for deciding whether NIPD should be included in the SHI catalog. For it, this is a question of innovation regulation
Huster: NIPD in the system of medical care

[24], or more precisely: whether NIPD procedures should be included in the maternity guideline (Section 92[1] Sentence 2 No. 4 SGB V) and thus be available in SHI-accredited care.

In 2014, the G-BA initiated the consultation procedure for issuing a trial guideline for “non-invasive prenatal diagnostics to determine the risk of fetal trisomy 21 by means of molecular genetic tests” in accordance with Section 137e SGB V [25]. This provision, introduced by the GKV-VStG [26], allows the trial use of new examination and treatment procedures that have not yet proven their (additional) benefit but have the “potential of a necessary treatment alternative”. The G-BA has already been severely attacked for this decision. The criticism misses the point, however, because an application was submitted by the manufacturer of the Praena test and the G-BA was obligated under Section 137e (7) sentence 3 SGB V to decide on this application within three months. And in view of the fact that NIPD is regarded as a major advance in medicine, there was nothing else to do in the matter but to assume a corresponding “potential”.

The G-BA then went one step further in August 2016 by suspending this trial procedure and initiating a method assessment procedure in accordance with Section 135 of the German Social Code, Book V [27]; the reason for this is probably that numerous studies on NIPD procedures are now available, so that an upstream trial procedure has become unnecessary. In this method evaluation procedure, which as a rule must be completed within three years (cf. Section 135[1] sentence 5 SGB V), “the recognition of the diagnostic and therapeutic benefit of the new method as well as its medical necessity and cost-effectiveness – also in comparison with methods already provided at the expense of the health insurance funds – must be examined according to the respective state of scientific knowledge in the respective therapeutic direction” (Section 135 [1] sentence 1 no. 1 SGB V).

The G-BA is responsible for the Methods Assessment Subcommittee, which commissioned the Institute for Quality and Efficiency in Health Care (IQWiG, cf. Section 139a SGB V) with the evidence assessment of NIPD on January 26, 2017 [28]. At the same time, the commenting procedure was opened according to Section 6 (2) of the G-BA’s Regulation.

In addition, the G-BA has now commissioned IQWiG to prepare information for insured persons on prenatal diagnostics, which is expected to include NIPD [29].

There could hardly be any doubt that the NIPD procedures fulfill these requirements in principle. However, it had to be clarified in which cases of a “high-risk pregnancy” which test should be used at the expense of the SHI – an application in every pregnancy should not be considered for cost reasons alone – how information and counseling before and after the test should be designed and to what extent NIPD can replace invasive procedures. The latter question arises on the one hand because NIPD offers a very high, but not 100% certainty, so that in the case of a positive test result, clarification is currently still carried out by means of an invasive procedure (whereby it must be taken into account that the test result is negative in the vast majority of cases, so that invasive examinations can then be dispensed with). Secondly, NIPD so far only covers trisomies 13, 18 and 21; other malformations and developmental disorders can still only be detected by means of invasive procedures.

2. The consideration of ethical reservations in the method evaluation process?

The G-BA has also been criticized for its decision to initiate the method assessment procedure: Here, a controversial medical technology with possible social effects and ethical problems is anchored in the health care system without prior discussion [30]. However, the fact that the Federal Joint Committee may not block or delay a method assessment “arbitrarily or for irrelevant reasons” is not taken into account here either, if it does not want to produce a “system failure” – with the consequence of a cost reimbursement claim by the insured according to Section 13 (3) of the German Social Code, Book V: New methods are also part of the scope of services provided by the SHI system (cf. Section 2 [1], Sentence 3 of the German Social Code, Book V); insofar as they fulfill the legal requirements, the Federal Joint Committee must decide on their inclusion in the benefits catalog [31].

The impartial chairman of the G-BA has attempted to counter this inaccurate but expected criticism with the assurance that the G-BA is aware that “in addition to the standard medical aspects to be examined, this procedure touches in a special way on fundamental ethical issues that must also be considered” and that it therefore intends to involve “in addition to the scientific societies, other social organizations, for example the German Ethics Council” in the consultation procedure [32]. If this is not to be merely an inconsequential appeasement, it must mean that the G-BA at any rate considers it conceivable that NIPD will not be included in the SHI supply catalog, or only very restrictively, because of “fundamental ethical” aspects. However, this now raises the question of whether the ethical and social justifiability of a medical procedure can be the
subject of the method evaluation pursuant to Section 135 (1) SGB V. Even at first glance, this would be peculiar: Why should a body of joint self-administration in SHI suddenly decide on the ethical aspects and sociopolitical effects of a method? Even if one were to see a special need for ethics here, it would be the medical associations that would come into view in this respect, as they traditionally deal – and with their own problems – with questions of professional law and ethics in reproductive medicine [33].

However, there is no need to discuss the much-discussed [34–39] legitimacy of the G-BA here, because the answer can be found in the law: Section 135 (1) of the German Social Code, Book V (SGB V) conclusively defines the criteria – diagnostic and therapeutic benefit, medical necessity, and cost-effectiveness – on which the evaluation of methods must be based. The view that non-invasive prenatal diagnostics procedures cannot have any benefit within the meaning of the German Social Code, Book V, because no therapeutic interventions are possible to correct the genetic defect, which is also occasionally expressed in the political debate, is completely absurd. The suggestion that the G-BA should be particularly critical of the benefits of NIPD from the point of view of the ethical and social reservations about it [30] misses the point of the structure of the method assessment procedure: the G-BA does not assess the benefits itself, but must “obtain an overview of the published literature and the opinion of the relevant professional circles and then determine whether there is a consensus, adequately supported by scientific studies, on the quality and efficacy of the treatment method in question” [40].

This is exclusively a matter of quality assurance [41]; neither Section 135 (1) of the German Social Code, Book V (SGB V) nor any other norm authorizes the G-BA to conduct an ethical or social justifiability review in the method evaluation procedure. However, such a legal basis would be required already because of the relevance to fundamental rights of the regulation to be decided by the G-BA, which affects the conditions of realization of the professional freedom of the test manufacturers, the freedom of therapy of physicians, and especially the reproductive autonomy of women. In other areas of law with special reference to ethical issues, the examination of ethical justifiability (cf. § 7a para. 2 no. 3 TierSchG) or the involvement of an ethics committee (cf. §§ 40, 42 AMG) are then also expressly regulated. A “freehand” addition of ethical and social aspects to the legal program of action in order to appease political concerns and arrive at an exclusion of benefits is not permissible: The G-BA is also subject to the binding force of law (Art. 20 (3) GG).

The further development was therefore not surprising. The Institute for Quality and Efficiency in Health Care (IQWiG), commissioned by the G-BA, soon came to the conclusion that there was little to criticize about the test to be evaluated from a technical point of view: its sensitivity and specificity were widely convincing [42]. On this basis, the G-BA took the decision in September 2019 to include NIPD in the maternity guideline – albeit limited to “justified individual cases”, i.e. cases of – albeit unspecified – “high-risk pregnancies” (whereby a purely statistically increased risk of trisomy should not be sufficient) [43]. Since education and counseling of the affected persons play a central role for this review of the use of the test in the respective individual case, this decision will only come into force when IQWIG has developed a corresponding information for insured persons. This has been submitted in December 2020 [44], so that nothing stands in the way of a final decision by the G-BA, which would then finally anchor NIPD in the maternity guideline. An orientation debate in the Bundestag in April 2019 [45] has not yet led to any concrete legislative initiatives.

**IV Options for action**

The G-BA could not be trusted to “deal with” the – real or perceived – ethical and social problems of NIPD in the method evaluation process. If it had done so, it would have exceeded its competences.

What would this mean for the regulation of NIPD? The legislator could try to ban their procedure completely in Germany. However, this would be constitutionally tricky and would also hardly be politically acceptable to a majority; moreover, it would only be likely to induce those affected to circumvent this ban by sending a blood sample abroad and then being left without any information and counseling before and after the test.

If one wants to avoid this and instead regulate SHI financing, two options are conceivable. One could consider providing the G-BA – for method evaluation or on an even more general level – with a legal basis for considering ethical and social consequential problems in its decisions.

However, already in view of the anyway disputed legitimacy of the G-BA, this is not seriously considered; also the G-BA itself should not be happy about such a politicization and “ethicization” of its activities.

This leaves only an explicit legal exclusion of NIPD from SHI care. This would represent a certain break with the general rules and procedures that otherwise guide the composition of the SHI coverage catalog, but the legislature would undoubtedly be authorized to do so in principle; after all, it has already made individual exclusions of benefits in other cases – from lifestyle drugs to vision...
V Conclusions

The real problem is not NIPD, which is to be evaluated now, but the possible development that in the future numerous genetic characteristics of the embryo can be easily determined via non-invasive testing [50]. Here, the community will indeed have to consider whether it makes sense that information about all possible characteristics – perhaps up to physical characteristics that have little to do with disease and health, but a great deal to do with ideals of beauty – is available and can be used as a basis for the decision to continue or terminate a pregnancy. In this respect, § 15 Para. 1 Sentence 3 GenDG prohibits, for example after a prenatal diagnostic examination, the communication of the sex of the embryo before the end of the twelfth week of pregnancy, so that an abortion without penalty (§ 218a StGB) cannot be used to select the sex. According to Section 15 (2) GenDG, prenatal diagnostic testing for late-manifesting diseases is generally inadmissible; this is rightly met with criticism [10, 51].

On the one hand, however, this is still future music to be decided on when it is played out; such fears do not allow a procedure to be banned now that does not provide any more information than the tests that have already been available for some time, but only does so much more gently. The boundaries between disease prevention and efforts to “perfect” may not be easy to draw here on occasion, but that does not mean that there are no boundaries and no clear cases here. If the politicians do not want to trust the citizens here and leave them extensive freedom of decision – which would speak for something, because apocalyptic developments do not seem to be just around the corner – the legislators themselves must take action in any case.

On the other hand, such considerations, which address the consequences of comprehensive knowledge about genetic characteristics of the embryo for social coexistence, touch on social and political issues that go far beyond traditional bioethics and medical ethics [50]. This makes it even more implausible that they would be well served by a body such as the G-BA, which is entirely focused on controlling the system of medical care. In this respect, too, the following therefore applies: If the funding of NIPD by the health insurance funds is to be generally excluded, this can only be done by the legislature itself. This does not, of course, answer the question of what one would think politically and morally about the procedure of denying SHI funding to a medically superior procedure that is unpopular for ideological and extremely speculative reasons and then hoping that there will be enough women who cannot or do not want to afford the test and then run the risk of miscarriage. Perhaps this would be more of a topic for a social and ethical justifiability test.

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**Article note:** This essay is an updated and translated version of “Der Gemeinsame Bundesausschuss als Ethikbehörde? On the Regulation of Prenatal Diagnostics by Health Insurance Law”, MedR 2017, pp. 282–286.
Abstract: Experimental and clinical studies suggest that prenatal experiences may influence health trajectories up to adulthood and high age. According to the hypothesis of developmental origins of health and disease exposure of pregnant women to stress, nutritional challenges, infection, violence, or war may “program” risks for diseases in later life. Stress and anxieties can exist or be provoked in parents after fertility treatment, after information or diagnosis of fetal abnormalities and demand simultaneous caring concepts to support the parents. In vulnerable groups, it is therefore important to increase the stress resilience to avoid harmful consequences for the growing child. “Enriched environment” defines a key paradigm to decipher how interactions between genes and environment change the structure and function of the brain. The regulation of the fetal hippocampal neurogenesis and morphology during pregnancy is one example of this complex interaction. Animal experiments have demonstrated that an enriched environment can revert consequences of stress in the offspring during critical periods of brain plasticity. Epigenetic markers of stress or wellbeing during pregnancy might even be diagnosed by fragments of placental DNA in the maternal circulation that show characteristic methylation patterns. The development of fetal senses further illustrates how external stimulation may impact individual preferences. Here, we therefore not only discuss how maternal stress influences cognitive development and resilience, but also design possibilities of non-invasive interventions for both mothers and children summarized and evaluated in the light of their potential to improve the health of future generations.

Keywords: creative interventions to support stress resilience; fetal programming; maternal stress; prevention of psychiatric diseases.

Introduction

Aristotle already mentioned that our sensory development starts antenatally to be prepared for the challenges of extrauterine life. He postulated epigenetic processes and compared the influence of the mother’s environment with how the earth supports the development of plants [1]. Therefore, in ancient times it was recommended that pregnant women should live in a stimulating environment and avoid harmful influences.

It was not until the 20th century that new biophysical tools allowed to directly approach the fetus and to observe early fetal reactions towards maternal and external stimuli. As a pioneer, Prechtl described the continuous development from prenatal to postnatal life [2]. The care of pregnant women became a matter of public health concerns with regular controls of pregnant women; it was then that maternal-fetal medicine became a subspecialty of its own. Epigenetic studies of fetal programming such as proposed by the concept of developmental origins of health and disease (DOHaD) have demonstrated a harmful impact of maternal undernutrition on cardiovascular, metabolic, and mental health in the offspring up to adulthood [3–5]. It was recognized that not only prenatal or early postnatal exposure to undernutrition, but also maternal stress may reprogram brain development and increase risk of behavioral and neurological disorders later in life. Long-term follow up of humans whose mothers had been tested positive for maternal stress, anxiety, or depression even...
from the first trimester onwards demonstrated delayed cognitive development and impaired mental health in later life [6].

Unfortunately, pregnancy assessments usually do not involve screening tools for maternal stress, anxiety depression, although validated questionnaires such as the perceived stress scale (PSS), the stress trait anxiety inventory (STAI) or the Edinburgh postnatal depression scale (EPDS) readily exist and could be easily implemented. Maternal-fetal specialists have rather concentrated on the detection of risks of chromosomal abnormalities, fetal abnormalities pregnancy complications, or emergencies and sometimes even induce maternal stress instead of recognizing their chances to prevent the fatal consequences on the fetus up to adult life. The fetal brain seems to be a sensitive target for maternal stress effects because the differentiation of major brain structures occurs during prenatal life [7]. It is speculated that 17% of the variance of later psychological disease in adulthood are caused prenatally [8]. In pregnancies after artificial reproductive techniques, with chromosomal abnormalities or congenital heart defects (CHD), when pregnant women are exposed to natural disasters, the COVID-19 pandemic, social deprivation, violence, or war, maternal stress levels are even more increased and therefore initiate a vicious circle for the offspring [9–12] (Figure 1).

Interventions that counteract the transgenerational transmission of stress have not yet been developed although they would be desperately needed mainly in identified focus groups. Work in animal models has proven that the effects of artificially induced transgenerational maternal stress can be “reversed” by increasing stress resilience. Many of these interventions follow the model of “environmental enrichment” (EE) and have been developed in rats and mice [13]. In this review we summarize experimental and clinical findings related to transgenerational stress, sensory and cognitive development and discuss their relevance for future pregnancy care.

**Stress factors of pregnancy and fetal programming**

Maternal well-being determines fetal and postnatal cognitive and psychosocial development. Numerous clinical studies have summarized the consequences of high anxiety and stress levels in pregnant women on the mental health of their offspring, but unfortunately did not translate into screening or care concepts [6, 14–17]. Meanwhile, only one European region has introduced a screening concept for maternal stress and the risks for the offspring [18]. Recent epigenetic studies have shown that early deviations in temperament and cognitive development were initial indicators of previous maternal stress. Maternal stress and anxiety or depression can persist or even increase after birth and be associated with a negative attitude towards parenthood [19]. This may have an additional impact on the offspring, which is modified by the genetic disposition or additional challenges in later life. Each stress factor can shorten the telomere length, a prominent marker of biological aging, in women by 35 base pairs [20].

**Figure 1:** Maternal stress measured by the perceived stress scale (PSS), anxiety measured by the stress trait anxiety inventory (STAI) or depression measured by the Edinburgh postnatal depression scale (EPDS) as it is distributed in normal pregnancies (left columns), after the diagnosis of a congenital heart defect (CHD) (centered columns) and during COVID-19 (right columns). Modified according to ref. [10] and unpublished data from a Zoom lecture of Catherine Limperopoulos from the Center for the developing brain children’s’ health system Washington, 2020.
During pregnancy, stress factors may increase pro-inflammatory markers and thereby even shorten telomere length in newborns [21]. It is estimated that globally, 250 million children (43%) under five years are at high risk of not reaching their physical, intellectual, and creative potential to become healthy and happy adults [14].

Acute symptoms of maternal stress are not uncommon during pregnancy and activate the “stress axis” (HPA axis) from the hypothalamus to the pituitary gland and to the adrenal cortex in both mothers and children. The fetal brain is thought to cope better with acute challenges, although in rats acute maternal stress impacted psychomotor functions in terms of motivational changes in the central-object variations of exploratory tasks in the offspring [22]. Brief maternal stress can cause sudden changes in uterine blood flow, fetal heart rate (FHR) and fetal movement patterns. The effects of stress on the HPA axis depend on age, gender, and duration of the stressor. Short-term stress also affects the HPA axis, corticosteroid levels, psychomotor function, and exploratory behavior in offspring in ref. [22].

Chronic stress can disrupt basic physiological and metabolic functions and adversely affect health. Such chronic stress situations can be simulated repeatedly over a long period of time in different generations, e.g., through social isolation. Chronic stress predisposes fetuses to changes in growth, metabolism, structure, and function of their brains and later in life even life expectancy [23–25]. Children of mothers with anxiety symptoms show a doubling of behavioral problems compared to a normal population [14]. But not only experience within a single lifetime, but also ancestral experience affects health trajectories and chances of successful aging or disease incidence by formation of an epigenetic memory [26]. Without prevention it can take too much time for interventions of social support and sensual stimulation (“EE”) to reverse the negative consequences. Mediators are mainly cortisol, but also catecholamines, cytokines, serotonin/tryptophan, oxygen radicals, and finally the microbiome [27] (Figure 2). Epigenetic mechanisms are the link in this complex process. Biological indicators could help to identify risks and initiate early stimulation programs. Finally, even fetuses themselves are thought to stimulate the maternal sympathetic system that prepares mothers for their care through fetal movements [17].

Prenatal stress experience increases the sensitivity of the developing organism to postnatal influences [28] and explains the different outcome by a pre-existing context [29]. This may offer important opportunities for early intervention strategies.

Low birth weight also programs future mental health and was shown to be associated with hostility in later life [30]. Studies of the Dutch Hunger Winter showed that children of pregnant women who were starving during their first trimester (and certainly exposed to stress) showed increased rates of schizophrenia, depression, or inadequate stress responses in later life [31]. Since the association between birth weight and ADHD has not been confirmed in selected communities, it is likely that maternal care can break this link [32, 33]. Gestational age and birth weight explain only 1% of the variance in emotional behavioral abnormalities, but maternal stress

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**Figure 2:** Main mediators of maternal stress via the placenta to the fetus. Modified according to ref. [14].
explains 17% mainly when the socioeconomic status is also considered [14]. Intensified maternal care can modify the outcome in groups affected by fetal growth restriction (FGR) [34]. Parental care compensates for hippocampal hypofunction in low birth weight children, thereby supporting the effective regulation of the stress axis [34]. A high socioeconomic status also reduces the effects of FGR on mental health in children [35], while a low socioeconomic status increases the negative effect of glucocorticoids and stress on long-term memory [23]. In all populations, the duration of breastfeeding promotes cognitive development even more significantly in children with FGR as compared to children with normal birth weight [36, 37].

Even chronic exposure to modern media or death of a loved one is associated with low birth weight [38, 39]. Endocrine factors such as $\beta$-human chorionic gonadotropin ($\beta$-HCG) or progesterone are possible mediators of sex-specific effects. In a multivariable regression model, an increase in maternal progesterone of 1 ng/ml in the first trimester increased girls’ birth weight by 10.17 g (95% CI 2.03–18.31); in male offspring, stress during pregnancy caused growth retardation independent of progesterone concentrations [40].

The concept of environmental enrichment

The early development of animal and human offspring is determined by unchangeable (genetic) and dynamic (epigenetic) factors. From conception to old age, experiences and activities cause continuous anatomical and functional changes in our brain both in a negative and positive way. The EE paradigm was introduced by a Canadian neuropsychologist Donald Hebb in the 1940s to understand the role of experience on brain development. He compared rats under standardized laboratory conditions with rats raised like pets in his own home showing improved memory performance [41]. Mark Rosenzweig defined EE as a combination of inanimate and/or social stimuli [13]. The experimental design has been modified in rats or mice when animals were raised in multimodal laboratory conditions that included toys, tunnels, running wheels, ladders or larger cage space (Figure 3) [42]. Thus, the animals experience a greater range of sensory, cognitive and motor stimuli compared to standard housing conditions [43]. Neuroanatomical studies in rats showed higher brain weights, stronger cross-linking of dendrites [44] and an increase in brain-derived neurotrophic factor (BDNF) expression responsible for facilitated neuroplasticity in EE [45, 46]. It was also shown that EE causes a higher degree of histone acetylation at the BDNF gene [47–49]. These mechanisms explain how EE promotes the development of the fetal brain, later counteracting premature aging, and supporting lifelong learning and stress resistance.

Animal studies can unravel the complex relationships of unfolding our genetic potential up to old age. Early experiences during developmental periods of high plasticity modify our personality. Accordingly, in pregnant mice, maternal EE accelerated cell migration in the temporal lobe [50], cell proliferation in the hippocampus [51] and earlier opening of the eyes in the offspring [52]. Neurological reflexes and motor coordination are milestones of neuromotor development [53]. Reflexes on auditory and sensorimotor stimuli developed two days earlier in the offspring of stimulated pregnant rats as compared to offspring of pregnant rats under standard conditions (p<0.05). They also showed better motor functions (e.g., to bend or stand upright) up to 3 weeks after birth (p<0.05).

Epigenetic mechanisms respond to environmental changes transmitting transgenerational stress by altering gene expression [54, 55]. This can occur via paternal and maternal transmission. Thus, the experience of previous generations may favor adaptations in behavior and physiology in their offspring that ensure their survival. However, stress adaptation can also harm other important
functions: Stress in male rats during spermatogenesis can cause DNA methylation passed on to the next generation (F1), leading to reduced stress reactivity and impaired motor development [56, 57]. Since exposure to stress from previous generations is irreversible and hard to control, there is considerable interest in the extent to which EE can reduce or reverse such risks. Breeding several generations in animal models can provide more feasible and practical approaches than studies in humans.

Recently developed animal models can distinguish between stress in only one preceding generation (“trans-generational”) or cumulative stress (“multigenerational”) in several preceding generations [58, 59]. In experimental designs, the effects on the offspring of both situations can then be compared with those of control groups that grew up with and without EE. It has been shown that repeated or cumulative stress can lead to limited stress resilience or adaptation at the expense of premature biological aging with a high risk of chronic disease [60, 61]. Overall, psychosocial and/or physical stress of varying duration and the EE interventions (e.g. stimulation of motor skills with or without social factors) may differ within the models [60]. An example of effective therapy with EE is the study of neuromotor function of the offspring in rat models after different stress of previous generations [58]. Animals were observed walking over a ladder (Figure 4). With increasing ancestral stress, the number of unsuccessful attempts by front or hind legs to reach the ladder rungs increased. The results were reversed after EE, so that the animals with originally high risk performed better than animals from the control group with EE (Figure 4 right). Interestingly, female animals react more positively to social EE components by the release of oxytocin which serves as a “cuddle hormone” supporting bonding and social contacts. It also has a stress-reducing effect, increases BDNF expression and reduces aging processes [62]. The studies suggest that social networks or creative interventions can promote neurodevelopment into adulthood.

Sensory development and previous intervention models

The fetus not only responds to maternal stress or well-being, the increasing integrity of the sensory system allows to become aware of an outside world, whereby stimuli are first projected to subcortical areas and associated with behavioral patterns via neurons [63].

Already in the sixth week of pregnancy (SSW) skin receptors develop in the mouth region and are found on the entire skin surface until the 20th week of pregnancy. In 1952, Hooker described reactions to touch after therapeutic abortions at the end of the first trimester [64]. By this time, synapses develop in the posterior horn of the spinal cord, into which the nerve endings lead. Between 20 and 24 weeks of gestation, switch points and fibers from the thalamus to the cerebrum are formed, which are prerequisite for the experience of touch and pain [65]. Fetuses react to pain stimuli during invasive procedures [66]. After surgery on the fetus itself, a 590% increase in β-endorphin and an 183% increase in cortisol was measured; the

Figure 4: Rat crossing the ladder, mean number of wrong attempts of the rear extremities as compared to the total number of steps without (red) and with (yellow) EE.

*Significance of EE p<0.05. Values represent mean value ± SD, according to ref. [53].
increase in norepinephrine was associated with the duration of the procedure [67]. Reactions to the touch of a co-twin were observed from 8 to 10 gestational weeks onwards in mono-amniotic twin gestations. Before 16 SSW, male fetuses showed faster but less complex reactions than female or mixed couples [68], suggesting early influences of testosterone [69]. Somatosensory evoked potentials were described in preterm infants from 28 weeks onwards prerequisite for the memory of sensory sensations [70, 71]. Pre- and postnatal experiences are not necessarily comparable. Haptonomy where parents are introduced to contact their children prenatally by touch has never poorly evaluated. However postnatally premature babies have lower rates of infection and mortality when the kangaroo procedure was applied which also promoted breastfeeding rates and skull growth [72].

The outer ear is visible from the 10 gestational weeks onwards. Bones of the middle ear have already the same size as in adulthood at 18 weeks. The organ of Corti in the inner ear starts to develop at 10 gestational weeks and contains sensory and supporting cells including inner and outer hair cells with synapto- and ciliogenesis. At around 20 weeks, the morphology corresponds to the onset of cochlear function [60], Cells of the auditory nerve enter the brainstem and pass eight synapses before entering the cerebrum. Many auditory abilities are attributable to subcortical processing.

The intrauterine world is determined by frequencies <500 Hz and sound intensities from vascular pulsations, maternal respiration, or digestion (imprinting effect) of up to 90 dB. Music and voices are audible at a volume of 8–12 dB, with male voices at 125 Hz at 125 Hz at 125 Hz being less absorbent and female voices at around 220 Hz more distinguishable. When fetuses were exposed to sounds from 100 to 3,000 Hz, initial reactions were seen at 22 weeks and 500 Hz, at 27 weeks and 100–500 Hz, and from 31 weeks on at 1,000–3,000 Hz [73]. They can also be detected by changes in electric potentials to acoustic stimuli or stimulus-related neuromagnetic fields with decreasing latency of 300–150 ms from 34 weeks of gestation to term [74].

Short behavioral responses in terms of the fetal heart rate (FHR), fetal movements or eye blinking can be observed by ultrasound. Reactions are modified by fetal behavioral stages [75]. Repeated exposure to sound has been associated with fetal conditioning: Experiments in “habituation” show that the fetus can remember and compare sounds [76]. The memory exceeds the threshold of pre- to postnatal life [77] and shapes postnatal preferences. It has been proven that third trimester fetuses are familiar with their mother’s language [78]: Newborns prefer to hear the mother’s voice or the language or melodies spoken or sung by the mother which was demonstrated by sucking with a “sucky-dummy device” [79]. Sounds that resemble the intrauterine environment, but also music, encourage sucking and falling asleep of newborns [80, 81]. Pilot studies have also shown fetal behavioral changes when mothers listen to music with headphones only [82]. Whether fetuses are “enriched” more by direct exposure or maternal relaxation is difficult to distinguish when both are directly and simultaneously exposed to music after 22 weeks. In any case, music exposure during pregnancy promotes neuromotor skills in childhood [83] and stable behavior as compared to controls [83]. Prenatal musical experiences – mainly rhythmic elements – are still remembered after one year [84], although the time span of acoustic memory is shorter in newborns than in adults [85].

“Music is my first love, it will be my last”. This song by John Miles still applies in different cultures, as a number of proto-rhythms seem to be of biological prenatal origin [86]. The maternal voice represents a continuity from pre- to postnatal life [87, 88]. This relationship is “musical” since the child does not yet understand the meaning of language. Listening has an influence on voice formation, hence spectrographic images of the first cry of a newborn child are already similar to the patterns of the maternal voice [89]. Various devices are commercially available to expose fetuses to music programs, but we doubt that the music produced will reach the fetus, and the band to the mother is missing [90]. Lubetzki et al. [91] played Mozart music for premature babies between 32 and 37 weeks: As compared to a control group, energy consumption was reduced in those who listened to Mozart. In children with disabilities, music therapy was able to improve development, especially communicative skills [92]. Studies in adults support the hypothesis that musical abilities are inherent in every brain [93]. Even more important for a lifelong effect of music exposition are studies in which motor, sensory and cognitive abilities were examined in old age and classified according to whether the subjects had received music instruction in their youth for at least one year. Thus, it was confirmed that early stimulation of neuronal connections plays an essential role in maintaining cognitive abilities throughout lifetime. The longer the instruction took place, the less symmetrical and asymmetrical motor skills deteriorated [94].

About 1–2% of the human genome is assigned to the receptors of the olfaction and taste [95]. After the first trimester, the receptors of the olfactory organ in the upper nasal cavity are mature and connected to the brain by olfactory nerves [95, 96]. The dendrites grow into the mucosa of the mouth and nose binding chemical substances; the
signals are transmitted to the paleocortex and hippocampus [95]. Taste buds are scattered throughout the oral cavity from 12 SSW onwards, mainly on the tongue and the front palate [97]. During the second trimester, sensory cells spread on the nasal septum and transmit hormonal responses through pheromones. During the third trimester the olfactory organ is mature. From 10 gestational weeks onwards, amniotic fluid with odorous substances from mother and child pass through the nasal cavity by fetal respiratory movements [98]. Aromatic substances of the maternal and child pass through the nasal cavity by fetal respiratory movements [98].

Alimentary tract development: The presence of Smell and taste experiences might have therapeutic consequences to stabilize breastfeeding, adaptation, and bonding, and can also represent an extended form of “enrichment”.

**Implications for future projects**

Physical, mental, and social health is more than the absence of suffering but implies that people can unfold their genetic capabilities. Scientific projects help to link the fetal development with new insights of epigenetic processes and their significance for public health concepts. Exposure to adverse environments in early life, such as abnormal nutrition and maternal stress may reprogram organ development with potentially lifelong consequences and disrupt cellular functions contributing to accelerated aging and the potential risk of disease in older age [26].

Both animal and human data show that the uncontrollable impact of even ancestral adverse stress and trauma can potentially be offset by a beneficial experience throughout life [26].

Our motivation for designing creative projects was increased from a study showing that newborns of pregnant women with positive pregnancy experiences had increased telomere lengths, which may improve their chances of a longer life [104]. The bush fire in Alberta, Hurricane Harvey in Houston, and migrant family stress in Pforzheim were identified as study populations of vulnerable populations [12].

Creative writing of pregnant women has been used and shown that short episodes of expressive writing can improve cognitive outcome of the offspring [105, 106]. In a review by Olson et al. [12] it is described that children will be later examined for neuromotor outcome, metabolic biomarkers, and the risk for a later premature birth.

A Canadian team tracked the children of pregnant women who were exposed to increased stress before or during pregnancy during the 1998 ice storm in Quebec (“Project Ice Storm”). Between the ages of 2 and 10 years, the stress experience explained differences in speech characteristics, especially at early exposure, increasing rates of obesity, autism, pro-inflammatory markers, and altered DNA methylation up to 15 years. Exposure of pregnant women to flooding in Iowa (US) and in Queensland (Australia) found similar effects on cognitive and motor development or even obesity rates in the offspring [12].

Currently, the outbreak of the coronavirus disease exposes pregnant women to increased risks and fears. A systematic review found 3,166 papers on this topic and then included 24 studies reporting negative psychological effects such as post-traumatic stress symptoms, confusion, and anger. Stressors included longer quarantine duration, infection fears, frustration, boredom, inadequate supplies, or financial loss. Some researchers have suggested long-lasting effects [107]. It has been shown that the exposure to COVID-19, combined with quarantine measures adversely affected the thoughts and emotions of mothers, worsening her depressive symptoms [11].

This all means that the need for screening for anxiety, stress, and depression in pregnant women who – as pointed out – may transmit the negative consequences to following generations has even increased in the whole population and not only the described vulnerable subgroups.

Already in 2002, the first author of this article proposed the design of trials addressing not only the wish to study the influence of music on developing children but also the desire to create concepts of a caring relationship by musical interventions and thus to fulfill the concept of
environmental, sensory and social enrichment. A variety of ideas how future interventions could be realized and evaluated was given, such as to evaluate parents’ preferences, their wish to move or to sing and to perform these studies cross-culturally to evaluate further insights regarding anthropological perspectives. Simultaneously, it was proposed to focus on specific risk groups, to use questionnaires and biophysical methods to document instantaneous and long-term effects [108]. Thereafter, we have evaluated the musical behavior of mothers during pregnancy and proposed to compare intervention with control groups [109].

Unfortunately, as much as screening for genetic aberrations has been pushed forward and is combined with enormous costs but comparably only few options of therapy rather than pregnancy terminations, the screening for maternal characteristics that cause epigenetic diseases in the offspring which could be followed by preventive interventions are neglected.

Although the concept of the fetus as a patient demands that we have preventive ethical obligations not only for visible diseases but also for environments limiting potentials of healthy development and aging of the offspring, the most frequent reaction of obstetricians towards the importance of early interventions is rather characterized by “passive aggressive resistance” [110]. In contrast, it took only a noticeably short time to convince the Berlin Philharmonics and dedicated artists to help to create, design and realize acoustic enrichment programs for parents-to-be. Thus, we have the chance to offer concerts and workshops at two-week intervals from early pregnancy onwards within the Foyer of the Berlin Philharmonic chamber concert hall within a cohort and feasibility study and to evaluate psychological and biological consequences.

We needed time and perseverance to find and construct a research group of a satisfactory artistic and scientific level by integrating dedicated maternal-fetal medicine specialists, psychologists, epidemiologists, and artists. The initial common goal is to determine the compliance of parents-to-be, and to compare results of an intervention group with a pre-existing cohort. Further goals are whether creative interventions can counteract the harmful effects of maternal stressors and then to focus on specific interventions in vulnerable subgroups. Finally, we have the vision, to demonstrate the “survival value” of musical and social interventions, to decrease inequality and to extend the concept to a cross-cultural movement.

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Arabin et al.: Maternal stress, interventions to reduce consequences


First trimester screening with biochemical markers and ultrasound in relation to non-invasive prenatal testing (NIPT)

Abstract: Non-invasive prenatal testing (NIPT) is often erroneously received as a diagnostic procedure due to its high discriminatory power in the field of fetal trisomy 21 diagnosis (wording: “NIPT replaces amniocentesis”). Already a look at the methodology of NIPT (statistical gene dose comparison of a primarily maternofetal DNA mixture information at selected sites of the genome) easily reveals that NIPT cannot match the gold standard offered by cytogenetic and molecular genetic analysis procedures from the matrix of the entire human genome (origin: vital fetal cells), neither in diagnostic breadth nor in diagnostic depth. In fact, NIPT in fetal medicine in its current stage of development is a selective genetic search procedure, which can be applied in primary (without indication) or secondary (indication-related) screening. Thus, NIPT competes with established search procedures for this field. Here, the combined nuchal translucency (NT) test according to Nicolaides has become the worldwide standard since 2000. The strength of this procedure is its broad predictive power: NT addresses not only the area of genetics, but also the statistically 10 times more frequent structural fetal defects. Thus, NIPT and NT have large overlaps with each other in the field of classical cytogenetics, with slightly different weighting in the fine consideration. However, NIPT without a systematic accompanying ultrasound examination would mean a step back to the prenatal care level of the 1980s. In this respect, additional fine ultrasound should always be required in the professional application of NIPT. NIPT can thus complement NT in wide areas, but not completely replace it.

Keywords: combined NT-test; NIPT; prenatal genetic screening; test coverage; test performance.

Introduction

The introduction of Non-invasive prenatal testing (NIPT) into clinical medicine from 2012 was greeted with great acclaim by physicians and patients. There was talk of breakthrough, NIPT replacing amniocentesis, diagnostic testing procedure and much more. However, clinical research over the past eight years has succeeded in painting a more realistic picture of what the NIPT method can actually do, where its opportunities lie, but also its methodological limitations. This also makes it possible to draw a comparison of the value of NIPT with the standard method “combined NT test”, which has been established at this point, that better reflects the real conditions in everyday life.

NIPT is an innovative, sophisticated genetic determination method: it thus stands at the interface between laboratory medicine, genetics, pediatrics, and prenatal medicine. The experience of the last eight years in dealing with NIPT has shown that not only the view of unborn life itself, but also the technical language and medical concepts of these disciplines vary slightly from each other at this point. Therefore, in order to understand each other well beyond our medical specialties, it is essential that we use unambiguous terminology across disciplines. We should also have an unambiguous, clear, common concept about which epidemiological key data characterize the field of prenatal medicine.

Epidemiology of congenital malformations

About 130 million children are born worldwide each year (Figure 1) [1]. The UN puts the proportion of children with birth defects at just under 8 million per year [2]. This corresponds to 6% of all births. Of these 8 million, 3.2 million are disabled for life [3]. Disabled children account for a large proportion of pediatric mortality [4]. Over 3.3 million children die annually from congenital defects before reaching the age of five [5]. Interestingly, the rate of congenital anomalies appears to be lower in developed
countries: it is approximately 3% in the United States as well as in Germany [6].

The causes of congenital anomalies can be divided etiologically into three groups: The first group is that of genetic causes. Here, it can be further roughly divided into chromosomal disorders and single gene disorders. The next group concerns exogenous teratogenic factors. These include infections, substance deficiencies, substance abuse-toxic factors, diabetes, and in the broadest sense, maternal age. The third group includes cases of unknown cause [7, 8]. This includes structural malformations in the embryonic phase and thus a large proportion of fetal malformations diagnosed prenatally. Quite a few malformations also result from the combination of the above causes: This is the model of multifactorial disease genesis.

As a result of these acting factors, there may be a disturbance of the structure of the body or its function. Often one causes the other and we observe an overlapping of both forms. As a consequence, these disorders can lead to physical, intellectual and developmental impairments. Due to the mutual dependencies, such impairments are often combined (Figure 2).

This etiological-taxonomic classification cannot be consistently applied to the prenatal situation: Prenatally,
the possibilities are limited to assess the functional impairments that may result from a recognizable structural defect – the view ahead is clouded. Prenatal medicine recognizes three major groupings of fetal disorders: The group of disturbance of fetal structure, the group of genetic defects, and the group of disturbance of growth as an expression of the stability of the maternoplacental axis of supply (Figure 3). Biologically-practically, these three pathological conditions are closely intertwined. They are mutually dependent. Here is the classic example: A fetus with trisomy 21 has a structural heart defect in about 50%. At the same time, his risk of developing growth retardation or placental insufficiency is significantly increased.

Conversely, this means for the practical prenatal medical procedure: Whenever the fetus is diagnosed as belonging to one of the three groups of fetal pathologies, simultaneous involvement of the other group of fetal pathologies should be excluded with maximum possible certainty. The more pathology groups the fetus combines, the more probable is the causal presence of a common genetic cause.

Two of these three prenatal pathology groups can be diagnosed authochtonously only by sonography. Even genetic disorders can be detected with high sensitivity by fetal nuchal translucency (NT) measurement and fetal echocardiography.

In a clinical weighting, it should be noted that clinically relevant, prognosis-determining structural defects of the fetus generally occur 10 times more frequently than chromosomal disorders. Therefore, the first commandment of prenatal medicine is: No genetics without fetal ultrasound examination!

From the year 2000: combined NT screening

The turn of the millennium saw the introduction of NT measurement [9, 10]. This was initially done as NT-stand alone, then as a combined NT test with pregnancy-associated plasma protein A (Papp-A) and free beta human chorionic gonadotrophin (free ßHCG). This test was initially intended to be genetic only: it yielded unprecedentedly high sensitivities of around 90% for the three classical trisomies [11]. It soon became apparent, moreover, that the combined NT test could also be predictive for rare chromosomal disorders and occasionally for other genetic diseases [12–15]. Thus, NT already exceeded all expectations in this field. What was not foreseeable to this extent in the early 2000s was the increasingly clear realization that increased NT as a screening method in conjunction with early systematic ultrasound examination could also detect up to 80% of relevant structural malformations [16–19]. Thus, NT was a door opener toward systematic early sonographic malformation diagnosis between 11 and 14 gestational weeks. It has now established itself as an integral part of a professional approach to the question of fetal health in prenatal centers worldwide [20].

The core of this concept is the application of early fetal echocardiography [21]. This represents the cornerstone of the diagnosis in a holistic health assessment. This is based on the following biological relationship: the heart anatomy is closely linked to the genetic constitution of the unborn child. Genetically healthy fetuses have structurally normal hearts in the vast majority. Genetically diseased fetuses have a high proportion of structural heart defects.

**Figure 3:** Prenatal fetal pathologies: origin, effect.
IUGR, intrauterine growth restriction.
The combined NT test, in conjunction with early malformation exclusion, detects a large proportion of chromosomal defects and simultaneously a large proportion of structural malformations in fetuses at the biologically earliest possible time (completed embryonic phase) (Figure 4). Thus, in a holistic approach, this combined sonographic-biochemical screening procedure was and is the best, most applicable reasonable approach to the regularly recurring question of the mother: Is my child healthy? This question, too, is holistic in nature and goes far beyond considerations of fetal genetics alone.

In the years between 2000 and 2012, a systematic, stepwise expansion of NT occurred: by introducing additional sonographic markers, the test sensitivity could be expanded to 95% for trisomy 21 [22–24].

From 2012: NIPT and combined NT screening

In 2012 NIPT was introduced into prenatal medicine. It has become firmly established worldwide in non-invasive prenatal genetic diagnostics as a robustly applicable search procedure for trisomy 21 [25–27]. Studies have shown a slight increase in sensitivity in trisomy 21–99% compared to NT at 95% [28, 29]. The detection rates of NIPT in trisomy 18 and 13 range between 90 and 97% and are thus comparable on the level of sensitivity with NT in experienced examiner’s hands [30, 31]. Rare chromosomal anomalies are not addressed by NIPT in its current standard configuration. Therefore, in comparison, the total number of genetic disorders considered, and thus the diagnostic breadth, is lower with NIPT than with the combined NT test. In a comparative outcome analysis of the detection (test sensitivity) of all fetal pathologies (structural malformations and genetic disorders), NIPT without simultaneous application of ultrasound is inferior to the combined NT test (sensitivity) when viewed in this way. The better detection of trisomy 21 with NIPT has slightly shifted the focus of consideration toward trisomy 21 compared with NT (Figure 5).

The actual superiority of NIPT compared to NT [32] is found in the significantly higher discriminatory power of the procedure in trisomy 21 due to the impressive reduction of the false positive rate (type 1 error) and thus increase in specificity. But also the false negative rate (type 2 error) decreases by at least one power of 10 compared to NT. This significantly increases the positive predictive value (PPV) when considering test performance figures for trisomy 21.

![Combined (NT-)Test: Scope of application](image_url)
2000 NT -> 2010 NT

Figure 5: NIPT and NT: cytogenetic coverage and development.

Table 1: Test performance combined NT-test in T21 – low risk population.

<table>
<thead>
<tr>
<th>Test performance T21 combined NT-test</th>
<th>Reality - Outcome</th>
<th>Reality - Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany 800,000 births/year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calculation based upon observational study by Kagan 2008, projected on low risk population (PPV original paper 0.17 in high risk)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence 1:1,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conspicuous (test-positive)</td>
<td>739</td>
<td>23,976</td>
</tr>
<tr>
<td>Unconspicuous (test-negative)</td>
<td>61</td>
<td>775,224</td>
</tr>
<tr>
<td>Sum</td>
<td>800</td>
<td>799,200</td>
</tr>
</tbody>
</table>

| Sens | 0.924 |
| Spec | 0.97  |
| PPV  | 0.03  |
| NPV  | 0.999 |
| FPR  | 0.03  |

PPV, positive predictive value; NPV, negative predictive value; FPR, false positive rate; Sens, sensitivity; Spec, specificity.

(Tables 1, 2). Thus, NIPT has the potential to replace NT on the genetic-chromosomal side of a combined sonographic-genetic search strategy between 11 and 14 gestational weeks. This does not affect the potential of NT on the morphological side of this holistic screening concept.

NIPT for microdeletions

Around 2015, there was an expansion of the spectrum of genetic disorders addressed by NIPT towards microdeletions in professional investigation kits. For the five most common microdeletions (DiGeorge, Cri-du-Chat, Wolf-Hirschhorn, 1p36, Prader-Willi/Angelman), in high-risk collectives, the sensitivity of NIPT is 75% [33] for DiGeorge and over 90% for the others. All disorders have a steeply decreasing disease prevalence starting from DiGeorge with 1:1,000–1:4,000. This has a statistical effect in search procedures such that the false positive rate is relatively high and the PPV is relatively low (5–10%). A high false positive rate means a high unnecessary puncture rate. Thus, NIPT for microdeletions is scientifically-statistically effective in detection, but not efficient in practical prenatal life (cost-benefit consideration). Thus, the efforts of the laboratories, which are quite successful on the marketing side, to give NIPT a broader profile by including microdeletions, come to a dead end medically. This is reflected in the
current DEGUM recommendations: The use of NIPT in screening is currently not recommended [34].

NIPT - effect of test failure rate on real test performance in primary screening

One aspect that is often left out of the scientific analyses and marketing strategies of laboratory providers is the everyday reality of NIPT screening in a normal or low-risk population. This is envisaged as a model of care by statutory health insurers in Germany from 2021. Here, a factor comes into play that is usually primarily excluded in study collectives and thus leads to significantly better test performance figures than in prenatal everyday reality. This is the test failure (no-call) rate. Taken into account, this leads to a significant increase in the false positive rate of NIPT in trisomy 21, because a test that is not interpretable even when repeated often results in a puncture with good medical and psychological reasons [35]. Conversely, the increased false positive rate means a significant decrease in the positive predictive value of NIPT for trisomy 21.
According to meta-analyses, these effects decrease the test sensitivity of NIPT for trisomy 21 in a normal population to 96%, for trisomy 18–87%, and for trisomy 13–77% [36]. Thus, NIPT screening for trisomy 13 and 18 in the normal population no longer meets the quality criteria that are internationally applied to a screening procedure.

**Summary – conclusion**

NIPT is a high-performing procedure at the trisomy 21 level for indicated screening in high-risk populations and is superior to the combined NT test, particularly at the level of specificity at this point. Due to the high NPV, an inconspicuous test result at T21 predicts a non-T21 fetus with an extremely high probability. However, non-T21 does not mean genetically healthy or even generally healthy. In this respect, the wording “NIPT replaces amniocentesis” is philosophically-epistemologically and medically-practically incorrect and misleading.

NIPT is thus, from a practical point of view, a highly selective search procedure for trisomy 21. In all other respects, it is at best equivalent to the combined NT test with systematic ultrasound examination in genetic terms. NIPT without systematic ultrasound examination of the fetus means a diagnostic relapse into the 1980s for practical prenatal medicine.

NIPT has thus expanded the spectrum of available diagnostic methods in the practical day-to-day work of prenatal medicine, but has not completely displaced NT: Depending on the individual counseling situation, the expectations of the pregnant women seeking advice, and their economic possibilities, NT and NIPT are currently two valuable search methods in prenatal medicine that differ slightly in their breadth and depth of information (Figure 6).

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**Ethical approval:** Not applicable.

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Opinion Paper

Samantha J. Leonard*

Reproductive genetic screening for information: evolving paradigms?

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Abstract: Reproductive genetic screening has introduced the possibility for pregnant women to learn, during the pregnancy or sometimes earlier, about the likelihood of their baby being affected with certain genetic conditions. As medicine progresses, the options afforded by this early information have expanded. This has led to a shifting paradigm in prenatal screening, wherein the early knowledge is seen as useful not solely for its inherent value to the pregnant woman, but also as enabling an expansion of conditions whose identification may allow early intervention and clinical impact. This article discusses this paradigm against the backdrop of prenatal genetic screening that is available today.

Keywords: carrier screening; non-invasive prenatal testing (NIPT); prenatal screening.

Introduction

Reproductive genetic screening has introduced the possibility for pregnant women to learn, during the pregnancy or sometimes earlier, about the likelihood of their baby being affected with certain genetic conditions. As medicine progresses, the options afforded by this early information have expanded. This has led to a shifting paradigm in prenatal screening, wherein the early knowledge is seen as useful not solely for its inherent value to the pregnant woman, but also as enabling an expansion of conditions whose identification may allow early intervention and clinical impact. As the landscape of prenatal screening tests evolves, and the list of available target genetic conditions increases, it is worthwhile to evaluate what can be accomplished with today’s technology. There are three interesting areas of reproductive-related screening which will be considered here: expanded carrier screening, non-invasive prenatal screening (NIPS) for aneuploidies and selected microdeletions, and NIPS for single gene disorders.

What conditions do we want to screen for?

Trisomy 21 forms part of a routine offer of prenatal screening in a number of countries. Trisomy 21 was one of the first genetic conditions for which a cytogenetic cause was identified and it became possible to identify this prenatally using amniocentesis and karyotyping even in the early days of cytogenetics [1]. The association between altered levels of various serum markers and likelihood of trisomy 21 then allowed screening to be carried out to refine the risks for a pregnancy before offering amniocentesis [2]. This offering eventually expanded to include trisomies 13 and 18. However, these three trisomies only represent a small proportion of all of the genetic conditions which may affect an individual. Therefore, there is an argument that prenatal screening options should be expanded to include conditions that fulfill a considered set of criteria that make them appropriate for prenatal screening. Such criteria could include, for example, prevalence, penetrance, severity of phenotype and conditions where early knowledge could affect management, and have the potential to improve outcomes. This is particularly pertinent at this point in time when gene therapies are becoming available for a selection of genetic conditions. In general, the earlier a medical issue is identified and treatment is started, the better the likelihood of an improved outcome. With genetic conditions such as spinal muscular atrophy (SMA) this difference can be dramatic: without specific treatment, the progression of the disease can be rapid and devastating, whereas with early treatment the child may achieve milestones that would have been unthinkable previously [3].

Additionally, early information is valuable for a number of other reasons:

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(1) Information given in pregnancy allows the woman or couple time to prepare and to plan for the birth of a child who may have difficulties. This planning could be practical, such as meeting doctors who will be involved in their child’s care, or contacting associations, it could be financial, particularly in systems where there is no or limited public health care available, and it could be psychological, for example coming to terms with altered expectations and preparing the wider social circle for the new arrival.

(2) In some circumstances the pregnant woman or couple may decide, having learned about the presence of a genetic condition in the fetus, that they will not continue with the pregnancy. Learning about the condition during pregnancy is the only way that they would have the option to exercise this aspect of reproductive autonomy.

(3) For certain conditions, preimplantation genetic testing is available, involving undergoing IVF and testing embryos prior to implantation for a known genetic condition in the family.

(4) For some conditions, immediate postnatal interventions are required for optimal outcomes, but appropriate screening tests may not be routinely available after birth, or results may only be available days or weeks after birth. In these cases, prenatal testing is the only way to ensure that these interventions are available in a timely manner. For example there is an expression that ‘time is motor neurons’ [4], referring to the importance of and advantage of early identification and commencement of treatment to maximize the benefits of knowledge and appropriate management.

## Carrier screening

Carrier screening, which is designed to identify genetic variants in prospective parents that are associated with affected children, forms part of the prenatal screening paradigm as it can give information about the risk of passing on a genetic condition. It may be the only opportunity of finding out of such risk ahead of the birth of an affected child, as most of the conditions detectable by carrier screening are not screened for by routine prenatal screening. These conditions affect single genes rather than chromosomes. Common conditions seen on carrier screens include SMA or cystic fibrosis. It has been shown that as many as 88% of carriers of cystic fibrosis, SMA and fragile X syndrome have no known family history of the condition [5]. Carrier screening has traditionally been offered on the basis of ethnicity, so would be offered for specific conditions to groups known to be at increased risk of those conditions, for example Tay-Sach’s disease in the Ashkenazi Jewish population which was first introduced in the 1970s [6]. However there is increasing awareness that such an approach can miss a significant proportion of carriers, reflected in recent ACOG guidelines to offer screening for certain conditions, including cystic fibrosis and SMA, to all patients who are pregnant or considering pregnancy regardless of ethnicity [7]. The possibility of missing carriers with non-typical ethnicities for the condition applies even for conditions that have been strongly associated with particular populations. This has come to light partly because the advent of more widely available screening has made it possible to find carriers in populations that would previously not have been offered testing [8]. As ancestry DNA tests are showing, people may not be fully aware of the specific risk groups they may belong to, so they would not be offered appropriate screening for their ethnic background [9].

The value of carrier screening can be shown through the example of SMA screening. SMA, one of the most common autosomal recessive diseases, is a progressive neurodegenerative condition which is associated with muscle weakness and respiratory difficulties [3]. It is due to a deletion of the SMN 1 gene [3]. The carrier rate is around one in 50, and this is a pan-ethnic condition [10]. Until recently, the management of this condition was primarily supportive, but there have been two major developments. The first is a medication called Nusinersen, an antisense oligonucleotide that binds RNA. This targets a gene (SMN2), which is very similar to SMN1 and causes it to function more like SMN1 [11]. It has been shown to be associated with improvements in motor milestones and a reduction in mortality and there was indication that the efficacy might be improved by early therapy initiation [11]. Further developments have led to the development of a gene therapy for SMA [3]. Again data indicates that very early treatment is associated with better outcome [3]. Another example is cystic fibrosis, which now has a number of treatments available, including four designed to help to restore gene function [12]. Duchenne Muscular Dystrophy, another example, also has an increasing number of therapies that target gene function, and gene therapy trials are underway [13].

### Why screen for a condition that has treatments available?

One question that could be asked is ‘why should we offer carrier screening for conditions where treatments are
available?’. A goal of prenatal screening is to identify medical conditions to help to make choices regarding care and treatment during the pregnancy or after the baby is born [14]. Carrier screening offers this, and in fact goes further, providing information that allows couples to make decisions at every stage of the reproductive process. Carrier screening offers couples the opportunity to have information before even becoming pregnant, about what their chances might be of having a baby with certain specific genetic conditions. This allows them to decide whether they wish to progress with pregnancy naturally or whether to select other options that may be available to them such as preimplantation genetic diagnosis, adoption, or egg/sperm donation. If they do opt for natural pregnancy, they then have the option to confirm whether or not their baby will inherit the condition. Having this knowledge then gives them the opportunity to decide whether or not to continue the pregnancy and if so, to have the chance to prepare themselves and others. It also gives the opportunity for the baby to be given appropriate treatment at the earliest possible opportunity. Not all conditions screened for by carrier screening are currently offered as routine postnatal screens, and in some places no or little postnatal screening is available. It could thus be weeks, months, or years before the condition is detected.

If we accept that having the option to obtain information about important potential genetic conditions in the fetus is a valuable endeavor, then carrier screening can be considered an option that women and their partners should be informed about, ideally before pregnancy, and in fact this is the recommendation of the American College of Obstetrics and Gynecology [7].

Expanding the offer of non-invasive prenatal genetic screening

In 2011 tests using cell-free DNA, known as ‘NIPS became available to screen for trisomy 21 [15]. This approach represents a significant advance: rather than using proxy markers, DNA originating directly from the pregnancy is assessed for the genetic evidence of the additional chromosome material that is the hallmark of trisomy [15]. Although this technique targets the DNA that defines the condition, it is considered a screening test rather than diagnosis. One reason for this is that it is looking at cell-free DNA from the placenta and not directly from the fetus, and confined placental mosaicism can confound results [16]. Regardless, a head to head comparison of NIPS and standard first trimester screening incorporating maternal serum markers demonstrated significantly superior performance for NIPS for trisomy 21 [17].

More recently, some NIPS tests added a set of key microdeletions to their offering [18], and some NIPS have started offering genome-wide screening for large, unselected copy number variants [19]. If we adhere to the principles for prenatal screening outlined above, we might consider the addition of at least some microdeletions to the offer of prenatal genetic screening. Let us consider the case for microdeletion 22q11.2, now offered as part of several NIPS tests. This condition is the most common human microdeletion syndrome. Studies have indicated an incidence of between 1/1,000 and 1/6,000 [20], although the true prevalence is unknown as not all cases are detected. This is a serious condition which is associated with congenital cardiac defects, developmental delay and learning difficulties, immune deficiencies, palate malformations, hypocalcaemia, and psychiatric disorders among other clinical features [21]. The condition is variable, with some individuals being severely affected whereas others may be mildly or asymptomatic, but penetrance is complete in the majority of cases [21]. Whilst performance rates will vary according to the specific test used, detection rates for the common 2.91 Mb deletion of 90% have been published for the SNP NIPS technology [22], and a false positive rate of 0.07% [23]. It is important when thinking of expanding prenatal genetic screening to consider false positive rates, which are higher for copy number variants than for the common trisomies.

The advantages of prenatal screening for 22q include early information for parents and healthcare professionals to manage the pregnancy and prepare for the birth and potential health issues. In the immediate postnatal period, there are a number of interventions which may improve outcome, such as doing a detailed cardiac scan before the baby leaves hospital, and checking for hypocalcaemia, immune deficiency, and palatal anomalies [22]. Early intervention in speech and motor development, which has been advised to start before 12 months if possible [24] can be put into place. Children with undiagnosed 22q11 deletion may undergo a diagnostic odyssey in which multiple healthcare providers are consulted before an underlying explanation for the various developmental and health issues is found, and again prenatal screening could help to avoid this and maximize opportunities for early and appropriate management [22]. It is important to note that counseling for microdeletion 22q screening should include the fact that this is a variable condition, the severity of which cannot be determined in advance on an individual level, and that around 10% of cases are inherited [21]. A parent may therefore find out that they also have 22q11...
deletion. This in turn has benefits as they can seek appropriate surveillance and also be given more accurate information about the likelihood of 22q11 in future pregnancies (50% for affected parents).

**Single gene testing**

One of the most recent advances in NIPS is the possibility to offer NIPS for some monogenic conditions [25]. Many of these would not be detected by routine prenatal screening, may be detected late, or involve non-specific ultrasound findings. Early knowledge of the likelihood of such a condition may help to avoid uncertainty when non-specific signs are detected, and to inform about the likelihood of a condition for which no ultrasound signs would be present, such as Rett syndrome [26]. This information may guide pregnancy and delivery management and care in the neonatal period and beyond. This type of testing may be of particular interest when there is advanced paternal age (generally considered to be 40 or above) [27], where there are non-specific ultrasound signs and diagnostic testing is unavailable or is refused by the couple, as well as prospective parents who want to increase the range of conditions that they are screening for in pregnancy.

**Conclusions**

Prenatal genetic screening has developed rapidly over the past decade. As it becomes possible to screen for more conditions, it is important to reflect on the risks and benefits of adding each condition. Just as it would be wrong to add a condition purely because it is technically possible, it is also important to review whether there are additional conditions which should be included, for the value of the information itself and for the clinical actionability. As genetic screening technology advances, there will be more options for prenatal genetic screening, which offer exciting opportunities to improve outcomes through early diagnosis and appropriate management. A well-thought-out offer of screening can include different types of genetic conditions – selected whole chromosome conditions, copy number variants and single gene changes, with the aim of maximizing the availability of useful information. Appropriate counseling is vital to help to support prospective parents to understand their options and to make informed decisions about what screening is right for them.

**Competing interests:** Samantha J. Leonard is an employee of Natera Inc.

**Informed consent:** Not applicable.

**Ethical approval:** Not applicable.

**References**


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**Author contributions:** Single author contribution.
Opinion Paper

Isabel Filges, Peter Miny*, Wolfgang Holzgreve and Sevgi Tercanli

How genomics is changing the practice of prenatal testing

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Abstract: New genomic laboratory technology namely microarrays and high throughput sequencing (HTS) as well as a steady progress in sonographic image capture and processing have changed the practice of prenatal diagnosis during the last decade fundamentally. Pregnancies at high risk for common trisomies are reliably identified by non-invasive prenatal testing (NIPT) and expert sonography has greatly improved the assessment of the fetal phenotype. Preconceptional comprehensive carrier screening using HTS is available for all parents, if they should wish to do so. A definite fetal diagnosis, however, will still require invasive testing for most conditions. Chromosomal microarrays (CMA) have greatly enhanced the resolution in the detection of chromosome anomalies and other causal copy number variations (CNV). Gene panel or whole exome sequencing (WES) is becoming the routine follow up of many anomalies detected by ultrasound after CNVs have been excluded. The benefits and limitations of the various screening as well as diagnostic options are perceived as complex by many who find it challenging to cope with the need for immediate choices. The communication of facts to ensure an informed decision making is obviously a growing challenge with the advent of the new genomic testing options. This contribution provides an overview of the current practice and policies in Switzerland.

Keywords: genomics; NIPS; NIPT; prenatal diagnosis; prenatal screening.

Introduction

For decades and until today the prenatal diagnosis of chromosomal anomalies and monogenic conditions relies on testing cells obtained by an invasive procedure which poses a small risk to the fetus. Therefore, the access to these procedures has traditionally been more or less strictly limited to pregnancies with an increased risk mainly for aneuploidies as defined by advanced maternal age as the sole parameter for many years. Only a small proportion of pregnancies were tested due to familial genetic conditions or following carrier testing in high risk populations. The performance of risk screening for aneuploidies improved steadily over the years by inclusion of maternal serum parameters in the second trimester and later of the sonographic measurement of the nuchal translucency plus maternal serum parameters in the first trimester (first trimester screening) [1, 2]. High throughput sequencing (HTS) of DNA fragments in the maternal circulation, however, has – unexpectedly – during the past decade set a new performance standard in prenatal screening for aneuploidies which became the first large-scale clinical application of this technology. HTS also for the first time permits the short term diagnostic testing of significant parts of the fetal genome when malformations are found on ultrasound and copy number variants are excluded [3].

Non-invasive prenatal testing or screening (NIPT, NIPS)

The rapid implementation of non-invasive prenatal testing or screening (NIPT, NIPS) in the developed world was driven by commercial providers mainly from China and the US and the tests became soon extremely popular with parents to be and their attending obstetricians. The initial promise, however, that the NIPT might be diagnostic turned out to be overoptimistic mainly due to a biological phenomenon well-known since the introduction of chorionic villus sampling, i.e. confined placental mosaicism (CPM) which may cause false positive as well as false
negative test results [4, 5]. A number of maternal factors may cause false-positive test results [6]. The negative predictive value, however, for trisomies 21, 13 and 18 is very high and a mainstay of the superior performance of NIPT as a screening tool which has caused a significant decrease of invasive procedures worldwide. All screenpositive test results, however, require a confirmation by an invasive procedure [7]. NIPT has been implemented without regulatory guidance in many countries and followed strictly formal protocols in others.

Switzerland was among the first countries where the obligatory health insurance covered the cost for NIPT under certain conditions (contingent screening approach) starting in 2015. In a joint effort of health administration and the professional organisations involved detailed criteria were defined and published (current version as of March 2018 [8]). They basically restrict the coverage to the screening for trisomies 13, 18, and 21 and a risk of more than 1 in 1,000 in the first trimester combined test and also specify quality criteria for nuchal translucency measurements and risk calculation for the first trimester test. Another requirement is that the test must be performed within the country which induced a collaboration of major providers with local laboratories. First trimester combined testing is part of the routine prenatal care and offered in all pregnancies [9, 10]. Non-invasive test approaches, however, covering the sex chromosomes, selected microdeletion syndromes or any larger CNV have been successfully marketed, are a frequent choice [11] and billed to the patient. The debate on the clinical utility of expanded NIPT options is ongoing for years and remains controversial [12]. In practice both options have to be addressed in some detail and reimbursement is just one of several aspects relevant to the decision. The future of the current contingent screening approach also remains a matter of controversy which is likely to resolve when testing costs come down.

Carrier-screening

In the past prenatal or ideally preconceptional carrier screening has been recommended for populations with a known increased risk for recessive conditions. The textbook example is hemoglobinopathies where cost-effective non-genetic screening is available by a red blood cell count and hemoglobin-electrophoresis. In some countries screening for the more frequent recessive conditions is recommended such as cystic fibrosis, spinal muscular atrophy and others [13, 14]. Carrier screening uptake is traditionally high in the Jewish population and a national program provides testing free of charge in Israel [15]. HTS opens up a new dimension of testing options which may be useful for consanguineous couples [16] or in families with a suspected genetic condition when the index patient is not available. The popular direct to consumer tests cannot be recommended, however, for various reasons and test results must be confirmed [17].

For the time being there are no specific national recommendations in Switzerland. Carrier tests are not covered by the health insurance and the demand for cost intensive genomic test approaches remains low.

Ultrasound

In the last two decades fetal phenotyping by prenatal sonography improved significantly. Prenatal physical and functional symptoms of a growing number of genetic conditions were identified and correlated to specific copy number or DNA sequence variants. Hygroma colli in early pregnancy was one of the first anomalies investigated and confirmed as an important marker of chromosomal and others fetal disorders since the end of the 80s [18, 19]. During the 90s the risk assessment for chromosomal anomalies was based on the so-called genetic sonogram which included the search for major fetal anomalies and softmarkers [20, 21]. The screening performance increased further with the introduction of the combined test earlier in pregnancy at 11–14 weeks [22, 23]. The standardized measurement of the nuchal translucency (NT) became the best and critical marker in first trimester risk screening and required continuous quality control policies [22].

Following the implementation of the NIPT the role of sonography in the screening for common trisomies was occasionally questioned. All relevant advisory boards, however, stressed the fundamental role of ultrasound in screening for other genetic and non-genetic conditions. For decades two or more ultrasound scans are an established part of antenatal care in most developed countries. In Switzerland and other countries NIPT was integrated in the existing antenatal care schemes i.e. ultrasound scans and NT measurement are recommended as the first step prior to all further testing [9, 24].

The main intention of this policy is to not reduce antenatal screening to common trisomies and use the potential of diagnostic ultrasound for fetal phenotyping. An increased NT has been found as an early sign of a variety of fetal malformations and more than 50 rare syndromes [25, 26]. In a recent study abnormal ultrasound findings in general were associated with copy number variation (CNV) not detected by NIPT in 16.3% of pregnancies [27]. The single most important ultrasound marker
for CNVs as well as monogenic conditions is an increased NT (Figure 1) [25, 26]. Numerous groups reported a wide range of CNVs and DNA-sequence variants in presence of major isolated or multiple fetal abnormalities namely increased nuchal translucency (NT≥3.5 mm), cardiac, skeletal, urogenital, renal and central nervous system anomalies (3.5–80%) (Figures 2 and 3) [28–30]. Based on these findings invasive testing is recommended in Switzerland whenever a fetal structural anomaly is diagnosed, or the NT is increased, or the risk in the combined test is higher than 1 in 10 [8] because the estimated detection rates of advanced genomic testing may be as high as 30% [29, 31, 32].

**Diagnostic testing**

**Microarrays**

Since the implementation of NIPT in clinical practice the number of diagnostic procedures, CVS or amniocentesis being the most common, decreased significantly particularly for interventions related to an increased risk for the frequent trisomies based on advanced maternal

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**Figure 1:** Noonan syndrome in a 34 years old primigravida at 12 + 5 weeks of gestation with increased NT (3.4 mm; A), agenesis of the ducutus venosus (B) and persisting lateral nuchal cysts at 14 + 3 weeks (C).

NIPT and CMA normal. Prenatal panel testing or WES denied. Postnatal diagnosis of missense mutation in RIT1 (c.170C>G).

**Figure 2:** Coffin Siris syndrome in a 28 years old primigravida with mild intellectual disability at 22 + 6 weeks of gestation. Mild ventriculomegaly and absent cavum septi pellucidi due to agenesis of corpus callosum. CMA normal, WES on DNA from amniotic fluid cells: c.1488dupG in ARID1B gene.
age only or other low risk indications such as e.g. parental choice. The advantage of the very high negative predictive values of NIPT for the frequent trisomies is the best argument in favour of this approach, and limits invasive testing to confirmation of NIPT findings indicating an increased risk by rapid testing methods such as QF-PCR, FISH or MLPA on digested chorionic villi or amniotic fluid cells, and to differentiate between free trisomies from unbalanced translocation trisomies by consecutive microscopic karyotyping on cultured cells [33].

However, in the presence of fetal structural anomalies different considerations apply. There is consensus that NIPT should only be offered in combination with a certified ultrasound scan. Increased nuchal translucency is associated with a higher risk of numerical but also structural chromosome abnormalities causing fetal malformations particularly cardiac, genitourinary, skeletal, but also others, not necessarily apparent in first trimester ultrasound scan.

In most countries molecular karyotyping by chromosomal microarray (CMA) has now replaced the conventional microscopic chromosome analysis because of its superior detection rate including clinically relevant submicroscopic structural chromosome changes also termed copy number variants (CNV). Additional 6–10% of clinically relevant CNVs are identified in the presence of increased NT, intrauterine growth restriction and/or one or more fetal structural anomalies, and the risk is increased also following positive FTT screening results due to altered PAPP-A and free beta-HCG levels without fetal anomalies [34, 35]. The detection rate is particularly high in the presence of multiple anomalies or when specific organ systems are affected as e.g. in the presence of brain, cardiac or renal anomalies, or in fetuses with NT > 3.5 mm [29, 36–38]. NIPT, as a screening tool, has poor positive and negative predictive values for CNVs, and therefore is not indicated in pregnancies at high risk for chromosomal anomalies other than the frequent trisomies. An 1.7% baseline risk for CNVs in low risk pregnancies without fetal anomalies was assessed in pregnancies examined for advanced maternal age and pathogenic CNVs were identified in 0.86–1.7% in pregnancies without any risk factors.

The diagnosis of an unbalanced structural chromosome anomaly, recurrent or rare microdeletion or -duplication syndrome may significantly change the prognosis since global developmental delay and/or intellectual disabilities may be associated, and the etiologic diagnosis influences parental decisions and pregnancy management. Obviously such functional abnormalities cannot be detected by ultrasound. After the exclusion of the frequent trisomies by rapid testing using QF-PCR, FISH or MLPA on the invasive sample, CMA analysis is performed on DNA extracted from digested chorionic villi, native amniocytes or cultured cells depending on the quantity of DNA available from the native sample provided. All other considerations for standard karyotyping including quality measures minimizing the risk for maternal contamination as well as guidelines assessing and interpreting mosaicism of the fetoplacental unit also apply for CMA analysis. In addition to the detection of CNVs using common oligo-arrays for array comparative genomic hybridization, also known as array-CGH, microarrays including additional single nucleotide polymorphisms (SNPs) allow the detection of triploidy and uniparental isodisomy. In most diagnostic laboratories CNVs up to a 100–200 kb size, representing a resolution 100× higher than microscopic karyotyping, are reported. Balanced chromosomal abnormalities cannot be detected by CMA, since there is no loss or gain of genomic material in a truly balanced rearrangement.

In many countries, including Switzerland, CMA has now replaced conventional karyotyping in the presence of ultrasound anomalies or on parental request. Pre- and posttest counselling remains important and gets more complicated regarding today’s multiple testing options in various clinical settings. Besides benefits and limitations challenges of genomic testing by CMAs such as copy number variants of unknown significance need to be addressed, although estimated to occur in only about 1% now with the increasing experience on CNV interpretation.
Genome-wide sequencing

When there is no chromosomal abnormality or pathogenic CNV identified, HTS now facilitates the parallel sequencing of multiple genes to identify pathogenic sequence variants causing monogenic disorders. While such sequencing approaches allow to sequence the coding genome (the exome, representing about 1% of the genome) or even the entire genome, in only 7,000 of the 22,000 genes of the exome multiple, but not all, variants are known to cause a monogenic disorder for the time being, often also called the «mendeliome»). Balancing the wealth of data technically obtainable against the primary goal of prenatal diagnosis to identify a reliable etiologic and prognostic information in a reasonable time frame several HTS approaches can be used. These include the interpretation of variants in a restricted and predefined number of disease genes for which there is evidence for a causal relationship to the phenotype, often also termed panel-sequencing. This approach has e.g. been used for the diagnosis of skeletal dysplasias which are a heterogeneous group of diseases with overlapping clinical signs identified by ultrasound scan [39] achieving a high diagnostic yield when combining the analysis of sequence data with expert clinical genetics reviews. Another strategy is to include variants present in all known disease genes in a clinical exome (CES) as opposed to all genes in a whole exome (WES) including those not yet linked to a human phenotype. Trio-exome sequencing including samples of the parents is often used to facilitate variant interpretation and shorten turn-around-time.

Panel and CES approaches are on the verge of being implemented into routine clinical practice when there is increased NT, hydrops, intrauterine growth restriction and/or a single or multiple congenital anomalies in the presence of a normal CMA result as a sequential test. The consideration is based on postnatal WES which allows a diagnosis in about 25% of patients with various indications [40] and such will be present already prenatally. There are so far only a few prospective studies assessing the prenatal diagnostic yield for monogenic disorders which varies considerably according to the clinical phenotype. The PAGE study (and substudies) revealed the high detection rate of 15.4% for fetuses with multiple congenital anomalies, skeletal and cardiac defects [31, 32, 41, 42].

Monogenic causes for isolated increased NT in the first trimester were identified in 3.2% of pregnancies and 25% in non-immune hydrops fetalis phenotypes. Pathogenic variants in genes involved in the rasopathy pathway causing hydrops as the severe end of the Noonan syndrome phenotype spectrum seem to account for the majority of cases in the current studies [41, 43]. Retrospective studies for selected indications and in small patient series using various sequencing approaches show diagnostic yields between 6.5 and 80% (reviewed by [44]). It is important to mention that neither CMA nor genome-wide sequencing approaches will detect all genetic disorders or exclude them entirely. The residual risk for a rare disorder, especially in the presence of multiple congenital anomalies, is an important aspect of patient counselling. Particularly sequencing approaches for monogenic disorders are still incomplete by missing certain types of variants in known disease genes, and by the presence of variants of unknown significance which we cannot reliably interpret in the context of human disease. Furthermore, our knowledge about phenotype-genotype correlation so far mainly relates to postnatal experiences, and the fetal phenotype presentation may be more severe, lethal, different or incomplete as compared to the postnatal presentation even if caused by variants in the same gene or even identical variants [45].

Reporting or disclosure of incidental or secondary findings or pathogenic variants for late-manifesting disorders in the fetus and the parents remain a challenge particularly in a prenatal application [46–49]. Several professional societies have established recommendations for prenatal exome sequencing and counselling trying to standardize the clinical implementation and address all these uncertainties [50, 51].

Perspectives

There is now a multitude of screening and testing options in prenatal medicine (Figure 4). Emerging technologies such as optical mapping [52] or whole genome sequencing as the ultimate «one test for all» will overcome the technical difficulties of applying several methods sequentially by its ability to detect chromosome abnormalities, CNVs and sequence variants at the same time but will likely require an invasive procedure. Non-invasive prenatal diagnosis is established to determine the fetal sex or Rhesus type and is offered in some specialized laboratories for more frequent dominant new mutations and some specific familial variants. Prenatal medicine is turning into precision medicine which, however, will only be beneficial for patients when there is a close interdisciplinary collaboration of maternal fetal medicine specialists, clinical
geneticists and genomic laboratories in order to maximize the benefit of technological advances for a specific clinical question and to limit the potential harms, ensuring appropriate patient counselling and care.

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Mini Review

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Postnatal gene therapy for neuromuscular diseases – opportunities and limitations

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Abstract: During the last decade a number of innovative treatments including gene therapies have been approved for the treatment of monogenic inherited diseases. For some neuromuscular diseases these approaches have dramatically changed the course of the disease. For others relevant challenges still remain and require disease specific approaches to overcome difficulties related to the immune response and the efficient transduction of target cells. This review provides an overview of the current development status of mutation specific treatments for neuromuscular diseases and concludes with an outlook on future developments and perspectives.

Keywords: antisense oligonucleotide; Duchenne muscular dystrophy; gene therapy; myotubular myopathy; spinal muscular atrophy; viral vector.

Introduction

During the last decade several mutation specific treatments for monogenetic neuromuscular diseases have been approved or are in advanced stages of clinical development. These treatments include approaches that modify the splicing or translation of mRNA or introduce additional genetic material. Somatic gene therapy is defined as the addition, removal, or modification of genetic information in a patient’s somatic cells for the purpose of treating or preventing disease. For the treatment of neuromuscular diseases, gene augmentation or gene addition is currently the most advanced modality. This therapy adds a functional copy of the defective gene to facilitate production of the target protein. Beyond these first-generation gene therapies, gene editing technologies are enabling an entirely new modality for treatments based on precise modification of human genome sequences. These technologies are only currently beginning to be tested clinically [1].

Viral vectors are the most frequently used agents for gene therapy owing their capabilities to deliver many copies of the therapeutic gene to the target cells. Among the most commonly used types are adenoviral vectors, retroviral vectors, lentiviral vectors and adeno-associated vectors. Lentiviral vectors have the capability to integrate their genetic information into the genome of the target cell, while adeno-associated vectors do not integrate into the genome of the target cells. Instead, the genetic information remains in the nucleus as an episome. These vectors can thus express therapeutic genes without changing the genome in host cells, but their use is mainly limited to non-dividing cells.

Gene transfer can be performed ex vivo or in vivo (Figure 1). The most advanced use of ex vivo gene therapy is the modification of hematopoietic stem cells to treat inherited diseases such as thalassemia using lentiviral vectors. The in vivo approach, mostly based on adeno-associated vectors (AAV), is currently used for the treatment of neuromuscular diseases, retinopathies or haemophilia [2].

Key limitations of AAV-based gene therapies include the immune response to gene delivery vectors and to products of the foreign transgene. These reactions often require a prophylactic or reactive immunomodulatory treatment. Some patients are currently excluded from AAV-based gene therapies due to pre-existing antibodies to the vector capsid.

This paper will review the current development status of innovative and mutation specific treatments for neuromuscular diseases and discuss the implications for diagnosis and counselling of affected patients and their families.

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Therapeutic approaches for neuromuscular diseases

Spinal muscular atrophy

Spinal muscular atrophy (SMA) is an autosomal recessive disease caused by biallelic mutations of the SMN1 gene. The resulting reduction of survival motor neuron (SMN) protein production mainly affects spinal motoneurons and leads to a progressive loss of muscle strengths. The clinical phenotype associated with SMA covers a broad spectrum of disease severity from SMA type 1 with onset during the first six months of life to cases with onset during later childhood or adolescence (SMA types 2, 3 and 4). The main reason for the differences in disease severity between patients is the number of SMN2 gene copies. SMN2 is a nearly identical gene located next to SMN1, which also produces SMN protein. However, due to a single nucleotide exchange that affects the splicing, the production of functional protein is reduced to about 10% compared to SMN1. While SMN2 has no relevance in healthy humans, it serves as a back-up gene in patients with SMA and can partially rescue the phenotype. Higher SMN2 gene copy numbers are thus associated with a milder phenotype. Two SMN2 copies are most prevalent in the population and are typically associated with the severe phenotype of SMA type 1. Without treatment patients with SMA type 1 die within the first two years of life or require permanent ventilation due to severe muscle weakness [3, 4].

Nusinersen was the first drug that has been approved for the treatment of all types of SMA. It is an antisense oligonucleotide that specifically modifies the splicing of SMN2 and leads to an increase of SMN protein production. As nusinersen does not cross the blood-brain barrier it requires repeated lumbar punctures every four months for intrathecal administration. Double-blind, sham-controlled trials have shown a clear benefit compared to the control group in infants with SMA type 1 and children with SMA type 2, respectively [5, 6]. Very recently, risdiplam has been approved as the second splicing modifier for the treatment of SMA. In contrast to nusinersen, risdiplam is a small molecule that crosses the blood-brain barrier and can be administered orally. In Europe it has been approved for the treatment of SMA patients aged two months and older [7].

The gene therapy approach for the treatment of SMA makes use of an adeno-associated viral vector type 9 (AAV9) to introduce a functional copy of the SMN1 gene. Onasemnogene abeparvovec is administered through a single intravenous infusion. Based on open-label clinical trials in infants the drug has received FDA approval for the treatment of patients with SMA up to the age of two years. For Europe, EMA has approved onasemnogene abeparvovec for the treatment of patients with up to three SMN2 copies.
copies without defining a clear age or weight limit. As the total dose used is proportional to the body weight and clinical trial experience is limited to infants, there are ongoing discussions about the potential use of the treatment in older children [8]. According to the product information it is recommended to use an immunosuppressive treatment with prednisolone starting on the day before administration for at least four weeks. Most commonly observed side effects include increase of transaminases and thrombocytopenia.

There are no randomized trials comparing the different treatments for SMA and cross-study comparison is difficult due to distinct inclusion criteria and baseline characteristics. However, all studies have shown that early initiation of treatment is most relevant to achieve best outcome. As most patients with SMA do not show any symptoms during the first weeks of life, some studies have explored the pre-symptomatic initiation of treatment and shown that this can facilitate almost normal motor development for many patients [9]. As a consequence newborn screening for SMA has been explored in several pilot projects and is introduced in an increasing number of countries [10, 11].

**Duchenne muscular dystrophy**

Duchenne muscular dystrophy (DMD) is the most common neuromuscular disease during childhood. DMD is caused by mutations of the dystrophin gene on the X-chromosome. Due to the X-linked inheritance, DMD mainly affects boys and leads to a progressive loss of muscle strength. First symptoms, such as difficulties with climbing stairs or standing up from the floor, are typically noticed between two and four years of age. The progressive course of the disease leads to loss of ambulation between 10 and 14 years of age and respiratory failure during adolescence or early adulthood. In addition, most patients develop a dilative cardiomyopathy, which contributes to early mortality. In DMD the lack of the dystrophin protein causes disintegration of a membrane associated protein complex, which leads to cell death and replacement of muscle tissue by fat and fibrous tissue. Creatine kinase in serum, a marker of muscle necrosis, is invariably markedly increased from birth and serves a convenient screening marker for the disease. Underlying mutations include deletions or duplications of one or several exons of the dystrophin gene in about two thirds of cases and smaller mutations affecting only one or a few nucleotides in the remaining cases [12].

One treatment approach is the use of antisense oligonucleotides which bind to the splicing site of a specific exon and thus lead to so-called “exon-skipping”. If used in appropriate patients the skipping of an additional exon can help to restore the reading frame and thus allow for the production of partially functional dystrophin protein. Some of the exon skipping products have been approved by the FDA based on increased production of dystrophin observed in clinical trials. However, as clinical efficacy has not been proven convincingly, these drugs are currently not approved in Europe [13].

Ataluren is a specific treatment for premature termination codon (nonsense) mutations, which account for about 10% of the DMD cases. Although the primary endpoint was not met in a double-blind placebo-controlled trial, subgroup analysis showed lesser decline in the treatment group compared to the placebo group [14]. Ataluren has been approved in Europe for the treatment of ambulant patients with nonsense mediated DMD, who are at least two years old.

A major limitation for the use of gene therapy for the treatment of DMD is the size of the dystrophin gene which exceeds by far the packaging capacity of AAV-based vectors. One possible solution is the construction of truncated forms of the dystrophin gene, which contain the minimal functional regions of the protein. Several of these micro- or mini-dystrophins a currently in clinical development using AAV-vector based gene therapy [15]. Due to the limitations of this traditional gene augmentation therapy, genome editing is also explored for the treatment of DMD. In most cases these strategies are designed to change a DMD out-of-frame mutation into an in-frame mutation, which is associated with the milder phenotype of Becker muscular dystrophy. Currently, genome editing technologies like CRISPR/Cas9 are studied in DMD animal models [16].

**Myotubular myopathy**

X-linked myotubular myopathy (XLMTM) is caused by mutations of the myotubularin 1 gene (MTM1) located on the X-chromosome. The severe form of XLMTM, which is also the most common form, is characterized by severe muscle weakness, ophthalmoplegia and respiratory insufficiency from birth. Reduced fetal movement and polyhydramnios often indicate prenatal onset. Nearly all patients require respiratory support at birth and the mortality is about 50% during the first years of life. Most patients who survive require tracheostomy [17].
An open label treatment study in 12 patients described improvements in motor and respiratory function after AAV8 based gene therapy including weaning from artificial ventilation in a significant number of patients [18]. However, later three children who had received a higher dose of this gene therapy died from fatal hepatic dysfunction and sepsis [19]. It is assumed that this might have been related to pre-existing hepatobiliary disease, which had been reported in XLMTM. The use of the therapy has therefore been temporarily stopped.

Clinical implications and future developments

Mutation specific treatments and gene therapy have reached clinical development and clinical practice for a number of neuromuscular diseases. However, treatment strategies, clinical efficacy and safety profiles can be very different from disease to disease and might even be mutation specific. While treatment of SMA with splicing modifiers or gene therapy has already shown remarkable benefit, treatment of other neuromuscular diseases might be more complex and still requires additional research.

Treatment of SMA is particularly effective when initiated in the pre-symptomatic phase and the disease should ideally be diagnosed through newborn screening or even prenatally. However, if diagnosed in this stage, counseling is still challenging. The prognosis for SMA type 1 has changed from an almost inevitably lethal disease to long term survival without respiratory support and close to normal motor development. Nevertheless, the use of splicing modifiers requires lifelong treatment either orally or by regular intrathecal injection and AAV-based gene therapy is a one-time treatment, but it is not yet known if the efficacy might decline after several years. Thus, prognosis is potentially very positive for the first years of life but cannot always be guaranteed into adulthood.

For other neuromuscular diseases the future impact of innovative treatments is even more difficult to predict. The modification of vectors and gene constructs might help to reduce immune response and increase transduction of target cells. For some diseases gene augmentation therapy might not be sufficient and gene editing technologies like CRISPR might be needed to correct or modify existing genetic information. In some pathologies post-natal treatment might already be too late due to irreversible prenatal damage. In these cases, in utero gene therapy can be discussed. However, this is associated with new challenges such as potential transduction of maternal cells or immune response of the mother.

In conclusion, it is very likely that gene therapies will be used for an increasing number of diseases during the coming years. However, due to the complexities of individual diseases and the associated host responses, it is not possible to predict future breakthroughs or setbacks. Nevertheless, these new developments will not only be of interest for a small number of experts, but will be of increasing relevance for the whole medical field.

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