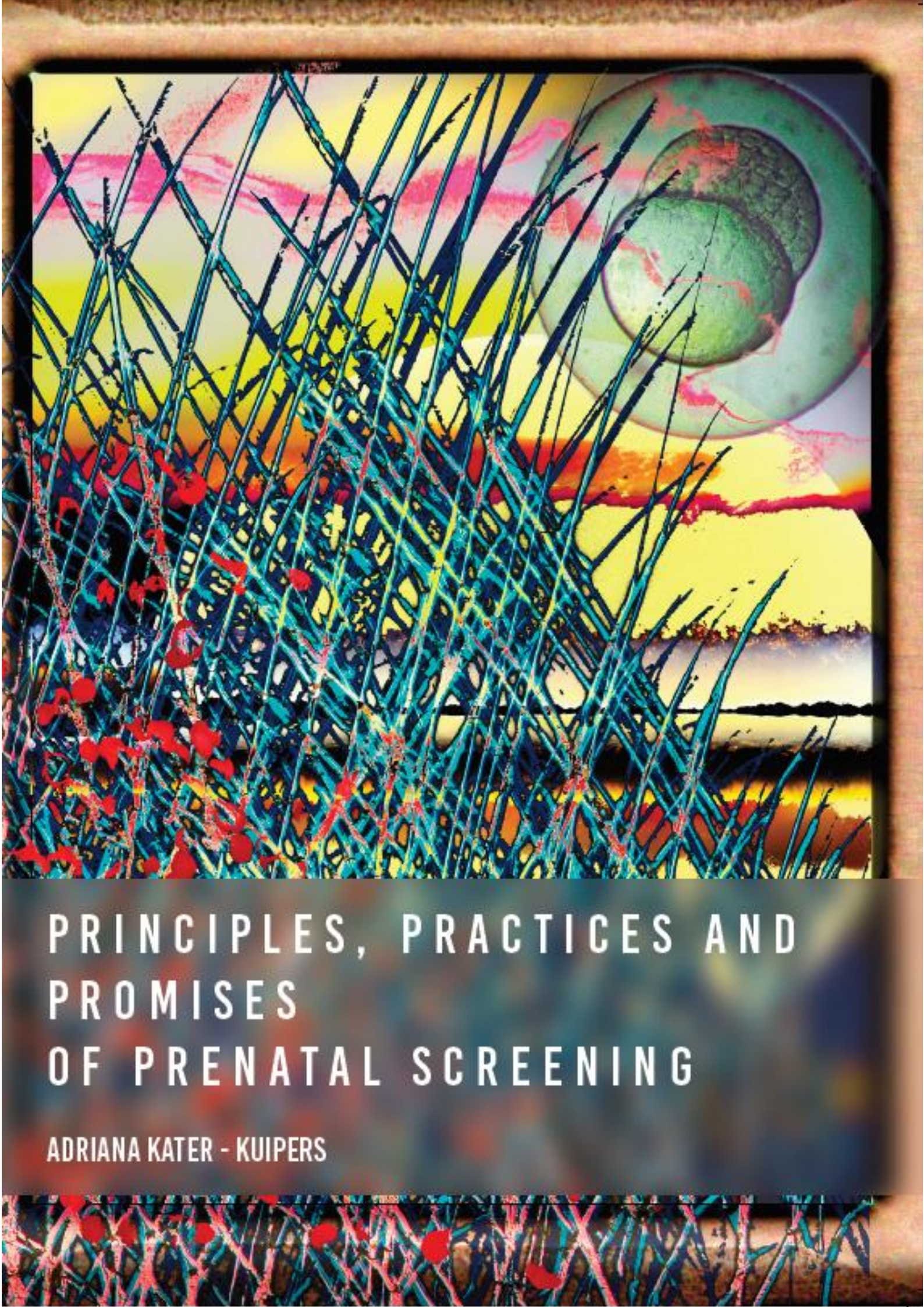

PRINCIPLES, PRACTICES AND PROMISES OF PRENATAL SCREENING

ADRIANA KATER - KUIPERS

Principles, practices and promises

of

prenatal screening

Ethical and social aspects of non-invasive prenatal testing (NIPT)

and the expansion of the scope of prenatal screening

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Principles, Practices and Promises of Prenatal Screening

Ethical and social aspects of non-invasive prenatal testing (NIPT) and the expansion of the scope of prenatal screening

Principes, praktijken en beloften van prenatale screening

Ethische en maatschappelijke aspecten van niet-invasief prenataal testen en de uitbreiding van de scope van prenatale screening

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Table of contents

Chapter 1|

Introduction

Over the past few years, the Dutch newspapers paid a lot of attention to the introduction of non-invasive prenatal testing (NIPT) for Down's syndrome, Edwards' syndrome and Patau's syndrome. They fuelled the debate about the introduction of this promising test, which will provide much more reliable test results compared to existing prenatal screening tests and prevent uncertainty for women. The newspapers also published articles headed like for example "Born, despite the NIP-test" or "Who chooses for a child with Down's syndrome" addressing ethical and social issues of NIPT.(1, 2) The first mentioned article draws a portrait of three couples with a child with Down's syndrome who made different decisions about prenatal screening for Down's syndrome. Two couples did not accept NIPT and one couple accepted it after an indication from the 20 weeks ultrasound. One couple did not opt for NIPT because, as the parents explained, they had no reasons for having prenatal screening: she was doing well and moreover, they thought that every child should be welcomed. The news that their new-born son has Down's syndrome was thus totally unexpected and the parents began to doubt their decision to decline NIPT. They explained that it felt as if they had chosen for a child with Down's syndrome by declining NIPT: "It was not something that just happened to us. You cannot go back to a sort of innocence." Nevertheless, they are not sure whether they will opt for NIPT in a next pregnancy and they question what they would do in case of an abnormal result, also because they still, after six months have to adapt to the new unexpected situation: "I love him but still I rather would have a child without Down's syndrome. It feels very tricky to say this". The other couple declined NIPT because they would welcome every child. The second article reports the dialogue between a mother who decided to terminate the pregnancy after receiving the diagnosis of Down's syndrome and a mother of a son with Down's syndrome. Both mothers explained how difficult it is to talk about your choice, because there are always people who have judgements about it. Nevertheless there are also people who are helped with sharing these opinions. These mothers therefore thought that it is important to have such dialogues, to create understanding for both decisions to accept or decline prenatal screening and terminate or continue the pregnancy after a diagnosis of Down's syndrome.

These newspaper articles reported parents' personal considerations concerning prenatal screening and termination of pregnancy and how they deal with the decision. The articles also pointed at the social dilemmas concerning the availability of prenatal screening: does

create this availability a certain responsibility for having a healthy child? Is it still accepted to give birth to a child with a disability? The Dutch social debate in newspapers and on television about the pros and cons of prenatal screening and the introduction of the relatively new non-invasive prenatal test (NIPT) are supported by these personal stories about deciding about prenatal screening as well as deciding about termination of a pregnancy of a child with Down's syndrome in order to make the related dilemmas concrete.

In the media these pros and cons of particularly NIPT are strongly contrasted and sometimes inflated. The reasons to learn about possible abnormalities, including psychological and practical preparation for the birth of a disabled child or the option to terminate the pregnancy, are contrasted with the negative consequences of a prenatal screening offer, including the a lack of freedom of choice and stigmatization or discrimination of people with the relevant disabilities. Firm statements about a lack of informed decision-making, routinisation, societal pressure to test and an expanded scope mark the debate. Also in the scientific debate these benefits and possible disadvantages of NIPT are mentioned, discussed and analysed. However, in both the social and scientific debate the reflection on the validity of the several arguments and concerns is limited. This thesis aims to clarify and justify these issues and related arguments, inform and nuance the scientific and social debate about prenatal screening and contribute to a responsible implementation of NIPT and its possible expansion.

1.1 Aim of prenatal screening

The aim of prenatal screening for aneuploidies is formulated as promoting reproductive choices or reproductive autonomy or providing courses of action to pregnant women and couples.(3-5) Prenatal screening enables pregnant women to obtain information about the health of their unborn child in order to have the possibility to terminate the pregnancy or to prepare for the birth of a child with a disorder in case of an abnormal test-result. This aim is formulated as an alternative for the general aim of other population screening programmes which is prevention.(3) Prevention-aimed screening intends to promote health and reduce morbidity or mortality. Prenatal screening programmes also include preventive screening tests to improve pregnancy outcomes and to gain health benefit, for example tests for the Rhesus-D status, hepatitis B or HIV. However, with prenatal screening for aneuploidies no health benefit can be reached because there are no treatments available for the disorders

included in the test. Prevention as an aim of such screening is therefore problematic: termination of an affected pregnancy would then be a preventive measure and the success rate of the prevention programme would be the amount of terminations. This might pressure women to terminate a pregnancy of a child with a disability.(3) Therefore the aim of prenatal screening is formulated as promoting reproductive autonomy and termination of an affected pregnancy is explicitly mentioned as one course of action among other options.(6) The success of the programme should be measured in terms of informed consent which is seen as the operationalization of the aim.(3) This aim is underlined in the ongoing debate about (selective) abortion as the consequence of prenatal screening. Opponents argue against prenatal screening because it provides women with reasons for abortion, which they reject for three reasons. Firstly, some people are against abortion because they believe that life starts at conception and is therefore from that moment on worth protecting. Others rejects abortion because they believe that one should accept life as it comes, without having religious convictions as underlying reasons for it. These two groups therefore disagree with the starting point of the Dutch Health council and Dutch legislation that the protection of unborn life of the foetus increases during the pregnancy. According to this starting point, a foetus is viable from a gestational age of 24 weeks on and in principle abortion is allowed until the 24th week.(5)

A third view opposes prenatal screening because it provokes selective abortion, which sends a discriminatory message about lives of people with the conditions included in the prenatal test. This is known as the 'expressivist argument', held by representatives of the disability rights critique, which argues that techniques which lead to prevention of the birth of children with disabilities send discriminatory messages about people with disabilities.(7) Others refuted this argument with stating that pregnant women and couples do not decide for selective abortion to judge the life of disabled people but because of the impact of raising a child with a disability on their own lives or to prevent severe suffering for the child.(6) However, in practice this argumentation does not take away the parents' concerns that prenatal screening and particularly NIPT affects the life of disabled people. Parents of children with Down's syndrome for example gathered negative experiences of judgment of others and of being confronted with critique on having a child with Down's syndrome in a Blackbook.(8) They presented it to the Dutch House of Representatives in order to provide

an illustration of the negative consequences of prenatal screening for children with Down's syndrome and their family and to feed the debate about the possible consequences of NIPT.

Informed choice

To reach the aim of reproductive autonomy, in the practice of prenatal screening professionals aim at women's informed decision-making by providing information about the prenatal test and the tested disorders.(3, 9) Informed choice as used in the context of prenatal screening is defined as "one that is based on relevant knowledge, consistent with the decision-maker's values and behaviourally implemented".(10) Information includes the conditions tested for, characteristics of the test and the implications of undergoing a test. A woman's attitude comprises her values concerning prenatal screening. 'Behaviourally implemented' means the actual choice.(9)

The multi-dimensional measure of informed choice (MMIC) is the instrument most used in the field of prenatal screening to measure the informedness of women's choices based on a self-report questionnaire about someone's knowledge and attitude.(11) A woman is thought to have sufficient knowledge when approximately at least half of the questions about the provided information concerning prenatal screening are answered correctly. Attitudes towards prenatal screening are assessed with questions such as for example "For me prenatal screening for Down's syndrome would be beneficial/harmful". Studies measuring informed choice showed various percentages of informed choice for first-trimester prenatal screening.(12) That 37%(13), 43%, 51%(14), 59%(11), or 68%(15) of the participating women made an informed choice for the first-trimester combined test and 75.6(16), 77.9%(17) and 89.0(18) for NIPT were promising results, although it also indicates that there is room for improvement. The recent introduction of NIPT was one of the reasons to start with this improvement and to again emphasize the importance of informed choice, also -or specifically- for this new practice changing test.

1.2 The introduction of non-invasive prenatal testing (NIPT)

NIPT is based on the finding that maternal blood contains cell-free DNA of the placenta.(19) Testing cell-free DNA was already conducted prenatally for foetal sex determination and rhesus D screening.(20) Genome wide sequencing techniques now also enable detection of

aneuploidies in this cell-free DNA which led to the introduction of NIPT for trisomy 21, 18 and 13 into the prenatal screening practice.(21) In 2011 NIPT became available in the United States and Western-Europe and thereafter also other in parts of the world.(22) It is proved to be an accurate test providing very reliable results compared to the first-trimester combined test(21, 23) with 98% sensitivity and a positive predictive value of 96% for Down's syndrome in a general obstetric population.(24) The first-trimester combined test has been offered to Dutch women since 2007 and includes a blood test and an ultrasound. The blood test measures maternal serum markers (PAPP-A end free betaHCG) and the ultrasound examines the nuchal translucency, the nuchal fold thickness. The obtained results, combined with the maternal age provide a risk estimate for Down's syndrome. In the Netherlands the cut-off point for a high risk for Down's syndrome is 1:200. A risk higher than 1:200 is an indicator for invasive follow-up testing. Women with a high risk result are eligible for an amniocentesis and chorionic villi sampling, both invasive follow-up diagnostic test with a very small miscarriage risk. The first-trimester combined test has a considerable amount of false positives, leading to unnecessary invasive follow-up diagnostic tests. With NIPT it is aimed to reduce the number of false positive screening results and therewith the number of unnecessary invasive follow-up tests.(25) NIPT can be introduced as first test or as second test after the first-trimester combined test. In case of NIPT as a second-tier screening women who received a high risk result from the first-trimester combined test can first opt for NIPT before they undergo invasive diagnostics. NIPT as first step replaces the first-trimester combined test and is also offered to women without an increased risk for Down's syndrome.

NIPT does not provide a fully reliable result because amongst others a lower foetal fraction, a confined placental mosaicism or a maternal tumour could cause false positive or negative results. Therefore an abnormal NIPT result still needs to be confirmed with a diagnostic invasive test.(26) According to several studies NIPT's reliability and easiness are seen by women and professionals as advantages, compared to the combined test. Besides, only a blood draw from the mother is needed to conduct the test and it can be done earlier in the pregnancy, from 9 weeks on.(27-30)

An expanding scope of prenatal screening

With whole genome sequencing techniques NIPT technically allows for testing the entire

genome of the foetus.(24) This enables the expansion of the scope of prenatal screening and the detection of an increasing number of lethal, severe and milder chronic disorders, including other trisomies like trisomy 8, 9, 15, 16 and 22, microdeletions like for example 12q or 22q11 deletion causing DiGeorge syndrome, variants of unknown significance (VOUS) and placental chromosome aberrations.(24, 31-33) NIPT can also reveal aneuploidies which are associated with pregnancy loss or maternal preeclampsia.(34, 35)

Ethical aspects of NIPT

The introduction of NIPT and the promising improvement of first-trimester prenatal screening for aneuploidies however raised clinical and ethical questions about its impact on informed decision-making, about the scope of prenatal screening and about the possible negative consequences for freedom of choice in prenatal screening and for giving birth to a child with a disability.

A simple blood draw eases the access to prenatal screening for women. This fuelled the fear that NIPT might foster women to routinely accept the prenatal screening offer, without thinking about its consequences. This might lead to what is called routinisation of prenatal screening which refers to the concern that a prenatal test is offered and accepted routinely.(36, 37) A routine uptake might impede informed decision-making and with that thus hinders the aim of prenatal screening.

Another indicated problem for informed choice is the possible expansion of the scope and the technical possibility to detect more abnormalities. The expanded pre-test information might hinder a well-informed decision-making and it can be questioned whether women will understand the possible rare and unknown test results including unknown phenotypes.(3) The possibility to expand the scope of prenatal screening also raises questions and concerns regarding how to define the scope ethically. Although it is seen as positive that an expanded scope removes the focus on Down's syndrome, it is questioned where the line should be drawn and which disorders would be included and which not. This question includes the difficulty that a defining list of disorders is susceptible to discrimination,(5) as explained above in the discussion of the purpose of prenatal screening. But the practice of prenatal screening needs some guidance to determine the scope and distinguish between serious and trivial disorders.

The indicated questions and concerns are not unique for NIPT but were previously indicated

in the context of other screening and diagnostic tests.(38-40) This thesis builds on previous debates and aims to clarify, verify and if necessary rectify several arguments within this debate which are raised in the context of the introduction of NIPT.

1.3 Dutch context of prenatal screening

Legislation and policy

First the Dutch context of prenatal screening and related legislation and policy will be described. In the Netherlands screening of (a category of) the population is regulated by the Population Screening Act (Wet op het Bevolkingsonderzoek, WBO, (1992). This act aims to protect citizens against potential physical or psychological risks of screening and requires that some screening programmes should have a license, including screening which uses ionic radiation, cancer screening and screening for severe disorders or abnormalities for which no treatment or prevention is available. Prenatal screening for aneuploidies, for which no treatment is available, falls within the latter group and thus needs a license.(41) For this license prenatal screening should meet the quality requirements. An important requirement concerns the pre-test information about the characteristics of the screening test, its consequences and possible follow-up, which is the basis for a well-informed choice. Although prenatal screening is not offered by the Dutch government prenatal screening all pregnant women receive information about prenatal screening as part of the standard healthcare during the pregnancy. The quality of the screening and the information is monitored by the RIVM (National Institute for Public Health and Environment) which is responsible for the coordination and implementation of the prenatal screening programme.
In the Netherlands since 2007 first-trimester prenatal screening is offered to women older than 38 and later 36. Women younger than 36 had to pay for the screening test. Since January 2015 this age limit is abandoned and all pregnant women have to pay €165,- for the first-trimester combined test. This age limit was amongst others abandoned because it possible might lead to misconceptions about the age-related risks.

NIPT in the Netherlands

In 2014 NIPT became available within the Netherlands and was offered to high-risk women within a nationwide study, the TRIDENT-1 study (Trial by Dutch laboratories for Evaluation of Non-Invasive Prenatal Testing). This study aimed to assess the clinical impact of NIPT

including uptake, test results, test performance and pregnancy outcomes.(25) This study has shown promising results concerning the performance of NIPT and the clinical aspects(25) and therefore besides TRIDENT-1 since 1 April 2017 TRIDENT-2 started. In the TRIDENT-2 study NIPT is offered to all pregnant women as an alternative for the first-trimester combined test.(24) Both TRIDENT studies not only assess clinical aspects but also study women's preferences and considerations concerning prenatal screening and NIPT as well as ethical, social and psychological aspects, including informed choice.(17, 42)

1.4 The aim and research questions of the thesis

In the ethical and social debate about prenatal screening and particularly NIPT informed choice, routine acceptance of a prenatal screening offer, societal pressure to test, reimbursement and the expansion of the scope are recurring and pressing themes. However, the related arguments, that NIPT might 1) impede informed choice or lead to routine acceptance of prenatal screening, 2) that NIPT might lead to routinisation of prenatal screening or societal pressure to test and that 3) reimbursement might lead to better informed choices, have limited empirical and ethical support. The aim of this thesis is to explicate and clarify these ethical and social arguments concerning prenatal screening and specifically NIPT. Furthermore, it aims to search for empirical and conceptual evidence to support or criticize these arguments in order to contribute to the scientific and social debate about a responsible implementation of NIPT and the possible expansion of the scope of prenatal screening.

The following research questions are addressed in this thesis.

Part I: The ethical framework for prenatal screening: theory and practice

1. What is the ethical framework of prenatal screening and how could this guide the expansion of its scope? (Chapter 2)
2. What do pregnant women think about ethical and social aspects of NIPT and the possible expansion of its scope? (Chapter 3)
3. What do parents of children with Down's syndrome think about NIPT and the possible expansion of its scope? (Chapter 4)

Part II: Conceptual and empirical analyses of ethical and social issues of prenatal screening.

1. How could informed consent and pre-test counselling serve the aim of prenatal screening at best? (Chapter 5)
2. What is meant with the concept of routinisation? Are the related routinisation arguments valid? (Chapter 6)
3. What are the Dutch public's attitudes towards prenatal screening and could they lead to societal pressure? (Chapter 7)
4. Should prenatal screening be fully reimbursed? (Chapter 8)

1.5 Methodology

In this thesis several methodologies are used to answer the research questions including ethical analysis of concepts and practices and empirical research methods. Qualitative and quantitative methods were used to study the attitudes of pregnant women, partners, parents of children with Down's syndrome and the Dutch public towards non-invasive prenatal testing.

The role of empirical research in ethics could be defined in at least two ways: firstly it can inform normative ethics in assessing which ethical questions arise in practice and how to deal with these questions. Empirical research could indicate which aspects of a certain practice need normative reflection. This approach of empirical ethical research sees empirical studies as source of normatively relevant facts not of normative claims as such. Secondly, empirical research in practice could be seen as source of moral beliefs or "normative-ethical knowledge" and therefore opinions of those working in practice could be seen as morally relevant. Practical experiences are then part of the ethical deliberation process.(43, 44)

Authors indicated several levels and categories of empirical research that could inform bioethics, ranging from defining current practices to improving care, from finding out who is involved in the specific practice to changing ethical norms.(45, 46) Empirical research can for example reveal who is the person that is expected to make an ethical decision and who is object of the decision.(45)

In this thesis empirical research is used in both ways and on several levels. Empirical information is gathered about stakeholders' attitudes towards NIPT. Health professionals, pregnant women, parents and the public were asked about their moral attitudes in order to

see which ethical questions arise from the clinical practice, the intended users of NIPT and the public. This might contribute to the deliberation about an ethical valid introduction of NIPT and about the scope for prenatal screening. Another aspect in ethics of prenatal screening are "foreseeable effects"(45): empirical research can help to study what already can be known about possible consequences of introducing NIPT, including social pressure or consequences for people with for example Down's syndrome. Precisely in the debate about prenatal screening, in which the preferences from pregnant women and professionals and also the possible impact of NIPT are highly relevant for the way the tests are offered, empirical research can contribute significantly. Therefore I made use of a mixed method approach of both conceptual analysis and empirical methods. This approach aims at giving more insight in arguments like slippery slope arguments, routinisation arguments and arguments concerning societal pressure to test. It enables the ethical analyses to be more explicit and concrete about the possible consequences of NIPT in order to further the debate. On the other hand, conceptual analyses will provide clarity in arguments which will not come to surface by empirical studies and might provide direction to the debate.

1.6 Clarifications of words and concepts

In advance I first will clarify some concepts or notions that are frequently used in the debate and in this thesis. Firstly, when it comes to decision-making about prenatal screening often only pregnant women were mentioned instead of women and partners or women and couples. Also in studies on prenatal screening mostly women participated and measurements of informed choice were conducted amongst women. However, in practice it is mostly a decision of both the pregnant woman and her partner which should be kept in mind when thinking and writing about informed decision-making and pre-test counselling, although the partner is not explicitly mentioned.

Terms for indicating disorders

When writing about prenatal screening several words are used to indicate a disorder. In this thesis 'abnormality', 'congenital abnormality or disorder' and 'disorder' are interchangeably used to indicate the presence of a (chronic) disorder in the foetus.(47) The concept of 'disability' is also used which relates to more than the clinical aspects of having disorder. It also includes the (social) context in which people with a disorder live. It comprises the

interaction between the social environment and living with a disease including the impact of de disorder on major life activities.(48, 49)

Prenatal screening and diagnosis

The concept of screening in general is used to indicate an unsolicited test offer to whole population groups or selected groups and aims and refers to "the presumptive identification of unrecognized disease or defect by the application of tests examinations or other procedures".(50) Prenatal screening for congenital disorders is a selective screening and is offered to all pregnant women. In this thesis I use 'prenatal screening' or 'prenatal testing' to indicate the unsolicited offer of a prenatal screening test for congenital disorders.

Prenatal screening differs from prenatal diagnosis which refers to diagnostic tests that are conducted on indication after obtaining an abnormal test result from NIPT or the first trimester combined test. Prenatal diagnosis is then offered to women as a follow-up test to confirm the prenatal screening result.

1.7 Outline

The first part of this thesis discusses the ethical framework for prenatal screening (chapter 2). The various ethical aspects in this framework were discussed with professionals (chapter 2) pregnant women (chapter 3) and parents of children with Down's syndrome (chapter 4) in individual interviews and focus groups.

In the second part of this thesis four specific ethical and societal issues and their related arguments are addressed, concerning informed consent (chapter 5) routinisation of prenatal screening (chapter 6), societal pressure to test (chapter 7) and reimbursement of prenatal screening (chapter 8).

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Chapter 2|

Limits to the scope of non-invasive prenatal testing (NIPT): an analysis of the international ethical framework for prenatal screening and an interview study with Dutch professionals

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Abstract

Background: The introduction of non-invasive prenatal testing (NIPT) for foetal aneuploidies is currently changing the field of prenatal screening in many countries. As it is non-invasive, safe and accurate, this technique allows for a broad implementation of first-trimester prenatal screening, which raises ethical issues, related, for instance, to informed choice and adverse societal consequences. This article offers an account of a leading international ethical framework for prenatal screening, examines how this framework is used by professionals working in the field of NIPT, and presents ethical guidance for the expansion of the scope of prenatal screening in practice. **Methods:** A comparative analysis of authoritative documents is combined with 15 semi-structured interviews with professionals in the field of prenatal screening in the Netherlands. Data were recorded, transcribed verbatim and analysed using thematic analysis. **Results:** The current ethical framework consists of four pillars: the aim of screening, the proportionality of the test, justice, and societal aspects. Respondents recognised and supported this framework in practice, but expressed some concerns. Professionals felt that pregnant women do not always make informed choices, while this is seen as central to reproductive autonomy (the aim of screening), and that pre-test counselling practices stand in need of improvement. Respondents believed that the benefits of NIPT, and of an expansion of its scope, outweigh the harms (proportionality), which are thought to be acceptable. They felt that the out-of-pocket financial contribution currently required by pregnant women constitutes a barrier to access to NIPT, which disproportionally affects those of a lower socioeconomic status (justice). Finally, professionals recognised but did not share concerns about a rising pressure to test or discrimination of disabled persons (societal aspects). **Conclusions:** Four types of limits to the scope of NIPT are proposed: NIPT should generate only test outcomes that are relevant to reproductive decision-making, informed choice should be (made) possible through adequate pre-test counselling, the rights of future children should be respected, and equal access should be guaranteed. Although the focus of the interview study is on the Dutch healthcare setting, insights and conclusions can be applied internationally and to other healthcare systems.

Introduction

Non-invasive prenatal testing (NIPT) is based on the analysis of cell free foetal DNA for chromosomal abnormalities.(1) Non-invasiveness refers to the way the foetal DNA sample is obtained: not from the placenta or amniotic fluid, which requires an invasive procedure, but from a blood sample of the mother.

NIPT for chromosomal abnormalities was first offered in 2011, in the United States of America, Western-Europe and China.(2) In the Netherlands, prenatal screening for untreatable disorders is subjected to licensing under the Population Screening Act. NIPT has been offered to high-risk women, exclusively within the context of the TRIDENT-1 study (Trial by Dutch laboratories for Evaluation of Non-Invasive Prenatal Testing) since early 2014.(3) When a woman received a high-risk outcome (chance ≥1:200) from the first trimester combined test (FCT) and wanted further testing, she was offered the choice between NIPT or invasive testing.(3) Low-risk pregnant women who wanted NIPT could not access NIPT in the Netherlands, and went abroad. Since April 2017, NIPT is also offered within the TRIDENT-2 study to low-risk pregnant women, who are given a choice between FCT and NIPT. The current NIPT-based prenatal test includes detection of trisomy 21 (Down syndrome), trisomy 18 (Edwards syndrome) and trisomy 13 (Patau syndrome). Compared to the FCT the sensitivity, the specificity and the positive predictive value of NIPT are remarkably high for those trisomies.(3) The positive predictive value is slightly lower in low-risk pregnant women but still higher than the positive predictive value of the FCT.(1, 4, 5) However, NIPT is not a diagnostic test. This is because of several factors. First, cell free foetal DNA circulating in maternal blood originates from the placenta, not the foetus. The presence of a chromosomal anomaly can be limited to the placenta in case of confined placental mosaicism without affecting the foetus, thus resulting in a false positive NIPT outcome. Furthermore, the presence of maternal chromosomal anomalies, including those originating from a maternal tumour, false-negative NIPT due to a low foetal DNA fraction in maternal blood, and a vanishing twin (6, 7), may still lead to inconclusive, false positive or false negative results.(8) Yet NIPT leads to fewer unnecessary invasive follow-ups tests - through amniocentesis and the chorionic villus sampling - than the FCT. These invasive tests have a 0.1%-0.2% miscarriage risk respectively.(3) To minimize the need for invasive testing – and the associated risk of miscarriage – has been one of the major reasons for implementing NIPT in current screening programmes.

When genome-wide sequencing techniques are used to perform NIPT, they allow for the detection of chromosomal abnormalities other than trisomy 13, 18 and 21, and thus for an expansion of the current scope of prenatal screening.(3, 9) Several studies have indicated that additional findings could include other full trisomies, sex-chromosomal abnormalities, and sub-chromosomal aberrations, associated with rare diseases.(3, 10-12) However, the possibility to find more abnormalities has raised questions, notably the policy question whether the screening offer should be expanded to include all those abnormalities. When discussing the question whether or not to include additional conditions, experts have brought up considerations of clinical utility and concerns related to the consequences of a broader test for informed choice.(13-15) These concerns were raised ten years ago, when genome-wide arrays were introduced in prenatal diagnosis, and are raised again with renewed urgency in the context of the introduction of NIPT.(16)

Various statements and position papers about prenatal screening, issued by governmental organisations and ethical committees, have addressed ethical issues of prenatal screening.(15, 17-24) Together with scholarly studies of ethical issues in prenatal screening (25-30) these statements and position papers could be seen as an – unofficial, but broadly shared and often referred to – international ethical framework for prenatal screening. An ethical framework can be defined as a specification of general principles in a specific context, through which the scope of general principles is narrowed by spelling out why and how actions should be undertaken or avoided.(31) The aim of an ethical framework is to "provide practical guidance for public health professionals and to highlight the defining values of public health."(32)

The aim of this article is firstly to reconstruct and analyse the main tenets of the ethical framework for prenatal screening and then to compare these with the practice of prenatal screening, by interviewing professionals in the field of prenatal screening. Secondly, this article examines whether and how the ethical framework can guide the introduction of an expansion of the scope of prenatal screening.

Methods

For this study we used a combination of methods, a literature study and a qualitative interview study. We conducted a comparative analysis of ethical statements about

requirements for (non-invasive) prenatal testing formulated by national and international organisations or committees. Also, we conducted in-depth interviews with Dutch professionals in the field of prenatal screening. The interviews serve to illustrate how the ethical framework for prenatal screening is translated into practice, and to offer insight into professionals' moral views on recent developments in prenatal screening.

Document analysis

To identify important documents that represent an ethical framework we started with an authoritative article of the European Society of Human Genetics (ESHG) and the American Society of Human Genetics (ASHG), which offers a consensus view of responsible innovation in prenatal screening, which is also endorsed by the Human Genetics Society of Australasia and other related professional associations in Europe.(15) We built on this consensus view and postulated four pillars of an ethical framework: the aim of prenatal screening, proportionality of testing, justice, and societal aspects. Other studies and documents – notably from the World Health Organisation (WHO), UNESCO International Bioethics Committee (IBC), German Ethics Council (Ethikrat) and the Dutch Health Council (GR) – were reviewed to corroborate, adapt and complement the ethical framework. We selected these four other documents for our analysis because – in contrast to other publications we have reviewed – these documents contain discussions of issues related to all four pillars.

Interviews

For the qualitative interview study, professionals in the field of prenatal screening and follow-up diagnostic testing from six academic centres in the Netherlands were invited. In total 15 individual in-depth interviews were conducted with two midwives, seven medical specialists (three gynaecologists, four clinical geneticists specialised in prenatal diagnosis), two lab specialists working with NIPT, two test developers and two policy makers. The interviews were conducted at the respondents' work places or at Erasmus MC. A semi-structured interview guide was used. This guide included five themes: informed decision-making, proportionality, access to NIPT, societal aspects and the scope of prenatal screening. Interviews were digitally recorded, transcribed verbatim and analysed with Atlas.ti using thematic analysis, based on the five indicated themes.

Results

The documents each point at the four pillars - the aim of screening, the proportionality of the test, justice, and societal aspects - but differ in some aspects of their interpretations. Table 1 presents an overview of interpretations of the four pillars in the five documents. Below we present the four pillars of the ethical framework for the practice of prenatal screening, complemented with results from the interviews.

Aim of prenatal screening

The first pillar of the ethical framework for prenatal screening pertains to the aim of prenatal screening for foetal abnormalities. Prenatal screening differs from other areas of public health, where the aim is reduction of morbidity and mortality associated with disorders in the population.(15) Translating this aim to prenatal screening might imply that the success of a prenatal screening programme would be defined in terms of maximisation of the termination rate of foetuses with abnormalities, which would be problematic, as abortion is often a point of controversy.(15, 17, 19, 20) Besides, prenatal screening is thought to imply discriminatory messages about the value of the lives of people living with the relevant conditions.(15, 17-19) The widely supported view therefore is that governments can only justifiably offer prenatal screening when the aim is to enable pregnant women and their partners to make autonomous reproductive choices.(15, 17, 19)

Although interviewed professionals recognised informed choice as the aim of prenatal screening, some of them pointed out that prenatal screening also provides the opportunity to prepare for the birth of a disabled child and to improve the care for it. Several respondents thought that the latter should be emphasised more during pre-test counselling and that it should be made clear that prenatal screening is not exclusively aimed at offering women the opportunity to terminate an affected pregnancy.

The right not to know about the options of prenatal screening is considered to be very important. In the Netherlands, this has been formalised in the obligation of professionals to present women with an 'information offer' first (33), in order to stress the fact that prenatal screening for aneuploidies is not mandatory. When a pregnant woman visits the midwife or obstetrician, the professional must first ask whether the woman wants to be informed about prenatal screening at all. The woman is free to decline this information offer.

Table 1: An ethical framework for prenatal screening

	ESHG/ASHG (2015)	WHO (2003)	Ethikrat (2013)	Dutch Health Council (2013)	UNESCO (2015)
Aim of prenatal screening	The aim is to enable autonomous reproductive choices, i.e. meaningful choices, related to serious health problems. The aim is achieved when women are enabled to make informed choices. Prenatal screening has a different goal than other forms of screening, because of the 'morally sensitive practice' of (selective) abortion and the stigmatisation of disabled people.	The aim is to obtain information and to promote freedom of choice and autonomy. Being able to prepare for the birth of a child with a disability is also seen as a way to exercise reproductive autonomy. Free choice requires: 1) adequate, unbiased information; 2) availability of relevant alternatives, including availability of healthcare services for disabled children or the (legal) possibility of abortion.	The aim is not specified, but prenatal screening is linked to self-determination and autonomy: "If a pregnant woman makes decisions about her pregnancy, these must be seen *inter alia* in the context of her right to reproductive self-determination." Reproductive decisions affect the unborn child and are thus not unlimited.	The aim is to enable and promote choice concerning terminating or continuing the pregnancy. "Informed choice is not a condition for, but the aim of prenatal screening." The aim is not to maximise reproductive choice as such. If informed choice is not reached, the aim is not achieved.	The aim is "not health gain but to decide (…) whether to carry a pregnancy to term." Furthermore, "it allows those involved to prepare for the birth of a sick or disabled child." There is controversy about the limits of reproductive autonomy in the light of a child's right to an un-manipulated genetic make-up. Prevention, focused on "reducing care costs for people with congenital con-ditions or disabilities, cannot be the goal of such screening. That would imply a discriminatory practice that sends the message that these people are unwelcome in society."

Proportionality	Proportionality is defined as a balancing of benefits and harms. Benefits of NIPT include reassurance, assistance in making informed reproductive decisions, and less invasive testing. Harms of prenatal screening generally include false reassurance, stress and anxiety, and risk of miscarriage in follow-up diagnostic testing. Balancing of benefits and harms includes consideration of quality aspects of the test and adequate counselling.	Proportionality is not discussed. Benefits and burdens are included in a cost-benefit analysis. Benefits are the chance to prepare for the birth of a child that will need medical treatment or a relief of maternal anxiety. Burdens include selective abortion of a wanted pregnancy.	Proportionality is not discussed, although it is stated that quality assurance is a precondition to meeting the aim of prenatal screening. Balancing benefits and harms is difficult: "The effect of a differentiated prenatal diagnosis is ambivalent. It may relieve the pregnant woman of fears, but on the other hand there is the danger that the (...) associated burden of deciding make the couple affected (...) and may even overstrain them." It is seen as a great risk that women may be insufficiently aware of the consequences of testing and subsequent decisions they will have to make.	Proportionality is a central requirement for prenatal screening. Screening is only justified when the value or utility of the offer is established and the benefits outweigh the disadvantages. Benefits of NIPT include reassurance, informed reproductive decisions and less invasive testing. 'Disadvantages' of screening include false reassurance, test-related stress and anxiety and risk of miscarriage.	Proportionality and proven usefulness are preconditions for a justified prenatal screening offer. The advantages should outweigh the disadvantages. Benefits are having freedom to choose and fewer invasive tests. Disadvantages are "routinization and institutionalization of choice of not giving birth to an ill or disabled child." If a test becomes self-evident women might feel pressured to test or stigmatised when they will not test.
Justice	Justice refers to the distribution of costs: "As	Justice refers to the "equitable distribution	Justice refers to equal access to prenatal	Justice refers to an appropriate use of	Justice refers to the organisation of

	health budgets are inevitably limited (…), opportunity costs will have to be taken into account as well." The requirement of just distribution of healthcare costs will demarcate the scope of prenatal screening.	of genetics services, including prenatal diagnosis, is owed first to those with the greatest medical need, regardless of ability to pay, or any other considerations." Relief of maternal anxiety has lower priority than medical indications for prenatal screening, in the just distribution of healthcare resources.	screening and to the danger of "discrimination and stigmatization of people with particular genetic characteristics."	healthcare resources. Prenatal screening can be used appropriately by couples wishing to prepare for the birth of an affected child, which is considered a justified aim of screening. Justice is also mentioned in the context of equal access to an expanded scope of prenatal screening: screening for abnormalities other than trisomy 21, 18 and 13 should not only be available for high-risk women (through invasive follow-up testing).	of healthcare systems, so that innovations are shared with society as a whole, without becoming a new source of inequality and discrimination. Justice also pertains to education: people should be actively enabled to exercise their freedom and autonomy. Finally, it refers to proper distribution of costs and investments in various fields within the healthcare system (e.g. care for people with disabilities).
Social aspects	As a public health programme, prenatal screening might have "consequences for other individuals and groups (including those living with the relevant conditions)". To avoid discriminatory messages, the aim of	Prenatal screening may have negative effects for people with disabilities, but does not lead to the birth of fewer people with disabilities, as long as chromosomal and single gene disorders account for only a	Prenatal screening generates genetic information and could have social consequences including stigmatisation and discrimination. There is a (shared) duty to create a society without discrimination,	Prenatal screening programmes may have social impact but are not necessarily discriminatory, because they aim at reproductive choice and not at prevention. However, concerns related to the social	Prenatal screening is often not a therapeutic intervention but likely to lead to abortion and it might lead to discrimination and stigmatisation. "The adding up of a lot of individual choices to the 'acceptability' of

	screening (reproductive autonomy) should be stressed. NIPT might be seen as a routine procedure, which might lead to routinisation of prenatal screening, affecting the informed choices of pregnant women.	minority of disabilities present at birth. Healthcare for people with disabilities will and should not be reduced, also to prevent 'economic eugenics' which would hinder voluntary decision-making. Although "cultures or medical settings may be implicitly coercive," these problems are seen as part of the general sociocultural context and not attributed to prenatal screening specifically.	which will be a result of interactions between people and does not depend on the presence or absence of one test. Routine offer of prenatal screening might have negative consequences for reproductive freedom and put pressure on women to test: the idea that pregnant women should take their parental responsibility and opt for testing should be avoided.	impact of screening on people with a disability are realistic. Therefore ongoing ethical monitoring of screening practices is necessary. Also, the state should guarantee good-quality care for people with a disability. A simple and safe test could possibly lead to routinisation, including pressure to test. This might affect reproductive autonomy.	aborting certain kinds of embryos (…) brings forward a societal phenomenon, which resembles a kind of eugenics in the search for a 'perfect child'." Non-discrimination should be emphasised and guaranteed. Prenatal screening as 'A routine measure' might negatively affect society's perception of disability and societal solidarity with disabled people and the women who give birth to them.

Not all professionals agreed with this policy, and some argued - contra current policy - that this first question should be skipped,

> "because many people actually do not know what it (prenatal screening) entails. How could you say 'yes' or 'no' to this question when you do not exactly know what this test is for?" (I3 medical specialist)

In order to reach the aim of prenatal screening, it is of paramount importance that pregnant women or couples can make informed choices for or against a screening offer.(15, 17-20) Informed choice is often defined as "a choice that is based on relevant knowledge, consistent with the decision maker's values and behaviourally implemented".(34, 35) This means that women should understand the purpose of the test and its potential risks and implications (36), because they may be confronted with "a large number of further decisions which (they) might have wished to avoid if (they) had been aware of the consequences before screening".(18) To help women make informed choices pre-test counselling is offered. During pre-test counselling women are presented with information about the purpose, nature, scope and validity(18) and complete information about diseases, including e.g. "name(s) and general characteristics of the major disorder(s)", possible treatments, possible unexpected or unclear findings of the test and kinds of test-outcome.(20) Furthermore, pre-test counselling for first-trimester prenatal screening should be conducted at a designated moment, clearly separated from information provision about other aspects of antenatal care, such as lifestyle, health aspects (e.g. screening for HIV) and birth planning.(15)

Many professionals noticed that when women talked about their reasons for choosing prenatal screening, they often mentioned wanting to be reassured about the health of their child. Professionals thought that women sometimes do not realise in advance what kinds of outcomes they might face and difficult choices they might have to make:

> [women] "have to realise that if [they] opt for NIPT and a congenital disorder is found, [they] kind of jump on a train on which [they] might not want to be [… I] hear people say that they are in a rollercoaster." (I8, medical specialist)

Some professionals thought that especially in the case of NIPT this might be a problem. The previous screening programme in the Netherlands was step-wise: the first step was a FCT,

which provided only a risk estimate for aneuploidies. Then women had to think carefully about invasive follow-up testing, taking into account the risk of miscarriage. Women could choose whether or not to undergo invasive testing to obtain a diagnostic result. Professionals thought that this step-wise process gradually prepared women for the obtaining of an abnormal test result. They thought that, with NIPT, by contrast, women will opt for an easy test and – in one single step – may be confronted with an almost 'diagnostic outcome' at once. NIPT "*gives the idea of a decisive outcome*."(I10, midwife) As said, this idea is not accurate, as diagnostic follow-up testing is required also with NIPT. The odds that the result turns out false positive, however, are much lower.

In order to protect women from the negative consequences of uninformed choices, professionals emphasised that counselling plays a crucial role. Counselling serves to explain women's options and to correct misunderstandings of tests and disabilities, but should also explore the norms and values and the attitudes of women towards having a child with a disability. During counselling women should be encouraged to think about their views about testing, about having a child with a disability and termination of pregnancy:

> "Yes, I think, that with a few standard questions [the counsellor] will [be able to] achieve a lot. Just to trigger [women], let's say [to think about the consequences of NIPT]. That does not necessarily take a lot of time. [… As a counsellor, you could ask women:] What does Down syndrome mean to you?" (I3, medical specialist)

Respondents took the view that the current quality of counselling in the Netherlands is moderate, and needs improvement: professionals should pay more attention to and spend more time on pre-test counselling. Dedicated counselling sessions will help women understand that the aim of prenatal screening for chromosomal abnormalities is different from those of antenatal care (i.e. maintaining and/or improving the health of the pregnant woman and the foetus). Some respondents, who were medical specialists, feared that professionals underestimate the importance of (non-directive) counselling for NIPT and should be aware that the ease of the test, requiring only a maternal blood sample, and its high reliability may lead to less informed choices. One study suggested that professionals might indeed attach less importance to informed consent for a non-invasive test compared to an invasive test.(37)

To conclude, in order to reach the aim of prenatal screening - reproductive autonomy - informed choice is of crucial importance. Counselling should be non-directive and of high quality, and include deliberation on personal values of women, in order to achieve informed choice and promote this aim.

Proportionality

In the identified ethical framework, the pillar of proportionality of screening programmes entails balancing benefits and harms, following the original screening criteria for population screening formulated by Wilson and Jungner, complemented with additional criteria from the WHO.(15, 19, 38). To assess benefits and harms, the quality of the test and the test offer, including the laboratory procedures, counselling and education of professionals should be evaluated.(15) According to the ESHG/ASHG and the Dutch Health Council, the benefits and harms or costs depend on the way NIPT will be offered, as a first-tier screening test or second-tier screening test, after FCT.(15, 17) When NIPT would replace FCT as a first-tier test, it might have the benefit of fewer false positive results for trisomy 21, 18, and 13, but on the other hand might also lead to a loss of other findings that can be identified on ultrasound as part of FCT. Experts must decide whether the benefits of a better test performance of NIPT regarding the three trisomies will outweigh this loss of diagnostic yield when the first-trimester ultrasound is removed from the screening programme.

For pregnant women or couples, prenatal screening for foetal abnormalities has the benefit of offering reproductive choices regarding an affected pregnancy, including termination of pregnancy or being able to prepare for the birth of an affected child, relief from anxiety in case of a negative test result and the reduction of invasive follow-up tests.(15, 17-20) Harms for pregnant women are related to false reassurance, burden of decision making and anxiety in case of false-positive outcomes and incidental findings, which can be of unclear clinical significance and might cause needless worries.(15) Respondents held that these harms are inevitable but acceptable. Yet the possibility of incidental findings needs to be explained during pre-test counselling. It has been suggested that making the choice to terminate a desired pregnancy after receiving an abnormal test result may be harmful, as well.(20)

According to professionals, women might be faced with unwanted choices they have to make, because they may not have been fully aware of the consequences of prenatal screening beforehand, as some medical specialists indicated in the interviews:

> "But sometimes I see people saying: 'I never would have wanted this choice. This is a horrible choice you're giving me. I don't want it. This is a wanted pregnancy. If I had not known that this child has Down syndrome I would go for [continuation of this pregnancy], I am sure. But now I have a choice and I am going to hesitate'." (I7, medical specialist)

Justice

The third pillar of the ethical framework is justice. The principle of justice in prenatal screening relates to equal access to prenatal screening for all pregnant women, to policy questions concerning reimbursement of prenatal screening, and to equal distribution of healthcare resources.(15, 17-20) Equal access to prenatal screening means that differences in personal resources may not cause disparities in access to prenatal screening programmes: women's choices not to participate in screening should not be based upon a lack of financial resources.(15, 17-20) That would imply that prenatal screening should be offered, especially to women with limited financial resources, either free of charge or against a small fee. On the other hand, it could be argued that a (small) payment might serve the aim of reproductive autonomy as it may "increases awareness that there is truly a choice to be made".(15)

Professionals recognised this dilemma concerning the reimbursement of prenatal screening. Respondents mentioned the impact of payment on the uptake of prenatal screening. A midwife suggested that the fee that is currently asked for FCT in the Netherlands (165 euros) has much impact and might explain the large difference in the uptake of FCT as compared to the 20-week ultrasound, which is offered free of charge:

> "I am curious, when [NIPT] will be reimbursed and [as a counsellor] you explain to people the possibility of having a NIPT, whether they would say: 'If it is reimbursed and it gives information about the health of my child, of course I want [to use NIPT].' They do the same for the 20 week scan. I really wonder whether the difference (in uptake for the FCT and the 20-week ultrasound) is that big because people say: 'I [do want to] give birth to a child with Down syndrome but not to a child with spina bifida'. I do not believe that [differences in attitudes explain the] difference between 30% [the uptake of the FCT] and 95% [the uptake of the 20-week ultrasound]." (I10, midwife)

Some professionals suggested that a financial contribution by women might serve as a helpful barrier, making women aware of the importance of the choice. It could prevent women from opting for a test 'just because it is possible and does not cost any money', and thus protect them against ill-considered testing. On the other hand, respondents mentioned two objections to payment as a barrier for test uptake. Firstly, professionals thought that some women refrain from screening because of lack of money:

> "There are a lot of people for whom [165 euros] is a lot of money that can buy a lot of baby clothes.".(I13, medical specialist)

They thought that lack of money is not a good reason to decline screening. Professionals think that when screening is offered, it should be reimbursed to guarantee unhindered access. Secondly, asking a contribution is in contradiction with equality in healthcare:

> "Yes, it is a barrier, but for whom are you creating a barrier? For a specific group of people who cannot pay for it." (I3, medical specialist)

Experts should understand that while requiring a personal financial contribution may serve a purpose (i.e. improving informed choice), it may also, and more importantly, create disparities in access to prenatal screening, which is undesirable and contrary to one of the moral pillars of prenatal screening: justice.

Societal aspects

Self-determination is not only a matter of individual freedom, but also has a societal dimension, and it may be threatened by for example group pressure or societal views about testing.(18, 19) One of the concerns related to group pressure is that it might lead to less-autonomous choices among pregnant women. This would be problematic, it is argued, because the aim of prenatal screening, reproductive autonomy, will not be reached when women fail to make informed choices.(15, 17-20)

Furthermore, it is thought that the offer of prenatal screening for chromosomal abnormalities might also imply a discriminatory message to individuals and groups living with specific diseases.(15, 17-20) This objection is known as the 'disability rights critique' of prenatal screening and holds that discriminatory messages are inseparable from prenatal screening.(15, 17) This critique may apply both to the sheer societal availability of prenatal

screening programmes and to individual women's choices. In response, it is underlined that the aim of prenatal screening is not preventing the birth of disabled people, but promoting reproductive autonomy.(17) Also, studies have shown that women's reasons for the selective termination of their pregnancies include prevention of a life of severe suffering and not being able to create the best conditions to care for a child with a disability (17, 39-43), which does not support this critique. However, with the introduction of NIPT, the uptake of first-trimester screening might increase and the number of persons with disabilities might decrease. This is not in itself problematic, but it might become problematic if a low prevalence of disabilities will negatively affect the position of persons with disabilities, and render the option to continue an affected pregnancy less attractive. Therefore the practice of prenatal screening should be evaluated continuously in comparison to its aim.(17) Moreover, a negative perception of people with a disability can be redressed with public information and education.(19) The WHO concludes that just non-discriminatory societal settings are important for making a free choice: "It is important to prevent discrimination and to provide improved support services for individuals and families with genetic conditions. The absence of adequate services for people with hereditary disabilities undermines the principle of free choice for couples at risk of having children with such disabilities."(20)

Professionals did not think that the uptake of prenatal screening would increase dramatically, although they suggested that an easier test is less likely to be declined and might become self-evident. They observed however that the need to participate in prenatal screening is not as self-evident to many pregnant women as the need for other tests in pregnancy.

> Besides, "there will always be people who do not want to know [about health risks of their foetus], who just want a care-free pregnancy, and (who feel that) every child is welcome,"(I13 medical specialist)

Moreover, professionals think that women will not choose to terminate pregnancies more often because women who participate in prenatal screening generally have desired pregnancies, and do not wish to undergo termination of pregnancy for trivial reasons.(18) Also, according to respondents, specific cultural aspects in the Netherlands might in part

explain the low uptake of NIPT, as compared to other countries. In the Dutch prenatal screening programme, midwives play important roles in pre-test counselling, rather than medical specialists.(44) Among midwives, there is a tendency to avoid medical interference in the pregnancy. Also, in society, a rather positive public image of Down syndrome prevails. Professionals held the opinion that the fear that fewer people with Down syndrome will be born when NIPT is introduced, is not justified. Respondents thought that people with a disability are accepted in the Netherlands and that there is good care available for handicapped people. However, they agreed that care and support should be guaranteed to counteract possible negative consequences of prenatal screening, including discrimination.

In sum, societal aspects and concerns such as an increase in test uptake and a decrease in people born with disabilities are recognized, but disputed in the literature as well as among professionals. However, it is acknowledged that arrangements should be made (i.e. ensuring quality of care for the disabled) to counteract possible negative consequences.

Discussion: the expansion of the scope of prenatal screening

The four pillars of the ethical framework can be used to evaluate the potential expansion of the scope of NIPT. Below, four limits are proposed to the responsible expansion of the scope of NIPT in the future. These limits provide ethical guidance for professionals and policy-makers who are working in the field of NIPT and will be shaping its development and further implementation in the future.

Limits set by the aim of prenatal screening

In the five documents it is explicitly stated that although the aim of prenatal screening is not to maximise reproductive choice indefinitely, there is room for expansion of the screening offer.(15, 17, 20) In the interviews several professionals indicated that a broader test will contribute to the aim of prenatal screening because an expanded NIPT allows for detecting more disorders than trisomy 21, 18 and 13:

> "People do not want a test for Down syndrome, but a test for a healthy child." (I15)

However, an expanded scope might affect informed choice as a precondition of reproductive autonomy. When NIPT includes a high number of diseases, it will be difficult in pre-test

counselling to discuss all possible test outcomes in detail, "including the full range of variability in the manifestations" of these diseases.(15) Testing for more abnormalities might thus "paradoxically undermine rather than serve or enhance reproductive autonomy."(15) A clinical professional feared that

> "People have no idea what the results [of NIPT] can be and what these could mean to them. I am sure about this, because for Down syndrome it is already the case [that people do not understand what the outcome means to them]." (I7, medical specialist)

This raises the question how to best inform pregnant women prior to the test. It has been suggested in documents and by some of our respondents that information about the possible outcomes of prenatal screening should be presented as categories of disorders: the scope of NIPT can be narrow or broad, with results pertaining to severe or non-severe disorders and early- or late-onset disorders. When the scope of NIPT expands to such an extent that it becomes impossible to describe in detail all possible test outcomes during pre-test counselling, the counsellor "should describe the general characteristics of the categories of disorders tested for (e.g., mental disability or neurological impairment). Women will receive intensive counselling after a foetal diagnosis."(20) This model of informed choice is sometimes referred to as 'generic consent', which is thought to be a solution for complex counselling and has already been discussed in the context of genetic screening. Generic consent aims to prevent 'information overload' and to avoid the provision of information that is "pointless or counterproductive".(45) The question arises whether generic consent offers enough information to enable people to make a truly informed choices.(46, 47) The ESHG/ASHG and the Dutch Health Council have their reservations about generic consent (15, 17), because "the feasibility of this model has not yet been empirically tested in the prenatal context" and it remains unclear how *informed* generic consent would be.(15) The extent to which generic consent can be informed consent should be studied in line with previous studies on informed choice in the context of prenatal screening. These studies showed highly variable percentages of women having made informed choices: 89%, 77,9%, 51% and 44%.(35, 48-50) Some of that variation might be explained by variation in the nature and the quality of pre-test counselling practices, which will likely affect the 'informedness' of women's choices to a great extent, also in the context of an expanded NIPT. In practice, it is

not clear whether a sufficient number of professionals will be available to counsel large numbers of pregnant women and their partners, and whether they will have enough time to explain the details of the test and facilitate informed decision-making. In some countries, measures have been put in place to counter this problem, including the use of decision aids and the additional training of midwives in NIPT counselling.(51) Another solution might be a change in the *focus* of counselling, from technical-medical aspects to women's values or goals related to screening. As respondents suggested too, counselling is more than providing information; women should be triggered to think about why they would want prenatal screening and what they would do in case of an abnormal test result, to make them more aware of their attitude towards undergoing prenatal screening. Attitude is defined as the general feeling of 'favourableness' or 'unfavourableness' for testing.(34) Triggering women to think about testing might lead to a process of deliberation and evaluation of pros and cons, which, according to several authors, should be part and parcel of an informed choice.(49) Professionals could play a role in this deliberation and help women to formulate their values, for instance in accordance with the interpretive model of the physician-patient relationship, as described by Emanuel and Emanuel.(52) This model entails that the healthcare professional helps to elicit the norms and values of a patient.

We would suggest that in this process, the necessary technical information about the test could support or influence the attitude, but is not sufficient or even essential to the quality of decision-making. Shifting the focus of counselling from 'conveying knowledge about screening' to 'exploring women's attitude towards screening' might improve women's and their partners' decision-making processes, even in the context of an expanded scope of screening and, in combination with decision aids, takes away the time pressure to explain all clinical and technical details of NIPT.

Professionals differed in their opinions about whether women should be given a say in decisions regarding the scope of the screening offer. Some professionals suggested that a list of options should be offered from which women could choose, whereas others believed that experts should determine which (categories of) disorders should be included in the test. The main reason for preferring a predetermined offer was that women might not have the information – or the capacity to understand the information – required to make a decision about the adequate scope of NIPT. Another study of opinions of professionals showed that a

majority of respondents preferred a predetermined offer or a fixed list of disorders to be tested.(53)

A second category of problems arises with the dual aim of prenatal screening within antenatal care systems.(15) Some routinely offered prenatal screening tests are used to improve pregnancy outcomes or the health condition of the mother or the baby, such as the blood test for rhesus status in RhD-negative women. The rhesus test is currently offered as a separate test but could – for reasons of efficiency – be combined in one test with NIPT for autosomal aneuploidies. An objection to a combination of this test with screening for aneuploidies is the possible confusion in women about what test they should accept or decline, and for what reasons. Prenatal screening for aneuploidies is aimed at reproductive autonomy and requires non-directive counselling.(15) The term 'non-directiveness' refers to the absence of coercion or the withholding of advice, in order to respect the autonomy of a patient.(54) According to Ten Have, as cited in Oduncu, non-directiveness means that the expert who provides information about genetic conditions "should not, in any respect, try to influence the decision made by the persons who are counselled or screened. (…) his aim is merely to provide information and to help the patients or clients to work through possible options."(54) For prevention-aimed screening in antenatal care (e.g. screening for hypertension or rhesus status), it may not be objectionable for health professionals to recommend or insist on participation, because this type of screening promotes the health of the mother and the foetus, but for autonomy-aimed screening, directive counselling is not appropriate.(15, 55) In sum, one (expanded) NIPT that combines two aims and two - opposed - modes of counselling is not desirable.

NIPT is meant to offer reproductive options, but not to screen foetuses for all kinds of medical problems. For instance, children are usually not allowed to undergo predictive testing for (untreatable) late-onset diseases because this might affect their right to an open future and their right not to know unwanted predictive information.(15, 17-20) The principle to defer testing until adulthood applies to unborn children as well. Prenatal screening is not meant as a medical screening of future children: its scope should thus be limited to those conditions for which expecting parents may consider terminating the pregnancy. To protect the unborn child's right not to know, 'conditional access' models have been proposed for women who want information about late-onset diseases: testing for late-onset diseases,

including some sex chromosomal aneuploidies, will only be offered if women "expressed the clear intention to choose abortion if a predisposition for a late-onset diseases is found."(56) However, as termination of a pregnancy is, and should continue to be, the result of a voluntary decision, women who change their minds about an earlier expressed intention cannot be forced to terminate an affected pregnancy. Therefore, it cannot be excluded that children may be born in the knowledge of carrying a mutation for a late-onset disease. Further research should focus on the consequences of living with this information for both parents and children and on its effects on their relationship.(18, 19)

NIPT may contribute to the aim of prenatal screening: the promotion of reproductive autonomy. On the basis of the first pillar of the ethical framework for prenatal screening, however, limits can be set to the morally responsible expansion of the scope of NIPT: NIPT should generate only test outcomes that are relevant to reproductive decision-making, and informed choice should be (made) possible through adequate pre-test counselling.

Limits set by proportionality

The expansion of the scope of NIPT also raises questions concerning proportionality. According to the Dutch Health Council, proportionality is an important requirement of prenatal screening, and benefits of each 'test' (for each condition) to be included in the screening offer should outweigh the harms.(17) Professionals noted that it may be beneficial to include more disorders in a test because that means that more reproductive choices can be made:

> "There are children who are born with a severe disorder. Then we do an exome analysis to see what the cause is. Then we find, say, in 40% of the cases, a new mutation, in a crucial gene, which the parents do not have. In the future it may be possible to detect that [mutation] in maternal blood."(I15, lab specialist)

Several professionals gave the example of the 22q11 deletion, which is associated with a severe phenotype. Studies on the attitudes of pregnant women towards an expanded scope of prenatal screening showed that women thought that it may be valuable especially to include severe disorders with no or short life expectancy in a screening test.(57, 58) Women also wanted to learn about sex chromosomal aneuploidies (59, 60) and about specific other aneuploidies, but were hesitant about learning about conditions with unknown or variable

phenotypic expression. They were uncertain about what the benefit would be of knowing about such conditions.(59)

Proportionality concerns might limit the expansion of the scope, on at least three points. Firstly, when genome-wide analyses are used in NIPT, it might be difficult to assess the clinical validity of many among the huge number of abnormalities that can be detected. Offering a test for disorders without knowing the validity might lead to false positives and false negatives, cause harm to pregnant women, and challenge the proportionality of including the disorders.(17) Professionals mentioned that outcomes should be actionable for pregnant women. When tests are not reliable (i.e. clinically valid), they provide few actionable options. Moreover, uncertain test outcomes might lead to unnecessary anxiety or insecurity in pregnant women, which is objectionable:

> "I think that, when you introduce uncertainty in the pregnancy, it will become difficult. If you [can say that you] are sure that the child is disabled, then this is understandable for people, and they will be able to prepare [for the birth of a disabled child] or to decide that they do not want this. But if you say, 'we actually do not know what it means exactly; (…) it can turn out better than expected, but the child can also turn out severely disabled.' Well, what should you do, as parents?"(I3, medical specialist)

Several other professionals stated that in practice this should not pose a big problem, as only a small number of abnormalities that are currently being detected in labs are of unknown or little-known clinical validity. These will need to be discussed between expecting parents and clinical geneticists specialised in prenatal diagnosis.

A second point that several respondents stressed is that NIPT has shortcomings: NIPT is not a diagnostic test, and it still requires invasive follow-up. An expanded scope might lead to an increasing number of positive test results for a wide range of disorders, which will include false positive results that need confirmation by (unnecessary) invasive diagnostic testing. This is problematic, because a reduction of invasive tests as compared to FCT is seen as one of the important benefits of NIPT.(15, 18, 19)

A third point that might limit the scope of NIPT is the burden of the decision to terminate a pregnancy. Some disorders may not be sufficiently severe to justify their inclusion in the

NIPT; they may not meet the first screening criterion of Wilson and Jungner: "The condition sought should be an important health problem."(61) However, professionals mentioned that it is hard to define what 'serious' or 'non-serious' diseases are. In the documents it is stated, for instance, that severity should not be determined at all: "It would be dangerous to create medical, legal, or social definitions of "serious", because these could infringe on couples' lives in several ways."(20) Expecting parents are the ones who should indicate whether they consider a disorder to be serious or not, in their life situation.(20) Although it will be difficult in practice to draw the lines, the seriousness of disorders can serve as an (arguable) limit to the expanding scope of NIPT.

From the pillar of proportionality a few additional limits can be derived for the expansion of the scope of NIPT: in order for tests to be included in an expanded scope of NIPT, they should be clinically valid. Especially the positive predictive value should be high, as confirmatory testing through invasive procedures will still be required and is associated with risks, costs and burdens. NIPT should not be offered for trivial conditions.

Limits set by justice aspects

When using the ethical framework to evaluate an expansion of the scope NIPT, the pillar of justice is less prominent than the other three pillars. However, there are three issues that arise from the pillar of justice. Firstly, when NIPT is offered as an expanded test, it should be available equally for every pregnant woman.(17) Equal access to healthcare is considered to be a fundamental right that should preclude the exclusion of specific groups from healthcare services.(62) Women should not face restrictions to having reproductive options. Ideally, all women should have access to the same information about their foetus, and the scope of first-trimester prenatal screening should be equal for all women. When expanded NIPT is made available only to women who have an increased risk of trisomy 21, 18 or 13 as a second-tier test after FTC, for instance, low-risk pregnant women will not have access to information about the foetus other than the three more common trisomies detected through FCT, whereas high-risk women will.(17) For this reason, justice would require making NIPT available as a first-tier test to all women (or restricting the scope of NIPT as a second-tier test). Also, it is important to note that diagnostic follow-up testing should be made available to women who have undergone NIPT, in line with the criterion of Wilson and

Jungner that in screening programmes, diagnostic follow-up testing should be available to those found to be at risk.(38) This is of special importance in countries in which access to follow-up testing is not self-evident.

A second aspect, according to the International Bioethics Committee, is that education is a matter of justice: "Persons with a lower education level and lower health literacy are denied the information which is required to exercise their freedom and autonomy."(19) Some women may not be able to understand all relevant information pertaining to the screening offer, which is necessary to make an informed choice. The expansion of NIPT will only exacerbate this inequality (19), it is feared, as the test becomes more elaborate and more complex, and decision-making places higher demands on women's health literacy.

A third concern is that an expanded NIPT could challenge a justifiable distribution of healthcare resources. As resources are scarce and should be distributed equally, efforts must be taken to demarcate the scope of prenatal screening tests to prevent unnecessary follow-up of clinically insignificant findings. Besides, when prenatal screening is offered within the context of a public health programme and is upheld by taxpayers, there should be transparency with regard to the utility of the test.(15) This also underlines the importance of ensuring the proportionality of a test.

When considering the costs of prenatal screening it should be noted that a widespread implementation and uptake of prenatal screening programmes is likely to lead to the birth of fewer affected children, which reduces the costs associated with their healthcare and support. Although this should not be an aim of prenatal screening, these long-term costs savings are undeniably part of a cost-effectiveness analysis of new screening tests.(15)

From the pillar of justice another limitation can be derived: expanded NIPT should be available for all pregnant women, which may increase the costs of the programme. This limitation may change over time as the technology improves and becomes cheaper.

Limits set by societal aspects

In discussions on the expansion of the scope of NIPT, concerns are reiterated that have already been raised in the context of earlier prenatal screening programmes, such as discrimination and stigmatisation of people with chronic diseases. New societal aspects, unique to expanded NIPT, are raised as well. Professionals noted in the interviews, for

instance, that a benefit of an expanded scope could be a removal of the focus of prenatal testing on Down syndrome. Down syndrome is the most common of the three trisomies and in the Netherlands first-trimester screening for chromosomal abnormalities is often referred to as a 'test for Down syndrome'. By expanding the scope of prenatal screening this focus could shift, which might reduce concerns related to discriminatory messages conveyed by the screening programme. This benefit of the expansion is also acknowledged by parents of children with Down syndrome, who experience the focus on Down as stigmatising for their children.(63) On the other hand, the Dutch Health Council mentioned that expanded NIPT is not free from the allegation of stigmatisation either, as, for instance, a list of selected disorders can be thought of as 'subjective' and vulnerable to stigmatisation of specific groups, too.(17) According to some professionals, an expanded scope might reduce the acceptance of children with a disability:

> "With 22q11 deletion, [children] can be mentally retarded, etc. When people hear a story like that, they tend to terminate [the pregnancy]. I find it very hard. Everybody wants a healthy child, I understand that. So it is good to have these options. On the other hand, I am afraid that, when more [screening] becomes possible, what space is there for children with a disability? I find it terrible that there may be no respect or no care [for these children]."(I10, midwife)

Adverse societal consequences of an expanded scope are also mentioned by pregnant women and parents of children with Down syndrome, who fear a loss of diversity in society and a 'slippery slope', implying that people might want to start testing for increasingly trivial abnormalities.(57, 63) However, respondents questioned whether these consequences of an expanded scope will occur and denied that society will eventually be without children with a disorder or disability. Although it is difficult to predict the societal consequences (if any) of NIPT or how these would limit the expansion of its scope, it is clear that negative consequences for people with disabilities should be mitigated, and the practice of prenatal screening should be monitored continuously, not only with a focus on the risks and benefits for individuals, but also for its wider societal implications.

Conclusion

An expansion of the scope of NIPT fits the aim of prenatal screening, as it contributes to

more reproductive options for pregnant women and couples. However, drawing on the broadly shared ethical framework for prenatal screening as well as on the findings of our qualitative study of professionals' opinions and experiences of the translation of the pillars of this framework in practice, we conclude that expansion of the scope of NIPT is not unlimited. Four moral limits can be set to demarcate a responsible expansion of the scope of NIPT. Firstly, informed choice as a central precondition for prenatal screening should limit its scope: when NIPT is expanded to include more chromosomal or sub-microscopic abnormalities, and relevant pre-test information about the test becomes more elaborate and more complex, counsellors will need to improve pre-test counselling to uphold its quality. This requires new models for counselling, with a special focus on generic information about possible test outcomes and on expecting parents' attitudes and values in relation to prenatal screening. Secondly, any expansion of NIPT should be proportionate: the test should be clinically valid and useful to women. Findings that generate mainly anxiety and for which no courses of action are available, do not meet the criterion of proportionality. Thirdly, respect for the right of the future child to an open future excludes testing for late-onset disorders when women or couples know beforehand that they will not terminate the pregnancy based on the results. Finally, healthcare resources should be justly distributed: when possible, NIPT should be made available to all pregnant women either free of charge or for a small sum. At the same time, any expansion of the scope of NIPT should be based upon a favourable assessment of the benefits of including additional 'tests' for additional disorders in proportion to the costs and burdens. Both in the literature and in our interview study of professionals' opinions, we observed differences in the sense of urgency or importance that is attributed to each of the four limitations. We contend that the criterion of reproductive autonomy as the aim of prenatal screening as well as that of proportionality – or a positive balance between the benefits and burdens for pregnant women and their future children – should together be guiding in decisions whether particular disorders should be tested or communicated to women or couples. This means that for example, depending on the test performance, disorders that are comparable to trisomies 13, 18 and 21 in terms of severity could be included in the NIPT. Over the next decade, those working in the field of NIPT may strive to maximise the potential benefits of NIPT and include more abnormalities in the screening test, keeping these moral limits to a justified scope of NIPT in mind.

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Chapter 3|

Implementing non-invasive prenatal testing (NIPT) in the Netherlands: An interview study exploring opinions about and experiences with societal pressure, reimbursement, and an expanding scope

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Abstract

The noninvasive prenatal test (NIPT) as the first trimester prenatal screening (FTS) for trisomies 21, 18, and 13 is offered to all pregnant women in the Netherlands. NIPT using genome sequencing allows for an expansion of the scope of FTS and the introduction of NIPT gives rise to ethical and societal concerns about deliberated decision-making, pressure to engage in screening, and possible lack of equal access due to the financial contribution (€175) to NIPT. We explored the opinions and experiences of pregnant women, who were offered FTS, about these concerns, and the possibility of a broadened scope. Nineteen pregnant women representing a diversity of backgrounds were interviewed using a semi-structured interview guide. Eight women did not opt for prenatal screening while 11 did (NIPT = 4, combined test = 7). Women experienced a free choice to accept or decline prenatal screening, despite sometimes receiving advice from others. Prior to pretest counseling, some women had already deliberated about what an abnormal test result would mean to them. Others accepted or declined FTS without deliberation. The current Dutch policy of requiring a co-payment was acceptable to some, who believed that it functioned as a threshold to think carefully about FTS. Others were concerned that a financial threshold would lead to unequal access to screening. Finally, pregnant women found it difficult to formulate opinions on the scope of FTS, because of lack of knowledge. Life expectancy, severity, and treatability were considered important criteria for the inclusion of a condition in NIPT.

Introduction

The noninvasive prenatal test (NIPT) provides an easy form of first trimester prenatal screening (FTS). In the Netherlands, NIPT screens for trisomies 21, 18, and 13 and is offered to all pregnant women, costing them €175. When using genome sequencing, NIPT allows for an expansion of the scope of FTS. The introduction of NIPT gives rise to ethical and societal concerns about deliberated decision-making, pressure to engage in screening, and possible lack of equal access due to the financial costs of NIPT. This study examines to what extent these concerns matter to pregnant women and explores their opinions and experiences concerning FTS.

In the Netherlands, all pregnant women can choose to have a screening test to determine their chance of fetal trisomies 21 (Down syndrome), 18 (Edwards syndrome), and 13 (Patau syndrome).(1) From 2007 until April 1, 2017 this screening was mainly conducted with the first trimester combined test (ftCT). If the ftCT determines an increased likelihood (>1:200) of (one of) these common aneuploidies, pregnant women could choose either invasive prenatal genetic testing or refrained from further testing.(2, 3) On the April 1, 2014, the possibility to opt for the noninvasive prenatal test (NIPT) in a national implementation study 'trial by Dutch laboratories for evaluation of non-invasive prenatal testing' (TRIDENT-1) was added.

Since April 1, 2017, all pregnant women in the Netherlands have a choice between no first trimester screening (FTS), the ftCT, or NIPT within the TRIDENT-2 study. First (and second) trimester screening is mainly offered by primary care midwives, in a separate consultation with a funded duration of 30 min.(4) At the moment all pregnant women in the Netherlands must pay out of pocket for the ftCT (€170), and NIPT also requires a €175 contribution. Second-trimester screening sonography scans are fully reimbursed.(5)

The introduction of NIPT provides easy accessible FTS using genome sequencing, NIPT allows for an expansion of the scope of FTS. Pregnant women opting for the ftCT still have a choice, in case of an increased risk, between NIPT or invasive prenatal genetic testing as the follow-up test. NIPT entails important benefits for pregnant women: first, it is more sensitive and specific as compared to the ftCT. The sensitivity of NIPT is 97% for Down syndrome, 90% for Edwards syndrome, and 90% for Patau syndrome, while the combined test has sensitivities

of r 85%, 77% and 65% (6) respectively. Second, the use of NIPT will reduce the need for invasive procedures and the concurrent risks of miscarriage. However, the introduction of NIPT also raises some concerns.

First, it is feared that NIPT as a first-tier screening test may lead to routinization. The routinization argument is a container concept, which has been conceptually and empirically unraveled elsewhere.(7) Routinization may refer to: (a) that NIPT may lead pregnant women to venture into first trimester prenatal screening less thoughtfully, (b) that in the absence of a risk of miscarriage, NIPT may lead to societal pressures to participate in prenatal screening and to stigmatization of those who
forego screening (8 2013), and (c) because NIPT can be conducted early in the pregnancy, it may result in the trivialization of abortion (9, 10). However, concerns about informed decision-making, pressure to test, and stigmatization lack empirical evidence, which questions their validity.(7)

Second, there are concerns about the influence of reimbursement policies on pregnant couples' views and uptake of prenatal screening. Pregnant couples might easily or thoughtlessly opt for reimbursed screening, whereas non-reimbursed screening may lead to unequal access.(11) As said before, at the moment all pregnant women in the Netherlands must pay a contribution for the first trimester screening. In contrast, second trimester screening sonography scans are fully reimbursed.(5) The uptake of first trimester screening is around 45% whereas over 90% of pregnant women choose the fetal anomaly scan in the second trimester. The difference in reimbursement policies might be one of the reasons why the uptake of these tests is different, besides the fact that many women opt for an ultrasound to see their unborn child.(12)

Third, whole genome NIPT can detect a wide range of fetal chromosome abnormalities in addition to trisomies 21, 18, and 13.(13) At the moment, pregnant women in the Netherlands can choose for a NIPT that only reveals trisomies 21, 18, and 13, or a NIPT that also reveals abnormalities in other chromosomes, indicated as secondary findings. However, in the Netherlands fetal sex and sex chromosomal abnormalities are not communicated, because the ministerial license does not allow analysis of the sex chromosomes.(2)

Expanding the scope of NIPT could be beneficial for pregnant couples, be- cause more pathogenic abnormalities in the fetus can be detected.(14) However, concerns on this expanding scope of NIPT have been voiced. Several studies have suggested that an expanded scope of NIPT may undermine informed decision-making because of the increased quantity and complexity of pretest information counselors have to offer.(15) Moreover, people fear that with an expansion of the scope, prenatal screening is on a 'slippery-slope' towards screening for minor abnormalities and cosmetic traits. Different studies have shown that both professionals and pregnant women have difficulty deciding where to draw the line for an expanded NIPT.(14, 16) In practice, the expansion of NIPT has already started in many clinics in many developed countries, including the United States and the Netherlands. (2, 17) An expanded NIPT includes other trisomies in addition to trisomies 21, 18, and 13 and also subchromosomal aberrations and microdeletions. Professionals indicate an urgent need for ethical guidance to determine an appropriate scope of NIPT.(14) In this context, knowledge of women's preferences with regard to the scope of NIPT is indispensable.

The aim of the study at hand is to examine the ethical and societal concerns about routinization, societal pressure, reimbursement, and an expanded scope of NIPT. Interviews with pregnant women regarding their views about NIPT, its characteristics, its (lack of) reimbursement, and its scope were conducted. Previous interview studies on attitudes of pregnant women and partners regarding NIPT mainly focused on how pregnant couples view NIPT and its different aspects, but remain hypothetical on the aspects of that is, societal pressure and reimbursement.(8, 16) Furthermore, most studies were conducted a couple of years before the introduction of NIPT as a first-tier screening test, making the results less applicable to present day pregnant couples. This study will give a more in-depth insight of the views and opinions of pregnant women who have made the decisions about whether or not to engage in such prenatal screening tests.

Methods

For this study a qualitative research design was used. Semi-structured individual interviews were held to explore the experiences and opinions of pregnant women regarding first trimester pre- natal screening and in particular NIPT. Ten interviews were con- ducted before the availability of NIPT to all pregnant women in the Netherlands, whereas nine

interviews were conducted after this implementation. All women provided written informed consent be- fore participating in this study. The research ethics review commit- tee (METC) of Erasmus MC, University Medical Centre Rotterdam, exempted this study (MEC-2016-399).

Participants

Individual semi-structured interviews were conducted with 19 pregnant women from four midwifery practices between June 2016 and June 2017. After 19 interviews no new information was attained and therefore data saturation was reached, no further interviews were conducted. Women were recruited through four different midwifery practices across the country. The researchers deliberately sought to include women with different ethnic and religious backgrounds, educational levels, and socioeconomic status. However, women who signed up for the study were mostly Caucasian, highly educated women. Women were interviewed throughout all phases of their pregnancy. All 19 women were offered first trimester prenatal screening; 11 of them opted for prenatal screening (NIPT or ftCT), whereas eight did not. None of the pregnant women who chose for first trimester prenatal screening obtained high-risk results. Characteristics of the participants can be seen in Table 1.

Table 1: Characteristics of interviewed pregnant women

Characteristic	N (%)
Nationality	
Dutch	18 (94.7%)
Other	1 (5.3%)
Screening	
No	8 (42.1%)
Yes, ftCT	7 (36.8%)
Yes, NIPT	4 (21.1%)
Education level[a]	
Highly educated	12 (63.2%)
Lower educated	7 (36.8%)
Religious	
Yes	5 (26.3%)
No	14 (73.7%)
Children	
Yes	10 (52.6%) (mean = 1.8)
No	9 (47.4%)

[a]Education level: Highly educated: College educated or higher.

Procedure

Pregnant women were recruited and interviewed by two of the re- searchers (IMB and AKK). Nine interviews were held in person and the other 10 by telephone. The interviews were guided by an interview guide, and if necessary follow-up questions were asked. The individual interviews lasted between 30 and 60 min. The pregnant women received a €10 gift card for their participation.

An interview guide was developed in a multidisciplinary team of clinical geneticists, gynecologists, medical ethicists, and medical psychologists. The themes found to be relevant for the interviews were discussed and appropriate questions were formulated. The interview guide made sure that the interviews entailed a reflection on women's own choices with respect to screening, their views on the different screening modalities (ultrasound, combined test, NIPT), the appropriate scope of NIPT, and their experiences (if any) of societal pressure to undergo prenatal screening or to terminate an affected pregnancy. Furthermore, we included questions about the reimbursement policies for the various screening tests and asked the pregnant women what influence—if any—the reimbursement policy had on their choices for prenatal screening.

Data analysis

All interviews were audio taped and transcribed verbatim by IMB afterwards. After transcription, the interviews were analyzed using Nvivo software. Data analysis was conducted using thematic analysis.(18) Responses in the interviews were coded independently by AKK and IMB. Afterward, these codes were com- pared and any discrepancies were discussed until consensus was reached. From these codes topics were extracted, and clustered into main topics and subtopics in order to identify important themes in the interviews. Representative quotes from the interviews were translated from Dutch to English and presented to illustrate the different themes.

Results

The four themes that were examined during the interviews were pregnant women's: (a) reasons for choosing first trimester prenatal screening or not (routinization), (b) experiences of pressure from the social environment and society, (c) thoughts and expectations about

payment for prenatal screening, and (d) views on the possible expansion of the scope of prenatal screening. These four themes will be presented consecutively below.

Women's views regarding prenatal screening and NIPT

Women who participated in the interviews had various reasons to accept or reject prenatal screening. Some women did not opt for screening because they did not think about it at all, they believed they were too young and not at risk, or thought the test result of the ftCT is difficult to interpret, or a combination of these considerations. Others preferred a worry-free pregnancy above knowing the health status of their fetus, or would not take action after an abnormal test result. For some, abortion was not an option because of their religious beliefs or because they thought they would not be able to handle its psychological burden.

> "Well, at my age anyway, the chance is just a bit smaller [for Down syndrome]. Besides, I would not terminate my pregnancy if it [the unborn child] does have Down syndrome. They could also see it at the 20-week scan, so I can still prepare myself for it." (I9, age 20, no pre- natal screening)

The pregnant women who opted for first trimester screening also gave various reasons. Some chose screening because they wanted information about the health of their child, because they wanted to have the possibility to end their pregnancy in case of an abnormal test result, or because they wanted to be able to prepare for the birth of a disabled child.

> "I just really wanted to know if it [the unborn child] was healthy. I really wanted that little piece of certainty, I really liked that." (I7, age 27, combined test)

The characteristics of the NIPT, such as its reliability and easiness compared to the ftCT, make testing more attractive to women. Ten women were interviewed before NIPT became available as a first-tier test in the Netherlands. Most of these women indicated that they would have opted for NIPT if it was available for them during their pregnancy. The interviewed women expected an increase in uptake with the introduction of NIPT, although women also thought that when pregnant women do not want to participate in prenatal screening they still will not opt for it.

> "You are going to find out whether your child is healthy or not [with the ftCT and NIPT], and many people do not want to know that. (…) There might be somewhat more [women who opt for NIPT than with the ftCT], because it is easier and more accessible (…). That could be the case, but I think that it [the uptake of ftCT vs. NIPT] would not differ very much." (I17, age 39, combined test)

A few participants made their choice concerning prenatal screening before they received pretest counseling, based on information on the internet, or flyers, or peers' experiences. At the same time some women had a general concern that other pregnant women might not think through their choice for NIPT, that some accept the NIPT offer thoughtlessly, viewing it as part of standard procedure, without reading information leaflets or thinking about the information they received during counseling. As one woman indicated:

> "Because I think, they already take so much blood, why do you not add that [NIPT] to that [those tests]. (I3, age 32, no prenatal screening)

Therefore, pretest counseling for FTS should emphasize choice awareness among pregnant women. According to the interviewed women, good counseling should further include medical information about the test, such as its process, the reliability and explanation about trisomies 21, 18, and 13, and the possible next steps. A few participants also mentioned that it is important to discuss the emotional impact of screening, including knowing in advance what they want to do with the test result. However, other women indicated that they did not think about what to do with the test result before engaging in prenatal screening. They first wanted to wait and see what the test result would be.

Experiences of pressure from social environment and society

Women had different thoughts about and experiences with social and societal influence on their choice for first trimester prenatal screening. Most of the women indicated that their social environment did not influence their opinion about prenatal screening. However, some women indicated that their social environment did influence their choice. These pregnant women did not experience this influence as pressure: they stated that they could still make

their own individual choice. Most women, furthermore, stated that the counseling by the midwife did not change their opinion, but more so strengthened it.

> "Yes I told her [the midwife] in advance [that I did not want to opt for screening]. But she said she wanted to explain everything about the screening to me, so she did. But that did not make me change my mind. (I15, age 35, no prenatal screening)

A few younger women (age range: 24–30) in our sample expected influence from family or friends on their choice when they would be older, because then they would be at higher risk and family and friends would stimulate them to opt for screening. Some of these women also indicated that friends and family asked them the question why they opted for screening while they were young. Two women mentioned a certain influence toward testing from healthcare professionals and got the idea that testing is more self-evident to professionals.

> "Nobody said [during the counseling session]: you can also do nothing." (I11, age 40, NIPT)

A few women believed that society participation in prenatal screening is portrayed as being self-evident amongst others caused by media attention for the introduction of NIPT. It is presented as a very reliable test, and as an improvement of prenatal screening. It is expected that every woman would opt for it. Some women also had certain worries that being pregnant becomes medicalized, or that utilizing available tests becomes the social norm. Furthermore, concerning the termination of pregnancy, a few women had the opinion that there is certain societal pressure, in two directions: one woman's opinion was that terminating a pregnancy is more self-evident than to carry an affected pregnancy to term.

> "You will be judged [by society] when you decide to keep a baby with a severe disorder while you had the possibilities to detect the disorder." (I12, age 33, NIPT)

Another woman had the opinion that it is less acceptable to choose termination of pregnancy and stressed the importance of complete in- formation in the counseling.

> "I think that people are opposed to it and look at you and ask if you are sure to do it [terminating the pregnancy]. I think that people do not easily opt for it and also do not easily accept from others that they choose it. (…) Because people do not really know the consequences of having such a child [with a disability]." (I17, age 33, combined test)

Most of the participants did not experience pressure from the society to test or not test. Most women experienced that there is sufficient freedom to refrain from screening, and most women believed that you are free to either carry an affected pregnancy to term or to choose termination of the pregnancy. The pregnant women also believed that in society there is not one major opinion on the termination of pregnancy; there are different opinions, influenced by, amongst others, culture and religious beliefs.

Thoughts and expectations about payment for prenatal screening

Opinions on the role of payment for prenatal screening were quite diverse. Some women thought that having to pay for a test did not have any impact on their decision about prenatal screening. Others thought that asking a fee might have impact on their personal choice for screening. They expected to be influenced by the price of the test, and probably would not opt for it if it were expensive. Some thought that if the tests were free of charge they would certainly opt for screening, whereas they would not take part if they were asked to pay.

> "If I did not have to pay I would definitely do it [the combined test]. But the fact that I have to pay really makes me think it is a lot of money. I almost did not want to do it [the combined test]." (I2, age 29, combined test)

A few women thought €175 is a lot of money for people with limited financial resources, while others thought that it is acceptable to ask that fee. Some women indicated that they think that a reimbursement of the test carries the message that it is a standard practice.

> "But if it is free of charge, then it is more as if it is included in the total package [of tests during pregnancy], like the ultrasounds. You do not feel obliged, but it seems that it is included." (I8, age 26, combined test)

Moreover, women thought that more pregnant women would opt for screening if it was free of charge and the uptake would increase. Therefore several women suggested that asking a fee might function as a threshold and makes pregnant women aware that it is an import- ant choice they have to make.

> "I do not know, if it is completely reimbursed it is accessible for everybody [NIPT]. I think that people would take the test more often. But on the other hand you do have to think about it very well, about the con- sequences. Maybe if it is too accessible people do not think about it good enough. So maybe asking money [for NIPT] could help." (I10, age 29, NIPT)

A few women stated that it is your own choice to become pregnant and therefore you have to pay for a prenatal screening test yourself. Other women thought that prenatal screening should be free of charge in order to eliminate any threshold and make the test equally accessible for all women.

> "People differ in their incomes and then [by asking a fee] you get involved in the rich versus poor argument. I believe that in healthcare income should not matter, especially not in the case of an unborn child." (I18, age 33, no prenatal screening)

Expansion of the scope of prenatal screening

The discussion on the expanding scope of prenatal screening was often difficult to understand for women. When asked about their preferences, benefits, and disadvantages of an expanded scope, women found it difficult to formulate their opinions because of lack of knowledge.

> "I do not dare to say something about that. I did not learn about what kind of abnormalities there could be, because I assume that it [the child] was just healthy. In case of an abnormal test result of course you are going to look at what it means." (I7, age 27, combined test)

Some women expressed reservations regarding the expansion of prenatal screening. One woman mentioned that pregnant women (and their partners) would not have worry-free pregnancies anymore if abnormalities were detected. Others thought that it is a step too far or felt it would be like playing God. Furthermore, a few women thought that society wants to exclude all possible abnormalities and feared that society tends to select perfect children and would not accept people with a disability anymore. Moreover, they feared that abortion for less severe abnormalities might also become accepted.

> "Just in general, I am opposed to everything being placed in a medical framework. That you can already know so many things in advance [before the baby is born]. The question is of course where this [expansion] will stop. (…) So I think I am just against it [the expansion] going on and on." (I18, age 30, no prenatal screening)

Other women thought that an expansion of the scope of prenatal screening is positive, because it provides certainty, or they were in favor of an expansion because it might prevent a long search for a diagnosis when a child is born with unexplained symptoms.

> "I would appreciate it when the test becomes expanded. I think it is something good because it just provides more certainty. You know, you are giving birth to a whole new life." (I7, age 27, combined test)

Especially the question on the kind of fetal abnormalities pregnant women want to know was difficult for women to answer, because of unfamiliarity with such abnormalities. In the interviews several categories of disorders were discussed such as early onset, late onset, and neurological disorders, based on categories as used in clinical genetics practice. Women who positively evaluate (a certain) expansion of the scope often indicated that disorders with limited or no life expectancy should be considered for inclusion in the test. Other considerations related to the question on which disorders should be included in the test, are the severity of the disorder, and the child's prospects of living an independent and happy life.

> "It is difficult. My idea would be that it [NIPT] should concern severely disabled children. Children who could never live independently, who need a lot of medical care, where you ask yourself if they could be happy at all." (I11, age 40, NIPT)

However, women said that it is hard to say something regarding such a difficult and hypothetical situation of expecting a child with a severe disorder and regarding what they would do with such knowledge. They did not know what they would decide in the case of an abnormal test result. However, the different perceptions pregnant women have of, for example, Down syndrome suggest that women have different perceptions of severity and quality of life. Some women believed that Down syndrome is not sufficiently severe and they would not terminate the pregnancy for it. Others would terminate a pregnancy for Down syndrome because the child will always need care and might have many problems.
Another important argument was life expectancy, which is often a reason not to include late onset disorders in a screening test. They believed that one can have a joyful life until your 40s or 50s, without knowing about the disease, and maybe there will be new treatments discovered in the meantime. In contrast, a few women indicated that they probably would want to know late onset diseases because it enables you to prepare for your own future and the child's future. Some women believed that an expanded test might enforce striving for a perfect child and also mild disorders might be included in pre- natal screening in the future. They were worried about where the expansion would stop.

Discussion

Pregnant women gave various reasons to accept or reject the first trimester prenatal screening. Women mainly chose for FTS to pre- pare for the birth of an affected child, or to terminate an affected pregnancy. Preferring a worry-free pregnancy or not wanting to take action after an abnormal test result was the main reason for declining FTS. In concordance with other studies, NIPT was preferred over the ftCT by most women because of its reliability.(19, 20) Some participating women would terminate a pregnancy in case of an abnormality; others would never consider a termination.

With regard to the influence of pretest prenatal counseling on the decision whether or not to participate in FTS, some pregnant women already made their choice about screening

before visiting their obstetric caregiver, whereas others made this choice after counseling. Most women indicated that counseling for first trimester screening should both include information on the tests, the process, and the conditions screened for, as well as a discussion on the emotional impact of screening and the possibility of receiving an abnormal test result, which has been described before.(21)

Pregnant women indicated that it is important that women think about what they would do with the results from prenatal screening beforehand, which is also underlined by healthcare professionals.

Deliberation, defined as the weighing and considering of what prospective parents consider to be a worthy life for their child and what a termination of pregnancy would mean to them, is seen as a key aspect of informed decision-making.(22) However, a few interviewed women stated that they did not deliberate themselves, even not after pretest counseling, because they want to take the screening process step by step and would only start considering what they would do with an abnormal test result when they actually receive one. To our best knowledge this discrepancy is not found in previous studies, although one study did find that not wanting to think about what to do with a possible abnormal test result can be a reason for pregnant women to decline prenatal screening.(23) This discrepancy gives rise to the question what should be the focus of the prenatal screening counseling. Currently, the main focus of pretest counseling is pro- viding information (21), but our results suggest that merely providing information is outdated: some women prioritize deliberation about their choice. Other studies also found that pregnant women want more than only information provision. They would like to have decision-making support or even advice from their midwives, whether or not to test.(24) These results also show that women's personal information needs and preferences regarding deliberation differ. This requires personalized counseling in which the counselor addresses such personal needs. Previous research found that midwives feel more comfortable with providing in- formation than with inquiring about the feelings and thoughts of the pregnant couple.(21) Future research could focus on the best way to layout a pretest counseling session for first trimester prenatal screening, to balance information provision and deliberation support, and make midwives' task a little less complex. Also, a deliberation-focused approach to pretest counseling might need to be differentiated, as a subgroup of women want to take part in the first trimester prenatal screening without imagining what a detected abnormality might mean to them and

deliberating what reproductive decision they would make in response. To respect the autonomy of these women, they should be allowed to access screening without partaking in deliberation.

Pregnant women feel like they are free to have their own opinion about the first trimester prenatal screening. They made different choices with regard to first trimester prenatal screening, but all felt that they could make these decisions independently, without pressure from others. Some of the women indicated that their surroundings influenced their choice, such as their partner, parents, friends, or family with (shared) beliefs or views of life, or their obstetric care- givers. These pregnant women did not experience this influence as pressure: they stated that they could still make their own individual choice. This phenomenon was described in the literature before, in a study in which it was examined whether prenatal screening programs allow pregnant women to make autonomous choices. The women in that study also stated that they were influenced by others during the decision-making process, such as their partners, their midwives, and society, but they made their own choices without pressure by others.(25, 26) These results suggest that the concern that NIPT will lead to a societal pressure to take part in screening and/or to terminate an affected pregnancy (27), is contradicted in this study. This suggests that, for the women pretest counseling in the context of NIPT, emphasized freedom of choice.

So, pregnant women do not personally experience any pressure to (not) engage in prenatal screening, however, some of them did express the concerns that in society there are certain expectations with regard to participation in screening and either termination of an affected pregnancy, or carrying this pregnancy to term. Earlier research has also shown that pregnant women are worried that NIPT may lead to pressure to engage in screening; however, none of these studies described pregnant women experiencing this pressure themselves.(8, 16)

Pregnant women differed in their opinions regarding the re- imbursement of first trimester prenatal screening. These different views could be explained by differences in test choice, personal (financial) situation, and other aspects. Pregnant women did agree that a lack of reimbursement could result in unequal access to healthcare.

Furthermore, pregnant women agreed that reimbursing a screening test carries the message that the test is standard practice, as can be seen with the second trimester sonography scan, of which the uptake is over 90% in the Netherlands.(28). Pregnant women believed that by

reimbursing first trimester screening, the uptake will increase and women might venture into prenatal screening less thoughtfully. Some women indicated that asking a (small) fee made them think about their choice. They believed that it would also make other pregnant women aware that prenatal screening is a personal, important choice. However, they did feel that for some women even a small fee might be too much, therewith causing these women to forego participating in screening, even if they wanted to. In sum, women underlined the importance of informed choice, to which a small fee might be conducive, but that should not be at the expense of equal access. This again stresses the influence of how screening is organized on the women's choices, and demands that in the screening offer and pretest counseling the choice aspect is emphasized.

These results show that both scenarios, a reimbursed screening offer and a non-reimbursed screening offer, might challenge the non-directiveness of the screening offer and the related counseling, whereby nondirective means 'withholding any normative judgment regarding the obtaining and application of genetic information'.(29) Reimbursed first trimester prenatal screening might imply for pregnant women that the screening test is a good quality test, and participating in this test is self-evident and part of routine antenatal care. By contrast, a non-reimbursed screening offer might imply that the test offered is not seen as an important or of good quality by the healthcare providers, and therefore pregnant women would not want to opt for it. The effect of either message should be minimized in the counseling by explaining that while the test is reimbursed, women are still free to not opt for the test, or that while the test is not reimbursed, it is a good test that might provide options to women. Adequate pretest counseling is the most important resource we have to counteract any negative effects of (not) reimbursing first trimester prenatal screening.

Finally, a possible expanding scope of NIPT turned out to be a difficult discussion point for pregnant women. Pregnant women found it difficult to make statements about the expansion of NIPT because they were unfamiliar with other disorders than the common trisomies currently included in first trimester screening. In the discussion, various categories were used, that is, early onset/late onset and actionable/non-actionable. Pregnant women were also not al- ways familiar with these categories, in such cases examples to explain the categories were used, but the categories did make it easier for them to elaborate on the screening offer.

Some women were enthusiastic about an expansion because they thought that obtaining more information is something good. Others, however, were hesitant toward the expansion of NIPT and expressed the fear of a possible slippery slope. The interviewed pregnant women were made aware of the existence of a large number of serious conditions other than trisomies 21, 18, and 13 through this discussion, and some of them linked this to their own unborn child. Having this discussion could be burdensome for pregnant women, who could start questioning whether they are the ones having to decide on the screening offer.

Analysis of the responses given by the pregnant women on the questions regarding the scope of NIPT showed that they consider three things to be important in deciding whether or not to screen for a certain condition: (a) severity, (b) life expectancy, and (c) the possibility of an independent and happy life. If a condition would have (one of) these characteristics most women agreed that it should be included in the screening.

In the literature, to help women make individualized decisions about the scope of prenatal screening, it has been suggested that women should choose from a menu of options (30), with different categories of conditions included in the screening offer. Also, in another interview study pregnant women favored 'pure choice' model for expanded NIPT, wherein reproductive autonomy and informed choice are used to justify any prenatal screening decision a women wants to make.(31) According to the findings of this study, such models would lead to practical problems: women had different interpretations of categories and found it hard to imagine what learning particular test results might mean to them and their child. Moreover, women had little knowledge of—or experience with—conditions that could potentially be included in the test, which raised the question whether women can make an informed, autonomous choice. From this the conclusion could be derived that the scope of NIPT should mainly be determined by experts, not by women themselves. Which experts should decide on the scope of NIPT should be determined by future research. Based on earlier re- search an expert panel in the Netherlands could include midwives, gynecologists, clinical geneticists, laboratory specialists, policy makers, and ethicists.(30, 32) Nevertheless, opinions of women on the scope of prenatal screening, as found in this study, are important inputs for the determination of the scope.

A second issue raised by the expanded scope and its related in- formed choice is that some interviewed women wanted to receive the test results first, and only after something of relevance has been found, they would wish to learn more detailed information on the

condition detected. These findings suggest that in case of an expanded NIPT women might prefer a layered counseling wherein information in several stages can be provided to women in order to prevent information overload, as is proposed in a layered consent model for personal genetic tests.(33) Personal preferences regarding informational need and deliberation could therewith be taken into account.

Strengths and limitations

The strength of this study is that we included pregnant women from different regions in the Netherlands, aiming to include varying opinions within our sample. Furthermore, we included women with different test choices, to make sure that all choices (no prenatal screening, NIPT, and the ftCT) were well represented within our sample. Finally, we held these interviews right before and right after the introduction of NIPT as a first trimester screening test for all pregnant women in the Netherlands, making it a current and non-hypothetical matter for all interviewed pregnant women.

For this study women signed up themselves, which may have caused a bias in our pregnant population. Women who are willing to participate in an interview about prenatal screening, might have different characteristics and opinions compared to pregnant women willing not to be interviewed. This might explain why in our pregnant group more than half (11 out of 19) of the interviewed pregnant women opted for NIPT or the ftCT, whereas in the entire Dutch pregnant population less than half (45%) opts for first trimester screening. Therefore, the interpretation of these results must be performed with caution, as these might not be generalizable to the entire Dutch pregnant population. Furthermore, al- though we actively sought other target groups, mostly Dutch, highly educated, nonreligious women participated, which may also cause problems in the generalizability of the results. Also, some of the interviews were conducted before the availability of NIPT to all pregnant women in the Netherlands, whereas other inter- views were conducted after its implementation, which may have elicited different opinions. Finally, in our pregnant group most women were highly educated (12 out of 19) of which most (9 out of 12) chose for either the combined test or NIPT. In the lower educated group (7 women) only two women chose for first trimester prenatal screening. Because we conducted a qualitative interview study, we are not able to draw conclusions or elaborate on the fact that more highly educate women opted for first trimester prenatal screening than lower educated women. However, this finding is in line

with previous research which concluded that higher educated women opt for NIPT more often.(34)

Conclusion

Our study shows that there is a varying and broad range of opinions about first trimester prenatal screening, NIPT, pressure to test, the reimbursement of screening and the expanding scope among pregnant women in the Netherlands. Women feel that they have a free choice to opt for or decline prenatal screening, even though they sometimes receive advice from others for their decision. Adequate pretest counseling is important to maintain this experience of choice liberty now that NIPT has become part of the screening offer. However, counseling might need a shift in focus toward deliberation about what women want to know about the health of their child and what they want to do with the results, taking into account personal informational needs—which is already started in all Dutch training institutions and midwife practices. The significance of pretest counseling for first trimester screening continues to be a factor of great attention. However, our study clearly shows two important social issues that should be addressed in counseling. First of all, freedom of choice should be emphasized and second, possible messages deriving from either reimbursed or non-reimbursed screening should be minimized. Most women felt that not fully reimbursing screening could prevent the routinization of NIPT, but that this may also cause unequal access to healthcare. Furthermore, women had difficulty making statements about expanding the scope of NIPT, but agreed that determining the scope should mainly be based on severe, life-threatening disorders. Finally, our results suggest that the scope of NIPT should be determined by experts (in the Netherlands these could include midwives, gynecologists, clinical geneticists, laboratory specialists, policy makers, and ethicists), not by women themselves.

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Chapter 4|

What do parents of children with Down syndrome think about non-invasive prenatal testing (NIPT)?

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Abstract

This study explores the attitudes of parents of children with Down syndrome towards non-invasive prenatal testing (NIPT) and widening the scope of prenatal screening. Three focus groups (*n*=16) and eleven individual interviews with Dutch parents (and two relatives) of children with Down syndrome were conducted. Safety, accuracy and earlier testing were seen as the advantages of NIPT. Some participants were critical about the practice of screening for Down syndrome, but acknowledged that NIPT enables people to know whether the fetus is affected and to prepare without risking miscarriage. Many feared uncritical use of NIPT and more abortions for Down syndrome. Concerns included the consequences for the acceptance of and facilities for children with Down syndrome, resulting in more people deciding to screen. Participants stressed the importance of good counseling and balanced, accurate information about Down syndrome. Testing for more disorders might divert the focus away from Down syndrome, but participants worried about "where to draw the line". They also feared a loss of diversity in society. Findings show that, while parents acknowledge that NIPT offers a better and safer option to know whether the fetus is affected, they also have concerns about NIPT's impact on the acceptance and care of children with Down syndrome.

Introduction

Non-invasive prenatal testing (NIPT) using cell-free placental DNA is increasingly being used to test for fetal aneuploidy. By using a maternal blood sample, NIPT can test for Down syndrome with a sensitivity of more than 99% and a false-positive rate of less than 0.1%.(1) For women with an elevated risk based on the first-trimester combined test (FCT), NIPT is a safe alternative to invasive testing, although invasive testing will be required to confirm a positive NIPT result. Due to its high accuracy, NIPT can also be used as a first-tier screening test for all pregnant women, thereby replacing the FCT (2), although the positive predictive value is significantly lower in lower-risk women as compared to high-risk women.(3) The introduction of this innovative test is having great impact on the prenatal landscape. Furthermore, it has been proven possible to scan the whole fetal genome with NIPT.(4) so future use is likely to expand to testing for a wider range of genetic disorders.

Several studies have investigated the attitudes towards NIPT of important stakeholders such as health professionals and pregnant women. Overall, these studies show that both pregnant women(5-7) and health professionals (8, 9) have great interest in NIPT due to its ability to test early in pregnancy with high accuracy and no miscarriage risk. However, concerns were expressed about potential "routinized" or uncritical use of NIPT, women feeling pressure to test, and the possible impact of NIPT on acceptance of people with a disability (6, 7). Alongside these concerns, the introduction of NIPT in routine prenatal care has been criticized (10), on the basis of the disability rights critique.(10, 11) It has been argued that prenatal screening for Down syndrome sends out a message that emphasizes the negative aspects of living with Down syndrome, and implementing NIPT runs counter to the hope of improving attitudes towards Down syndrome.(10)

Very little is known about what parents of children with Down syndrome think about prenatal screening and, in particular, about NIPT. Using an online survey, Kellogg et al.(12) studied the attitudes of 73 US mothers of children with Down syndrome towards NIPT. They showed that the majority of mothers agreed that NIPT should be available to all pregnant women, and that NIPT was a good thing because it allows people to prepare themselves for a child with Down syndrome. However, most of the mothers also expected NIPT to cause an increase in pressure to test and in social stigma for having a child with Down syndrome.(12) When looking at the attitudes of parents of children with Down syndrome towards prenatal testing in general, it seems that most believe prospective parents should have autonomy

and reproductive freedom.(13, 14) However, studies have shown cultural and religious differences in attitudes towards prenatal testing and termination of pregnancy amongst parents of children with Down syndrome.(15, 16) A study of 78 women who had a sibling with Down syndrome showed that they overall had a positive experience of having a brother or sister with this condition, but around one-third would still consider prenatal testing and termination of pregnancy since they experienced a negative impact on themselves and their family.(17)

Decisions in a national screening system need political support, thus taking account of many perspectives. Since the introduction of NIPT could have an impact on the way society perceives Down syndrome and the lives of people living with this condition, it is important to further investigate what parents of children with Down syndrome think about introducing NIPT into a national prenatal screening system and which consequences they think this will have. This information can be used to establish a responsible implementation of NIPT, taking account of all stakeholder perspectives. This study therefore addresses the following research questions: 1) What do parents of children of Down syndrome think are the advantages and disadvantages of using NIPT for prenatal screening?; 2) What are important requirements for a responsible NIPT offer according to them?; and 3) What do they think about widening the scope of prenatal testing with NIPT?

This study was performed in the Netherlands, where the uptake of prenatal screening for Down syndrome (and trisomy 18 and 13) is relatively low (~27%) (18) compared to nearby countries like Denmark (90%) (19) or England (74%).(20)The low uptake of screening might be partially explained by the way screening is offered to women, with a clear emphasis on the “right not to know,” women having to pay for FCT (21), and the rather positive attitudes towards Down syndrome in the Netherlands.(22, 23)

Methods

A qualitative research design was used. Focus groups were formed to explore multiple perspectives and to stimulate discussion. Additional individual, semi-structured interviews were held to allow for a more private environment to explore the attitudes and (often emotional) experiences of parents of children with Down syndrome. Ethical approval for this study was obtained from the Medical Ethical Committee of the VU University Medical Center

Amsterdam (VUMC). Informed consent was obtained from all individual participants included in the study.

Participants

Participants were recruited with help of the Dutch Genetic Alliance (VSOP). An invitation for participation was placed on the website of the Dutch Down Syndrome Foundation (SDS, parent organization). As this produced no responses, another invitation was placed on a closed Facebook group consisting of about 900 members sharing experiences of having a child with Down syndrome. In total, 58 parents responded to the invitation, and two parents were recruited through the researchers' network. A total of 27 people took part in the study; 16 participated in the three focus groups (each consisting of 5 to 6 participants) and 11 in an individual interview. The parents who participated in the focus groups were not related. Two of the focus group participants were not parents but relatives of a child with Down syndrome (sister and aunt). Participant characteristics are summarized in Table 1. After three focus groups and 11 interviews no new information was obtained, and therefore data saturation was reached.

Instrumentation and procedures

In April 2014 NIPT became available in the Netherlands in public healthcare as a second-tier screening test. The first two focus groups were conducted prior to this period, in September 2013, in a community center in the middle of the Netherlands (Utrecht). The last focus group was in April 2015 at the VUMC in Amsterdam. The individual interviews were conducted by A.K.K. between March and April 2015, and took place at participants' home, workplace or by telephone. The focus group sessions were conducted using a semi-structured interview guide based on the one used in our previous study of pregnant women and their partners. (7) The guide included the following topics: participants' perceptions of the current Down syndrome screening using the FCT and invasive tests; perceptions of the advantages and disadvantages of NIPT, especially when NIPT would become available as a first-tier screening test; and opinions about testing for a wider range of disorders using NIPT. Via a PowerPoint presentation, participants were given a brief explanation of the characteristics of the current screening program and characteristics of NIPT, including testing for more genetic disorders. The focus groups were managed by an experienced moderator, together with an assistant

Table 1: Characteristics of participants in the three focus groups and individual interviews

Characteristic	Focus groups (*n* = 16)	Individual interviews (*n*= 11)
Sex		
Female	14	9
Male	2	2
Mean age, years (range)	39.7 (29-50)	41.1 (31-48)
Level of education[a]		
Low	0	0
Medium	1	4
High	15	7
Religion		
None	12	9
Christian	4	2
Mean number of children (range)	2 (0-3)	2 (1-4)
Number of children with DS		
0	2[b]	0
1	13	10
2	1	1
Mean age of child with DS, years (range)	6 (1-17)	6 (1-16)
Prenatal screening during pregnancy of child with DS		
Yes:		
Low-risk FCT result	2	2
Low-risk FCT result, invasive test after ultrasound abnormality	1	0
High-risk FCT result, no invasive test	2	0
High-risk FCT result, invasive test	0	1
FCT (result unknown)	1	0
No:		
Not interested	5	7
Not offered	3	0
Declined screening because of the costs	0	1
Not applicable:	2 [b]	0

[a]Low: elementary school, lower level of secondary school, lower vocational training; Medium: higher level of secondary school, intermediate vocational training; High: higher vocational training, university.

[b]Two relatives of children with DS, a sister and an aunt.

taking notes and observing group interactions. For the individual interviews, the same semi-structured interview protocol, with some minor changes, was used. During the individual interviews, information about the current screening program and NIPT was provided verbally, supported by illustrations.

Data analysis

Focus groups and interviews were audiotaped and transcribed verbatim. After transcription, a thematic content analysis was performed using the qualitative software program ATLAS.ti 5.2. Responses in the text were coded independently by R.v.S. and A.K.K., and ranked and clustered into main topics and subtopics in order to identify important themes. Themes and codes were discussed with a third researcher (L.H.), and discrepancies were discussed until consensus was reached. Representative quotes from the focus groups (FG) and interviews (I) were translated from Dutch and are presented to illustrate the themes.

Results

Participants' own experiences with prenatal testing for Down syndrome varied widely as did their attitudes towards prenatal screening and NIPT. Participants discussed four main themes: NIPT test characteristics; consequences of a lower barrier for prenatal screening; requirements for a responsible NIPT offer; and widening the scope of prenatal screening. The findings are summarized below.

Theme 1: NIPT test characteristics: accuracy, safety, earlier testing

Although not all participants necessarily agreed with prenatal screening, their first impressions of NIPT were positive. Different advantages of NIPT related to its test characteristics were discussed.

Accuracy and safety

The high accuracy of NIPT was seen as an advantage, as participants felt that the test currently used for prenatal screening, the FCT, had limited accuracy, causing unnecessary invasive tests and a false sense of security in women with a low-risk estimation.

> "I had a chance of 1 in 800 [after FCT], well, I had some friends who had a chance of 1 in 20. They did not have a child with Down syndrome, and I did. I was totally not prepared for it, because I actually thought that my child would not have Down syndrome, because I had excluded that with the test [FCT]." (I11)

Participants stated that NIPT's ability to reduce the number of invasive procedures, and thus miscarriages, is a great advantage since these tests are risky and stressful, both for pregnant women and obstetricians.

> "Lower risk of miscarriages, and that is of course, the big advantage I think […] I have had chorionic villus sampling, but that's just not nice. It was a very bad experience […] it was painful but also emotionally a bad experience." (FG1)

Most participants argued that because NIPT is accurate and safe, it is easier for women to test whether the fetus has Down syndrome. In the case of a positive test result, this allows women to prepare themselves emotionally for the birth of a child with special needs, arrange adapted perinatal care, or terminate the pregnancy if they feel they are not able to cope with a child with Down syndrome.

> "For me that is the biggest advantage, that without the risk of a miscarriage you know what the situation is and from there on can think: What do I choose?" (FG2)

> "If NIPT had been available back then, I would have liked to have had it, because then at least I would have known [that the fetus had Down syndrome]. Our child had a very narrow escape [at birth]; there would have been less risk if we had known." (FG3)

Testing earlier

The fact that NIPT can test earlier in pregnancy than the FCT was seen as an advantage because participants expected less maternal-fetal bonding during the early phase of pregnancy. Should the fetus have an abnormality, and prospective parents wish to terminate, it was thought that this would be easier to deal with because they are less attached to the child.

> "Yeah I think the earlier you know, the less difficult an abortion will be probably, for me I think, because a child develops so quickly […] I think I would be able to live with it [termination of pregnancy] better if it's done as early as possible." (FG2)

Participants also mentioned that testing early in pregnancy is better because fewer people are aware of the pregnancy, which means that a potential termination of pregnancy would be easier for the parents socially as they would not have to explain it to others. While most agreed that earlier testing is an advantage of NIPT, some argued that this could also be a disadvantage. They thought that women (and their partner) would terminate the pregnancy less thoughtfully since they are less involved in the pregnancy at this stage, feel less of a bond with the child, or do not have enough time to think carefully about what they want. They expected this could even lead to regret afterwards.

> "You are maybe less involved with your pregnancy. […] you have thought less well about the consequences of aborting it, while later on you may feel sorry about it." (FG1)

Theme 2: Consequences of a lower barrier for prenatal screening

Most participants felt that because of the better test characteristics, NIPT would lower the barrier for participation in prenatal screening. Some saw this as an advantage since prenatal screening will become easier as only a blood sample is required, and there is no risk of miscarriage.

> "It is just more accessible because of the fact that there is less risk of a miscarriage […] you can just give blood, so in that sense it is more accessible […] it lowers the barrier." (FG1)

Most participants, however, saw this lessened barrier as a disadvantage. Since NIPT is such an easy and risk-free test, it might become more "normalized" to screen for Down syndrome, and Down syndrome would become less accepted.

> "It will become more normal to test for Down syndrome with the consequence that Down syndrome becomes even more undesirable, because the fact that you screen for something means it is undesirable, otherwise you wouldn't screen for it." (FG1)

Moreover, participants thought that pregnant women and their partner might feel pressured by society to have NIPT. Participants stated that already with the FCT some parents of children with Down had the experience of being judged on their choice not to screen. Since NIPT is a better test, women who decline NIPT might feel the need to explain their decision. Having a child with Down syndrome might be regarded as their own responsibility for which society would then be justified to hold them (financially) accountable.

> "Your freedom of choice will be limited in such a way that you have to explain the fact that you don't want to screen." (FG3)

> "Like, you consciously decided not to test, so it's kind of your own fault…so then you also will carry the burden of it. So everything it [having a child with Down syndrome] costs, yeah: Sorry madam, you should been tested then." (FG3)

Participants thought that the uptake of prenatal screening would increase with NIPT, and more people would terminate their pregnancy. This would cause a decline of the population with Down syndrome, leading to a potential loss of acceptance and facilities for affected individuals. They also were concerned that because of the decreasing number of people with Down syndrome there would be less research on Down syndrome-related complications, thereby eroding the knowledge concerning treatments and care for people with Down syndrome. In this scenario women would not really have a choice anymore to turn down prenatal screening, which would lead to an even higher uptake. This supposed self-reinforcing process is illustrated in Figure 1.

> "The moment you make screening more accessible and lower the barriers [...] more people will do it […], and as a consequence of that, the population [of people with Down syndrome] will decline. I am sure of that." (FG1)

> "What has been fought for, for so long, that those people finally, yeah, are more accepted in society, […] that will all go, well, it might deteriorate." (FG2)

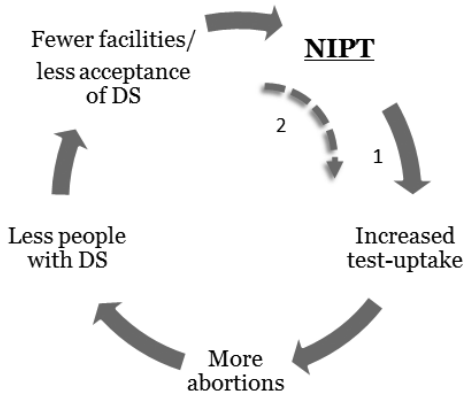

Figure 1. Self-reinforcing process of impact of NIPT, based on expectations of Dutch parents of children with Down syndrome (DS)

Participants hypothesized that the advantages of NIPT are mostly applicable to the individual woman. In contrast, the disadvantages of NIPT are more likely to affect society as a whole. For example, they feared it would lead to a loss of diversity in society. They thought that people with Down syndrome were valuable to society, and that people could learn from them.

> "The way he [son] has contact with other people, everybody can take it as an example. […] he gives a lot of joy, and it sometimes brings you back to reality." (I3)

Participants indicated that having a disability could become less acceptable by society.

> "[Screening] affects people with a disability.[…] There is a negative attitude towards people with a disability, and this is stimulated [by the introduction of NIPT]."(I2)

In addition, participants thought that people may get the idea that life can be controlled by using NIPT, and that this might lead to unrealistic expectations about having children.

> "It's not like: Okay, I did the test and I am done now, and everything will be fine. Having a child is not easy, and a lot of things can be wrong with the child, and there are external factors that influence child development. Now [with NIPT] it seems like, well you can exclude everything […]. That's just not true."(I7)

Lastly, participants felt that prenatal screening puts a lot of focus on Down syndrome, while trisomy 13 and 18 can also be identified. They felt that with NIPT, the focus is even more on Down syndrome. They stated that in the (Dutch) media NIPT is being called "the Down-test" (24), which in their opinion suggests that Down syndrome is the worst thing that can happen to your child.

> "It [prenatal screening] makes it seem as if the most important thing is to avoid having Down syndrome […] like, when it [the child] has Down syndrome then your world will fall apart, there is nothing worse than that […]. I am not saying it is not a handicap. But it is not the worst in the world, no." (FG2)

> "Actually it's already becoming standard: NIPT equals Down syndrome, which equals terminating the pregnancy." (FG3)

Some participants wondered why Down syndrome is still screened for at all. They felt that people with Down syndrome can have a valuable life, and that there has been significant medical progress, giving children with Down syndrome much fewer medical problems nowadays.

> "I support screening if there is something one can do, and if suffering can be avoided. We therefore did the FCT because trisomy 13 or 18…we wouldn't wish that on a child. But a child with Down syndrome […] overall can have a valuable life in society." (FG3)

> "I often wonder for what medical reason they screen for Down syndrome [..] the reason why those children did not survive was primarily because of their heart disorder, and there has been so much medical progress on that." (FG1)

Theme 3: Requirements for a responsible NIPT offer

NIPT in public healthcare

Although not all participants agreed with screening for Down syndrome, most did think it is unrealistic to stop offering prenatal screening. Therefore, when prenatal screening is being offered anyway, they felt that it would be better to screen with a safe and accurate test like

NIPT and to embed this in public healthcare with proper counseling, instead of women going to a commercial setting where they might receive poor counseling and information.

> "You're better off starting to offer it [NIPT] within public healthcare and making sure there is proper counseling than having it offered anyway in some kind of commercial setting." (FG1)

Reimbursement of NIPT

Participants had trouble deciding whether NIPT should be reimbursed. They felt that by doing so, you send out a certain message that would encourage all people to do this test without thoroughly thinking about it. However, the present cost of NIPT could create double stigmatization, where children with Down syndrome are only born in lower social economic classes, because those people cannot afford NIPT.

> "People with a low income, yeah, they cannot do it [NIPT]. Yeah, it will be like when you could recognize someone's poverty by the state of his teeth." (FG3)

Information and counseling

Almost all participants mentioned that improving information provision during the implementation of NIPT is important to support informed decision-making and avoid routinization. Participants felt improvement to be necessary because they thought there was a lack of good counseling and up-to-date, balanced information about Down syndrome. They also felt that in society Down syndrome is portrayed as being either too negative or too optimistic.

> "We are programmed to think it is terrible to have a child with Down syndrome. But if you see how normal a child with Down syndrome can be, if you, in some way, can incorporate that [in counseling], then you get more balanced information than there is now." (FG1)

> "There is a group that portrays it [Down syndrome] as very positive, but they want to counterbalance all those negative stories […] I would like to see a midway, the reality […] just show how it really is, and that is very diverse." (FG1)

Several participants mentioned that the government contributes to the negative image of Down syndrome by providing the possibility to test for Down syndrome.

> "Down syndrome really gets labelled as a disorder that should not exist. At least, that's how many parents [of children with Down syndrome] perceive it, and for that we blame the government." (I9)

They indicated that the government therefore has the responsibility to correct the negative image of Down syndrome by, for example, information campaigns, and that the government should not spend money on the implementation of a new test without improving the information provision.

To achieve balanced and complete counseling for NIPT, many parents stated that, in addition to medical information, more information about living with Down syndrome should be given.

> "Yes, also the counseling, […] I think that obstetricians and midwives can still learn a lesson about that when NIPT gets implemented. […] I think counseling is very important. To portray a realistic picture (of) what it's like to live with a child that has a disorder." (I10)

> "I think you should highlight all sides (of Down syndrome). The current counseling for Down syndrome is like 'high risk of heart disease,' 'higher risk for this' […] you are just getting a list of symptoms. […] When you offer it [NIPT] to people, you should also offer all information […], all sides of it. Make sure that people really get an honest picture." (I6)

Several participants mentioned that parents of children with Down syndrome could have a role as an information source. They could share their experiences of having a child with Down syndrome and make people understand what it is like.

> "Not to convince them [prospective parents], but to tell the truth, to show the reality." (I8)

Some participants also thought there was unfamiliarity with Down syndrome amongst healthcare professionals. They were concerned because professionals play a major role during counseling and can have a significant impact on parents' decisions, as parents might feel uncertain and anxious after receiving test results. Some participants also mentioned that for some obstetricians, a termination of pregnancy is the obvious next step after a Down syndrome diagnosis. Participants therefore stressed the importance of a non-directive attitude of the health professional.

> "That people hear like 'Well you had amniocentesis, you carry a child with Down syndrome, so when are we going to set the appointment to terminate the pregnancy?'" (FG1)

> "I can imagine that, when you are pregnant and have a lot of hormones and emotions and whatever, and then you hear that your child has Down syndrome and you know nothing about it, then you get the opinion of a doctor. The question is whether all doctors will have the same opinion. I think not." (I1)

Theme 4: Widening the scope of prenatal screening with NIPT

Participants had conflicting thoughts about testing for more disorders with NIPT. They agreed it had a number of advantages, like being able to prevent suffering, to arrange adapted perinatal care, or starting soon after birth with a certain diet to lessen the pathology of the disorder.

> "If people indeed happen to have a disorder that you can, for example, partly prevent with a lifestyle or diet […] yeah that of course has its advantages." (FG1)

Some participants mentioned that it would give parents the option to decide whether they would be capable of caring for a child with a disorder.

> "I find the freedom of choice of parents very important. Like, can I handle this? Will we be able to deal with this in my family?" (FG2)

Some participants also felt that testing for more disorders could lessen the focus on Down syndrome, which they saw as a benefit.

> Moderator: "Expanding the offer [of NIPT] to other disorders, what do you think about that?"
> Respondent: "Well, I think, that as long as it [a broader NIPT test] goes along with good information provision...look, what I find wrong at this moment is that the focus is so much on Down syndrome […] and if there will be more [disorders], […] as long as the information provision is right, everyone should be able to decide for themselves." (FG1)

Participants expected it to be difficult to decide where to draw the line when testing for a broader range of disorders, and to avoid that this line getting crossed over time.

> "Yeah, what would worry me a lot is how to guard that line […] what we can all test for. We are curious by nature you know, there will always be people that will want to cross that line." (FG1)

Some participants noted that it is not up to prospective parents to decide about everything since we cannot control everything in life. Some also mentioned that society would not benefit from eliminating everything that differs from the "normal standard."

> "I find it very dangerous that as a society we more and more make value judgments on everyone who doesn't fit the strict definition of normality." (FG3)

Other participants mentioned that people would be faced with even more difficult decisions to deal with during pregnancy. Moreover, they worried what kind of impact it would have on eligibility for healthcare insurance or housing mortgages.

Discussion

Parents of children with Down syndrome considered the accuracy, safety and possibility to test earlier as advantages of using NIPT in prenatal screening. However, they thought that prenatal screening in general, and the use of NIPT in particular, put too much focus on Down

syndrome, making it seem like Down syndrome is the worst thing that can happen to one's child. They expected that NIPT would lower the barrier for participation in screening, which has both advantages and disadvantages. Participants argued that NIPT gives people a more accurate option to test for Down syndrome without having to risk a miscarriage; but because of that, testing for Down syndrome and terminating the pregnancy could also become more normal. They feared the latter could erode the acceptance, facilities and research for Down syndrome, which in turn leaves women with little room to decline testing (self-reinforcing process illustrated in Figure 1). Participants stated that, when implementing NIPT, the counseling should be improved by giving more balanced, accurate information, including more information about living with Down syndrome. Although participants assumed that testing for more disorders with NIPT diverts the focus away from Down syndrome and allows for early medical intervention, they worried about where to draw the line. They also feared a loss of diversity in society.

This study describes the views of a sample of parents and relatives of children with Down syndrome in the Netherlands, a country with relatively low uptake of prenatal screening. When compared with the attitudes of pregnant women in the Netherlands as well as pregnant women in other countries (5-7), it seems that parents of children with Down syndrome often perceive similar advantages and disadvantages of NIPT. Like pregnant women, they believe NIPT lessens the barrier for participation in screening because it is a simple and safe test that can be done early in pregnancy. Similar to the study by Kellogg et al.(12) of mothers of children with Down, participants agreed the lower barrier is beneficial because it allows people to test without risk and decide whether or not to continue the pregnancy based on that information.

The notion that it could also lead to an increase in termination of pregnancies also corresponds to findings of Kellogg et al.(12), where the majority believed NIPT would lead to the termination of more pregnancies. A study by Natoli et al.(25) on termination rates after a Down syndrome diagnosis showed that higher termination rates were associated with earlier gestational age. This finding supports the assumption that NIPT's ability to test earlier could lead to more termination of pregnancies, although others have suggested that with NIPT the percentage of women who opt for termination of pregnancy in the case of an affected pregnancy may decrease.(26)

The fear expressed by participants that fewer children with Down syndrome being born could lead to stigmatization and fewer facilities, is a concern that was also observed in several other studies.(6, 7, 27, 28) Due to the lower barrier for NIPT, participants indicated that good quality counseling and informed decision-making are of great importance. This awareness also exists amongst health professionals, for example, genetic counselors from the UK, who stated that because NIPT has the potential to become routinized, it is the professional's role to make sure that women understand what they are consenting to.(29)

To help healthcare professionals facilitate meaningful discussions between themselves and prospective parents, Sachs et al.(30) have developed a framework for pre-test counseling about NIPT, especially focusing on its capabilities and limitations. Participants in our study, however, felt that already in current screening practice, information and counseling were not up to standard. They were especially critical of the quality of the information about Down syndrome given at different stages of the screening trajectory. Studies in other countries suggest that knowledge of Down syndrome among healthcare professionals could be improved (31), and that some parents perceive the information about what it may mean to live with this condition, both for the individual and for the parents, as insufficient (32, 33) or overly negative.(12) It was also noted that the information leaflets for those considering screening for Down syndrome should provide more accurate information about this.(34) Participants in our study thought that parents of children with Down syndrome could play a valuable role in this respect as well.

Similar to pregnant women (7), parents of children with Down syndrome think that testing for more disorders with NIPT can have some advantages. Interestingly, one of the advantages mentioned was that it would shift the focus away from Down syndrome, thus avoiding the impression of Down syndrome as a disorder for which screening would somehow be more justified than for other (including more serious) conditions, something that many of these parents find unjust and hurtful. Participants, however, feared testing for more disorders would confront prospective parents with even more difficult decisions. This fear was also expressed in our previous questionnaire study of Dutch pregnant women, who stated that "testing for a broad range of disorders may complicate the decision-making process beyond what most couples are able to comprehend".(35) Although it was not explicitly mentioned in this study, widening the scope of testing will also make it increasingly

difficult to meaningfully discuss prior to testing what it is like to have a child with any of the conditions screened for. Participants in our study also feared a loss of diversity in society, which is in line with findings from a previous study in the UK that highlighted public fears of fueling a problematic quest for perfection if NIPT were to be used to screen for an ever wider range of disorders.(36)

Study limitations and research recommendations

A strength of this study is the qualitative approach, which allows for exploring in-depth views about NIPT. Using both focus groups and individual interviews allowed us to explore opinions in both a group context and more private environments, which strengthened the credibility of the results. As far as we know, this is the first qualitative study of the attitudes of parents of Down syndrome children towards NIPT. A limitation of the study is that almost all participants were recruited from one source, a Facebook group which consisted of people with relatively young children. Moreover, participants were Caucasian and highly educated. This might have led to biased responses. Additionally, previous discussions on this Facebook page might have influenced participants' opinions. Moreover, attitudes of parents might have been influenced by the strongly articulated opinions in the Dutch media. In the focus group and individual interviews held in 2015, participants seemed more negative about NIPT than in the focus groups in 2013. However, the sample size is too small to draw conclusions on this point. The study was conducted in the Netherlands, where prenatal testing is offered in a nationally organized prenatal screening system, the uptake of which is relatively low. Attitudes of participants in this study may thus vary from those living in countries where NIPT is offered by individual (commercial) healthcare providers, or in countries with other cultures and religions. Finally, qualitative data are not intended to be generalized to the population of interest. Future studies might include larger samples of males and females. Moreover, should NIPT be introduced as a first-tier screening test, it would be interesting to see whether and how it affects parents' opinions.

Conclusion and practice implications

The findings from this study provide insight into the expectations and concerns that parents of children with Down syndrome have about introducing NIPT into a national prenatal

screening system. It can be concluded that parents of children with Down syndrome may have ambivalent attitudes towards NIPT. While they do not necessarily all agree with prenatal screening, they do acknowledge that NIPT offers a better option than the combined test to know whether the fetus has Down syndrome. However, they also expressed concerns for the future of children with Down syndrome and emphasized the need for good counseling and information provision, including more information about living with Down syndrome.

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Chapter 5|

Rethinking counselling in prenatal screening: An ethical analysis of informed consent in the context of non-invasive prenatal testing (NIPT)

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Abstract

Informed consent is a key condition for prenatal screening programs to reach their aim of promoting reproductive autonomy. Reaching this aim is currently being challenged with the introduction of non-invasive prenatal testing (NIPT) in first-trimester prenatal screening programs: amongst others its procedural ease –it only requires a blood draw and reaches high levels of reliability– might hinder women's understanding that they should make a personal, informed decision about screening. We offer arguments for a renewed recognition and use of informed consent compared to informed choice, and for a focus on value-consistent choices and personalized informational preferences. We argue for a three-step counselling model in which three decision moments are distinguished and differently addressed. 1) Professionals explore women's values concerning whether and why they wish to know whether their baby has a genetic disorder. 2) Women receive layered medical-technical information and are asked to make a decision about screening. 3) During post-test counselling, women are supported in decision-making about the continuation or termination of their pregnancy. This model might also be applicable in other fields of genetic (pre-test) counselling, where techniques for expanding genome analysis and burdensome test-outcomes challenge counselling of patients.

Introduction

In many countries, when a pregnant woman first visits an obstetric care provider, she will be offered information about several prenatal screening tests. Some tests are offered to promote the health of mother or child, for example screening for Rhesus factor. Other prenatal screening tests, however, are aimed at the detection of foetal abnormalities for which no therapeutic or preventive interventions are possible or available.(1) Rather, testing for these foetal abnormalities provides reproductive options to pregnant women or couples, with the aim of promoting reproductive autonomy.(2) These tests enable future parents 1) to obtain information about their future child, and 2) decide about whether to continue or terminate a pregnancy in case of a genetic disorder.

Non-invasive prenatal testing (NIPT) is being introduced widely as a screening test for three common foetal aneuploidies: trisomy 21, 18 and 13, leading to Down's, Edwards' and Patau's syndrome, respectively. NIPT is an alternative for and an improvement of the first-trimester combined biochemical test for these trisomies.(3) It is based on the assessment of cell-free DNA in the blood of the mother and has better test characteristics compared to the first-trimester combined test, being more accurate and reliable. However, these advantages of NIPT have raised several ethical questions and concerns.(4) For instance, an increase in uptake of NIPT is feared to lead to an increased abortion rate and to social exclusion of people with a disability. Moreover, next-generation sequencing technologies allow for a future expansion of the scope of NIPT. Some people are concerned that NIPT may come to include trivial conditions or findings that are difficult to interpret.(5) Prenatal clinics today are already confronted with - sometimes difficult to interpret - incidental findings resulting from the use of next-generation technologies in NIPT.(4)

Another frequently mentioned problem is that NIPT may lead to problems for informed decision-making: NIPT might be considered by pregnant women as 'just another blood test'(6) easy to conduct and very reliable. Women might routinely accept NIPT as a screening test for trisomy 21, 18 and 13 and may not be prepared for abnormal test results.(7) Besides, it is feared that women would step into what is called a 'screening trap'.(8) This means that NIPT might put women on a pathway to invasive follow-up diagnostic testing and potentially termination of the pregnancy, while they not have fully assessed the consequences beforehand.

These problems are considered to challenge the 'informedness' of NIPT-related decisions and consequently to undermine the aim of reproductive autonomy.(2) Counselling is the generally preferred instrument to promote informed decisions and includes providing information and decision-making support.(9) How can counselling be used to counter some of the ethical and practical problems for informed consent raised by the introduction of NIPT? What should be the focus of counselling, and how can women best be supported in decision-making for or against first-trimester prenatal screening?

We first discuss the aim of prenatal screening (reproductive autonomy), the definition of informed consent and its operationalization in counselling. We offer arguments for a renewed recognition and use of the term informed consent – rather than informed choice – in ethical discussions of prenatal screening, and a different understanding of what it means to give or ask for informed consent for first-trimester screening.

The aim of prenatal screening: promoting reproductive autonomy

The aim of prenatal screening programs is formulated as promoting reproductive autonomy.(10) By explicitly stating this aim, health care systems try to make clear that prenatal screening is different from other forms of screening in the public health context, such as breast or cervical cancer screening, the aims of which are the (secondary) prevention of disease or the promotion of health.(1) It would be problematic for prenatal screening programs to be aimed at prevention, for this implies that the birth of affected children ought to be avoided. If that were so, states or healthcare systems might appear to be promoting or encouraging abortion in case of genetic disorders. Abortion would turn into a (eugenic) public health instrument.(2) Also, it would carry the discriminatory message that children with the conditions screened for should not be born and their lives are worth less than those of citizens without genetic conditions. Thirdly, it might put pressure on women to terminate the pregnancy of an affected foetus.(2, 7) Pressure is precisely what should ideally be avoided in decision-making with regard to NIPT: women must be free to decide whether or not to take part in screening, and whether or not to terminate a pregnancy because of detected abnormalities. To distance prenatal screening from these problems, its aim is formulated as the provision of health-related information about the foetus in order to offer courses of action to pregnant women and couples in case of a foetal abnormality, or the promotion of reproductive autonomy.(7) This means that the decision to reject prenatal

screening, too, is and should be part of reproductive autonomy, in recognition of "patients' individual right(s) to decide whether or not they wish to receive testing and then to make reproductive choices based on test results".(11)

Informed consent in the context of NIPT

The aim of prenatal screening is operationalized through informed consent. Through the instrument of informed consent, healthcare professionals seek to ensure that women make autonomous decisions for or against a screening offer.(12, 13) According to the seminal theory of informed consent by Faden and Beauchamp, an "informed consent is given if a patient or a subject with (1) substantial understanding and (2) in substantial absence of control by other (3) intentionally (4) authorizes a professional."(14) Firstly, a decision whether or not to take part in screening should be based on 'substantial understanding'. This implies that women should be informed about characteristics of the tested condition, potential risks and benefits of the test and implications of possible test outcomes.(15) Secondly, women should be free to make a voluntary decision about screening and not be coerced or pressurized by others. Thirdly, women should have the capacity to consent. Most women do, and healthcare professionals are expected to presume that all patients are decisionally competent to decide unless they have reason for doubt. Traditionally, someone is believed to have the capacity to consent when she demonstrates the following four competencies: understanding of relevant information, reasoning based on this information, appreciating her situation and the consequences of her choice, and communicating a choice.(16) Fourthly and finally, the woman must in fact make a choice. It is noteworthy that in the field of prenatal screening the term 'informed choice' is frequently used instead of informed consent, which is ubiquitous in medical ethics and medical practice generally. (17) In one dominant model, 'informed choice' is defined as "one that is based on relevant knowledge, consistent with decision-maker's values and behaviourally implemented."(18) In the context of NIPT, informed choice is achieved when a woman has sufficient knowledge and either a positive attitude towards undergoing a test while opting for screening, or a negative attitude while refusing screening.

One of the rationales offered for preference of the term informed choice is that it distances prenatal screening programmes from unwanted eugenic associations.(17) Another rationale is that informed choice suggests that decision-making is less active than in informed consent,

and that informed consent requires a more elaborate discussion with a health professional.(19) Also, it is claimed that "informed consent is not explicitly concerned with the understanding of those not consenting."(20) Informed consent would suggest that patients should accept the option that is proposed or preferred by the healthcare professional. The withholding of consent to this preferred option might be considered ill-advised or irrational. By using the term informed *choice* in lieu of informed *consent*, it is emphasized that accepting and rejecting of prenatal screening are evaluated as equally valuable options. Both the choice to accept and the choice to reject prenatal screening are an expression of reproductive autonomy.(21) Finally, it has been suggested that informed consent "is not explicitly concerned with the consenting individual's values" while informed choice includes someone's values reflected in attitudes.(20) Also, in the literature on prenatal screening, the term 'informed decision-making' is being used. Informed decision-making often refers to the pre-decisional process, "the process of arriving at a decision" (22) and includes a process of deliberation and of weighing of pros and cons (23), while informed choice refers to the decision itself for or against a screening offer.

We contend that there is no ethical need for the use of the terms informed choice or informed decision-making in the context of prenatal screening. Traditional notions of informed consent encompass the criterion of voluntariness, and thus forestall concerns related to a lack of opportunity to withhold consent or related to state-enforced eugenics. They imply that patients (or pregnant women) understand relevant information about the proposed (or offered) screening test, and that this may require elaborate discussion with a healthcare professional. Also, when a woman is reasoning based on relevant information or appreciating her situation and the consequences of her choice, she is deliberating and evaluating. As a complement to their 'autonomous authorisation' model, Faden and Beauchamp propose a condition of authenticity: "An authenticity condition would require actions to be consistent with a person's reflectively accepted values and behaviour in order to be autonomous. Authenticity in this usage requires that actions faithfully represent the values, attitudes, motivations, and life plans that the individual personally accepts upon due consideration of the way he or she wishes to live."(14) With this condition, the traditional model of informed consent incorporates the consenting individual's values and attitudes. Ultimately, in this 'autonomous authorisation plus authenticity' model, informed consent in

the context of prenatal screening would require women's choices to be deliberate and consistent with their values as reflected in their attitudes. Thus, the rationales offered in the literature for preferring the term informed choice (or decision-making) over the term informed consent, do not hold.

Besides, a rehabilitation of the notion of informed consent in the context of prenatal screening may offer the added benefit of embedding it in the broader basis of existing ethical literature concerning the principle of respect for autonomy, which plays an especially important role in ethical discussions of NIPT as its main aim.

Limitations of current models for 'informed consent'

Given the aim of prenatal screening, to evaluate the success of screening programs for aneuploidies including pre-test counselling, the *informedness* of women's decisions for or against screening must be assessed, rather than uptake or detection rates.(2) Various measures of informed consent and informed choice have been developed in the past to measure the 'informedness' of women's choices with regard to screening offers.(18, 24, 25)

The knowledge component of these models, however, is problematic for NIPT. Firstly, the necessity of knowledge might get too little attention amongst women because, as said, the procedural ease of NIPT could hinder women's understanding that they have to provide informed consent for first-trimester prenatal screening, leading to routine acceptance of the test.(26) Furthermore the next-generation sequencing technologies used for the test and its possible outcomes – trisomy 21, 13 and 18, and incidental findings – are increasingly complex. There are concerns that women may lack understanding of relevant information about its aim, procedures, possible outcomes and consequences. Also, it may not be possible to redress these concerns by having healthcare professionals provide more and more – written and verbal – information to pregnant women. In fact, the provision of a lot of medical-technical information during pre-test counselling may overwhelm women and cause 'information overload', which may hinder them in becoming aware of what prenatal screening might mean for them.(27) When measurement scales focused on information and knowledge are being used to assess the quality of informed consent, such assessments are likely to result in high percentages of 'uninformed' decisions. But is that to say that women have not given valid informed consent for screening, or that their decisions were not

autonomous?

Providing or 'disclosing' information may not be a primary requirement for informed consent in the context of prenatal screening. Manson and O'Neill have pointed out the complexities of the disclosure or what they call the 'conduit' of information in the context of consent. Information, for instance, is 'inferentially fertile' (28): when a pregnant woman receives a bit of information about a test, she may consciously or unconsciously go on to make a range of inferences about the test, which may or may not overlap with the counsellor's understanding of the test and may or may not be correct or relevant. Moreover, when she enters the counselling session, she may have already made her decision about participation in screening.(29) She may have gathered her information from various types of sources (e.g. magazines, acquaintances, social media). Thus, when she consents, she may consent to something (slightly) different than that which is envisioned and disclosed to her by the counsellor.

Pre-test counselling should therefore not focus on the knowledge component of informed consent, but on supporting pregnant women and their partners in making personal, value-consistent decisions about prenatal screening. This is how reproductive autonomy is best served. Offering decision-making support can at the same time be used to counter the problem of routine acceptance of prenatal screening: although NIPT is not a diagnostic test, and any abnormal results must be confirmed through invasive follow-up testing, it is much more sensitive and specific than previous technologies. It further requires only a single blood draw. As women may thus have fewer reasons to refuse screening, they may accept it automatically, without full consideration. Focussing on personal decision-making might help women to make a personal decision about prenatal screening.

Screening is offered to help women to plan their lives according to their values – if they want to, with use of prenatal screening. Women therefore should make considered decisions for or against first-trimester screening, for it may have great impact on their lives. The decision to take part or not to take part in screening should be informed but above all authentic. To respect women's autonomy and enable them to decide about prenatal screening according to their personal values they should be enabled to think about the question why they would want to know whether their baby has a genetic disorder. Women should be prompted to think about whether they want to have the options (termination or preparation in case of a

genetic disorder) which prenatal screening provides them in order to plan their lives. This is in line with the notion that informed consent includes a more active decision-making than informed choice.(19) Reproductive autonomy not only involves sufficient knowledge as argued by previous authors but also "involves (…) encouraging self-reflection to act in accordance with broader life goals"(30) which emphasizes autonomous decision-making. This aim is more in line with the definition of informed consent including the authenticity requirement, as it focuses on self-determination and the broader ideal of planning one's life according to one's values.

A three-step counselling model

To reach an authentic choice according to someone's life plan requires a restructuring of the current approach to counselling, and requires primarily a dialogue about the pregnant woman's or couple's values, instead of providing 'value free'(31) medical technical information as is suggested by several professional committees.(32, 33)

We propose a re-focusing of pre- and post-test counselling and a re-envisioning of the decision-making process, consisting of three central decision moments for women and their partners (Figure 1). These three decision moments are derived from the current counselling practice in the Netherlands, in which pregnant women are already presented with three decision moments. In the Netherlands pregnant women first receive an 'information offer'. With this offer, a woman is asked whether she would want to receive information about prenatal screening at all. When a woman declines, the counsellor will explore her motivation and will not inform her any further about first-trimester prenatal screening options.(34) The information offer is meant to promote the moral *right not to know* about the options of prenatal screening for foetal aneuploidies, in order to stress the fact that this screening is not mandatory.(35)

Critics of the information offer suggest that it is not possible to make an informed choice to decline screening when one does not know about the options for prenatal screening. This criticism touches upon a realistic problem, but we think that the solution is not to provide complete information in this first step. Instead, the health professional first should explore women's motivations and related values to determine whether the declination is either the result of an autonomous decision or on misunderstanding of prenatal screening.

Step 1: Exploration. The first decision moment of our proposed counselling model focus on

women's personal attitudes towards prenatal screening and its meaning to their life planning, instead of providing medical-technical information. The main goal of this first step is that health professionals will explore women's values, discussing with them why they do or do not want to know about genetic disorders at this stage of pregnancy. This might enable women to make their values explicit in context of this decision. We acknowledge that in this step women might want some information about prenatal screening, for example to imagine what possible results might mean to them. But foremost, in this first step it must become clear to women that opting for - or against - prenatal screening is a free and personal choice: it should focus on promoting choice awareness. More than the information offer, this first step might infringe upon the presumed right not to know about screening options. This first step does not replace the information offer, because in this step it is about accepting or declining the screening offer, not an information offer. An information offer could take place beforehand, but might entail the same exploration questions to find out whether women or couples have deliberated about their decision.

Step 2: Information. The second step in the counselling is that, when women would like to have prenatal screening, they will receive information about the test, its procedures, its possible outcomes and the consequences thereof, and risks and benefits. At this stage medical-technical information becomes more important and provides women the option to compare this information with their values. Information provision can be done through multiple modalities, including written materials, video materials, individual and/or group-based face-to-face discussions with healthcare professionals, according to women's personal needs, to ensure that key information on the (increasingly) complex test is conveyed. In this step it should again be stressed that women are free to withdraw from taking part in screening.

In the current Dutch practice of offering NIPT, wherein women can choose to learn about incidental findings, the question raises whether women need to know everything about the abnormalities included in the test, before they opt for screening, or whether they could wait to receive a full explanation of the implications of detected abnormalities when it turns out that one has been detected. We suggest that in order to make an informed choice, in the second decision moment women do not necessarily need to know medical-technical information about the test, such as the percentage of women that has a low risk based on first-trimester screening or which follow-up test are available beforehand. They primarily

should understand that first-trimester prenatal screening may yield information about serious diseases for which often no treatment is available. They should know that this may be a reason for women or couples to consider termination of an affected pregnancy, and should consider whether or not they wish to make use of the possibility of obtaining such information about their foetus. However, women's preferences, concerning which information is provided, how much and in what way, might differ. To design the second step, a tiered-layered-staged model for informed consent, which has been proposed in the context of genomic testing, might provide direction, proposing a choice between specified categories of diseases.(36) In the context of prenatal screening and pre-test counselling, categories of incidental findings can be based on characteristics of abnormalities, e.g. pathogenic for the foetus, variants of unknown clinical significance, benign findings and incidental findings, as proposed for diagnostic genetic tests.(37) Based on these categories women and couples can be informed about possible outcomes according to their needs, to make a personal informed decision about prenatal screening. Furthermore, in the second step, information about the prenatal test and its outcomes could be presented in a layered fashion, offering more detailed information (written materials, websites, group information meetings) to women on request, in order to keep the first layer of information (offered during the face-to-face counselling discussion with the healthcare professional) limited and focused on key messages, preventing information overload. Besides, information provision could be spread over time to promote elaboration about the information and reflection on it (36), although in the context of prenatal screening counsellors should take account of the fact that during a pregnancy, the time of having courses of action, including the possibility to terminate the pregnancy, is limited and thus the time to reflect on information is limited.

Ultimately, in step two, women should again be encouraged to reflect on the information provided based on their personal values. Therefore, the information given in step two should foremost support value-consistency, and not be aimed of providing as much objective technical-medical information as possible.

Step 3: Follow-up and support. The third step takes place when women receive an abnormal test result. This step does not differ from the current practice after receiving an abnormal result from prenatal screening. Women will receive post-test genetic counselling from one or

more relevant professionals, in most cases a clinical geneticist, about the detected abnormality, its prognosis and possible courses of action. After considering this information women and their partners should obtain information about follow-up tests including amniocentesis or chorionic villus sampling, the consequences of carrying the pregnancy to term or terminating the pregnancy. They should be free to decide whether or not to opt for follow-up tests and termination or continuation of the pregnancy and receive professional support during their decision-making.

This three-stage choice process covers the problem which NIPT might cause for informed consent. It moves towards resolving the problems of routine uptake of prenatal screening by emphasizing the personal-choice aspect, focusing on women's or couples' personal values. This stepwise counselling model, including the layered information provision might also be applicable to other types of prenatal screening like the 20-week ultrasound scan, and also to other types of genetic testing as for example parents with a known family history of a genetic history. Furthermore, this restructuring of pre-test counselling could address the concern that reproductive autonomy could be hindered by future expansions in conditions screened for prenatal screening test. It is feared that therewith NIPT will involve too much information about many abnormalities, which might cause an information overload for women during pre-test counselling. Women might not understand what a broad NIPT might disclose, hindering them to give informed consent about whether or not to participate in screening.(2)

But for the first of three decisions moments, the width of the scope and the technicalities of the test are of less importance. The most important question is whether women want the options prenatal screening might provide to them, including preparation and termination of pregnancy in case of a genetic disorder.

The three-step model in practice

Our proposal to change the focus of pre-test counselling from information provision towards elaborating women's values is not fully new. Studies amongst pregnant women found that not only information about a test but also personal circumstances(6) and ethical beliefs influence their decision. Furthermore women want to have time to deliberate (38), and prefer a form of advice besides non-directive health education.(39) Professionals indicated

that they should "trigger women to think"(40) and midwives thought that it is important to ask exploring questions that make women think.(41) However, they indicated that they experience a lack of time to ask them. The lack of time could be solved with decision-aids, which can help women to prepare the counselling and already obtain information about prenatal screening, or to resume what is discussed in the counselling, facilitating a staged process. Although some women might wish to receive information about prenatal screening in a separate visit, step one and two of the counselling model could take place in a single visit. Nevertheless, two separate counselling moments do not necessarily demand very many additional resources because it often can take place in visits wherein other topics are discussed and measurements are done. But, as professionals already underlined, to provide women with time to consider, the prenatal test should not take place at the same visit as the pre-test counselling.(42)

The three-step counselling model might fulfil women's needs of support in making a decision according to their beliefs and help counsellors to facilitate reflection on women's choices for or against prenatal screening. Furthermore, it might protect those women who are less able to understand information and formulate their personal values and promote their reproductive autonomy, corresponding to what is stated by O'Neill: "Informed consent procedures protect choices that are timid, conventional and lacking in individual autonomy (variously conceived) just as much as the protect choices that are self-assertive".(43) In the Dutch context, it may help to avoid the moral discomfort experienced by professionals when they do not provide any information at all to those who decline the information offer. The present article shows that there are also ethical arguments for a revised approach of pre-test counselling for prenatal screening, which should focus on personal decision-making.

Finally, as reproductive autonomy also includes relational aspects(30), enabling women to give informed consent and reaching the aim of prenatal screening program is successfully, is not only the responsibility of counsellors. As argued elsewhere, also the context in which a decision is made matters.(44) Women or couples should have the feeling that accepting or rejecting prenatal screening are equally valuable options. This is not only established by counselling but also by the broader societal context, in which provision of care and support should be in place for those who choose to continue a pregnancy when it is known that the child born will have a disability, as well as for those who choose to terminate the pregnancy.

Conclusion

The introduction of NIPT is associated with several ethical problems including negative consequences for informed consent. Because of its procedurally ease, NIPT is believed to hinder women's understanding that they have to personally decide about a first-trimester prenatal screening offer. Furthermore, the potential for future expansion of NIPT might pose challenges for sufficient information provision. The current way of counselling focuses on the non-directive provision of practical and medical-technical information about the test, and may not be equipped to counter these problems. Informed consent in prenatal screening should be characterized as the decision to participate or not participate in screening, based on an understanding that screening may yield information about serious disorders in the foetus, which may be a reason for women and their partners to consider termination of the pregnancy. In our view, having knowledge about the test itself, its possible outcomes and the consequences thereof may be conducive to the informed consent process for some women, but it is not of central importance to all women.

We have proposed a three-step counselling model, in which three decision moments are distinguished and recognized as different types of decisions, for which different types of counselling should be offered to women and their partners. The primary decision should focus on the values concerning obtaining knowledge about whether the baby has a genetic disorder and the courses of option this knowledge provide. The second step involves layered information provision about the test and the final decision to test or not test, adapted to women's personal informational need. In case of an abnormal test result, in a third step, women will need to decide about follow-up tests and the continuation of their pregnancy. We have argued that reaching the aim of prenatal screening not necessarily lies in having sufficient knowledge, but in making a personal choice, according to one's life plan.

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Chapter 6|

The ethics of routine: A critical analysis of the concept of 'routinization' in prenatal screening

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Abstract

In the debate surrounding the introduction of non-invasive prenatal testing (NIPT) in prenatal screening programmes, the concept of routinization is often used to refer to concerns and potential negative consequences of the test. A literature analysis shows that routinization has many different meanings, which can be distinguished in three major versions of the concept. Each of these versions comprises several interrelated fears and concerns regarding prenatal screening and particularly regarding NIPT, in three areas: 1) informed choice, 2) freedom to choose and 3) consequences for people with a disability. Three of the strongest arguments raised under the flag of routinization are assessed for their validity: the threat that NIPT poses to informed choice, the potential increase in uptake of first-trimester prenatal screening and its consequences for social pressure to participate in screening or terminate affected pregnancies, and the negative consequences for disabled people. These routinization arguments lack empirical or normative ground. However, the results of this analysis do not imply that no attention should be paid to possible problems surrounding the introduction of NIPT. At least two problems remain and should be addressed: there should be an ongoing debate about the requirements of informed choice, particularly related to an expanded scope of prenatal screening. Also, reproductive autonomy can only be achieved when expecting parents' options are variegated, real and valuable, so that they can continue to choose whether or not to screen or to terminate a pregnancy.

Introduction

For several years, first-trimester prenatal screening for chromosomal abnormalities has been available for pregnant women and their partners. With the first-trimester combined test (FCT), which includes a blood test and an ultrasound scan, the foetus can be assessed for its risk of trisomy 21, 18 or 13, or Down's, Edwards' or Patau's syndrome, respectively. The introduction of non-invasive prenatal testing (NIPT) now changes the field of first-trimester prenatal screening. NIPT is based on the possibility to analyse cell-free foetal DNA in the blood of the mother for chromosomal abnormalities in the foetus. With a simple maternal blood draw, the foetus can be assessed for trisomy 21, 18 and 13.(1) NIPT can be performed throughout the pregnancy, from ten weeks onwards, and provides more reliable test results for these trisomies than the FCT.(2) Further, as genome-wide sequencing techniques and the bioinformatics analyses of the data are improving, more abnormalities other than trisomy 21, 18 and 13 can be detected through NIPT.(1) In theory, this allows for the expansion of the number of disorders that can be included in the test.

The favourable test characteristics of NIPT - early, reliable and safe - make the test attractive to pregnant women.(3) But pregnant women and professionals have also indicated that these improved test characteristics might raise ethical concerns.(4, 5) It is feared that the test is 'too easy' and influences the way the test is perceived and presented, namely as a routine offer, which a pregnant woman will accept as a matter of course.(6-9) This might impede the informed choice of women (7-9), or lead to pressure to test.(10, 11) In the literature this concern is often referred to as *routinization* of prenatal testing.(7, 9, 12) Routinization is thought to affect the generally acknowledged single justified aim of prenatal screening: to promote reproductive autonomy.(13) Reproductive autonomy in the context of prenatal screening presupposes that women make informed choices (13), and also that they are free to choose from a range of options (14), which should be varied, realistic and valuable.(15) This implies that women or couples should have the freedom to choose between screening and not-screening, and, more importantly, between termination and continuation of the affected pregnancy. Routinization of prenatal screening is not only thought to negatively affect the precondition of autonomous choice, but can also indicate other concerns, such as adverse consequences for people with Down's syndrome, including discrimination and stigmatization.(11, 16) Routinization is presented either as a

disadvantage of first-trimester prenatal screening in general, or as an argument against a widespread implementation of NIPT.(13, 17) The literature about prenatal screening encompasses a large number of interpretations of the concept of routinization. Routinization refers to concerns that having a prenatal test might be self-evident to pregnant women or couples or that their choices for prenatal screening are uninformed and not well-considered, but it may also refer to the trivialization of abortion or to the consequences of prenatal screening for people with Down's syndrome or other disabilities. Routinization serves as an umbrella term for many kinds of concerns and consequences of prenatal screening. Moreover, using an umbrella term as an argument in an ethical discussion is usually not productive, as it may be unclear what concern or problem exactly, is being referred to. Also, when a problem is not clearly defined, it is difficult to devise or assess possible solutions.

This paper explores the various meanings of the concept of routinization as it is used in the ethical and psychosocial literature on prenatal screening. It further examines the validity of three prominent versions of routinization as arguments in the debate about a responsible implementation of NIPT, both normatively and empirically. It contributes to the current debate not only by clarifying the routinization argument and dispelling some of the public fears for routinization in the current prenatal screening landscape, but also by pointing out possible solutions to some of the more serious concerns that routinization may refer to.

Different interpretations of *routinization* in the literature

In order to find different interpretations of the concept of routinization we conducted a literature search. We collected publications that include 'routinization'/'routinisation' or 'routinize' and 'prenatal screening' in the full text from the following databases: Embase, PsycINFO OvidsSP, Google Scholar and Pubmed. Search strings included 'prenatal screening', 'antenatal screening', 'prenatal test*' and routini*. Results included empirical studies, ethical analysis and governmental documents. Interpretations of routinization were listed, coded and clustered in several themes.

Table 1 provides an overview of the various meanings of routinization. Three clusters of interpretations of routinization were identified: informed choice, freedom to choose and consequences for people with a disability.

Table 1: Interpretations of routinization in the literature

Version	Definition	Articles
1. Informed choice		
Unconsidered choice	Pregnant women do not deliberate their choice and they are not aware of the consequences of testing.	(7-9, 12, 18-20)
Presentation by healthcare professional	Professionals present a prenatal test, especially NIPT, as routine.	(4, 18, 21)
2. Freedom to choose		
Self-evidence of testing and increase in uptake	Prenatal screening becomes self-evident. With the introduction of NIPT more pregnant women opt for prenatal screening.	(11, 22)
Pressure to test	Pregnant women feel a (social) pressure to take part in prenatal screening,	(2, 9-11)
Normalization of termination of pregnancy	Termination of pregnancy after a positive test result becomes a matter of course.	(17, 23)
3. Consequences for people with a disability		
Decrease in number of people with disabilities	Prenatal screening decreases the birth of children with disabilities.	(11, 24, 25)
Consequences for people with a disability and their family	Acceptance of children with disabilities decreases and they become discriminated and stigmatized.	(26, 27)

Informed choice

Firstly, routinization refers to the potential negative consequences of a routine offer of prenatal screening for the informed choice of pregnant women. Routinization means that giving consent is an 'act of routine' or 'habitual'.(19) According to authors first-trimester prenatal screening has already become routinized (9, 12) or the introduction of the NIPT might lead to routinization of prenatal screening.(7, 18, 28) Routinization of the decision about prenatal screening means that women or couples do not deliberate their choice for prenatal screening.(9, 20) In contrast to FCT, NIPT is perceived by many women as a one-step process rather than a multi-step process: in FCT, women are offered risk estimates for trisomies 12, 18 and 13, while NIPT is seen as providing yes-or-no answers.(7) A one-step process, it is feared, might shorten the time for deliberation about the choice for or against prenatal screening and its implications.

Women's informed choice also depends on the way prenatal screening is offered and discussed by healthcare professionals.(22) Routinization is thought to negatively influence counselling and decision making: professionals may offer less or incomplete information, present prenatal screening as a standard procedure that is offered to all pregnant women as part of standard antenatal care (29), or might even counsel women directively and encourage them to undergo screening.(22) It is thought that the easier and more risk-free the test is, the less importance healthcare professionals will attribute to offering adequate pre-test information which is thought of as routinization of pre-test counselling.(21)

Freedom to choose

A second cluster of meanings of routinization includes the obviousness of testing and the consequences of routine testing for a pressure to test and a normalization of abortion. When prenatal screening becomes routinized, the social norm might become that women should use prenatal screening and that it is responsible to do so, which might generate a social pressure to test.(9) Routinization also refers to normalisation of the termination of affected pregnancies.(11, 17) When prenatal screening becomes unquestioned, it is suggested, more people will opt for termination of affected pregnancies, not as a result of well-considered choices, but, likewise, as a matter of course, or because of social pressure.(11)

It is feared that when NIPT becomes widely available and is less invasive and free from risks these consequences will be enforced.(10, 11) NIPT might become part of routine procedure in antenatal screening as "just another blood test" (6) and might be accompanied with an increase in uptake, social pressure to test and an increase in terminations of affected pregnancies.(25)

Consequences for people with a disability

Thirdly, some authors have used routinization to refer to the consequences of the offer of first-trimester prenatal screening for people with a chromosomal abnormality or other disability. The total number of people with a disability might decrease over time, and this might provoke discrimination and stigmatization of people with a disability.(26, 27)

The three clusters of versions of routinization are not separated but relate to and reinforce each other:(16) an increase in uptake of first-trimester prenatal screening might lead to an increase in abortions, which might lead to fewer children with Down's syndrome. This might have consequences for the existing group of people with Down's syndrome, including

discrimination or less or lower-quality healthcare. These consequences might also have implications for women's freedom to choose or decline prenatal screening. The existence of only limited (health) care for people with Down's syndrome or of a negative public image of Down's syndrome could pressure women into choosing prenatal screening and into abortions of affected pregnancies.(16) Routinization as used in the literature can thus also refer to more than one version at the same time and these versions can be interrelated or affect one another.

Analysis of three leading routinization arguments

We have seen that routinization can refer to a variety of ethical concerns related to prenatal screening. Some of these concerns are introduced as arguments in the ethical and societal debate about the introduction of NIPT as a first-trimester prenatal screening test. We will now critically assess three of the most prominent routinization arguments in relation to the introduction of NIPT: the threat that NIPT poses to informed choice, the potential increase in uptake of first-trimester prenatal screening and its consequences for a pressure to test and abortion rates, and the negative consequences for disabled people. We will examine the validity of these arguments, and see if there is any empirical or normative support for them.

1. Informed choice: The challenges of NIPT for informed choice

The first identified routinization-argument is that NIPT could threaten the informed choice of pregnant women for prenatal screening because of the favourable test characteristics of NIPT. Besides, women might be less aware of potential consequences of prenatal screening, such as unwanted and difficult choices regarding invasive diagnostic testing and the termination of pregnancy.(18) Uninformed choices about prenatal screening are normatively problematic because the aim of prenatal screening is to promote reproductive autonomy, for which informed choice is an important requirement.(13) Moreover, a high level of knowledge about a test and its implications is associated with an improved psychological management of decisions and a better personal well-being.(30)

Informed choice for prenatal screening has been studied empirically, with varying results. Research groups have measured the 'informedness' of pregnant women's or couples' choices regarding first trimester prenatal screening, and reported varying outcomes: 51%, 59%, 77,9% and 89% of women or couples, respectively, were found to have made informed choices with regard to first-trimester prenatal screening.(20, 31-33) Part of the differences in

outcomes may be explained by the different methods for measurements employed: some studies measured knowledge, attitude and actual choice(31-33) and others also studied the decision-making process and included deliberation in the measurements.(20, 33) Besides, these studies mentioned limitations related to the feasibility of measuring informed choice. Authors questioned which elements determine informed choice and whether elements of knowledge, value-consistency and deliberation should be weighed equally.(20, 31) This should be taken into account when considering these results in the context of NIPT. The empirical studies on informed choice for NIPT suggest that NIPT does not lead to uninformed choices, showing that a majority of women, 77, 9% and 89%, were capable of making informed choices regarding NIPT.(32, 33) However, a comparative study suggest that informed choice rates may be lower in routine prenatal care than in a study setting; 89.0% versus 75.6%.(34) This difference emphasizes the importance of continuous improvement of informed choice in practice. Efforts are underway to train midwives in counselling for NIPT(35) and to develop decision aids for pregnant women.(36)

In conclusion, recent studies of informed choice do not offer convincing reasons to expect a critical effect on informed choice for prenatal screening. Attention to counselling and information provision may further relieve some of the concerns related. The introduction of NIPT could be an opportunity to continue work on the methodological difficulties of measuring informed choice and the content and quality of counselling.

2. Uptake screening & freedom to choose: NIPT and an increase in the uptake of prenatal screening

A second prominent routinization argument is that the introduction of NIPT could lead to an increase in the uptake of first-trimester prenatal screening.(11)

Empirical studies that investigated women's motivations for opting for first-trimester screening do support the expectation that the uptake of screening will increase significantly with the widespread availability of NIPT.(37-39) Foremost, women take part in screening because they wish to be reassured about the health of their baby (40), and NIPT can facilitate that, free from risk and on the basis of a reliable test result. Women also indicated that they would choose NIPT even if they would not choose FCT, because of the favourable test characteristics of NIPT.(5, 39) On the other hand, women do not seem to overwhelmingly opt for prenatal screening in all countries. Studies showed that for instance

in the Netherlands and in the US women or couples decline prenatal screening, because they are against abortion or wish to accept a child with Down's syndrome.(37-40) The uptake of screening will not become 100% as long as women are free to decline prenatal screening for these reasons.

Furthermore, an increase in uptake is not normatively problematic in itself, but becomes problematic when it is caused by a lack of freedom for pregnant women to act according to their own motivations or the existence of (perceived) pressure to opt for prenatal screening. Pressure could arise in the communication with the healthcare professional, the set-up of the screening offer itself and in the social context.(9, 41) Pressure to test undermines reproductive autonomy and jeopardizes the freedom not to participate in screening.(13) Reproductive decisions should be the result of autonomous choice, without coercion or control by others.(19) Pressure to take part in screening should therefore be counteracted.

Empirical evidence for the existence of pressure to test is limited. Studies report that some women feared social reactions (41) or experienced pressure to accept the test.(22) Some women who declined a prenatal test had the feeling that they had to explain or justify their decision to others.(42) On the other hand, this does not apply to all women: many women do not experience pressure to test, not by the screening offer itself nor by others.(41, 42) Probably the experience of pressure is highly personal and its causes are complex. Because of the importance of reproductive autonomy further research should be directed at women's experiences of pressure, the causes thereof and ways to mitigate these.

An increase in the uptake of prenatal tests is also thought to be problematic because it might result in an increase in the abortion rate, which is a major concern to several groups of people: some believe that abortion is morally unacceptable because of the sanctity of early human life and argue that prenatal screening is questionable by association, as it may lead to abortion.(2) Others argue that particularly the *selective* abortion, of children with certain disabilities, is a problematic consequence of prenatal screening.(27) The concern that NIPT will lead to an increase in abortions is probably premature as research and clinical practice show that there are also women or couples who choose not to terminate affected pregnancies. Instead, they use the information about the health of their foetus to prepare for the birth of an affected child.(6) This emphasizes the importance of sensitive

communication about screening and a responsible set-up of screening programmes, highlighting individual, autonomous reproductive choice as the central measure of success in screening programmes.

The absence of pressure is also important for another group of people, who may have less principled objections against prenatal screening but may still feel a reaction of disgust (moral intuition or emotion) towards prenatal screening and believe that 'nature should run its course'.(5) They also should be free and autonomous in their choices regarding prenatal screening and abortion. In the Netherlands, for instance, the uptake of first-trimester prenatal screening, therefore, is relatively low (38), under 30%.

To conclude, the expectation that the introduction of NIPT might increase the uptake of prenatal screening because of its benefits can be empirically supported. An increase in the uptake of first-trimester screening in itself is not necessarily problematic, when women and couples make informed, autonomous choices regarding prenatal screening and follow-up reproductive options. There is little supporting empirical evidence for an increase in social pressure to take part in screening or to terminate affected pregnancies. Further research is needed of public attitudes towards prenatal screening and people with disabilities, and the influence of these attitudes on women's and couples' decisions-making.

It is important to note that women's and couple's decision-making may be affected by funding arrangements, as well. It is sometimes suggested that reimbursement of prenatal screening by the health care system may 'legitimize' the screening offer and gives women the (false) impression that screening is important and/or necessary, and thus that all pregnant women should or must participate in screening.(43) Letting women pay out of pocket could help to underline that participation in screening is voluntary and elective. The meaning of this financial barrier merits further discussion, including its ethical implications e.g. for women with limited financial resources, for whom this barrier may not promote but rather restrict freedom to choose with regard to screening.

3. Social aspects: Consequences for people with a disability

The third routinization argument relates to societal consequences of the introduction of NIPT for people with a relevant abnormality. A routine offer of NIPT and a related routine choice for testing and abortion might lead to a reduction in the number of people with Down's syndrome.(3, 5, 16, 24) Parents and pregnant women suggested that a decrease in

the number of people with a disability might result in an impoverished care and support system for people with disabilities.(3, 16) Besides, routinization of testing might negatively influence public perception of Down's syndrome.(27)

Whether these effects will occur will partly depend on the effect of NIPT on the number of children born with Down's syndrome. To our best knowledge these results are not available yet for NIPT. Previous studies on first-trimester screening showed that in Europe between 1990-2009 47% of the pregnancies affected with Down's syndrome were terminated, but due to an increase in incidence of Down's syndrome because of an increase in maternal age, the overall prevalence stayed the same.(44) Other studies showed a decrease in life born of Down's syndrome of 28-50% in the Netherlands and 18%-59% in Western Australia.(25, 45) The fear of an increase of the abortion rate is also supported with referring to high numbers of abortion as for example in Denmark, but due to cultural differences between countries it might be hasty to suggest that in the Netherlands the uptake and abortion rate will increase until same numbers.(46) This remains to be seen in practice.

Another aspect that will influence social consequences of NIPT is the public's perception of Down's syndrome. Studies have shown that parents of children with Down's syndrome experienced negative consequences in their social environment, such as being judged for not having done a test, receiving negative reactions after deciding to continue an affected pregnancy or failing to find help from organisations.(16, 47, 48) More widespread availability of NIPT - and more positive attitudes towards NIPT - may exacerbate such consequences: positive attitudes towards screening have been found to correspond with negative attitudes towards individuals with Down's syndrome.(49) NIPT might thus exacerbate discrimination of individuals with Down's syndrome. Wider education and information provision about chromosomal abnormalities will be indispensable to build and maintain nuanced public attitudes towards these conditions, and thus help to counter discrimination and stigmatization. Patient, parents and patient organisations have an important role to play in public education about the implications of chromosomal abnormalities for patients and their families. While it is unclear whether and to what extent public attitudes towards Down's syndrome and other chromosomal abnormalities will deteriorate with the implementation of NIPT, this is something that can – and should – be monitored over the next couple of years.

In conclusion, we have discussed three prevalent versions of the routinization argument in the context of NIPT, for which support is limited. Current studies showed high percentages of informed choice and the improvement of counselling, information provision and decision aids might counter potential negative effects of NIPT. Furthermore, the uptake of first-trimester screening may increase with the wide availability of NIPT, which however does not contradict the aim of prenatal screening. It is not yet clear whether NIPT will spur any rising social pressure to participate in screening, and whether this affects women's freedom to choose to decline prenatal screening. This is an area of concern that will need to be addressed over the next couple of years. The rate of selective abortions might increase as a result of an increased uptake of first-trimester screening, which is considered undesirable by individuals or groups who believe that the intentional termination of a pregnancy is morally unacceptable. This dilemma, however, is not new. Nor is it significantly affected by the introduction of NIPT as compared to existing first-trimester screening programmes, such as the FCT or the 20-week ultrasound.

Finally, as many arguments under the denominator of routinization are either not valid or not fully convincing as arguments against the implementation of NIPT, the term routinization is losing some of its force in ethical discussions. Although the umbrella term routinization has been exposed as largely ineffectual, its usage does reveal the existence of concerns or fears among stakeholders. Some of these concerns need to be addressed or can be overcome.

NIPT and the problems that remain: informed choice and an expanded NIPT, and freedom to choose

We now have seen that routinization is an umbrella term that is frequently used within the ethical debate surrounding the introduction of NIPT and that it can refer to a variety of concerns. Some of these concerns have an empirical component that can largely or partly be refuted. Other concerns are based on ethical principles or values, such as the sanctity of early human life, and are not new or specific to NIPT nor in any significant way affected by NIPT, which is, in the light of this discussion, simply a more reliable and safe alternative to FCT within existing first-trimester prenatal screening programmes.

However, our analysis does not provide grounds to discard all concerns related to the

introduction of NIPT. From the analysis it follows that at least two ethical issues should be taken seriously when implementing NIPT.

Firstly, the effects of NIPT on society are an area of concern. For its ease, safety and accuracy, pregnant women may feel pressured to take part in prenatal screening or forced to account for their choice to decline. The feeling of no longer 'having a good reason not to' participate in screening may negatively affect women's freedom to make (autonomous) choices or their *experience* of this freedom. If women are blamed for bringing children with chromosomal abnormalities into this world or if children are discriminated against or lacking in appropriate healthcare and social support, it will no longer be an (equally) valuable or realistic option to continue a pregnancy following the detection of an abnormality. The precondition of equally valuable options is not met. It should be (and feel) feasible – socially, financially, practically for women and couples to choose not to participate in screening and to carry a child with a chromosomal abnormality to term. Otherwise, participation in prenatal screening is no longer the result of an (autonomous) *choice*, and the screening programme will not meet its aim: that of promoting reproductive autonomy. NIPT can be seen as an improvement of existing programmes as long as valuable options are created and maintained for children with disabilities and their families.

Secondly, informed choice is not only thought to be affected by the easiness of NIPT but also by the potential expansion of its scope, which comes closer with NIPT.(13) Genomic sequencing techniques will allow for the detection of other chromosomal abnormalities including microdeletion syndromes like DiGeorge and Prader Willi/Angelman.(13) Moreover, women are interested in additional information on microdeletion syndromes and sex chromosome aneuploidies.(50) Several studies suggested however that an expanded scope undermines an informed choice because of the quantity and complexity of pre-test information, including information test results with unknown clinical significance.(6, 13, 50) Especially sufficient knowledge levels may be difficult to reach in the context of a broad range of abnormalities of varying clinical significance. There the question is whether knowledge should be equally valued as value-consistency or deliberation in order to reach informed choice. The weighing of these elements should change and deliberation should get more attention, in order to counter routine uptake as well as an uninformed uptake for an expanded NIPT.

Conclusion

In the ethical debate on the introduction of NIPT, routinization is used as an umbrella term that is used to refer to various potential negative consequences of the test. When the meaning of the term is unclear, it is difficult to devise or discuss ways to counteract specific negative consequences of NIPT. Unqualified usage of the term routinization does not serve the debate: rather, the underlying concerns should be specified and made explicit.

On further consideration, many specifications or versions of the routinization argument are not valid because they lack empirical or normative foundations. Empirical studies have shown, for instance, that there may be no need to fear an increase in the uptake of screening or a significant threat to informed decision-making among pregnant women or couples. Furthermore, an increase in uptake is not normatively problematic in itself. This paper directs attention to two areas of serious concern related to the wider availability of NIPT and its potential expanded scope, and suggests ways of mitigating these concerns. High-quality pre-test counselling focusing on attitude-consistency could help safeguard informed, autonomous choice. Also, reproductive autonomy can only be achieved as long as declining participation in screening and carrying an affected pregnancy to term remain realistic options for pregnant women and their partners. This means that support and care systems for disabled people should be in place and that social pressure to test or to terminate an affected pregnancy and stigmatization should be actively counteracted through public education and information provision about chromosomal abnormalities.

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Chapter 7|

Non-invasive prenatal testing (NIPT): societal pressure or freedom of choice? A vignette study of Dutch citizens' attitudes

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Abstract

The introduction of the accurate and procedurally easy non-invasive prenatal test (NIPT) raises ethical concerns that public attitudes towards prenatal screening may change, leading to societal pressure to participate in aneuploidy screening. This study examined Dutch citizens' attitudes towards a pregnant woman's decision to 1) decline NIPT in the context of two different funding policies and 2) to terminate or continue a pregnancy affected by different disorders. The attitudes of 1096 respondents were assessed with the contrastive vignette method, using two pairs of vignettes about declining NIPT and termination of pregnancy. Most respondents either agreed with a woman's decision to decline NIPT or were neutral about it, stating that this decision should be made independently by women, and does not warrant judgment by others. Interestingly, funding policies did influence respondents' attitudes: significantly more respondents disagreed with declining NIPT when it was fully reimbursed. Respondents had similar attitudes to the vignettes on termination and continuation of pregnancy in case of Down's syndrome. In case of Edwards' or Patau's syndrome, however, significantly more respondents disagreed with continuation, citing the severity of the disorder and the child's best interests. This study demonstrates broad acknowledgment of women's freedom of choice in Dutch society; a finding that may help to rebut existing concerns about societal pressure for pregnant women to participate in prenatal screening. As the reimbursement policy and the scope of NIPT may influence people's attitudes and elicit moral judgements, however, maintaining freedom of choice warrants sustained efforts by health professionals and policy-makers.

Introduction

The aim of offering prenatal screening for aneuploidies is promoting women's and couples' reproductive autonomy.(1) This implies that women and couples make their personal decision about prenatal screening according to their life plan and values, and it precludes any form of pressure to accept or decline prenatal screening. However, women's freedom of choice is subject of concern with the introduction of non-invasive prenatal testing (NIPT).(2) The current study explores whether there are public attitudes towards NIPT in the Netherlands which might give rise to societal pressure to participate in screening.

NIPT is offered as an alternative to – or in lieu of – the first-trimester combined test for trisomy 21, 18 and 13, or Down's, Edwards' and Patau's syndrome respectively. NIPT allows for the analysis of cell-free foetal DNA in maternal blood using genome-wide sequencing techniques. It only requires a blood draw from the mother, while the first-trimester combined test also includes an ultrasound scan. Furthermore, NIPT is more reliable than the first-trimester combined test which provides a risk estimation for these three trisomies.(3) With both testing modalities, abnormal test results must be confirmed by an invasive follow-up diagnostic test. Because of its higher specificity, NIPT leads to fewer follow-up tests than the combined test. These favourable characteristics of NIPT however raise ethical and social concerns and are amongst others believed to change the informed decision-making process and lead to self-evident acceptance of NIPT – a concern often referred to as 'routinisation'.(4) It is feared that NIPT takes away reasons for women to deliberate or reject the screening offer (5) or provokes the feeling that women have to justify themselves when they decline an easy and reliable prenatal test.(6, 7) These consequences are thought to lead to societal pressure to test. Such societal pressure poses a threat to a reproductive autonomy and thus to the aim of prenatal screening.(4)

Testing this hypothesis is a challenge, because it is difficult to assess whether societal pressure to participate in screening exists at all – or what exactly societal pressure is. We interpret societal pressure not as pressure exerted by the state (e.g. mandatory screening programs) or by health professionals (e.g. directive counselling). In the countries in which NIPT is currently being introduced, screening is offered on a voluntary basis and women are not forced or coerced by their health professionals to take part.

Instead, we take societal pressure to be associated with explicit positive societal attitudes

towards prenatal screening,(8) negative explicit or implicit societal attitudes towards people with a disability,(9) holding parents (financially) accountable for the birth of a disabled child or with suggesting that raising a disabled child is one's own (financial) responsibility.(10) Moreover, societal pressure can be associated with pressure to abort an affected pregnancy, e.g. fearing that people may perceive giving birth to a disabled child as irresponsible.(5, 10) Dutch parents of children with Down's syndrome, for example, have collected their experiences with societal critique on having a child with Down's syndrome in a book titled 'Blackbook Down's syndrome, all people are unequal and similar'.(11)This book for example includes judgements that parents 'could have known that their child has Down's syndrome with prenatal screening' and that 'it is not necessary to have such a child because they could have terminated the pregnancy'. The experienced or feared societal pressure to test and to terminate a pregnancy of a child with Down's syndrome was also mentioned in qualitative studies amongst parents of children with Down's syndrome.(10, 12, 13)

Besides, in the Netherlands, women must make a co-payment of €175,- for NIPT. Funding policies are thought to influence the routine practice of prenatal screening(14) and possibly therewith societal pressure to test: a prenatal screening offer which is paid with government subsidies might strengthen the message to the public that it is important to have that test. And vice versa, a test that is not reimbursed might send a message that it is an unnecessary test. Additionally, it is evident that women decide about NIPT in a social context, and may take the perspectives of partners, family members and friends into account, but that does not inevitably amount to societal pressure.

To our knowledge little is known about the influence of public attitudes on women's decision-making concerning prenatal screening. In the field of social psychology, research is done on the effects of group pressure on people's opinions. Several experimental studies found that when people face a majority's or an expert's opinion different from their own opinion, they adopt this opinion, even when it includes a wrong judgment.(15, 16) Translating this to the context of decision-making in prenatal screening, pregnant women and couples might (unreflectively) adopt a dominant societal attitude towards NIPT, also when it would not fit their personal attitude towards this test. To assess whether this pressure from societal attitudes might arise it is firstly important to investigate public moral attitudes towards prenatal screening. This might provide insight into the possible presence

of predominant attitudes that might lead to pressure to test or to abort an affected pregnancy. The objective of this study was therefore to examine the attitudes of Dutch citizens towards the decision to decline NIPT and to study the possible impact of funding policies on citizens' attitudes. Furthermore, this study investigated the assumption that women and couples are expected by society to terminate the pregnancy when they learn about the presence of a disorder. It additionally explored respondents' underlying reasons for their attitudes.

Secondly for the assessment of societal pressure and its impact on women's decision making it is also important to assess pregnant women's experiences of pressure. Studying women's experiences falls outside the aim of this study but is already done elsewhere.(17, 18)

Method

In this study we used the contrastive vignette technique (CVT) in order to prevent soliciting socially desirable responses.(19) With this technique, respondents are presented with one of two contrastive vignettes, while unaware of the contrastive condition and the hypothesis of the study. The vignettes are contrastive in one condition while other variables are kept constant, enabling the identification of factors that affect people's attitudes towards moral issues.(19) The outcome measure of the CVT is the difference in group means between contrastive situations. In this study the decision to decline a state-funded NIPT was contrasted with the decision to decline a non-reimbursed NIPT and termination of an affected pregnancy was contrasted with continuation of an affected pregnancy.

Sample population and survey

We searched for a sample population representative of the Dutch population. Respondents were recruited via an external Dutch market research agency, Motivaction. Motivaction has an online research panel consisting of 65.000 Dutch members (reference date: April 2018), who participate in (market) research.(20) With filling in online questionnaires on the website www.stempunt.nu panel members earn credits which can be exchanged for gift cards. For this study Motivaction randomly invited members from their panel until 1096 panel members filled in the questionnaire: for their surveys Motivaction always use groups of approximately 1000 participants whereby they strive for a representative sample. The response rate for this survey was 36%. The panel members did not know the topics of the

survey beforehand.. The study was conducted in September 2017, shortly after the introduction of NIPT as a first-trimester prenatal screening test in the Netherlands.

Design of the vignettes

In a multidisciplinary team we designed two pairs of contrastive vignettes (appendix A). In the vignettes we introduced a third person, a fellow citizen in the person of Hanna, who is pregnant for the first time and has to decide whether or not to take part in NIPT, and, when an abnormality is detected, whether to continue or to terminate the pregnancy. We introduced a third person and not for example 'your sister' or 'your friend' in order to prevent the influence of relationships.

The first pair of vignettes involved the decision to decline NIPT including varying funding conditions (i.e. the test is fully reimbursed contrasted with a test offered at a price of €175,-). In the second set of vignettes the decision to terminate the pregnancy was contrasted with the decision to continue, primarily in case of Down's syndrome and subsequently in case of Edwards' or Patau's syndrome. The vignettes were pilot tested among acquaintances of the researchers and 23 students following a university minor programme in genetics, and were optimized after this pilot.

Procedure

Respondents first read a short introduction about NIPT and about Down's, Edwards' and Patau's syndrome. Then every respondent received one vignette of the first pair about declining a reimbursed or non-reimbursed NIPT or of the second pair about termination or continuation of pregnancy. Respondents were randomly assigned to the vignettes. They were asked to indicate on a 7-point Likert scale to what extent they agree with Hanna's decision ('completely disagree' = 1, 'disagree'= 2, 'disagree a little' = 3, 'do not disagree/do not agree'= 4, 'agree a little' = 5, 'agree'= 6 and 'completely agree' = 7). Respondents were asked to explain their answers in a follow-up free-response question. Subsequently, we investigated whether people's attitudes changed when confronted with the contrastive condition, as an additional investigation of the effect of varying reimbursement or disorder-severity conditions. In question 1c and 2c respondents were asked what their attitude would be when the situation was the opposite, thus declining a fully reimbursed NIPT instead of co-

payment, or vice versa. In question 3c and 4c respondents were asked what their attitude would be when it concerned a pregnancy affected with Edwards' or Patau's syndrome (appendix A). It should be noted that the answers on these follow-up questions might be influenced by the preceding questions. When respondents answered a question and clicked through, they could not go back to previous questions. The vignettes were part of a survey from Motivaction consisted of 20-23 questions about several other topics including cheese, internet domains and elevators.

Statistical analysis

Differences in demographic characteristics were tested between groups for each vignette pair: independent sample t-tests were used to test mean age differences and the Chi-square statistic was used to test differences with respect to the remaining variables. We tested for each vignette the possible impact of sex, education and income on mean agreement, with a one way ANOVA and correlation between age and agreement. To investigate differences in agreement between groups within each pair of vignettes, independent sample t-tests were conducted. Differences in agreement within groups, between questions a and c, were tested with paired sample t-tests.

We were specifically interested in 'disagreement' with the choice presented in the vignette because when people disagree with each other, particularly when a majority holds a different attitude, this might affect the individual's attitude, not because of a change in this person's own values but because of the values of others.(15) To compare the group who disagreed with those who did not agree or disagree and those who agreed, in a second step we transformed the 7-point Likert scale into three distinctive subcategories: "Disagree" (1-3), "Do not disagree/do not agree" (4), and "Agree" (5-7), to see how many people agreed, did not disagree/did not agree and disagreed with the decisions.

For comparing the between sample difference in proportions choosing the 'Disagree' subcategory we used the 2-sample z-test available in Epitools at http://epitools.ausvet.com.au. Data were analysed with IBM SPSS Statistics 25. The effect size for between and within groups mean differences, was expressed as Cohen's d for respectively independent and paired means(21) and interpreted according to Cohen's

standard rules of thumb: 0.20 = "small", 0.50 "medium", 0.80 = "large". The level of significance was defined as $p < 0.05$.

All free-response answers were exported from the data set. X and X coded the answers independently. Afterwards the codes and discrepancies were discussed until consensus was reach. Then the dataset was recoded which result in a list of 14 different explanations of participants concerning their attitudes towards NIPT or termination of pregnancy. The codes and therewith the different explanations were quantified in order to obtain numbers and percentages of how many participants expressed a certain attitude.

Results

Sample Characteristics

In total 1096 panel members participated in the study. The mean age of this group was 50.6 years, 49.4% was man and 50.6% woman (Table 1). This is representative for the Dutch population. No significant differences were found in demographic variables between the two groups of each pair of vignettes. Some demographic variables were significantly related to attitudes: in vignette 1 and 2 significantly more women agreed with the decision to decline NIPT than men. And in the vignettes 1c, 2a and 2c in the northern and eastern regions of the Netherlands respondents agreed significantly more with the decision to decline NIPT than in the western and southern regions. In vignette 3c people from the south agreed significantly more with termination for Edwards' or Patau's syndrome than people in the north.

The results provide insight firstly in differences in participants' attitudes towards declining a reimbursed or a non-reimbursed test and towards the decision to continue or terminate a pregnancy of a child with Down's syndrome. They furthermore reveal that respondents frequently mentioned four important explanations for their stated attitudes including freedom of choice, necessity of testing, valuing life, and quality of life.

Attitudes towards declining NIPT and the impact of reimbursement

Respondents' attitudes in vignette 1 and 2 revealed that the mean agreement with Hanna's choice to decline NIPT in vignette 1, in which NIPT was fully reimbursed, was significantly

lower than in vignette 2, where NIPT required an out of pocket co-payment of €175,- ($p = .006$, Table 2). In line with this finding, the subgroup percentages showed that significantly more people disagreed with declining a reimbursed NIPT ($p = .002$, Table 2). The first of the four most indicated explanations in the total sample for agreeing or being neutral (not agreeing and not disagreeing) was that this decision to decline is someone's personal choice (Appendix B, Table B1):

> "It is her decision, I should not have an opinion about that."

Furthermore, most of the respondents who disagreed with the decision to decline a fully reimbursed as well as a non-reimbursed NIPT did so because they thought that availability of a test offers courses of action, creates a responsibility to test, or costs society too much money (Appendix B, Table B1):

> "It is not necessary anymore to bring a handicapped child into the world. Firstly from a moral point of view, secondly because of the costs (healthcare is already unaffordable)."

The second of four most offered explanations for agreeing or being neutral was a perceived lack of necessity. Some respondents expected a low chance of having a disabled child or a low risk because of the younger age of Hanna – Hanna's age was not mentioned in the vignette, but people thought that she was young, because she was pregnant for the first time. They therefore thought that it was not necessary to test and consequently agreed with declining NIPT.

When both groups of respondents were confronted with the contrastive condition in question 1c and 2c no significant changes occurred within vignette 1, in which then NIPT cost €175,-. But within vignette 2, in which then the NIPT was fully reimbursed the mean of the Likert-scale answer in 2c was significantly lower than in 2a ($t(265) = 4.74$, $p < .001$, $d = 0.22$). As a result, the difference between vignette 1 and 2 was not significant ($p = .791$, Table 2). Apparently, when respondents first read about a NIPT costing €175,- and then about a reimbursed NIPT, they tended to agree less with declining a reimbursed test. A X2 test showed that there were no significant differences between vignette groups with respect to

different income groups (X2(9) = 2.98, p = .965) Most of those respondents indicated that availability creates a certain responsibility (Appendix B2, Table B1):

> "Then [when NIPT is reimbursed] it belongs to standard prenatal screening and there will be good reasons to offer it to every pregnant woman. A waste of opportunity to reject it."

Besides, fewer respondents agreed with declining a reimbursed NIPT than with declining a non-reimbursed NIPT because of a perceived lack of necessity of the test (2c: 12.8 % resp. 2a: 22.7%, Appendix B, table B1). This suggests that perception of necessity is influenced by reimbursement policy. It is noteworthy that fewer respondents disagreed with declining NIPT because 'testing provides courses of action' in 1c compared to 1a (10.4% resp. 31.3%, Appendix B, table B1) which also suggests that reimbursement policy affects respondents' attitudes:

> "When it costs money, I understand it better. Maybe Hanna cannot pay €175,-. That is a lot of money."

Exploratory additional analysis showed that the difference between "state-funding vs. non-reimbursement" was not significantly associated with income.

In sum, the most important explanation respondents gave for agreeing with or being neutral about declining NIPT is that it is someone's personal decision. Secondly, the perceived lack of necessity of testing was a frequently indicated reason to agree with declining NIPT. But reimbursement affected respondents' attitudes: when NIPT was fully reimbursed respondents were less likely to agree with declining NIPT.

Attitudes towards termination or continuation of pregnancy and the impact of severity

Respondents' agreement with the decision to terminate a pregnancy in case of Down's syndrome (vignette 3a) did not differ significantly from agreement with the decision to continue a pregnancy in case of Down's syndrome (vignette 4a), p = .080 (Table 3). Neither did the subgroup percentages show any difference in agreement. This suggests that the public does not prefer one course of action above the other: the decision to terminate or continue a pregnancy after a prenatal diagnosis of Down's syndrome would meet the same

public attitude. As with the previous pair of vignettes, respondents indicated that the decision to terminate or continue an affected pregnancy is someone's own choice to make. The most frequently indicated reason to disagree with termination was that someone has to accept life as it comes and should accept every child (Appendix B, Table B2). This was also the third of the top four explanations in general. Within this group most respondents thought that every child should be accepted because they were against abortion.

In the group that agreed with termination of the pregnancy or disagreed with continuation the most frequently indicated reason was that it is in the child's or parents' best interest to end the pregnancy, respectively 33.3% and 37.2%, which is the fourth most frequently indicated explanation in the total sample. Respondents thought that it takes too much from parents to raise a disabled child or that the child is awaiting a low quality of life, being always dependent on the parents and the community.

We further wanted to know in question 3c and 4c whether respondents' attitudes would change when the decision to terminate or continue concerns more severe disorders, i.e. Edwards' or Patau's syndrome. Most children with these aneuploidies are not viable. The severity of a disorder affected respondents' attitude: respondents were more likely to disagree with continuation of a pregnancy in case of trisomy 13 or 18, or agree more with termination of a pregnancy in case of such severe chromosomal aberrations ($p < .001$, Table 3).

The mean attitudes towards the decision to terminate or continue the pregnancy also changed significantly within both groups: respondents changed their mind in case of more severe disorders. Respondents in vignette 3 agreed more with termination of pregnancy in case of trisomy 13 or 18 compared to trisomy 21 ($t(303) = -5.04$, $p < .001$, $d = .15$). Likewise, in vignette 4, more people disagreed with continuation of pregnancy in case of trisomy 13 or 18 compared to trisomy 21 ($t(257) = 9.45$, $p < .001$, $d = .47$). Most respondents stated that a reason for them to agree with termination or disagree with continuation of pregnancy in case of trisomy 13 or 18 was that termination is in the best interest of the child, sometimes indicating that Edwards' or Patau's syndrome is more severe:

> "A child with Down's syndrome can still be happy but with this handicap you cannot. There is no life expectancy [for children with Edwards' or Patau's syndrome]."

In sum, the detected attitudes towards the decision to decline NIPT and the decision to terminate or continue an affected pregnancy revealed not one but at least four major societal attitudes towards NIPT: "It is someone's own choice", "It is not necessary to test", "One must accept every child" and "Testing is in the best interest of parents and child". Besides, 13.1% gave no explanation and 13.8% gave somewhat generic or just personal explanations, like 'I would make the same decision', 'I would never have a handicapped child', and 'I do not have enough information about Hanna's personal situation', which were classified as 'other'.

Discussion

This contrastive vignettes study provided valuable insights into public attitudes in the Netherlands towards the decision of a pregnant fellow citizen to decline NIPT and towards termination or continuation of pregnancy. Also, it sheds light on the impact of reimbursement policies and of the severity of disorders included in NIPT on these attitudes. The most remarkable finding was that a majority of the respondents either agreed with or did not have an outspoken opinion about the decision of a pregnant woman to decline either a fully state-funded NIPT or a NIPT requiring a co-payment of €175,- because these decisions are considered to be personal in nature. This suggests that Dutch citizens acknowledge the importance of free choice, and that society leaves room for personal decision-making concerning prenatal screening, which is a prerequisite for autonomous reproductive choices. The results of this study may help to rebut the ethical concern that NIPT leads women to be pressured into accepting the prenatal screening offer. Furthermore many respondents did not have a dominant preference for either termination or continuation of pregnancy in case of a diagnosis of Down's syndrome – which also supports this. Moreover, respondents' explanations revealed some degree of diversity in public attitudes towards NIPT and termination of pregnancy. The existence of a range of public attitudes – we have identified four major attitudes and many (minor) others – regarding NIPT theoretically provides pregnant women and couples with room to conceive personal attitudes.

This study also showed that funding policies affect public attitudes towards NIPT. Respondents agreed less with declining a fully funded NIPT and agreed more with declining a

NIPT for which a co-payment was required. This suggests that state funding of NIPT might influence public attitudes towards declining prenatal screening. Offering a fully reimbursed test seemed to provoke amongst a small group the idea that NIPT becomes an offer one cannot refuse, suggesting a legitimizing effect for accepting prenatal testing. This finding might fuel the fear which was previously indicated in the literature by pregnant women and parents of children with Down's syndrome namely for self-evident acceptance of NIPT among pregnant women, and societal moral judgements on those who decline screening.(5, 6, 10) But whether pregnant women will be influenced by a funding policy and the possible related public attitudes should be asked to women themselves. In one interview study women suggested that state-funding might carry the message that prenatal screening is standard practice but this is still hypothetical, further study of women's personal decision-making is necessary.(18) On the other hand, requiring a co-payment might contribute to the misunderstanding that reimbursed tests are important and non-reimbursed tests are unnecessary or not applicable to certain (younger) women. Further research should address the influence of funding policies on public attitudes and societal pressure to test.

Attitudes towards termination or continuation of a pregnancy in case of Down's syndrome or Edwards' or Patau's syndrome seemed to be shaped in first instance by attitudes towards abortion. Secondly, they were shaped by how respondents perceived living with these syndromes. This study's findings about the impact of the severity of the disorder and its expected burden for children and their parents are relevant in light of recent discussions on the technical possibilities for expanding the scope of NIPT, allowing for the assessment of many more genetic disorders. Societal support for inclusion of more disorders in a prenatal screening program will vary with the severity of the disorders. This might be relevant when thinking about the possible expansion of the scope of prenatal screening.

Furthermore, the current study showed that a small subgroup within the Dutch population has a negative attitude towards declining NIPT or giving birth to a disabled child, pointing at parental responsibility or social costs. The finding that this is a small group might fend off existing fears of future societal pressure as expressed by pregnant women, professionals and parents of children with trisomy 21, 13 or 18.(5, 10, 22, 23) Nevertheless, since these attitudes exist, during counselling, professionals could investigate whether women experience pressure from societal attitudes and pay extra attention to women's free and

personal decision-making. The current study does not provide insight in the extent to which women recognize or feel influenced by these kinds of expressed attitudes. Whether these experiences are present amongst women should be asked to women themselves as already done in previous studies: In these studies women reported that they felt free to decide about prenatal screening independently.(8, 17, 24). But the question is whether women will always be aware of societal pressure if it exists. Therefore, the interaction between women's and public attitudes merits further scrutiny to understand the effects of societal pressure and ways to counter it.

The strengths of this study are the large representative sample population, the heterogeneity within groups and comparability between groups. However, demographic information on respondents' views on life or religious convictions was not asked. Religious convictions are known to influence attitudes towards prenatal screening and termination of pregnancy.(25) This might explain that in the current study, respondents from the eastern region agreed significantly more with the decision to decline NIPT, as the population in the eastern region of the Netherlands is more conservatively religious than in the western region. Previous research found a low uptake of the first-trimester combined test in this region.(25) Furthermore, we found that termination and continuation met the same public attitudes, but the distribution of those who agreed with termination actually differed between the vignettes: in vignette 3 more people were pro termination and in vignette 4 more people were pro continuation. In vignette 4a we used the phrase 'continuing the pregnancy and keeping the baby'. Possibly the word 'baby' made the vignette feel more personal to respondents and elicited moral intuitions about the life of the future child. For the formulation of the vignettes we had to deal with on the one hand the comparability of the vignettes and on the other hand natural language. Although 'continuation' and 'termination' are more neutral opposite terms, the phrase 'to continue the pregnancy' is not often used in Dutch natural language to describe a decision to 'keep the baby'. This dilemma shows that terminology in vignettes may be value-laden and steering. It is outside the scope of this paper, but it would be interesting to study if and how framing and terminology used by counsellors influence pregnant women's decision-making.

To conclude, this study showed that within a representative sample of Dutch citizens, personal choice is broadly acknowledged. Also, Dutch society appears to allow for a wide

range of attitudes regarding NIPT, which could help to nuance the concern that in the Netherlands, one moral attitude may become predominant and lead to societal pressure to take part in screening and to terminate pregnancies affected by chromosomal abnormalities. However, opinions are partly influenced by the funding policy and by the severity of the disorder. Thus, continued focus on personal decision-making in pre-test counselling and responsible screening-policy decisions will be required to serve reproductive autonomy. Also, further research in this area should help to maintain freedom of choice with regard to prenatal screening.

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Characteristics		Total		Vignet 1		Vignet 2		Vignet 3		Vignet 4	
		Mean	% (n)	Mean	% (n)	Mean	% (n)	Mean	% (n)	Mean	%(n)
Age		50.59 (15-70)	1096	51.04 (15-70)	268	50.06 (18-70)	266	50.72 (15-70)	306	50.51 (17-70)	258
Sex	Man		49.4 (541)		50.7 (136)		46.2 (123)		50.3 (153)		50.0 (129)
	Woman		50.6 (555)		49.3 (132)		53.8 (143)		49.7 (151)		50.0 (129)
Residence	3 biggest cities[3]		10.9 (119)		9.7 (26)		11.3 (30)		11.8 (36)		10.5 (27)
	West[4]		29.2 (320)		27.6 (74)		30.8 (82)		28.3 (86)		30.2 (78)
	North [5]		9.1 (100)		7.5 (20)		10.2 (27)		9.2 (28)		9.7 (25)
	East[6]		19.7 (216)		20.9 (56)		19.9 (53)		19.1 (58)		19.0 (49)
	South[7]		26.5 (290)		29.9 (80)		23.3 (62)		27.0 (82)		25.6 (66)
	Border towns[8]		4.7 (51)		4.5 (12)		4.5 (12)		4.6 (14)		5.0 (13)
Education [1]	High		28.8 (316)		26.1 (70)		32.0 (85)		28.6 (87)		28.7 (74)
	Middle		52.1 (571)		54.5 (146)		47.7 (127)		54.3 (165)		51.6 (133)
	Low		19.1 (209)		19.4 (52)		20.3 (54)		17.1 (52)		19.8 (51)
Income [2]	Below median		32.9 (361)		31.7 (85)		32.7 (87)		31.9 (97)		35.7 (92)
	Median		12.4 (136)		14.6 (39)		11.3 (30)		11.8 (36)		12.0 (31)
	Above median		29.7 (326)		29.9 (80)		30.5 (81)		30.9 (94)		27.5 (71)
	Unknown		24.9 (273)		23.9 (64)		25.6 (68)		25.3 (77)		24.8 (64)
How many children do you have	0		32.7 (358)		34.0 (91)		33.8 (90)		30.9 (94)		32.2 (83)
	1		12.4 (136)		13.8 (37)		10.2 (27)		12.8 (39)		12.8 (33)
	2		33.7 (369)		28.4 (76)		36.5 (97)		34.5 (105)		35.3 (91)
	3		13.3 (146)		14.9 (40)		12.4 (33)		14.1 (43)		11.6 (30)
	≥4		7,9 (87)		9.0 (24)		7.1 (19)		7.6 (23)		8.1 (21)

Table 2

[1] High: Master/ Bachelor, Middle: High school, (preparatory) secondary vocational education, Low: practice-oriented vocational education primary school, no education.

[2] Median income is €33 500. 00 - €39 999.00

[3] 3 bigger cities: Amsterdam. Rotterdam. Den Haag

[4] West: Utrecht. Noord-Holland. Zuid-Holland, excl. 3 bigger cities and border towns

[5] North: Groningen, Friesland, Drenthe

[6] East: Overijssel, Gelderland, Flevoland

[7] South: Zeeland, Noord-Brabant, Limburg

[8] Border towns: Diemen, Ouder-Amstel, Landsmeer, Amstelveen, Schiedam, Capelle aan den IJssel, Krimpen aan den IJssel, Nederlek, Ridderkerk,
Barendrecht, Albrandswaard, Leidschendam, Voorburg, Rijswijk, Wassenaar, Wateringen.

Table 2: Comparison of vignette 1 and vignette 2, reimbursed NIPT vs. co-paid NIPT

Vignette version	Agreement § M (SD), Mdn	Difference M1 vs M2, t (df)	Difference M1 vs M2 Effect size (d)	Agree % (*n*)	Do not disagree/ not agree % (*n*)	Disagree % (*n*)	Disagree % 1 vs 2
1a Declining a reimbursed test *n* = 268	4.35 (1.80), 4	*p* = 0.006, -2.75 (532)	*0.240*	44.8 (120)	24.3 (65)	31.0 (83)	3.1**
2a Declining a test which costs €175.- *n* = 266	4.77 (1.75), 5			53.0 (141)	27.4 (73)	19.5 (52)	
1c Declining a test which costs €175.- *n* = 268	4.41 (1.73), 4	*p* = 0.791, .27 (525.67)	0.022	46.3 (124)	28.7 (77)	25.0 (67)	0.8*
2c Declining a reimbursed test *n* = 266	4.37 (1.92), 4			47.0 (125)	24.8 (66)	28.2 (75)	

Note. § Measured on a 7-point Likert scale;

* p < .05, ** p < .01, *** p < .001;

Cohen's (1992): d = 0.20 small; 0.50 = medium; 0.80 = large.

Table 3: Comparison of vignette 3 and vignette 4, termination vs. continuation of pregnancy

Vignette version	Agreement § M (SD), Mdn	Difference M1 vs M2, t (df)	Difference M1 vs M2 Effect size (d)	Agree % (*n*)	Do not disagree/ not agree % (*n*)	Disagree % (*n*)	Disagree % 3 vs 4 z
3a Deciding to terminate the pregnancy of a child with Down's syndrome. *n* = 304	4.64 (1.817), 5	*p* = 0.080, -1.75 (560)	0.146	53.3 (163)	25.0 (76)	21.7 (66)	1.5*
4a Deciding to continue the pregnancy of a child with Down's syndrome *n* = 258	4.90 (1.752), 5			57.4 (149)	26.0 (67)	16.7 (43)	
3c Deciding to terminate the pregnancy of child with Edwards' or Patau's syndrome *n* = 304	4.90 (1.729), 6	*p* < .001, 5.58 (547.76)	0.472	54.9 (168)	29.9 (91)	15.1 (46)	3.7***
4c Deciding to continue the pregnancy of a child with Edwards' or Patau's syndrome *n* = 258	4.09 (1.703), 4			34.1 (89)+	38.0 (98)*	27.9 (72)	

Note. § Measured on a 7-point Likert scale;

* p < .05, ** p < .01, *** p < .001;

Cohen's (1992): d = 0.20 small; 0.50 = medium; 0.80 = large.

Appendices

Appendix A: Vignettes

Vignettes as presented to the respondents, including the introduction about non-invasive prenatal testing (NIPT) and Down's syndrome, Edwards' syndrome and Patau's syndrome.

Introduction

What is NIPT?

The non-invasive prenatal test (NIPT) is a screening test in the pregnancy. Since April 1st, 2017 NIPT is offered to all pregnant women within a study. Every pregnant woman has the choice to opt for this test. To conduct NIPT a blood sample is taken from the pregnant woman which is used to find out whether the unborn child has Down's syndrome (trisomy 21), Edwards' syndrome (trisomy 18) or Patau's syndrome (trisomy 13). In case of an abnormal test result there are strong indicators that the unborn child has Down's syndrome, Edwards' syndrome or Patau's syndrome. However, the test does not provide a 100% reliable test result. Therefore in case of an abnormal test result a chorionic villus sampling or an amniotic fluid test is necessary, to confirm the test result. **Reference:** **www.meerovernipt.nl**

What are Down's syndrome, Edwards' syndrome and Patau's syndrome?

Down's syndrome is a congenital anomaly. People with Down's syndrome have learning disabilities. Therefore a child with Down's syndrome may learn skills more slowly than their peers. These children often also have physical handicaps and health problems. The severity of these problems varies from one child to another. Also Edwards' syndrome and Patau's syndrome are congenital anomalies. Children with Edwards' syndrome and Patau's syndrome have a very fragile health and severe intellectual disability. Most children also will have a serious congenital heart defect. Besides, in many cases, other organs are also affected such as the kidneys (in case of Edwards' syndrome) and the brain (in case of Patau's syndrome). Most children with Edwards' or Patau's' syndrome die during the pregnancy or shortly after birth or in the first year. **Reference:** **www.rivm.nl**

What we would ask you

You are going to read a short story. After this story three questions will be asked. We would want to ask you to answer each question. When you have answered a question and go to the next question, you cannot go back to the previous question.

Vignette 1	**Vignette 2**
Hanna is expecting a baby for the first time and is 11 weeks pregnant. The midwife has told her that she can opt for NIPT, to find out whether her child has Down's syndrome, Edwards' syndrome or Patau's syndrome, and that this test is reimbursed. Hanna chooses to not have a NIPT.	Hanna is expecting a baby for the first time and is 11 weeks pregnant. The midwife has told her that she can opt for NIPT, to find out whether her child has Down's syndrome, Edwards' syndrome or Patau's syndrome, and that this test costs €175,-. Hanna chooses to not have a NIPT.
a. What is your opinion about Hanna's choice? I… r***eally disagree – disagree - disagree a little – do not disagree/do not agree - agree a little – agree - really agree***. b. Explain your answer.	a. What is your opinion about Hanna's choice? I… r***eally disagree – disagree - disagree a little – do not disagree/do not agree - agree a little – agree - really agree***. b. Explain your answer.
c. What would you think about Hanna's choice when she had to pay €175,- for the test? I… r***eally disagree – disagree - disagree a little – do not disagree/do not agree - agree a little – agree - really agree***. d. Explain your answer.	c. What would you think about Hanna's choice when she had to pay nothing for the test? I… r***eally disagree – disagree - disagree a little – do not disagree/do not agree - agree a little – agree - really agree***. d. Explain your answer.

Vignette 3	**Vignette 4**
Hanna is expecting a baby for the first time and is 11 weeks pregnant. She had a NIPT to find out whether her child has Down's syndrome, Edwards' syndrome or Patau's syndrome. From the test result it turns out that her child possibly has Down's syndrome. This result is confirmed with a chorionic villus sampling. Hanna and her partner choose to terminate the pregnancy.	Hanna is expecting a baby for the first time and is 11 weeks pregnant. She had a NIPT to find out whether her child has Down's syndrome, Edwards' syndrome or Patau's syndrome. From the test result it turns out that her child possibly has Down's syndrome. This result is confirmed with a chorionic villus sampling. Hanna and her partner choose to continue the pregnancy.
a. What is your opinion about Hanna's choice? I… r***eally disagree – disagree - disagree a little – do not disagree/do not agree - agree a little – agree - really agree***. b. Explain your answer.	a. What is your opinion about Hanna's choice? I… r***eally disagree – disagree - disagree a little – do not disagree/do not agree - agree a little – agree - really agree***. b. Explain your answer.
c. What would you think about Hanna's choice when it concerns Edwards' or Patau's syndrome? I… r***eally disagree – disagree - disagree a little – do not disagree/do not agree - agree a little – agree - really agree***. d. Explain your answer.	c. What would you think about Hanna's choice when it concerns Edwards' or Patau's syndrome? I… r***eally disagree – disagree - disagree a little – do not disagree/do not agree - agree a little – agree - really agree***. d. Explain your answer.

Appendix B: Supplementary tables vignettes study NIPT

Table B1: Respondents' explanations of question 1a, 2a, 1c and 2c

Vignette version		Availability of NIPT creates responsibility to test *% (n)*	Testing offers courses of action *% (n)*	It's someone's own choice *% (n)*	No explanation *% (n)*	A disabled child can also have valuable life *% (n)*	In child's or parents' interest *% (n)*	The test is too expensive *% (n)*	A disabled child is too expensive for the society *% (n)*	You must accept life as it comes *% (n)*	Others *% (n)*	It is unnecessary to test *% (n)*	It concerns a more severe abnormality *% (n)*	The choice does not depend on costs *% (n)*	The test have to be reimbursed *% (n)*
1a: Declining a reimbursed test (*n*= 268)	Agree 44.8% (120)	0	2.5 (3)	33.3 (40)	9.2 (11)	0	0.8 (1)	0	0	19.2 (23)	17.5 (21)	17.5 (21)	0	0	0
	Do not disagree/do not agree 24.3% (65)	0	0	63.1 (41)	26.2 (17)	0	1.5 (1)	0	0	1.5 (1)	7.7 (5)	0	0	0	0
	Disagree 31.0% (83)	16.9 (14)	31. 3 (26)	9.6 (8)	8.4 (7)	0	7.2 (6)	0	2.4 (2)	0	21.7 (18)	2.4 (2)	0	0	0
2a: Declining a test which cost €175.- (*n*= 266)	Agree 53.0% (141)	0.7 (1)	1.4 (2)	23.4 (33)	8.5 (12)	0	1.4 (2)	14.2 (20)	0	19.1 (27)	8.5 (12)	22.7 (32)	0	0	0
	Do not disagree/ do not agree 28.7% (73)	0	0	42.5 (31)	30.1 (22)	0	0	8.2 (6)	0	1.4 (1)	13.7 (10)	4.1 (3)	0	0	0
	Disagree 19.5% (52)	11.5 (6)	26.9 (14)	5.8 (3)	11.5 (6)	0	1.9 (1)	7.7 (4)	1.9 (1)	7.7 (4)	23.1 (12)	1.9 (1)	0	0	0
1c : Declining a test which costs €175.- (*n*= 268)	Agree 46.3% (124)	0	0.8 (1)	19.4 (24)	11.3 (14)	0	0	24.2 (30)	0	8.9 (11)	8.9 (11)	8.9 (11)	0	12.9 (16)	4.8 (6)
	Do not disagree/ do not agree 28.7% (77)	0	1.3 (1)	35.1 (27)	31.2 (24)	0	0	10.4 (8)	0	0	10.4 (8)	1.3 (1)	0	6.5 (5)	3.9 (3)
	Disagree 25.0% (67)	3.0 (2)	10.4 (7)	3.0 (2)	11.9 (8)	0	9.0 (6)	4.5 (3)	4.5 (3)	0	17.9 (12)	1.5 (1)	0	23.9 (16)	10.4 (7)
2c: Declining a reimbursed test (*n*= 266)	Agree 47.0% (125)	1.6 (2)	0.8(1)	25.6 (32)	12.0 (15)	0	1.6 (2)	2.4 (3)	0	20.8 (26)	9.6 (12)	12.8 (16)	0	12.0 (15)	0.8 (1)
	Do not disagree/ do not agree 24.8% (66)	1.5 (1)	0	43.9 (29)	36.4 (24)	0	0	1.5 (1)	0	0	9.1 (6)	1.5 (1)	0	6.1 (4)	0
	Disagree 28.2% (75)	20.0 (15)	16.0 (12)	5.3 (4)	12.0 (9)	0	4.0 (3)	4.0 (3)	2.7 (2)	4.0 (3)	16.0 (12)	0	0	13.3 (10)	2.7 (2)

Table B2: Respondents' explanations of question 3a, 4a, 3c and 4c

Vignette version		Availability of NIPT creates responsibility to test *% (n)*	Testing offers courses of action *% (n)*	It's someone's own choice *% (n)*	No explanation *% (n)*	A disabled child can also have valuable life *% (n)*	In child's or parents' interest *% (n)*	The test is too expensive *% (n)*	A disabled child is too expensive for the society *% (n)*	You must accept life as it comes *% (n)*	Others *% (n)*	It is unnecessary to test *% (n)*	It concerns a more severe abnormality *% (n)*	The choice does not depend on costs *% (n)*	The test have to be reimbursed *% (n)*
3a: Deciding to terminate the pregnancy (*n*= 304)	Agree 53.4% (162)	0.6 (1)	3.7 (6)	27.8 (45)	13.0 (21)	0	33.3 (54)	0	1.9 (3)	1.2 (2)	17.3 (28)	1.2 (2)	0	0	0
	Do not disagree/ do not agree 24.9% (76)	0	0	61.8% (47)	21.1 (16)	0	0	0	0	3.9 (3)	11.8 (9)	1.3 (1)	0	0	0
	Disagree 21.6 % (66)	0	0	1.5 (1)	3.0 (2)	16.7 (11)	0	0	0	65.2 (43)	12.1 (8)	1.5 (1)	0	0	0
4a: Deciding to continue the pregnancy (*n*= 259)	Agree 57.5% (149)	0	0.7 (1)	25.7 (38)	6.1 (9)	18.9 (28)	1.4 (2)	0	0	37.2 (55)	9.5 (14)	0.7 (1)	0	0	0
	Do not disagree/ do not agree 25.9% (67)	0	0	68.7 (46)	20.9 (14)	0	0	0	0	0	9.0 (6)	1.5 (1)	0	0	0
	Disagree 16.6% (43)	0	0	9.3 (4)	16.3 (7)	0	37.2 (16)	0	9.3 (4)	2.3 (1)	18.6 (8)	7.0 (3)	0	0	0
3c: Deciding to terminate the pregnancy in case of Edwards' or Patau's syndrome (*n*= 304)	Agree 55.1% (167)	1.2 (2)	2.4 (4)	18.6 (31)	13.2 (22)	0	37.1 (62)	0	1.8 (3)	0.6 (1)	16.8 (28)	1.2 (2)	7.2 (12)	0	0
	Do not disagree/ do not agree 29.8% (91)	0	0	44.0 (40)	39.6 (36)	0	1.1 (1)	0	0	3.3 (3)	12.1 (11)	0	0	0	0
	Disagree 15.1% (46)	0	0	0	19.6 (9)	0	6.5 (3)	0	0	63.0 (29)	10.9 (5)	0	0	0	0
4c: Deciding to continue the pregnancy in case of Edwards' or Patau's syndrome (*n*= 259)	Agree 34.4% (89)	0	3.4 (4)	31.8 (28)	12.5 (11)	0	1.1 (1)	0	0	34.1 (30)	11.4 (10)	1.1 (1)	4.5 (4)	0	0
	Do not disagree/ do not agree 37.8% (98)	0	0	42.9 (42)	35.7 (35)	0	3.1 (3)	0	0	1.0 (1)	17.3 (17)	0	0	0	0
	Disagree 27.8% (72)	0	1.4 (1)	2.8 (2)	11.1 (8)	0	55.6 (40)	0	4.2 (3)	1.4 (1)	12.5 (9)	1.4 (1)	9.7 (7)	0	0

Chapter 8|

Should pregnant women be charged for non-invasive prenatal screening? Implications for reproductive autonomy and equal access

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Abstract

The introduction of non-invasive prenatal testing (NIPT) in health care systems around the world offers an opportunity to reconsider funding policies for prenatal screening. In some countries with universal access health care systems, pregnant women and their partners are asked to (co-)pay for NIPT. In this paper, we discuss two important rationales for charging women for NIPT: 1) to prevent increased uptake of NIPT, and 2) to promote informed choice. Firstly, given the aim of prenatal screening (reproductive autonomy), high or low uptake rates are not intrinsically desirable or undesirable. Using funding policies to *negatively* affect uptake, however, is at odds with the aim of screening. Furthermore, co-payment disproportionally affects those of lower socio-economic status, which conflicts with justice requirements and impedes equal access to prenatal screening. Secondly, we argue that although payment models may influence pregnant women's choice behaviours and perceptions of the relevance of NIPT, the co-payment requirement does not necessarily lead to better-informed choices. On the contrary, external (i.e. financial) influences on women's personal choices for or against prenatal screening should ideally be avoided. To improve informed decision-making, health care systems should instead invest in adequate non-directive, value-focused pre-test counselling. This paper concludes that requiring (substantial) co-payments for NIPT in universal access health care systems fails to promote reproductive autonomy and is unfair.

Introduction

A new first-trimester prenatal screening test commonly referred to as non-invasive prenatal testing (NIPT) is in the process of being implemented in countries around the world. With NIPT, chromosomal abnormalities can be detected in cell-free DNA circulating in maternal blood, giving pregnant women the opportunity to consider reproductive options – either prepare for the birth of a child with a disability or terminate the pregnancy. In some countries, including the United Kingdom, France, Canada and the Netherlands, NIPT is available in implementation research settings.(1, 2) In the United States of America, Israel and Australia, NIPT is available primarily through commercial providers.(3) In other countries, such as Belgium, Denmark and Singapore, it is either already part of routine antenatal care (4) or offered through publicly funded screening programs.(5) NIPT is procedurally safe and simple, and its test performance for trisomy 21 (Down syndrome), 18 (Edwards syndrome) and 13 (Patau syndrome) is better than that of the conventional combined test based on nuchal translucency ultrasound, blood tests and maternal age. Even in low-risk pregnancies, NIPT is characterized by high sensitivity and specificity.(6) It requires only a blood draw from the pregnant woman at 9-11 weeks of gestation. NIPT is not a diagnostic test; as cell-free DNA is derived not from the foetus but from the placenta, an abnormal NIPT result requires confirmation through invasive follow-up diagnostic testing (i.e. chorionic villus sampling or amniocentesis). Because of its better test performance for trisomies 21, 18 and 13, however, NIPT requires fewer invasive follow-up tests than does the combined test, and thus leads to fewer iatrogenic miscarriages.

First-trimester prenatal screening has traditionally been offered free of charge in many countries. A survey conducted in 2015 across 28 countries around the world shows that conventional first-trimester screening was generally covered in full or in part by public health programs, with the exception of Argentina, Ireland, India, the Netherlands, Mexico, Qatar and the United States.(4) Funding policies for screening are likely to affect its uptake; in countries where first-trimester prenatal screening is fully publicly funded, the uptake is usually high, such as in Denmark (90%) and Belgium (80%) (7), whereas in countries like the Netherlands, where women paid out of pocket for the combined test, the uptake has traditionally been lower, at around 30%.(8) NIPT costs approximately 400 US dollars (9) and insurance coverage for NIPT is variable.(3) In a recent study, US obstetricians indicated that

the cost of NIPT is currently hampering its utilization.(10) Health care professionals in Canada, too, observe that financial cost is "an important barrier" to accessing NIPT. (11)

The introduction of NIPT raises ethical quandaries. Notably, there are discussions with regard to the appropriate scope of NIPT.(12-14) Dutch laboratories are licensed to screen for trisomies 13, 18 and 21 only, although pregnant women can choose to have incidental findings reported as well. These findings pertain mostly to other chromosomal abnormalities, which may be rarer, but can be equally or more severe, and of sufficiently understood clinical significance. In some countries, the scope of NIPT has expanded to include sex-chromosomal abnormalities and microdeletion syndromes. In this paper, when we write about NIPT, we consider the use of NIPT primarily as a first-tier ('universal') or second-tier ('contingent') screening test for trisomies 13, 18 and 21. The argument may be extended to other chromosomal abnormalities that are "markedly severe"(15), or "serious congenital conditions and childhood disorders".(13) We do not consider the use of NIPT for the detection of other medical or non-medical conditions (including sex determination), for which there has thus far been less public support.(16) Also, we proceed from the notion that prenatal screening programs are acceptable, and that allowing women to terminate a pregnancy in case of a serious foetal health condition, is acceptable.

The ongoing introduction of NIPT around the world requires a reconsideration of funding policies for first-trimester prenatal screening. Should pregnant women and their partners be charged for NIPT, and on what grounds? There are practical as well as principled reasons to charge women for NIPT. In resource-constrained settings, societies may not have sufficient funds to offer NIPT free of charge. Universal NIPT is both more effective than the first-trimester combined test in detecting trisomies and more costly.(17) In most 'cost-effectiveness' studies, however, the costs of the care and support required for children with chromosomal abnormalities are not taken into account. Furthermore, although the costs of NIPT may currently be among the main reasons for states to charge women, these costs will likely decrease in the future as the technology develops.

This paper, therefore, focuses on principled reasons for charging – assuming that the practical reasons for doing so (i.e. lack of resources, organizational challenges) need not be decisive. We critically discuss two principled rationales for asking pregnant women and their partners to (co-)pay for NIPT: to prevent increased uptake of screening and to improve

informed decision-making. First, a financial contribution can function as a hurdle, making prenatal screening more difficult to obtain, and discouraging women from taking part. Some of those who oppose widespread uptake of prenatal screening and/or abortion may not only wish to refrain from screening themselves, but may also prefer others to forego screening. Asking a significant sum may help in maintaining or decreasing the number of women who participate in screening. A second moral justification for charging women is to promote informed and well-considered choices for or against the prenatal screening offer. Charging is believed to help women understand that first-trimester screening is not part of routine antenatal care, but something different. Co-payment is believed to help create 'choice awareness' and to ensure well-considered participation in screening. Both rationales merit further scrutiny, as it is not self-evident that charging for NIPT is justifiable from a justice perspective or contributes to well-considered choices.

Rationale 1: Charging women to prevent increased uptake of screening

One reason for charging pregnant women for NIPT is to prevent an increase in uptake of prenatal screening, and thus to prevent an increase in the number of abortions. Although commentators do not usually explicitly mention this rationale, it follows from the reverse concern that public funding of NIPT may encourage women to take part in prenatal screening. If the state offers prenatal screening free of charge, it gives the impression that it condones screening as a form of routine care among other antenatal care services. An *offer* of NIPT would lead to a higher uptake of screening, and – following this rationale – a higher uptake is perceived to be problematic.

With the start of the NIPT implementation study in April 2017, for instance, it was feared that pregnant women would 'rush' to Dutch academic medical centres to obtain NIPT.(18) The notion that all Dutch women would engage in screening was seen as intrinsically undesirable. Pregnant women and mothers of children with Down syndrome were concerned that abortion rates would rise, and that Down syndrome might disappear from society.(19-21)

This is not likely. In the Netherlands, the majority of women decline first-trimester screening altogether, even today, now NIPT is widely available. Moreover, not all prenatal screening results in abortion. In the period 2000-2013, around 85% of pregnancies with a confirmed

diagnosis of Down syndrome resulted in termination, (22) which means that a substantial minority chose to continue the pregnancy. Certain groups in Dutch society hold a relatively high acceptance and positive image of Down syndrome; some Dutch women do not consider Down syndrome 'severe enough to justify termination of pregnancy'.(23) The number is consistent with termination rates found in other countries, such as the US (24), the UK (25), and other European countries (26), but lower than the rates reported elsewhere, such as 93% in Australia (27) and 98% in Denmark.(28) Overall, the prevalence of Down syndrome has been relatively stable around the world since the early 1990s.(29) This is not likely to change with the introduction of NIPT, as in countries like the UK and the Netherlands, some women continue to opt for first-trimester prenatal screening 'for information only' (1), and refrain from abortion. A recent review of studies from the US, Asia and Europe suggested that termination rates following the introduction of NIPT were unchanged or even decreased.(30)

Even if Down syndrome would disappear from society, this may be considered a loss in terms of social diversity, but it may not be a soluble problem or a moral wrong as long as terminations resulted from pregnant women's autonomous decisions. A related – and possibly valid – concern is that if fewer children are born with Down syndrome, the acceptation of persons with Down syndrome and the quality of their medical care and support might decrease(20, 21) and discrimination and stigmatization of affected persons and families might increase. Pregnant women and their partners may indeed feel less free to carry an affected pregnancy to term if good-quality medical care and support were not available for disabled children. Reproductive autonomy, the stated aim of first-trimester prenatal screening (12), presupposes that disabled children receive the support they need. Therefore, the existence of "decent, fair, inclusive and supportive policies with regard to the abilities and conditions of all people"(15) is a precondition for a responsible prenatal screening program.

Charging money can be thought of as a political compromise to those who oppose widespread use of prenatal screening and/or abortion and believe that first-trimester screening may (need to) be available to women who actively and purposively request it, but should not be *too readily* available. (Co-)payment thus serves as a barrier to access, aimed at *discouraging* women from taking part. However, this is not consistent with the aim of

prenatal screening. Women should not be withheld from screening, just as those who oppose screening should not be put under pressure to take part. In Dutch counselling practices, women are presented with an 'information offer' about screening first, which they are free to refuse, to safeguard their 'right not to know'. Also, the ethical requirement of non-directiveness in counselling is meant to safeguard the voluntariness of participation. Such measures should be in place in screening programs around the world to avoid any pressure on women to participate in screening just because it is 'the norm'.(31)

In countries where screening and/or abortion are morally controversial, so it is argued, it is not obvious that society should bear the costs.(32) Other health care priorities may be more important than sustaining screening programs aimed at promoting reproductive "liberty and autonomy".(15) In response, we would like to stress that prenatal screening does not aim at promoting unrestricted reproductive liberty and autonomy, but at offering information about severe health conditions in the foetus that could be a reason for pregnant women to consider terminating the pregnancy, so as to prevent the birth of an affected child. Children born with trisomy 13 or 18 are severely ill, and most children die before birth or within days, weeks or months after birth. There is less consensus on Down syndrome as a justified reason to terminate an affected pregnancy; some children born with trisomy 21 may lead relatively contented lives, while others develop severe cognitive delays and somatic conditions. A life with Down syndrome, "even if it does not involve major medical problems, is fraught with intellectual disabilities and (…) it is, in most cases, a life that is shorter than other human lives."(33) Some prospective parents may wish to prevent this in their families. Empirically, there is broad societal support for public funding of NIPT for trisomies. A Canadian study found that the majority of women (66,9%) thought that all pregnant women should have access to NIPT free of charge.(11) Also women in Australia (93% of respondents) have been found to support public funding of NIPT.(34)

Finally, by putting up a barrier that is higher for less affluent women than for more affluent women, the (co-)payment requirement raises intractable justice concerns and hinders equity of access to first-trimester prenatal screening. Charging for NIPT affects disproportionally those who are least well off financially, which challenges the principle of equal access to first-trimester prenatal screening. The (co-)payment requirement may in part explain the especially low uptake among groups of lower socio-economic status and minority ethnic

groups vis-à-vis groups of higher socio-economic status, which have been found to be unrelated to attitudes towards screening.(35) Rather, socio-economically disadvantaged women are less likely to act upon their (positive) attitudes towards screening than socio-economically advantaged women when confronted with financial and physical barriers, such as requiring extra visits to the midwifery clinic. Women from minority ethnic groups may also be less aware of Down syndrome (36), and other chromosomal abnormalities. Putting up a financial barrier may exacerbate these differences in uptake (37), and therewith, it may exacerbate choice disparities among groups of higher and lower socio-economic status. Offering NIPT free of charge is likely to reduce these disparities. Alternatively, differentiated funding policies could be considered, in which women who can afford (co-)paying for NIPT would be asked to do so, while those who cannot would be offered NIPT free of charge, or would be partly reimbursed afterwards. Although other ways to promote equal access to prenatal screening can thus be imagined, practical and logistical issues are likely to limit the feasibility of, for instance, differentiated pricing schemes.

Finally, in countries such as the Netherlands, where all pregnant women are offered a free ultrasound scan for structural anomalies at 20 weeks of gestation, charging for NIPT seems strikingly inconsistent. Despite morally relevant differences between the two screening tests (notably, although the 20-week ultrasound is aimed primarily at reproductive autonomy, it also aims to improve maternal health and pregnancy outcomes), we find it remarkable that NIPT tends to elicit ethical discussions, whereas the 20-week ultrasound does not.

In sum, funding policies should support prenatal screening programmes in achieving their aim of promoting reproductive autonomy. They should not be used to negatively affect uptake rates.

Rationale 2: Charging women to improve informed decision-making

A second argument brought forward in public discussions for charging money for NIPT is that it will improve decision-making.(38) A financial contribution to NIPT is thought to have the benefit of signalling to pregnant women and their partners that screening is optional: screening is an offer that may have far-reaching implications that should be considered beforehand.(39) Because NIPT requires only a simple blood draw, just like other routine screening tests offered during the pregnancy, such tests for HIV, hepatitis B, syphilis, blood

type, Rhesus factor or antibodies, observers are concerned that women will thoughtlessly accept NIPT.(12) Also, they may feel less justified in forsaking screening, as NIPT "removes the risk to pregnancy as a reason for declining testing" (40), and may experience societal pressure to take part in screening. Meeting the aim of reproductive autonomy is generally considered to require 'informed choice' for or against a screening offer. Participation in screening should be the result of such adequately informed, voluntary and value-consistent decisions (41), not of passive acceptance or acquiescence to societal pressure.

It is feared that because of the non-invasive character of NIPT, health professionals may treat the informed choice process differently – less stringently – than they would in the context of invasive testing, requiring less time to consider, or not asking for written informed consent.(42) NIPT would be presented by counsellors as a routine procedure and would consequently be perceived as such by pregnant women and their partners; a concern referred to as 'routinisation'.(43) If women may not appreciate the significance of the test, it would "become more difficult to achieve the aim of enabling autonomous reproductive choices."(12) In sum, in the absence of accepted reasons *not* to take part in first-trimester prenatal screening, such as safety or financial considerations, pregnant women may consider less thoroughly whether or not to take part. Also, state funding is believed to send a 'legitimizing' message about the importance of NIPT, implying that the government encourages screening (38), making pregnant women more likely to participate without deliberation.

Putting up a (small) barrier by charging women, on the other hand, so it is argued, may help reinstall well-considered decision-making.(39) If women must pay 175 euro, the fee required in the Netherlands, or the small sum of 8,68 euro, the fee required in Belgium, for NIPT, they will deliberate the benefits, risks and implications of screening. Especially in countries like the Netherlands, where all 'medically necessary' health care services are offered free of charge, including the 20-week ultrasound scan, the co-payment requirement may signal to women that NIPT is a different test, and help them understand that NIPT "is an *offer* that can be declined."(44) At the same time, however, it may signal that first-trimester screening is less relevant and lead women to (mistakenly) believe that screening is "not necessary"(23) because of an assumed low risk of foetal abnormalities.

Thus, reimbursement policies are not neutral and may influence women's choice behaviours. But is charging a substantial or a 'symbolic' sum an effective way to promote informed choices? Does it not have adverse moral implications? Are there no subsidiary and better ways to prompt women to make informed choices?

Although many women are willing to co-pay for NIPT (45), for some women, the costs of first-trimester screening withhold them from taking part.(23, 46) Personally incurred costs significantly influence pregnant women's choices whether or not to undergo screening. (47, 48) For a majority of Canadian women (66.4%), costs have 'a lot of impact' (5 on the 1-5 scale) on their decision use screening.(11)When a prenatal screening offer is declined on the basis of financial constraints, in fact quite the opposite from the ideal of informed choice is being realized: women are not choosing for or against NIPT based on their values, but because of financial constraints.

To illustrate the caveat, imagine that an opposite policy would be proposed: women who do *not* take part in prenatal screening are asked to pay a fee of 175 euro. Policy makers would claim that this fee was introduced to prompt women to more thoroughly consider their decision. The fee, however, will likely be perceived by pregnant women as a discouragement or a punishment for the decision not to take part. This policy would signal that participation in screening is the preferred option and may limit women's freedom to decline screening, thus failing to promote informed choice. Strictly speaking, if a fee is considered instrumental in promoting informed choice, it should apply to both options (screening and not screening). For if reproductive autonomy is the justified aim of prenatal screening programs, both options should be considered equally valuable and equally acceptable. A fee should be asked for both options or none.

In sum, it is unclear how funding policies best serve reproductive autonomy. We have seen that there is no reason to assume that either a financial barrier or a fully reimbursed test will promote informed choice. To help women make choices regarding screening that are well-informed, voluntary and consistent with their values, other solutions must be sought.

To make informed choices, women need time to become informed about screening, to talk to health care professionals and others, to imagine futures with children with disabilities, and to deliberate their options. Repeat discussions with health care professionals, over time, may be preferable to "only one point of contact."(3) Another requirement may be good

information about the implications of screening, offered individually and/or collectively, and through multiple modalities, including written information material and audio-visual material, and – if requested – balanced narratives from parents of children with disabilities to illustrate the range of experiences of living with and caring for children with disabilities.(49) Further, women may need to be assisted in explicating their values and in making decisions in accordance with these values. In the Netherlands, obstetricians and midwives are specifically trained to focus on *deliberation* in pre-test counselling. Counsellors are expected to conduct 30-minute dedicated face-to-face discussions with pregnant women to facilitate informed choice for or against the NIPT offer.(50)

To help increase choice awareness regarding first-trimester prenatal screening, pre-test counselling may therefore need to focus on conveying key information about the aim and utility of prenatal screening, and foremost on the question whether women and their partners wish to start on the trajectory of reproductive decision-making (at all). The decision (not) to take part in screening should be based on women's values, not on their financial resources – although pregnant couples may reasonably ask themselves whether they have the social, practical and financial means to care for a child with a disability. Health professionals should discuss with pregnant women and their partners the reasons why they would wish to use screening, and what they would do in case of abnormalities.(50) Not making people pay, but offering adequate pre-test counselling should thus be (part of) a solution to safeguard informed choice. The offering of value-based pre-test counselling will likely be more effective in promoting reproductive autonomy than the asking of a co-payment for NIPT.

Conclusion

We have argued that the (co-)payment requirement for NIPT is not a necessary nor a subsidiary approach to the promotion of informed choice among pregnant women and their partners, and does not serve reproductive autonomy. While informed choice remains of paramount importance in all prenatal screening programs, there are no indications that charging women for NIPT will prove effective in accomplishing this. In fact, it may lead to the opposite of reproductive autonomy, when women forego screening not based on well-considered choice, but simply because of financial constraints. Although reimbursement

policies will likely affect pregnant women's and their partners' choice behaviour, neither full reimbursement nor the asking of a co-payment is fully neutral, and neither will in and of itself improve informed choice. Rather, informed choice should be accomplished through adequate information provision and value-based pre-test counselling focused on the promotion of choice awareness and deliberation.

Funding policies should not be used to prevent increased uptake of first-trimester prenatal screening. Financial barriers will disproportionately affect those of lower socio-economic status, which is not in line with general justice requirements nor with the aim of prenatal screening. Instead, full reimbursement of NIPT for trisomies 13, 18 and 21 – and in future, possibly for other serious childhood disorders – will help to guarantee equal access to prenatal screening and reproductive options.

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Chapter 9|

General discussion

In both the scientific and social debate about the implementation of non-invasive prenatal testing (NIPT), scientists, health professionals, pregnant women, parents of children with Down's syndrome and the general public extensively discuss the pros and cons of this relatively new and promising prenatal screening test for Down's, Edwards' and Patau's syndrome. Both debates address the ethical and social aspects of implementing NIPT in a national prenatal screening programme, including the possible negative consequences of NIPT for individuals and society. These negative consequences include the negative effects of NIPT on informed choice, routinization of prenatal screening, societal pressure to test and reimbursement of prenatal screening. These concerns are often referred to by those who have reservations regarding the implementation of NIPT and are used as arguments in both debates. However, empirical or ethical support for them is limited. In this thesis these arguments are analysed and provided with supporting or refuting ethical and empirical argumentation. The aim of these analyses is to advance and nuance the scientific and social debate about prenatal screening, especially about NIPT and the expansion of its scope: in the future, whole genome sequencing technologies may be used to screen the foetus for conditions other than trisomies 21, 18 and 13, based on NIPT.

Main findings of this thesis

Reconsidering pre-test counselling

Firstly it is argued in several analyses of the ethical and social aspects of introducing NIPT that its procedural easiness and strong validity might lead to routine acceptance of NIPT: compared to the first trimester combined test which combines a blood test and an ultrasound to provide a risk estimate NIPT provides a more clear and easy understandable test result. Women might therefore accept NIPT routinely without making an informed choice, or professionals might present NIPT as a routine test.(1-3) An uninformed decision about prenatal screening is seen as problematic for reaching the aim of prenatal screening which is formulated as promoting reproductive autonomy. Pre-test counselling is the preferred instrument to reach informed decision-making and therewith reproductive autonomy and to counter these negative consequences of NIPT. But several studies suggested that the introduction of NIPT might pose challenges for pre-test counselling as counsellors sometimes had difficulties with having or taking enough time to for pre-test counselling (4), underestimated the importance of pre-test counselling about NIPT

compared to invasive tests(5) or framed information when discussing different test options.(6) Furthermore, professionals, women and parents of children with Down's syndrome interviewed for this thesis (chapter 2, 3 and 4) indicated that informed consent should be improved for the implementation of NIPT.(7-9) Interviewed professionals in the 'framework study' (chapter 2) for example questioned the focus on information provision in pre-test counselling and suggested that the focus of pre-test counselling should shift to deliberation on personal values. Besides, the current focus on objective or 'value-free' information provision in pre-test counselling (10-12) might complicate counselling especially in the context of the expansion of the scope of prenatal screening. The next generation sequencing technologies and related possible test outcomes are increasingly complex and women might feel overwhelmed and unable to understand the relevant information necessary for the decision. In that case, an expansion of the scope might hinder the aim of prenatal screening because information overload impedes rather than fosters informed decision-making and autonomous reproductive choices.(13) To be able to deal with these current and future aspects of prenatal screening we proposed a three step counselling model the priory of which is exploring women's personal values towards prenatal screening and related follow-up, including termination of pregnancy or caring for a child with a disability (chapter 5). In the first step of the counselling counsellors will explore women's values and discuss them in order to enable women to make their values explicit and find out what is important to them. Medical technical information provided in the second step might support these considerations or maybe change it. In this second step women could weigh the information in the context of their values. With this counselling model women would be supported to provide informed consent for prenatal screening, also in case of an expanded scope.

An analysis of routinisation

A second argument introduced in the debate about possible consequences of NIPT is that this test might induce *routinisation* of prenatal screening. In chapter 6 we showed that this concept has several meanings when used in the context of prenatal screening, which consequently makes it unclear to what kind of problems the concept refers and how these can be counteracted.(14) Three versions of the concept were distinguished which comprise several inter-related fears or negative consequences of NIPT: 1) a reduced informed choice,

2) a lack of freedom to choose and 3) negative consequences for people with a disability. We found that empirical studies limitedly support the first version because in general women did make informed choices and experienced freedom to choose not to accept prenatal screening, although the found percentages leave room for improvement. We also argued that to guarantee freedom of choice, actions should be taken to continue to evaluate (societal) pressure to test amongst pregnant women, and when it arises, to counteract it. Furthermore, we argued that when using the concept of routinisation it is necessary to specify to which kind of consequence it refers in order to devise strategies to counteract this consequence.

Studying public attitudes with contrastive vignettes

A third argument is that the test characteristics of NIPT could lead to societal pressure to accept prenatal testing: prospective parents might have the feeling that they cannot decline prenatal testing anymore, because its easiness and reliability compared to the first trimester combined test take away good reasons for declining it.(14) Furthermore, in contrast to invasive diagnostic tests (chorionic villus sampling and amniocentesis) NIPT holds no risks of miscarriage. This might contribute to positive public attitudes towards NIPT, which, it is feared, could lead to societal pressure to accept prenatal screening. But little is known about what the public attitudes towards prenatal screening are. It is furthermore difficult to study attitudes of the public without eliciting socially desirable responses. Therefore, to study public attitudes towards prenatal screening and termination of pregnancy, we made use of the contrastive vignette method which is designed to prevent socially desirable responses from participants (chapter 7). This vignette study revealed that a majority of participants thought that a decision about prenatal screening is a personal one that should not warrant judgment by other people. This result could help to reduce existing fears that current public attitudes lead to social pressure. Furthermore, this finding is, I think, strong result because the question we asked participants, about what they think about the decision of another person, precisely provokes a normative judgment about someone's decision. Therefore, this finding reflects a normative public attitude towards how someone should relate to these personal decisions.

Reimbursement of prenatal screening does not promote informed choice

The fourth argument in the debate about NIPT concerns co-payment of prenatal screening. It

is argued or assumed by amongst others healthcare professionals (7), pregnant women (8) and parents of children with Down's syndrome (9) that asking a co-payment could make women aware of the importance of the decision and improve informed decision-making. However, as shown in the ethical analysis in chapter 8 this assumption lacks ethical support: given the aim of prenatal screening (promoting reproductive autonomy) we argue that although payment models may influence pregnant women's choice behaviours and perceptions of the relevance of NIPT, the co-payment requirement does not necessarily lead to better informed choices and thus does not promote the aim of prenatal screening (Chapter 8).(15)

Reflection on the framework of prenatal screening and the expansion of the scope

Based on existing reports and statements about the ethical and social aspects of prenatal screening a framework was distilled consisting of four pillars: 1) the aim of prenatal screening for congenital disorders, 2) the proportionality of the test, 3) justice and 4) social aspects (chapter 2).(7) The main findings in this thesis provide specification or reconsideration of these pillars in the ethical framework of prenatal screening, especially in the context of the possibility to expand its scope.

1. The aim of prenatal screening for congenital disorders

Firstly the aim of prenatal screening, the first pillar of the framework, is formulated as offering reproductive choices or promoting reproductive autonomy.(13) In the practice of prenatal screening this aim should be reached by enabling parents to make an informed decision. The fear related to the expansion of the scope of prenatal screening is that an increase in the number of disorders included in the test affects informed decision-making.(13) An information-overload might make it difficult for women to make an informed choice, particularly when the focus of pre-test counselling is the provision of objective or 'value-neutral' information.(11) But, when the aim of pre-test counselling primarily is to elicit pregnant women's values and norms towards prenatal screening and its follow-up, as proposed and argued in chapter 5, the amount of technical and medical information might have less impact on decision-making. This approach of pre-test counselling and obtaining informed consent complements the first pillar of the framework and contributes to the promotion of reproductive autonomy. It provides direction in how this aim still can be reached when the scope of prenatal will expand and might counter the objection of

information-overload when more disorders will be included in the test. In sum, within the first pillar we specified that the aim of reproductive autonomy is not reached primarily by providing objective information during pre-test counselling but by exploring women's values.

Furthermore, in practice the process of informed decision-making may start before pre-test counselling. Women gather information on the internet and in their social environment. Some women already made a decision concerning prenatal screening before they visited the midwife.(8) The impact of the news media and social media on this decision should not be underestimated I think. Therefore I would suggest that the public debate about prenatal screening could be used to provide women with different kinds of values and information concerning prenatal screening and its possible follow-up decisions. In the introduction of this thesis I mentioned two newspaper articles which for example might be helpful to pregnant women who are thinking about prenatal screening. To enhance informed decision-making health professionals and scientists as well as women and parents of children with a disability could contribute to this debate with sharing their information and values in order to create a social context wherein all values are mentioned. This might help women to reflect on their personal considerations. This possibly also might contribute to the freedom to accept or decline prenatal screening and to terminate or continue a pregnancy in case of a diagnosis of a congenital disorder.

2. The proportionality of the test

The second pillar of the prenatal screening framework concerns proportionality of the test and includes the balance between benefits and harms of prenatal screening. The question how this balance should be found is particularly relevant when thinking about the expansion of the scope of prenatal screening. The possibility to include more disorders not only increases women's courses of action but might also have disadvantages. In our interview studies, health professionals and pregnant women mentioned the possible limited clinical validity of some test results and the related unnecessary anxiety, an increase in unnecessary invasive testing (which would undo the positive effects that NIPT limited to trisomies 13, 18 and 21 currently has on the number of invasive follow-up tests), and the difficulty to define which disorders are 'serious' enough to include (chapter 2 and 3). Related to the question which disorders should be seen as serious enough, in the WHO framework document it was

argued for example that parents should personally decide which disorders should be included.(16) Also some of the interviewed professionals in our study thought that pregnant women should decide themselves whether a disorder is serious enough to test for, taking into account their personal situation and personal views.(7) We therefore asked pregnant women in interviews which kind of disorders they would include in prenatal screening (chapter 3). We discussed several categories of disorders with them, including early onset, late onset, and neurological disorders, based on categories as used in clinical genetics practice.(17) These interviews showed that for every woman the balance between benefits and disadvantages of prenatal screening as well as the personal considerations differ. Women furthermore indicated negative psychosocial aspects of an expanded scope: women might not have 'worry-free' pregnancies anymore, the children with all kinds of abnormalities might be excluded from societies and abortion might be asked for less severe abnormalities. Besides, they found it difficult to assess the impact of prenatal screening for the several categories of disorders that could be included in prenatal screening and they had difficulties to demarcate the scope (chapter 3). However, another study on preferences of women concerning NIPT and its scope showed that 78% chose to learn about incidental findings including other trisomies or microdeletions which might have variable clinical implications.(18) And previous studies on women's preferences for prenatal diagnosis indicated that most women opted for the option which provides a maximum of information.(19, 20) If pregnant women prefer a maximum of information, how should that be combined with the qualitative studies which found that women feared a slippery slope or questioned where to draw a line?(21, 22) Additionally, other studies showed that potential users of prenatal screening had doubts about having the choice between a smaller or broader test because it might be a burden to decide.(23, 24) The question will be whether women are able to make informed decisions for themselves about which disorders they would wish to have included in their prenatal test.

In sum, besides the clinical test requirements for performance and validity of the offered test, which are necessary for a responsible implementation of a prenatal test, in the pillar of proportionality another balance must be sought: the balance between on the one hand the benefit of having reproductive options in order to make informed autonomous reproductive decisions and on the other hand the burden of having too many options which does not help women to make autonomous reproductive decisions. And the related difficulty is that this

balance might be personal for every woman. Those who offer prenatal screening have to decide between promoting autonomous decisions on one hand and doing no harm with providing too many difficult decisions on the other hand, without being paternalistic.

3. Justice

The third pillar *justice* addresses the specific issue of access to prenatal screening, including reimbursement of the tests. We argued in chapter 8 that asking a co-payment is not a measure to improve informed decision-making. On the contrary it hinders autonomous decision-making for those for whom the co-payment is too high to pay.(15) We also stated that the role of money in decision-making will not be neutral but could carry a message both in case of a fully reimbursed test as well in case of a co-paid test: a fully reimbursed test might carry the message that the government stimulates screening and that women should accept the test. A co-paid test might carry the message that the government does not endorse screening and does not consider it important or necessary to offer the test.

The findings from the vignette study on public attitudes towards prenatal screening (chapter 7) also suggested an impact of asking a co-payment: more people agreed with declining NIPT when the test was not reimbursed. This possible impact of reimbursement policy should be addressed in the framework and at least be considered when deciding about a reimbursement policy because, although asking a co-payment will not promote well-informed choices, it could influence women's decision-making and also public attitudes towards prenatal screening.(15)

Another issue of justice is the equality in people's ability to understand the necessary information, according to the UNESCO international bioethics report about human genome and human rights.(25) It is feared that an increase in pre-test information for an expanded prenatal test might enlarge the difference between those who are able to understand the information and to make an informed decision and those who are not. The counselling model as proposed in chapter 5 might render the concerns regarding inequality of information less important, because it focusses on women's values (not on technical or medical information about the screening test) as a key component of informed consent. In combination with a layered approach to information provision women might be helped with understanding the information necessary to make

4. Social aspects

In this thesis routinisation of prenatal screening and societal pressure to test, two of the *social aspects of prenatal screening* from the fourth framework pillar, are ethically and empirically addressed. The analyses of routinisation showed the importance of specifying the concept in order to make clear to which problem it refers. One of these problems which are referred to as routinisation is a lack of freedom to choose or the presence of societal pressure (chapter 6). In the vignette study we empirically examined this concern by studying public attitudes towards prenatal screening in the Netherlands (chapter 7).

Societal pressure to test is a recurring theme in the discussion about societal aspects of prenatal screening (7, 14), but also in the discussion about the aim of promoting reproductive choices(14) and reimbursement policy for prenatal screening.(8)

However, the vignette study on public attitudes towards NIPT and termination of pregnancy (chapter 7) and also the interview studies amongst professionals, pregnant women and parents about prenatal screening and NIPT (chapter 2, 3 and 4) raise the question how societal pressure actually should be defined. In for example the interview study amongst pregnant women most participants declared that they did not experience pressure themselves. They explained that there is freedom to choose in the Dutch society, that there are different public opinions present about prenatal screening and termination of pregnancy and there is not one major opinion that steers pregnant women into accepting or declining prenatal screening. This is in line with previous studies which assessed reasons for prenatal screening. These studies revealed that the opinion of others was one of the least mentioned reasons to accept or decline a prenatal test.(26, 27)

But, in the context of societal pressure we also discussed with pregnant women the possible influence of opinions of others on decisions about prenatal screening and then they referred to several societal attitudes that might influence women's decision. Firstly, some women mentioned the possibility that opting for a test and termination of pregnancy is taken as self-evident in society which might steer decision-making. Others related societal pressure to a perceived pressure not to terminate the pregnancy after receiving an abnormal diagnostic test result. Women also mentioned critical questions from friends and relatives as sources of pressure or the influence or pressure from a healthcare professional who offered the prenatal test (chapter 3).

Societal pressure could thus refer to different kinds of pressure including firstly outspoken positive or negative judgments concerning prenatal screening from other people in society or from family and friends or the 'trusted' health professional, sources which were also mentioned in the literature.(21, 28, 29) Secondly, societal pressure could refer to explicit public opinions that disabled children should not be born, because for example they are too expensive for society. Some of the parents of children with Down's syndrome for example referred to being held responsible for raising a child with a disability and a few parents feared that in the future this might also include the financial costs.(9) In another qualitative study this is defined as a 'social reaction of intolerance'(28): participants who declined prenatal screening feared that they will be held accountable for negative consequences of their decision. Related to that feelings of pressure could be fed by the suggestion that accepting a test belongs to responsible parenthood and not accepting a test might be seen as 'irresponsible'.(21, 30)

A third interpretation of societal pressure indicated in several empirical studies is that women may have the feeling that they cannot decline prenatal screening because it is simply available or, in case of NIPT, because it is 'just another blood test'.(21, 31) Furthermore, women might feel the need to justify their decision to not accept NIPT because it is expected that they participate in prenatal screening.(32) These kinds of pressure are linked to routinisation of prenatal screening and are not new or specific for NIPT but were previously associated with prenatal screening and reproductive choices.(28, 33, 34)

This short overview of several meanings of societal pressure has similarities with the outcomes of the analysis of the container concept of routinisation (chapter 6). In the analysis of the concept of routinisation we have already argued that using such a container concept does not provide enough information to analyse the specific possible problems of prenatal screening or to find possibilities to counteract these problems. Our analysis showed that the distinct problems that routinisation may refer to may require different solutions. We therefore argued for a specified use of the concept routinisation. The same conclusion might follow from a comparable analysis of the concept of societal pressure. Also for the arguments concerning societal pressure it would be an important first step to clarify what people's fears exactly are.

The second step in the analysis of societal pressure is to examine whether these fears can be supported with empirical evidence. People assume that the societal attitudes are mainly positive towards prenatal screening and therefore could pressure women to accept prenatal testing. But it was not studied yet what the attitudes of the Dutch public are towards prenatal screening. Therefore we conducted a contrastive vignette study on the Dutch public attitudes towards prenatal screening and termination of pregnancy (chapter 7). This quantitative study revealed that the vast majority of participants had a neutral attitude towards someone else's decision about prenatal screening, explaining that it is someone's own choice that should not be influenced by other people's opinion. Nevertheless, some participants had outspoken normative judgements concerning accepting or declining prenatal screening including that when prenatal screening is available there is no reason to not accept it, especially when it is fully reimbursed. Other participants thought that prenatal screening is in the interest of the child and might prevent severe suffering for the child and close family. A few participants thought that it is 'not necessary' to have a child with a disability and that it costs too much money for society. The group of participants who held these opinions was very small but our study indicates that these kinds of judgements exist. However, revealing these public attitudes is not enough to disprove or prove societal pressure. The presence of indicators of pressure within the public attitudes does not mean that women indeed experience pressure regarding accepting or declining prenatal screening: it is possible that, although there are outspoken opinions regarding prenatal screening being indicators for societal pressure, women do not experience that pressure. Therefore the follow-up question is to what extent these positive or negative public opinions would influence women's decision-making or lead to a perceived pressure to test. But it will be more difficult to measure these experiences of pressure. To measure this personal experience other measurement scales for pressure are necessary. However the development of these measurement scales or the operationalization of societal pressure might raise several problems. Firstly, the way women describe pressure might be very personal as shown in the interviews (chapter 3) and difficult to define in general terms, within a scale. Secondly, it is unclear to what extent women might experience pressure concretely: is it also possible that societal pressure is more subtle present in women's decision-making? Related to the latter point it might be questionable whether it is still pressure when women do not experience pressure and have the feeling that they could make an autonomous choice, while

they are maybe unconsciously influenced by for example their social environment. Does it still affect the aim of reproductive autonomy, when women do not feel pressure and have the feeling that they could make an autonomous choice?

To conclude, the argument of societal pressure needs at least more specification about its sources and related fears. The argument also requires new measures to examine and monitor pressure which include as much as possible the possible variability in personal experience of pressure.

Conclusion

In sum, the main findings of this thesis are that there is a set ethical framework for prenatal screening of which the pillars and moral starting points provide ground for the current prenatal screening offer and future expansion of its scope, including the possible negative consequences such as challenges for women's informed consent, information overload, routine acceptance of prenatal screening and societal pressure to test.

Reflections on the aim of prenatal screening

This thesis has shown that there is a well formulated aim of prenatal screening within the ethical framework. This framework provides guidance to deal with the challenges of reaching the aim of promoting reproductive autonomy. But one new challenge is not mentioned yet in this framework, the future availability of foetal treatment for congenital disorders. In this section I want to reflect further on the aim, its position within this framework and the possible consequences of enabling foetal treatment.

Offering reproductive options or promoting reproductive autonomy

The aim of prenatal screening as we have discussed throughout this thesis is formulated as 'promoting reproductive autonomy' or 'offering reproductive options'. Both definitions of the aim refer to offering women the possibility to decide about termination of pregnancy in case of a congenital abnormality, or to prepare for the birth of a child with a disability. This aim requires autonomous informed decision-making, which is attained by offering sufficient information to women and promoting their informed decision-making.(13, 16, 25, 35, 36) Therefore, to assess the 'effectiveness' of the program of prenatal screening scales are developed to measure women's reproductive autonomy(37) and to measure women's informed consent(38, 39) or informed choice.(40-42) The studies on informedness of

decision-making provided different conclusions about whether the aim of prenatal screening is reached, from high percentages of informed consent or informed choice to relatively low percentages.

However, the analyses of the four pillars of the framework in chapter 2 and in this discussion section also refer to other requirements for a responsible offer of prenatal screening. These requirements also affect the aim of prenatal screening: proportionality of the offered test might restrict the number of courses of action women may have, reimbursement policies should minimally influence women's decision-making and freedom of choice should be guaranteed. These requirements of the framework are comprehensive and show that merely offering prenatal screening does not promote reproductive autonomy and thus might not reach the aim.

In this paragraph I would therefore argue for a distinction between *offering reproductive options* as the aim of a prenatal screening offer and *promoting reproductive autonomy* as the justification of the prenatal screening offer.

Future parents make many reproductive choices before and during pregnancy. Prenatal screening aims to contribute to having reproductive options, firstly in the offer of a prenatal test in order to learn about congenital abnormalities and secondly in opting for termination or continuation of the pregnancy in case of a detected abnormality.

These reproductive options promote women's autonomy when they are enabled to decide about these options personally and well informed, according to the Western perspective on autonomy.(43)

Autonomy is amongst others about self-governing agents who formulate their own ideals and undertake actions according to these ideals. Prenatal screening could support women to act according their personal ideals by providing courses of action in case of an abnormality in a foetus and therewith support their reproductive autonomy. However, in the field of prenatal screening it is acknowledged that this formulation of the aim meets some challenges.(3) Firstly, there are problems with saying that the aim of prenatal screening is maximizing the number of options, like the 'Pure Choice paradigm' or the pure autonomy paradigm' do.(3, 44) These paradigms advocate for a maximization of choice without limitations. But the aim of a public prenatal screening offer cannot be formulated as simply maximizing reproductive options because then it is not justifiable to limit the scope to for

example severe or untreatable health conditions.(3) Also in the context of the expansion of the scope of prenatal screening it is mentioned that the scope should not be determined based on the maximization of the choice, but that informed consent, benefits and harms, aspects of justice and social consequences should guide the expansion of the scope.(7, 13)

This thesis furthermore showed that reproductive autonomy not only depends on the existence of a prenatal screening offer but is also determined by the way pre-test counselling is offered and conducted and the extent to which freedom of choice is experienced or guaranteed (chapter 2, 5 and 6). The framework for a responsible prenatal screening offer also includes absence of societal pressure, availability of equal valuable options, and access to care for people with a disability as requirements for a responsible implementation of prenatal screening (chapter 2).(7, 13) Offering reproductive options without such a framework cannot be seen as a justified and responsible prenatal screening offer. A framework for prenatal screening provides guidance and requirements in order to justify and regulate this offer and its aim. This justification is especially important when it concerns a public prenatal screening programme, with course of options linked to the moral sensitive practice of (selective) abortion.(13)

A distinction between the aim of prenatal screening formulated as *offering reproductive options* and the justification of a prenatal screening programme formulated as *promoting reproductive autonomy* could contribute to the clarification how offering reproductive options can be justified.

According to this distinction the aspects elaborated on within the framework's first pillar of the aim of prenatal screening, including promoting informed decision-making and pre-test counselling, would then be part of the requirements for the justification of prenatal screening and not requirements for the aim of prenatal screening. Furthermore, the fact that a prenatal screening offer also should be justifiable, underlines the importance of guaranteeing autonomous reproductive choices by addressing and monitoring continuously the four different pillars of the framework.

Nonetheless, the aim of prenatal screening also should meet certain requirements I think. Test results should for example be valid and provide enough clear information to really offer reproductive options. These are proportionality requirements related to the second pillar

which might be on the borderline of the distinction between the aim and the justification of prenatal screening.

Treatment of congenital disorders, just another course of action?

A new challenge for promoting reproductive autonomy is the finding that in the future several congenital abnormalities could be treated with foetal treatment.(45-48) Recently researchers have studied in utero surgery for spina bifida, a defect that can be detected with the 20-week ultrasound.(49, 50) Another new kind of foetal therapy is therapy for Down's syndrome: it might become possible to improve neurocognitive skills of people with Down's syndrome as some pre-clinical studies suggested.(45) A basic science study presented results which suggested that it might become possible to inactivate the third copy of chromosome 21 of the foetus and which therefore could lead to normal development.(51)

The availability of foetal treatment raises several ethical questions and concerns. It is for example argued that the 'expressivist' critique on prenatal screening for Down's syndrome also applies to foetal therapy. This argument includes objections against prenatal testing because of its discriminatory message to people with a disability. In line with this critique someone could argue that offering foetal treatment sends the same discriminatory message that lives of people with this disability are less worth living.(46) Besides, foetal treatment might affect an individual's personality which could be seen as a negative consequence of this treatment, changing the benefits and harms for this person.(46)

Another problem is that availability of treatment might challenge women's decision-making regarding prenatal screening and thus challenge promoting reproductive autonomy. Prenatal screening is currently offered to provide women with an option to terminate the pregnancy in case of an untreatable congenital disorder. How women value this current option differs for each person, there is no good or wrong decision in this: in the current framework for prenatal screening accepting or declining a test and termination and continuation of pregnancy after receiving the diagnosis of Down's syndrome are seen as moral equal options.(7) The availability of treatment for the syndrome might change this. One consideration is that if parents choose to decline prenatal screening for Down's syndrome they will not be aware that their child has Down's syndrome and thus they could deny their child with Down's syndrome a better health. This might put pressure on women to accept prenatal screening even when they do not want to be confronted with these decisions. This

challenges the freedom to decline prenatal screening and thus women's autonomy.

A second challenge of the availability of foetal therapy for women's freedom of choice is that when she receives a test result that her child has a congenital disorder, she might be expected to accept treatment rather than forego this, although she might have personal reasons to refrain from treatment.

Treatment could also be seen as a preferable option above termination of the pregnancy, while some women might prefer the latter course of action. Although foetal therapy can be seen as an ultimate goal of prenatal diagnosis as argued by some authors (52), other authors argued that presenting foetal treatment in this way might be ethically problematic.(46) They stated that foetal treatment should not be presented as 'the morally preferred option' because whether it is a morally preferred option depends on the moral status attributed to the foetus.(46) On this issue, however, the pro-life and pro-choice visions differ(46) and values of pregnant women differ.(53, 54) Taking these differences into account the option to accept foetal treatment is then just another course of action after prenatal diagnosis about which a woman will decide according her own values. To help women to decide autonomously, the explication of values as proposed in chapter 5 might become even more important. In the context of decision-making about foetal treatment women might in particular need a personal moral ground on the basis of which she can reflect on the available information and options of prenatal screening and its possible follow-up. If women have the feeling that they are in a rollercoaster after receiving the diagnosis of Down's syndrome and have to think about follow-up diagnose and further steps, it might be helpful to her to rely on what they had deliberated in the context of accepting screening.

A third challenge is that the moral complexity of foetal treatment makes it less easy to present it just as another course of action. Professionals might present it as doing everything that is possible.(55) Or women might experience pressure because of a sense of responsibility and feel they are obliged to accept foetal treatment in the interest of the child.(46)

It is imaginable that the availability of foetal treatment affects the freedom of choice and provokes certain judgements in society and increases societal pressure to test. Would the result of a new vignette study on the public attitudes towards prenatal screening then still be that the vast majority indicates that it is someone's own choice? The plea for monitoring effects of offering prenatal screening should receive more attention as well as studying how

to achieve an environment wherein women can freely choose according to their own values. This study would also regard policy measurements including guaranteeing care for people with a disability, ensuring equal access to foetal treatment as well as to safe and affordable pregnancy termination services in order to have equal valuable courses of action for women who have to decide about prenatal screening.(56)

In conclusion, there is a set framework for prenatal screening including requirements for a responsible implementation of non-invasive prenatal screening. These requirements, including informed decision-making, availability of equal valuable options, absence of societal pressure, and access to care for people with a disability are essential for the justification of offering prenatal screening because they are essential for women's reproductive autonomous decision-making in case of congenital abnormalities.

Besides, new techniques, which enable an expansion in courses of action including the possibility of having better pregnancy outcomes with foetal treatment, raise challenges for the aim of promoting reproductive autonomy and for informed and autonomous decision-making which amongst others can be addressed by a refocus in pre-test counselling.

Recommendations for further research

The first unsolved difficulty in this thesis is the determination of the scope of prenatal screening based on the justification and proportionality requirements of the ethical framework. The question is who should determine the balance between on the one hand the benefit of having reproductive options in order to make an informed autonomous reproductive choice and on the other hand the burden of having too many options which leads to an inability to make an autonomous reproductive choice. Those who offer prenatal screening have to decide between guaranteeing personal autonomous choices on the one hand and doing no harm with providing too (many) difficult decisions on the other hand, without being paternalistic.

A first step towards addressing this dilemma might be to study whether and how women experience these decisions in practice, before and after accepting an expanded test and after receiving an abnormal test result. There are for example upcoming studies which will evaluate how pregnant women look back on the process of prenatal screening and on receiving information about an incidental finding.(57) The findings of this kind of studies might provide counsellors with more background information to help pregnant women

decide about a broader prenatal test which implies a greater likelihood of incidental findings, or choose between a smaller or broader test.

A second recommendation for further research concerns the clarification of the concept of societal pressure as it is used in the arguments for a restricted implementation of NIPT. As shown in this discussion, the concept of societal pressure has more than one meaning and therefore possibly needs more than one solution. To deal with this possible negative aspect of offering prenatal screening and particularly NIPT it is important to clarify what critics mean with this concept and what their concerns are. Furthermore, it should be found out how best to measure and monitor societal pressure. For this question it is important to define societal pressure. Is it something that can be measured through a scale or with a questionnaire whereby pregnant women or the public are explicitly asked for their opinions? Or should the study design be more implicit like the contrastive vignette method we used in our study (chapter 7). A final topic for further study is how societal pressure can be counteracted. Is pre-test counselling enough or are there other measures necessary like for example a public education programme?

Finally, because of the increase in possible courses of action after a prenatal diagnosis, including having better pregnancy outcomes and availability of foetal treatment more reflection on the aim of prenatal screening and on the offer of prenatal screening in general is needed.

It was previously argued that to women the aim of prenatal screening should be clear also when it concerns screening for different purposes including prevention or offering reproductive options:(13) a distinction should be made between screening for the purpose of prevention, for example for the Rhesus D status on the one hand and screening for congenital abnormalities, for example for Down's syndrome on the other hand. One of the solutions for this distinction is that two separate screening moments are provided, in order to make clear to women that it concerns different screening programmes with two different aims. In case of foetal treatment for congenital disorders a new course of action is added. But as argued above, the decision to consent to this action is not the same decision as to terminate a pregnancy in case of an abnormal diagnostic test result or the decision to learn about congenital disorders in order to prepare for the birth of a child with a disability. Therefore new kinds of these (practical) solutions might become necessary to distinguish

between the different courses of action. Furthermore, ethical reflection is needed on how the availability of foetal treatment could affect the aim of prenatal screening and whether it is just a new course of action after prenatal screening or that it should be presented apart from the other courses of action.

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Addendum

Summary

The ethical and social debate about prenatal screening and particularly about NIPT address several recurring and pressing themes concerning informed choice, routine acceptance of a prenatal screening offer, societal pressure to test, reimbursement and the expansion of the scope of prenatal screening. However, the relevant arguments appeared to need more clarification, soundness or evidence. The aim of this thesis is to contribute to the debates with explicating arguments and searching for evidence in ethical and empirical literature to support or criticize the relevant arguments.

Chapter 2 offers an account of the leading international ethical framework for prenatal screening and analyse it in the context of an expansion of the scope of prenatal screening. A comparative analysis was conducted of four authoritative international and national statements and position. Furthermore it was examined how this framework is used by professionals working in the field of NIPT. 15 professionals in the field of prenatal screening in the Netherlands were interviewed. The current ethical framework consists of four pillars: the aim of prenatal screening, the proportionality of the test, justice, and societal aspects. Respondents recognised and supported this framework but they also expressed some concerns. They felt that pregnant women do not always make informed choices, while this is seen as central to reproductive autonomy which is *the aim of prenatal screening*. Pre-test counselling practices therefore stand in need of improvement and more attention could be paid to women's personal values. This becomes especially important in the light of the expansion of the scope of prenatal screening when more information becomes available. New forms of counselling should therefore be studied.

Related to *proportionality* respondents believed that the benefits of NIPT outweigh the harms. The mentioned harms of an expanded scope were false positive and negative or unclear test results. Therefore proportionality might limit the expansion.

Justice relates to equal access for prenatal screening. Professionals felt that the out-of-pocket financial contribution currently required by pregnant women on one hand can be a helpful barrier for making women aware of the importance of the choice. But on the other hand it constitutes a barrier to access to NIPT which disproportionally affects those of a

lower socioeconomic status.

Social aspects that where mentioned related to the framework were amongst others discrimination and stigmatisation of people with a disability and societal pressure to test for pregnant women. Professionals recognised but did not share concerns about a rising pressure to test or discrimination and stigmatisation. Although it is difficult to predict whether these social consequences will occur, the practice of prenatal screening should also be evaluated for these social implications.

Chapter 3 The non-invasive prenatal test (NIPT) as first trimester prenatal screening for trisomies 21, 18, and 13 is offered to all pregnant women in the Netherlands. NIPT using genome sequencing allows for an expansion of the scope of prenatal screening and the introduction of NIPT gives rise to ethical and societal concerns about deliberated decision-making of pregnant women, pressure to engage in screening, and possible lack of equal access due to the financial contribution (€175) to NIPT. Pregnant women's opinions were explored about these concerns and about the possibility of a broadening the scope of prenatal screening. Nineteen pregnant women representing a diversity of backgrounds were interviewed using a semi-structured interview guide. Eight women did not opt for prenatal screening while 11 did (NIPT = 4, combined test = 7). Women experienced a free choice to accept or decline prenatal screening, despite sometimes receiving advice from others. Prior to pre-test counselling, some women had already deliberated about what an abnormal test result would mean to them. Others accepted or declined prenatal screening without deliberation. The current Dutch policy of requiring a co-payment was acceptable to those who believed that it functioned as a threshold to think carefully about prenatal screening. Others were concerned that a financial threshold would lead to unequal access to screening. Finally, pregnant women found it difficult to formulate opinions on the scope of prenatal screening, because of lacking knowledge about the different disorders. Life expectancy, severity, and treatability were considered important criteria for the inclusion of a condition in NIPT.

Chapter 4 explored the attitudes of parents of children with Down syndrome towards non-invasive prenatal testing (NIPT) and widening the scope of prenatal screening. Three focus groups of in total sixteen Dutch parents and eleven individual interviews with Dutch parents (and two relatives) of children with Down syndrome were conducted. Parents saw safety,

accuracy and earlier testing as the main advantages of NIPT. Also the reduction of the number of invasive procedures, and thus miscarriages was mentioned as great advantage. However, many feared uncritical use of NIPT and more abortions for Down syndrome. Parents expected unwanted consequences of this uncritical use including a limitation in freedom to choose not to have prenatal screening and negative consequences for the acceptance of and facilities for children with Down syndrome. They feared that this might result in more people who accept screening and termination the pregnancy of a disabled child. Participants stressed the importance of good counselling and balanced, accurate information about Down syndrome instead of a too negative or too optimistic portrait of Down's syndrome. Testing for more disorders might divert the focus away from Down syndrome, but participants worried about "where to draw the line". They also feared a loss of diversity in society. Findings in this chapter showed that, while parents acknowledge that NIPT offers a better and safer option to know whether the foetus is affected, they also have concerns about NIPT's impact on the freedom to accept or decline prenatal screening and on the acceptance and care of children with Down syndrome.

Chapter 5 proposes a rethinking for pre-test counselling and provided an ethical analysis of informed consent in the context of NIPT. Informed consent is a key condition for prenatal screening programs to reach their aim of promoting reproductive autonomy. Reaching this aim is currently being challenged with the introduction of non-invasive prenatal testing (NIPT) in first-trimester prenatal screening programs: amongst others its procedural ease –it only requires a blood draw and reaches high levels of reliability– might hinder women's understanding that they should make a personal, informed decision about screening. We offer arguments for a renewed recognition and use of informed consent compared to informed choice, and for a focus on value-consistent choices and personalized informational preferences. We argue for a three-step counselling model in which three decision moments are distinguished and differently addressed. 1) Professionals explore women's values concerning whether and why they wish to know whether their baby has a genetic disorder. 2) Women receive layered medical-technical information and are asked to make a decision about screening. 3) During post-test counselling, women are supported in decision-making about follow-up testing and the continuation or termination of their pregnancy. This model might also be applicable in other fields of genetic (pre-test) counselling, where techniques

for expanding genome analysis and burdensome test-outcomes challenge counselling of patients.

In **chapter 6** the concept of routinisation is critically assessed as well as the related arguments. In the debate surrounding the introduction of non-invasive prenatal testing (NIPT) in prenatal screening programmes, the concept of routinisation is often used to refer to concerns and potential negative consequences of the test. A literature analysis shows that routinisation has many different meanings, which can be distinguished in three major versions of the concept. Each of these versions comprises several inter-related fears and concerns regarding prenatal screening and particularly regarding NIPT in three areas: (1) informed choice, (2) freedom to choose and (3) consequences for people with a disability. Three of the strongest arguments raised under the flag of routinisation are assessed for their validity: the threat that NIPT poses to informed choice, the potential increase in uptake of first-trimester prenatal screening and its consequences for social pressure to participate in screening or terminate affected pregnancies, and the negative consequences for disabled people. These routinisation arguments lack valid empirical or normative ground. However, the results of this analysis do not imply that no attention should be paid to possible problems surrounding the introduction of NIPT. At least two problems remain and should be addressed: there should be an ongoing debate about the requirements of informed choice, particularly related to an expanded scope of prenatal screening. Also, reproductive autonomy can only be achieved when expecting parents' options are variegated, real and valuable, so that they can continue to choose whether or not to screen or to terminate a pregnancy.

Chapter 7 provided an insight in public attitudes towards prenatal screening through the contrastive vignette method. The introduction of the accurate and procedurally easy non-invasive prenatal test (NIPT) raises ethical concerns that public attitudes towards prenatal screening may change, leading to societal pressure to participate in aneuploidy screening. This study examined Dutch citizens' attitudes towards a pregnant woman's decision to 1) decline NIPT in the context of two different funding policies and 2) to terminate or continue a pregnancy affected by different disorders. The attitudes of 1096 respondents were assessed with the contrastive vignette method, using two pairs of vignettes about declining NIPT and termination of pregnancy. Most respondents either agreed or did not agree or

disagree with a woman's decision to decline NIPT stating that this decision is someone's own to make and does not warrant judgment by others. However, funding policies did influence respondents' attitudes: significantly more respondents disagreed with declining NIPT when it was fully reimbursed.

Respondents had similar attitudes to the vignettes on termination and continuation of pregnancy in case of Down's syndrome. In case of Edward's or Patau's syndrome, however, significantly more respondents disagreed with continuation, citing the severity of the disorder and the child's best interests. This study demonstrates broad acknowledgment of women's freedom of choice in Dutch society; a finding that may help to rebut existing concerns about societal pressure for pregnant women to participate in prenatal screening. As the reimbursement policy and the scope of NIPT may influence people's attitudes and elicit moral judgements, however, maintaining freedom of choice warrants sustained efforts by health professionals and policy-makers.

Chapter 8 addresses the reimbursement question of prenatal screening. The introduction of non-invasive prenatal testing (NIPT) in healthcare systems around the world offers an opportunity to reconsider funding policies for prenatal screening. In some countries with universal access healthcare systems, pregnant women and their partners are asked to (co)pay for NIPT. In this chapter two important rationales for charging women for NIPT were discussed: (1) to prevent increased uptake of NIPT and (2) to promote informed choice. First, given the aim of prenatal screening (reproductive autonomy), high or low uptake rates are not intrinsically desirable or undesirable. Using funding policies to negatively affect uptake, however, is at odds with the aim of screening. Furthermore, co-payment disproportionally affects those of lower socioeconomic status, which conflicts with justice requirements and impedes equal access to prenatal screening. Second, it is argued that although payment models may influence pregnant women's choice behaviours and perceptions of the relevance of NIPT, the co-payment requirement does not necessarily lead to better-informed choices. On the contrary, external (i.e., financial) influences on women's personal choices for or against prenatal screening should ideally be avoided. To improve informed decision-making, healthcare systems should instead invest in adequate non-directive, value focused pre-test counselling. This chapter concludes that requiring (substantial) co-payments for NIPT in universal access healthcare systems fail to promote reproductive autonomy.

Concluding remarks

A set framework for prenatal screening is defined including preconditions for a responsible implementation of non-invasive prenatal screening. New techniques, which enable an expansion of the scope prenatal screening including the possibility of having better pregnancy outcomes and possibly provide availability of foetal treatment, raise challenges for the aim of promoting reproductive autonomy and how informed and autonomous decision-making should be reached. Therefore more reflection on the consequences of these new possibilities for the aim of prenatal screening is necessary. Besides, the aim of prenatal screening is associated with some preconditions including informed decision-making, absence of societal pressure, availability of equal valuable options, and access to care for people with a disability. These preconditions, comprised in a framework for prenatal screening, are the justification of promoting reproductive autonomy which should be distinguished from its aim of offering women reproductive choices in case of congenital abnormalities in their unborn child.

Samenvatting

Het ethische en publieke debat over prenatale screening, in het bijzonder over NIPT, gaat over geïnformeerde keuze, routineuze aanvaarding van het aanbod van prenatale screening, maatschappelijk druk om te testen, vergoeding van de test en uitbreiding van de reikwijdte van prenatale screening. De relevante argumenten vragen echter om meer verheldering of bewijs. Het doel van deze thesis is een bijdrage te leveren aan dit debat door middel van het expliciteren van argumenten en het zoeken naar bewijs in ethische en empirische literatuur om daarmee de relevante argumenten van onderbouwing of kritiek te voorzien.

Hoofdstuk 2 biedt een uitwerking aan van een toonaangevend internationaal ethisch kader voor prenatale screening en analyseert het in de context van een uitbreiding van de scope van prenatale screening. Er is een vergelijkende analyse uitgevoerd van vier gezaghebbende nationale en internationale documenten en stellingnamen. Vervolgens is onderzocht hoe het kader gebruikt wordt door professionals die werkzaam zijn in het veld van NIPT. Er zijn semigestructureerde interviews gehouden onder vijftien professionals uit het veld van prenatale screening in Nederland. Het huidige ethische kader bestaat uit vier pijlers: het doel van screening, de proportionaliteit van de test, rechtvaardigheid en maatschappelijke aspecten. Respondenten herkenden en onderschreven dit kader in hun praktijk maar uitten ook hun zorgen. Ze denken dat zwangere vrouwen niet altijd een geïnformeerde keuze maken terwijl dit als cruciaal gezien wordt voor reproductieve autonomie, wat het *doel is van screening*. De counseling voorafgaand aan de test valt dus nog te verbeteren waarbij meer aandacht uit zou kunnen gaan naar de persoonlijke waarden van vrouwen. Dit is extra belangrijk in het licht van de uitbreiding van de scope van prenatale screening waarbij nog meer informatie over de foetus beschikbaar komt. Daarom zou er onderzoek gedaan moeten worden naar nieuwe vormen van counseling. Als het gaat om *proportionaliteit* dachten respondenten dat de voordelen van NIPT opwegen tegen de nadelen. De genoemde nadelen van een bredere scope waren fout- positieve, fout-negatieve of onduidelijke testresultaten. Om die reden zou proportionaliteit de uitbreiding van de scope kunnen begrenzen. *Rechtvaardigheid* gaat over gelijke toegang tot prenatale screening. Professionals hadden het gevoel dat de eigen financiële bijdrage die momenteel vereist is voor zwangere vrouwen enerzijds een behulpzame drempel kan zijn om vrouwen bewust te

maken van het belang van de keuze. Anderzijds kan het een drempel opwerpen voor toegang tot NIPT die degenen met een lagere sociaaleconomische status onevenredig raakt. *Maatschappelijke aspecten* die genoemd werden in relatie tot het ethisch kader waren onder andere discriminatie en stigmatisering van mensen met een aandoening en sociale druk voor zwangere vrouwen om te testen. Professionals herkenden de zorgen over toenemende druk om te testen of over discriminatie en stigmatisering maar onderschreven die niet. Ondanks dat het moeilijk is om te voorspellen of deze maatschappelijke consequenties daadwerkelijk voor zullen komen moet de praktijk van prenatale screening ook voor deze sociale implicaties tegen het licht gehouden worden.

Hoofdstuk 3 De niet-invasieve prenatale test (NIPT) voor de trisomiën 21, 18 en 13 wordt aangeboden aan alle zwangere vrouwen in Nederland. Omdat NIPT gebruik maakt van genoomsequencing is het mogelijk om de scope van de prenatale screening te vergroten. De introductie van NIPT geeft aanleiding tot ethische en maatschappelijke zorgen over weldoordachte besluitvorming van zwangere vrouwen, druk om deel te nemen aan screening en ongelijke toegang tot NIPT vanwege de financiële bijdrage van € 175,-. De meningen van zwangere vrouwen over deze zorgen zijn onderzocht, evenals hun standpunten over de mogelijke uitbreiding van de scope van prenatale screening. Negentien zwangere vrouwen die verschillende achtergronden representeerden zijn geïnterviewd aan de hand van een semigestructureerde interviewleidraad. Acht van de vrouwen nam geen deel aan de prenatale screening en de andere elf wel (NIPT = 4, combinatietest = 7). De vrouwen ervoeren een vrije keuze om de prenatale screening te accepteren of te weigeren, hoewel sommigen aangaven advies gekregen te hebben van anderen. Voorafgaand aan de pre-test counseling hadden sommige vrouwen al nagedacht over wat een afwijkend testresultaat voor hen zou betekenen. Anderen accepteerden of weigerden prenatale screening voor de trisomieën zonder erover na te denken. Het huidige Nederlandse beleid waarbij een eigen bijdrage gevraagd wordt was voor sommigen acceptabel. Zij dachten dat het zou kunnen functioneren als drempel om tot nadenken aan te zetten over prenatale screening. Anderen waren bezorgd dat een financiële drempel zou leiden tot ongelijke toegang tot screening. Ten slotte vonden de zwangere vrouwen het moeilijk om een mening te formuleren over de scope van de prenatale screening vanwege een gebrek aan kennis

over de verschillende aandoeningen. Levensverwachting, ernst en behandelmogelijkheden werden als belangrijke criteria genoemd voor het includeren van een aandoening in NIPT.

Hoofdstuk 4 geeft de mening weer van ouders van kinderen met downsyndroom over de introductie van de niet-invasieve test en de uitbreiding van de scope van prenatale screening. Drie focusgroepen met in totaal 16 deelnemers en 11 individuele interviews zijn uitgevoerd met ouders en twee familie leden. Ouders zagen de afwezigheid van een miskraamrisico, de mogelijkheid om vroeg te testen en de betrouwbaarheid van de uitkomst als belangrijke voordelen van de test. Ze maakten zich wel zorgen over een ondoordacht gebruik van NIPT en een afname in keuzevrijheid om de test te weigeren. Verder vreesden ze negatieve consequenties voor de acceptatie van kinderen met downsyndroom en een afname in de beschikbaarheid van zorg voor deze kinderen. Ze vreesden dat hierdoor meer ouders zullen testen en de zwangerschap zullen beëindigen in het geval van een gevonden afwijking. Ouders benadrukten het belang van goede counseling en volledige informatie over downsyndroom. Met betrekking tot de scope noemden ouders als voordeel dat de focus op downsyndroom minder zou worden. Wel vroegen ze zich af waar de grens getrokken moet worden van de scope. Sommige ouders noemden de mogelijkheid van verlies van diversiteit in de samenleving als nadeel van een bredere scope van prenatale screening.

Hoofdstuk 5 introduceert een nieuw model voor pre-test counseling voor prenatale screening in de context van NIPT. Pre-test counseling is de manier om geïnformeerde keuze te bevorderen. Geïnformeerde keuze is belangrijk voor het bereiken van het doel van prenatale screening, het bevorderen van reproductieve autonomie. De introductie van NIPT brengt echter uitdagingen met zich mee voor dit doel. De angst is dat een eenvoudige test zoals NIPT, die alleen een bloedafname vereist, er toe leidt dat vrouwen niet nadenken over hun keuze voor prenatale screening. In dit hoofdstuk worden argumenten besproken voor het gebruik van het concept geïnformeerde toestemming boven het concept van geïnformeerde keuze, omdat dit beter aansluit op de bestaande ethische literatuur over besluitvorming en autonomie. Verder wordt er een nieuw counselingmodel voorgesteld dat focust op de waarden van de zwangere vrouw in plaats van op informatievoorziening. Dit model bestaat uit drie stappen. 1) de counselor bespreekt met de zwangere vrouw wat haar waarden met betrekking tot prenatale screening zijn. 2) vrouwen ontvangen informatie over prenatale screening, op basis van hun informatiebehoefte en ze besluiten of ze prenatale

screening willen. 3) in de post-test counseling worden vrouwen begeleid in de beslissing om al dan niet vervolgtesten te ondergaan en de zwangerschap te beëindigen of uit te dragen. Dit model maakt het ook mogelijk om vrouwen te ondersteunen in een beslissing over een NIPT wanneer meer aandoeningen zijn toegevoegd aan de test. Dit model is niet alleen geschikt voor prenatale screening maar zou mogelijk ook in andere gebieden van genetische counseling gebruikt kunnen worden.

Hoofdstuk 6 biedt een analyse van het concept van routinisatie van prenatale screening. Dit concept wordt vaak gebruikt om zorgen aan te duiden met betrekking tot mogelijk negatieve gevolgen van de introductie van NIPT. Een literatuuranalyse laat drie verschillende betekenissen van dit concept zien die allen verschillende zorgen omvatten met betrekking tot NIPT. 1) NIPT zou de geïnformeerde keuze van vrouwen kunnen beïnvloeden. 2) NIPT zou de keuzevrijheid van vrouwen kunnen aantasten. 3) NIPT zou negatieve consequenties kunnen hebben voor mensen met een (chromosomale) aandoening. Deze drie zorgen en gerelateerde argumenten zijn in dit hoofdstuk onderzocht op hun validiteit en beschikbare empirische of conceptuele bewijs. Hoewel de resultaten laten zien dat er maar beperkt bewijs is voor deze zorgen neemt dat niet weg dat er aandacht aan besteed moet worden. In de eerste plaats moet er blijvend aandacht geschonken worden aan het bereiken van geïnformeerde keuze in het bijzonder met het oog op de uitbreiding van prenatale screening. En alle opties voor zwangere vrouwen, zowel het accepteren als afwijzen van prenatale screening en het beëindigen of uitdragen van de zwangerschap moeten gelijkwaardige opties zijn. Vrouwen moeten te allen tijde emotionele en materiële steun ontvangen bij de keuze die ze maken.

Hoofdstuk 7 geeft inzicht in de mening van de Nederlandse bevolking over prenatale screening. De zorg is dat de NIPT, die eenvoudig uit te voeren is er voor zorgt dat vrouwen sociale druk zullen ervaren om de test te accepteren en daaraan gerelateerd om de zwangerschap af te breken. Om te onderzoeken of deze zorg terecht is moet er eerst gekeken worden naar hoe het Nederlandse publiek denkt over prenatale screening en zwangerschapsafbreking na prenatale screening. Dit hoofdstuk onderzoekt ten eerste de houding van een representatieve onderzoeksgroep ten opzichte van het afwijzen van NIPT in de context van verschillende vergoedingen: helemaal vergoed of inclusief een eigen bijdrage van €175,-. Ten tweede wordt onderzocht hoe deze groep staat tegenover

zwangerschapsafbreking. Deze houding is in kaart gebracht met de contrastieve vignetten methode die is ontwikkeld om sociaal wenselijke antwoorden te voorkomen. De grootste groep van de deelnemers gaf aan geen mening te hebben over de keuze van een ander om NIPT af te wijzen of de zwangerschap af te breken omdat dit iemands eigen keuze is die niet beoordeeld moet worden door anderen. Verder bleek dat het vragen van een eigen bijdrage wel invloed heeft op de mening van een aantal respondenten: significant meer respondenten waren het niet eens met het afwijzen van NIPT wanneer deze volledig vergoed werd vergeleken met een afwijzing van NIPT in het geval van een eigen bijdrage. Met betrekking tot het afbreken of uitdragen van de zwangerschap was er geen verschil in de houding van de respondenten tussen deze twee opties. Wel waren er meer respondenten die het niet eens waren met het uitdragen van de zwangerschap in het geval van edwards- of patausyndroom omdat dit niet in het belang van het kind is. De keuzevrijheid die in dit onderzoek hoog gewaardeerd wordt moet wel actief in stand gehouden worden en mogelijke negatieve invloeden van het vergoedingsbeleid of morele oordelen ten aanzien van de ernst van de ziekte moeten actief worden voorkomen door degenen die NIPT aanbieden.

Hoofdstuk 8 behandelt de vraag met betrekking tot de vergoeding van prenatale screening. In sommige landen, waaronder Nederland, wordt aan zwangere vrouwen een eigen bijdrage gevraagd voor prenatale screening. Hiervoor zijn twee redenen te geven. Ten eerste zou een eigen bijdrage de toename in uptake van prenatale screening kunnen tegengaan en ten tweede zou een eigen bijdrage de geïnformeerde besluitvorming kunnen bevorderen. Het doel van prenatale screening, het bevorderen van reproductieve autonomie, geeft echter geen aanleiding om een hoge uptake te willen voorkomen of te bevorderen. Het vragen van een eigen bijdrage om de uptake te beïnvloeden kan juist niet samen gaan met dit doel. Verder heeft het vragen van een eigen bijdrage vooral effect op diegenen met een lagere sociaal economische status of een lager inkomen. Dit is in strijd met het principe van rechtvaardigheid en gelijke toegang tot prenatale screening. Daarnaast leidt het vragen van een eigen bijdrage niet tot een geïnformeerde keuze. In tegendeel, zowel het vragen van een bijdrage als een volledige vergoeding van NIPT zou geen invloed moeten hebben op de keuze van een zwangere vrouw.

Concluderende opmerkingen

Een vastgesteld kader voor prenatale screening omvat verschillende voorwaarden voor een verantwoorde implementatie van de niet-invasieve prenatale test. Nieuwe technieken die de uitbreiding van de scope van prenatale screening mogelijk maken en daarnaast ook de mogelijkheid gaan bieden om onder andere neurocognitieve kenmerken van downsyndroom foetaal te behandelen roepen vragen op ten aanzien van het doel van prenatale screening. De vraag is hoe vrouwen voor deze nieuwe mogelijkheden een geïnformeerde, persoonlijke en autonome keuze kunnen maken. Daarom moet er meer onderzoek gedaan worden naar hoe deze technieken het doel kunnen beïnvloeden en hoe een autonome keuze gewaarborgd kan worden.

Daarnaast zijn er in het ethisch kader verschillende voorwaarden geformuleerd voor het aanbod van prenatale screening en het bereiken van het doel van het bieden van reproductieve keuzeopties. Dit kader vormt de rechtvaardiging van het doel van prenatale screening en moet onderscheiden worden van het doel vrouwen reproductieve keuzeopties te bieden in het geval van een aangeboren afwijking bij hun ongeboren kind.

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Curriculum Vitae

Adriana Kuipers was born on November 21, 1990 in Gouda, the Netherlands. In 2009 she finished secondary school at the Driestar College in Gouda (VWO). She obtained a Bachelor's degree in Biomedical Sciences (2013), a Master of Science degree in Health Sciences (2015) and a Master of Arts degree in Philosophy, Bioethics and Health (2015) at the Vrije Universiteit Amsterdam. During a graduate internship at the department of Clinical Genetics, section Community Genetics she conducted a qualitative research on the opinions of parents of children with Down's syndrome about the non-invasive prenatal test (NIPT). This was a starting point for a thesis about ethical and social aspects of prenatal screening.

In 2015 she started working on the department of Medical Ethics and Philosophy and participated in two projects about the ethical and social aspects of prenatal screening, particularly of non-invasive prenatal testing.

Since 2019 she is working as a post-doc on the department of Clinical Genetics, section Community Genetics at the Amsterdam University Medical Centre location VUmc. She is working on a project about the psychosocial aspects of newborn screening and the expansion of it.

List of publications

Kater-Kuipers A, Bunnik EM, de Beaufort ID, et al. Limits to the scope of non-invasive prenatal testing (NIPT): an analysis of the international ethical framework for prenatal screening and an interview study with Dutch professionals. *BMC Pregnancy Childbirth.* 2018;18(1):409. doi: 10.1186/s12884-018-2050-4

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PhD Portfolio

Adriana Kater-Kuipers PhD period: November 2015 - Mei 2020

Promotor: I.D. de Beaufort Copromotoren: E.M. Bunnik en R.J.H. Galjaard

Congresses and presentations	**Date**	**Activity**	**ECTS**
NVHG Najaarssymposium	November 2015		0.5
NIPT-symposium	Maart 2016		0.5
IAB Edinburgh	June 2016	Poster presentation	1
Symposium counseling en prenatale screening (De Vervolmaakte mens)	August 2016		0.5
EACME Leuven	September 2016	Oral presentation	2
NACGG	December 2016	Oral presentation	1
BMFMS	March 2017	Poster presentation	1
RIVM congress	April 2018		0.5
NVBe	April 2018		0.3
EACME 2018	September 2018	Oral presentation	2
Conference on Social Inclusion (UvH)	May 2019		0.5
			9.8
Courses	**Date**		**ECTS**
Workshop 'omgaan met groepen'	13 March 2017		0.5
OZSW Springschool 2017 - Ethical Theory and Moral Practice	April 2017		5
Good clinical practice	June 2017		0.5
Journal club (30 meetings of an hour = 1ECTS)	2016/2017		0.5
Wetenschappelijke integriteit	December 2018		0.5
			7
Education	**Date**		**ECTS**
Coaching minor student in writing.	September-October 2016	Coaching a bachelor student in writing an essay	0.5
VO prenatal screening (minor)	24 October 2016	Teaching	0.5
Minor clinical genetics	September 2016	Teaching	0.3
VO's dilemma arts-patiënt relatie	2-3 November 2016	Teaching	1
VO prenatal screening clinical genetics	8 December 2016	Teaching	0.5
Nascholing clinical genetics	June 2017	Teaching	0.5
Minor clinical genetics	October 2017	Teaching	0.5
Bacheloressays/ Tweedejaars essays	June 2017-2019	Correction	2
			6.3

Total ECTS: 23.1