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## **Implementing Non-Invasive Prenatal Testing (NIPT): Perspectives of patients and professionals**

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## **CHAPTER 10.**

### **GENERAL DISCUSSION**



Non-invasive prenatal testing (NIPT) using cell-free DNA in maternal plasma has created a significant change in the prenatal testing landscape. To reach a responsible implementation of NIPT in Dutch prenatal care, careful consideration, exploration of the attitudes of key stakeholder groups and close collaboration between these groups is required. The overall aim of this thesis was to get insight into the perspectives of various stakeholder groups involved in the implementation process of NIPT. This thesis is divided into two parts: 1) an exploration of the attitudes towards NIPT, for fetal aneuploidy and for a wider range of disorders, of pregnant women (and their partners), health professionals and parents of children with Down syndrome, and 2) a reflection on the implementation process of NIPT in the Netherlands and evaluation of the impact of NIPT on informed choice, emotional well-being and satisfaction in high risk pregnant women offered NIPT as an alternative option to invasive testing.

In this chapter the main findings of this thesis will be addressed and discussed in the context of relevant scientific literature. At the end of this chapter, the methodology, implications for practice and recommendations for further research will be discussed.

## **DISCUSSION OF MAIN FINDINGS**

### **NIPT for fetal aneuploidy**

Results of this thesis showed that key stakeholders believe NIPT is an improvement for prenatal care as it allows for accurate, risk-free testing earlier in pregnancy. A study by Hill et al. (1) that reviewed multiple studies among stakeholders showed similar, largely positive, attitudes about the introduction of NIPT. In this thesis, both pregnant women and parents of children with Down syndrome thought that if NIPT would replace the first-trimester combined test (FCT) the barrier for participating in prenatal screening would become lower (Chapter 2 & 6). Stakeholders assumed that the lower barrier would cause an increase in the uptake of prenatal screening (Chapter 2, 5 & 6). This expectation was portrayed by the finding that a third of women who had previously declined FCT expressed interest in having NIPT in their next pregnancy (Chapter 3). Other studies from the Netherlands showed similar results(2) and indicate that an increased uptake of prenatal testing with NIPT can be expected.(3) While the current uptake of prenatal screening in the Netherlands is relatively low(4;5;6) implementing NIPT in Dutch prenatal care might thus increase the proportion of women accepting screening and possibly increase the proportion of women choosing to terminate their pregnancy for Down syndrome. However, Verweij et al.(3) suggested that the percentage of women opting for termination of pregnancy might as well decrease with NIPT since this test will be accepted by a more diverse group, including more women willing to continue a pregnancy affected by Down syndrome. This finding is confirmed by this thesis, firstly by demonstrating that pregnant women in general believe prenatal screening with NIPT to be of value for those only wishing to prepare themselves.

Secondly, by the finding that some women who declined the FCT because they are opposed to termination of pregnancy, considered having NIPT for information purposes (Chapter 4), and thirdly by the finding that women opting for NIPT after a high-risk FCT result had less intention to terminate the pregnancy for Down syndrome than those undergoing invasive testing (Chapter 8). Results of this thesis thus suggest that with the introduction of NIPT there might be an increase in the uptake of prenatal testing as well as an increase in women electing it purely to obtain information so they can prepare themselves.

As in other studies (7;8,9) stakeholders also perceived potential disadvantages of NIPT. Concerns were raised about the potential uncritical or routinized use of NIPT and increased societal pressure to test. Interestingly, when comparing our findings with studies performed after the introduction of the national screening program for Down syndrome in The Netherlands in 2007 (10;11) it appears that there were similar worries back then. This implies that these are recurrent (deeply rooted) concerns that are related to prenatal screening in general, although they might be more significant for NIPT. Parents of children with Down syndrome worried that, since NIPT allows women to test earlier in pregnancy, they might terminate an affected pregnancy more thoughtlessly. They also feared that with NIPT there would be more abortions for Down syndrome, leading to less acceptance, facilities and research for children with Down syndrome (Chapter 6). According to these parents, and as was described by others (1), this would create a scenario in which women are left with little room to decline prenatal screening, leading to even more prenatal tests and abortions.

### **How to responsibly implement NIPT for aneuploidy?**

The aim of offering prenatal screening in a public healthcare program is not to prevent the birth of children with an abnormality, but to enable pregnant women and their partners to make an autonomous reproductive choice.(12) This aim should be reflected in the way prenatal testing for fetal aneuploidy is offered and carried out.(12) According to Dondorp et al.(12) the measure of the 'effectiveness' of a prenatal screening offer should be to which extent women are able to make informed choices rather than the technical performance of the test.

There is an ongoing debate (1;13) on whether to offer NIPT as a first-tier screening test (replacing the FCT) or to offer it like a contingent (second-tier) screening test as in the TRIDENT study. Both this thesis and a study from the UK (14) show that when NIPT is offered as an contingent screening test, accompanied by sufficient pre-test counseling, the majority of women is able to make an informed choice (Chapter 8). Moreover, women were glad to have been offered NIPT, were reassured by a normal NIPT result and experienced no regret about their choice (Chapter 9).(15) Offering NIPT in this way thus allows women to get certainty after a high-risk FCT result without risking a miscarriage and does not seem to undermine informed decision-making.

However, the downside of this two-step procedure is that it keeps women in a prolonged state of anxiety which is undesirable, especially since anxiety is associated with potential negative obstetrical outcomes.(16;17)

The health professionals questioned in this thesis about the position NIPT should have in the prenatal screening program largely favored to replace the FCT with NIPT (Chapter 5). Offering NIPT as a first-tier test will reassure most women early in pregnancy and will cater those currently travelling abroad to have immediate testing at their own costs. Of course only a small subgroup is able to afford the latter. Stakeholders also mentioned that replacing the FCT with NIPT would lower the barrier for screening, allowing prospective parents to decide about prenatal testing without being influenced by fear of a miscarriage risk or the uncertainty of results of the (less accurate) FCT. Offering NIPT as a first-tier test accessible to all women would therefore better serve the aim of prenatal screening. In contrast to offering NIPT to high risk women who already reflected on prenatal testing, if NIPT becomes a first-tier test this will be the first decision-making moment about prenatal screening. Therefore, it is especially important to be wary of potential routinization or uncritical use of NIPT. In order to do so, the need for comprehensive counseling on NIPT has been expressed,(1;12) and health professionals in this thesis stated that counseling and sampling of maternal blood should not take place on the same day. The results show that women who declined FCT because of their attitudes towards Down syndrome and termination of pregnancy are more likely to decline NIPT as well. These findings suggest that if women are given the opportunity to reflect on their personal values, there is no need to fear uncritical use of NIPT. Ensuring effective counseling and autonomous, informed-decision making is thus the fundamental condition for offering NIPT as a first-tier test to all pregnant women.

To facilitate informed decision-making on NIPT, Sachs et al.(18) have developed a framework for key points to be discussed during pre-test counseling, for example that NIPT is a screening test and a positive result needs to be confirmed with invasive testing or that findings other than trisomies 21, 18 or 13 can be found. Moreover, Allyse et al.(19) have developed a set of best ethical practices for offering NIPT, highlighting the importance of an informed decision-making process. Others have suggested the use of decision aids to help health professionals support pregnant women making an informed choice. Decision aids are tools designed to help people in the decision-making process by providing information and helping to clarify their personal values.(20) Counselors could therefore incorporate the (additional) use of (online) decision aids made available to women prior and following prenatal testing. However, there is a need for development of these decision aids.(20) First attempts to do this have been made by Skoth et al.(21) and Beulen et al.(22) Nonetheless, adequate face-to-face counseling remains most important as research has shown that prospective parents still prefer to receive information about prenatal testing in this way

instead of receiving it online.(23) During counseling it is important to give special attention to women with inadequate health literacy or lower levels of education as this thesis and a study by Farrell et al.(24) showed that those women less often make an informed choice about prenatal testing.

To further aid informed decision-making, the need for accurate, up-to-date information provision about Down syndrome was stressed in this thesis. Some information sources about NIPT do not yet provide all the content and balanced information recommended in professional guidelines.(1) However, equally important for safeguarding informed choice is that, irrespective of what will happen to the number of children with Down syndrome being born after implementation of NIPT, there is a guarantee that adequate care and facilities for people with Down syndrome are sustained. Only in a society in which there is good care for people with a disability do pregnant women really have the capacity of making an informed reproductive choice. The proportion of women using NIPT and the proportion choosing termination of pregnancy are of secondary importance. What counts first and foremost is protecting the aim of prenatal screening, which is to enable autonomous reproductive choices.

Lastly, when trying to support reproductive autonomy it is important that all women have equal access to NIPT. Rolfes et al.(25) have stated that financial barriers, like a high price for NIPT, can potentially counteract reproductive autonomy. Although stakeholders in this thesis have suggested that a financial barrier can act as a tool to make women think more thoroughly about the choice they are making, the need to pay may on the other hand limit the access to NIPT to those who are able to afford it.(26)

### **Widening the scope of prenatal screening with NIPT**

It has been shown that NIPT can be used to sequence the entire fetal genome,(27;28) opening up opportunities to screen for a much wider range of disorders in future. The findings from this thesis show that stakeholders see value in testing for a wider range of disorders with NIPT, since it can avoid suffering or help reduce the pathology of a disorder through early medical intervention. Pregnant women mostly agreed to screening for severe genetic disorders associated with premature death, severe physical or mental disability or disorders for which the child can already be treated during pregnancy (Chapter 2 & 3). Health professionals agreed mostly to screening for disorders characterized by neonatal death or death within the first year of life (Chapter 5). Other studies also have shown support among stakeholders for testing for more disorders with NIPT.(1;29;30)

It is important to note that there are discrepancies in the preferences of pregnant women and health professionals with regard to the method of offering broader screening, and the extent to which women have an individualized choice. Results of this thesis, as well as other studies,(8;31) show that women wish to make their own decision ('free choice') for which disorders is tested for. In contrast, health

professionals rather offer a test for multiple disorders as a closed offer (i.e. fixed list of disorders), probably because they expect that explaining each different disorder would be infeasible.(8) A potential solution could be to offer a 'happy medium' in which women can choose from optional packages each testing for disorders similar in type and severity, but both pregnant women and health professionals seemed to prefer this the least. This implies that there is a need to further investigate ways to offer a broader test that would satisfy both groups.

Irrespective of how it should be offered, testing for a broader range of disorders would greatly challenge counseling and informed-decision making. This thesis showed that stakeholders fear that it would potentially confront prospective parents with choices, the implications of which would be difficult to grasp. The risk of information overload is especially noteworthy when considering the fact that, as gene sequencing advances, screening for multiple disorders will lead to results that indicate varying risks or probabilities of developing a disorder or even findings of unknown clinical significance.(26;32) These type of results will be difficult to interpret and burden prospective parents with difficult decision-making.(26) Or as argued by De Jong et al.(33) 'may lead to undermining rather than promoting reproductive choices'. Therefore, introducing a broader NIPT test would call for an adapted counseling process that assures understanding of disorders tested for and the possibility of receiving uncertain results or incidental findings. This means that we need to gain more insight in ways to deliver this type of information that are practicable for health professionals and would not cause information overload for prospective parents. A suggested solution is that of 'generic' informed consent, where pre-test information is grouped in general categories of type of disorders.(29;32;34) This would help to keep pre-test counseling and informed decision-making feasible.

Besides testing for more disorders, NIPT also has the potential to test for fetomaternal risk factors which negatively influence the course of pregnancy (i.e. preeclampsia or preterm birth), although stakeholders showed less support for this. If this type of testing does get implemented it would create a test offer with two different aims of screening; supporting reproductive choice by testing for various disorders and supporting a healthy outcome of pregnancy (prevention) by testing for fetomaternal risk factors (35). This would request different counseling styles, with counseling for screening for disorders being non-directive, but counselors being more directive when it comes to screening for fetomaternal risk factors in order to protect the pregnancy from potential harm.(33) De Jong et al.(33) therefore suggest that, in order to avoid confusing moral messages, counseling and information provision for these two different type of screening should be separated.

Lastly, the idea of testing for a wider range of disorders made stakeholder question 'where to draw the line'. They wanted to avoid a slippery slope which would lead to people eventually testing for minor abnormalities, gender and cosmetic traits.

The fear that people will terminate the pregnancy for trivial matters was also expressed in other studies.(36;37) Another fear was that expanding the use of NIPT could lead to less acceptance of those living with or giving birth to a child with a disorder.

Overall, it can be argued that although stakeholders seem interested in a broader NIPT, there are still many questions that need to be answered before initiating such a test. Dondorp et al.(35) stated that there is need for more ethical reflection on the issues arising from prenatal screening for multiple disorders and therefore we should not expand the scope of prenatal screening just yet. As a society we need to understand for what type or disorders we think testing is warranted for, and also how we are going to guarantee that there will be no stigmatization of those living with a disorder or those deciding to continue a pregnancy of an affected child. Moreover, we need to find a way to offer a broader test that is both practical and able to safeguard informed decision-making. For now, it is wise to focus on implementing NIPT for aneuploidy in a responsible manner, but since gene sequencing technology develops at a fast rate we need to start thinking and discussing about the future use of NIPT in the Netherlands.

## **REFLECTIONS ON METHODOLOGY**

To answer the research questions both qualitative as well as quantitative research methods were applied. Using focus groups, individual interviews as well as questionnaires allowed us to extensively explore the attitudes of different stakeholders involved in the implementation of NIPT. Both low risk and high risk pregnant women were included in the study, which ensured that a variety of experiences in prenatal testing could be explored. Another strength of the studies is that it gave more insight in the attitudes of partners of pregnant women and parents of children with Down syndrome. Both groups were underrepresented in the literature on NIPT when the study started. A limitation is that the level of education of participants was relatively high and participants were predominantly white. This might have biased the results as people with a lower socio-economic status or other ethnicity might have different attitudes or interest in NIPT. Moreover, it is conceivable that those accepting to participate in the study did so because they had interest in the topic of prenatal screening, which could have also led to bias.

A strength of the research on women's experiences, described in part II of this thesis, was the large sample size and response rate of the questionnaire study among high risk women being offered NIPT as an alternative to invasive testing. Another strength was the prospective study design, where, during the first five months of the TRIDENT study, psychological variables could be measured before testing and after receiving NIPT results. This design made it possible to study the development of psychological outcomes over time and prevented bias that can occur during a retrospective study. Not all women choosing invasive testing over NIPT were given a questionnaire and

were therefore potentially underrepresented in the study. Moreover, also in the questionnaire study the majority of participants was highly educated and therefore maybe not representative for the pregnant population of the Netherlands. However, it can also be explained by the fact that highly educated women often delay childbearing and are thus more likely to have a high risk FCT result and be referred to follow-up testing and counseling in the TRIDENT study. Lastly, the use of the MMIC (Multi-dimensional Measure of Informed Choice) in this study to measure informed choice was not ideal as it is not developed to measure informed choice among women choosing between different tests. Moreover, the MMIC is a rather simple measure for the complex process of making a decision for prenatal testing. Unfortunately, there is no alternative measure for informed choice as of yet.

### **IMPLICATIONS FOR PRACTICE**

In the Netherlands, the TRIDENT study created a learning phase where pregnant women could be offered NIPT, whilst in the meantime the offer and experiences of pregnant women could be evaluated and developed further. Other countries aiming to implement NIPT in public healthcare could also benefit from such a learning phase as it stimulates responsible implementation. Results of this thesis show that with good counseling and information provision, most women can make an informed choice for NIPT as a contingent screening test. If NIPT will be offered as a first-tier test to all pregnant women, new information material and counseling techniques should be developed in order to safeguard informed decision-making in this situation. Decision aids could play an important role, since they have a positive effect on the decision making process in the prenatal context, and help decrease feelings of anxiety and decisional conflict.<sup>(20)</sup> Continuous attention for counseling is required, especially for low-educated and less health-literate women. While the proposed idea of testing for a wider range of disorders is received positively, there is a strong need for professional, political and societal debate on the impact of a broader screening offer.

### **RECOMMENDATIONS FOR FUTURE RESEARCH**

This thesis shows that key stakeholders are interested in NIPT. However, there are concerns about NIPT's impact on informed decision-making. Therefore, the following recommendations for research can be drawn from this thesis.

1. More research should be done on strategies and tools (i.e. decision aids) that can secure adequate counseling and informed-decision making when offering NIPT as a first-tier test.
2. Research is needed on the impact of testing for a wider range of disorders, including strategies that safeguard informed decision-making but prevent 'information overload'.

3. In order to generalize findings of this thesis, research is needed among more representative study populations including people with lower SES and different ethnic backgrounds.

## **CONCLUSION**

This thesis shows that key stakeholders groups are interested in NIPT for aneuploidy as well as testing for a wider range of disorders with NIPT. Introducing NIPT within a study context assisted a responsible implementation in Dutch prenatal care and led to an offer that satisfied high-risk women and allowed them to make an informed choice. However, there are concerns about informed decision-making if NIPT becomes a first-tier test and even more if it will screen for multiple disorders in the future. These concerns call for safeguarding informed decision-making through training of health professionals and realizing good pre-test counseling. Innovative strategies and counseling aids could be helpful, especially, but not exclusively, for women with low educational levels and/or inadequate health literacy. When testing for a wider range of disorders it is important to find a way that facilitates rather than undermines well-informed decision-making.

Even though NIPT has excellent test characteristics, stakeholders are highly aware of the potential for NIPT to put informed decision-making at stake. This strong awareness in itself will likely help to avoid a scenario of routinization and to protect the aim of prenatal screening.

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