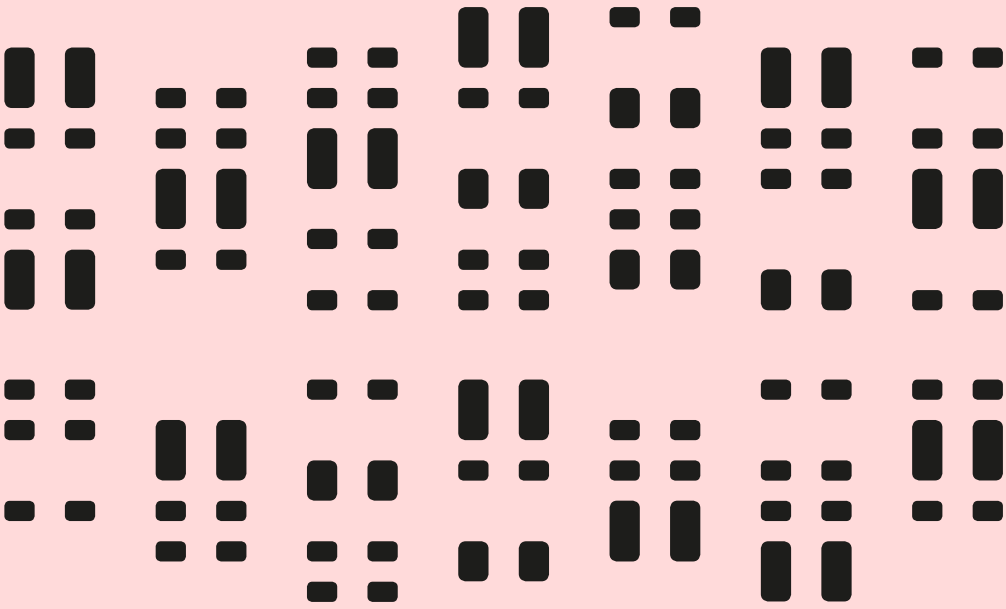
The new era of prenatal genetic testing

Considerations regarding the scope, psychological consequences & pregnant couples' preferences



Sanne Leanne van der Steen

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The New Era of Prenatal Genetic Testing

Considerations regarding the scope, psychological consequences and pregnant couples' preferences

Het Nieuwe Tijdperk van Prenataal Genetisch Testen

Overwegingen betreffende de reikwijdte,
psychologische gevolgen en de voorkeuren
van zwangere stellen

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam

op gezag van de rector magnificus
Prof. dr. R.C.M.E. Engels

en volgens besluit van het College voor Promoties

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Table of contents

Chapter 1

General introduction

Prenatal testing: screening and diagnosis

The field of prenatal testing has rapidly developed over the past decades. Until 1970 women would get pregnant and have babies without knowing anything about the health of their pregnancy or future health of their child. In the seventies and eighties techniques that allowed to gain more knowledge of the (future) health of the baby, before birth were developed. It was these techniques that made the introduction of prenatal testing possible. Since the 1970's, prenatal chromosomal testing has become available by means of an amniocentesis (AC) or chorionic villus sampling (CVS), both invasive procedures with an associated miscarriage risk of 1:200, or 1:300. With AC, a sample of amniotic fluid (fluid around the baby) is removed from the uterus. CVS removes a small sample of placenta tissue from the uterus. The amniotic fluid or placental tissue can be genetically analysed in the laboratory.

Originally, chromosomal testing was performed with karyotyping and was only targeted at the detection of Down's, and later also for Edwards, and Patau syndrome. Down's syndrome is the most common chromosomal abnormality and occurs in around 1 in 500 pregnancies in the Netherlands. From the 1970's onwards, chromosomal testing has been the golden standard in prenatal chromosomal testing until the introduction of first trimester screening (FTS) in the Netherlands in 2007. FTS, by means of the combination test, allowed pregnant women to screen for the presence of Down's syndrome, Patau syndrome and Edwards syndrome, that is, trisomy 21, 18 and 13. Pregnant women with an increased risk based on FTS have a higher probability (for example ± >1:200) of a child with one of these syndromes and may opt for further testing in their pregnancy by means of prenatal genetic testing.

Reproductive rights are relating to reproduction and reproductive health. The World Health Organization defines these rights as follows: Individuals or couples have the right of reproductive autonomy, meaning they are free to decide if they want to have children, how many, the spacing between children and at which time in their life.

Prenatal screening programs were designed to give women more control over their reproductive autonomy. The goal of prenatal screening is thus to enable women or couples to make informed decisions about the course of their pregnancy.[1] Informed choice is a prerequisite for engaging in medical procedures

in the Netherlands. Informed choice is different from informed consent. The concepts of informed consent and informed choice are disentangled; informed consent is used to protect both patients and doctors, whereas informed choice is mostly used to evaluate counselling (Retel Helmrich, 2017). A choice is considered informed when there is sufficient knowledge and a consistent attitude. Michie et al. defined an informed choice as 'based on relevant knowledge, consistent with one's attitudes and behaviourally implemented' (2001).[2]

Informed choice is especially relevant in the l field of prenatal testing and screening and is viewed as very important for coping with the test results. In the case of a pregnant woman engaging in prenatal screening, her choice would be considered informed if she knows what the aim of prenatal screening is, if she has knowledge about the test and its' characteristics, the possible outcomes, if she has deliberated whether or not the information that FTS might generate is important to her, and if she consequently decides to engage in FTS or not.

Before 2014

Before 2012, chromosomal testing was performed with conventional karyotyping at a resolution of 5–10 megabases (Mb) for all indications. Since 2012, the Erasmus Medical Center has replaced karyotyping with microarrays (single nucleotide; SNP array) at 0.5 Mb resolution.[3] SNP array allows for the detection of microdeletions and duplications at a very detailed level. As a metaphor, one could compare the level of detail with the mere design of a book case. With karyotyping you look at the bookcase from a distance. You can see the shelves and whether they are filled with books, but you cannot see the books separately, nor read the titles. With microarray, you stand very close to the bookcase. You see the individual books and you can even read the titles. Using the same metaphor, with karyotyping you can see whether shelves are missing or empty, whereas with microarrays you can see whether individual books are missing and even read their titles. Thus, microarray yields much more information about the health of the unborn child.

A next step would be next generation sequencing (exome or genome sequencing) which metaphorically speaking would mean that we read the books and determine whether text is correct.

Erasmus Medical Center offers microarray to all pregnant women engaging in prenatal diagnosis as a first-tier follow-up genetic test after abnormal first trimester screening results.[3] This broad scope microarray is only available when

performing invasive prenatal diagnosis by means of an amniocentesis or chorionic villus sampling with an associated miscarriage risk.

After 2014

Since 2014, non-invasive prenatal testing (NIPT) has been introduced in the Netherlands. With NIPT, it is possible to test with a high probability (92–99% certainty) for trisomies 21, 18 and 13 at *no risk* of a miscarriage.[4] NIPT has a resolution of ±20 Mb, which is less detailed than karyotyping and microarray. Thus, it provides less genetic information about the fetus when compared to NIPT is offered as an alternative for invasive PND. Pregnant women with an increased risk based on FTS could opt for either NIPT or invasive PND as a follow-up genetic test. The Erasmus Medical Center had a different policy regarding invasive prenatal testing than the other genetic centers in the Netherlands. Whereas other academic centers in the Netherlands performed only Quantitative Fluorescence-Polymerase Chain Reaction (QF-PCR) on fetal DNA to examine chromosomes 13, 18 and 21, we perform high resolution SNP array at 0.5 Mb to analyze all chromosomes at a submicroscopic level. The Erasmus Medical Center has completely replaced karyotyping by a whole genome SNP array for all indications since July 2012. SNP array is faster and less costly than karyotyping, but most importantly; it provides much more detailed additional information on other chromosomal aberrations. The broader scope of possible outcomes requires more extensive pre-test counselling to enable informed decision-making.

Consequences of a broader scope

The increasing scope of possible findings provided by SNP array and NIPT complicates sound prenatal genetic counselling and may subsequently influence the pregnant couple's informed decision-making process negatively.[5] As techniques in the prenatal field are developing rapidly, concerns were raised about the attainability of informed choice due to the more complex information women or couples are presented during counselling.[6–9] An informational overload could put burden on pregnant women and couples, and the information might hinder instead of promoting reproductive autonomy.[10, 11] It is voiced that the informational overload could lead to anxiety, heightened levels of stress and doubts which might

put further psychological burden on pregnant women or couples. Moreover, the complexity of information challenges the communicational skills of counsellors and might tread heavily on the principle of shared decision-making.

For this reason, the research described in this thesis focuses on the increased scope of prenatal genetic testing and on the psychological consequences for pregnant women or couples.

Aim and research questions

The aim of this thesis is to address the psychological consequences of the introduction of new techniques in prenatal testing for pregnant women or couples which as a consequence may lead to the identification of many more clinically relevant findings with which couples have to deal with. The option of microarray testing in a prenatal setting has been left unexplored so far and has not yet been evaluated in earlier studies. Part 1 of this thesis addresses the preferences of pregnant women or couples regarding the scope of invasive prenatal diagnosis, in the pre-NIPT era. The psychological consequences, such as anxiety and doubts of a broader scope and level of informed choice are studied. Part 2 of this thesis focuses on the psychological consequences of the additional, non-invasive option of NIPT, and on the level of informed choice. Finally, it was explored whether the preference of counsellors regarding testing options affected the decision-making. This led to the following research questions:

Part 1: Era before NIPT was introduced, solely invasive PND

1. What do pregnant women or couples choose; a broad or narrow scope of microarray regarding invasive PND? (Chapter 2)
2. Do they wish to be informed of uncertain outcomes?
3. Are there differences between participants opting for broad or narrow microarray regarding: the level of informed choice, anxiety and doubts? (Chapter 3)
4. What is the psychological impact on parents of receiving uncertain outcomes from invasive prenatal diagnosis? (Chapter 4)

Part 2: Era after introduction of NIPT

1. What do pregnant women or couples choose; NIPT or invasive PND? (Chapter 5)
2. Are there differences between participants opting for NIPT or PND regarding: the level of informed choice, anxiety and doubts? (Chapter 5)
3. Are there differences between women or couples who are counselled in non-academic vs. academic hospitals regarding their choices for NIPT or PND? (Chapter 5)
4. Do counsellors differ in the content and approach of their counselling regarding the level of information-centeredness, patient-centeredness, and the level of non-directivity? (Chapter 6)
5. Does the counsellor preference for NIPT/PND affect patients' choice? (Chapter 6)
    a. Were patients aware of the counsellor's preference?
    b. Were there differences in patients' knowledge and attitude scores *between* counsellors?

References

1. Gezondheidsraad. *Prenatale screening. Downsyndroom, neuralebuisdefecten, routine-echoscopie.* Den Haag: Gezondheidsraad; 2001.
2. Marteau T.M., Dormandy E., Michie S. A measure of informed choice. *Health Expect.* 2001;4(2):99–108.
3. Srebniak M.I., Mout L., Van Opstal D., Galjaard R.J. 0.5 Mb array as a first-line prenatal cytogenetic test in cases without ultrasound abnormalities and its implementation in clinical practice. *Hum Mutat.* 2013;34(9):1298–1303.
4. Oepkes D., Page-Christiaens G.C., Bax C.J., et al. Trial by Dutch laboratories for evaluation of non-invasive prenatal testing. Part I-clinical impact. *Prenat Diagn.* 2016;36(12):1083–1090.
5. Sachs A., Blanchard L., Buchanan A., Norwitz E., Bianchi D.W. Recommended pre-test counselling points for noninvasive prenatal testing using cell-free DNA: a 2015 perspective. *Prenat Diagn.* 2015;35(10):968–971.
6. de Jong A., Dondorp W.J., Macville M.V.E., de Die-Smulders C.E.M., van Lith J.M.M., de Wert G.M.W.R. Microarrays as a diagnostic tool in prenatal screening strategies: ethical reflection. *Human Genetics.* 2014;133(2):163–172.
7. Dondorp W., de Wert G., Bombard Y., et al. Non-invasive prenatal testing for aneuploidy and beyond: challenges of responsible innovation in prenatal screening. Summary and recommendations. *Eur J Hum Genet.* 2015.
8. McGillivray G., Rosenfeld J.A., McKinlay Gardner R.J., Gillam L.H. Genetic counselling and ethical issues with chromosome microarray analysis in prenatal testing. *Prenat Diagn.* 2012;32(4):389–395.
9. van den Berg M., Timmermans D.R., ten Kate L.P., van Vugt J.M., van der Wal G. Informed decision making in the context of prenatal screening. *Patient Educ Couns.* 2006;63(1–2):110–117.
10. de Jong A., Dondorp W.J., De Wert G.M. The scope of prenatal diagnostic testing for chromosomal aberrations: broad or narrow? Ethical considerations on the choice of tests. *Ned Tijdschr Geneeskd.* 2009;153:A1060.
11. Dondorp W., Sikkema-Raddatz B., de Die-Smulders C., de Wert G. Arrays in postnatal and prenatal diagnosis: An exploration of the ethics of consent. *Hum Mutat.* 2012;33(6):916–922.

Chapter 2

Pregnant couples at increased risk for common aneuploidies choose maximal information from invasive genetic testing

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Abstract

Genomic array detects more pathogenic chromosomal aberrations than conventional karyotyping (CK), including genetic variants associated with a susceptibility for neurodevelopmental disorders; susceptibility loci (SL). Consensus regarding the scope of invasive prenatal diagnosis (PND) pregnant couples should be offered is lacking. This study examined pregnant couples' preferences, doubts and satisfaction regarding the scope of invasive PND.

Eighty-two couples choosing prenatal screening (PNS) and 59 couples choosing invasive PND were offered a choice between 5 Mb (comparable to CK) and 0.5Mb resolution array analysis outcomes, the latter with or without reporting SL. A pre-test self-report questionnaire and post-test telephone interview assessed their choices in-depth.

Actual (PND) and hypothetical (PNS) choices differed significantly ($p < 0.001$). Ninety-five percent of the couples in the PND group chose 0.5Mb array, versus 69% in the PNS group. Seven percent of the PND group wished not to be informed of SL. Ninety percent was satisfied with their choice and wished to decide about the scope themselves. Pregnant couples wish to make their own choices regarding the scope of invasive PND. It therefore seems justified to offer them a choice in both the resolution of array and disclosure of SL.

Introduction

Genomic array analysed at high resolution detects more pathogenic anomalies compared to conventional karyotyping (CK) (resolution 5–10 Mb).[1–4] However, it may also reveal pathogenic findings not related to the indication, genetic variants with incomplete penetrance and variable phenotype associated with a susceptibility for neurodevelopmental disorders; susceptibility loci (SL) or variants of unknown significance (VOUS).[5] Analysis with higher resolution (e.g. 0.5 Mb) detects common trisomies and known (micro)deletion/duplication syndromes that match the indication, but also potentially reveal more unexpected diagnoses and uncertain results such as SL than CK (resolution 5–10 Mb). The advantages of SNP array in invasive PND are evident for pregnancies with ultrasound anomalies,[1,2] but the implementation of SNP array in invasive PND for other indications has raised concerns among professionals.[6–9]

First, informed consent is believed to be untenable due to the higher incidence of findings not related to the indication.[6,10] Some have argued that array might complicate informed decision-making.[6,7,8,11] Generic consent has been proposed as an alternative,[6,11] which we temporarily implemented by offering pregnant couples a choice between predefined categories of genetic outcomes when we started using SNP array in case of ultrasound anomalies.[12] However, whether generic consent will provide sufficient basis for decision-making has not yet been established. Second, first trimester screening (FTS) is intended to identify pregnancies at risk for the most common aneuploidies (Down, Edwards and Patau syndrome), while SNP array as a follow-up test may detect many more genetic aberrations for which the a priori risk is not increased.[13]

Third, when using SNP array, genetic variants associated with susceptibility for neurodevelopmental disorders such as developmental delay, and/or behavioural/learning problems, autism spectrum disorders or seizures are found in about 1% of pregnancies without foetal ultrasound anomalies.[1,2] If found prenatally, the risk of developing the disorder is not yet quantifiable. The phenotype of the foetus is difficult to assess due to phenotypic heterogeneity of the carriers and functional and some structural foetal anomalies cannot be detected by ultrasound examination. The phenotype may vary from normal to severely affected, probably depending on a second hit[14] or genetic/environmental background. Thus, the use of array also ensues the dilemma whether to inform pregnant

couples of SL or not. It has been argued that pregnant couples may not wish to be informed of findings of uncertain nature[3] and that such findings should be withheld in order not to put burden on the pregnant couple.[15,16] On the other hand, it has been proposed that couples should be informed of any finding in order to be able to exert their reproductive autonomy8 and that better tools for dealing with uncertainty should be developed.[9,15,17,18]

Previous research on patients' choices has demonstrated quite consistently that when offered a choice regarding the number of genetic conditions tested in one test, pregnant couples preferred a maximum of conditions.[19,20] However, the latter study concerned hypothetical preferences and did not concern SNP arrays. Remarkably, few studies investigated the actual choices concerning invasive prenatal testing in a real-life setting.

The aim of this study was to investigate whether pregnant couples at increased risk for an aneuploidy prefer 5 or 0.5Mb array, to assess whether couples who engage in PNS or PND differed in this choice (theoretical vs. actual choice) and to assess whether pregnant couples wished to be informed about uncertain information such as SL. Additionally, we investigated whether participants opting for higher resolution experienced more doubts regarding their choice and whether participants were satisfied regarding their choice four weeks after the test result.

Materials and methods

Participants

Pregnant women or couples were approached from February 2012 to September 2013 in the clinic of the department of prenatal medicine in the Erasmus Medical Center in Rotterdam, the Netherlands. We included partners of pregnant women since we were interested in both partners' decision processes. Other studies focused mainly on pregnant women. This study was exempted by the medical ethical committee of the Erasmus University Rotterdam. Inclusion criteria for participation were a) increased risk on common trisomies (advanced maternal age (AMA), increased risk based on FTS or combined indication), b) the woman or couple was participating in first-trimester prenatal screening (PNS) or invasive prenatal diagnosis (PND) and c) fluency in Dutch language. The exclusion criteria were a) presence of ultrasound anomalies and/or b) language barriers. The

sample (N = 250) consisted of 141 female and 109 male participants (see Figure 1 and 2). Women were approached at the intake of their first ultrasound, around 9–11 weeks gestational age (GA) and counselled by a clinical geneticists (together with partner), after which both pregnant women and their partners filled out questionnaires individually. Between 16–23 weeks GA, participants were approached for follow-up by phone. See Figure 3 for a timeline of the study.

Methods

An information leaflet about the study was added to the invitation letter pregnant women received before attending the outpatient clinic. A research-assistant was present at the clinic to approach pregnant couples meeting the inclusion criteria and provide information concerning the study and its further procedure. After consenting, an additional genetic counselling with a clinical geneticist by telephone was planned in in advance of the next appointment for PNS or PND in order to enable informed decision-making. Face-to-face counselling was not practically feasible in this study.

Counselling

We offered participants a choice between a SNP array analysed at 5 Mb resolution (comparable to CK) and a SNP array analysed at 0.5 Mb resolution (higher resolution). Participating couples received counselling from (or under the supervision of) a clinical geneticist by telephone. Extensive information was provided. In addition to the background of genetics, participants were informed of the difference between 5 Mb resolution and 0.5 Mb resolution. Examples of what could be detected additionally by 0.5 Mb testing over 5 Mb testing was illustrated with Wolf-Hirschhorn syndrome, Duchenne muscular dystrophy and examples of SL. SL were explained as 'risk factors', genetic variants that give an elevated but unquantifiable chance on mainly neurodevelopmental disorders, such as autism, learning disabilities, epilepsy and/or psychiatric disorders. The geneticist explained these 'risk factor variants' could occur in both healthy and affected individuals and that they have a variable expression, ranging from no expression at all to severe expression.

Five Mb resolution array was presented as a 'narrower test' and it was specified that trisomy 13, 18 and 21 and other microscopically visible deviations could be found. The last part of the counselling consisted of a dialogue about the

couples' concerns, questions and preferences. Couples were asked whether they already knew what test they preferred and whether they needed additional information to make a decision. Within three days after counselling but *before* their PND or PNS appointment, all participants filled out a questionnaire individually.

Participants engaging in PND were contacted by the researcher one day before their appointment to ascertain their choice (0.5 Mb or 5 Mb analysis). The laboratory was informed of the couples' choice and performed their array resolution of choice. Participants engaging in PNS and not proceeding with PND made a hypothetical choice. PNS participants filled out the questionnaire hypothetically, they were asked 'If you should engage in invasive PND by means of amniocentesis or chorionic villus sampling, what array resolution would you choose?'. Then, the PNS group filled out the same questions as participants in the PND group, while keeping their hypothetical choice for the array resolution in mind. Additionally, if participants in the PNS group were undecided, they could opt for 'I cannot choose'.

Data

Socio-demographic data were collected, see Table 1. Pregnant couples' choices and willingness to choose between 0.5 and 5 Mb array PND were assessed (options: 'I want to decide myself', 'I think the doctor should decide', 'I want to make a decision in consultation with the doctor' or 'I do not have an opinion about this'). One question assessed whether pregnant couples would be interested in whole exome sequencing (WES) in the near future ('If there would be a test that could detect even more anomalies, do you feel this test should be offered?', options of answer: yes/no/no opinion). Furthermore, the questionnaire comprised the Decisional Ambivalence Scale (DAS) which was designed for this study. The DAS measured doubt or confidence regarding the choice with ten items (see Table 2). All items had a 10-point response format and ranged from 1 (not at all) to 10 (very much so). DAS total score ranged 10–100, a higher score indicated a higher level of experienced doubts.

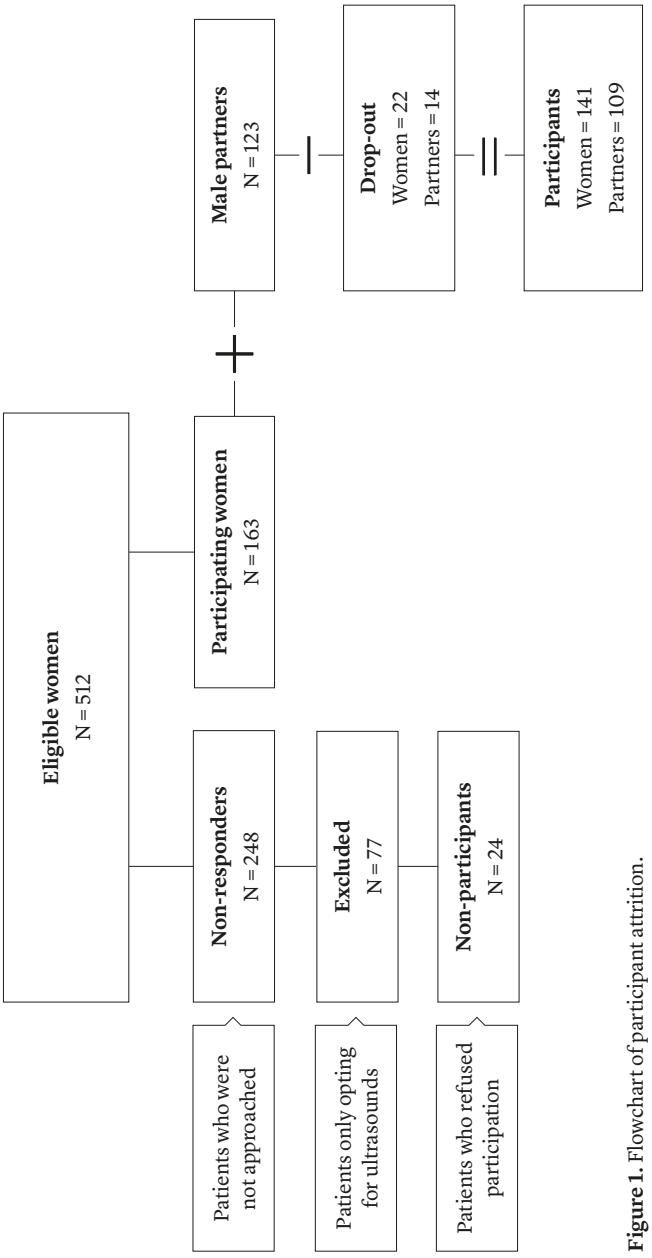

Figure 1. Flowchart of participant attrition.

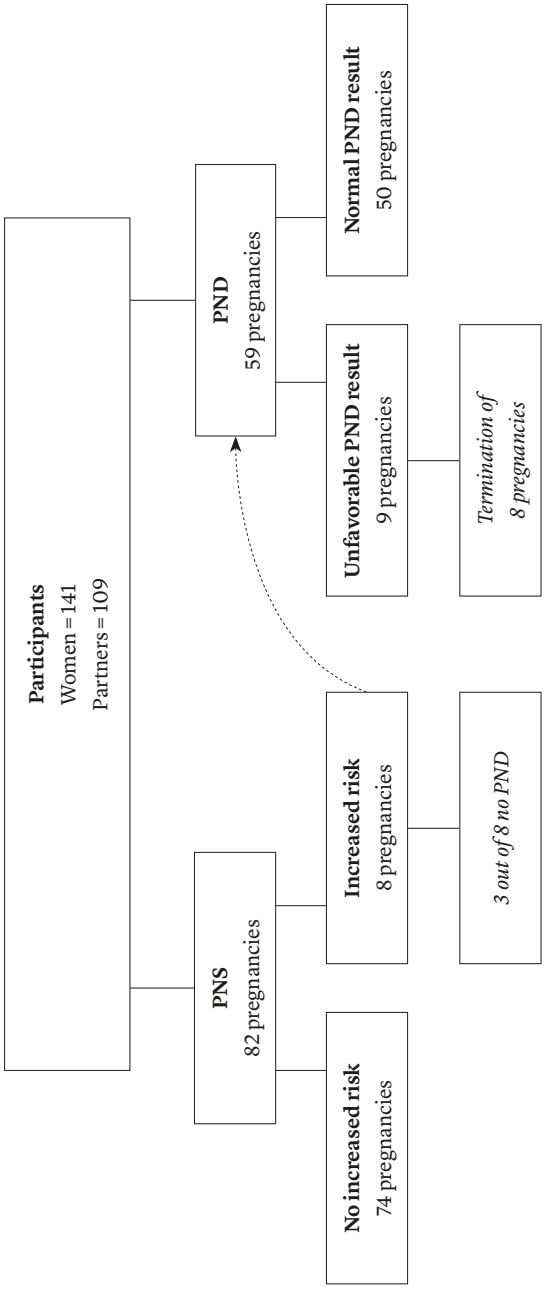

Figure 2. Flowchart of the outcomes from PNS and PND.

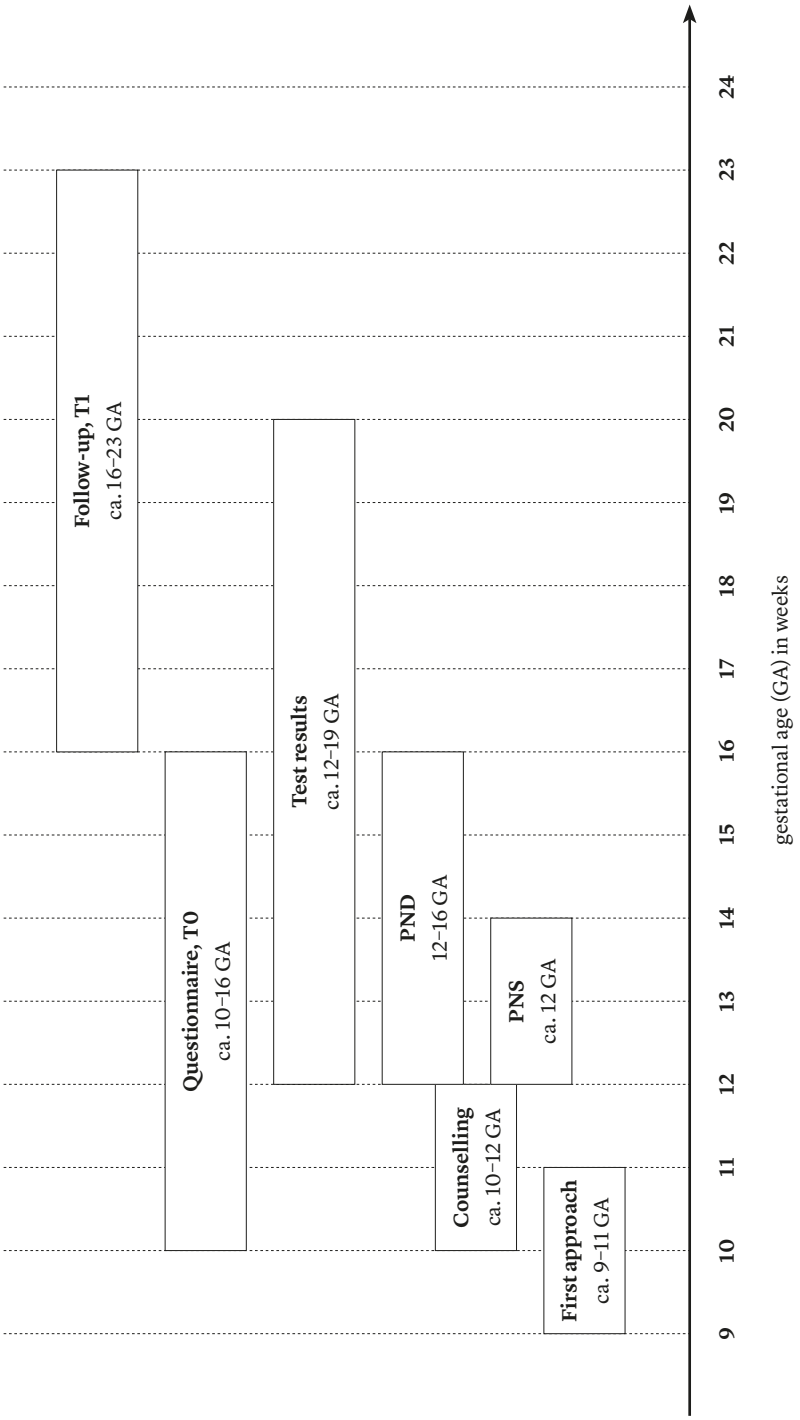

Figure 3. Timeline of the study.

	N	%	PNS			PND		p(χ^2) PNS/PND	p(χ^2) 5/0.5 Mb
			0.5Mb	5Mb	No choice	0.5Mb	5Mb		
Sex								.991	.506
Women	141	56	49	24	3	61	4		
Men	109	44	47	12	1	46	3		
Indication (pregnancies)								**.001****	**.026***
Advanced maternal age	103	77	37	16	3	43	4		
ICSI pregnancy	16	11	7	6	0	3	0		
Increased risk (after PNS)	8	5	0	0	0	8	0		
Combined indication	14	7	5	2	0	7	0		
Miscarriages (previous)								.662	.962
Yes	55	38	20	9	1	24	1		
No	86	62	27	15	0	36	3		
PNS or PND (pregnancies)									**.001****
Prenatal screening	144 (82)	58	50	29	3	55	4		
Prenatal diagnosis	106 (59)	42							

Children								**.047***	.342
Yes	143	56	49	19	0	64	4		
No	107	44	47	16	3	42	3		
Educational level								.189	.962
Low/intermediate	87	35	26	16	3	38	1		
High	159	64	67	17	6	62	2		
Missing	4								
Nationality								.421	.991
Dutch	229	92	90	33	9	96	3		
Other	21	8	4	3	0	7			
Religion								.700	.110
Yes	41	16	14	9	4	21	0		
No	150	60	59	18	4	63	3		
Missing	59	24							

* P < .05 (Pearson Chi-square)

** P < .001 (Pearson Chi-square)

Table 1. Socio-demographic characteristics of sample by group and choice (N = 250).

Items		Mean	SD
a.	I have made the right choice about the test	8.39	1.55
b.	I accept the consequences of my choice	8.73	1.52
c.	I am happy to make this choice myself	8.84	1.36
d.	I have doubts about my choice	3.06	2.36
e.	I am worried about the possible consequences of my choice	4.65	2.82
f.	I would prefer the doctor to make this choice	2.07	1.81
g.	My partner supports me in this choice	9.15	1.71
h.	The choice I have made, feels like my own choice	8.94	1.66
i.	My choice seemed to have the doctors preference	3.21	2.49
j.	I have had sufficient information to make my choice	8.25	1.78

Table 2. Items and Range of Decisional Ambivalence Scale.

Statistical analyses

Before analysing the data for this study, assumptions for ANOVA were checked. A significance level of p <0.05 was used for all analyses. Outliers were detected, reverse-scored items were recoded and total scores have been calculated. To validate the instruments, Cronbach's alpha was used to examine the internal consistency of the DAS. To assess if there was a relationship between background variables and the choice of test separate Pearson's Chi-square tests were performed. To assess whether the choice for 5 or 0.5 Mb differed between the PNS and PND group a Pearson Chi-square test was used. We performed Pearson's Chi-square tests on socio-demographic data to determine whether we could analyse the results for the PNS and PND group as a whole (to test if background variables differed in the PNS and PND group). A one-way ANOVA was performed to assess if level of doubt differed between educational level. To assess whether the choice for 5 or 0.5 Mb differed between educational level a Pearson's Chi-square test was used. A one-way ANOVA was performed to assess whether 0.5/5 Mb array analysis and PNS/PND differed in levels of experienced doubts on T0 (after the counselling, but before their first appointment for PND or PNS) and T1 (four

weeks after their test result). Furthermore, correlation between choice and level of doubt was calculated. Lastly, we assessed whether pregnant couples were satisfied with their choice for the array resolution four weeks after their test results. IBM SPSS Statistics 21.0.0.1 was used to analyse data.

Results

Women's mean age was 37.7 (SD = 3.1) and men's 39.8 (SD = 5.6) years. Internal consistency of the DAS was $\alpha = .85$ in a sample of 250 participants.

There was a significant association between the test type (PNS/PND) and already having children ($\chi^2(4) = 9.65$, $p < 0.05$), as well as the test type (PNS/PND) and the indication ($\chi^2(3) = 34.00$, $p < 0.001$), see Table 1. Pregnant couples who already had children opted for invasive PND more often, as well as women with an AMA indication. Furthermore, there was a significant association between the choice of array resolution (5 Mb/0.5 Mb) with indication ($\chi^2(9) = 18.96$, $p < 0.05$) and with test type (PNS/PND), ($\chi^2(3) = 45.18$, $p < 0.001$). Pregnant women with an AMA indication opted for 0.5 Mb more often, as well as for invasive PND.

There were no other significant differences regarding the socio-demographic and obstetric background variables, see Table 1.

Pregnant couples' decisions regarding the choice of test

Seventy-nine percent of the participants wished to decide about the scope of invasive prenatal testing solely themselves, 19% wished to decide about this in consultation with a doctor whereas 1% wished the doctor to decide for them (1% missing).

Ninety-four per cent of the PND group and 69% of the PNS group chose testing at higher resolution (0.5Mb array), and of these groups 84% and 44% resp. wished to be informed of SL if detected (see Figure 4 and 5). The PND group chose 0.5 Mb SNP array analysis significantly more often, $\chi^2(2) = 18.49$, $p < 0.001$, and also chose to be informed of SL significantly more often, $\chi^2(2) = 44.79$, $p < 0.001$. In the PNS group, 7% of the participants was unable to make a hypothetical choice.

Seventy-eight percent of all participants appreciated the option of whole exome sequencing (WES) in the near future. Only 8% would not like to know as much as possible and 14% did not have an opinion about WES.

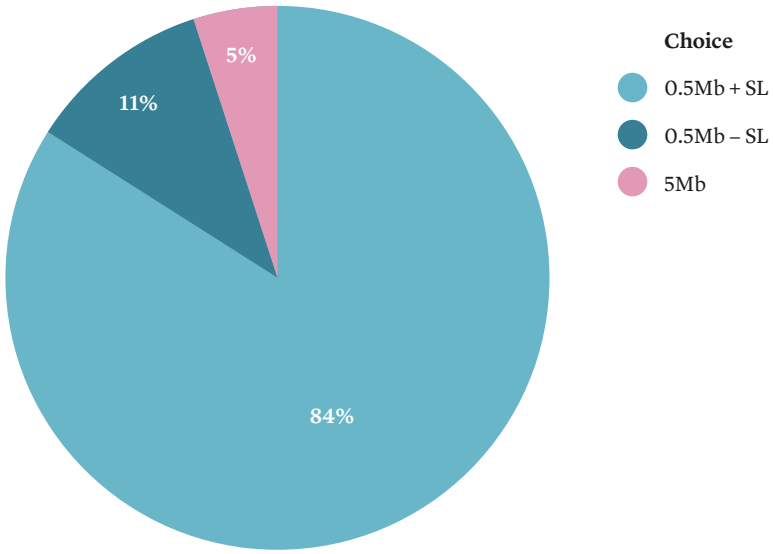

Figure 4. Actual choice of all participants in the invasive prenatal diagnosis group.

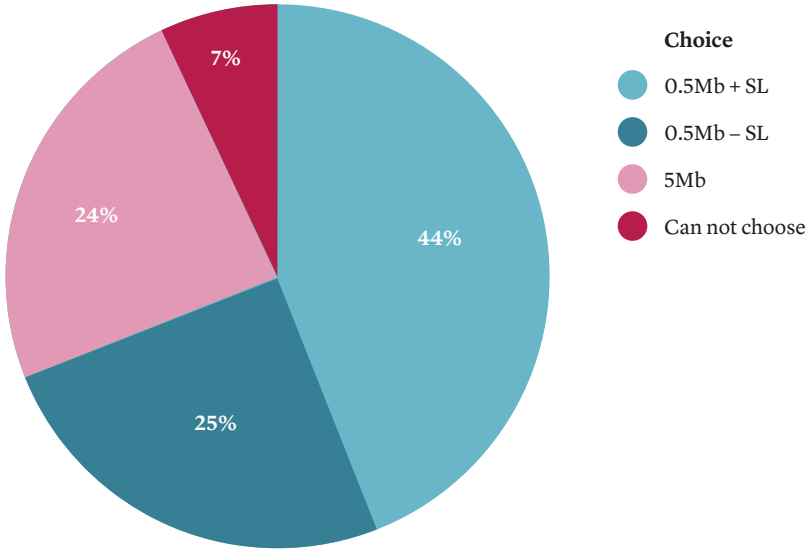

Figure 5. Hypothetical choice of all participants in the prenatal screening group.

Educational level

We identified three levels of education; low (primary to low secondary education), intermediate (higher secondary to low tertiary education) and high (bachelors, masters and above). A one-way ANOVA was performed to test if level of experienced doubts (T0 and T1) differed between educational level. There was no significant effect of educational level on level of experienced doubts nor in choice of array resolution.

PNS vs. PND group

The PNS and PND group did not significantly differ in level of doubts.

0.5 Mb vs. 5 Mb

There was a significant effect of choice on T0 doubts, F (3,239) = 3.76, p<.05. The 5 Mb group (M = 35.10, SD = 9.80) experienced significantly more doubts on T0 than the 0.5 Mb group (M = 30.44, SD = 9.21). The correlation between choice of test and level of doubts was R = 0.046, r = 21, p<.05, showing a significant, small to medium positive relationship. On T1 (four weeks after the test result) this effect was not significant.

Of all participants, 90% was satisfied with their choice, however 27% of these had doubts and 19% was worried about the possible consequences of their decision four weeks after the test result.

Discussion

Since the availability of prenatal whole genome SNP array analysis, there is much discussion whether this genetic test should be offered to pregnant couples for other indications than foetal ultrasound anomalies. The aim of this study was to investigate the real-time diagnostic preferences of pregnant couples at increased risk for common trisomies.

Both the PNS and PND group preferred broad scope testing, which is congruent with earlier findings.[7] It seems that the pregnant couples are not withheld in their choice by concerns voiced by professionals in the field such as the right to self-determination, the right not to know etc.[6-8] Since the majority of the PNS group also preferred higher resolution testing, it would seem that it is not

just the miscarriage risk of invasive testing that prompted pregnant couples to want to learn as much as possible about the (future) health of their unborn child. Pregnant couples may have a greater information need than what is commonly offered. It is important to emphasise that pregnant couples appreciated being offered a choice, which is consistent with our 21 and other's experience.[7, 22] Several studies have previously demonstrated that professionals were more conservative than pregnant couples with regard to what PND should detect.[7, 23] An earlier study explored the views and preferences of professionals and potential users concerning PND.[7] In this study, most potential users and midwives preferred individualised choice in PND, whereas physicians (gynecologists, clinical geneticists and cytogeneticists) would prefer rapid aneuploidy detection (RAD) for efficiency and financial reasons. In congruence, we were also more conservative than the pregnant couples since we anticipated that couples would decline SL, because knowledge of SL might lead to increased stress and worries.[6, 8, 16] It was striking that most pregnant couples wished to be informed of the presence of SL should these be detected. Apparently, pregnant couples value information to the extent that they are willing to bear the uncertainty caused by SL. In our sample none of the couples received an SL as a test outcome. Thus, it was not possible to reflect on how couples dealt with SL in the current study. In due course we will report on the psychological impact of uncertain outcomes such as SL.

Most of the research into broadening the scope of PND concerned hypothetical choices.[19] In the only two studies offering a real choice, pregnant couples preferred CK over targeted testing for common occurring aneuploidies (RAD standalone).[20, 22] The current study is unique in offering pregnant couples an actual choice between 5 Mb (comparable to CK) and 0.5 Mb array resolution analysis. Couples who made a real-time choice more often chose for higher resolution array, thus, our outcomes suggest that a hypothetical choice may not be a good predictor of the choice couples make once they actually engage in PND.

Although most participants were satisfied with their choice, about one third of these reported doubts or feelings of worry regarding this choice. Couples opting for the higher resolution experienced less doubts regarding their choice than did couples opting for a lower resolution. These couples may have felt more reassured that severe genetic anomalies would not be missed. In contrast, couples opting for a lower resolution analysis may already have been more doubtful about the possible outcomes of prenatal genetic testing. Alternatively, it may be

that the doubts pregnant couples experienced in our sample are influenced by the degree of informed decision-making, since making uninformed decisions is associated with experiencing psychological distress.[24]

Although the PND group almost unanimously opted for 0.5 Mb array analysis, most also indicated that they wished to decide about the scope of PND themselves. Thus, instead of suggesting it may be justified to merely offer 0.5 Mb array analysis in pregnancies without ultrasound anomalies, we suggest that couples should be offered a choice regarding the scope of invasive PND. We realise that offering this choice is not only a challenge for counselling and informed decision-making, but also for routine management of large numbers of patients. It may become necessary to start offering and counselling these options earlier in pregnancy, for example in primary care.

The current study had a number of limitations and strengths. A limitation in this study was the non-random, observational design and a homogeneous group of participants. The great strength of our study was that we were able to assess the actual choices of couples engaging in invasive PND.

Conclusion

In conclusion, offering pregnant couples an individualised choice regarding the scope of invasive PND seems an appropriate approach that is highly valued by patients. As most pregnant couples preferred a maximum of information (including SL) and wished to make their own decision about the scope of invasive PND, we suggest that patients without ultrasound anomalies may be offered a choice regarding the scope of invasive PND, including the option of a higher resolution array and disclosure of SL.

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References

1. Wapner R. J., Martin C. L., Levy B., Ballif B. C., Eng C. M., Zachary J. M., et al. Chromosomal microarray versus karyotyping for prenatal diagnosis. N Engl J Med. 2012 Dec 6;367(23):2175–84.
2. Fiorentino F., Caiazzo F., Napolitano S., Spizzichino L., Bono S., Sessa M., et al. Introducing array comparative genomic hybridization into routine prenatal diagnosis practice: a prospective study on over 1000 consecutive clinical cases. Prenat Diagn. 2011 Dec;31(13):1270–82.
3. Hillman S. C., McMullan D. J., Silcock L., Maher E. R., Kilby M. D. How does altering the resolution of chromosomal microarray analysis in the prenatal setting affect the rates of pathological and uncertain findings? J Matern Fetal Neonatal Med. 2013 Aug 19.
4. de Wit M. C., Srebniak M. I., Govaerts L. C., Van Opstal D., Galjaard R. J., Go A. T. Additional value of prenatal genomic array testing in fetuses with isolated structural ultrasound abnormalities and a normal karyotype: a systematic review of the literature. Ultrasound Obstet Gynecol. 2014 Feb;43(2):139–46.
5. Srebniak M. I., Diderich K. E., Govaerts L. C., Joosten M., Riedijk S., Galjaard R. J., et al. Types of array findings detectable in cytogenetic diagnosis: a proposal for a generic classification. Eur J Hum Genet. 2014 Jul;22(7):856–8.
6. Bunnik E. M., de Jong A., Nijsingh N., de Wert G. M. The new genetics and informed consent: differentiating choice to preserve autonomy. Bioethics. 2013 Jul;27(6):348–55.
7. de Jong A., Dondorp W. J., Krumeich A., Boonekamp J., van Lith J. M., de Wert G. M. The scope of prenatal diagnosis for women at increased risk for aneuploidies: views and preferences of professionals and potential users. J Community Genet. 2013 Jan;4(1):125–35.
8. McGillivray G., Rosenfeld J. A., McKinlay Gardner R. J., Gillam L. H. Genetic counselling and ethical issues with chromosome microarray analysis in prenatal testing. Prenat Diagn. 2012 Apr;32(4):389–95.
9. Vetro A., Bouman K., Hastings R., McMullan D. J., Vermeesch J. R., Miller K., et al. The introduction of arrays in prenatal diagnosis: a special challenge. Hum Mutat. 2012 Jun;33(6):923–9.

10. Bernhardt B. A., Soucier D., Hanson K., Savage M. S., Jackson L., Wapner R. J. Women's experiences receiving abnormal prenatal chromosomal microarray testing results. Genet Med. 2013 Feb;15(2):139–45.
11. Dondorp W., Sikkema-Raddatz B., de Die-Smulders C., de Wert G. Arrays in postnatal and prenatal diagnosis: An exploration of the ethics of consent. Hum Mutat. 2012 Jun;33(6):916–22.
12. Srebniak M., Boter M., Oudesluijs G., Joosten M., Govaerts L., Van Opstal D., et al. Application of SNP array for rapid prenatal diagnosis: implementation, genetic counselling and diagnostic flow. European Journal of Human Genetics. 2011;19(12):1230–7.
13. de Jong A., Dondorp W. J., Frints S. G., de Die-Smulders C. E., de Wert G. M. Advances in prenatal screening: the ethical dimension. Nat Rev Genet. 2011 Sep;12(9):657–63.
14. Girirajan S., Rosenfeld J. A., Cooper G. M., Antonacci F., Siswara P., Itsara A., et al. A recurrent 16p12.1 microdeletion supports a two-hit model for severe developmental delay. Nat Genet. 2010 Mar;42(3):203–9.
15. Rigter T., Henneman L., Kristoffersson U., Hall A., Yntema H. G., Borry P., et al. Reflecting on earlier experiences with unsolicited findings: points to consider for next-generation sequencing and informed consent in diagnostics. Hum Mutat. 2013 Oct;34(10):1322–8.
16. de Jong A., Dondorp W. J., Macville M. V., de Die-Smulders C. E., van Lith J. M., de Wert G. M. Microarrays as a diagnostic tool in prenatal screening strategies: ethical reflection. Hum Genet. 2013 Sep 28.
17. Wolf S. M., Paradise J., Caga-anan C. The law of incidental findings in human subjects research: establishing researchers' duties. J Law Med Ethics. 2008 Summer;36(2):361–83, 214.
18. Stark Z., Gillam L., Walker S. P., McGillivray G. Ethical controversies in prenatal microarray. Curr Opin Obstet Gynecol. 2013 Apr;25(2):133–7.
19. de Jong A., Dondorp W. J., De Wert G. M. The scope of prenatal diagnostic testing for chromosomal aberrations: broad or narrow? Ethical considerations on the choice of tests. Ned Tijdschr Geneeskd. 2009;153:A1060.
20. Boormans E. M., Birnie E., Oepkes D., Boekkooi P. F., Bonsel G. J., Van Lith J. M. Individualized choice in prenatal diagnosis: the impact of karyotyping and standalone rapid aneuploidy detection on quality of life. Prenat Diagn. 2010 30 928–36.

21. Srebniak M., Boter M., Oudesluijs G. V. O., D. , Joosten A., Govaerts J., Galjaard R. Application of SNP array for prenatal diagnosis -counselling and diagnostic flow. Eur J Hum genet 2011 submitted.
22. Kooper A. J., Smeets D. F., Feenstra I., Wijnberger L. D., Rijnders R. J., Quartero R. W., et al. Women's Attitudes towards the Option to Choose between Karyotyping and Rapid Targeted Testing during Pregnancy. Obstet Gynecol Int. 2013;2013:636459.
23. Boormans E. M., Birnie E., Bilardo C. M., Oepkes D., Bonsel G. J., Van Lith J. M. Karyotyping or rapid aneuploidy detection in prenatal diagnosis? The different views of users and providers of prenatal care. BJOG. 2009;116:1396–9.
24. Dormandy E., Michie S., Hooper R., Marteau T. M. Informed choice in antenatal Down syndrome screening: a cluster-randomised trial of combined versus separate visit testing. Patient Educ Couns. 2006 Apr;61(1):56–64.

Chapter 3

Choosing between higher and lower resolution microarrays: do pregnant women have sufficient knowledge to make informed choices consistent with their attitude?

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Abstract

Developments in prenatal testing allow the detection of more findings. SNP arrays in prenatal diagnosis (PND) can be analyzed at 0.5 Mb resolution, detecting more clinically relevant anomalies, or at 5 Mb resolution. We investigated whether women had sufficient knowledge to make informed choices regarding the scope of their prenatal test that were consistent with their attitude. Pregnant women could choose between testing at 5 or at 0.5 Mb array.

Consenting women ($N = 69$) received pre-test genetic counselling by phone and filled out the Measure of Informed Choice questionnaire designed for this study. Choices based on sufficient knowledge and consistent with attitude were considered informed. Sixty-two percent of the women made an adequately informed choice, based on sufficient knowledge and attitude-consistent with their choice of microarray resolution. Women who made an informed choice, opted for 0.5 Mb array resolution more often. There were no differences between women making adequately informed or less informed choices regarding level of experienced anxiety or doubts. Over time on T0 and T1, anxiety and doubts significantly decreased.

While previous studies demonstrated that knowledge is an important component in informed decision-making, this study underlines that a consistent attitude might be equally important for decision-making. We advocate more focus on attitude-consistency and deliberation as compared to only a strong focus on knowledge.

Introduction

Prenatal genetic screening and follow-up diagnostic testing confront pregnant women with often difficult decisions. One of the first decisions women make is whether or not to participate in prenatal screening. When deliberating whether or not to participate in prenatal screening programs, many women may find it difficult to understand the characteristics of the test, to weigh its benefits and risks and to grasp the possible implications.[1]

The use of new, increasingly complex techniques, it is feared, may further hinder informed choices.[2-4] To date, there has been little empirical evidence to support or falsify the concern that women may no longer be able to make informed decisions regarding more complex prenatal tests. While techniques in prenatal screening and diagnosis are developing rapidly, the need for insight into whether pregnant women are making informed choices about prenatal genetic testing becomes ever more pressing.

The stated aim of prenatal screening is to offer reproductive options, allowing pregnant women to choose the best course of action if their unborn child is affected.[5] These actions may include preparing for the future, altering pregnancy management or terminating a pregnancy. Prenatal screening and diagnosis should thus provide information about the fetus that is relevant to reproductive decision-making. Information that is not relevant to reproductive decision-making, it is argued, consequently falls outside the scope of prenatal screening.[6] Information outside of this scope can be unwanted, for it may be burdensome and could lead to worry or anxiety for pregnant women. Moreover, such information may needlessly infringe upon their child's right not to know its genetic risk.[3, 6] Although the scope of prenatal screening should thus be limited to information that is relevant to reproductive decision-making, what is considered to be relevant is a topic for debate.

At present, in the Netherlands, prenatal screening is limited to detecting an increased risk of trisomies 13, 18 and 21. However, in our center we employ whole genome SNP arrays for prenatal diagnosis. One of the major consequences of using SNP array instead of more targeted techniques (such as rapid aneuploidy detection or conventional karyotyping) is that many more genetic aberrations may be detected (e.g., early onset diseases such as Williams syndrome, and Duchenne muscular dystrophy). Genetic aberrations may even include susceptibility loci (SL: 1.4%).[7]

SL are complicated test results because although they are defined as 'likely pathogenic',[8] the associated risk of expression and severity is yet unquantifiable. SL are associated with neurodevelopmental disorders such as learning disabilities, behavioral problems and/or seizures.[7,9] We reported on the first parents' experiences with prenatal disclosure of SL in a previous study.[10] Outcomes like these may be equally relevant to reproductive decision-making. There is tension between the legal scope of prenatal screening in the Netherlands and its stated aim of enabling reproductive autonomy. There is also a tension between the scope of SNP array for follow-up diagnostic testing at our clinic, and the scope of screening in the national prenatal screening program, which is much narrower.

This contentious topic leads to much discussion amongst professionals and ethicists about which test to employ and what to report to pregnant women regarding prenatal genetic test outcomes. Some emphasize that test results which fall outside the scope of prenatal screening might put an unnecessary burden on pregnant couples,[3] while others argue that withholding any kind of information is paternalistic and should be avoided.[11]

A prerequisite for reproductive autonomy is making an informed choice. Marteau et al. (2001) state that 'An informed decision is one where all the available information about the health alternatives is weighed up and used to inform the final decision; the resulting choice should be consistent with the individual's values. An effective decision is one that is informed, consistent with the decision maker's values and behaviorally implemented' (p. 100). Well-informed choices are psychologically beneficial.[12,13] Psychological management of prenatal test decisions is better when knowledge is adequate,[14] while uninformed choices increase decisional conflict and decrease feelings of personal wellbeing.[15] Psychological coping and informed choice were more difficult for pregnant women who were not prepared for the possibility of an abnormal prenatal screening result.[16] Studies reported that a majority of pregnant women did not make informed decisions regarding prenatal screening. and most women did not have sufficient knowledge to prepare them for the possibility of abnormal outcomes of prenatal screening.[17,18] Without adequate information provision and counselling, offering prenatal diagnosis with a wider scope could indeed burden the pregnant couple and undermine their reproductive autonomy instead of enhancing it. Making informed choices is meant to prevent the harms that too much unwanted information could cause.

What pregnant couples wish to learn about the health of their fetus is underreported thus far. The few studies on this subject indicate a preference among pregnant couples to learn as much as possible from prenatal diagnosis (PND).[19, 20] We have recently reported that the vast majority of pregnant couples to whom we had offered the choice between array at higher (0.5 Mb) or lower resolution (5Mb, comparable to CK), chose higher resolution array. In our experience, most pregnant couples at increased risk for common aneuploidies chose to learn as much as possible about the (future) health of their unborn child.[21] We furthermore offered couples a choice whether they wished to be informed of SL if detected. Eighty-four percent of the pregnant couples engaging in PND chose to be informed of SL should these be detected.[21] Using SNP arrays as a diagnostic prenatal test leads to the poignant question of the extent to which pregnant couples have sufficient knowledge to make informed decisions regarding its scope.[19]

In this study we report on one member of pregnant couples, that is, pregnant women at increased risk for common aneuploidies who were offered a choice between 0.5 and 5 Mb SNP array testing. We investigated whether they had sufficient knowledge to make an informed decision consistent with their attitude. Furthermore, we explored whether level of informed choice was associated with anxiety and doubts.

Materials and methods

Participants

Pregnant women ($N = 69$) consented to participate from February 2012 to September 2013 at our outpatient prenatal clinic. Inclusion criteria were:

a. advanced maternal age (>36 years), and/or
b. the woman participated in first-trimester prenatal screening (PNS) or PND, and
c. fluency in Dutch language.

Women were approached at the intake of their first ultrasound, around 9–11 weeks gestational age (GA) and counselled by a clinical geneticist (see Figure 1 for a timeline of the study). After counselling, women filled out a questionnaire about their choice. The Measure of Informed Choice, see Measures section, was filled out by a subsample of women that participated in our previous study.[21]

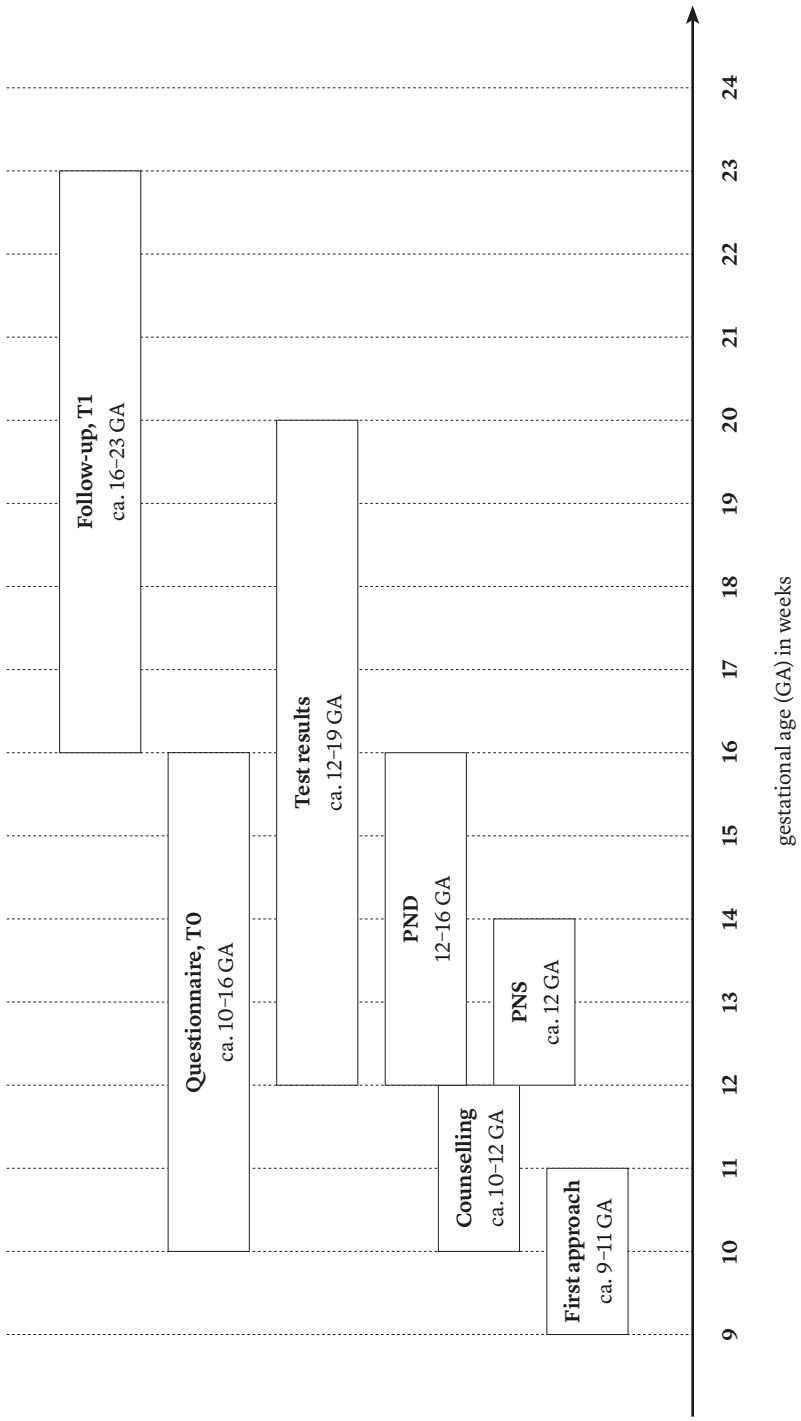

Figure 1. Timeline of the study.

Procedure

This study was waivered by the local Medical Ethical Testing Committee (METC). An information leaflet about the study was added to the invitation letter pregnant women received before attending the outpatient clinic. A research-assistant was present at the clinic to approach pregnant women meeting the inclusion criteria and provide information concerning the study and its further procedures. After consenting, an additional genetic counselling session with a clinical geneticist by telephone was planned in advance of the next appointment for PNS or PND. We combined women engaging in PNS (hypothetical choice) and PND (real choice) in our sample to obtain a larger number of participants. Face-to-face counselling was not practically feasible in this study.

Women were approached at the intake around 9–11 weeks gestational age (GA) and counselled by a clinical geneticist, after which they filled out a questionnaire (T0) (see Figure 1). Between 16 and 23 weeks GA, women were approached for follow-up by phone. This was four weeks after their prenatal test results (T1).

Content of genetic counselling by telephone

Participating women received a 30–45 minute counselling from a clinical geneticist (or a resident) by phone. Extensive information was provided. In addition to the background of genetics, participants were informed of the difference between 5 Mb and 0.5 Mb array. The 5 Mb array was presented as a 'less broad test,' and it was specified that trisomy 13, 18 and 21 and other microscopically visible deviations could be found, comparable to the scope of a karyotype. The 0.5 Mb array was presented as a 'broader test,' and examples of what could be detected additionally by broader testing compared to less broad testing was illustrated with Williams syndrome, Duchenne muscular dystrophy, and susceptibility loci for neurodevelopmental disorders (SL); these were counselled as incidental findings. Initially, participants could choose between 5 Mb testing and 0.5 Mb testing. The 0.5 Mb array resolution was presented as a broader test that also included susceptibility loci. During data collection, an increasing number of participants wished to learn the results of 0.5 Mb resolution array, but without disclosure of susceptibility loci. Therefore, we adopted the policy that participants could also opt for 0.5 Mb (broader testing) without being informed of susceptibility loci. The last part of the counselling comprised a dialogue about the women's concerns, attitudes towards the scope of testing, questions and preferences. Women were

asked whether they already knew what resolution they would choose. If necessary, additional information or explanation was provided.

Measures

Demographics

Socio-demographic data were collected (living situation, educational level, nationality, religion, and age).

Measure of Informed Choice

To explore informed decision making regarding the scope of PND, we developed the Measure of Informed Choice (MIC). The MIC is based on the Multidimensional Measure of Informed Choice instrument [MMIC, Knowledge Scale ($\alpha = .68$), and Attitude Scale ($\alpha = .78$)] by Michie, Dormandy and Marteau (2002), which measures knowledge and attitude towards PNS. Our MIC contains 7 items measuring knowledge (see Table 1) and 6 attitude items regarding the scope of PND (see Table 2). A decision was considered to be adequately informed if it was based on sufficient knowledge and if the decision was consistent with the attitude towards testing with higher or lower resolution array. The knowledge scale comprised multiple-choice items, and we determined a cut-off score of 5 or more correct answers to qualify as 'adequate knowledge' (see Table 1). We used a very strict criterion because the choice we offered is controversial, and we wanted to maintain a high standard to evaluate our counselling. Michie et al. used a midpoint score (4.5) on 8 knowledge questions for knowledge to be qualified as sufficient. Thus, our criterion for 'sufficient knowledge' is stricter. This should be taken into account when interpreting our results.

We developed the MIC questions based on the content of the counselling participants received. During counselling, there was a strong emphasis on explaining what the differences between 0.5 Mb and 5 Mb testing were, and what the respective scopes might and might not detect, with realistic examples of certain conditions. A team of clinical geneticists, psychologists and a statistician were involved with the development of the questions. The attitude scale comprised six statements with a 10-point response format and ranging from 1 (useless/not important) to 10 (very useful/very important) (see Table 2). A higher score indicated a more positive attitude towards broader scope array (0.5 Mb), a lower score

Item (multiple choice)		Incorrect/ correct	M	SD
Q1	Which conditions can be excluded by CVS or AC?	0/1	.78	.42
Q2	What is the risk of having a miscarriage?	0/1	.82	.39
Q3	Which conditions may the less broad test detect?	0/1	.50	.50
Q4	Which conditions are not detectable with the less broad test?	0/1	.79	.41
Q5	Which conditions may the broad test detect?	0/1	.88	.33
Q6	What is a susceptibility locus?	0/1	.53	.50
Q7	What could be the added value of the broad test for pregnant women?	0/1	.79	.41
Total knowledge score		**0–7**	**4.78**	**2.88**

Table 1. Item descriptives of MIC knowledge scale, 7 items (Cronbach's. α =.55, N = 69).

Item		Range	M	SD
1.	*For me, knowledge about Down syndrome is…*			
a.	(1) Not of added value … (10) Useful	1–10	8.86	1.64
b.	(1) Unimportant … (10) Important	1–10	9.08	1.51
2.	*For me, knowledge about a small, but severe chromosomal abnormality is…*			
a.	(1) Not of added value … (10) Useful	1–10	9.00	1.39
b.	(1) Unimportant … (10) Important	1–10	9.04	1.46
3.	*For me, knowledge about a susceptibility locus is…*			
a.	(1) Not of added value … (10) Useful	1–10	6.45	3.29
b.	(1) Unimportant … (10) Important	1–10	6.66	2.97
Total attitude score		**6–60**	**47.90**	**11.1**

Table 2. Item descriptives of MIC attitude scale (Cronbach's. α =.78, N = 69).

indicated a more negative attitude. Based on design of the MMIC from Marteau et al. (2001), we created three categories of outcomes of informed choice;

1. completely informed (adequate knowledge and consistent attitude),
2. partly uninformed (poor knowledge and consistent attitude, or good knowledge and inconsistent attitude) and
3. completely uninformed (poor knowledge and inconsistent attitude).

Decisional Ambivalence Scale

The questionnaire furthermore comprised the previously published Decisional Ambivalence Scale (DAS; (Cronbach's $\alpha = .85$).[21] The DAS contain ten items that measure doubts and confidence regarding the choice. All items had a 10-point response format and ranged from 1 (not at all) to 10 (very much so). Summed scores on the DAS can range from 10–100, with a higher score indicating a higher level of experienced doubts.

State-Trait Anxiety Inventory

Anxiety was measured using the short version of the Dutch State-Trait Anxiety Inventory (STAI), which was validated for pregnant women in the Netherlands.[22] The scores ranged from 1 (not at all) to 4 (very much so). STAI total scores can range from 20–80. Higher scores indicate greater feelings of anxiety.[21]

Statistical analyses

To obtain a larger sample, women engaging in PNS (hypothetical choice) and PND (real choice) were both included in our analyses. It should be noted that these are two different groups of women, and that the PND group is a 'high stakes' group compared to the PNS group, that has lower stakes. Women in the PND group had made a real choice that led to real prenatal test results, and therefore they could have, arguably, paid more attention to the counselling. However, as there were no statistically significant differences in informed choice between the two groups of women, we analyzed the sample as a whole.

Before analyzing the data for this study, assumptions for ANOVA were checked. A significance level of $p < 0.05$ was used for all analyses. Outliers were detected,

reverse-scored items were recoded, and total scores were calculated. To examine the internal consistency of the MIC, Cronbach's alpha was used.

To assess whether participants made an informed choice, we calculated total MIC Knowledge and Attitude scores. Correct answers on the Knowledge scale were coded into dichotomous scores (1 = correct; 0 = incorrect),[1] thus summed to a maximum of 7 points. For the Attitude scale, with six statements, scores ranged from 6 (very negative) to 60 (very positive). Those were summed and divided by 6 to produce an attitude score between 1 and 10. Similar to other studies on this subject,[13, 23, 24] we employed a midpoint score for the attitude scale; participants with an attitude score below 5.5 were categorized as having a negative attitude, scores above 5.5 were categorized as a positive attitude. Attitudes were checked for their congruence with the choice of array resolution. For example, if a participant indicated that knowledge about SL was important/useful, 0.5Mb array resolution including disclosure of SL was expected as a choice. Attitudes were linked to choice of test for (in)consistency.

To examine the relationship between nominal variables, separate Pearson chi-square tests were used for decision outcome and actual (PND) and hypothetical (PNS) choice, decision outcome and broad (0.5 Mb) or less broad (5 Mb) array, and for decision outcome and wanting to be informed about SL (+SL/-SL).

We assessed differences in background variables (age, level of education) for women making an informed vs. an uninformed choice using separate Pearson chi-square tests.

Using the decision outcome (completely informed/uninformed) as dichotomous factors, we performed separate independent samples t-tests for continuous variables (STAI/DAS total scores) to test for differences between groups. To assess differences in anxiety and doubts (DAS/STAI) between women opting for or against disclosure of SL, independent t-tests were performed. For anxiety and doubts over time (T0 & T1), we used paired samples t-tests.

Results

Demographic variables

The mean age of women was 37.9 years. The demographic variables (see Table 3) of women making informed or uninformed choices did not differ significantly,

although the relationship between educational level and informed/uninformed choices was marginally significant ($p = 0.055$).

	Total N (%)	Informed N (%)	Uninformed N (%)	$p(\chi^2)^*$
Previous children				.28
Yes	42 (60)	25 (66)	17 (53)	
No	28 (40)	13 (34)	15 (47)	
Education				.055
Low-intermediate	25 (35)	12 (29)	12 (46)	
High	44 (65)	30 (71)	14 (54)	
Nationality				.07
Dutch	64 (93)	38 (88)	26 (100)	
Other	5 (7)	5 (12)		
Religious				.83
Yes	17 (25)	11 (26)	6 (23)	
No	51 (75)	31 (74)	20 (77)	
Test type				.25
PNS	39 (56)	22 (51)	17 (65)	
PND	30 (44)	21 (49)	9 (35)	

*2-sided Chi square tests performed.

Table 3. Demographic characteristics of women who made informed versus uninformed choices (N = 69).

Measure of Informed Choice

Tables 1 and 2 present the items and descriptives of the MIC knowledge and attitude scales. The internal consistency reliability of the MIC Knowledge scale was $\alpha = .55$, which is insufficient. This was caused by the fact that most women answered the questions with the same answers, resulting in lower variances, which led to a lower Cronbach's alpha. The MIC Attitude scale had a reliability of $\alpha = .78$.

Figure 2 shows the percentage of correct and incorrect answers for the MIC Knowledge questions (see Table 1 for the specified questions). Most questions were answered correctly by the majority of women. Question 3, 'Which diseases may the less broad test detect?' and question 6 'What is a susceptibility locus?' were answered correctly by approximately 50% of the women.

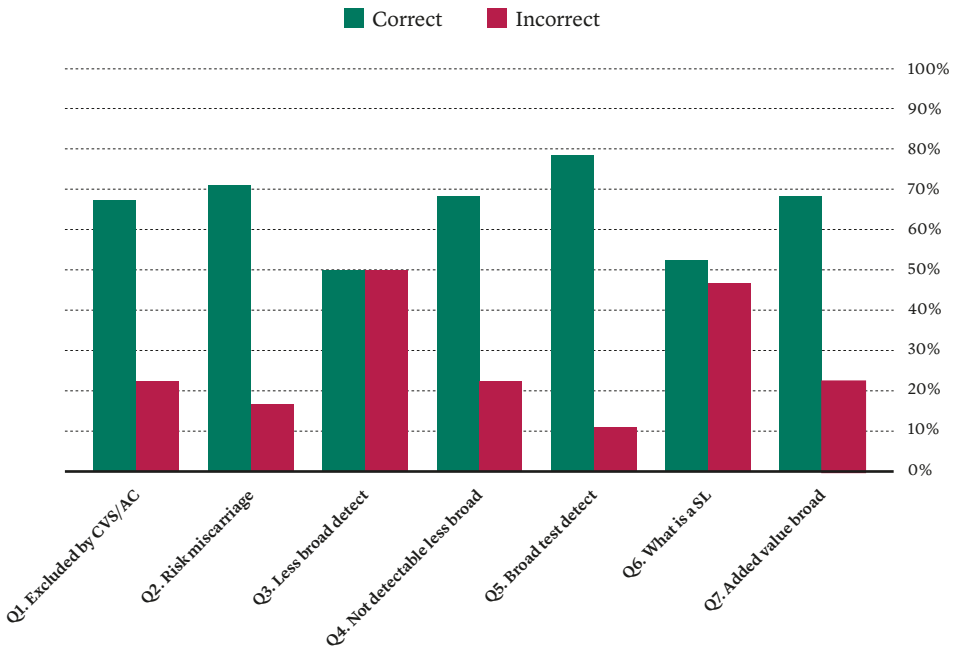

Figure 3. Percentage of women's correct/incorrect answerson the MIC Knowledge scale (N = 69).

Informed choice outcomes

Figure 3 presents a pie chart of the outcomes of informed choice. Overall, 62.3% made a completely informed choice. A partly informed choice was made by 33.3% of women; 24.6% had poor knowledge, but a consistent attitude, and 8.7% had good knowledge, but an inconsistent attitude. Lastly, 4.3% made a completely uninformed choice.

For statistical analyses, level of informed choice was dichotomized in two levels, informed and uninformed.

Relationship between decision outcome and demographic variables

There was a marginally significant association between educational level and informed/uninformed choices ($p = 0.055$). Women who had a higher educational level tended to be more likely to make completely informed choices than women who had a lower educational level. There were no other statistically significant differences in demographic variables (see Table 3).

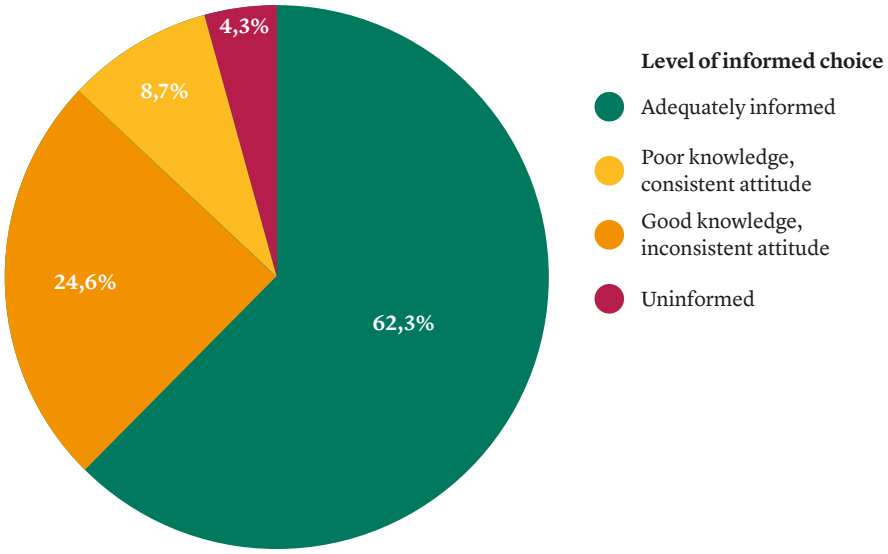

Figure 3. Piechart of decision outcomes of all women (N = 69).

Relationship between decision outcome and actual/hypothetical choices

As mentioned earlier, there was no significant association between informed/uninformed choices and actual versus hypothetical choice. Thus, women choosing for PNS or PND made equally informed choices.

Relationship between decision outcome and choosing broader or less broad testing

There was a significant association between informed/uninformed choices and choice of array resolution χ^2 (1) = 19.29, $p < 0.001$, $V = 0.71$ (large effect size), OR = 0.36 (95% CI 0.17 — 0.79). Women who made a completely informed choice, opted for broader testing more often.

Relationship between decision outcome and disclosure of SL

There was no significant association between wanting to be informed about SL and informed/uninformed choices. Thus, women opting for or against disclosure of SL made equally informed choices. There were no significant effects of wanting to be informed of SL on either anxiety or doubts.

Anxiety & doubts and decision outcome

There were no significant differences in anxiety level (STAI) and informed versus uninformed choices. There was no significant difference in levels of doubts (DAS) and informed versus uninformed choices. Thus, there were no differences in level of anxiety and doubts between women making informed versus uninformed choices. Mean anxiety and doubt scores for all women are displayed in Table 4.

There was a significant difference in anxiety (STAI) for women opting for PNS versus PND. Women who opted for PND, had a higher level of anxiety. There was no significant difference in level of doubt for women opting for PNS versus PND (see Table 5). There were no differences in anxiety and doubts between women opting for or against disclosure of susceptibility loci (see Table 6).

Overall the anxiety and doubt scores decreased significantly between T1 and T2 (see Table 7). There were no significant differences in the course of anxiety and doubts between informed and uninformed decision-makers or between the PND and PNS subgroups.

	Informed choice	**Uninformed choice**	***t***	***p***
	n = 37; 51%	n = 32; 58%		
Mean STAI score	34.05	34.95	n.s.	
Mean DAS score	25.11	25.81	n.s.	

Table 4. Mean anxiety (STAI) and doubts (DAS) score by decision outcome for all women (N = 69).

	PND	**PNS**	***t***	***p***
	n = 29	n = 40		
Mean STAI score	37.20	33.75	6.802	.012
Mean DAS score	22.90	26.86	n.s.	

Table 5. Mean anxiety (STAI) and doubts (DAS) score of women opting for PND/PNS (N = 69).

	+SL	–SL	*t*
	n = 39	n = 23	
Mean STAI score	36.49	32.22	n.s.
Mean DAS score	22.73	24.10	n.s.

Table 6. Mean anxiety (STAI) and doubts (DAS) score of women opting for or against disclosure of SL (N = 62).

	T0	T1	*t*	*p*
	n = 69	n = 69		
Mean STAI score	35.03	26.82	5.390	<.001
Mean DAS score	28.86	18.32	5.135	<.001

Table 7. Mean anxiety (STAI) and doubts (DAS) score of women after counselling (T0) and 4 weeks after disclosure of prenatal test results (T1) (N = 69).

Discussion

The aim of the current study was to assess whether pregnant women had sufficient knowledge to make an informed decision regarding the scope of their invasive prenatal genetic test using SNP microarray that was consistent with their attitude. Furthermore, we explored whether level of informed choice was associated with anxiety and doubts.

Informed choice implies making a value-consistent decision based on sufficient knowledge. Although the majority of women made a 'completely informed' choice (sufficient knowledge and consistent attitude), a substantial subgroup made a choice that was at odds with their personal values. Michie et al. (2002) showed that knowledge plays no role in whether women undergo screening or whether they act in line with their attitudes. Our study supports this finding; women who did not have sufficient knowledge were able to make a choice that was consistent with their attitudes, and vice versa. A small percentage of women with sufficient knowledge were still choosing value-inconsistently.

Anxiety and doubts were not higher in women who made an uninformed choice. These findings are in contrast to previous studies showing that making uninformed choices is associated with adverse psychological outcomes. Women who made uninformed choices had more decisional conflicts/doubts and felt more anxious when making a choice whether or not to engage in prenatal screening.[12, 24] Therefore, we would have expected that making an uninformed choice (lack of knowledge) might bring more worries about choosing the right test, and that these worries may lead to more anxiety or stress. Alternatively, it is possible that the women who made an uninformed choice were not able to grasp the potential detrimental consequences of their choice. A lack of knowledge may only be stressful if one is aware of what is lacking. The percentage of informed choices are concordant with other studies on informed choice in prenatal *screening,* although those studies used less stringent criteria, such as the midpoint score.[23, 25, 26]

The concepts of adequately informed and uninformed choices are evident. However, partly informed choices lie in a more 'grey area,' which needs to be reflected upon. We found that most women who made partly informed choices based their choice on insufficient knowledge but with a consistent attitude. It could be argued that partly informed choices can still be considered autonomous choices: women may not need the complete detailed facts and specifications about the test characteristics to make a choice that is in line with their values (or an expression of self-determination). In line with this, it may be argued that reproduction/recall of knowledge after counselling is less of a condition for autonomous choice than agreement with one's personal values.

Choices based on sufficient knowledge, but with an inconsistent attitude, were less prevalent. In line with an earlier study, our results show that knowledge indeed played no role in whether or not the women acted in accordance with their attitudes (Michie et al., 2003). We argue that value-inconsistent choices might be the most worrisome type of decision. If a woman chooses a scope of testing that does not fit her personal values, despite having sufficient knowledge about the test characteristics, this might lead to adverse psychological outcomes. It has to be taken into account that subtle signs of attitude inconsistency are easily missed. The counsellors' preferences may have (inadvertently) influenced the pregnant women's decision-making, leading women to make choices that were inconsistent with their own values despite enough knowledge.

Actual versus hypothetical choices

No differences were found in the level of informed choice between the PNS and PND groups. This might indicate that women who made a hypothetical choice, have gone through a similar decision (making) process as women who underwent PND. However, there is a difference between the women engaging in PNS and PND: women engaging in PND made a real choice that was actually performed by our lab, and thus had higher stakes than women making a hypothetical choice (PNS). Our results show that women opting for PND indeed experienced more anxiety than women engaging in PNS. It might be that level of anxiety is associated with informational needs. Alternatively, it could be that women engaging in PND are more anxious because of the miscarriage risk associated with the invasive procedure27. It must be noted that in our sample 19% of the pregnant women experienced anxiety at clinically relevant levels, and these women were distributed equally across the PNS/PND groups. At follow-up, four weeks later and after they received test results, almost all anxiety scores were back to normal levels,[22] except for three women who experienced enduring anxiety.

Broad or less broad microarray and susceptibility loci

Women who opted for broad scope PND made informed choices significantly more often. Being fully aware of the possible outcomes, they preferred to gain information about susceptibility loci in their unborn child. This might be related to the 'sense of personal ownership' of genomic data.28 Patients may be inclined to want ownership and/or control over their — or in this case their baby's — genomic data. This may contribute to choosing a maximum of information from a genomic test, even if that means the test would include uncertain outcomes such as susceptibility loci.[21] Our first impressions were that women in our clinic appeared to be able to handle this kind of information. Moreover, women indicated that they could use this kind of information in the future, if their child would develop abnormally. They indicated that they would know where to start looking for help and/or mobilize adequate care.

The majority of well-informed women chose to be informed of susceptibility loci if detected. The finding that the majority of women make informed decisions about susceptibility loci might seems in contrast with the often expressed fear/concern among professionals that these results are too difficult to grasp for patients.[2, 29] However, the two positions are not mutually exclusive. Women may

be able to make an informed decision at the time, but not able to fully grasp/understand the long-term consequences of a rather abstract test outcome. On the other hand, professionals might underestimate the resiliency of their patients. We found that the women in our study did not have a heightened level of anxiety compared to other Dutch pregnant women at high risk of an abnormal fetus.[22] This finding is also incongruent with professionals' worries of burdening pregnant women with an overload of information.[2, 6, 11, 29]

In conclusion, despite all of the controversy regarding prenatal microarrays, our study shows that the majority of women were capable of making an informed choice regarding the scope of their invasive prenatal genetic test. And most importantly, they made informed choices in the absence of severe anxiety or doubts. Our data have shown that overall levels of anxiety and doubts decreased significantly over time, regardless of the choices (broad, less broad, SL or no SL) or level of informed decision-making. This decreasing pattern of anxiety is in accordance with previous studies.[22]

It should be noted that choice/consent cannot and need not be *completely* informed.[30] People may differ with regard to their informational needs and the level of detail they require for decision-making.[31] For some, knowing that testing may generate 'information about severe, incurable conditions' may be sufficient, whereas others may need to know what conditions exactly are included in the test, in order to make an informed decision. To accommodate differences in informational needs among individual women, pre-test counselling can be conducted in a layered fashion, where basic, crucial information is offered to all women, and further, more detailed information is given if needed or desired.[32] The level of knowledge required for informed choice, it can be argued, may thus vary among individual decision-makers. Attitude consistency, on the other hand, is less of a spectrum, but rather a necessary condition for informed choice.

In the literature, efforts aimed at improving informed choices mostly target the knowledge component.[17, 25, 33] We stress the importance of attitude consistency, and recommend that the choices of pregnant women regarding the scope of their genetic test should fit their personal values well in order to facilitate informed choice. Thus, interventions aimed at improving informed choices through attitude consistency may be more effective than those targeting knowledge only.[12, 23] We suggest that attitude and values need to be explored and discussed in the pre-test counselling sessions.

The telephone counselling enabled the majority of women to make an informed choice. It must be taken into account, however, that this counselling was extensive and time-consuming, and therefore will not be feasible in everyday practice. It would be interesting to compare the level of informed choices with telephonic versus routine face-to-face counselling. Face-to-face counselling has a more personal aspect, and therefore might be capable of more adequately addressing attitude inconsistency or miscomprehension.

The future: the expansion of prenatal genetic information

Prenatal screening and follow-up diagnostic testing are likely to expand in the future, and to become more complex, as more and more findings/conditions could be included in the test. This might not only be possible with invasive testing, but also with non-invasive prenatal test (NIPT). Some state that in order to keep informed consent feasible, unnecessary complications should be avoided: screening should only be used for trisomies 13, 18 and 21. However, complications may not always be unnecessary: tests may come to include other conditions that are *as relevant* to women or couples in reproductive decision-making as is Down syndrome. Multiple studies have shown that a majority of pregnant women prefer an individualized choice, and prefer to learn as much as possible from prenatal tests.[2, 21, 34] Broadening the scope of prenatal diagnosis should — at minimum — be considered. To facilitate informed choices, pre-test counselling remains of great importance. Since extensive face-to-face counselling might not always be feasible, the next step may be to develop decision-aids that comprise both knowledge and attitude and personal values. This could be especially helpful for women who may otherwise make choices that are inconsistent with their attitudes. Such solutions and new models of informed consent are more and more widely applied in healthcare systems, and they may indeed have the potential to improve complex decision-making regarding the prenatal screening and follow-up diagnostic testing offer.[35]

Strengths & limitations

It should be noted that the women who present at the prenatal clinic of our university medical center are of above-average educational level. Furthermore, participating women were already motivated to seek prenatal screening or diagnosis (on the basis of either advanced maternal age or abnormal first trimester

screening), and may thus be more inclined to prefer to learn about genetic risks in their fetuses than other pregnant women. Our results might be further biased due to the unequal distribution of ethnicity; only 7% of the women was not Dutch.

A strength of this study is that, to our knowledge, we are the first to have assessed informed choice regarding invasive PND performed with microarrays. Further, we allowed participants to make an individualized choice of array resolution that best suited their preferences.

Conclusion

We found that the majority of pregnant women were capable of making an adequately informed choice about the scope of invasive PND, including whether or not they wanted to be informed of SL. A justified course of action based on this result could be that laboratories perform broad analysis and counsellors provides patients with an opting in or out possibility. Knowledge has already been established as an important component in informed choice. However, our study underlines that a consistent attitude might be equally important. We anticipate that in the future, regardless of more complex or new techniques, the majority of women will still be able to make informed choices, as long as adequate information provision and counselling are provided. For counselling practices, we advocate a stronger focus on attitude-consistency instead of only a focus on knowledge.

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References

1. van Schendel R.V., Dondorp W.J., Timmermans D.R., et al. NIPT-based screening for Down syndrome and beyond: what do pregnant women think? *Prenat Diagn*. 2015;35(6):598–604.
2. de Jong A., Dondorp W.J., Krumeich A., Boonekamp J., van Lith J.M., de Wert G.M. The scope of prenatal diagnosis for women at increased risk for aneuploidies: views and preferences of professionals and potential users. *J Community Genet*. 2013;4(1):125–135.
3. de Jong A., Dondorp W.J., Macville M.V., de Die-Smulders C.E., van Lith J.M., de Wert G.M. Microarrays as a diagnostic tool in prenatal screening strategies: ethical reflection. *Hum Genet*. 2013.
4. Dondorp W., de Wert G., Bombard Y., et al. Non-invasive prenatal testing for aneuploidy and beyond: challenges of responsible innovation in prenatal screening. *Eur J Hum Genet*. 2015.
5. Dondorp W., de Wert G., Bombard Y., et al. Non-invasive prenatal testing for aneuploidy and beyond: challenges of responsible innovation in prenatal screening. Summary and recommendations. *Eur J Hum Genet*. 2015.
6. Dondorp W., Sikkema-Raddatz B., de Die-Smulders C., de Wert G. Arrays in postnatal and prenatal diagnosis: An exploration of the ethics of consent. *Hum Mutat*. 2012;33(6):916–922.
7. Van Opstal D., de Vries F., Govaerts L., et al. Benefits and burdens of using a SNP array in pregnancies at increased risk for the common aneuploidies. *Hum Mutat*. 2015;36(3):319–326.
8. Srebniak M.I., Diderich K.E., Govaerts L.C., et al. Types of array findings detectable in cytogenetic diagnosis: a proposal for a generic classification. *Eur J Hum Genet*. 2014;22(7):856–858.
9. Srebniak M., Boter M., Oudesluijs G., et al. Application of SNP array for rapid prenatal diagnosis: implementation, genetic counselling and diagnostic flow. *European Journal of Human Genetics*. 2011;19(12):1230–1237.
10. van der Steen S.L., Riedijk S.R., Verhagen-Visser J., et al. The Psychological Impact of Prenatal Diagnosis and Disclosure of Susceptibility Loci: First Impressions of Parents' Experiences. *J Genet Couns*. 2016;25(6):1227–1234.

11. McGillivray G., Rosenfeld J.A., McKinlay Gardner R.J., Gillam L.H. Genetic counselling and ethical issues with chromosome microarray analysis in prenatal testing. *Prenat Diagn.* 2012;32(4):389–395.
12. van den Berg M., Timmermans D.R., ten Kate L.P., van Vugt J.M., van der Wal G. Informed decision making in the context of prenatal screening. *Patient Educ Couns.* 2006;63(1–2):110–117.
13. Kleinveld J.H., Ten Kate L.P., van den Berg M., van Vugt J.M., Timmermans D.R. Does informed decision making influence psychological outcomes after receiving a positive screening outcome? *Prenatal Diagnosis.* 2009;29(3):271–273.
14. Dahl K., Hvidman L., Jørgensen F.S., Kesmodel U.S. Knowledge of prenatal screening and psychological management of test decisions. *Ultrasound Obstet Gynecol.* 2011 38:152–157.
15. Dahl K., Hvidman L., Jorgensen F.S., Kesmodel U.S. Knowledge of prenatal screening and psychological management of test decisions. *Ultrasound in Obstetrics & Gynecology* 2011;38(2):152–157.
16. Kleinveld J.H., Ten Kate L.P., van den Berg M., Van Vugt J.M., Timmermans D.R.M. Does informed decision making influence psychological outcomes after receiving a positive screening outcome? *Prenatal Diagnosis.* 2009;29:271–273.
17. Schoonen H.M., Essink-Bot M.L., Van Agt H.M., Wildschut H.I., Steegers E.A., De Koning H.J. Informed decision-making about the fetal anomaly scan: What knowledge is relevant? *Ultrasound Obstet Gynecol.* 2010 [Epub ahead of print].
18. McCoyd J.L. Preparation for prenatal decision-making: a baseline of knowledge and reflection in women participating in prenatal screening. *J Psychosom Obstet Gynaecol.* 2013 34:3–8.
19. van der Steen S.L., Diderich K.E.M., Riedijk S.R., et al. Offering a choice between 5 Mb and 0.5 Mb prenatal whole genome SNP array analysis: are pregnant couples able of making informed decisions? *European Journal of Human Genetics.* 2014;22s1:357.
20. Riedijk S.R., Diderich K.E.M., van der Steen S.L., et al. The Psychological Challenges of Replacing Conventional Karyotyping with Genomic SNP Array Analysis in Prenatal Testing. *Journal of Clinical Medicine.* 2014;3(3):713–723.

21. van der Steen S.L., Diderich K.E., Riedijk S.R., et al. Pregnant couples at increased risk for common aneuploidies choose maximal information from invasive genetic testing. *Clin Genet*. 2014.
22. van der Bij A.K., de Weerd S., Cikot R.J., Steegers E.A., Braspenning J.C. Validation of the dutch short form of the state scale of the Spielberger State-Trait Anxiety Inventory: considerations for usage in screening outcomes. *Community Genet*. 2003;6(2):84–87.
23. Michie S., Dormandy E., Marteau T.M. The multi-dimensional measure of informed choice: a validation study. *Patient Educ Couns*. 2002;48(1):87–91.
24. Dahl K., Hvidman L., Jorgensen F.S., Kesmodel U.S. Knowledge of prenatal screening and psychological management of test decisions. *Ultrasound Obstet Gynecol*. 2011;38(2):152–157.
25. Schoonen M., Wildschut H., Essink-Bot M.L., Peters I., Steegers E., de Koning H. The provision of information and informed decision-making on prenatal screening for Down syndrome: a questionnaire- and register-based survey in a non-selected population. *Patient Educ Couns*. 2012;87(3):351–359.
26. Rowe H.J., Fisher J.R., Quinlivan J.A. Are pregnant Australian women well informed about prenatal genetic screening? A systematic investigation using the Multidimensional Measure of Informed Choice. *Aust N Z J Obstet Gynaecol*. 2006;46(5):433–439.
27. Muller C., Cameron L.D. Trait anxiety, information modality, and responses to communications about prenatal genetic testing. *J Behav Med*. 2014;37(5):988–999.
28. Kimball B.C., Nowakowski K.E., Maschke K.J., McCormick J.B. Genomic data in the electronic medical record: perspectives from a biobank community advisory board. *J Empir Res Hum Res Ethics*. 2014;9(5):16–24.
29. de Jong A., Dondorp W.J., De Wert G.M. The scope of prenatal diagnostic testing for chromosomal aberrations: broad or narrow? Ethical considerations on the choice of tests. *Ned Tijdschr Geneeskd*. 2009;153:A1060.
30. Manson N.C., O'neill O. *Rethinking Informed Consent in Bioethics*. Cambridge University Press; 2007.
31. Vos J., Menko F.H., Oosterwijk J.C., van Asperen C.J., Stiggelbout A.M., Tibben A. Genetic counselling does not fulfill the counselees' need for

certainty in hereditary breast/ovarian cancer families: an explorative assessment. *Psychooncology.* 2013;22(5):1167–1176.

32. Bunnik E.M., Janssens A.C., Schermer M.H. A tiered-layered-staged model for informed consent in personal genome testing. *Eur J Hum Genet.* 2013;21(6):596–601.
33. Schoonen H.M.V.A., H. M. , Essink-Bot M.L., Wildschut H.I.J., Steegers E.A., De Koning H.J. Informed decision-making in prenatal screening for Down's syndrome: What knowledge is relevant? *Patient Educ Couns.* 2010 [Epub ahead of print].
34. van Schendel R.V., Dondorp W.J., Timmermans D.R., et al. NIPT-based screening for Down syndrome and beyond: what do pregnant women think? *Prenat Diagn.* 2015.
35. Vlemmix F., Warendorf J.K., Rosman A.N., et al. Decision aids to improve informed decision-making in pregnancy care: a systematic review. *Bjog.* 2013;120(3):257–266.

Chapter 4

The psychological impact of prenatal diagnosis and disclosure of susceptibility loci: first impressions of parents' experiences

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Abstract

Genomic microarray may detect susceptibility loci (SL) for neurodevelopmental disorders such as autism and epilepsy, with a yet unquantifiable risk for the fetus. The prenatal disclosure of susceptibility loci is a topic of much debate. Many health care professionals fear that reporting susceptibility loci may put a psychological burden on pregnant couples. It is our policy to disclose prenatal susceptibility loci as we recognize them as actionable for prospective parents. The aim of this report was to evaluate the psychological impact of disclosing a prenatal diagnosis of susceptibility loci.

The psychological impact of disclosing susceptibility loci was evaluated in the first patients who received such results. Eight out of 15 women who had a susceptibility locus disclosed and four of their partners consented to share their experiences through a telephonic evaluation (n = 12). Follow-up time ranged from 3 to 15 months after their prenatal test result.

The reporting of susceptibility loci was initially 'shocking' for five parents while the other seven felt 'worried'. Ten out of 12 participants indicated they would like to be informed about the susceptibility locus again, two were unsure. Most had no enduring worries. Participants unanimously indicated that pregnant couples should have an individualized pre-test choice about susceptibility loci (non)disclosure.

We observed no negative psychological impact with the prenatal diagnosis and disclosure of SL on participants. A key factor in mitigating parental anxiety with SL disclosure appears to be post-test genetic counselling. Our report confirms that pregnant women and their partners prefer an individualized choice regarding the scope of prenatal testing.

Introduction

Genomic microarray may detect more copy number variants (CNVs) that cause clinically relevant abnormalities and generates results faster than conventional karyotyping (CK).[1–3] Therefore, we use SNP array instead of conventional karyotyping (CK) for routine cytogenetic analysis for all indications since July 2012.[4, 5] Next to known microdeletion syndromes such as Prader-Willi syndrome, or Duchenne muscular dystrophy, array testing may also reveal susceptibility loci (SL) for neurodevelopmental disorders. Susceptibility loci (SL) were defined as following by Girirajan et al.: 'SL are copy number variants (CNVs) with an extreme phenotypic heterogeneity and/or of variable expressivity'6–8 associated with an unquantifiable risk of neurodevelopmental disorders such as epilepsy, autism and psychiatric disorders and can be found in about 1.4% of fetuses without ultrasound anomalies.[9, 10] SL are often inherited from (apparently) unaffected parents, but are more frequently detected in affected individuals as compared to control populations.[8, 11–13] Genetic counselling in pregnancies where SL is found is challenging as it is difficult to estimate the chance of expression and/or to predict the phenotype because most likely a second hit like another genetic or even non-genetic factor, like environment, may also influence the expression of the phenotypes.[14, 15] Almost all information about SL phenotypes and penetrance that is available is based on postnatal ascertainment. There is currently no information available about the development of children in whom a SL was found prenatally.

The value of SNP array in fetuses who were prenatally diagnosed with ultrasound anomalies has been widely accepted,[2, 3] but its implementation for other indications has raised concerns among health care professionals, causing much debate regarding the disclosure of SL.[16–18] Some classify these CNVs as variants of unknown clinical significance (VOUS),[2] but because of their association with an abnormal phenotype, we have classified SL as pathogenic.[8] In our opinion, SL are different from VOUS because the phenotypic effect of VOUS is unknown, whereas for an SL the association with a specific phenotype is known but has a highly variable penetrance and expression.

It has been argued that pregnant couples may wish not to be informed on findings of uncertain expression19 and that such findings should be withheld in order not to put burden on the pregnant couple.[20, 21] It has also been said, both

for susceptibility loci and VOUS, that reporting them may create a false sense of autonomy,[22] because an overload of information could deteriorate reproductive autonomy, or raise possible emotional harm such as distress.[23] Some ethicists argued that genetic information of unclear meaning interferes with reproductive autonomy and should not be provided for this reason.[21]

On the other hand, others argue that it is paternalistic to try to prevent women from emotional harm and potential termination of a pregnancy, and that pregnant women are entitled to be informed of all genetic information[23] and that better tools for dealing with uncertainty should be developed.[20,24-26]

Although we are well aware of the burden that SL may represent psychologically for the pregnant couple, for several reasons we have chosen to disclose SL when prenatally detected. Firstly, we consider most SL to be actionable during and/or after pregnancy. For example, SL may be associated with congenital heart disease and an expert ultrasound examination during pregnancy can be offered. Secondly, if neurodevelopmental problems occur (either early or late onset), rapid diagnostics and more adequate care may be mobilized when parents have the knowledge of the SL (Govaerts et al., manuscript in preparation).[27]

Since we implemented SNP array for all indications, we encountered 14 cases of SL in 1330 pregnancies without ultrasound abnormalities.[5] To date, no patient experiences regarding the psychological impact of SL on pregnant couples has been reported. To explore whether disclosure of SL indeed puts a heavy burden on the parents,[20-23] we feel it is important to understand how SL disclosure affects pregnant couples. We report on the narratives of 12 parents' experiences with a prenatally disclosed SL.

Materials and methods

Pre-test counselling by a senior obstetrician

All patients undergoing invasive prenatal diagnosis (PND) received pre-test counselling by a senior obstetrician and received a patient information leaflet which specified that 'all pathogenic results will be reported'. Pregnant couples were informed about array testing. The occasional occurrence of unexpected findings was discussed. These could either be pathogenic CNVs not related to the prior indication for invasive testing or susceptibility loci (SL), Patients received

no detailed information regarding SL. Unexpected findings were discussed, but there was no strong emphasis on SL as a category of outcomes of invasive prenatal testing. SNP array testing was performed as a first-tier diagnostic test as described before.[4,9]

Disclosing the prenatal test result

When a SL was diagnosed pregnant couples were contacted directly by a clinical geneticist informing them that there was no causative chromosomal abnormality found, but a deviant finding that may require special attention. They were invited for extensive post-test counselling available the next day. For extensive information about our counselling methods and pregnancy management, see Govaerts et al. (manuscript in preparation), in short:

1. The nature of the particular SL was explained. Phenotypic examples (including pictures) from the postnatal literature were available.
2. An expert ultrasound examination was offered if the SL was associated with structural abnormalities.
3. We offered targeted parental SNP array in all cases because knowing whether an SL was inherited aided in evaluating the clinical implications of the SL within the family.
4. The couples were informed about the possibility for early postnatal intervention programs (www.mee.nl), and the option to terminate the pregnancy was discussed.
5. The pregnant women and their partners were offered support from a medical psychologist specialized in prenatal care.

Inclusion for the psychological evaluation

In this report we describe the experiences pregnant couples had when a susceptibility locus was found after invasive genetic testing, in the absence of ultrasound anomalies. Between July 2012 and

December 2013, fourteen couples received a prenatal diagnosis of a SL, and all of them were contacted. A clinical geneticist informed on their situation and asked them whether they were willing to share their experiences by phone in order to assess the impact of disclosing a prenatal susceptibility locus. This interview was part of aftercare in order to learn about the long term psychological

impact of SL disclosure in pregnancy. All patients proceeding with invasive prenatal testing, signed consent for further follow up during pregnancy and after delivery. Eight women and four of their partners agreed to share their experiences, see Figure 1 for the participants. The prenatal testing indication and array findings in 8 fetuses of the parents that took part in the interview are shown in Table 1. None of the participants decided to terminate the pregnancy. The parents of live born children reported no congenital anomalies or dysmorphic features that were detected at birth. In Table 2, array results are displayed with phenotype and incidences based on the information the parents received. All couples were offered psychological support in dealing with the outcome after disclosure of SL, but none of them indicated they wanted to make use of this.

The follow-up interview period between invasive PND and the contact ranged between three and eighteen months. The mean time before the follow-up interview was 10 months after disclosure. Three participants were still pregnant at the time of follow-up.

Measures

Consenting participants were approached for a follow-up interview by phone, using semi-structured questions (mean duration: 30 minutes). Women and their partners were interviewed individually. In Table 3, all questions are summarized. All interviews were transcribed verbatim and translated from Dutch to English. Worries about the health and development of the child were measured on a scale of 1 to 10 (1 — not at all to 10 — very much so).

Analysis

Qualitative analysis was performed on the answers of all participants. A posteriori, three independent judges (SL; JV; SR) categorized the answers to the open-ended questions (see Table 4). Subsequently, the judges came to a consensus regarding which categories emerged from which questions. The three judges independently assigned a dichotomous score (0 not present; 1 present) to each theme per question.

The observed inter-judge agreement varied between $\alpha = .44$ and $\alpha = 1.00$. The inter-judge reliability ranged from acceptable to excellent, except for question 1, which had a poor inter-judge reliability ($\alpha = .44$).[28]

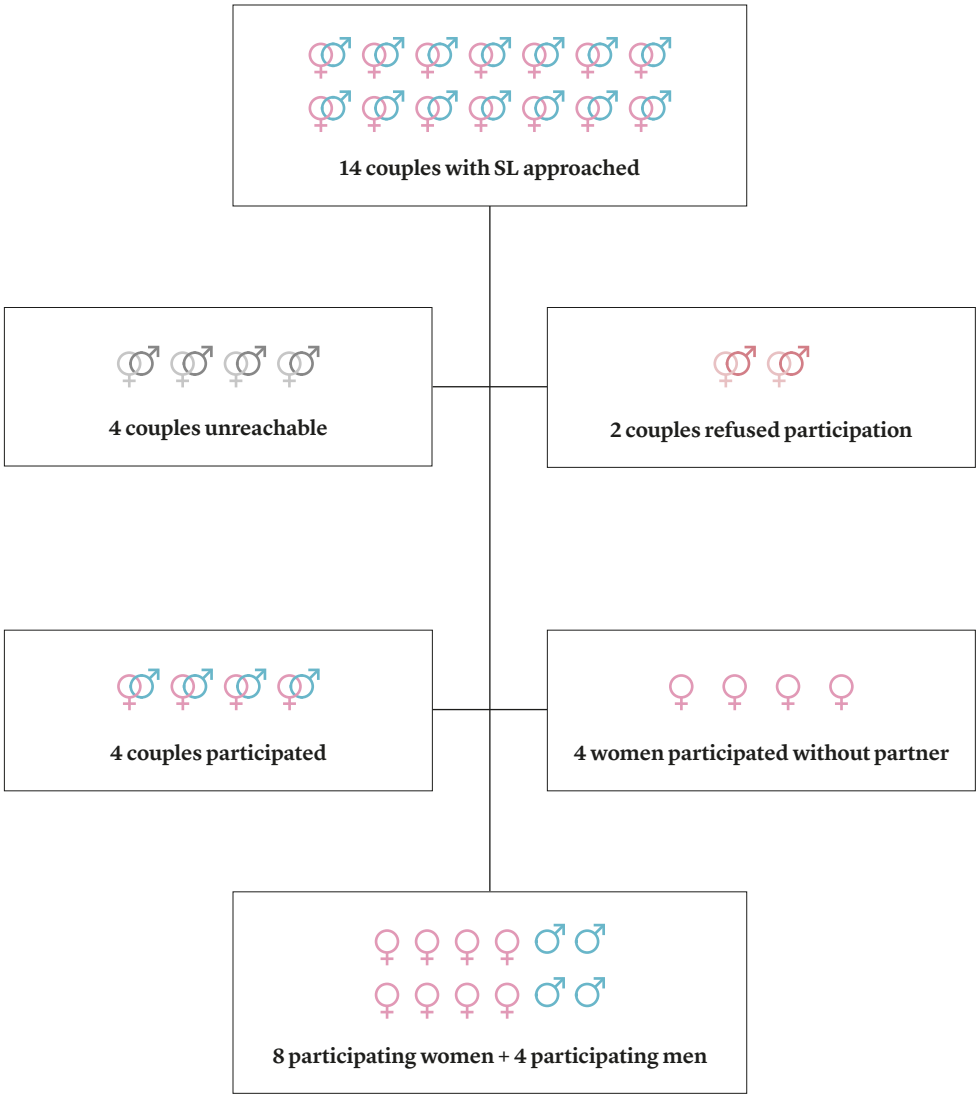

Figure 1. Flowchart of participants.

Fetus	Participant	Age	Sex	Indication	Follow-up (months)	CNV(hg18) and inheritance
A	1	41	F	AMA	9	15q11.2(20,191,584–20,710,960)x1 mat
B	2	41	F	aFTS	13	22q11.21(17,249,767–19,959,004)x3 ukn
C	3 4	35 35	F M	aFTS	8	16p11.2(29,548,278–30,171,562)x3 dn
D	5 6	23 33	F M	aFTS	15	15q11.2(20,191,584–20,698,860)x1 ukn
E	7* 8	38 37	F M	AMA	4	15q11.2(20,191,584–20,698,860)x1 dn
F	9*	37	F	AMA	5	1q21.1(144,959,767–146,307,651) x1 dn
G	10* 11	37 38	F M	aFTS	3	15q11.2(20,070,582–20,718,150) x1 mat
H	12	39	F	aFTS+AMA	15	3q29(197,141,069–198,793,022)x3 mat

* Still pregnant during the interview.

AMA = advanced maternal age, aFTS = abnormal first-trimester combined test.

Table 1. Participants' age, sex, prenatal testing indication, time of follow up interview after disclosure and array results with mode of inheritance; inherited from the mother (mat), de novo (dn), unknown in cases where parents refused testing (ukn).

Array result	N	Incidences affected vs. controls*	Phenotype**
15q11.2 microdeletion	4	0.60% vs. 0.20% (Cooper et al., 2012) 0.41% vs. 0.37% (Burnside et al., 2011)[29]	Intellectual disability, neurodevelopmental delay, behavioral problems, autism, facial dysmorphism (Girirajan et al., 2012 & Rosenfeld et al., 2013)[6,30]
22q11.2 microduplication	1	0.21% vs. 0.05% (Kaminsky et al., 2011)	Intellectual disability, hypotonia, hearing loss, epilepsy, cardiac malformations, urinary tract anomalies, growth retardation, facial dysmorphism (Firth et al., 2013)[31]
16p11.2 microduplication	1	0.18% vs. 0.02% (Cooper et al., 2011) 0.25% vs. 0.04% (Kaminsky et al., 2011)	Intellectual disability, schizophrenia, autism (Cooper et al., 2011 & Kaminsky et al., 2011)[32,33]
3q29 microduplication	1	0.0005% vs. 0.00009% (Kaminsky et al., 2011)	Intellectual disability, hypotonia, occular anomalies, congenital heart defects (Ballif et al., 2008 & Goobie et al., 2008)[34,35]
1q21.1 microdeletion	1	0.35% vs. 0.03% (Kaminsky et al., 2011) 0.28% vs. 0.018% (Rosenfeld et al., 2012)	Intellectual disability, microcephaly, cardiac malformations, cataracts, schizophrenia, renal and urinary tract anomalies, autism (Rosenfeld et al., 2012)[30]

* Incidences as counselled by the clinical geneticist in 2012–2013.

** Phenotype: postnatal ascertained proband.

Table 2. Array results with incidences and postnatal ascertained phenotype.

1. What was it like for you when you were told about the SL that was found?
2. What was your first reaction?
3. How do you feel about the SL at this very moment?
4. Would you choose to be informed of SL again?
5. Do you think that pregnant women should have a choice regarding the disclosure of SL?
6. Please indicate on a scale of 1 to 10 how worried you are about the health/development of your child? (1: not worried at all, 10: very worried)

Table 3. Open-ended questions about the psychological impact of prenatal SL disclosure.

Results: participant's narratives

Initial experience when the SL was disclosed

Qualitative analysis of the interviews showed that 7 out of 12 participants said they were 'worried', while the other 5 participants said 'it was real shock' to hear about the SL. We provide quotes to the answers by category. Participants marked with an asterisk (*) were still pregnant during follow-up.

Question 1 and 2

What was it like for you when you were told about the SL that was found? What was your first reaction?

Quotes of parents who were worried (7 out of 12)

'It startled me, you just don't want to hear that about your baby. But I thought that our baby would develop normally, maybe a bit slower than others, but healthy in the end.' (Participant 2, female)

'It was unpleasant, because we thought everything would be fine. Thus far, it appears as such.' (Participant 4, male)

'We were a little shocked at first, but we understood that there was only a very small chance that something could really be wrong. So we were not too worried.' (Participant 6, male)

'We were a bit upset the first days. When we had an advanced ultrasound, everything looked normal, that was a relief to us.' (Participant 8, male)

'It came very unexpectedly, I was a little overwhelmed, but I wasn't really, really alarmed.' (Participant 10*, female)

'At first we were not too alarmed, because the baby did not have Down syndrome. But we felt the SL diagnosis was slightly worrisome, because we did not know what we could expect at all.' (Participant 11, male)

'I was upset, because they could not tell me exactly how high the risk of developing the clinical features was. I just sat there stared at the geneticist and asked what it was, and if it was dangerous.' (Participant 12, female)

💬 *Quotes of parents who were shocked (5 out of 12)*

'To us, it was very unclear at first. We heard something was wrong and it came as a shock, I was nervous. When we had an appointment with the geneticist to talk about it, we understood that the risk was quite low. I thought; 'we'll have to wait and see', but my husband was really worried. There was a picture of a patient with the same deletion, clearly showing something was wrong. This was very upsetting to us. We didn't really know what to do with the provided information. I wasn't expecting it and did not think about the possibility of this kind of outcome when we engaged in prenatal diagnosis, only about the possibility of a trisomy. Maybe our older daughter has this deletion too, but she is a healthy, normal girl.' (Participant 1, female)

'That was a real shock. It was quite upsetting. We thought; What is going to happen next? It was not a very nice time. ' (Participant 3, female)

'We were startled, it was quite something. But we were informed of the possibility of such results.' (Participant 5, female)

'Unpleasant. It came as a shock. We did an amniocentesis hoping to hear that everything is alright, and then this susceptibility locus came as a test result. I was very emotional.' (Participant 7*, female)

'That was a real shock. It was not clear what was wrong, that made me worry a lot. The more I thought about it, the more worried I became. I had a lot of questions. I kind of panicked. Luckily, we had an appointment with the geneticist the next day. After that, I felt calmer.' (Participant 9*, female)

Question 3
How do you feel about the SL at this very moment?

💬 *Quotes of parents that do not think about it often anymore (11 out of 12)*

'I don't think about it too much now.' (Participant 2, female)

'I don't think about it anymore. I think I just have a normal, healthy son.' (Participant 3, female)

'I don't look back on it. I gave birth to a healthy son.' (Participant 4, female)

'I like to think that nothing is wrong. At the moment, I don't see any reason to think there is.' (Participant 5, male)

'During pregnancy I was worried about other physical abnormalities. But now that I gave birth, I am not worried anymore.' (Participant 5, female)

'I don't think about the SL anymore. I think I coped with the information quite well.' (Participant 6, male)

'Most abnormalities were excluded with expert ultrasound examinations. We are only unsure of other neurodevelopmental symptoms like behavioural problems. But we think everything will be fine.' (Participant 7*, female)

'After the expert ultrasound examinations we felt reassured. The SL does not have to mean anything.' (Participant 8, male)

'I think the chance of expression of the SL is very small. And if it will express itself, I think it will be mild and actionable.' (Participant 9*, female)

'We will have to wait and see. I think it is nothing very severe, since I carry it myself and do not have any symptoms. I am not too worried anymore.' (Participant 10*, female)

'I think it might be something very mild. My wife has it too. Maybe we will not even notice it.' (Participant 11, male)

'I do not see anything out of the ordinary regarding my daughter at this point.' (Participant 12, female)

💬 *Quote of a parent that experienced a stigma (1 out of 12)*

'It is something that you keep carrying with you. If she behaves weirdly, then I immediately think that this behaviour is related to the SL. I also do not like the fact that she already had a medical file before she even was born.' (Participant 1, female)

Question 4
Would you choose to be informed of SL again?

💬 *Yes (10 out of 12 parents)*

'I want to know as much as possible. That is the reason I chose for invasive prenatal diagnosis in the first place.' (Participant 2, female)

'Yes, even though it was distressful when we first heard about the susceptibility locus. But if something might be wrong with your child, you want to know about it.' (Participant 4, male)

'If I could choose, than I would like to know.' (Participant 6, male)

'Absolutely.' (Participant 8, male)

'Yes, I think so, because I prefer to know as much as possible.' (Participant 10*, female)

'Personally, I want to know everything, but I have an academic degree. I can imagine that this kind of information might be very confusing for people with a lower educational level.' (Participant 11, male)

'Of course. Especially with regards to my advanced maternal age.' (Participant 12, female)

💬 *Hesitant (2 out of 12 parents)*

'If I would get pregnant again, I might not want to know. But in this pregnancy, I would not want to have missed this information.' (Participant 1, female)

'It depends if it really matters. It did give us a lot of stress, because we thought it was something very severe at first. But I would be very curious in the future (next pregnancy). A friend of mine, who had children at a young age, did not have any genetic information about her children at all. But her son has a neurodevelopmental disorder and she did not know about it in advance. It can be useful, because you know where it might come from.' (Participant 9*, female)

Worries about the health and development of the child ranged from 2 to 7 on a 10-point scale (see Table 4). Most participants mentioned that they now '*just have the normal worries any parent has*'.

Nr.	1, 2. First reaction	3. How do you feel about the SL now?	4. Would you choose to be informed again?	5. Pregnant women should have a choice?	6. Assume child is healthy?	7. Worried about health child (1–10)
1	shocked	stigma	hesitant	yes	yes	2
2	shocked	not thinking about it often	yes	yes	yes	3
3	shocked	not thinking about it often	yes	yes	yes	3
4	worried	not thinking about it often	yes	yes	yes	2
5	shocked	not thinking about it often	yes	yes	yes	6
6	worried	not thinking about it often	yes	yes	yes	3
7*	shocked	not thinking about it often	yes	yes	yes	7
8	shocked	not thinking about it often	yes	yes	yes	6
9*	worried	not thinking about it often	hesitant	yes	yes	1
10*	worried	not thinking about it often	yes	yes	yes	2
11	worried	not thinking about it often	yes	yes	yes	3
12	worried	not thinking about it often	yes	yes	yes	2

* Still pregnant during follow-up.

Table 4. Overview of the answers of participants.

Discussion

Since it has been suggested that disclosure of SL may raise emotional harm, we evaluated the psychological impact of prenatal SL disclosure on pregnant couples. Women and their partners initially felt worried and shocked. Most parents indicated that the SL was not what they had expected from invasive PND, however some recalled being informed on such possibility during the pre-test counselling. Previous research showed that pregnant women are hardly ever ready for receiving abnormal prenatal test results, even if they are well informed.[36–38]

After their initial reaction, parents were confused and had a high need for understanding these outcomes. Most were quite alarmed by the phone call of the geneticist telling them that there was a 'peculiar finding that needed explanation'. All parents indicated they appreciated that the post-test counselling was available the next day. Due to the highly variable penetrance and expression, the meaning of the particular finding remained uncertain for the parents. A few parents noted that this uncertainty was stressful to them at first. However, none of the parents made use of the psychological support they were offered. None of the participants felt that a termination of pregnancy was a personal option for them. The interviews revealed that some parents adopted a wait-and-see policy; that they will have to wait and see in which way their child will develop, with a positive state of mind. These parents seemed less distressed when talking about their experiences.

Parents seemed to have recovered from their initial feelings, and are now handling the knowledge about their child having a SL fairly well. They seem to base this on a seemingly normal phenotype, either after giving birth to a 'normal appearing' child or with the reassurance of a 'normal' expert fetal ultrasound examination. At the moment of the follow-up interview (mean time 10 months after disclosure), all born children had no congenital anomalies or dysmorphic features, but were still too young to be examined for neurological development. None of the fetuses had ultrasound anomalies. It is yet unknown whether these children will develop neurodevelopmental symptoms in the future. Most parents did not have lingering worries regarding the SL, except for one woman who experienced a stigma regarding her seemingly normal and healthy born daughter. She told that each time her daughter behaved aberrant, she immediately feared it might be caused by the SL. This is something that is also encountered

in other studies on abnormal prenatal diagnoses, even if the child has seemingly normal appearance.[36] Other parents did not report stigma or enduring worries about the child's development, and mentioned they just have 'normal parental worries' now. The interviewed parents indicated feeling relieved after advanced ultrasound scanning revealed no visible anomalies. We also found that parents, identified as SL carriers themselves, were in a way relieved, because they had the feeling the child could be 'normal' like themselves. These parents used themselves or their partner as a reference for the interpretation of the SL in their fetus. The psychological reaction reported by the individuals in our clinic may have been milder as compared to the study of Bernhardt et al. (2013). In that study, 23 participants were interviewed after disclosure of abnormal prenatal microarray results, of which 9 were known pathogenic results and 14 were variants of unknown clinical significance (VOUS). As in our study Bernhardt observed that participants initially felt shocked and worried, and had a problem with understanding the uncertainty and unquantifiable risks. Participants also shared a high need for support to manage and understand their prenatal microarray results with the help of a health care professional. However, in our study all women and their partners were counselled by a senior geneticist, whereas in the study of Bernhardt such support was not offered in all cases which might explain to the enduring concerns and a lack of support to manage decisions about termination of pregnancy and/or birth.. In both Bernhardt's study and our own, a key factor in mitigating parental anxiety with SL disclosure appears to be post-test genetic counselling.[36] However, in our study, participants reactions seem milder. In the study of Bernhardt, most participants indicated that they felt their test result was 'toxic knowledge'. In our study however, most participants indicated that they 'just have normal parental worries now', which clearly is a different outcome. The fact that all but one woman would choose to be informed of prenatal SL again, is a strong indicator of this.

Nearly all parents indicated they would want to be informed of SL again if offered a choice. Parents who said they preferred to know about SL, said they did so because they could quickly mobilise adequate care if needed. For instance, if developmental problems would occur, they could have access to early interventions for i.e. autism. These findings are congruent with our earlier study in which we found that a vast majority of pregnant couples, when offered a choice during pretest genetic counselling, opted for SL disclosure.[39] The parents we discussed

in this study indicated that they would prefer to have a choice regarding the (non) disclosure of SL. This study supports earlier reports[16, 39, 40] that parents highly appreciate individualized choice on the scope of prenatal testing. We have not observed psychological burden, however it has to be taken into account that the number of interviewed patients is small. Furthermore, some participants were still pregnant at the time of the interview. It is therefore difficult to make long-term conclusions. In our study, there was no distinction between prenatal de novo and inherited findings, however, due to their different nature parents might cope with them in another way. It would be interesting to evaluate this. Research on a larger scale is much needed to gain more insight in how pregnant couples are coping with this type of prenatal information.

Conclusion

This small study showed that in our setting, there was no long-term psychological burden for pregnant couples whose fetus was diagnosed with a susceptibility locus. A key factor in mitigating parental anxiety with SL disclosure appears to be post-test genetic counselling. This study confirms that parents highly appreciate an individualized choice on the scope of prenatal testing. We believe that if genomic microarray testing is offered, a chance of the detection of results like susceptibility loci should be routinely mentioned during pre-test counselling. An opt-out possibility may be sufficient to support the reproductive autonomy of pregnant couples.

References

1. Wapner R., Jackson L: Chromosomal microarray analysis for prenatal diagnosis: a prospective comparison with conventional cytogenetics. *Prenatal Diagnosis* 2008; 28: s8, 15–14.

2. Wapner R.J., Martin C.L., Levy B *et al*: Chromosomal microarray versus karyotyping for prenatal diagnosis. *N Engl J Med* 2012; 367: 2175–2184.

3. Fiorentino F., Caiazzo F., Napolitano S *et al*: Introducing array comparative genomic hybridization into routine prenatal diagnosis practice: a prospective study on over 1000 consecutive clinical cases. *Prenat Diagn* 2011; 31: 1270–1282.

4. Srebniak M.I., Mout L., Van Opstal D., Galjaard RJ: 0.5 Mb array as a first-line prenatal cytogenetic test in cases without ultrasound abnormalities and its implementation in clinical practice. *Hum Mutat* 2013; 34: 1298–1303.

5. Van Opstal D., de Vries F., Govaerts L *et al*: Benefits and burdens of using a SNP array in pregnancies at increased risk for the common aneuploidies. *Hum Mutat* 2015; 36: 319–326.

6. Girirajan S., Rosenfeld J.A., Coe BP *et al*: Phenotypic heterogeneity of genomic disorders and rare copy-number variants. *N Engl J Med* 2012; 367: 1321–1331.

8. Srebniak M.I., Diderich K.E., Govaerts LC *et al*: Types of array findings detectable in cytogenetic diagnosis: a proposal for a generic classification. *Eur J Hum Genet* 2014; 22: 856–858.

9. Van Opstal D., de Vries F., Govaerts L *et al*: Benefits and burdens of using a SNP array in pregnancies at increased risk for the common aneuploidies. *Hum Mutat*. 2015 36: 319–326.

10. Srebniak M.I., Diderich K., Joosten M *et al*: Prenatal SNP array testing in 1000 fetuses with ultrasound anomalies: causative, unexpected and susceptibility CNVs. *Manuscript in preparation* 2015.

11. Kaminsky E.B., Kaul V., Paschall J *et al*: An evidence-based approach to establish the functional and clinical significance of copy number variants in intellectual and developmental disabilities. *Genetics in Medicine* 2011; 13: 777–784.

12. Rosenfeld J.A., Coe B.P., Eichler E.E., Cuckle H., Phil D., Shaffer LG: Estimates of penetrance for recurrent pathogenic copy-number variations. *Genetics in Medicine* 2013; 15: 478–481.

13. Srebniak MI: Types of array findings detectable in cytogenetic diagnosis: a propaosal for a generic classification. *European Journal of Human Genetics* 2013.

14. Veltman J.A., Brunner HG: Understanding variable expressivity in microdeletion syndromes. *Nat Genet* 2010; 42: 192–193.

15. Girirajan S., Rosenfeld J.A., Cooper GM *et al*: A recurrent 16p12.1 microdeletion supports a two-hit model for severe developmental delay. *Nat Genet* 2010; 42: 203–209.

16. de Jong A., Dondorp W.J., Krumeich A., Boonekamp J., van Lith J.M., de Wert GM: The scope of prenatal diagnosis for women at increased risk for aneuploidies: views and preferences of professionals and potential users. *J Community Genet* 2013; 4: 125–135.

17. McGillivray G., Rosenfeld J.A., McKinlay Gardner R.J., Gillam LH: Genetic counselling and ethical issues with chromosome microarray analysis in prenatal testing. *Prenat Diagn* 2012; 32: 389–395.

18. Vetro A., Bouman K., Hastings R *et al*: The introduction of arrays in prenatal diagnosis: a special challenge. *Hum Mutat* 2012; 33: 923–929.

19. Hillman S.C., McMullan D.J., Silcock L., Maher E.R., Kilby MD: How does altering the resolution of chromosomal microarray analysis in the prenatal setting affect the rates of pathological and uncertain findings? *J Matern Fetal Neonatal Med* 2013.

20. Rigter T., Henneman L., Kristoffersson U *et al*: Reflecting on earlier experiences with unsolicited findings: points to consider for next-generation sequencing and informed consent in diagnostics. *Hum Mutat* 2013; 34: 1322–1328.

21. de Jong A., Dondorp W.J., Macville M.V., de Die-Smulders C.E., van Lith J.M., de Wert GM: Microarrays as a diagnostic tool in prenatal screening strategies: ethical reflection. *Hum Genet* 2014; 133: 163–172.

22. Brady P.D., Delle Chiaie B., Christenhusz G *et al*: A prospective study of the clinical utility of prenatal chromosomal microarray analysis in fetuses with ultrasound abnormalities and an exploration of a framework for reporting unclassified variants and risk factors. *Genetics in Medicine* 2013.

23. McGillivray G., Rosenfeld J.A., McKinlay Gardner R.J., Gillam LH: Genetic counselling and ethical issues with chromosome microarray analysis in prenatal testing. *Prenat Diagn* 2012; 32: 389–395.

24. Wolf S.M., Paradise J., Caga-anan C: The law of incidental findings in human subjects research: establishing researchers' duties. *J Law Med Ethics* 2008; 36: 361–383, 214.

25. Stark Z., Gillam L., Walker S.P., McGillivray G: Ethical controversies in prenatal microarray. *Curr Opin Obstet Gynecol* 2013; 25: 133–137.

26. Vetro A., Bouman K., Hastings R *et al*: The Introduction of Arrays in Prenatal Diagnosis: A Special Challenge. *Human Mutation* 2012; 33: 923–929.

27. Dababnah S., Parish SL: Feasibility of an empirically based program for parents of preschoolers with autism spectrum disorder. *Autism* 2015 25: Epub ahead of print.

28. Field A: Discovering statistics using SPSS Sage Publications Ltd., 2009.

29. Burnside R.D., Pasion R., Mikhail FM *et al*: Microdeletion/microduplication of proximal 15q11.2 between BP1 and BP2: a susceptibility region for neurological dysfunction including developmental and language delay. *Hum Genet* 2011; 130: 517–528.

30. Rosenfeld J.A., Coe B.P., Eichler E.E., Cuckle H., Shaffer LG: Estimates of penetrance for recurrent pathogenic copy-number variations. *Genet Med* 2013; 15: 478–481.

31. Firth HV: 22q11.2 Duplication 1993.

32. Kaminsky E.B., Kaul V., Paschall J *et al*: An evidence-based approach to establish the functional and clinical significance of copy number variants in intellectual and developmental disabilities. *Genet Med* 2011; 13: 777–784.

33. Cooper G.M., Coe B.P., Girirajan S *et al*: A copy number variation morbidity map of developmental delay. *Nat Genet* 2011; 43: 838–846.

34. Ballif B.C., Theisen A., Coppinger J *et al*: Expanding the clinical phenotype of the 3q29 microdeletion syndrome and characterization of the reciprocal microduplication. *Mol Cytogenet* 2008; 1: 8.

35. Goobie S., Knijnenburg J., Fitzpatrick D *et al*: Molecular and clinical characterization of de novo and familial cases with microduplication 3q29: guidelines for copy number variation case reporting. *Cytogenet Genome Res* 2008; 123: 65–78.

36. Bernhardt B.A., Soucier D., Hanson K., Savage M.S., Jackson L., Wapner RJ: Women's experiences receiving abnormal prenatal chromosomal microarray testing results. *Genet Med* 2013; 15: 139–145.

37. Statham H., Solomou W., Chitty L: Prenatal diagnosis of fetal abnormality: psychological effects on women in low-risk pregnancies. *Baillieres Best Pract Res Clin Obstet Gynaecol* 2000; 14: 731–747.

38. Lalor J., Begley C.M., Galavan E: Recasting Hope: a process of adaptation following fetal anomaly diagnosis. *Soc Sci Med* 2009; 68: 462–472.

39. van der Steen S.L., Diderich K.E., Riedijk SR *et al*: Pregnant couples at increased risk for common aneuploidies choose maximal information from invasive genetic testing. *Clin Genet* 2014.

40. Boormans E.M., Birnie E., Oepkes D., Boekkooi P.F., Bonsel G.J., Van Lith JM: Individualized choice in prenatal diagnosis: the impact of karyotyping and standalone rapid aneuploidy detection on quality of life. *Prenat Diagn* 2010 30 928–936.

Chapter 5

Non-invasive or invasive prenatal testing: safety for the fetus overrides the need for broad scope genetic information

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Chapter 6

Offering a choice between NIPT and invasive PND in prenatal genetic counselling: the impact of counsellor characteristics on patients' test uptake

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Abstract

Testing options for pregnant women at increased risk of common aneuploidies are non-invasive prenatal testing (NIPT) and invasive prenatal diagnosis (PND). Counsellors are challenged to comprehensively discuss the complex information in a patient-centered and non-directive manner, to allow for patients' informed decision-making. This study explored the information-centeredness, patient-centeredness and level of non-directivity of different counsellors and examined group differences between their patients. First, semi-structured interviews with four senior obstetricians and one senior nurse were held regarding their information provision, their adaptation of a patient-centered attitude, and their practice of non-directivity. Interviews were transcribed verbatim and rated by four independent judges. Secondly, 181 pregnant women were included in the study, of whom 82% opted for NIPT and 18% chose PND. Between counsellors, we assessed the distribution of choice ratios, patients' impression of counsellors' test preferences, and patients' knowledge scores. The results indicate that counsellors do not differ in their level of information-centeredness, but do differ in their level of patient-centeredness and their level of non-directivity. Significant differences in patients' NIPT/PND ratios were observed between counsellors, with the largest difference being 35% versus 4% opting for invasive PND. Between 9% and 22% of the patients had an impression of their counsellor's preference and chose in accordance with this preference. Patients' overall knowledge scores did not differ across counsellors. In conclusion, the differences in NIPT/PND ratios between counsellors indicate that counsellors' differences affect the choices their patients make. The interviews indicate a possible framing effect which may unintentionally steer the decision-making process.

Introduction

Because of recent developments in prenatal genetic testing, more testing options have become available for pregnant women. Women with an abnormal first trimester screening (FTS) result need to make important decisions about how they wish to proceed in their prenatal care. As of now, pregnant women in the Netherlands have three options as depicted in Figure 1:

1. no further testing,
2. invasive prenatal diagnosis (PND), and
3. non-invasive prenatal testing (NIPT).

The primary goal of pre-test counselling is to enable the pregnant woman and her partner to make an informed choice and to give informed consent for either NIPT or invasive PND, or refrain from further testing. The eventual decision should be based on relevant knowledge, consistent with the couple's values, and behaviorally implemented.[1] During pre-test counselling, information is provided about the benefits and limitations of both NIPT and invasive PND, as well as the potential to detect findings other than the indication for testing.

Besides informing pregnant women and their partners, the counsellor should address individual attributes of the patient, such as emotions and resilience.[2] A focus on patient-centeredness in prenatal counselling is expected to lead to more well-deliberated choices and less psychological distress for patients. Kessler[3] has differentiated between the teaching model and the counselling model. Whereas the teaching model aims for educated patients, the counselling model aims for patients to feel understood, in control, and competent. These outcomes are desirable, but also require a much broader set of counselling skills. The counsellor should then not only inform, but should also elicit information from patients about their needs and use this information to guide the counselling session.[3,4]

Genetic counselling traditionally implies a non-directive attitude. According to Kessler 5, non-directive counselling aims to facilitate patients to think about their considerations, which is different from directive counselling, aiming to prescribe and influence the patients' behavior. While directive counselling involves persuasive coercion, thereby targeting the decision outcome, non-directive

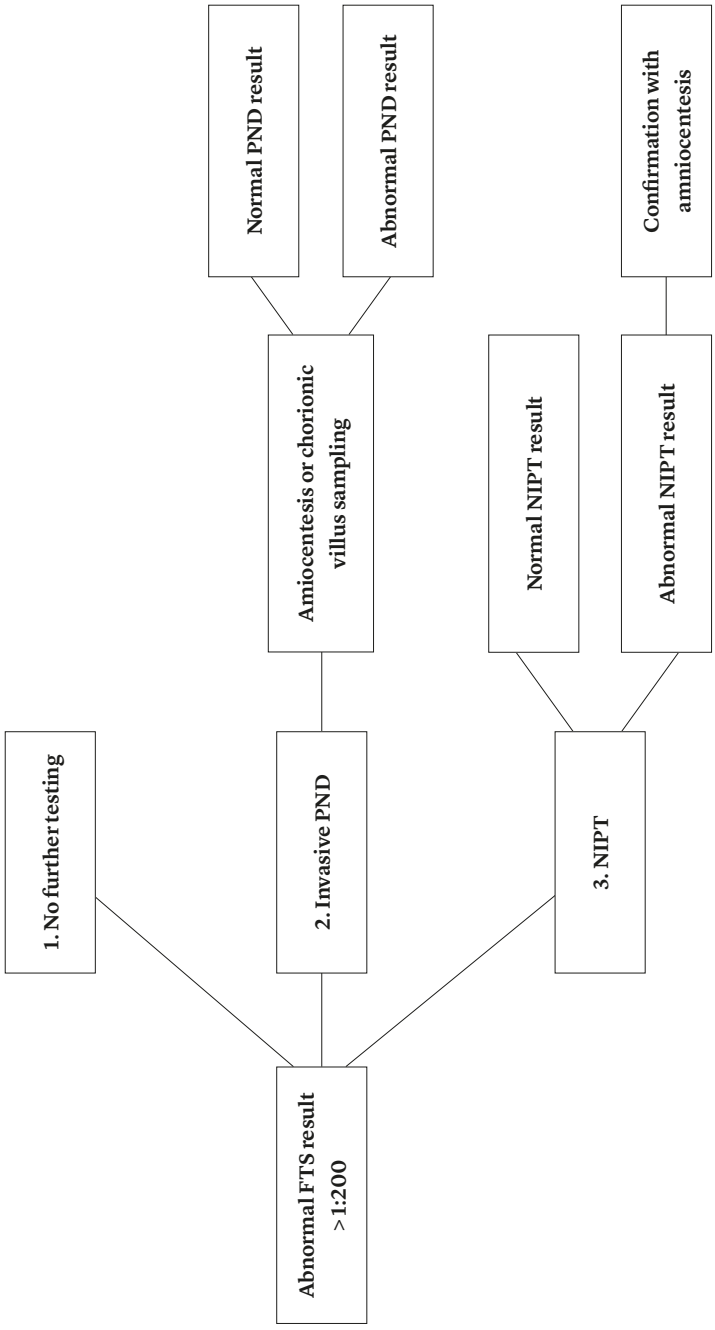

Figure 1. Flowchart of prenatal testing options after abnormal first trimester screening results (FTS)

counselling promotes the patient's autonomy and self-directedness, so that the decision-making process is optimized.[3,4]

A recent Dutch study demonstrated that nationwide, about 3% of pregnant women with an increased FTS result chose invasive prenatal testing while about 97% chose NIPT.[6] At the Erasmus Medical Center in the Netherlands, nearly 20% of the pregnant women opted for invasive PND while around 80% chose NIPT.[7] The difference in choice ratio may be explained by this center's different policy regarding invasive prenatal testing. Whereas other academic centers in the Netherlands perform Quantitative Fluorescence-Polymerase Chain Reaction (QF-PCR) on fetal DNA to examine chromosomes 13, 18 and 21, here, high resolution SNP array at 0.5 Mb is performed to analyze all chromosomes at a submicroscopic level.[8] This microarray provides much more detailed information on additional chromosomal aberrations.

The increasing scope of possible findings provided by SNP array and NIPT may jeopardize sound prenatal genetic counselling.[9] As the complexity of genetic counselling increases, it may become demanding for pregnant women and their partners to understand the test characteristics and implications.[10-12] Subsequently, the informed decision-making process of pregnant women and their partners requires more extensive pre-test counselling.

The higher invasive PND uptake rate at the Erasmus Medical Center compared to other academic centers, and the even more challenging task of counsellors to comprehensively discuss the different testing options and test outcomes of PND with their patients, increases the need to explore the approach of the different counsellors in this center and the content of their prenatal genetic counselling. Therefore, we explored the information-centeredness, patient-centeredness and level of non-directivity of different counsellors by means of semi-structured interviews. We used data analysis to compare the ratio of patients' choices for either NIPT or invasive PND between counsellors and we examined whether patients had an impression of their counsellors' preferences. Finally, we assessed whether there were group differences in patients' knowledge scores between counsellors.

Materials and methods

For this study, qualitative and quantitative data were collected. Qualitative data about counsellor characteristics were obtained by semi-structured interviews with prenatal genetic counsellors. Quantitative data about group differences between patients of different counsellors were obtained from previously collected data.[7]

Qualitative data

Counsellors working at the Erasmus University Medical Center in Rotterdam who provided counselling to more than 15 patients in an earlier study[7] were eligible for the qualitative interview study (N = 5). All five counsellors had senior positions, with 15+ years of experience in the prenatal genetic testing field. One counsellor was a senior nurse, the other four counsellors were senior gynecologists/obstetricians. The senior obstetricians performed chorionic villus sampling and amniocentesis themselves, whereas the senior nurse did not. The age range of counsellors was 42–51 years. All counsellors were familiar with providing counselling for invasive PND, and when NIPT was introduced in the Netherlands, they were formally trained in a Dutch national program about offering this choice alongside invasive PND as part of the Trial by Dutch laboratories for Evaluation of Non-invasive Prenatal Testing (TRIDENT). The counsellors welcomed pregnant women who had an increased risk based on first trimester screening and who subsequently had to choose between no further testing, NIPT, and invasive prenatal testing. In total, 181 pregnant women were counselled in this study. Counsellor one counselled 49 patients, counsellor two 71 patients, counsellor three 23 patients, counsellor four 15 patients, and counsellor five 23 patients. The interviews focused on three important themes of prenatal genetic counselling, as previously described in the introduction: 1) information-centeredness, 2) patient-centeredness, and 3) non-directivity.

First, the counsellors were asked how and to what extent they inform pregnant women and their partners about the choice between NIPT and invasive PND (information-centeredness), i.e. the different choice options, goals and methods of testing, test characteristics and limitations, risk-communication, turnaround time of results, and possible outcomes and implications. Veach et al. stated that 'presentation and discussion of relevant information allows patients to gain improved understanding and develop a new or different perspective'.[2] Second, it

was explored how and to what extent the counsellor addresses the pregnant women and their partners' thoughts, feelings, values, family dynamics, and psychosocial context and promotes emotional well-being by giving support, validation, and assistance with coping; patient-centeredness.[2] The balance between patient-centeredness and information centeredness was discussed. Third, it was explored to what degree counsellors adopted the concept of non-directivity in their counselling. In the exploration of this concept, directiveness and non-directiveness were not used as categorical opposites, but rather as extremes on a continuum related to the level of patient autonomy.[13] Counsellors elaborated on the existence and definition of non-directivity and on how this concept was implemented in their counselling. We asked counsellors whether at times they were inclined to provide directive advice about the best option for the patient and whether counsellors had a personal preference towards a specific test.

To illustrate counsellor characteristics scores, we have selected several quotes from each counsellor regarding his/her level of information-centeredness, patient-centeredness and non-directivity. Although these quotes are fragments of the answers counsellors gave during the interviews, we consider them to be archetypical of the counsellor's approach.

Qualitative Analysis

The interviews were conducted in Dutch and transcribed verbatim. The transcriptions of the interviews were scored by four independent judges (SS; DH; SR; AT). Using a five-point Likert scale, the judges each formed an individual evaluation of the counsellors' level of information-centeredness (1 = very low to 5 = very high), patient-centeredness (1 = very low to 5 = very high), and the degree of non-directivity (1 = fully directive, i.e. low patient autonomy to 5 = fully non-directive, i.e. high patient autonomy). Four judges rated the five counsellors on three categories, resulting in 15 ratings per judge. More than two points difference between judges' ratings was regarded as substantial, and a consensus meeting was held to discuss these differences. Subsequently, judges could adjust their individual scores, eliminating these substantial differences. After adjustment of the scores, for each counsellor, the mean score on each of the three concepts was calculated. Finally, for all 15 sets of four ratings we calculated both the percentage absolute agreement between judges and the percentage of ratings with not more than one point difference (on the five-point scale) between judges.

Quantitative Data

Pregnant women and their partners who visited the outpatient clinic of prenatal medicine in the Erasmus MC, University Medical Center Rotterdam, between April 2014 and November 2015 were invited to participate in a study 7 measuring informed choice for patients opting between NIPT and invasive PND. For the present study, we made use of the same data, however, we compared patients scores *between counsellors* instead of *between test choice*.

Inclusion criteria for the patients were: a) an elevated risk on common aneuploidies based on first-trimester screening and b) engaging in either NIPT or invasive PND. Exclusion criteria were:

1. a recurrence risk for trisomies based on earlier pregnancies or heredity,
2. a fetal nuchal translucency >3.5 mm, and
3. patients who were counselled in satellite hospitals in the South-West region of the Netherlands. One-hundred and eighty-one pregnant women were included in the study.

Consenting participants completed a questionnaire that assessed:

1. their choice for either NIPT or PND,
2. their impression of the counsellor's preference, and
3. their level of knowledge.

Social demographic background, level of education, nationality, age, religiosity and obstetric history were collected. The ratios of patient's choices for either NIPT or invasive PND between counsellors were computed. Whether the patients had an impression of the counsellor's own preference for either NIPT or invasive PND was measured by one item ('I feel like the choice I made had the doctor's preference'), answered on a 10-point visual analogue scale. We were especially interested in the distribution of high scores per counsellor, indicating that the patient followed a clearly expressed preference of the counsellor. Therefore, we reported scores >8 on this item per counsellor. The Measure of Informed Choice (MIC) was part of the questionnaire and previously designed to assess the level of informed decision-making after pre-test counselling.[7] The MIC consists of two scales; Knowledge (with a reliability of $\alpha = .55$ [ref. 7]) and Attitude (with a

reliability of $\alpha = .78$ [ref. 7]). The Knowledge scale has nine multiple-choice questions regarding the test capacities of NIPT and invasive PND.

Quantitative analysis

To analyse the data, the multiple-choice answers of the Measure of Informed Choice (MIC) knowledge scale were dichotomized, where '0' represented an incorrect answer and '1' a correct answer. Sufficient knowledge was determined to be seven (7/9 = 77.8%) or more correct answers on the MIC Knowledge scale. We chose such a conservative criterion because we place great priority on thorough and extensive provision of information during counselling. Chi square tests were used to test differences in patients' total knowledge scores between counsellors on the MIC knowledge scale. To evaluate the differences on *individual items* of the MIC between counsellors, McNemar tests were conducted. Paired samples t-tests were used to investigate the differences in total knowledge score of patients between counsellors. Chi square tests were used to test differences in the uptake ratio of NIPT or PND between counsellors and to test for differences in patient characteristics between counsellors. For all statistical tests, a significance level of $\alpha = .05$ was used.

Results

Counsellor characteristics

The mean scores on the categories of level of information-centeredness, patient-centeredness and non-directivity per counsellor are displayed in Table 1. The average percentage of absolute agreement between judges was 61.7% (Min = 50%, Max = 100%) and the percentage of ratings with not more than one point difference between judges was 83.3% (Min = 75%, Max = 100%). Counsellors do not differ in their level of information-centeredness, but do differ in their level of patient-centeredness and their level of non-directivity. Figure 2 shows interview findings and quotes to illustrate and support the findings in this study.

Counsellor	Information centeredness (scale 1–5)	Patient centeredness (scale 1–5)	Level of non-directivity (scale 1–5)
1	4.3	4.5	4.5
2	4.5	3.8	3.0
3	4.0	4.0	2.8
4	3.3	2.5	3.5
5	4.0	3.8	5.0

Table 1. Counsellors and their individual characteristics* as derived from the semi-structured interviews.

* Counsellor characteristics were derived as the mean rating based on scoring of the interviews by 4 separate judges (SS; DH; SR; AT).

	N	%	C1	C2	C3	C4	C5	p-value (*x*)
Educational level								**.106**
Low/intermediate	59	33%	41%	28%	17%	27%	48%	
High	122	67%	59%	72%	83%	73%	52%	
Nationality								**.293**
Dutch	167	92%	94%	89%	96%	87%	100%	
Other	14	8%	6%	11%	4%	13%	0%	
Religiosity								**.007***
Religious	38	21%	10%	24%	4%	40%	35%	
Non-religious	143	79%	90%	76%	96%	60%	65%	
Previous children								**.001***
Yes	101	56%	71%	57%	57%	67%	17%	
No	80	44%	29%	43%	43%	33%	83%	
Previous miscarriages								**.793**
Yes	46	25%	32%	35%	43%	50%	31%	
No	82	45%	68%	65%	57%	50%	69%	
Missing	53	29%						

* = Significant (<.05)

Table 2. Demographic data of participating women (N = 181).

	Information-centeredness
Counsellor 1	'I am talking a lot! You must give patients a lot of information. I start with the invasive test. It is a diagnostic test and NIPT gives a probability of trisomy 21, 18 and 13. I ask them if they have heard about it. If they say yes, I do not go into a lot of detail about it. *I ask them if they know what it is, and what they are going to do in case of an abnormal result*.'
Counsellor 2	'I explain them there are three options; no further testing, NIPT or invasive PND and about the technical capacities of these tests. We are looking at *all the chromosomes on a detailed level and it is possible to detect thousands of other aberrations that might be equally relevant*, and that the background risk is the same for everyone in the population.'
Counsellor 3	'I start with the FTS result. Then I ask if they know what chromosomes are. *I explain that chromosomes are genetic building blocks*, and sometimes there is a bit too much or too little of it. If that's the case, then it might have consequences for the fetus. To test the chromosomes you can opt for NIPT or PND. *I weigh the patient's specific FTS result to the risk of a miscarriage due to the invasive procedure and the chance to detect something with NIPT.* I also talk about the family composition, and the personal values of the women or couple.'
Counsellor 4	'I start with the increased *FTS result and tell them that they can accept this risk and do nothing or proceed with NIPT/PND*. I tell NIPT is not that reliable and only for trisomy 21, 18 and 13. About *invasive PND I tell that we "just look at all the other chromosomes"* as well. I do not go into detail about this. I also tell them that there is a *very small risk of a miscarriage*.'
Counsellor 5	'*I tell them that NIPT, like FTS, is also a probabilistic test, no 100% certainty. Invasive PND does give certainty and is capable to detect more aberrations.* I tell them that NIPT has no miscarriage risk and is designed to detected trisomy 21, 18 and 13. *I also explain the symptoms of these trisomies and what it might mean for the fetus.*'

Figure 2a. Quotes to illustrate counsellors' answers and their individual scores on characteristics.

	Patient-centeredness
Counsellor 1	'I always start with; 'How are you? Did the abnormal FTS result come as a shock? How are you feeling about the result now? *Do you already know what your preference for testing is?' If I don't do this, then they are not open to my more technical information about NIPT/PND.*'
Counsellor 2	'I always ask: *Do you think it is important to have a definite result? Do you think it is important to have a fast result?* How much tolerance for uncertainty do you have? Are you afraid of risks? *What are you going to do with a normal/ abnormal test result?* Have you thought about a termination of pregnancy? *I am emphasizing they should make a choice that fits their personal values most.*'
Counsellor 3	'My story is always more or less the same, with small variations; I explain what chromosomes are, how the invasive PND procedure works, what the miscarriage risk is, what the pros and cons of both NIPT and invasive PND are.' '*I ask about the family structure and living situation. How many previous kids? Do those have special needs? What are your resources?*'
Counsellor 4	'It is not my job to explore which choice would be the best fit for the patient, right? *It is up to the couple to decide which road they could best take.*'
Counsellor 5	'*I open my counselling with informing about how the woman is doing when she enters my room.* I ask, "How are you? How do you feel about the abnormal FTS result? *What are you going to do with the outcomes of a follow-up test (in the case of NIPT/PND)?" I try to ask them about the way their choice feels for them, whether it be NIPT, PND or no further testing.*'

Figure 2b. Quotes to illustrate counsellors' answers and their individual scores on characteristics.

	Non-directivity
Counsellor 1	'Non-directive counselling. *Completely neutral. I don't know...* I think I am trying my best to do that. But *I have my own style and the way you communicate risks is of big influence on the patients' perception* of that risk. You always bring a piece of your personality into the counselling. I try to be as neutral as possible. *I take the patient and her background and emotions into account.*'
Counsellor 2	'I tell that with invasive PND, you test for more than just the common trisomies. I tell that *NIPT is a good screening test, and invasive PND provides certainty.* The additional *risk of a miscarriage is nihilistic*. I also talk about the expanded scope of invasive testing. *The extra information PND yields is a bonus.*' 'I believe in non-directivity, however, you cannot filter out things like non-verbal communication or unbalanced time distribution when explaining NIPT or invasive PND.'
Counsellor 3	'I do not give advice, I counsel people. They should make their own choice. *I do confirm them in their choices, but I never try to 'talk them into' anything. Sometimes you need to decide together with the patient.* It is important that people do not feel regret for their choices afterwards.' 'I think we should keep doing invasive tests and I am pro-invasive testing... oh, I am not only pro-invasive, I am also pro-NIPT by the way...'
Counsellor 4	'*I think non-directivity is a great principle, but that it is hard to maintain it all of the time.* But yes, I do think it is very desirable to counsel in a non-directive fashion. I try to counsel as non-directive as possible and to give the information about it as clearly as I can. When they ask me for advice, I say that it is not my child and I am not the one who is pregnant, but *I am willing to go through all information about the options again.* I tell them the *risk of a miscarriage is actually quite small, but when it happens, it is a great tragedy.*'
Counsellor 5	'*I think it is most important to explain people what both options comprise and what the consequences can be. I never ever give advice.* I tell them that they have to make their own choices, even if they ask me what I would do.' 'I do say that in the experience of my patients, chorionic villus sampling is often perceived as a more unpleasant procedure.'

Figure 2c. Quotes to illustrate counsellors' answers and their individual scores on characteristics.

Patients' group differences

Demographics

The mean age of patients was 34.6 years. Between patients of different counsellors, there were no significant differences in demographic variables, except for religiosity, and having previous children (as depicted in Table 2); 83% of patients from Counsellor 5 did not have previous children, while the other counsellors more often saw patients that did already have children, and 40% of the patients from Counsellor 4 were religious, versus 4% of the patients from Counsellor 3.

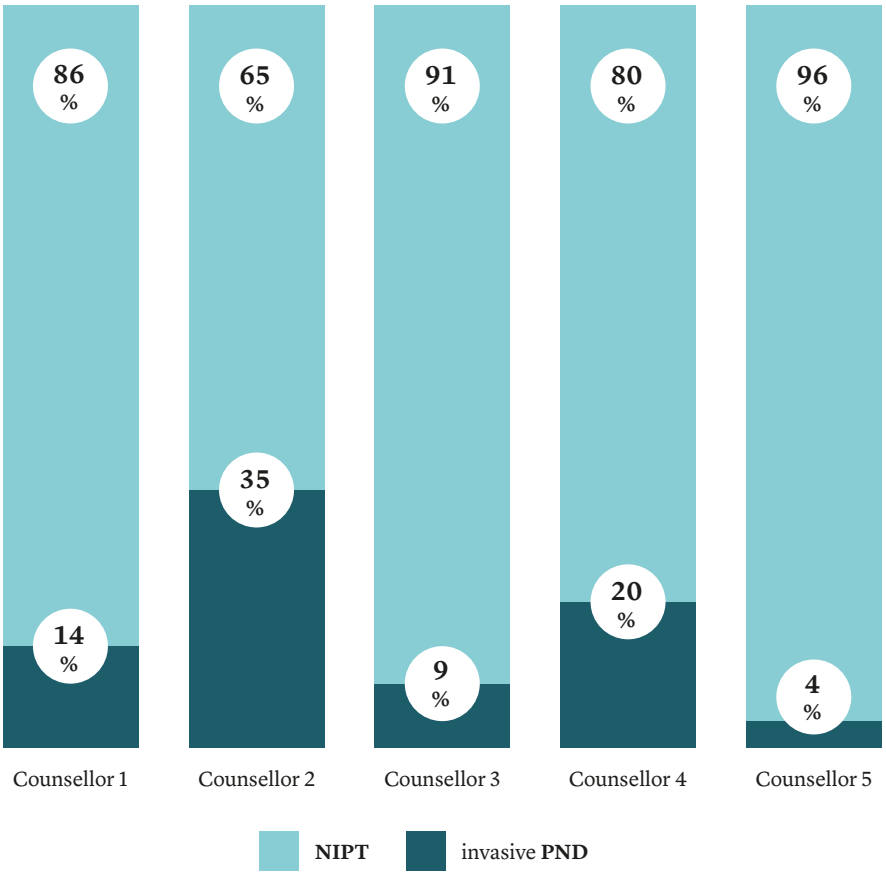

Figure 3. Ratio of patiens' choices for NIPT or invasive PND *between* counsellors (N = 181)

Choice ratios

Patients' choices for either NIPT or PND differed significantly between counsellors (χ^2 (4) = 11.98, p = 0.017). The largest difference was found between counsellor 2 and counsellor 5, being 35% versus 4% opting for invasive PND, as depicted in Figure 3.

Patients' impression of counsellor preference

The mean and median scores of the question 'I feel like the choice I made had the doctor's preference' are displayed between counsellors in Table 3. Table 3 also depicts the percentage of patients for each counsellor who indicated they had an impression of their counsellor's preference. Between 9% and 22% of the patients had an indication of the counsellor's preference and chose in accordance with this assumed preference.

	N	Mean	Median	Frequency score ≥ 8	Percent score ≥ 8
Counsellor 1	49	3.68	4.50	6	12.0%
Counsellor 2	71	4.04	4.00	16	21.6%
Counsellor 3	23	3.00	2.00	3	13.0%
Counsellor 4	15	4.00	5.00	2	13.3%
Counsellor 5	23	2.65	1.00	2	8.7%

Table 3. Mean and median item scores between counsellors and percentage of patients (N = 181) who indicated they had an impression (≥ 8, range 0–10) of the counsellor's preference and chose in accordance.

Patients knowledge scores

Patients' mean knowledge scores were high. Most pregnant women and their partners answered all questions correct and displayed good testing knowledge. Knowledge scores did not differ across counsellors. However, patients' individual item scores of either NIPT or PND questions differed significantly across counsellors, as depicted in Table 4.

Item	Total *N* = 181	C1 N = 49	C2 N = 71	C3 N = 23	C4 N = 15	C5 N = 23
1. Which material is used for NIPT testing?	.99	1.00	1.00	1.00	1.00	1.00
2. Which aberrations does the NIPT detect?	.99	1.00	.96	1.00	1.00	1.00
3. What is done to verify an abnormal NIPT result?	.96	1.00	.94	1.00	**.80***	.93
4. What is the miscarriage risk of the NIPT?	.98	1.00	.98	1.00	.90	1.00
5. After how many weeks of gestation can NIPT be performed?	.95	.95	.96	1.00	.90	.86
6. What is the reliability of the NIPT?	.85	.95	**.64***	.69	.80	.93
7. Which conditions or abnormalities can be detected with invasive PND?	.58	.65	.68	.69	.80	**.50***
8. What is a possible advantage of invasive prenatal testing for a pregnant woman and her partner?	.88	.89	.88	1.00	1.00	.79
9. What is a possible advantage of NIPT for a pregnant woman and her partner?	.80	.84	.82	.85	.80	.93
Total knowledge score	**7.97**	**8.27**	**7.86**	**8.23**	**8.00**	**7.93**

Note. C = Counsellor. For each item 0 = incorrect and 1 = correct. The range of the total score is 0 to 9.
* = significant difference

Table 4. Mean MIC Knowledge scores between counsellors. Significant differences on NIPT or invasive PND questions answered correct were observed between counsellors and marked with *.

Discussion

Prenatal genetic counselling has become increasingly demanding due to the more complex information resulting from technological progress. Consequently, for pregnant women and their partners, the decision-making process may be under more pressure than ever before. Such pressure requires thorough, high quality counselling. Assuming all counsellors commit to the recommendations made by the Dutch Health Council[14] in their counselling, overall uptake ratios and the counsellors' views on the content and approach of their counselling should be approximately equal in the grand total. All counsellors in our study provide and discuss the relevant information that is necessary to meet the first requirement of informed decision-making, which was validated by the high knowledge scores of pregnant women. However, in this study we found differences *between* counsellors in their level of patient-centeredness, non-directivity, and the test uptake of patients.

Regarding patient-centeredness, some counsellors stated that they actively explore the patient's values and attitudes, whereas others were less inclined to address the patient's feelings and cognitions about the test options of NIPT and invasive PND (as illustrated by the quotes). The patient-counsellor relationship (e.g., affective communication, collaboration, goal consensus, positive regard) accounts for a substantial part of the psychological outcomes in a prenatal care trajectory.[2, 15–17] We therefore consider this category to be of great importance. Providing space for patients to share their considerations and thoughts leads to a greater level of perceived patient-centeredness.[2] It is important for counsellors to provide guidance by eliciting information from their patients about their needs and by asking questions about their values and attitudes. Individual differences require counsellors to adjust, i.e. personalize, their counselling.

Regarding how counsellors valued non-directivity, we observed differences between counsellors, as indicated by their quotes. Although the concept of (non) directivity has been used for more than four decades, there is still no consensus about the definition of directiveness and non-directiveness. Kessler has argued that *not being* directive is not the same as being non-directive.[3, 5] He states that being directive involves a degree of persuasive coercion. However, the absence of persuasive coercion does not imply non-directivity. Non-directiveness is an active strategy that requires counselling skills that aim to support the patient's

autonomy and self-directedness and provides them with a way of thinking about their considerations. According to Evans, a misunderstanding of the concept of non-directivity may lead the counsellor to adopt a stance of passivity or defensive avoidance rather than engaged neutrality.[18]

Moreover, counsellors might be unaware of their directiveness.[3] In our study, counsellors' quotes show that a framing effect may implicitly be present in their counselling. For example, when they spend more time discussing one test than discussing the other. Differences in risk communication also become apparent from the interview quotes. Some counsellors frame their information by using words such as 'negligible', 'only 1/1000', and 'extremely small' when communicating the miscarriage risk. Other counsellors make it much more personal by stating that 'the risk is small, but when it happens, it is a great tragedy'.

Furthermore, all counsellors are about the same age (42–51 years) and have been active in their profession for a long time. For them, invasive testing has been the standard of prenatal genetic testing for years. This may lead some of them to describe invasive PND as such, while the testing options of either NIPT or PND are essentially different, since they have been designed for different purposes; invasive PND is a diagnostic test, while NIPT is a screening test. Counsellors also indicated that a substantial number of patients already have a strong preference for NIPT when they enter the counselling. As the counsellors reported, the information that is provided to them by primary or secondary care is often framed, shaped, or even flawed in favor of NIPT. This skewed level of prior knowledge may motivate some counsellors to elaborate more on both test options and to balance the knowledge of their patients. However, other counsellors may become demotivated, as they feel like they are repeatedly making up for other referrers' misconceptions. These matters of word choice and non-verbal communication may unintentionally steer the decision-making process of patients, which is hard to prevent. However, this framing effect may be counterbalanced by skillful counselling.

Counsellors in our study differed in the percentage of their patients opting for invasive PND and NIPT. Moreover, there was a group of patients who had an impression of their counsellor's preference for either test. The unique offer of high resolution microarray may incline the counsellors to guide their patients towards opting for invasive PND. The finding that nearly 20% of pregnant women opted for invasive PND in Erasmus Medical Center, compared to about 3% nationwide,

may indicate such a tendency. However, there is also contradictory data suggesting that the difference in uptake cannot be explained by the unique offer. This data was retrieved from non-academic centers in the region that offered the same high resolution SNP array to their patients by sending their genetic material to the Erasmus Medical Center's lab for chromosomal examination at submicroscopic level.[7] Remarkably, none of these pregnant women who were offered the same options as in Erasmus Medical Center chose invasive PND.[7] Whether the impression of the counsellor's preference had influenced the pregnant woman's eventual decision needs to be further investigated.

This study gave a first exploration of counsellors' differences affecting patients' choice. We combined both qualitative data from the interviews with counsellors and quantitative data of patients. Although we found differences in patient-centeredness and non-directivity between counsellors, we were unable to link these differences to differences in patients' test uptake. It may be that the differences in counsellor characteristics are too subtle to identify a clear pattern related to patients' choice based on such a limited number of counsellors. Also, counsellors' answers may have been subjected to what they thought was socially desirable. We suggest that further research finds a way to study the actual counselling provided by means of analyzing recorded counselling sessions in a larger, more powerful research design, to gain more insight into counsellors' approach and content. Also, given the higher invasive PND uptake rate in the Erasmus Medical Center compared to other academic centers, it would be interesting to compare counsellor approach and counselling content between different academic centers and/or hospitals.

Implications

Counsellors differed in their prenatal genetic counselling approach and content. Our results indicate that the information provision during counselling is sufficient. Patient-centeredness differs between counsellors and may be improved by putting more emphasis on exploring patients' meaning and personal significance during the counselling. We advocate that this theme should be elicited in training modules for counsellors. Another important theme to emphasize during training modules is the paradigm of non-directivity. The understanding of this concept should shift from emphasizing what counsellors *should not* do, i.e. persuasive coercion and giving advice, possibly inducing passivity, to what they *should* do,

i.e. promoting patient's autonomy and self-directedness by aiming for patients to feel understood, in control, and competent. The latter involves an active attitude and requires more counsellor skills.

Conclusion

To conclude, patients' choice ratio for either NIPT or invasive PND differed significantly per counsellor. The different choice ratios of NIPT/PND could not be explained by different levels of patients' knowledge or demographic factors, indicating that the approach and content of the counselling affect the eventual choices that patients make. In our study, counsellors seem to influence the choices their patients make. It is important that counsellors reflect on their potential impact on the patients' decision-making process. A framing effect may unintentionally steer the decision-making process of patients, which is hard to prevent. The challenge remains to affect the decision-making process in the most positive and skillful manner; to facilitate well-deliberated and informed choices, to determine the counselling needs of pregnant women and their partners, and to promote autonomy and self-directedness.

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References

1. Michie S., Dormandy E., Marteau T.M. The multi-dimensional measure of informed choice: a validation study. *Patient Educ Couns* 2002; 48(1): 87–91. doi:https://doi.org/10.1016/s0738–3991(02)00089–7

2. Veach P.M., Bartels D.M., Leroy B.S. Coming full circle: a reciprocal-engagement model of genetic counselling practice. *J Genet Couns* 2007; 16(6): 713–728. doi:10.1007/s10897–007-9113–4

3. Kessler S. Psychological aspects of genetic counselling. X.I. Non-directiveness revisited. *Am J Med Genet* 1997; 72(2): 164–171. doi:10.1002/(sici)1096–8628(19971017)72:2<164::aid-ajmg8>3.0.co;2-V

4. Farrelly E., Cho M.K., Erby L., Roter D., Stenzel A., Ormond K. Genetic counselling for prenatal testing: where is the discussion about disability? *J Genet Couns* 2012; 21(6): 814–824. doi:10.1007/s10897–012-9484-z

5. Kessler S. Psychological aspects of genetic counselling: V.I.I. Thoughts on directiveness. *J Genet Couns* 1992; 1(1): 9–17.

6. Oepkes D., Page-Christiaens G.C., Bax C.J., et al. Trial by Dutch laboratories for evaluation of non-invasive prenatal testing. Part I-clinical impact. *Prenat Diagn* 2016; 36(12): 1083–1090. doi:10.1002/pd.4945

7. van der Steen S.L., Bunnik E.M., Polak M.G., et al. Choosing between higher and lower resolution microarrays: do pregnant women have sufficient knowledge to make informed choices consistent with their attitude? *J Genet Couns* 2018; 27(1): 85–94. doi:https://doi.org/10.1007/s10897–017-0124–5

8. Srebniak M.I., Mout L., Van Opstal D., Galjaard R.J. 0.5 Mb array as a first-line prenatal cytogenetic test in cases without ultrasound abnormalities and its implementation in clinical practice. *Hum Mutat* 2013; 34(9): 1298–1303. doi:10.1002/humu.22355

9. Sachs A., Blanchard L., Buchanan A., Norwitz E., Bianchi D.W. Recommended pre-test counselling points for noninvasive prenatal testing using cell-free DNA: a 2015 perspective. *Prenat Diagn* 2015; 35(10): 968–971. doi:10.1002/pd.4666

10. de Jong A., Dondorp W.J., de Wert G.M. The scope of prenatal diagnostic testing for chromosomal aberrations: broad or narrow? Ethical considerations on the choice of tests. *Ned Tijdschr Geneeskd* 2009; 153: A1060.

11. de Jong A., Dondorp W.J., Krumeich A., Boonekamp J., van Lith J.M., de Wert G.M. The scope of prenatal diagnosis for women at increased risk for aneuploidies: views and preferences of professionals and potential users. *J Community Genet* 2013; 4(1): 125–135. doi:https://doi-org.eur.idm.oclc.org/10.1007/s12687–012-0126–9

12. Riedijk S., Diderich K., Srebniak G., et al. The psychological counselling challenge of broadening the scope of genetic prenatal diagnosis. *European Journal of Human Genetics* 2014; 3(3): 713–723.

13. Benkendorf J.L., Prince M.B., Rose M.A., De Fina A., Hamilton H.E. Does indirect speech promote nondirective genetic counselling? Results of a sociolinguistic investigation. *Am J Med Genet* 2001; 106(3): 199–207. doi:10.1002/ajmg.10012

14. The Dutch Health Council [internet]. NIPT: dynamics and ethics of prenatal screening. The Hague: Health Council of the Netherlands, 2013; publication no. 2013/34: 21–28. Available from: https://www.gezondheidsraad.nl/en/task-and-procedure/areas-of-activity/prevention/nipt-dynamics-and-ethics-of-prenatal-screening isbn = 978–90-5549–983-0

15. Bernhardt B.A., Biesecker B.B., Mastromarino C.L. Goals, benefits, and outcomes of genetic counselling: client and genetic counsellor assessment. *Am J Med Genet* 2000; 94(3): 189–197. doi:10.1002/1096–8628

16. Elwyn G., Gray J., Clarke A. Shared decision making and non-directiveness in genetic counselling. *J Med Genet* 2000; 37(2): 135–138. doi:http://dx.doi.org/10.1136/jmg.37.2.135

17. Sep M.S., van Osch M., van Vliet L.M., Smets E.M., Bensing J.M. The power of clinicians' affective communication: how reassurance about non-abandonment can reduce patients' physiological arousal and increase information recall in bad news consultations. An experimental study using analogue patients. *Patient Educ Couns* 2014; 95(1): 45–52. doi:https://doi.org/10.1016/j.pec.2013.12.022

18. Evans C. *Genetic Counselling: A Psychological Approach*. Cambridge University Press: New York, USA, 2006.

19. Evans C. 2006. Genetic counselling, a psychological approach. Cambridge, UK: Cambridge University Press. p 204.

20. Evans C. 2006. Genetic counselling, a psychological approach. Cambridge, UK: Cambridge University Press. p 204.

Chapter 7

General discussion

Answers to the research questions

The aim of this thesis is to address the psychological consequences of new techniques which lead to a much larger scope of possible prenatal genetic findings for pregnant couples. In Chapter 1, the research questions were formulated. Below, these research questions are answered.

Part 1:

1. **What do pregnant women, or couples choose; a broad or narrow scope of microarray regarding invasive PND? Do they wish to be informed of uncertain outcomes?**
   In Chapter 2 it is shown that an overwhelming majority of couples choose for a maximum of genetic information about their child, including uncertain outcomes.

2. **Are there differences between participants opting for broad or narrow microarray regarding: the level of informed choice, anxiety and doubts?**
   There were no differences in informed choice and anxiety, but participants opting for broad microarray have more doubts (Chapter 3).

3. **What is the psychological impact on parents of receiving uncertain outcomes from invasive prenatal diagnosis?**
   Initially parents were worried, but no sustained negative psychological impact was observed in this study. Note that this finding is under the condition of extensive post-test genetic counselling (Chapter 4).

Part 2:

1. **What do pregnant women or couples choose; NIPT or invasive PND?**
   We found that in non-academic hospitals all couples chose NIPT, whereas in the academic hospital 20% of patients opted for PND (Chapter 5). This suggests that: 1) there is a substantial group of pregnant women or couples with

interest in broad scope testing; 2) there are differences in counselling between the academic and non-academic hospitals.

2. **Are there differences between participants opting for NIPT or PND regarding: the level of informed choice, anxiety and doubts?**
   Consistent with the findings reported in Chapter 3, no differences were observed in informed choice and anxiety, but participants opting for PND had more doubts. It seems that both groups of patients were equally informed and felt more or less the same. Patients possibly receiving more detailed genetic information were however a little bit more ambivalent about their choice.

3. **Are there differences between women or couples who are counselled in the non-academic vs. academic hospitals regarding their choices for NIPT or PND?**
   Chapter 5 showed that the choice for either NIPT or PND was related to attending a non-academic vs. an academic hospital. In the non-academic centers, none of the women included in the study sample opted for invasive PND, whereas in the academic hospital almost 20% of all participants did. This could be due to differences in counselling, patient characteristics, or counsellor characteristic.

4. **Do counsellors differ in the content and approach of their counselling regarding the level of information-centeredness, patient-centeredness, and the level of non-directivity?**
   The content of the counselling was more or less equal, however the approach and specifically framing of information and the communication of risks did differ *between* counsellors (Chapter 6).

5. **To which extent does counsellors' preference for NIPT/PND affects patients' choice?**
   While counsellors' preference has limited influence, in Chapter 6 it was shown that framing of information affects patients' choice.

6. **Were patients aware of the counsellors' preference?**
   Yes, a small percentage of patients felt that the counsellor had a preference, see Chapter 6.

7. **Were there differences in patients' knowledge and attitude scores between counsellors?**
   Overall, patients had very high knowledge scores, however, at the level of individual items related to knowledge of NIPT or PND there were differences *between* counsellors. This shows that counsellors place different emphasis on information provision of either NIPT or PND.

The fear for information

The increasing scope of possible findings in genetic testing has led to a debate regarding the attainability of making informed choices among health professionals and ethicists.

As the number of possible outcomes increases, it may become difficult for patients to understand the characteristics of the test and its implications.[1, 2, 3, 4, 5] This increasing scope with added complexity of information may jeopardize counselling and might subsequently influence the informed decision making process.[3, 5–8] In the field of prenatal genetics, professionals fear that pregnant couples will suffer psychological burden because of informational overload due to new technological developments. According to de Jong et al. (2013)[9] and Dondorp et al. (2015),[10] the use of new, increasingly advanced techniques which provide much more genetic information about the fetus, may further hinder informed choices. Making an informed choice is a prerequisite for reproductive autonomy. Marteau et al. (2001) state that 'An informed decision is one where all the available information about the health alternatives is weighed up and used to inform the final decision; the resulting choice should be consistent with the individual's values.[10] An effective decision is one that is informed, consistent with the decision-maker's values and behaviourally implemented' (p. 100).[11] Well-informed choices have been reported as psychologically beneficial.[6, 12] Psychological management of prenatal test decisions is better when knowledge is adequate, while uninformed choices increase decisional conflict and decrease feelings of personal wellbeing.[13] These findings were not supported by the results of Chapter 3, where women that made uninformed choices had the same

level of anxiety and doubts as women that made informed choices. Interestingly, women who made an informed choice opted for broad scope testing more often.

Women who were at elevated risk of a fetus with a common trisomy such as Down's syndrome or Patau or Edwards syndrome could opt for either prenatal screening (PNS) or prenatal diagnosis (PND). In Chapter 2, we studied both hypothetical and actual choices regarding the scope of the prenatal test. We did so by including women who, only opted for PNS. These women were viewed as the hypothetical group; we asked them to think about their desired scope of PND if they would engage in PND in the nearby future. The other group, women opting for PND, made an actual choice regarding the scope of their prenatal microarray that was performed by our laboratory in real-time.

Women and their partners had a strong preference for broad information

New techniques in prenatal testing are developing rapidly. As a result, a much broader scope of information has become available for pregnant women with an increased risk after first trimester screening. The question was, however, if women and their partners would be interested in such broad scope information that might also reveal pathogenic findings not related to the indication, genetic variants with incomplete penetrance and variable phenotype associated with a susceptibility for neurodevelopmental disorders; susceptibility loci (SL). In this thesis, pregnant couples could opt-in for disclosure of SL in a research setting. Were pregnant couples inclined to obtain all genetic information that is available, or are they interested in less detailed information? When given the choice in the context of this thesis, almost all women choose for the widest scope of genetic information. Almost all women opting for invasive PND chose to be informed of all findings, including uncertain findings. This finding is not supportive of the reluctance expressed by professionals and ethicists who fear that the disclosure of such findings might be too burdensome for the pregnant women and their partners. Interestingly, when offered as a hypothetical option, pregnant women were less inclined to all genetic information about their child. The main motive for women choosing PND was to prepare for the future as much as possible. In the PNS group, women were less inclined to obtain all information about their fetus. This finding might be explained by the fact that women in this group do not, or do not yet, have such a strong need for information and certainty; hence their choice for prenatal screening which is only an estimation of risks and the fact that

it does not provide a diagnosis. Many of the research in the field of prenatal testing is performed with hypothetical questions for participants. Chapter 2 showed that hypothetical choices are not a good predictor of real, eventual choices that patients will make.

Informed choices in the light of prenatal testing options

Prenatal genetic screening and follow-up diagnostic testing confront pregnant women with often difficult decisions. One of the first decisions women make is whether or not to participate in prenatal screening. When deliberating whether or not to participate in prenatal screening programs, many women may find it difficult to understand the characteristics of the test, to weigh its benefits and risks and to grasp the possible implications.[14] In the Netherlands, only 27% of women engaged in prenatal screening in 2014. This is a lot lower than in, for example, France or Denmark, where the uptake of first trimester combined testing is >90%. After the introduction of NIPT in the Netherlands, the uptake of prenatal screening has increased to around 45% (TRIDENT-2, 2017).

The value of microarray in fetuses who were prenatally diagnosed with ultrasound anomalies has been widely accepted,[15,16] but its implementation for other indications has raised concerns among health care professionals, causing much debate regarding the disclosure of susceptibility loci.[3,17,18] Some argue that these findings should be withheld from pregnant women in order not to burden them, while others state that withholding information is paternalistic and should be avoided.[3] In our study participants who were disclosed an SL reported no negative psychological impact with the prenatal diagnosis and disclosure of SL on participants. They showed no enduring worries and unanimously indicated that pregnant couples should have an individualized pre-test choice about susceptibility loci (non)disclosure. It should be noticed that a key factor in mitigating parental anxiety with SL disclosure appears to be post-test genetic counselling. Yet, the resilience of patients should not be underestimated. Throughout this thesis, women and their partners consistently showed a strong preference for the broadest scope of information, even including uncertain outcomes which will not surely lead to an aberrant child now, or in the future.

The problem with measuring attitude in the context of informed choice

Traditionally, both knowledge, attitude and test choice are used when determining an informed choice. Our results showed that measuring attitude towards testing with NIPT or PND was not suitable for this kind of testing offer.

The multidimensional measure of informed choice (MMIC, as formulated by Michie et al. 2002) is a commonly used instrument in the prenatal testing environment. Michie et al. argue that the attitude towards testing and the act of engaging in a prenatal test should be congruent. This is self-evident in the case of not testing versus testing (0 versus 1), for instance whether or not to engage in prenatal screening. However, in the case of one specific test versus another specific test (NIPT versus PND), the attitude is not just about 'getting information about the health of the fetus; yes/no', but also about 'the scope of the information' and 'the risk of a miscarriage'. In that case, attitude is no longer a unidimensional trait, but a complex mix of attitudes about different topics. There is no logical argument whether a choice for NIPT or PND based on these measured attitudes are a consistent choice or an inconsistent choice. For instance, if a woman is inclined towards more information about the health of the fetus, but prefers a test that is completely safe, she could have a positive attitude towards obtaining a broad scope of information but still choose NIPT. Based on this thesis and earlier studies, we also suggest adding a deliberation scale to new measures of informed decision-making. According to van den Berg et al. (2005), deliberation is an evaluation of the alternatives, a process of deliberation about the alternatives and weighing up their pros and cons against each other. Bakkeren et al. are currently developing a new measure based on the Measure of Informed Choice from Chapter 3 of this thesis, that adds a deliberation scale for the choice between NIPT and invasive PND.

Safety for the fetus overrides 'the need to know'

Interestingly, after the introduction of non-invasive prenatal testing, women's choices have changed substantially. Before its' introduction, women unanimously opted for broad scope information. Many women stated; 'why would I opt to know less, when I can opt to know more?'. However, the number of invasive procedures has strongly decreased since the introduction of NIPT in April 2014. As much as 80% of all women in the Erasmus MC opted for NIPT instead of PND with a broad genomic microarray. It turned out that safety for the fetus overrides

the need to know. Women thus place a much higher priority on not being at risk of a miscarriage, even if it means that they will potentially miss important genetic information about their fetus. It was the fear of a miscarriage associated with invasive procedures that made most women prefer NIPT over invasive PND. Most pregnant women and their partners choosing NIPT did not refer to the limited scope of testing (trisomies 21, 13 and 18 only) as a motive for choosing NIPT. Rather, for most respondents, safety concerns were the single most decisive factor. However, 87% of the participants choosing NIPT would have wanted more information about other chromosomal aberrations and indicated they preferred a wider scope than is currently offered with NIPT. Our findings suggest that most women are not making value-inconsistent choices but rather experience value ambivalence; tension between wanting to obtain as much information as possible and on the other hand to warrant the fetus' safety. Our finding that women's informational need is high, is consistent with our earlier studies and other research.[14, 19, 20] The broader informational need of women should be taken into account with future techniques such as Whole Exome Sequencing (WES), which will potentially reveal even more genetic information about the unborn child. Due to the invasive nature of WES, not many pregnant women will opt for this due to wanting to be at risk of a miscarriage. Should they engage in WES, they are interested in obtaining as much information as possible.

Women and partners wanted maximal autonomy regarding their choice

Prenatal genetic counselling has become increasingly demanding due to the more complex information resulting from technological progress. Consequently, for pregnant women and their partners, the decision-making process may be under more pressure than ever before. Health professionals have different views on what to offer pregnant women. Should the offer of prenatal testing be restricted or are women or couples able to make individualized choices? Throughout this thesis, women and their partners have voiced that it is very important to them to make their own, individual choices, and to exert maximal autonomy over this choice; whether it be NIPT, invasive PND or no further testing.

The influence of the counsellor on patient choices

Because of the recent developments in the field of prenatal genetic testing, more testing options have become available for pregnant women. Counsellors

are challenged to comprehensively discuss the complex information in a non-directive, i.e. autonomy promoting, and patient-centered manner that allows patients to make an informed decision. These aspects are clearly desired, but they also require a much broader set of counselling skills. The counsellor is not only there to inform, but also to elicit information from patients and to use this information to guide the counselling session.[21, 22] We explored the level of information-centeredness, patient-centeredness and level of non-directivity between principal prenatal counsellors of the Erasmus Medical Centre and found significant differences *between* counsellors (Chapter 5). Patients' choice ratio for either NIPT or PND differed significantly per counsellor, indicating that the approach and content of the counselling affects the eventual choices that patients make. It should be noted that knowledge was very high in all groups of patients, indicating the counselling was of good quality. The different choice ratios of NIPT/PND could thus not be explained by different levels of patients' knowledge, differences in attitude towards prenatal testing, or demographic factors such as previous pregnancies. This thesis showed that counsellors are not non-directive, nor are neutral and seem to influence the choices their patients make. And that this especially applies with regards to a 'framing effect' of the information about prenatal testing such as risk communication. It is important that counsellors are aware of their potential impact on patients' decision-making processes.

The future: prenatal whole exome sequencing

The obvious next step in prenatal testing seems Whole Exome Sequencing (WES). With WES, it is possible to detect many more genetic changes, while the significance of much of this information is yet unknown. Not all genetic changes affect the health of the unborn child, and some changes will only result in late-onset diseases. Throughout this thesis, pregnant women and their partners had a strong wish to decide about the diagnostic scope of their genetic test. And, when given a choice, most pregnant couples opted for a maximum of information. However, WES at this moment can only be offered in an invasive setting. The fact that an invasive procedure is necessary to perform a WES might lower the choice for WES substantially as we learned that women opt for the test with the lowest change on a spontaneous abortion.

If pregnant couples still are interested in the offer of prenatal WES it needs a different protocol. Almost all women opted to be informed of uncertain outcomes

too (Chapter 2). In this light, it is expected that in the future pregnant couples would also tolerate and even prefer to be informed of uncertain outcomes from WES. However, due to the almost infinite range of outcomes from WES, it will not be possible to prepare pregnant couples for specific unfavorable outcomes. Thus, the question shifts to a more generic one; 'do prospective parents want to know if there is an increased chance that their child may have a genetic condition?'(Riedijk, Galjaard & Tibben, in preparation, 2018). With WES, counselling needs to be more focused on the individual's tolerance for uncertainty and one's view on what constitutes a satisfactory quality of life for a child with a condition. For counselling, there needs to be a shift from supplying information to a discourse about the pregnant couples' personal values and attitudes.

Informed choice as process and as result

Throughout the studies in this thesis, women were capable of acquiring sufficient levels of knowledge. The information provided during counselling thus was comprehensible for participants. We did identify a problem with measuring attitude in the context of informed choices. The multidimensional measure of informed choice (MMIC, as formulated by Michie et al. 2002) is a commonly used instrument in the prenatal testing environment. Michie et al. argue that the attitude towards testing and the act of engaging in a prenatal test should be congruent. That is self-evident in the case of *not testing* versus *testing* (0 versus 1), for instance whether or not to engage in prenatal screening. However, in the case of one *specific test* versus *another specific test* (NIPT versus PND), the attitude is not just about 'getting information about the health of the fetus; yes/no', but also about 'the scope of the information' and 'the risk of a miscarriage'. In that case, attitude is no longer a unidimensional trait, but a complex mix of attitudes about different topics. There is no logical argument whether a choice for NIPT or PND based on these measured attitudes are a consistent choice or an inconsistent choice. For instance, if a woman is inclined towards more information about the health of the fetus, but prefers a test that is completely safe, she could have a positive attitude towards obtaining a broad scope of information but still choose NIPT.

The attitude items are measured unidimensional, however, our qualitative data show that attitude is rather multidimensional. It is impossible to determine a score that synthesizes all the attitudes of women regarding prenatal testing in a 'positive-negative' spectrum qualification.

The safety of the test, i.e. not being at risk of a miscarriage, seems to be a single decisive factor for most pregnant women. In many cases, the safety for the fetus outweighs a broader informational need. Future multidimensional models should include such a criterion.

Recommendations for research

In the studies described in this thesis, the study population was a self-selected group of women who were willing to participate in scientific research on a voluntary, non-paid basis. It appeared that these women were mostly highly educated, of Dutch origin and non-religious. However, it may very well be that in a more diverse group of pregnant women, the preference for the scope of information and their counselling needs are different. Therefore, I propose that further research should focus on acquiring different populations of pregnant women and their partners.

It would also be interesting to develop a model that looks at new ways of how to determine the counselling needs of different groups of patients. Because of lower education, comprehension of the information provided during counselling could also be more limited, resulting in lower knowledge scores.

With regards to measuring informed decision-making, we think it is important to include a deliberation scale to the measure. This could help to get a better insight in the way choices are made, since measuring only knowledge and attitude is not sufficient when measuring between *types of a test,* instead of whether or not to engage in a test. Lastly, in Chapter 5 differences between counsellors were revealed, showing that the patient uptake of invasive PND was different between counsellors. Despite the counsellors preference being obvious to the patients, all of the women were supported by the counsellor and had acquired sufficient knowledge about NIPT or invasive PND. This thesis showed that counsellor preference is not harmful for patients, as long as proper counselling and information provision and sufficient patient knowledge is warranted. These findings were based on self-reported answers to semi-structured interviews of a small sample of counsellors, but doing a large-scale analysis of actual counselling conversations would be thoroughly interesting. We advocate for the development of skills training for counsellors and clinicians, in order to safeguard the principles of proper non-directivity and/or shared decision-making.

Implications for clinicians & healthcare policy

In 2017, approximately 55% of pregnant women did not opt for prenatal screening, whereas 45% of women did (TRIDENT-2, 2017). If they decide to engage in prenatal testing, women want to make their own choices regarding their prenatal test and its' scope, and most prefer a maximum of genetic information about their child. Even more so, most want to be informed of uncertain outcomes, despite the more conservative view of professionals to not disclose such information. This thesis shows that facilitating deliberation during counselling is very important. We advocate that attitude and deliberation should be elicited in training modules for counsellors. Another important theme to elicit during training modules is the paradigm of non-directivity. The understanding of this concept should shift from emphasizing what counsellors *should not* do, i.e. persuasive coercion and giving advice, possibly inducing passivity, to what they *should do*, i.e. promoting patient's autonomy and self-directedness by aiming for patients to feel understood, in control, and competent.

This thesis showed that disclosing broad scope genetic information to pregnant women was not psychologically harmful. In fact, most women had excellent understanding after pre-test counselling. Doubts about the choice were somewhat higher in the group of women that opted for a maximum of genetic information about their baby. However, it remains unclear if these women were not more doubtful beforehand, which led them to choose a broad scope test.

Under the current conditions of proper pre-test genetic counselling, this thesis showed throughout that disclosing broad scope information is something pregnant women *want*, choose, and can cope with. The existent safeguards of counselling function excellently. There is no need to worry that pregnant women cannot deal with broad scope information. Even more so, if genetic information would be expanded in the case of prenatal WES, it is expected that patients will be able to manage this.

Concluding, if proper counselling is warranted, the scope of prenatal genetic information can be further expanded. In any case, patients should be able to make their own choices for a prenatal test and its' scope.

References

1. Dondorp W., Sikkema-Raddatz B., de Die-Smulders C., de Wert G. Arrays in postnatal and prenatal diagnosis: An exploration of the ethics of consent. *Hum Mutat*. 2012;33(6):916–922.
2. de Jong A., Dondorp W.J., De Wert G.M. The scope of prenatal diagnostic testing for chromosomal aberrations: broad or narrow? Ethical considerations on the choice of tests. *Ned Tijdschr Geneeskd*. 2009;153:A1060.
3. McGillivray G., Rosenfeld J.A., McKinlay Gardner R.J., Gillam L.H. Genetic counselling and ethical issues with chromosome microarray analysis in prenatal testing. *Prenat Diagn*. 2012;32(4):389–395.
4. Oepkes D., Page-Christiaens G.C., Bax C.J., et al. Trial by Dutch laboratories for evaluation of non-invasive prenatal testing. Part I-clinical impact. *Prenat Diagn*. 2016;36(12):1083–1090.
5. Riedijk S.R., Diderich K.E.M., van der Steen S.L., et al. The Psychological Challenges of Replacing Conventional Karyotyping with Genomic SNP Array Analysis in Prenatal Testing. *Journal of Clinical Medicine*. 2014;3(3):713–723.
6. van den Berg M., Timmermans D.R., ten Kate L.P., van Vugt J.M., van der Wal G. Informed decision making in the context of prenatal screening. *Patient Educ Couns*. 2006;63(1–2):110–117.
7. Stark Z., Gillam L., Walker S.P., McGillivray G. Ethical controversies in prenatal microarray. *Curr Opin Obstet Gynecol*. 2013;25(2):133–137.
8. Bunnik E.M., de Jong A., Nijsingh N., de Wert G.M. The new genetics and informed consent: differentiating choice to preserve autonomy. *Bioethics*. 2013;27(6):348–355.
9. de Jong A., Dondorp W.J., Krumeich A., Boonekamp J., van Lith J.M., de Wert G.M. The scope of prenatal diagnosis for women at increased risk for aneuploidies: views and preferences of professionals and potential users. *J Community Genet*. 2013;4(1):125–135.
10. Dondorp W., de Wert G., Bombard Y., et al. Non-invasive prenatal testing for aneuploidy and beyond: challenges of responsible innovation in prenatal screening. Summary and recommendations. *Eur J Hum Genet*. 2015.
11. Marteau T.M., Dormandy E., Michie S. A measure of informed choice. *Health Expect*. 2001;4(2):99–108.

12. Kleinveld J.H., Ten Kate L.P., van den Berg M., van Vugt J.M., Timmermans D.R. Does informed decision making influence psychological outcomes after receiving a positive screening outcome? *Prenatal Diagnosis*. 2009;29(3):271–273.
13. Dahl K., Hvidman L., Jorgensen F.S., Kesmodel U.S. Knowledge of prenatal screening and psychological management of test decisions. *Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology*. 2011;38(2):152–157.
14. van Schendel R.V., Dondorp W.J., Timmermans D.R., et al. NIPT-based screening for Down syndrome and beyond: what do pregnant women think? *Prenat Diagn*. 2015.
15. Wapner R.J., Martin C.L., Levy B., et al. Chromosomal microarray versus karyotyping for prenatal diagnosis. *N Engl J Med*. 2012;367(23):2175–2184.
16. Fiorentino F., Caiazzo F., Napolitano S., et al. Introducing array comparative genomic hybridization into routine prenatal diagnosis practice: a prospective study on over 1000 consecutive clinical cases. *Prenat Diagn*. 2011;31(13):1270–1282.
17. de Jong A., Dondorp W.J., Macville M.V., de Die-Smulders C.E., van Lith J.M., de Wert G.M. Microarrays as a diagnostic tool in prenatal screening strategies: ethical reflection. *Hum Genet*. 2013.
18. Vetro A., Bouman K., Hastings R., et al. The introduction of arrays in prenatal diagnosis: a special challenge. *Hum Mutat*. 2012;33(6):923–929.
19. Farrell R.M., Nutter B., Agatisa P.K. Meeting patients' education and decision-making needs for first trimester prenatal aneuploidy screening. *Prenat Diagn*. 2011;31(13):1222–1228.
20. van der Steen S.L., Bunnik E.M., Polak M.G., et al. Choosing between Higher and Lower Resolution Microarrays: do Pregnant Women Have Sufficient Knowledge to Make Informed Choices Consistent with their Attitude? *J Genet Couns*. 2017.
21. Farrelly E., Cho M.K., Erby L., Roter D., Stenzel A., Ormond K. Genetic counselling for prenatal testing: where is the discussion about disability? *J Genet Couns*. 2012;21(6):814–824.
22. Kessler S. Psychological aspects of genetic counselling. X.I. Nondirectiveness revisited. *Am J Med Genet*. 1997;72(2):164–171.

Chapter 8

Summary

Prenatal genetic testing informs pregnant couples about health problems of their unborn child. The knowledge prenatal genetic testing generates may improve pregnancy care. In case of abnormal findings, it may also cause pregnant couples to decide about ending or continuing their pregnancy.

Over the last 10 years the possibilities for genetic testing in pregnancy have developed rapidly. Since the introduction of new techniques such as microarray analyses for invasive prenatal diagnosis (PND), the scope of possible findings from a prenatal test has increased at greatly. Since 2014, non-invasive prenatal testing (NIPT) has been introduced in the Netherlands. With NIPT, it is possible to test for common trisomies with a high probability, at no risk of a miscarriage. NIPT is offered as an alternative for invasive PND. Microarray and NIPT created a new landscape of choices for pregnant women. This thesis explored this new landscape from both the patient and the health care professionals' perspective.

The main objectives of this thesis are formulated in Chapter 1 as;

1. Assess the choice between broad or narrow scope microarray in invasive PND, and compare participants regarding the level of knowledge, anxiety and doubts,
2. investigate what the psychological impact of receiving uncertain prenatal outcomes is on prospective parents,
3. assess the choice between NIPT and invasive PND, and compare participants regarding the level of knowledge, anxiety and doubts and
4. investigate whether prenatal counsellors differed in the content and approach of their counselling, and if patients made different choices per counsellor.

In Chapter 2 we discuss the choice for a broad or narrow scope of microarray in invasive PND. Consensus regarding the scope of invasive prenatal diagnosis (PND) pregnant couples should be offered is lacking. Chapter 2 examined pregnant couples' preferences, doubts and satisfaction regarding the scope of invasive PND. A striking 95% of patients opted for broad scope array, including disclosure of uncertain results such as susceptibility loci. Ninety percent was satisfied with their choice and wished to decide about the scope themselves. Concluding, the majority of patients wanted to obtain as much information as possible, and highly appreciated the offer of an individualized choice. It therefore seems justified

to offer patients a choice; in both the scope of microarray and for the disclosure of uncertain outcomes such as susceptibility loci.

Chapter 3 investigates the choice between broad or narrow scope microarray, and assesses whether women that were offered this choice had sufficient knowledge and a consistent attitude. We found that both groups of women had equal knowledge. Knowledge was high among all participants in the study. However, attitude consistency was more complicated since not all women chose a test that was congruent with their attitude. While previous studies demonstrated that knowledge is an important component in informed decision-making, Chapter 3 underlines that a consistent attitude might be equally important for decision-making. Chapter 3 advocates more focus on attitude-consistency and deliberation during counselling as compared to only a strong focus on knowledge.

Chapter 4 takes a closer look at women and partners that actually received uncertain prenatal test outcomes, and aimed to assess the psychological impact of such findings. Since there were only few patients who had such a disclosed result, Chapter 4 provides a first insight of parents' experiences through semi-structured interviews with 13 participants. All participants reported feeling overwhelmed by the test outcome initially. After the initial shock, all participants seemed not to have enduring psychological burden. All but one participants would opt to be informed of these findings again in the future. Chapter 4 concludes that the resilience of patients should not be underestimated.

In Chapter 5 we discuss the choice between NIPT and invasive PND for women with an increased risk based on first trimester screening. NIPT is safer than PND, but has a limited scope for only trisomies 21, 13 and 18. We studied patients' choices for NIPT or PND, whether these choices were informed, and if were differences in level of knowledge, anxiety and doubts between patients opting for NIPT or PND. Our results show that in the academic hospital, 82% chose NIPT and 18% chose invasive PND. In the non-academic hospitals, all women chose NIPT. A big difference. The main motive for choosing NIPT was safety for the fetus. The main motive to choose PND was its reliability and faster disclosure of results, and to obtain more information. Women who chose PND were not more anxious, but had a higher level of doubts. Eighty-seven percent of women electing NIPT indicated they preferred a wider scope, were it not for the risk of miscarriage associated with PND. Concluding, Chapter 5 shows that for most women, safety for the fetus overrides 'the need to know'.

Chapter 6 describes non-directivity and the influence of the counsellors' preference on patient choices in prenatal genetic counselling. Counsellors are challenged to comprehensively discuss the complex information in a non-directive, i.e. autonomy promoting, and patient-centered manner that allows patients to make an informed decision. Semi-structured interviews with four senior obstetricians and one senior nurse were held regarding how they value provision of information, adopt a patient-centered attitude, and value non-directivity. Significant differences in NIPT/PND ratios of patient choices were observed *between* counsellors, with the largest difference being 35% versus 4% opting for invasive PND. Between 9% and 22% of the patients had an impression of their counsellor's preference and chose in accordance with this preference. Patients' overall knowledge and attitude scores did not differ across counsellors. Thus, all patients were equally well-informed. In conclusion, the differences in NIPT/PND ratios between counsellors indicate that counsellor differences affect the choices their patients make.

Lastly, Chapter 7 provides an overview of our main findings, an interpretation of these findings and the implications for both clinicians and healthcare policy. We also added recommendations for future research. The studies in this thesis have added insight into the patients' perspective in the ever changing prenatal testing environment. We addressed the psychological consequences of new techniques in prenatal testing for pregnant women and their partners. The main message of this thesis is that patients want to make their own, individualized choices regarding their prenatal test, and that most patients are capable of making such choices. Concluding, if proper counselling is warranted, the scope of prenatal genetic information can be further expanded without psychological damage for patients.

Samenvatting

Prenataal genetisch testen biedt zwangere stellen de mogelijkheid om informatie te verkrijgen over eventuele gezondheidsproblemen bij hun toekomstige kind. De kennis die prenatale testen kunnen opleveren, kan de zorg tijdens of na de zwangerschap bevorderen. Als er sprake is van afwijkingen, leidt de uitslag van een prenatale test voor sommige zwangere stellen tot de keuze om een zwangerschap al dan niet te beëindigen.

De afgelopen 10 jaar hebben de mogelijkheden voor prenatale testen zich in een razend tempo ontwikkeld. Sinds de introductie van nieuwe technieken, zoals microarray analyse voor invasieve prenatale diagnostiek (PND), is de reikwijdte van mogelijke bevindingen enorm toegenomen. Daarnaast werd in 2014 Niet-invasief Prenataal Testen (NIPT) geïntroduceerd in Nederland; een alternatief voor invasieve PND, waarbij het mogelijk is om met een hoge voorspellende waarde op de drie meest voorkomende aandoeningen (Down, Edwards en Patau syndroom) te testen zonder het risico op een miskraam. Microarray analyse en NIPT hebben een nieuw landschap van keuzes gecreëerd voor zwangere stellen. Dit proefschrift exploreert dit nieuwe landschap vanuit het perspectief van zowel de patiënt als de zorgverlener/counsellor.

De onderzoeksvragen van dit proefschrift zijn geformuleerd in Hoofdstuk 1 als zijnde;

1. Het onderzoeken van de keuze tussen een brede en een smalle reikwijdte van microarray bij invasieve PND, en het vergelijken van patiënten op de mate van kennis, angst en twijfel,
2. beoordelen wat de psychologische impact van onzekere prenatale resultaten is voor aanstaande ouders,
3. de keuze tussen NIPT en invasieve PND onderzoeken, en patiënten vergelijken op de uitkomstmaten van kennis, angst en twijfel en
4. exploreren of prenatale *counsellors* verschillen wat betreft de inhoud en aanpak van hun counselling, en of patiënten andere keuzes maakten per *counsellor*.

In Hoofdstuk 2 wordt de keuze tussen een brede en smalle reikwijdte van microarray analyse bij invasieve PND, en daarmee de beschikbare hoeveelheid informatie over het ongeboren kind, nader belicht. Tot op heden is er nog geen consensus bereikt over de reikwijdte van een test die zwangere stellen aangeboden

zouden moeten krijgen. Hoofdstuk 2 belicht de keuzes die stellen maakten, alsmede de twijfels over en tevredenheid met hun keuze. Het is opvallend dat maar liefst 95% van de patiënten kiest voor een brede reikwijdte van microarray, met alle informatie ínclusief onzekere uitkomsten, de zogenaamde *susceptibility loci*. Negentig procent was tevreden met hun keuze en wilde zelf beslissen over de reikwijdte van hun prenatale test. Concluderend wilde de meerderheid van de patiënten zoveel mogelijk informatie ontvangen over hun ongeboren kind. Bovendien vonden ze het aanbod om een gepersonaliseerde keuze te kunnen maken zeer prettig. Dit rechtvaardigt het aanbieden van een gepersonaliseerde keuze; zowel wat betreft de reikwijdte van de test als voor het prenataal vermelden van onzekere uitkomsten zoals *susceptibility loci*.

Hoofdstuk 3 bestudeert de keuze tussen een brede en smalle reikwijdte van microarray, en bekijkt of patiënten adequate kennis en een consistente attitude hadden. De uitkomst is dat beide groepen, dus zowel de groep die voor een brede als voor een smalle reikwijdte koos, evenveel adequate kennis hadden. Er was dus geen verschil in mate van geïnformeerdheid. Alle deelnemers (in beide groepen) hadden een zeer hoog kennisniveau. Qua attitude consistentie lag het gecompliceerder, omdat niet alle vrouwen een keuze maakte die overeenkwam met hun attitude ten opzichte van een prenatale test. Hoewel eerdere studies al aantoonden dat kennis een belangrijke component is van geïnformeerde besluitvorming, benadrukt Hoofdstuk 3 dat een consistente attitude minstens even belangrijk is voor het maken van een goed geïnformeerde keuze. Het onderstreept het belang van meer aandacht voor het belichten van de houding en attitude van de zwangere zelf tijdens de counselling, in plaats van enkel te focussen op het overbrengen van adequate kennis.

Hoofdstuk 4 zoomt in op zwangere stellen die daadwerkelijk een onzekere prenatale uitslag hebben gekregen, en brengt de psychologische impact van zulke bevindingen in kaart. Omdat er slechts een kleine groep patiënten was die een dergelijke uitslag hebben ontvangen, poogt Hoofdstuk 4 een eerste inzicht te geven in de ervaringen van 13 (aanstaande) ouders door middel van semigestructureerde interviews. Alle deelnemers gaven aan in eerste instantie geschrokken te zijn van de uitslag. Na de eerste schok leken alle deelnemers geen langdurige psychologische schade opgelopen te hebben. Alle deelnemers, op één na, wilde in de toekomst graag opnieuw geïnformeerd worden over een onzekere prenatale uitslag. Hoofdstuk 4 concludeert dat de veerkrachtigheid van patiënten niet onderschat moet worden.

Hoofdstuk 5 richt zich op de keuze tussen NIPT en invasieve PND in een groep vrouwen met een verhoogd risico op basis van eerste trimester prenatale screening. NIPT is veiliger dan PND, maar heeft een beperkte reikwijdte en test alleen op het syndroom van Down, Edwards en Patau. We bestudeerden de keuze tussen NIPT/PND, of het geïnformeerde keuzes betrof, en of er verschillen waren in de mate van kennis, angst en twijfel tussen NIPT/PND. Onze resultaten tonen aan dat er in het academisch ziekenhuis (Erasmus MC) andere keuzes worden gemaakt dan in niet-academische ziekenhuizen. In een academische ziekenhuis setting koos 82% voor NIPT en 18% voor invasieve PND. In de niet-academische ziekenhuis setting kozen alle patiënten voor de NIPT en dus 0% voor invasieve PND; een groot verschil. Het meest voorkomende motief voor NIPT was het ontbreken van een miskraamrisico c.q. de veiligheid voor het ongeboren kind. Vrouwen die voor invasieve PND kozen, gaven aan dit te doen vanwege de hogere betrouwbaarheid van de test, de snellere uitslagtermijn (2 vs. 3 weken), en de mogelijkheid om meer genetische informatie te verkrijgen. Vrouwen die voor invasieve PND kozen waren niet angstiger, maar hadden wel een hogere mate van twijfel over hun keuze. Van de vrouwen die NIPT kozen, gaf 78% aan geïnteresseerd te zijn in een bredere reikwijdte van de test, als er geen miskraamrisico aan verbonden zou zijn. Concluderend laat Hoofstuk 5 zien dat de meeste vrouwen bijzonder veel waarde hechten aan veiligheid voor het ongeboren kind, en deze veiligheid vele malen zwaarder weegt dan maximale informatie verkrijgen.

Hoofdstuk 6 beschrijft het principe van non-directiviteit en de invloed van de *counsellor* op de keuzes van patiënten in prenatale genetische counselling. Voor de counsellor is het een uitdaging om de complexe informatie op een begrijpelijke manier over te brengen. Dit moet op een non-directieve, autonomie bevorderende en patiëntgerichte manier, die zorgt dat patiënten een geïnformeerde, weloverwogen keuze kunnen maken. Er werden semigestructureerde interviews gehouden met vier ervaren counsellors en één ervaren verpleegkundige. Gevraagd werd hoe ze omgaan met het overbrengen van informatie, patiëntgerichtheid en met non-directiviteit. Er waren significante verschillen in de verhouding NIPT/PND ratio's *tussen* counsellors, met het grootste verschil van 35% vs. 4% van de patiënten die kiest voor invasieve PND. Van deze patiënten had 9% tot 22% het idee dat hun counsellor een voorkeur had, en maakte zij hun keuze voor NIPT of PND in overeenstemming met de voorkeur van de counsellor. De totale kennis en attitude scores verschilden *niet significant* tussen counsellors;

alle patiënten waren dus even goed geïnformeerd. Concluderend, de verschillen in NIPT/PND ratio's laten zien dat counsellors de keuze van de patiënt wel degelijk beïnvloeden.

Tot slot geeft Hoofdstuk 7 een overzicht van de bevindingen uit dit proefschrift, een interpretatie en de implicaties voor zowel clinici als gezondheidszorgbeleid. Tevens doen we aanbevelingen voor toekomstig onderzoek. De studies in dit proefschrift bieden inzicht in het patiënten perspectief, wat heel belangrijk is in het snel veranderende milieu van prenataal testen. We onderzochten de psychologische consequenties van nieuwe technieken van prenataal testen voor zwangere vrouwen en hun partners. De belangrijkste boodschap van dit proefschrift is dat patiënten hun eigen, geïndividualiseerde keuzes willen maken en dat de meeste patiënten goed in staat zijn om dit te doen. Concluderend, als goede counselling gewaarborgd is én blijft, kan de reikwijdte van prenatale genetische informatie verder worden uitgebreid zonder dat dit psychologisch schadelijk is voor patiënten.

Dankwoord

De afgelopen 5 jaar stonden in het teken van dit onderzoek en het verwezenlijken van mijn proefschrift. Ik ben zo dankbaar voor alles wat ik heb geleerd, de bijzondere mensen die ik heb ontmoet en de ervaringen die ik heb opgedaan met patienten. Onderweg kreeg ik steun en inspiratie van vele mensen die ik het liefst allemaal zou opnoemen, maar van wie ik er een paar in het bijzonder wil bedanken:

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Beste Aad, dank voor je promotorschap en je expertise als een van de eerste psychologen in het veld van de genetica. Voor je gelaagdheid, je geduld en je prachtige beschouwingen tijdens het sparren over de inhoud van mijn proefschrift. Ik koester de momenten dat ik met de trein naar het LUMC in Leiden ging om met jou te elaboreren. Daarna nam ik altijd de trein terug naar Rotterdam verrijkt met nieuwe inzichten.

Beste Jan, je verfrissende aanpak als promotor heeft mij scherp gehouden. Je was kritisch en doortastend en zorgde ervoor dat ik altijd op zoek ging naar de kern van het verhaal. Dankjewel voor de momenten waarop we mijn papers strak en duidelijk maakten, en voor je hulp bij het voortzetten van mijn promotietraject. Als er iets geregeld moest worden, dan was jij daar als eerste (met hulp van Hetty, waarvoor ook dank)!

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aangenaam. Iris, mijn medepromovenda, dank voor de toffe tijden en dat je mijn paranimf wilde zijn. Ik kijk al uit naar jouw promotie!

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Karin Diderich, Marieke Joosten, Lutgarde Govaerts, Diane van Opstal, Gosia Srebniak en alle andere co-auteurs; samen hebben we gezorgd voor gebundelde krachten en een sterk staaltje wetenschappelijke publicaties. Jullie inzichten hebben onze papers doordrenkt van mooie inzichten en formuleringen. Marike Polak, je statistische adviezen hebben mij en onze publicaties enorm geholpen. Diewertje, onze samenwerking was heel fijn; ik ben trots op jou, en op de publicatie die daaruit is voortgekomen!

Lieve familie — op elke verjaardag en gelegenheid werd er geïnformeerd naar de progressie van mijn onderzoek. Tijdens mijn promotie is onze familieslogan zeker van toepassing geweest; *when the going gets tough, the tough get going!*

Mama, papa en broertje, bedankt voor jullie liefde, steun en goede zorgen. Jullie staan altijd voor me klaar met raad en daad. Toen ik mijn eerste huis kocht in 2016, de drukste periode van mijn PhD bestaan, hebben jullie me enorm geholpen met de verbouwing en het klussen. Ik hoop dat ik later voor jullie mag zorgen, zoals er voor mij gezorgd is. Ik hou van jullie.

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Tot slot, mijn lieve Theo. Hoewel je pas als een van de laatsten insprong in mijn leven en mijn promotietraject, ben je in korte tijd ontzettend belangrijk voor mij geworden. Dankjewel voor je liefde & steun. Voor de mooie tijden die we samen al beleefd hebben. Voor het prachtige ontwerp van dit proefschrift; je hebt mijn levenswerk handen en voeten gegeven. Op naar de toekomst, samen met jou!

PhD Portfolio

Name Sanne Leanne van der Steen Erasmus MC Department: Clinical Genetics	**PhD period** November 2013 – December 2018 **Promotors** A. Tibben & J. van Busschbach **Supervisors** S.R. Riedijk & R.J.H. Galjaard

1. PhD training

	Year	Workload
Academic skills		
Systematic Literature Retrieval in PubMed and other databases, Endnote, Medical Library Erasmus MC	2013	1 ECTS
Biomedical English Writing and Communication	2014	4 ECTS
CPO course	2014	0.3 ECTS
BROK (Basic course Rules and Organization for Clinical researchers)	2015	1.5 ECTS
CPO course	2014	0.3 ECTS
Research Integrity	2015	2 ECTS
Presentations		
ESHG/EMPAG Milan, Italy	2014	2 ECTS
ISPD Brisbane, Australia	2014	2 ECTS
ESHG Barcelona, Spain	2015	2 ECTS
NIPT Consortium Amsterdam, The Netherlands	2015	2 ECTS
NAGCC Utrecht, The Netherlands	2017	2 ECTS
International conferences		
ESHG/EMPAG Milan, Italy	2014	2 ECTS
ESHG Barcelona, Spain	2015	2 ECTS
ESHG/EMPAG Copenhagen, Denmark	2017	2 ECTS

	Year	Workload
Seminars and workshops		
NACGG	2013	1 ECTS
VKGN	2014	1 ECTS
NACGG	2014	1 ECTS
ESHG/EMPAG	2014	1 ECTS
Workshop Grant writing 12C approach	2017	0.1 ECTS
Workshop elevation pitch	2017	0.1 ECTS
Other		
Journal Club, Department of Clinical Genetics, Erasmus MC	2013–2017	2 ECTS

2. Teaching activities

Lecturing		
Psychological aspects of genetic counselling, BA2 (VO)	2014–2017	6 ECTS
Lecture Horizon study, minor Genetics in Society	2015–2017	2 ECTS
Lecture PhD trajectory, minor Genetics in Society	2015–2017	2 ECTS
Decisions regarding prenatal genetic testing, BA3 (VO)	2015–2017	6 ECTS
Bereavement; dealing with loss (VO), BA3	2015–2017	6 ECTS
Samenwerken (SW), BA1	2015–2017	8 ECTS
Consultvoering (CV), BA1–2	2015–2017	8 ECTS
Communicatie & Attitude (CA), BA3	2015–2017	4 ECTS
Arts Patient Contact (APC), BA3	2015–2017	4 ECTS
Workshop Genetic Counselling, minor Genetics in Society	2017	2 ECTS
Supervising practicals		
Basic communication skills for medical students BA 1–3	2015–2017	8 ECTS
Supervising theses		
Several bachelor & master theses for Horizon Study/ Clinical Genetics	2015–2017	6 ECTS

List of publications

The psychological challenges of replacing conventional karyotyping with genomic SNP array analysis in prenatal testing.
✓ *Published in Journal of Clinical Medicine, July 2014;3(3):713-23. doi: 10.3390/jcm3030713.*

Pregnant couples at increased risk for common aneuploidies choose maximal information from invasive genetic testing
✓ *Published in Clinical Genetics, July 2015;88(1):25-31. doi: 10.1111/cge.12479.*

The psychological impact of prenatal diagnosis and disclosure of susceptibility loci: first impressions of parents' experiences
✓ *Published in Journal of Genetic Counselling, December 2016;25(6):1227–1234.*

Choosing between higher and lower resolution microarrays: do pregnant women have sufficient knowledge to make informed choices consistent with their attitude?
✓ *Published in the Journal of Genetic Counselling, February 2018;27(1):85-94. doi: 10.1007/s10897-017-0124-5.*

Offering a choice between NIPT and invasive PND in prenatal genetic counselling: the impact of clinician characteristics on patients' test uptake
✓ *Published by the European Journal of Human Genetics, October 2018; s41431-018-0287-z.*

Non-invasive or invasive prenatal testing: safety for the fetus overrides the need for broad scope genetic information
⌛ *Under review by Clinical Genetics*

Curriculum vitae

Sanne Leanne van der Steen was born in 1989 in The Hague, The Netherlands. After she graduated from the Montessori Lyceum in Rotterdam in 2006, she started to study Pedagogy & Child Development. During the first year, she found out she had a fascination for psychology in the broader sense. Therefore, she switched to studying Psychology at the Erasmus University Rotterdam in 2007. She specialised in Clinical Psychology, with a passion for Medical Psychology. She opted for a minor in Medical Psychology at the Erasmus Medical Center, where her interest in research and genetics started.

Her bachelor minor led to an internship during her master phase. During the internship, she became involved in the Horizon Study of the Erasmus MC as a research assistant, which ultimately led to her position as a PhD student. In 2013 she obtained her master's degree in Clinical Psychology, and straight after she started working as a PhD student in the department of Clinical Genetics, under the wings of prof. dr. Aad Tibben and prof. dr. Jan van Busschbach.

During the first PhD year in 2013, her main focus was on the inclusion of pregnant women for her research. She combined this with her work as a medical psychologist at the outpatient clinic of Clinical Genetics.

From 2013 onwards, she also got involved in teaching. In 2015 she became a university lecturer, training medical students and residents in genetic counselling and communication skills. She did this for both the Department of Medical Psychology & Psychotherapy and the Department of Clinical Genetics.

In 2018 she became a psychologist in specialized mental health care (S-GGZ/psychiatry) at Pameijer in Rotterdam. Her main focus is the psychological assessment and treatment of multi-problem patients, of which some have an underlying genetic abnormality leading to i.e. cognitive impairment and neurodevelopmental/psychiatric problems. She wants to start a training to become a health care psychologist (Gezondheidszorgpsycholoog) and would love to be able to combine this with scientific research in the future. She hopes to remain curious and is always open to new ideas.

The new era of prenatal genetic testing: *Considerations regarding the scope, psychological consequences & pregnant couples' preferences*

Prenatal genetic testing informs pregnant couples about the possible health problems of their unborn child. Over the last 10 years the possibilities for genetic testing during pregnancy have developed rapidly. Since the introduction of new techniques such as microarray analysis for invasive prenatal diagnosis (PND), the scope of possible findings from a prenatal test has increased greatly. In 2014, non-invasive prenatal testing (NIPT) has been introduced in the Netherlands. With NIPT, it is possible to test for common trisomies with a high probability, at no risk of a miscarriage i.e. safely. NIPT is offered as an alternative for invasive PND.

Both microarray and NIPT created a new landscape of choices for pregnant women and their partners. This thesis addresses their preferences, the psychological consequences such as anxiety and doubts and the level of informed choice. The studies in this thesis have added insight into the patients' perspective in the ever changing prenatal testing environment.

Sanne Leanne van der Steen (The Hague, 1989) obtained her master's degree in Clinical Psychology in 2013, with a passion for Medical Psychology. At the Erasmus Medical Center in Rotterdam, her interest in research and genetics started, which ultimately led to this thesis.

Next to being a psychologist, she became involved in teaching as a university lecturer, training medical students in genetic counselling and communication skills at both the Department of Medical Psychology & Psychotherapy and the Department of Clinical Genetics of the Erasmus Medical Center in Rotterdam.