

The **target** of testing

Dealing with **'unexpected'** findings
in prenatal diagnosis



Myra van Zwieten

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To Wangyal Lama and his family

*Prepare for the difficult while it is easy
Handle the great while it is small*

Lao Tzu



Source: Tao Te Ching – The Way of Virtue. Garden City Park: Square One Publishers, 2002.

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Thesis, University of Amsterdam, the Netherlands

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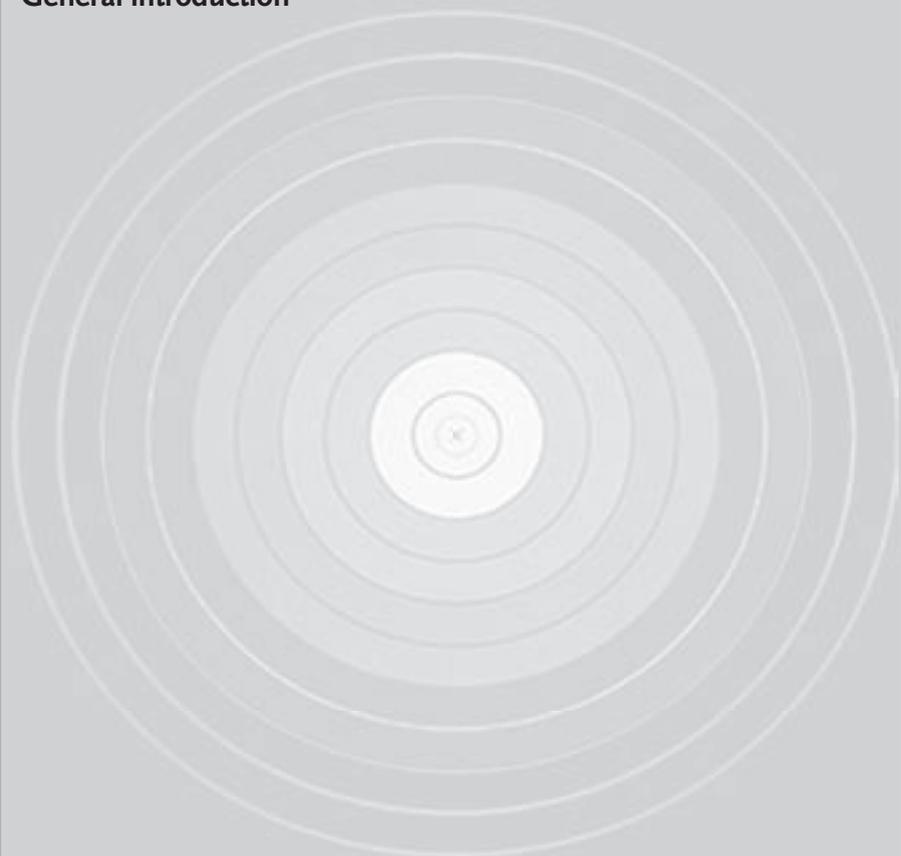
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Contents

Chapter 1	General Introduction	11
Chapter 2	How unexpected are unexpected findings in prenatal cytogenetic diagnosis? A literature review	19
Chapter 3	Constructing results in prenatal diagnosis. Reaching beyond technical matters	33
Chapter 4	Communication with patients during the prenatal testing procedure. An explorative qualitative study	51
Chapter 5	Problematic findings and the role of targeted testing in prenatal diagnosis	65
Chapter 6	Targeted testing or full karyotyping in prenatal diagnosis. A focus group study	81
Chapter 7	General discussion	91
	Summary	104
	Samenvatting	111
	Dankwoord	119
	Curriculum Vitae	125
	List of publications	126

Chapter 1

General introduction



General Introduction

Prenatal diagnosis may result in findings that were not specifically sought. Although providers are more or less familiar with this phenomenon, professional guidelines for dealing with 'unexpected findings' in prenatal diagnosis are lacking. Consequently, individual providers need to decide in each case of an unexpected finding what is the best way to handle this situation. The replacement of this *ad hoc* approach by a more structural strategy of dealing with unexpected findings could lead to an improvement in the quality of prenatal diagnosis practice.

This thesis searches for an answer to the question of what is the best way to deal with unexpected findings in prenatal diagnosis. As a starting point for this search we have examined both the providers' and clients' experiences with unexpected findings in current daily practice. Additionally, the consequences of new techniques for the prenatal diagnosis practice were considered, as these may diminish the occurrence of unexpected findings. Due to this second topic in particular, our study touches upon the basic assumptions of prenatal diagnosis as well. Therefore, apart from trying to find an answer to the question of how to deal with unexpected findings, this thesis also considers the more fundamental question of 'What is the target of testing in prenatal diagnosis?'

As a general introduction, this chapter will firstly provide the necessary background information about prenatal diagnosis, the clinical methods used in daily practice, and the category of unexpected findings. Next, the importance of the new technical developments for the question of how to deal with unexpected findings is explained. Then we describe how this study was carried out as an empirical ethical study. Finally, the aim and outline of this thesis are presented.

Prenatal diagnosis

Prenatal diagnosis is a way of testing during the pregnancy to search for possible abnormalities in the fetus. Trisomy 21 is the well known chromosomal abnormality occurring most frequently in the general population of older pregnant women. In case of trisomy 21 the genetic material of the fetus holds three chromosomes 21 instead of two, leading to Down's syndrome in the child.

Trisomy 21 can be detected through amniocentesis and chorionic villi sampling (CVS). In these procedures, fetal and placental chromosomal material respectively are acquired from the pregnant woman, and analysed in the laboratory. Women undergoing these procedures have a risk of about 1% that their pregnancy ends in a miscarriage induced by the invasive procedure.¹

Because of this miscarriage risk, amniocentesis and CVS are routinely offered only

to pregnant women with an increased risk of a congenital abnormality in their fetus. For many years, the increased age of the pregnant woman has been the main variable in establishing the increased risk for the occurrence of trisomy 21 in the fetus. Lately, several additional biochemical and ultrasonographic variables are being used to establish the increased risk for trisomy 21, as well as for neural tube defects.^{1,2} Nowadays, most Western countries have adopted prenatal screening programmes for Down's syndrome to select pregnant women of increased risk from the general population, to be able to particularly offer those women amniocentesis or CVS. However, in the Netherlands, prenatal screening can only be offered to individual women without them having personally requested this, to women over 35 years of age.³ For this reason, the main indication for prenatal diagnosis in the Netherlands is still the pregnant women's increased age. Although amniocentesis and CVS offered to women because of their age may be understood as a form of prenatal screening², we will regard this kind of testing as prenatal *diagnosis*. As opposed to prenatal screening, e.g. (a combination of) maternal serum screening or nuchal translucency measurement, which only provides an individualized risk estimation, prenatal diagnosis has the ability to detect a chromosome anomaly with certainty.

Due to a very accurate registration in our country, we know that about 70% of women undergoing prenatal diagnosis in the Netherlands have been offered this test because of their increased age.⁴ The remaining 30 % is offered amniocentesis or CVS because of a more specific indication, like a hereditary disorder in the family, or the (still)birth of a previous child with a chromosome abnormality.

The field of prenatal diagnosis discussed in this thesis particularly involves the invasive methods of prenatal diagnosis, i.e. amniocentesis and CVS, performed because of the pregnant woman's increased age. Dutch women undergoing prenatal diagnosis due to their increased age are rather similar to women in other countries having prenatal diagnosis because of their established high risk in screening programmes for Down's syndrome, as both referral indications are population-based rather than patient specific.

Amniocentesis and chorionic villi sampling (CVS)

Several health care professionals from different disciplines are involved in the procedures of amniocentesis and CVS.

Pre-test counseling is mostly performed by a midwife, family doctor or health practitioners of a prenatal diagnosis outpatient clinic.

A gynaecologist, assisted by a nurse, usually obtains the fetal material from the pregnant woman. In chorionic villi sampling, a sample from the placenta (chorionic villus) is taken transcervically or transabdominally under ultrasound guidance at 11-13 weeks of gestation. In amniocentesis, usually performed at 15-16 weeks of gestation, amniotic fluid is aspirated through a hollow needle inserted under ultrasound guidance through the abdominal wall.

All laboratory procedures to analyse the fetal chromosomes are performed by laboratory technicians, under the supervision of a clinical cytogeneticist. A clinical

geneticist helps interpreting the testing result from a clinical point of view.

When the testing result is available (within about a week and a half in case of CVS, and within two to three weeks in case of amniocentesis), it is initially communicated to the client by the gynaecologist or the clinical geneticist. Post-test counseling may also involve a social worker and a paediatrician with expertise about the congenital disorder at stake.

When a chromosome abnormality is detected after CVS or amniocentesis performed because of increased age, the decision for abortion is made in over 70% of these cases.⁴ At a gestation age until 12-14 weeks, abortion takes place by curettage. More advanced pregnancies until 24 weeks can be terminated by provoking an early delivery. Both kinds of abortions are performed by a gynaecologist.

‘Unexpected’ findings

The information generated in CVS and amniocentesis performed because of the pregnant woman’s increased age or her established high risk in a screening programme for Down’s syndrome, does not exclusively relate to trisomy 21. Instead, both procedures can lead to information about *any* chromosome abnormality, not only the one that was particularly sought. This is due to the kind of laboratory technique used in CVS and amniocentesis to analyse the chromosomes. In order to find out if the genetic material of the fetus holds three instead of two chromosomes 21, all 46 chromosomes of the fetus need to be analysed. Only when all chromosomes are graphically presented in a so called karyogram, can an anomaly like trisomy 21 be determined in a reliable way. Mainly due to this technical reason, 50% of the chromosome abnormalities detected through CVS and amniocentesis performed because of the woman’s increased age are anomalies other than trisomy 21.⁴ Referring to the fact that women undergoing prenatal diagnosis for some specific reason may not expect other chromosome anomalies to be found as well, the category of additional findings is usually indicated as ‘unexpected findings’.

In their own daily practice, providers of the Academic Medical Center in Amsterdam had observed that counseling of unexpected findings is more demanding.⁵ This observation led to their question of how these findings, once they were detected, should be communicated to clients of prenatal diagnosis. Another question was whether all clients should be informed in detail about *all* unexpected findings that could possibly be detected in prenatal diagnosis, or whether clients should only be informed in general terms about the phenomenon of unexpected findings.

These questions served as a starting point for this research project.⁶ In the orientation phase of this study it became clear that more understanding was needed of which testing results were exactly meant with the indication ‘unexpected findings’. Why did providers for instance often not include trisomy 13 and 18 in the category of unexpected findings category, while for clients, having prenatal diagnosis because of their increased risk for trisomy 21, these results are evidently unexpected? In other words, do providers who talk about unexpected findings really mean findings that are exceptional because they are unexpected or because of some other reason? To be able to answer the providers’ question of

how unexpected findings should be communicated, it was first of all necessary to find out to which findings they exactly referred in their question. Accordingly, it was not even certain if the term 'unexpected findings' was the most appropriate indication for this category of findings. Since this was yet not clear at the start of this research, and the final settling of this issue was made part of the research project, no consistent terminology could be applied throughout the project. Therefore, different terms for the category of unexpected findings are used in the following chapters, e.g. 'unclear findings', 'grey findings', 'preliminary findings', 'indefinite findings' and 'problematic finding'. This issue of terminology is the central topic in Chapter 2, and will be further elaborated on in Chapter 7, the general discussion.

Targeted testing

Some recent technical developments in prenatal diagnosis are highly relevant for answering the question of how providers should communicate about unexpected findings. As explained above, it is mainly due to technical reasons – detection of one chromosome abnormality requires analysis of *all* chromosomes – that unexpected findings occur in the first place. However, improvements in molecular diagnostic techniques may alter this situation. Prenatal tests applying for instance quantitative fluorescent polymerase chain reaction (QF-PCR)⁷ or multiplex-ligation-dependent probe amplification (MLPA)⁸ have the option to specifically focus the diagnostic process on the chromosome(s) suspected to be anomalous. The main advantages of this new way of targeted testing are speed and cost-effectiveness.⁹ Wide scale implementation is recommended for this reason, for instance by the UK National Screening Committee in 2004.¹⁰

However, there is another characteristic of targeted testing that makes it so relevant for this study. Naturally, in focusing on the chromosome abnormalities specifically being sought, targeted testing would exclude all anomalies that were *not* sought from detection.¹¹ In recent discussions, this characteristic is specifically presented as an advantage, because all kinds of counseling difficulties, related to the detection of unexpected findings, would not occur once targeted testing was implemented.¹² However, opponents of targeted testing do not merely consider the detection of unexpected findings a drawback, and it would be a great loss in their view when these additional testing results were not detected anymore. In fact, they fear for a deterioration of the quality of prenatal diagnosis when less chromosome abnormalities will be detected than in current practice.¹⁰ So far, advocates and opponents of targeted testing have not reached consensus about the desirability of a future scenario of targeted testing in prenatal diagnosis. Dutch prenatal diagnosis providers, represented in the Working Party Prenatal Diagnosis and Fetal Therapy (WPDT), are also still in discussion about whether targeted testing should be implemented in the Netherlands or not.¹³

Even so, the topic of targeted testing is highly relevant in relation to the question of how unexpected findings should be communicated. After all, unexpected finding findings might be prevented, fully or partly, in a future scenario of targeted testing. Therefore, although targeted testing is no part of the daily practice of prenatal diagnosis (yet), the topic

of targeted testing is given an important role in this thesis. With a view on the potential impact of targeted testing we therefore broadened the initial research question. Because the providers' original question of how to communicate unexpected findings might be (partly) outdated if targeted testing would indeed be introduced, we rephrased this question into how unexpected findings should be dealt with. The question of how unexpected findings should be *dealt with* also takes the possibility into account that unexpected findings need to be communicated completely differently – or not at all – in a future scenario of targeted testing.

This research

Because this research project was initiated by providers faced with unexpected findings in their daily practice, it was desirable that the project would lead to results that were specifically useful to them. An empirical approach, which carefully considered all available knowledge from this daily practice was therefore required. Aiming for thorough understanding and interpretation of the topic concerned, the research project was set up as a case study^{14,15}, consisting of qualitative research methods. The qualitative methods used in this project were observations, in-depth interviews and focus group discussions. Details about all these methods are described in the following chapters.

The perspectives of most providers involved in prenatal diagnosis were examined in this study, particularly in the focus group discussions. The providers included in the observations and in-depth interviews were laboratory technicians, cytogeneticists, clinical geneticist, gynaecologists and health practitioners from the prenatal diagnosis outpatient clinic.

With regards to the clients participating in this research, we invited both the pregnant woman for her participation, as well as the partner accompanying her. This approach led to client interviews with both the man and woman in the majority of cases.

Although the gathering and analysis of empirical data are definitely significant in this research, this project reaches beyond an empirical study of daily experiences only. Because the research question of how unexpected findings *should* be dealt with requires weighing the pros and cons of different ways of dealing with unexpected findings, an ethical reflection on these experiences was desired as well. An empirical-ethical approach was therefore chosen. Whilst this approach subscribes to starting from the question that was born in daily practice, it suggests to critically reflect on this question at the same time.^{16,17}

Aim and outline of the thesis

The question, raised in daily practice, of how providers should deal with unexpected findings, served as the starting point for this study. The importance of the topic of targeted testing led to the following **central research question**:

How to deal with unexpected findings, considering the potential role of targeted testing in this respect?

In order to be able to answer the central research question, the following three **subquestions** were formulated:

1. What exactly *are* unexpected findings?
2. How do providers deal with unexpected testing results before they communicate these to their clients?
3. What might be the impact of targeted testing on the problem of unexpected findings in prenatal diagnosis?

The first subquestion will be answered in Chapter 2, which presents a review of the literature about unexpected findings.

Chapters 3 and 4 will elaborate on the second subquestion. The same observation data were used in these two chapters, but these data were analysed from a different perspective. Chapter 3 focuses on the way providers 'construct' testing results, whereas Chapter 4 focuses on the providers' communication with their clients while this 'construction process' is still going on.

The third subquestion will be dealt with in Chapters 5 and 6. Chapter 5 can be understood as the empirical continuation of Chapter 2, as the central question in Chapter 5 is, 'What exactly are the problematic aspects of unexpected findings?' The answer to this question is relevant for establishing what might be the impact of targeted testing. Chapter 6 presents and analyses all relevant arguments used in the discussion about targeted testing.

Chapter 7, the general discussion, will provide reflections on the whole study and will aim to answer the central research question.

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Chapter 2

2

How unexpected are unexpected findings in prenatal cytogenetic diagnosis? A literature review

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Abstract

The objective of this review was to gain understanding about unexpected findings in prenatal cytogenetic diagnosis. This category of results might be excluded from prenatal testing when new molecular tests such as I-FISH and QF-PCR will be applied in a future scenario of targeted testing.

The literature was systematically searched for publications wherein the term unexpected or a synonym refers to testing results with specific problems. On the selected articles a qualitative analysis was performed, using the methods of cross-case analysis and within-case analysis.

Sixteen articles published between 1979 - 2003 were selected. Analysis led to the classification of four problems of unexpected findings:

1. Unexpected for professionals;
2. Unexpected for patients;
3. Uncertainty;
4. Other difficult counseling issues.

We conclude that currently, the problems of unexpected findings relate only slightly to their unexpected character. Instead, the main problems of unexpected findings relate to uncertainty and other aspects which create difficult counseling issues. As such, unexpected findings can be distinguished only gradually from standard results. Before targeted testing can be applied it is necessary to establish exact criteria in order to discern unexpected findings from standard testing results.

Introduction

Full karyotype analysis is the gold standard in current prenatal cytogenetic diagnosis¹. Within this practice, most professionals involved in the process of chromosome analysis of chorionic villi or amniotic fluid are aware of the fact that *any* kind of chromosome abnormality can be detected, not only the one for which the test is actually performed because of an existing high risk (i.e. trisomy 21 in the majority of cases). Still, some testing results in prenatal cytogenetic diagnosis are referred to as unexpected findings^{2,3}. Knowing the purpose of full karyotype analysis this seems rather peculiar; why call a specific testing result detected in a practice where *any* testing result might be expected, an unexpected finding? Although our research group has had a consistent interest in the topic of unexpected findings⁴⁻⁶, some confusion about the exact meaning of this specific term was also signalled within our own centre. When we recently started a new research project about how to communicate about unexpected findings – a project of which the results will be published later – we first tried to agree on the exact meaning of the term unexpected findings.

Although most professionals were familiar with the literature about this topic, this proved to be difficult. When asked about what an unexpected finding would be from their own practical perspective, most lab technicians and cytogeneticists replied: 'How do you mean, unexpected? The more peculiar the aberrations we find, the more excited we get, so why call an unusual marker chromosome or other rare structural aberrations an unexpected finding anyway?'

Clinical geneticists took a different stance because they tended to identify more with the patient's perspective. Still, they, too, have their doubts about the exact meaning of the term. Although they do differentiate between testing results because much more professional skills are needed to communicate for instance a mosaicism than to communicate a trisomy 21, they know on the other hand that for the patient any detected chromosome aberration is unexpected, even a 'standard' trisomy 21. So we acknowledged that – at least in our own centre – the meaning of the term unexpected findings is not so obvious.

Still, the word unexpected is regularly used in the prenatal diagnosis literature, even recently, for instance in publications about new possible applications of molecular tests like Interphase Fluorescent In Situ Hybridization (I-FISH) and Quantitative Fluorescent Polymerase Chain Reaction (QF-PCR). The initial reason to apply such molecular tests in prenatal diagnosis was to process testing results more rapidly⁷⁻⁹. QF-PCR has already been implemented within a routine service¹. Currently, such rapid testing of amniotic fluid or chorionic villi is always followed by the gold standard of full karyotype analysis, but the possibilities to apply these molecular tests as a stand alone technique are also being examined now¹⁰. Consequences perceived before as a disadvantage, i.e. that the molecular tests do not address the possible presence of unexpected chromosome abnormalities², are now sometimes presented as a possible benefit¹¹. One of the promises is that application

of such targeted testing would relieve parents of the burden of unexpected and incomprehensible results¹¹.

But which unexpected findings are exactly referred to in this context? Based on our own experiences with the concept of unexpected findings this is not clear. Therefore, we reviewed the literature to examine how the term unexpected findings has been used through the years. To be able to fully understand the possible benefits of targeted testing, presented as a solution for the problems of unexpected findings, we believe it is imperative to gain more insight into the topic of unexpected findings first.

Methods

Literature search

Literature was searched for articles in which problems of specific testing results of chromosome analysis were described under the heading 'unexpected findings'. First of all, four different PubMed searches were performed for the term unexpected(ly) and three of its synonyms. Searches were performed for Prenatal diagnosis (MeSH term) AND Unexpected(ly); Prenatal diagnosis AND Incidental(ly); Prenatal diagnosis AND Coincidental(ly); Prenatal diagnosis AND Unusual, limited for the English language only. These four searches respectively retrieved 119, 72, 25, and 392 publications, which were selected by reading titles and abstracts. Included were all publications which described problems of a specific category of testing results of chromosome analysis after amniocentesis or chorionic villi sampling under the heading 'unexpected findings' or a similar term. Excluded were publications which reported about results of other prenatal tests, e.g. ultrasound or DNA diagnostics; single case reports; follow up reports and/or specific indications.

Secondly we searched in our own archives of publications about sex chromosome abnormalities, which consisted of about 50 articles from the period 1978-2003, by using the same inclusion and exclusion criteria as in the PubMed search.

Thirdly, we searched in our own archives of reported series of amniocentesis (n=29; period 1966-1988) and chorionic villi sampling (n=27; period 1984-1995), by using the same inclusion and exclusion criteria.

Analysis

The selected articles were analysed both in a quantitative and qualitative way to examine how the term unexpected findings has been used in the literature. The concrete questions used in the analysis were:

- Which exact terms are used? How often? In which section of the article are the terms mentioned?
- Which problems are described under the heading 'unexpected findings' or its synonym?

Two types of qualitative analysis were used, i.e. a within-case analysis and a cross-case analysis¹². In the within-case method all publications were analysed one by one. The usage of the term 'unexpected findings' was examined in relation to the main message of the article and in relation to the different sections of the article, e.g. introduction, results and conclusion/discussion. Through the cross-case analysis the usage of the term 'unexpected findings' was compared between publications.

Results

Through the PubMed search for 'Prenatal Diagnosis AND Unexpected(ly)' we selected ten publications in which problems of specific testing results of chromosome analysis were described under the heading 'unexpected findings' or a synonym.^{2-5;13-18} No additional publications were selected from the other three PubMed searches. Another five articles were selected from our own archive of publications about sex chromosome anomalies.¹⁹⁻²³ One last article was found in our own archive of reported series of amniocentesis and chorionic villi sampling.⁶ Our analysis presented in this paper is based on these sixteen publications. **Table I** presents the most relevant details of the sixteen selected publications mentioning the word 'unexpected' or one of its synonyms.

In three of the sixteen publications the term unexpected(ly) was not mentioned, but a synonym was used instead, i.e. fortuitous(ly) or chance finding. Some of the articles which did mention the word unexpected also mentioned one or more synonyms, like incidental, coincidental or unanticipated. The sixteen articles we selected were published between 1979 and 2003, with a majority dated in the 1980s, and were published in specialised as well as in general medical journals. In ten of the sixteen publications the word unexpected or its synonym was mentioned in the title and/or the abstract, which indicates that the unexpected findings were an important topic of the publication. Other sections of the article in which the term unexpected or its synonym was mentioned were the introduction (n=5), results (n=5), discussion (n=6) and/or elsewhere in the article (n=5). Six of the sixteen articles mentioned the word unexpected or its synonym only once; in the other ten publications the term was used twice or more.

In five publications the word unexpected specifically referred to some kind of structural chromosome rearrangement.^{5;14-17} In six publications (some kind of) sex chromosome abnormality was specifically discussed.^{1;8-23} In the other five publications the term unexpected was used to label a mix of different kind of chromosome abnormalities, varying from trisomy 21¹³ and trisomy X⁶ to marker chromosomes⁴ and a collection of all kind of unexpected chromosome abnormalities in the two articles which give a more systematic overview of unexpected findings.^{2;3}

Our analysis of the literature led to the classification of four kinds of problems mentioned under the heading unexpected findings, which are described in the following section.

Table I. Publications (n=16) mentioning ‘unexpected’ or its synonym

Author and year of publication	Mentioned phrase	Testing result(s) referred to
Golblus et al, 1979 ¹³	Unexpected finding; Unexpected translocation; Coincidental finding	Translocations; Triploid; trisomy 18; trisomy 21 while tested for other indications
Crandall et al, 1980 ¹⁵	Unexpected translocation	Translocations
Verjaal et al, 1981 ⁶	Unexpected findings	De novo apparently balanced aberrations; Mosaicism; Trisomy X
Boué et al, 1982 ¹⁴	Unexpected chromosome rearrangement	Structural chromosome rearrangements
Gallannaugh, 1982 ¹⁹	(Detected) incidentally and unexpectedly	SCAs
Hook et al, 1984 ¹⁶	Unexpected/ Unsuspected/ Unanticipated structural chromosome rearrangement; (Detected) incidentally	Inherited structural chromosome rearrangements
Vejerslev & Friedrich, 1984 ¹⁷	Unexpected structural chromosome rearrangements	Structural chromosome rearrangements
Connor, 1986 ²⁰	Fortuitous diagnoses	Turner syndrome
Holmes-Siedle et al, 1987 ²¹	Unexpected and incidental (detection)	SCAs
Leschot et al, 1987 ⁴	Unexpected abnormalities	Equivocal laboratory findings in Chorionic Villi Sampling (CVS)
Leschot et al, 1989 ⁵	Unexpected balanced chromosome rearrangements	Balanced chromosome rearrangements
Schonberg, 1993 ²	Unexpected (laboratory) findings; Unexpected chromosome abnormality	De novo apparently balanced structural rearrangements; De novo marker chromosomes; Mosaicism; SCAs
Kelly, 1999 ³	Unexpected cytogenetic findings; Unexpected result; Unexpected aneuploidy	Trisomy 13 and 18; Structural abnormalities; Mosaicism; SCAs
Sagi et al, 2001 ¹⁸	Unexpected result	SCAs
Marteau et al, 2002 ²²	Discovered) fortuitously	Klinefelter syndrome
Hall et al, 2003 ²³	Chance finding	SCAs

Problems of unexpected findings

1. Unexpected for professionals

Several early publications report about testing results which were detected unexpectedly for professionals who were not yet acquainted with the new technique of analysing chromosomes derived from amniotic fluid or chorionic villi.

The earliest publication¹³ presents several testing results which did not match with the indication that had been the reason for testing. The abnormal results reported in this article were trisomy 18, triploidy and trisomy 21 when the indication was an increased risk for another aberration than the one detected.

Four other publications¹⁴⁻¹⁷ elaborate on the detection of a structural chromosome rearrangement which “occurs more frequently than expected from the results of studies of live born children”.¹⁴ To make professionals aware of the high frequency of structural anomalies found when testing is done for common indications like advanced maternal age, exact incidences were reported in these publications.

In 1982 it is discussed what should be done when a sex chromosome abnormality (SCA) is found, especially what to tell the parents in such a case. At that time it was not even obvious that professionals would inform their patients about this result. Once an SCA was detected, professionals faced the dilemma of choosing between not telling, which might be defensive in law, and discussing the finding of an SCA in full length with the parents. The latter option was problematic in the early times of prenatal diagnosis due to “the almost total lack of accurate and unselected information on the likely prognosis for affected individuals, resulting in confusion as to what parents are told and an understandable reluctance to transmit information which might prove to be erroneous”.¹⁹ In the last twenty years the knowledge about SCAs has enormously improved because several prospective studies have been conducted in which children with SCA from unselected populations were followed from birth.¹⁸

One publication reports the unexpected detection of some chromosome aberrations – of which the phenotypical consequences could not be predicted – which are not in accordance with the aim of prenatal diagnosis, a phenomenon that seems to have caught the authors by surprise: “As the aim of prenatal chromosome analysis is the diagnosis of severe congenital anomalies, we were struck by this high percentage of troublesome findings.”⁶ A similar problem is reported in an article which describes testing results like mosaicism and marker chromosomes found in the chorionic villi procedure but not in the subsequent amniocentesis.⁴ The aim of these publications at the time was to make professionals aware of that so far unknown phenomenon.

2. Unexpected for patients

Along with the awareness of professionals with regard to the phenomenon of detecting testing results which they had not foreseen, the awareness grew that these testing results would be unexpected for patients as well.

The problem that patients might not anticipate the detection of certain testing results is discussed most extensively in the literature about the SCAs. In 1982 it is already

signalled that it is “not common practice to discuss sex chromosome abnormalities, as a potential problem, before the test”.²¹ A more recent publication illustrates this is currently still the case: “While some parents are given information about the condition before testing, it seems that most are not”.²² To prepare parents for the unanticipated detection of an SCA it is already suggested in 1987 to mention this in the pre test counseling: “It might be better to incorporate such a topic into a pre-pregnancy counseling program, or into an educational programme linked with school leaving.”²¹

Not only for the SCAs it is suggested to make patients aware of through pre test counseling, but also with regard to other testing results which might be unforeseen for professionals as well as for patients: “In our team it is the practice to point out the possibilities of such unexpected findings when counseling the couple preceding amniocentesis.”⁶ For pre test counseling preceding a chorionic villi sampling the more specific advice is: “Counseling before chorionic villi sampling should include the possibility that subsequent amniocentesis may be needed should mosaicism or some other unexpected abnormality be detected.”⁴ More general advice is given in publication 3 “It seems prudent to point out during prenatal genetic counseling that while advanced maternal age with concerns for Down syndrome is usually known by the counselee, there exists an equal risk of some other aneuploidy which might carry a more or less severe prognosis than Down syndrome.”³

3. Uncertainty

In general terms, the problem of uncertainty of some testing results is already described rather boldly in 1979 as: “Prenatal diagnosis, in contrast to diagnostic cytogenetics, is “black box” cytogenetics, in that it is done without a known phenotype with which to correlate the results.”¹³

More specifically, this problematic aspect of the structural chromosome rearrangement was described by Boué et al by summing up the following three questions, raised when a structural anomaly is found in fetal cells: “Is this anomaly balanced or unbalanced? Is it inherited or de novo? If de novo and apparently balanced, is the fetus expected to be normal?”¹⁴ With regard to the last question it was already concluded in the 1980s that “each de novo reciprocal translocation is different from the others and no definite risk figures can be calculated”.¹⁴ This means that “it can never be decided with 100% certainty whether the child will be healthy or not”.¹⁷ In sum, for some testing results the situation is as follows: “For a de novo apparently balanced reciprocal translocation one can only cite an 8-10% risk of mental retardation which is not likely to be altered by further cytogenetic or ultrasonographic study.”³

The specific problems of uncertainty regarding mosaicism are summarized as follows: “The detection of mosaicism or suspected mosaicism in prenatal diagnostic specimens raises issues of two types. The first is related to the laboratory interpretation of the findings, that is, does the finding in culture represent the true status of the amniotic fluid or chorionic villi? The second is related to the clinical importance of the findings: How likely is it that the mosaicism detected in culture is representative of the true status of the fetus? and, What is the prognosis for the fetus after the finding of true mosaicism for the abnormality in question?”²

One conclusion in the literature is that this situation of uncertainty with regard to structural anomalies and mosaicism demands an “experienced and conscientious staff”.¹³ It is also concluded that when there is uncertainty about the exact meaning of the results, genetic counseling is complicated. The suggested strategy in this matter is: “To gather the best information available and to present it to the woman in a non-directive way. The aim is to allow her to make a fully informed decision which the counsellor then supports.”³ However, this is a difficult situation for both professionals and patient, as is illustrated in the following comment: “Once an unexpected result is obtained, prompt genetic counseling [has to be given] by an experienced counsellor who is prepared to provide the time and information necessary for couples to grapple with new information, considerable anxiety and a real measure of uncertainty.”³

4. Other difficult counseling issues

Beside the uncertainty of some testing results there are other reasons why some testing results lead to difficult counseling issues. These issues have been described specifically for the SCAs, but it is not easy to reveal the exact origin of these counseling difficulties. Apart from the fact that it is an unanticipated situation for the parents to learn about the diagnosis SCA, several other aspects are mentioned in the literature: “Sex chromosome abnormality is far less damaging to the phenotype”²¹. “For most SCAs, the prognosis is milder and less predictable than trisomy 21, and therefore parents are faced with a difficult decision regarding the option of pregnancy termination.”¹⁸ “In this unfamiliar and ambiguous situation they have to make a quick decision whether to continue or terminate the pregnancy.”¹⁸ So apart from the fact that an SCA is an unexpected result for parents, it is also pointed out that some typical aspects of the SCAs make it more difficult for the parents to decide about the continuation of the pregnancy.

As with the uncertain testing results (see category 3) some kind of (intensive) post test counseling is suggested to support parents in their difficult decision making once they have received the diagnosis SCA.²³ In addition to the literature about the uncertain testing results, the complex relationship between the professionals’ process of genetic counseling on one hand and the parents’ process of decision making on the other hand is specifically elaborated on: “Since most parents are unprepared for the diagnosis of an SCA and very few are familiar with these conditions, the information given by health professionals is likely to be of critical importance in guiding their decisions about the pregnancy”.²³

The more recent publications in our study have therefore examined some factors in post diagnostic counseling which might influence these decisions, like health professional’s specialty²² and the amount of positive or negative information about the SCA communicated by the health professional.²³ The overall conclusion is that the counseling following the diagnosis SCA should meet certain standards: “Lengthy and repeated genetic counseling may be required to ensure that the couple is prepared to make an informed decision about the pregnancy.”³ And: “Our results suggest an urgent need in training health professionals providing prenatal diagnostic services to ensure first, that they are well informed about the conditions that can be diagnosed as part of their services, and second, that they have the skills to present such information in ways that facilitate parents making an informed choice.”²³

Comment

The four kinds of problems discussed in the literature under the heading unexpected findings show a great variety and refer to different testing results. The problem of unexpectedness for professionals (category 1) has been mentioned specifically for the structural chromosome rearrangements and the SCAs. However, this problem does not exist anymore, since professionals are now fully acquainted with the technique of full karyotype analysis in prenatal cytogenetic testing. The problem of unexpectedness for patients (category 2) has been described specifically for the SCAs. The suggested solution for this problem is to mention the SCAs – and other unexpected findings – in the pre test counseling. The two other problems, i.e. uncertainty (category 3) and other difficult counseling issues (category 4) are problematic for both professionals and patients and less easy to solve. The problem of uncertainty has been discussed particularly for structural chromosome rearrangements and mosaicism. To handle this uncertainty it is suggested to gather the best information available and to present it in a non-directive way. Other difficult counseling issues have been described particularly for the sex chromosome anomalies. The suggested strategy in this matter is to counsel the patient in such a way that informed choice is facilitated.

Knowing the main problems of the unexpected findings, i.e. uncertainty and other difficult counseling issues, it is still hard to tell how unexpected findings could be distinguished from testing results which are apparently perceived as more standard. After all, how reasonable is it to assume that the problems of uncertainty and other difficult counseling issues play a role only in case of the unexpected findings? Is a standard aberration like trisomy 21 always indisputable? Down's syndrome can vary from a relatively mild to a more severe clinical picture, so even the prognosis of a trisomy 21 is ambiguous or unpredictable to some extent. And counseling in the more standard cases do not necessarily have to be easy. It would therefore be more realistic to conclude that the problems of uncertainty and difficult counseling issues are only *more* apparent in case of the unexpected findings. Instead of the existence of some sharply outlined category suggested by the common use of the term unexpected, we should perceive the difference between unexpected findings and standard results as a *gradual* distinction.

The common use of the term unexpected findings has not had a major influence on the practice of prenatal diagnosis so far. However, the application of targeted testing as described in the introduction would mean a radical change in this matter. Instead of intensifying professional procedures on an individual and ad hoc basis, as is the current strategy in case of an unexpected finding, targeted testing suggests a more structural solution to deal with this problem. In a future scenario of targeted testing the unexpected findings would simply be excluded from the practice of prenatal diagnosis, which would then only be targeted on a selective set of chromosomes, for instance the chromosomes 13, 18 and 21.

When assessing this idea of targeted testing, the following conclusions of our literature review should be taken into account.

Firstly, as said above, the literature about unexpected findings does not give a definite clue about the exact distinction between the unexpected findings and standard testing results. However, targeted testing can only be applied when a clear distinction can be made between the target, i.e. the results to be included into the practice of prenatal diagnosis, and the unexpected findings, i.e. the results to be excluded from prenatal diagnosis. Since clear criteria for this distinction can not be found in the literature, these criteria have to be established first.

Secondly, the two main problems of unexpected findings, i.e. uncertainty and other difficult counseling issues, are quite dissimilar. Therefore, an important question is: To which problems exactly would targeted testing be the solution? And how would this solution of targeted testing relate to other possible solutions, like the improvement of pre and post test counseling? The answer to these questions depends on the medical context in which prenatal diagnosis is performed, and different professionals may have a different focus in this matter. For instance, the obstetricians' attitude may have changed because of the increasing use of nuchal translucency measurement (NTM). The detection of Down's syndrome is a much more specific goal of NTM than it is for general cytogenetic diagnosis. So obstetricians may already be focused more exclusively on finding Down's syndrome than most cytogeneticists are in the current practice of prenatal diagnosis. So, as mentioned in the earlier publications, the category of unexpected findings remains related to the specific indication for which prenatal diagnosis is performed. Yet another complication is that application of targeted testing might lead to a new category of unexpected findings, associated with either new or familiar problems.

Thirdly, the literature about the problems of uncertainty and the difficult counseling issues does not always differentiate clearly between the professional's and the patient's perspective. Still, the consequences of these problems vary of course between professionals and patients. Therefore, both these perspectives need to be represented in the discussion about targeted testing in relation to unexpected findings. This is imperative because it still remains to be determined who may have to decide about the specific content of the target: the professionals, patients or other parties such as policy makers or financial institutes.

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Chapter 3

Constructing results in prenatal diagnosis: reaching beyond technical matters

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3

The Roothaan couple are sitting in the waiting room of the prenatal diagnosis outpatient clinic for their appointment with the clinical geneticist. Mrs. Roothaan (38) had a chorionic villi sampling a week ago. Yesterday, late in the afternoon she received a telephone call from the hospital that is still worrying her. Her clinical geneticist told her that the findings from the prenatal test showed that there was 'something wrong' with the chromosomes. When Mrs. Roothaan asked her about the exact nature of the problem, the physician said that things were a little too complicated to be explained over the telephone. The chromosome analysis did not reveal an extra chromosome 21, as is the case with Down's syndrome, but some of the cells did show another extra chromosome. The exact significance of this was still unclear for the time being, but the consequences would in any case be far less serious than with Down's syndrome, the doctor already reassured her. A clear result would require further diagnostic testing, so the physician suggested an appointment at the hospital. Mrs. Roothaan was to see her the next morning at nine, preferably along with her husband. There and then she would explain the findings in full so they could discuss the options to further clarify the findings to date.

What news awaits Mrs. and Mr. Roothaan in the consulting room of the clinical geneticist? When they decided to embark on this diagnosis trajectory they expected a clear result, either good or bad. But the way things have turned out, these findings seem to lie somewhere in between. The result is not really bad as there is no evidence of Down's syndrome. And that was after all their principal reason for chorionic villi sampling, in view of Mrs. Roothaan's age. On the other hand, the result can also not be 100% good, since they have to see the clinical geneticist...

Grey results

Mrs. and Mr. Roothaan in this case study^a are confronted with an unclear result; a finding that may indicate a problem but may also be insignificant. Actually, it is a preliminary or 'grey' result, i.e. a result of which it is still unclear whether it will turn out normal ('white') or aberrant ('black'). This type of result is a regular phenomenon in prenatal diagnosis. In addition to the fact that chromosome investigations may produce other 'black' results than the one that the test was done for (usually Down's syndrome), different kinds of grey results may be found (*see box 1*). Professionals do not apply a standard approach for dealing with grey results in the daily practice of prenatal diagnosis. From the few publications on the subject one might conclude that clarifying grey results is a mere technical matter.^b The literature does describe a number of technical procedures for the various types of grey results, but makes no mention of the fact that this approach may also differ per individual patient. Entirely in agreement with the model of nondirective counseling that is applied within prenatal diagnosis – as in other clinical genetics settings –, the recommended strategy for dealing with grey results is phrased as follows: 'To gather the best information available and to present it to the woman in a nondirective way. The aim is to allow her to

make a fully informed decision which the counselor then supports.⁷¹ This recommendation implies the assumption that the process of 'gathering the best information available' is a strict technical matter, and that the women (and their partners) concerned, only enter the equation when the process of 'gathering the best information available' has been completed, i.e. from the moment that the grey result is communicated. In other words: it would make no difference for the clarification process of a grey result as such whether these findings concern Mrs. & Mr. Roothaan or Mrs. & Mr. Jones or the Petersons.

But is this really the case? Is 'gathering the best information available' a purely technical matter? And does it make no difference for *whom* unclear prenatal diagnosis results have to be clarified? It is understandable that the literature on the subject presents a picture in which the result is not associated in any way with the individual for whom the findings are intended. Due to the value-related implications of prenatal diagnosis practice, which may involve terminating a pregnancy, professionals constantly and explicitly stress their non-involvement in the decision once the findings have been presented. They refrain from any form of influence over this decision, as it concerns the continuation of the pregnancy. The general picture of a result as purely technical information, with no relation whatsoever with the person for whom it is intended, perfectly matches the ideology of nondirectiveness.

However, this does not diminish the fact that prenatal diagnosis actually *is* a form of diagnosis. Gathering information can by definition never be a random process; it serves a certain purpose and takes place within a certain framework. In the same manner as with all diagnostic formats, the information gathered to obtain a result will have to be assessed. It will have to be decided whether the findings are or are not relevant in the light of the stated purpose within the diagnostic context. And the person for whom the result is intended is always intrinsically part of that context.

So how does the idea that a testing result consists of mere technical facts, and the fact that prenatal diagnosis is a form of diagnosis in which the individual patient matters relate to each other? Also, how is this linked up with the ideology of nondirectiveness? I will try to give some more insight in this matter by examining how professionals deal with grey testing results. Particularly I will examine whether clarifying a grey result indeed involves a strictly technical process or whether, during that process, the specific patient is kept in mind as well.

^a This case study has been composed from various case studies observed in this project.

^b In relevant literature, grey results are often categorized under the heading 'unexpected findings'. However, this term is somewhat confusing as the common feature of these types of results is not so much the unexpected element but rather the element of ambiguity.

Box 1: types of results of prenatal chromosome diagnosis

The majority (more than seventy percent) of prenatal chromosome diagnosis takes place due to the related elevated risk of trisomy 21 (Down's syndrome). Apart from trisomy 21, regularly other chromosome aberrations are recorded.

Some of these chromosome aberrations are generally considered as **more serious than trisomy 21** and result in very severe physical and mental disabilities. The most commonly known aberrations are trisomy 13 (in which three instead of two chromosomes 13 are present), trisomy 18 (three instead of two chromosomes 18) and triploidy (three chromosomes instead of two - for all chromosomes).

There is another group of chromosome aberrations that is generally considered as **less serious than trisomy 21**. Most common are the sex chromosomal aberrations, in which case there is something wrong with the X- or Y-chromosomes. Among these Turner's syndrome and Klinefelter's syndrome are quite familiar. With Turner's syndrome (45,X) we find one single X-chromosome instead of two sex chromosomes; with Klinefelter's syndrome (47,XXY) there is one X-chromosome too many. Most phenotypical problems in Turner's syndrome and Klinefelter's syndrome relate to infertility and/or secondary gender characteristics. In case of a 45,X or 47,XXY that appears in mosaicism, these phenotypical problems are less serious.

In addition to the various types of aberrant results ('black' results) we can make a general distinction between two types of grey results, i.e. mosaicism and structural aberrations

In **mosaicism** an individual shows two (or more) genetically different cell types. Forms of mosaicism have been observed of e.g. normal cells and cells with trisomy 21, or of normal cells and cells with an X-chromosome short, but mosaicism may appear in all kinds of variations.

Mosaicism is a relatively common phenomenon in chorionic villi sampling. As in chorionic villi sampling placenta material is examined and no fetal material, the observed mosaicism may be restricted to the placenta, but not manifest itself in the fetus. In that case one speaks of confined placental mosaicism. In chorionic villi sampling two different kinds of methods can be used to look at two types of cells of the placenta (see box 2 under heading 'cell culture' for more information on short and long-term cultures). When mosaicism is observed in the short-term culture of the chorionic villi sampling, additional testing can take place through a long-term culture. When mosaicism is not observed in the long-term culture, there is an increased chance that mosaicism is limited to the placenta, in which case it does not lead to phenotypical abnormalities.

In addition to mosaicism confined to the placenta, there may also be other explanations for mosaicism in laboratory material that cannot be found in the fetus. For instance because genetically deviating cells have developed in the cell culture (culture artifact) or because not only fetal cells but also cell material of the mother has been examined (maternal contamination). Culture artifacts and maternal contamination can both occur in chorionic villi sampling as well as in amniocentesis. In all these cases the detected mosaicism does not have phenotypical consequences.

In a **structural aberration** the problem concerns the form (structure) of the chromosomes. There are two kinds of structural aberrations. With an unbalanced structural aberration, the form of one or more of the chromosomes has been altered in such a way that the total amount of genetic material has also changed. In a balanced structural aberration, the total amount of (chromosomal) material has remained the same. Whereas an unbalanced aberration always leads to phenotypical aberrations, this is commonly not the case with a balanced aberration. To determine if the chromosome aberration would lead to phenotypical aberrations, the chromosomes of the parents are analyzed, as this may indicate whether the change of the chromosomes occurs within the family or is a new alteration. When one of the parents is carrier of the same chromosome anomaly, it is not to be expected that there will be phenotypical aberrations; for the parent with the same structural aberration is of normal health. But when it concerns a new aberration, it cannot be excluded that the structural aberration will have phenotypical consequences.

Constructing results

The notion that prenatal diagnosis results are straightforward technical issues has been challenged before. Rayna Rapp, a cultural anthropologist who has carried out an extensive observation study of the practice of prenatal diagnosis in the US, demonstrated that assessment of information is an intrinsic part of the process of producing results.² In the laboratories where the chromosomes are being examined – described by Rapp as ‘factories of fact construction’ – the technical information does not present itself unambiguously. According to Rapp, the work does not so much consist of observing and collecting facts but entails interpretation of ambiguous data. The daily responsibilities of laboratory staff include considering which data may be of importance to the testing result, and which is not:

Learning to muffle background noise in favour of the normalizing grid is a central skill of their work. At the same time, they must highlight each entity which differs from the norm, investigating its potential to move from background insignificance to foreground significance. (p. 205)

Rapp describes professionals active in the field of prenatal chromosomal diagnosis as ‘highly accomplished diagnostic disambiguators’. In other words, Rapp claims that a result obtained through prenatal diagnosis is not something that ‘presents itself’ but information that is constructed. And interpretation of technical information plays an important role in the construction process of the result concerned.

The next question is what drives professionals in their interpretation of technical information? More particularly, which weight is given to the individual patients in this process? As mentioned I will try to answer this question by specifically considering grey results. However, within this framework grey results are not so much viewed as *exceptions* to ‘standard’ (white or black) prenatal diagnosis findings, but as results in which the disambiguating process as described by Rapp has been *enlarged*. A grey result would then be a result in which disambiguating takes place much more emphatically than in ‘straightforward’ results, because in these cases the professionals explicitly question whether the technical information generated in the laboratory is eventually to be interpreted as normal (white) or abnormal (black).

Observational study

In order to examine how professionals operate in clarifying grey results, their daily activities at the Department of Clinical Genetics of the Academic Medical Center (AMC) of Amsterdam were observed. After becoming thoroughly acquainted with the health professionals involved and the way they work, the first step was to examine how a result of prenatal diagnosis is normally arrived at in the laboratory setting. Special points of attention in this respect were the various contacts and consultation moments between the different professionals with their respective tasks, i.e. the gynecologist, lab technician, cytogeneticist and clinical geneticist (*see box 2*).

The actual observations concerned the inter-disciplinary consultations between the professionals during the 'construction' of a result. This was based on the notion that the 'disambiguating process' described by Rapp, should be visible during the consultations between professionals and therefore open for study. Consequently, a procedure was agreed upon with the respective professionals to ensure that I could be present at the Department for observation at key moments.^c

The series of professional actions during which a result is constructed was viewed as a 'testing trajectory'. From the perspective of the parents who take part in prenatal diagnosis this testing trajectory already starts at an earlier stage and continues after that point. However, within the framework of this study of the clarification process of grey results, the intervention by the gynecologist and drawing up the final result are taken as the starting point and the end of the testing course, respectively. The observations were to answer the following question: 'What do professionals do to clarify grey results?', i.e. to make them black or white.

The observations, taking place in the period from July to September 2001 and in the period from April to May 2002, were reported in a so-called observation protocol.^d In order to enable analysis^e of the observation material, all documented and monitored result trajectories were considered as case studies, which were studied individually as well as in relation to each other. The analysis of the observation material aimed at providing an answer to the above-mentioned specific observation question, but the material was also analyzed in the light of this broader question: 'Does the way in which professionals deal with grey results correspond with the general idea of a testing result as a purely technical matter?'

^c As the large majority (some 95%) of the results in the daily practice of prenatal diagnosis concern normal outcomes, a signalling procedure was applied to enable me to be present at moments of significance. This way I could carry out my tasks as researcher without 'hanging round' at the Department. I had to be informed in case of any result that might be aberrant, i.e. both with 'grey' as well as 'black' results. All technicians were instructed to call me the moment they observed something in the laboratory that might produce an aberrant outcome. When a technician wanted to consult the cytogeneticist, all parties also agreed not to take any action before informing me. As soon as I received a telephone call from a technician, I went over to the Department and accompanied the technician to her meeting with the cytogeneticist. As of that moment I monitored the result in question and, if possible, attended all inter-professional consultations with respect to the outcome: between the technician and cytogeneticist; the cytogeneticist and clinical geneticist and/or between the clinical geneticist and gynecologist. I was also always present at the weekly inter-disciplinary meeting of the entire professional team involved in prenatal diagnosis in the AMC. Sometimes I attended the weekly technicians meeting.

^d During the observations and immediately afterward, I made notes of what I heard and saw during the professional consultations. If possible, I noted literal quotes. As soon as I returned to my own workstation, I worked up my notes into a comprehensive and detailed report of all my observations. In this way I developed an observation protocol; a description of all my experiences that was suitable for (external) third parties. The observation protocol contained factual and direct descriptions of the observed situation, e.g. in the form of quotes or indirect speech complemented by my own impressions and interpretations. In agreement with proper methodological standards, the different types of entries were clearly distinguished.

^e In order to analyze my observation data, I first structured all survey material per result trajectory. I put all fragments from the observation protocol relating to the same trajectory in chronological order. To this end, I made use of Kwalitan, a software program specially developed for analyzing qualitative research data. Consequently I reconstructed all observed result trajectories, partly based on additional file surveys. I had access to the relevant patient files with laboratory forms, the result letter and all other correspondence with medical specialists as well as the minutes of the weekly inter-disciplinary meeting. The next step was working out the reconstructed trajectories into a comprehensive report, always taking the primary survey data from the observation protocol into account. I submitted the descriptions of the observed result trajectories to a cytogeneticist and clinical geneticist of the AMC Department to check the reports for factual irregularities. I also wanted to know to what extent they recognized themselves in my account of the observed setting in their capacity as health professionals. This form of validation is known as *member check*; an important instrument in qualitative research to guarantee the validity of scientific research.

Box 2: constructing a result of prenatal chromosome diagnosis

Chorionic villi sampling is based on the fact that the cells derived from the placenta are genetically mostly identical with the fetal cells. Examination of the chromosomes of the placenta cells makes it possible to indirectly determine the chromosome pattern of the fetus. **Amniocentesis** makes use of the fact that the fetus as of a certain moment in the pregnancy secretes cells into the amniotic fluid. By examining these cells, the chromosome pattern of the fetus may be established.

In order to be able to carry out chromosome testing, **the cells to be examined must first be extracted from the body of the pregnant woman**. This is done by a gynecologist who, via the vagina or with a hollow needle through the abdomen retrieves some placenta tissue or amniotic fluid from the woman's body. There is a chance of around one percent that a miscarriage is initiated through this invasive procedure.

Consequently, a laboratory technician processes the testing material in a number of steps. With chorionic villi sampling the **fetal material** is first **dissected** from any other body material that is extracted during the procedure.

The next step is **increasing the number of available cells**. In the case of chorionic villi sampling the manner of increasing the number of cells (cell culture) depends on the analysis method applied. In the fast method - the short-term culture - the results are quickly available, but less reliable as the examined cells are not always genetically the same as the fetal cells. The results of the long-term culture are more reliable, but this method is more time-consuming. The most reliable results are reached through a combination of the fast and the slow methods, but this combination not only takes considerable time but also requires a lot of work. This is the reason why the AMC makes use of an alternative developed at the hospital.³ Part of the placenta material is directly used for the short-term culture and the remainder - if at all - is stored. Only when an aberration is found in the short-term culture, the remaining material will be cultured in a long-term culture. In the case of amniocentesis a cell culture takes about just as long as with the long-term culture of chorionic villi sampling (seven to ten days).

The technician performs the following actions to **make the chromosomes visible**. Once the cells have been manipulated to the division phase in which the chromosomes can be discerned optimally, the testing material is applied to a slide, which, after coloring, can be viewed under the microscope. Finally, the technician notes the microscope image in a **schematic representation of the chromosomes**. This is done in two different ways. First, the number of chromosomes of ten observed cells is recorded on a specially designed counting form. In order to optimize the chances that the schematic representation matches the fetal chromosome pattern, it is standard procedure for technicians to minimally count ten cells stemming from two different slides. In case one aberrant cell is found of the ten cells that are counted, the number of cells for examination is increased. In the second place, a schematic representation is made of all chromosomes of each of two cells. In such a diagram - a karyogram - the 22 chromosome pairs and the X- and Y-chromosome are arranged in a fixed order. To this end a photograph is made of the microscope image. All chromosomes are - literally - cut from this picture and pasted on a form by the technician in the prescribed order. Nowadays, a computer program is used to produce a karyogram.

The **chromosome diagrams** made by the technician are **summarized in a karyotype** by the cytogeneticist. The cytogeneticist checks the written material supplied by the technician and summarizes it in a karyotype, a standard notation of the chromosome pattern of one individual, in which 46,XY indicates a normal male and 46,XX a normal female karyotype.

After consultation between the cytogeneticist and clinical geneticist - who in the AMC are working on the same department, contrary to what is customary in most other centers - the found **karyotype is phrased as result**, for instance 'normal male karyotype'.

The result letter states the three last-mentioned steps. Under the heading 'examination findings' the exact number of analyzed cells is listed with accompanying chromosomes. Under 'karyotype' the karyotype is noted in the prescribed manner, e.g. 47,XY,+21. Under the heading 'conclusion' the karyotype is phrased in plain words, e.g. 'male fetus with Down's syndrome'. Under 'comments' there is room for various matters that are (or may be) of importance for a correct interpretation and/or communication of the result, for instance, whether and in what way the parents have already been informed of the result. Any technical details of the analysis can also be included. In the AMC both the cytogeneticist and the clinical geneticist sign the result letter.

3

Clarification of grey results in practice

A little more than half (22/39) of the testing trajectories monitored during the observational study produced an aberrant result in the manner as described in box 2. In these 'straightforward' trajectories, the inter-professional consultations were not related to the result itself, but concerned more practical matters as 'this result should be completed a.s.a.p.' or 'who will inform the couple of our findings?'

In a little less than half of the observed testing trajectories (17/39), a grey result was generated at some point in the route. The approach selected by the professionals to clarify these grey results – i.e. to make them white or black – corresponded with the literature on the subject. (see Chapter 2) The following summary describes the different kinds of follow-up procedures applied in the monitored testing trajectories in order to clarify the initial grey results.

The trajectories in which the grey result concerned mosaicism (14/17) mainly focused on the question whether the noted chromosome aberration would also occur in the fetus, or, in other words, whether the findings of the chromosome analysis were (sufficiently) representative for the fetal chromosome pattern (*see box 1*). Additional testing and analysis in these courses aimed at verifying whether the chromosome aberration could be found in other types of cells as well. If so, it would be more likely that the aberration also manifested itself in the fetus. In principle, mosaicism found in the short-term culture of chorionic villi sampling was followed by a long-term culture (*see box 2, under cell culture*). In case there was not sufficient material available, a new invasive test was generally suggested to the parents in the form of amniocentesis. Additional investigation of the chromosomes in other types of cells thus enabled clarification of a grey result into white or black.

In the observed testing trajectories, both possibilities were found: some grey preliminary findings became black results and others changed into white results. For instance, a grey result (mosaicism trisomy 21, i.e. a combination of a normal cell line and a cell line with trisomy 21) recorded in the short-term culture of the chorionic villi sampling e.g. turned black once a full trisomy 21 was found in the long-term culture. Another grey result (mosaicism of normal cells and cells with each three extra chromosomes 2, 6 and 7) became white once mosaicism was not confirmed in the amniocentesis test. The fact that an aberration was found in the (short-term culture of the) chorionic villi sampling that would not occur within the fetus itself was explained in this specific testing trajectory by regarding the original chromosome aberration as mosaicism confined to the placenta (*see box 1*).

In additional analysis, alternatives to chromosome testing were sometimes applied. In one trajectory this concerned an ultrasound scan; in this particular case the phenotype of the fetus was examined instead of the genotype. The grey result consisted of mosaicism in the amniotic fluid – a much rarer phenomenon than mosaicism in chorionic villi sampling. Moreover, as it concerned a type that is rarely found in humans (46,XY/46,XX: a combination of normal male and healthy female cells) the cytogeneticist as well as the clinical geneticist considered it unlikely that it would materialize in the fetus. The assumption therefore was that the chromosomes found in the laboratory were not representative for

the fetal chromosomes. In other words: the grey result should actually be white. However, this required an explanation as to why mosaicism had been observed in the laboratory. The first possible explanation was that the slides of two patients of a different sex had been mixed up. This implied that only XX-cells could have been found in one culture and that the other culture exclusively contained XY-cells. This was not the case, however, as the combination of XX- and XY-cells had been observed in two separate cultures. A second explanation was the possibility of maternal contamination: all XX-cells would then be derived from the mother and all XY-cells would originate from the fetus. Additional testing in this specific trajectory needed to support this hypothesis. An ultrasound scan was performed to determine whether the fetus had male genital organs. If so – reasoning back to the genotype – it could be assumed that the tested XY-cells definitely derived from the fetus. The ultrasound scan showed that the fetus indeed was male and as the scan revealed no further phenotypical aberrations with the fetus, it was consequently concluded that the XX-cells did not originate from the fetus, but were derived from the mother. By testing the actual phenotype of the fetus, the explanation of maternal contamination was thus confirmed and the preliminary grey result turned white.

In the remaining (3/17) testing trajectories, the grey result consisted of a balanced structural aberration. In these trajectories, the professionals did not opt for testing other fetal cells in order to clarify the results. Additional testing and analysis focused on the chromosomes of the parents instead. With a balanced structural aberration it is unclear whether the chromosome aberration (genotype) observed will have phenotypical consequences (*see box 1*). In all three trajectories, the result was clarified by testing the chromosomes of the parents. In each case the chromosome aberration of the fetus was found in one of the parents as well, the conclusion being that they were dealing with a familial structural aberration in which no phenotypical consequences were to be expected. Additional chromosomal examinations of the parents thus made these grey results white.^f

Hesitation to clarify grey results

A remarkable phenomenon was signaled in the observations of grey testing trajectories: in four trajectories (always with mosaicism as the preliminary outcome) clarifying the result was not considered the obvious next step in the process. In these cases, not only the patients, but professionals as well, were clearly embarrassed: there was an increase in professional contacts and in mutual consultations; cases were discussed at length at weekly meetings, etc. This embarrassment and hesitation with respect to clarifying initial findings was not based on technical matters, e.g. because it was unclear which approach to apply. It rather seemed to stem from the question of whether the current ambiguity actually *needed* clarification. While reflecting on the question of whether clarification of a

^f The chances that a child with a (familial) balanced structural aberration will later give birth to a child with an unbalanced structural aberration are larger, however.

grey result was (still) necessary or desirable, the professionals also took the future decision on continuation or termination of pregnancy into account. Therefore, the idea of clarifying a grey result being a purely technical matter did not seem to hold in these cases. For this reason we will describe these four cases in detail and indicate the specific reasons that prompted the professionals involved to ask (themselves) this question. In these descriptions we will show how in the clarifying process of a grey result the technical aspects and aspects related to the individual patient both had their influence.

Clarifying a grey result in case of a fixed decision to continue the pregnancy?

First case

In the case of a woman who had had chorionic villi sampling due to an ICSI pregnancy^g, and enlarged nuchal translucency^h, the diagnosis was mosaicism of normal cells and cells with 45,X (mosaic for Turner's syndrome: *see box 1*). Of the seventeen analyzed cells, two showed a single X-chromosome, the rest of the cells all had a normal 46,XX chromosome pattern. These findings constituted a grey result as the question remained whether the fetus would also show Turner's syndrome mosaicism (or that it would concern mosaicism confined to the placenta, *see box 1*). The cytogeneticist who had to summarize the chromosome diagrams drawn up by the technician in a karyotype (*see box 2*), decided to use a long-term culture to clarify the result.

So far, the testing trajectory went along the same lines as what happened when, for instance, a mosaic trisomy 21 found in the short-term culture, was followed by a long-term culture. In this case, however, the professionals were dealing with mosaicism of a sex chromosome abnormality, with much less severe symptoms than Down's syndrome. This was partly the reason that this testing route changed after contacting the parents. They were informed of the outcome of the short-term culture. It was explained to them that the final result would take some time due to the time-frame of the long-term culture. The parents, however, immediately indicated that they would not terminate the pregnancy now that Down's syndrome had been ruled out. For the professionals, this new situation raised the question of whether the result still needed clarification. The observation protocol demonstrates how the issue was brought up in the weekly inter-disciplinary meeting, when the clinical geneticist reported on her contact with the parents:

'With respect to this mosaicism, a thick nuchal translucency has been observed, and both 46,XX- as well as two 45,X-cells were found in the chorion. We may be dealing with

^g ICSI (Intra Cytoplasmic Sperm Injection) is a form of IVF in which a sperm cell is injected directly into the egg cell. ICSI is an accepted indication to perform prenatal diagnosis, because of a possible increased risk for chromosomal abnormalities.

^h Nuchal translucency measuring is a form of prenatal screening in which the thickness of the nuchal translucency is measured through an ultrasound scan.

Turner. I have phoned the parents but they were merely very pleased that their child did not have Down's syndrome; a girl with Turner would be quite acceptable to them.' One of the gynecologists present gave a somewhat worried response and wondered if the parents had a clear picture of Turner's syndrome. She mentions all the uncertain factors with respect to the current result. The cytogeneticist answers: 'That may be the case, but even when I find more cells with 45,X, it won't change my opinion as the result is acceptable to them.' The gynecologist remarks that she only hopes that the parents don't take the situation too lightly, whereupon the clinical geneticist reacts as follows: 'It is an ICSI pregnancy, and therefore a very costly one....'

After the weekly interdisciplinary meeting I asked C. [the cytogeneticist] for further comments. She explained the situation as follows: 'A long-term culture has been initiated with three possible outcomes: 46,XX [normal girl], 45,X [girl with Turner's syndrome] or 46,XX/45,X [Turner's syndrome mosaicism]. But even if the findings are not good, no additional testing will be carried out, as the parents have indicated that they will not terminate the pregnancy.'

Although the professionals considered the result of the short-term culture a grey result, needing clarification, it was decided not to proceed with the clarification process, as the parents had made it clear that they would continue the pregnancy anyway because they now knew positively that their child did not suffer from Down's syndrome. For them the initial outcome needed no further clarification.

Second case

In the case of a woman who had had chorionic villi sampling on the basis of DNA-diagnosisⁱ, the technician observed three of the sixteen cells counted with 45,X, the rest were normal 46,XY cells. This was a grey result because it was not clear if the 45,X cells would be present in the fetus or not. A long-term culture could not be performed because all material had been sent out for DNA analysis. The observation protocol states the following on this result:

The cytogeneticist and clinical geneticist discuss how to proceed. CG. [clinical geneticist] says that she will call the parents tonight to tell them that she has good news on the DNA analysis but that the outcome of the chromosome test is still unclear. She will also explain that there are two options, i.e. an amniocentesis or an ultrasound scan to determine whether normal male genitals are seen.^j

ⁱ When chorionic villi sampling or amniocentesis is performed because of an increased risk for a specific DNA abnormality, it is standard procedure – after consulting the patient – to screen the chromosomes as well.

^j The combination of mosaicism of cells with only one single X-chromosome and normal female cells gives a different situation than such mosaicism in combination with normal male cells. In case of a combination with normal female cells (45,X/46,XX) the phenotypical outcome is comparable to Turner's syndrome, but less severe; girls with this chromosome pattern may have a normal appearance. Mosaicism in combination with normal male cells (45,X/46,XY) leads to a more complex phenotypical situation because there may be ambiguity about the gender. In this trajectory the ultrasound scan was used to determine whether the fetus had normal male genital organs. If so, it would be improbable that this was a case of mosaicism 45,X/46,XY.

At the weekly interdisciplinary meeting the clinical geneticist reports on the conversation:

Early this week I heard that the child does not suffer from the hereditary metabolic disorder. We have examined the chromosomes and found mosaicism. In the past we have followed up with amniocentesis. I have discussed this with the parents on the phone but they do not agree to an amniocentesis. I have explained to them that there is a 90% chance that there is no problem at all. This means a 10% chance that there is something wrong with the genital formation. This was entirely acceptable to them. When she told her husband, he replied that they were more than willing to take their chances in this matter. They told me that they knew somebody with a similar problem. There was something wrong with the genital organs of that particular child as well. It turned out to be operable and, moreover, in relation to the possible problems for their child [hereditary metabolic disorder, the initial reason for prenatal diagnosis] these issues were no obstacle at all for continuing the pregnancy.

The position of the parents led to a similar situation as in the first case. The difference with this case was the lack of material, rendering a long-term culture impossible. Additional testing would therefore be subject to a second invasive test, with a new risk of miscarriage. The similarity with the first case is that the parents played a role in establishing the relative importance of a further examination of the chromosome aberration. They also assessed the seriousness of this possibility and related their assessment to their personal situation. But whereas in the previous trajectory, the personal context was primarily determined by the 'costliness' of the ICSI pregnancy, any problems in this case were related to the original worries of the couple, i.e. their problematic experiences with the metabolic disorder from which their first child was suffering. In the light of these circumstances, the parents did not feel that additional analysis was necessary, a feeling that grew even stronger when a second invasive procedure was required with a renewed risk of miscarriage. They were not prepared to take this risk, so they declined further clarification of the grey result, at least for the time being.

Clarifying a grey result in case of an assumed decision to terminate the pregnancy?

In the testing route of a woman who had had amniocentesis in view of her age trisomy 8 mosaicism was observed, whereas the technician had already found a trisomy 21. The trisomy 8 was recorded in two cells, which raised the question whether trisomy 8 mosaicism would be representative of the fetus. When a lab technician observes that two of the ten counted cells are aberrant, it is normal procedure that she analyses more than ten cells (*see box 2, schematic chromosome representation*). But the technician who found this trisomy 8 mosaicism, after already observing a trisomy 21, apparently took the possibility into account that this specific grey result needed no further clarification and put the matter whether or not to count more than ten cells to the cytogeneticist. The entry in the observation

protocol of the meeting between the technician and cytogeneticist states the following:

C. [cytogeneticist] says to T. [technician] that she will consult CG [clinical geneticist] as to whether it is of importance to clarify the trisomy 8 as well. T. remarks: 'Normally speaking we continue the analysis with a trisomy 8.' 'True', C. replies, 'but things may be different in this case because of the trisomy 21. So I am not sure that you should go the extra mile. And the trisomy 8 may be nothing more than a culture artifact; actually that's what I suspect. So finish those ten cells first, and then we will decide what to do next.'

The observation protocol mentions the following on the consultations between the cytogeneticist and clinical geneticist:

CG. asks: 'What do you normally do, that is to say when the trisomy 21 would not have been found?' C.: 'We would continue looking, but I am not sure if this is the right option in this particular case, also in view of our busy schedule.' CG.: 'I suspect that the pregnancy will be terminated anyway and that would make it a waste of time indeed.'

Just as in the previous cases we see the question arising whether the grey result (trisomy 8 mosaicism) should actually be clarified. This time, however, the question is not raised after or in response to the contact with the parents, but it originates with the professionals themselves. Moreover, in this trajectory the reason for hesitation is exactly opposite to the situation in the previous one. This time the professionals thought that the pregnancy would be *terminated* anyway, based on the observed trisomy 21. Therefore they considered the information on a possible trisomy 8 mosaicism as no longer relevant. Consequently, there is no mention of the mosaicism trisomy 8 in the result letter:

*Findings of the analysis: structural chromosomal aberrations: no recognizable (Q-banding)
Karyotype: 47,XX,+21
Conclusion: female fetus with trisomy 21*

Clarifying a grey result in case of a fixed decision to terminate the pregnancy?

This case concerns a woman who had an amniocentesis due to her age and an elevated risk based on the triple test.^k Seven cells 47,XXX and three cells 45,X were observed: not mosaicism of a normal and an aberrant cell line (as usual), but mosaicism of *two* aberrant cell lines. The cytogeneticist decided to clarify the grey result by applying

ⁱ The triple test is a measurement of three substances in the blood of the pregnant woman, which enables a prognosis of the risk of Down's syndrome.

an advanced analysis method, i-FISH¹, on the already available amniotic fluid. This method enabled her to gather more information on the number of aberrant cells. The advantage being that a second invasive test – with the risk of miscarriage – was not required. In consultation with the clinical geneticist it was decided to include an ultrasound scan in the follow-up route. This would provide data on the sex of the fetus and any heart abnormalities, which might be an indication of the presence of Turner's syndrome (45,X).

After the start of the additional testing, the clinical geneticist met with the parents to inform them on the preliminary findings and the way things went from there. In the weekly inter-disciplinary meeting after the appointment of the clinical geneticist with the parents, she reported that it looked as if the parents would probably continue the pregnancy. But in the next week this trajectory became entirely different from what the professionals had anticipated.

The observation protocol:

I call C. [cytogeneticist] to find out if she already has any information on the i-FISH. C. replies: 'No, but CG. [clinical geneticist] has pointed out in the meantime that the parents have decided over the weekend to terminate the pregnancy, rather unexpectedly I might say.'

The observation protocol on the weekly interdisciplinary meeting:

CG. explains the case of the woman with mosaicism karyotype for whom an i-FISH has been performed: 'Last week I talked to the parents and explained that it is difficult to come up with a reliable prognosis. I told them about the two possible phenotypes and mentioned the possibility that the ovaries might hardly develop, implying a possible infertility. I also mentioned the website of our Danish colleagues. It has a lot of balanced information that might be of importance to them. At the same time I warned them not to start looking for info on the internet on their own. The possible symptoms are presented far too seriously and I pointed out to them why these would not be relevant for their future daughter. On Monday, they saw G. (gynecologist) whom they told they had decided to terminate the pregnancy, in part because all the information on the net about Turner had really scared them. Well, you can imagine I was not very happy with what had happened. But then again, I simply had to tell them about the website....'

While the professionals were still working on clarifying the grey result, the parents had already decided to terminate the pregnancy. This implied that there was no reason for the professionals to follow-up on the initial grey findings. But in this particular instance,

¹ In conventional chromosome testing, as described in box 2, only cells can be screened that are presently in metaphase, as the chromosomes only become visible during that phase. Interphase Fluorescent In Situ Hybridisation (i-FISH) also enables screening of all cells in interphase. This makes a simple screening possible of a larger number of cells in order to answer a specific question..

things even went a little further. From the rest of the discussion it is clear that the clinical geneticist does not even *want* to clarify the grey result:

After a remark by someone else, CG. says: 'I have heard nothing else about it, but yes, G. made it quite clear that they would terminate. In that case we will have a skin biopsy. And in my opinion a post-mortem examination of the ovaries is undesirable, because if that turns out normal....'

D. [doctor-sonographer]: 'You just don't want to know...'

CG: 'No.'

D: 'The same goes for the heart, if that is normal...'

CG: 'No, and there is also no relevance for the follow-up, other forms of mosaicism have their own characteristics. I must say that I am very disappointed about it all, but what can I do...?'

Because the parents have already decided to terminate the pregnancy, the grey result does not need any clarification. In this case the professionals even pro-actively reject any clarification. For, when the heart and the ovaries turn out normal, this would indicate a healthy fetus without Turner's syndrome. It might be quite awkward to learn that the fetus did not have the suspected chromosome abnormality after all. The statement 'you just don't want to know' positively indicates that all additional information has become 'unwanted', not only for the parents but also for the professionals.

Conclusion

Regarding the question of what professionals do to clarify grey results, we can conclude that, in terms of technical procedures, the clarification process as we observed it is in line with the literature, with a distinction made between the most common grey results, i.e. mosaicism and balanced structural aberrations. But remarkably, some preliminary findings prompted the question whether a grey result needed clarification in the first place. This question clearly brought the individual patient for whom the testing result was meant into focus. In all four described cases there was doubt on the relevance of the outcome of the chromosome tests. The main issue was the question of whether the information about the result would (still) be of importance for the parents' decision about the pregnancy – a question that was mostly answered by the parents, but in one case also exclusively by the professionals.

Thus, the descriptions of these testing trajectories evidently go against the idea that clarifying a grey result is a strictly technical process in which the individual patient plays no particular part. Naturally, the moment the professionals consider the future decisions on termination of pregnancy, the individual patient appears - literally or figuratively - on stage. So, while still in the phase of constructing a testing result, in some of our observed cases the professionals did not focus on technical matters only, but also took the individual patient into account, particularly their - assumed - considerations regarding termination of pregnancy.

The goal of this study was to find out how professionals deal with grey results, but also to examine whether the observed practice of clarifying grey results would correspond with the general idea of a testing result as a purely technical matter. As indicated earlier, within the framework of this study a grey result was defined as a result of which it is still unclear whether it will turn out normal ('white') or aberrant ('black'). In case of mosaicism, the question was whether the observed chromosome aberration was representative for the fetal chromosome pattern. The grey mosaicism became a black result when it was *assumed* - based on further testing, if possible - that the chromosome aberration found in the lab was representative of the chromosome pattern of the fetus. With balanced structural aberrations the question was whether the observed chromosome aberration would have phenotypical consequences. The grey structural aberration became a black result when it was *assumed* - based on further testing, if possible - that the noted chromosome aberration would have phenotypical consequences (with a varying degree of seriousness).

So what can be deduced from the fact that in case of some grey results professionals doubted whether the chromosome aberration was actually relevant in the light of the decision on the continuation of the pregnancy? The logical conclusion would be that professionals apparently only considered clarifying the grey result of prenatal diagnosis when it was *assumed* - either by the parents or by the professionals - that the black outcome would be relevant for the decision on the termination of a pregnancy. It seems, then, that generally professionals do not only view an aberrant result as information on chromosomes that is representative for the fetal genotype and as information on chromosome aberrations with clinical consequences; they also tend to view an aberrant result of prenatal diagnosis as information which is relevant for the decision on continuing or terminating the pregnancy.

How does this conclusion relate to the idea that a testing result is a purely technical matter? Whereas the assessments regarding the representativeness and phenotypical consequences of chromosomal information can be considered as purely (medical-)technical matters, the assessment regarding the relevance of chromosomal information for the decision about termination of pregnancy cannot be considered as such. Instead, this assessment clearly has a *moral* dimension. Therefore, our observations challenge the general idea of a testing result as a strictly technical matter. In the four described cases our observations were at odds with this standard view, because in the process of disambiguating results the question regarding continuation of the pregnancy came up before the final results were in and even determined the extent to which results were actually disambiguated. This means that the technical work of producing a result (usually attributed to the professional) and the moral work of making a decision about continuation of the pregnancy (usually attributed to the patient) were more intermingled than is generally assumed. Moreover, while the model of nondirective counseling is applied to prevent any involvement in moral decisions *based* on the testing result, this paper shows that moral involvement can also occur in the process of *making* testing results.

Professional responsibility

The conclusion that the moral aspect regarding the decision on continuation or termination of pregnancy is an intrinsic part of prenatal diagnosis, is significant for at least two reasons. First of all, it is important for the communication with parents. Although professionals are quite reluctant to openly discuss the option of abortion with pregnant women in the early stages of prenatal diagnosis⁴, our empirical results illustrate that the idea that it is only necessary to explicitly refer to the subject of the decision on termination of pregnancy when a black result shows up is evidently superseded. After all, our observations show that when an indefinite grey result was processed, the parents can also be prompted to reflect on what this grey result might mean to them, which they can only do in relation to their decision on termination of pregnancy. More details of this kind of communication with parents about grey results are discussed in the next chapter but here we stress the professionals' responsibility to inform parents about the possibility that their personal ideas about continuation or termination of pregnancy may influence the course of an indefinite testing route. More generally, it is never too early to emphasize why prenatal testing results are generated in the first place. This applies for prenatal screening as well. Although promoting informed choice is commonly recognized as the chief purpose and benefit of prenatal screening⁵, the 'freedom-of-choice argument' is not always specified. Therefore, prenatal counseling should always explicitly discuss the fact that testing results of prenatal diagnosis are meant to serve as input for the parents' decision about continuation or termination of pregnancy.

Secondly, the conclusion that professionals, while constructing results, sometimes take the decision on termination of pregnancy into account also has its bearing on policy issues. Our empirical results challenge an essential foundation of the ideology of non-directiveness, namely the implication that prenatal diagnosis is a value-free form of information gathering. Consequently, we may carefully consider the words of Biesecker, who has stated that 'An insistence on nondirectiveness has stymied the process of policy making in prenatal genetic testing. (...) In the name of nondirectiveness, genetic counselors have avoided their professional and moral obligations to take a stand on the appropriateness of certain types of prenatal testing.'⁶ Would Biesecker's analysis be true? Let us hope not. Due to technical developments, it is not at all clear what the world of prenatal diagnosis will look like in the near future. There is an increasing range of genetic abnormalities to screen for, as well as increasing possibilities to exclude some of the grey results in a scenario of 'targeted testing'.⁷ It is our opinion that, in this turbulent situation, the providers of these services should wholeheartedly participate in the discussion about which tests should and should not be offered. Holding back from this discussion would indeed be a neglect of their professional responsibility. Moreover, from what we have seen in our observations, it would not correspond with their involvement in the daily practice of prenatal diagnosis, as the construction of testing results sometimes holds a moral dimension. After all, this study demonstrates that a result of prenatal diagnosis is not mere information for professionals, but information they consider relevant for the parents' decision to continue or terminate the pregnancy.

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Chapter 4

**Communication with patients during the prenatal testing procedure.
An explorative qualitative study**

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4

Abstract

Objective

While generally two phases of prenatal genetic counseling are distinguished, i.e. pre and post test counseling, we revealed a third form of communication *during* the testing procedure. The content of this intermediate communication was explored.

Methods

A secondary analysis was performed on data obtained in another observational study which was focussed on how indefinite testing results are clarified. Thirteen testing trajectories in which communication with parents took place during the testing procedure were further analysed.

Results

In the majority of cases the content of intermediate communication was similar to the content of pre test counseling. In four cases the content was different, because the communication involved the parents in decision-making about a testing result which was still being processed.

Conclusion

Communication in (prenatal) genetic testing is not always restricted to separate phases, but can be an ongoing process occurring parallel to, and sometimes even intertwined with, the testing process. The advocated model of shared decision-making might work better once it is determined if the decision concerns the area wherein the provider is the expert, or the patient.

Practice Implications

Further research into the process of continuing decision-making could clarify how providers' and patients' responsibilities regarding the diagnostic process are distributed. Meanwhile, the possible occurrence of continuous decision-making should be mentioned in (prenatal) genetic counseling.

Introduction

Our understanding of the genetic counseling process is far from ideal. Using the 'black box' metaphor, Biesecker and Peters recently stated that we know very little of the inside of the genetic counseling process.¹ There is little research documenting what counselors describe themselves as doing, or what they actually do, during the counseling process, nor is there a standard method of practice among prenatal clinic settings^{2,3}. Overall, there is an inconsistency in defining the exact nature of counseling and its intended goals.^{4,5}

However, there is a consistent tendency to distinguish different phases of the genetic counseling process. In prenatal testing, two phases are generally characterized, i.e. pre test counseling and post test counseling. Pre test counseling ideally includes information about the condition for which the testing is being offered, the characteristics of the test (including the chance of provoking a miscarriage), and the implications of possible test results. Post test counseling consists of providing information about the diagnosis of a fetal abnormality, and providing emotional and decisional support regarding possible termination of pregnancy.⁶

Another consistency in the literature is the idea of separating the genetic counseling interaction from establishing the medical genetics diagnosis.¹ Despite empirical studies showing clients often having difficulty distinguishing the counseling portion of the visit from the diagnostic or management portion⁷, the idea that the counseling part takes place separately from the diagnostic part is rarely objected to. Even when an integrated approach to genetic testing is proposed, the different elements of the model are still presented as occurring separately in time.⁸

Harper describes the genetic testing process as including three phases, i.e. 1) information, preparation and consent, 2) laboratory analysis, and 3) interpretation and support. In this model, the second phase starts when the first phase has ended, and the third phase starts when the second phase ends. Kessler, a well-known psychological expert in the field of genetic counseling, gives a similar description of the third phase of genetic testing: "The kind of genetic counseling session described here is one in which the data gathering and diagnostic activities have been completed and, following some unspecified period of time and/or rituals to mark off the session from what preceded it, the counsellors and counselees sit down together to discuss the diagnosis and its implication (including possible reproductive options) and attempt an integration."⁹

Presented in terms of pre and post test counseling, the theoretical model of the prenatal testing process could thus be characterised as:

- [A] Pre test counseling: information, preparation, consent.
- [B] Diagnostic procedure (e.g. amniocentesis or chorionic villi sampling) + laboratory analysis, leading to a testing result.
- [C] Post test counseling: interpretation, emotional and decisional support.

Most empirical research into prenatal genetic counseling will be focussed on either A or C, as these are the phases in the model in which physician-patient communication is expected to take place. However, in our observational study we also signalled some form of communication in phase B, i.e. *during* the testing procedure.

Because this had happened more than once we wondered if these observed kinds of communication between pre and post test counseling were just some rare exceptions to a model which was basically right, or if this model was perhaps too limited to reflect the day-to-day reality about prenatal genetic counseling. If the latter were the case, then the general distinction between pre and post test counseling, separated by the diagnostic procedure and lab analysis, might be an obstacle in our search for understanding the process of prenatal genetic counseling, and perhaps even of genetic counseling as such.

For this reason we decided to find out more about this communication with parents during the prenatal testing procedure. Was the communication in these contacts similar to what is normally discussed in pre or post test counseling, or was something else happening? And if so, how could this communication during the testing process be understood within the above mentioned A-B-C model of prenatal testing? Our research question was: "What was the content of the provider-patient communication in phase B of the prenatal testing process?"

More generally, we also examined if more insight into this communication during the testing process would possibly add to our overall understanding of the process of prenatal genetic counseling.

Methods

The above mentioned forms of communication were accidentally found in a larger observational study about which we have reported in Chapter 3. For the current study, we performed a secondary qualitative analysis on data we had already obtained in this larger study. Because we had not included the provider-patient communication in the original study design, we could only examine this data in an explorative way.

Data collection

The larger observational study took place in the periods April - June 2001, and July - September 2002. Observations were then focussed on results of which it was still unclear whether they would turn out to be normal or aberrant. These indefinite results, which we referred to as 'grey' results, are quite common in prenatal diagnosis (*see box 1, p.62*). The observations were used to examine what professionals do to clarify grey results, i.e. to make them black or white.

In that larger study, a procedure was agreed with the respective professionals to ensure that the researcher could be present at the department for observation at key occasions. The actual observations concerned the interdisciplinary consultations between the professionals during the process of clarifying the grey result. Consultations between technician and cytogeneticist, between cytogeneticist and clinical geneticist, and between clinical geneticist and gynaecologist were observed. The weekly interdisciplinary meeting of the entire professional team involved in prenatal diagnosis, and the weekly technicians meeting, if relevant, were also observed.

In terms of the theoretical model of prenatal testing, as mentioned in the introduction, our observations in the larger study had been focussed on phase B. We had therefore not included observations of any communication with parents in our original study design, as we had assumed that such communication would only take place either in phase A or C. So by the time we had found out that such communication did take place in phase B, we could only make use of indirect observations of this communication, i.e. through what the professionals had reported about their communication with parents in phase B. The clinical geneticists, who were the professionals communicating with the parents, had reported about these contacts either in the interdisciplinary meetings, or directly to the researcher. However, all these indirect reports had been included in the field notes, and were therefore available in the observation protocol.

Apart from these direct and indirect observation data, the patient files, containing laboratory forms, the result letter and all other correspondence with medical specialists, were also collected. Finally, the minutes of the weekly interdisciplinary meetings were examined.

Data analysis

All research material was structured by 'testing trajectory', i.e. the series of professional actions through which a grey testing result was clarified. To this end, all fragments from the observation protocol relating to the same testing trajectory were put in chronological order. Kwalitan, a software programme specially developed for analysing qualitative data, was used for this purpose.¹⁰ The next step was working out the reconstructed trajectories into comprehensive case reports, always taking the primary research data into account. These case reports were checked by a cytogeneticist (LK) and a clinical geneticist (NL) of the department, to detect factual irregularities, but also as a form of 'member checking', i.e. as a tool to guarantee the validity of qualitative research.^{11;12}

In thirteen of the observed grey testing trajectories some form of communication with parents had been taken place during the testing process. These thirteen grey trajectories were further analysed for this study. These trajectories were considered as case studies, which were both studied individually (individual case analysis) as well as in relation to each other (cross-case analysis).¹³ The qualitative analysis was directed by the research question. By carefully examining the reconstructions of the testing trajectories it was determined how the communication during the testing process related to the process of clarifying the grey result. This qualitative analysis was performed by the first author, and checked by NL and LK.

Results

In all thirteen analysed grey testing routes the timing of communication with parents differed from the phase in which pre or post test counseling normally occurs, as it took place during the testing procedure. Due to this different timing we refer to this as 'intermediate communication'. In all cases this intermediate communication procedure took place because the testing trajectory had resulted in an indefinite result for which clarification was needed.

However, the content of the intermediate communication with regard to the clarification of the indefinite testing result differed among the thirteen testing trajectories. Whereas in the majority of cases (9/13) the intermediate communication was about medical and/or technical matters only, in four cases more personal matters were discussed as well. *Table 1* gives an overview of all thirteen observed cases of intermediate communication during the testing procedure.

Communicating medical/technical matters only (n=9)

In two cases the parents were informed that the testing route would take a little longer because a second laboratory analysis was necessary to clarify the indefinite result. In the other seven cases the parents were not only informed about the delay of the laboratory procedure, but they were also informed about, and asked consent for a second diagnostic procedure, either amniocentesis (n=3), ultrasound examination of the fetus (n=1) or examination of the parents' blood (n=3).

Communicating a mix of medical/technical and personal matters (n=4)

In four cases, apart from medical/technical details, communication was also about the parents' personal evaluation of the testing result. Two of these cases were quite similar. The indefinite result found in trajectory 15 was a mosaic 45,X (mosaic Turner, *see box 1*), and in trajectory 19 it was a mosaic 46,XY/45,X. When the parents were informed about the additional testing necessary to clarify this result, the parents' personal considerations on this situation were also discussed.

The clinical geneticist who had contacted the parents of **trajectory 15** reported in the weekly interdisciplinary meeting that "*they were merely very pleased that their child did not have Down's syndrome; a girl with Turner's syndrome would be quite acceptable to them.*" The parents had let the clinical geneticist know that, while they might have terminated their pregnancy in case trisomy 21 (Down's syndrome) would have been detected, they would not do this for mosaic 45,X. This intermediate communication influenced the proceedings of the testing trajectory. Because the parents would not terminate this pregnancy, it was decided not to do amniocentesis to clarify the indefinite mosaic.

The clinical geneticist who had contacted the parents of **trajectory 19** had explained to the parents there was a 10% chance there would be something wrong with the genital formation. In the weekly interdisciplinary meeting the clinical geneticist reported: "*Well, this was entirely acceptable to them (...) they were more than willing to take their chances in this matter.*" Consequently, because these parents would continue this pregnancy anyway, no

matter if the amniocentesis would detect the mosaicism or not, it was decided not to do amniocentesis.

The indefinite result found in **trajectory 25** was a mosaic 47,XXX/45,X. Because of additional testing the parents needed to wait a little longer for a definitive testing result. They were also informed about the possible impact of the indefinite mosaic, i.e. the possibility that the ovaries might hardly develop, implying a possible infertility. Additionally, they were warned not to look for information on the Internet on their own, because the symptoms mentioned there were far too serious. However, a few days later these parents told their gynaecologist: “*We don’t dare to take the risk after all.*” According to the clinical geneticist: “*Among others, because all information on the net about Turner had really scared them.*” The parents’ personal considerations had made them decide to terminate the pregnancy, no matter the result of the additional test. Consequently, the result of this test was not communicated to the parents anymore.

The grey result in **trajectory 24** was not so much an actual detected aberration, but more the *suspicion* of mosaicism. Due to technical reasons the geneticists did not feel confident to give a definitive testing result, because they first wanted to exclude the possibility of mosaicism. The two options to do this were discussed with the parents, seemingly to find out how the parents would wish the testing procedure to continue. However, these parents did not seem to have any strong personal considerations regarding this matter. Consequently, it was decided to choose the option which was most reasonable from the professionals’ technical perspective.

Results in terms of the A-B-C model

The intermediate communication in the nine cases in which only medical/technical matters were discussed can be understood as a repeated form of pre test counseling. In terms of the A-B-C sequence this is what happened in these cases:

- [A] Pre test counseling
- [B] Diagnostic procedure + laboratory analysis, leading to an *indefinite* result
- [I] Intermediate communication = second pre test counseling [A2]
- [B2] Second diagnostic procedure and/or laboratory analysis, leading to a definitive testing result
- [C] Post test counseling

In the other four cases the content was very different to the content of pre or post test counseling as the intermediate communication (I) seemed to be *intertwined* with the proceeding of the diagnostic procedure and laboratory analysis (B2), as well as with post test counseling (C). Therefore, in terms of the A-B-C model, this is what happened in these four cases:

- [A] Pre test counseling
- [B] Diagnostic procedure + laboratory analysis, leading to an indefinite testing result
- [I+B2+C] Intermediate communication, intertwined with the proceeding of the diagnostic procedure + laboratory analysis, and with post test counseling

Decision-making during testing process

The intertwined intermediate communication with parents in the last four cases was directing the testing process, because through this communication the goal of prenatal diagnosis was specified. But why was the goal of prenatal diagnosis specified *during* the testing process? Due to technical characteristics, the goal of prenatal cytogenetic diagnosis is by definition not always very specific. Since full karyotype analysis is the 'gold standard', generally *all* chromosomes are examined in order to find a single chromosome abnormality. This means that chromosome analysis might lead to the detection of *any* kind of chromosome abnormality, not only the one for which the test is actually performed because of an existing high risk. In these cases, the detected aberration is an unexpected finding for the patient. In the four cases which have been described in detail, the chromosome abnormality found was grey (*see box 1*), but unexpected for the parents too. Because the detection of a so called unexpected finding is a well known phenomenon in prenatal diagnosis, it is advised to inform parents about this possibility in pre test counseling.¹⁴⁻¹⁷ However, in daily practice this is rarely done.¹⁸

We don't know if the parents in our observations were actually informed beforehand about these possibilities or not, but we do know from the observations that the parents were informed about the unexpected, grey result while the testing procedure was already going on. Whereas in nine cases the parents were indeed informed that this grey result needed to be further clarified, in the other four cases the communication with the parents dealt with the question if and how the grey result should be clarified. As such, the intermediate communication in these cases led to a process of decision-making, which was not located either in pre or post test counseling. Instead, this process of the parents' decision-making took place *during* the testing process.

Discussion and Conclusion

Discussion

The content of the provider-patient communication during the prenatal testing process was similar to the content of pre test counseling in the majority of cases. In four cases the content was different, because the parents were involved in decision-making about a testing result which was still being processed.

This study presents a secondary analysis on data that was already available through another study. Although the small number of cases limit the external validity of our study^{19;20}, our results may still help to better understand the process of genetic counseling in general.

Firstly, communication in prenatal genetic testing evidently does not only happen in separate phases before or after the test, but also during the testing process. The fact that parents sometimes have to make decisions during the testing process has been signalled before.²¹ Communication, including the parents' process of decision-making, may therefore be thought of as an ongoing process, occurring parallel to, and sometimes even intertwined with, the testing process.

Secondly, the cases in which the parents took part in deciding how to proceed with the testing process can be interpreted as examples of shared decision-making, a model which is recently being promoted to apply in genetic counseling.^{22,23} It is already acknowledged that shared decision making may also be applicable to negotiations about diagnostic pathways.²² However, based on the results of this study, we are not convinced that involving patients in the diagnostic pathway of their own testing results should be considered a goal in itself. On the contrary, we endorse the viewpoint that in cases of shared decision-making clients should not feel abandoned to make important decisions without sufficient support, when counsellors, for example, withdraw from any involvement.²² As professionals in genetic counseling are used to thinking of communication with their clients in terms of a consumer model, rather than the paternalistic model as is more common in other medical settings²⁴, this pitfall seems realistic. Therefore, when applying the model of shared decision-making in genetic testing settings, it could be kept in mind that the patient leads in areas where he is the expert, and the doctor leads in his domain of expertise.²⁵ Shared decision-making might work better once it is determined if the decision to be made concerns the area wherein the provider is the expert, or the patient. Doing this might prevent the parents to feel abandoned in an area like the diagnostic pathway which is, due to the complex technical character, primarily the doctor's domain of expertise.

Conclusion

This explorative study illustrates that parents could also be involved in decision-making while the testing result is still being processed. Due to some particular features of prenatal testing, e.g. uncertainty and the highly complex character of the testing procedures, it remains to be determined if parents experience this as a gain or as a loss. In evaluating the increasingly advocated communication model of shared decision-making, parents' appreciation of continuing decision-making should be weighed as well.

Practice implications

The occurrence of continuing decision-making shown in this study should be further examined. Particular attention should be focussed on how responsibilities between providers and patients are distributed in this process, for example along the lines suggested by Salmon and Young in their recent paper.²⁶ Meanwhile, counseling and education about (prenatal) genetic testing might emphasise that decision-making for parents involved in prenatal testing may exceed pre and post test counseling.

In this paper, we mainly focussed on the professionals' part of the communication process. However, an important step towards opening the 'black box' of genetic counseling might be to examine the clients' experiences with indefinite results of genetic testing. Further study of the communication following indefinite testing results and of other intermediate communication will definitely add to the overall understanding of the genetic counseling process.

Table 1: Cases of observed intermediate communication during testing procedure (n=13)

Content of communication	Indefinite (grey) testing result	Indication	Initial procedure
Medical/technical matters (n=9)	(20) ^a Mosaic ^b trisomy 21	Advanced maternal age	CVS ^c (STC ^d)
	(18) Mosaic trisomy 18	Advanced maternal age	CVS (STC)
	(29) Mosaic trisomy 18	Advance maternal age	CVS (STC)
	(27) Mosaic trisomy 2, trisomy 6, trisomy 7	Risk of DNA abnormality ^f	CVS (STC)
	(38) Mosaic trisomy 18 and trisomy 7	Advanced maternal age	CVS (STC)
	(17) Mosaic 46,XX/46,XY	Advanced maternal age	Amniocentesis
	(23) Balanced translocation ^g	Advanced maternal age	Amniocentesis
	(32) Balanced translocation	Previous child with chr. abn.	CVS
	(34) Balanced translocation	Advanced maternal age	Amniocentesis
Mix of medical/technical and personal matters (n=4)	(15) [*] Mosaic 45,X	ICSI ^h and NT ⁱ result	CVS (STC)
	(19) [*] Mosaic 46,XY/45,X	Risk for DNA abnormality	CVS (STC)
	(25) [*] Mosaic 47,XXX/45,X	Advanced maternal age and triple test ⁱ result	Amniocentesis
	(24) Fear of mosaicism	Advanced maternal age	Amniocentesis

a () = Number of observed trajectory. The trajectories marked with * are also described in detail in Chapter 3.

b See box 1 for explanation of mosaicism.

c CVS = chorionic villi sampling.

d STC = short-term culture; see box 1 under mosaicism for explanation.

e LTC = long-term culture; see box 1 under mosaicism for explanation.

f When prenatal diagnosis is performed because of an increased risk for a specific DNA abnormality, it is standard procedure – after the patient's consent – to analyse the chromosomes as well.

g See box 1 for explanation of balanced translocation.

h Intra Cytoplasmic Sperm Injection (ICSI) is a form of IVF in which a sperm cell is injected directly into the egg cell. An ICSI procedure is presumed to lead to an increased risk for chromosomal abnormalities.²⁷

Possible additional testing	Content of in-between communication: summary
LTC ^e	The parents were informed that their testing result would take a little longer because of the LTC
LTC	Idem
Amniocentesis (not enough material for LTC)	The parents were prepared and asked consent for amniocentesis
Amniocentesis	Idem
Amniocentesis (not enough material for LTC)	Idem
Ultrasound examination of the fetus	The parents were prepared and asked consent for ultrasound examination of the fetus
Parental chromosome analysis	The parents were prepared and asked consent for examination of the parents' blood
Parental chromosome analysis	Idem
Parental chromosome analysis	Idem
LTC, and amniocentesis if the LTC would show the mosaic 45,X/46,XX	The parents communicated that the uncertainty of this grey result was acceptable to them, now they knew their child did not have Down's syndrome. They would continue the pregnancy anyhow, independent of the testing result of the LTC, and did not want amniocentesis
Amniocentesis (not enough material for LTC)	The parents communicated that the uncertainty of this grey result was acceptable to them, now they knew their child did not have the DNA abnormality. They would continue the pregnancy, and did not want amniocentesis.
i-FISH ^k	The parents communicated that the uncertainty of this grey result was not acceptable to them. They did not wait for the i-FISH result, and decided to terminate the pregnancy.
i-FISH and/or amniocentesis	The parents communicated that for them there were no specific individual reasons to accept or not accept the uncertainty of this grey result. I-FISH was done to clarify this grey result.

- i Nuchal Translucency (NT) measuring is a form of prenatal screening in which the thickness of the nuchal translucency is measured through an ultrasound scan. A thickened nuchal translucency indicates an increased risk for Down's syndrome and other chromosomal abnormalities.
- j The tripletest is a measurement of three substances in the blood of the pregnant woman and results, combined with the age of the pregnant woman, in a calculated risk for Down's syndrome.
- k In interphase Fluorescent In Situ Hybridisation (i-FISH) more amniotic fluid cells can be analysed than with the conventional method of karyotyping, for which only dividing cells are used. I-FISH can be performed on cell material which is already available from amniocentesis, so there is no need for a second invasive procedure.

Box 1: Grey results in prenatal chromosome diagnosis

The most commonly found chromosome abnormality in prenatal diagnosis is trisomy 21, which means that every cell contains three instead of two chromosomes 21. A trisomy 21 found in prenatal diagnosis is a definite testing results. Apart from definite testing results, prenatal diagnosis can also lead to indefinite testing results.

Definite testing results

Trisomy 21 leads to a combination of physical and mental disabilities (varying in severity), which is known as **Down's syndrome**.

Other definite chromosome aberrations have phenotypical consequences which are generally considered as **more serious than Down's syndrome**. The most commonly known aberrations are trisomy 13 (in which three instead of two chromosomes 13 are present), trisomy 18 (three instead of two chromosomes 18) and triploidy (three chromosomes instead of two - for all chromosomes). All these chromosomal aberrations result in severe physical and mental disabilities. Another group of definite chromosome aberrations have phenotypical consequences which are generally considered as **less serious than Down's syndrome**. Most common in this category are the sex chromosomal aberrations, in which case there is something wrong with the X- or Y-chromosomes. Among these, Turner's syndrome and Klinefelter syndrome are quite familiar.

With Turner's syndrome (45,X) we find one single X-chromosome instead of two sex chromosomes; with Klinefelter syndrome (47,XXY) there is one X-chromosome too many. Most phenotypical problems in Turner's and Klinefelter's syndrome relate to infertility and/or secondary gender characteristics. In case of a 45,X or 47,XXY that appears in mosaicism these phenotypical problems are less serious (see the next section).

Indefinite (grey) testing results

In addition to the various types of definitive aberrant results, there are also chromosomal aberrations of which it still remains unclear if they will have phenotypical consequences. Among these indefinite, or grey, testing results, a distinction can be made between mosaicism and structural aberrations.

In **mosaicism** an individual shows two (or more) genetically different cell types. Forms of mosaicism have been observed of e.g. normal cells and cells with trisomy 21, or of normal cells and cells missing an X-chromosome, but mosaicism may appear in all kinds of variations.

Mosaicism is a relatively common phenomenon in chorionic villi sampling. As in chorionic villi sampling placenta material is examined and no fetal material, the observed mosaicism may be restricted to the placenta, but not manifest itself in the fetus. In that case one speaks of confined placental mosaicism. In chorionic villi sampling two different kinds of methods can be used to look at two types of cells of the placenta. When mosaicism is observed in the short-term culture (STC) of the chorionic villi sampling, additional testing can take place through a long-term culture (LTC). When mosaicism is not observed in the long-term culture, there is an increased chance that mosaicism is limited to the placenta, in which case it does not lead to phenotypical abnormalities. In addition to mosaicism confined to the placenta, there may also be other explanations for mosaicism in laboratory material that cannot be found in the fetus. For instance because genetically deviating cells have developed in the cell culture (culture artefact) or because not only fetal cells but also cell material of the mother has been examined (maternal contamination). Culture artefacts and maternal contamination can both occur in chorionic villi sampling as well as in amniocentesis. In all these cases the detected mosaicism does not have phenotypical consequences.

In a **structural aberration**, e.g. a **translocation**, the problem concerns the form (structure) of the chromosomes. There are two kinds of structural aberrations. With an unbalanced structural aberration, the form of one or more of the chromosomes has been altered in such a way that the total amount of genetic material has also changed. In a balanced structural aberration, the total amount of (chromosomal) material has remained the same. Whereas an unbalanced aberration always leads to phenotypical aberrations, this is commonly not the case with a balanced aberration. To determine if the chromosomal aberration would lead to phenotypical aberrations, the chromosomes of the parents are analysed, as this may indicate whether the detected change of the chromosomes occurs within the family or is a new alteration. When one of the parents is carrier of the same chromosome anomaly, it is not to be expected that there will be phenotypical aberrations; for the parent with the same structural aberration is of normal health. But when it concerns a new aberration, it cannot be excluded that the structural aberration will have phenotypical consequences.

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Chapter 5

**Problematic findings and the role of targeted testing
in prenatal diagnosis.**

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Submitted for publication

5

Abstract

Prenatal diagnosis may lead to the situation where parents have to decide about continuation or termination of their pregnancy. Testing results of mild or unknown clinical significance are considered problematic because the dilemmas for clients are bigger than in case of the more common results of severe or known clinical significance. In a new method of targeted testing, prenatal diagnosis could focus on common results and exclude the problematic results. To assess if targeted testing is the evident way to deal with problematic findings in prenatal diagnosis, the problems associated with these findings are systematically examined.

Providers from several disciplines were interviewed, individually and in focus group discussions, about their experiences with various testing results in general, and problematic results in particular. Clients were asked about their expectations and experiences regarding the same matter. Providers' and clients' experiences were analysed in comparison to search for themes related to problematic testing results.

Problematic results arise because providers, wishing to avoid underreporting, also report results of mild or unknown clinical significance. In a context where only two choices, i.e. continuing or terminating the pregnancy, are available, these results may lead to dilemmas. Because the decision about pregnancy is considered the clients' responsibility in the end, the decision burden for clients is relatively large in case of results of mild or unknown significance.

Compared to alternative solutions within the current scenario of testing, targeted testing can be considered the evident way to deal with problematic findings because it would diminish the decision burden for clients the most. Still, the implementation of targeted testing would require an explicit answer to the - morally laden - question of which testing results should be excluded from prenatal diagnosis. When providers are prepared to help answer this question, targeted testing may lead to a substantial improvement in the quality of the prenatal diagnosis practice.

Introduction

“Our baby is healthy but will not be able to have children. So what to do? It’s healthy, so terminating is difficult. But what happens when he’s a grown up, and we must tell him that he will never have children - that’s very difficult. Maybe he will be unhappy, and perhaps also angry to us because we knew about his condition, but still decided that he would be born. Oh, this is such a big responsibility!”

In our research project on unexpected findings in prenatal diagnosis we interviewed a Turkish couple, who were informed that in amniocentesis an extra X chromosome was detected with their male fetus, which would lead to Klinefelter’s syndrome, with infertility as a symptom, in their future baby. In this interview, several aspects of the difficult decision after an unexpectedly detected sex chromosome abnormality (SCA) were passed in review. Moreover, the importance of producing offspring for people living in a Turkish cultural context made the dilemma even more dramatic. The detection of a mild sex chromosome abnormality naturally leads to a difficult decision of having to choose between terminating the pregnancy of a healthy child, or continuing the pregnancy of a child with some failings which might prevent him/her to lead a normal, happy life. But in this particular case it seemed that the parents were faced with a decision that was almost impossible for them to make.

Inherently, prenatal diagnosis occasionally leads to troublesome situations. After all, any time a chromosome abnormality is detected, the parents need to decide about continuation or termination of their pregnancy. The problematic character of this situation, where parents need to make a decision they can account for - to themselves and others, including their future baby if they decide to continue the pregnancy - is widely recognized among prenatal testing providers. At the same time, providers expressly do not consider themselves responsible for the outcome of this difficult situation, as the actual decision to terminate or continue the pregnancy is considered being the parents’ ultimate responsibility.

Yet, voices are recently being raised to restrict the range of burdensome situations that are generated in prenatal diagnosis. Apart from reasons of rapidity, ‘targeted testing’ (see box 1) is increasingly being proposed as a new method of testing to prevent problematic situations like in the above case.^{1,2} Instead of intensifying professional procedures on an individual and ad hoc basis, as is the current strategy in prenatal diagnosis in case of a problematic testing result with an unknown or mild clinical significance, targeted testing suggests a more structural solution to deal with these problems.

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However, the idea of targeted testing is not undisputed. The recent recommendation of the UK National Screening Committee (UKNSC) to exclude the detection of SCAs from screening programmes for Down's syndrome was for instance strongly opposed by the UK Association of Clinical Cytogeneticists.³ Because the conflicting views on targeted testing reach beyond technical matters and are related to the goals of prenatal diagnosis, an ethical discussion about the pros and cons of this new approach in prenatal diagnosis is called for.⁴

If targeted testing would indeed be implemented, it is also important to determine which chromosome abnormalities should be included in this new method of testing. The literature on targeted testing refers to (some of) the problems that targeted testing might prevent, e.g. increased parental anxiety and possibly unnecessary terminations of pregnancy, and the SCAs are specifically mentioned in this respect.^{1;2;5;6} However, surprisingly, it is still an open question which testing results exactly would be excluded in a scenario of targeted testing. Evidently, the simple answer to this question, i.e. any testing result that is considered too problematic, is still difficult to interpret and therefore not satisfying. The more fundamental question that needs to be answered first is: 'which are the exact problems to which targeted testing intends to be the solution?'

The aim of this study was to find an answer to this question in the daily practice of prenatal diagnosis. The providers' and the clients' experiences with problematic testing results were systematically examined to find out which are the specific problems in the current practice of prenatal diagnosis to which targeted testing could be the solution. More insight in this matter may be helpful, we believe, for the discussion about whether a scenario of targeted testing would be the obvious way to deal with problematic testing results in prenatal diagnosis.

Box 1: Targeted testing in prenatal diagnosis

So far, in prenatal diagnosis *any* kind of chromosome abnormality can be detected, not only the one for which the test is actually performed because of an existing high risk, which is trisomy 21 (leading to Down's syndrome) in the majority of cases. The reason for this is a purely technical one. To find out if the woman undergoing prenatal diagnosis carries a fetus with three instead of two chromosomes 21, *all* 46 chromosomes of the fetus need to be analysed. Only when all chromosomes are graphically presented in a complete karyogram, can anomalies be determined in a reliable way.

New molecular diagnostic techniques could radically change the current practice of prenatal diagnosis. Contrary to the conventional method of full karyotyping, new molecular tests, using for instance quantitative fluorescent polymerase chain reaction (QF-PCR) or multiplex-ligation-dependent probe amplification (MLPA), have the option to focus the diagnostic process on the chromosome(s) suspected to be anomalous. Implementation of these techniques could change prenatal diagnosis into a form of 'targeted testing', where the detection would be focused on the high risk abnormality only, and not on other possible chromosome anomalies.

Methods

Data collection

Four kinds of (group) interviews were held in the period from April 2002 to July 2003. Firstly, clients scheduled in the Academic Medical Center in Amsterdam for amniocentesis or chorionic villi sampling because of increased maternal age were requested to participate. A letter was sent by their gynaecologist and included information about the aim of the research project. Only after a client indicated she was willing to participate, was her personal information passed on to the researcher (MvZ), who then contacted the client by telephone. In this telephone call some additional practical information about the interview was given, and clients were again explicitly asked for their willingness to participate. In-depth interviews (n=15) were held by MvZ and took place within an hour maximum of the invasive procedure taking place. In thirteen cases the woman and man were interviewed together in the hospital. In the other two cases the interview was held the following day with the woman only; one over the telephone, and the other at the client's home.

Secondly, clients who had received a testing result other than trisomy 21 while prenatal diagnosis was performed because of increased maternal age, were personally asked by their gynaecologist to participate, after having received written information about the aim of the research. Only clients who were willing to participate were contacted by the researcher. In-depth interviews (n=5) were held with clients who received three different kind of testing results: two clients had received a result which is generally considered more serious than Down's syndrome (trisomy 18), in two cases a sex chromosome abnormality was found (45,X and 47,XXX) and in one case the testing results was still unclear (balanced translocation). In three cases the interview was held with the woman and man together, in two cases with the pregnant woman alone. All interviews but one (in English) were held in Dutch, and were held at the clients' home by MvZ.

Thirdly, in-depth interviews were held with prenatal diagnosis providers (n=10) working in the Academic Medical Center, i.e. four gynaecologists; three midwives, doctors or ultrasound specialists doing the intake session preceding the invasive procedure; one clinical geneticist and two cytogeneticists. Interviews were held by MvZ in the providers' own working place.

Finally, focus group interviews were held with professionals (n=22) from all eight specialized Clinical Genetics Departments in the Netherlands, and a few other Dutch professionals specializing in the field of prenatal diagnosis, i.e. two cytogeneticists, three clinical geneticists, three gynaecologists, one ultrasound specialist, one medical ethicist, one general practitioner, three midwives, four social workers, three health politicians and one health researcher. Focus group discussions took place in the Academic Medical Center in Amsterdam in two groups of seven and one group of eight participants, each group moderated by one of the three authors.

Data of the focus group discussion that were specifically focused on the pros and cons of targeted testing are reported in Chapter 6.

All (group) interviewees were asked for their experiences with different testing results in general, and difficult results in particular. However, the topic list was adjusted for every different interview setting. All (group) interviews were audio-taped onto mini disc and transcribed verbatim. According to the Medical Research Involving Human Subjects Act (WMO), formal approval for this research project by a Medical Ethics Committee was not necessary.

Data analysis

Analysis was guided by the research question, “Which are the specific problems in the current practice of prenatal diagnosis to which targeted testing could be the solution?” The software program MaxQda⁷ was used to facilitate the process of coding. To optimize mutual comparison, the providers’ and the clients’ transcripts were analyzed simultaneously, through a cross-sectional code and retrieve method.⁸ In a framework approach, the first coding round started deductively from two main codes (‘kinds of results’ and ‘meaning of result’), and continued more inductively to add sub codes (about ten for each main code).⁹

Through selecting and retrieving fragments four different documents were generated, i.e., ‘kind of results’ for providers and for clients and ‘meaning of results’ for providers and for clients. In successive coding rounds, the selected material in these four documents was compared and analysed in a crystallisation style¹⁰ to discern different themes to which problematic testing results were related. Initially, mutual comparison of these four documents led to an early identification of four distinctive themes, i.e. difficult results; decision about termination of pregnancy; reason to do prenatal diagnosis and normativeness. Next, a matrix was created, holding these four themes in the vertical direction, and in the horizontal direction the responsibilities as perceived by clients and providers. Further examination of this matrix led to the final identification of four other themes that were considered most distinctive regarding the question which are the specific problems in the current practice of prenatal diagnosis to which targeted testing could be the solution.

In the results section the data are presented along the lines of these four themes, i.e. ‘avoiding underreporting’, ‘dichotomous choice’, ‘bigger dilemmas’ and ‘clients’ responsibility’.

Results

1. Avoiding underreporting

One of the reasons that problematic results arise in the current practice of prenatal diagnosis is the providers’ wish to avoid underreporting regarding the information detected in prenatal diagnosis. Also when providers doubt about whether some detected information would be significant, they will still want to report this in most cases, because in the providers’ opinion *any* detected information that clients might find significant should be reported to their clients:

Sometimes we wonder, is this something we should tell them? But I'm inclined to,

as soon as I have the idea that people have something to choose, that there's the need to tell them. I don't think you should make people work themselves up over nothing, but whenever they have a choice I think they should know. That's my firm conviction. (clinical geneticist 1)

An important motivation for providers to report everything that was detected originates from their fear to be accused afterwards, perhaps even in legal terms, of withholding information:

What I find most important is that they can tell, 'oh, but if this is the case then we don't do it', that they have the choice to terminate the pregnancy – that's what's important to me. [Int: Why?] Uhm, I think that's got to do with, perhaps that – the worst case scenario is that I'll be accused later on, like: 'you didn't tell me this and it's you that can be blamed for that', so that I do get blamed, that's why it's important. (clinical geneticist 1)

In the situation like this, where we're making full karyotypes, you can't say, if you feel uncertain about it, then you can't keep up appearance, you have to lay all your cards on the table. After all, the patient has access to his own file. So I do mention it, when I have three abnormal cells, even when I've got the feeling it won't be anything, I do report it in the result. (clinical cytogeneticist in focus group 3)

However, for the clients who are receiving such a - perhaps insignificant - result, this information will still be significant. After all, the single fact *that* the result is communicated will probably make it significant for the clients, who assume that the providers would only communicate significant information. This line of thought is expressed by the couple who were informed about a balanced translocation, for which further research was needed to find out if this was an innocent or a possibly harmful chromosomal abnormality:

Mr.1: But well, we'd also like to hear that calculation of probability.

Mrs.1: Yes, that percentage, wouldn't that be something they'd examine further?

Mr.1: Yes, I suppose so, because why would they have called the alarm in the first place? I mean, something was found, and in their view something's the matter with it.

II Dichotomous choice

Another theme that relates to problematic results in the current practice of prenatal diagnosis is the context of choice, determined by the setting of prenatal diagnosis itself. Because the prenatal diagnosis setting presents only two options of choice, i.e. either continuing or terminating the pregnancy, any prenatal testing result will naturally be evaluated within that context of choice. In the interviews, clients clearly expressed their awareness of this context. For them, doing prenatal diagnosis naturally implied being prepared to make this kind of choice. Although it was not yet specified in which cases they would decide to continue or to terminate the pregnancy, all the interviewed clients reported *some* preparedness to consider termination of pregnancy in case of a negative

result. After all, the option to decide for termination was the very reason for them for doing prenatal diagnosis; “otherwise I wouldn’t have done this test”. This is illustrated by the following fragments, reading three of the patients’ answers on the question of what had been their intention of doing the test:

Well, the reason we did it is because eventually, if it will turn out to have this defect, we will not keep the child. That’s easy for me to say right now, I know it will be very hard then, but otherwise I wouldn’t have done it, because then I would have just been pregnant for nine months and just found out if it were healthy. (Mrs. 4 after being tested)

And consequently, if this were the case, I mean Down’s or the most serious defects, uhm, that we would have it removed. (Mrs. 3 after being tested)

The objective is to know this, and if it’s clear it’s disabled because of this, or half dead or severely mentally disturbed, that you can still perform an abortion, even though it’s very late for that (...) Clearly, it’s about the decision to continue the pregnancy or not. (Mr. 1 after his wife being tested).

However, the opportunity of being able to decide about termination or continuation of the pregnancy may be perceived more as a *necessity* in case of the problematic results, where the clinical significance is mild or unknown:

It’s hard to help people decide about, let’s say, a Klinefelter’s, because the impact on the quality of life is not so big compared to triploidy, trisomy 13, 18 or 21, that’s why it’s so hard. (gynaecologist in focus group 2)

For myself a Turner’s or Klinefelter’s is not a difficult result because there’s so much information available, so you very well know what to tell them, it’s just that I wouldn’t like to be in the parents’ shoes to decide about this. (clinical geneticist 1)

III. Bigger dilemmas

Although generally speaking, clients are prepared to decide about continuation or termination of pregnancy, this decision is experienced as a bigger dilemma in case of the problematic results. Clients who were awaiting a testing result mentioned for example that for this reason *unclear* results are problematic for them:

Well, it’s positive if they say, we didn’t find any abnormalities. Uhm, negative, that’s more varied, from grey ‘till black. (...) And then I would prefer black, I suppose, even over grey. (...) Because then the decision would be easier. (...) Because grey, that’s when they say, well, we’ve found something, but it isn’t really life threatening, and then getting presented a whole range of possibilities... while they don’t know for themselves what it is. Getting additional research.... That would be my worst case scenario. (Mrs. 15 after being tested)

A woman who was indeed facing such a grey testing result (i.e. the balanced translocation mentioned above, for which further research of the parents' blood was needed to find out whether the translocation would be present in one of the parents' cells, in which case the grey result would be innocent), described what was so problematic for her about this unclear testing result:

What I find terribly difficult is that – oh I hope it won't come this far – I would have to decide, while nothing was found on the ultrasound, nothing was found in the blood, but still: it's our call (...) That's what I'm afraid of, that they will say, okay, we know things can go wrong, but it can be all right as well, but can you please decide, what is it you want? I find this an almost inhuman task. (...) So that's why I said, for God's sake, let's have the ultrasound show something, so then we know it's not okay. (Mrs. 1 after being tested)

So, clients who expect or who are actually faced with a grey result imagine that they would be better off with a black result, because in that case the dilemma would not be so big for them. This is consistent with the experiences of clients who have indeed received a black result like trisomy 13 or 18. Because these results are considered as more severe than Down's syndrome, clients experienced the dilemma they had to deal with in that case as relatively easy. It was for this reason that two women who were informed about the detection of trisomy 18 in their fetuses spontaneously indicated that they preferred this testing result over trisomy 21:

After I'd heard it from doctor X I looked it up on the Internet, which showed all the aberrations of these children. And I sort of appreciated to read that. Because that made it absolutely clear that it's really not okay. That you don't need to - I mean you don't need to decide. It just isn't okay. [Int.: How do you mean, you don't need to decide?] Well, unless of course you're against abortion, but it's not... You know, I can imagine that in case of trisomy 21 you think, well, that you'll have the option... because such a child has a chance to survive. But these children obviously don't have a chance to survive. (Mrs. 4 after being tested)
Now I think it's "a good result", because I know nature will be doing it anyway. And I'm going tomorrow for... to stop the pregnancy, but I still think, it doesn't matter if I'm doing this or nature will be doing it in two or three months. (...) If I'd for instance be told, it's a Down's child, then I would find it much harder to decide, because how far do you go? What's the point where you say, this is where I decide, and this is where I don't know, or where I can't do it (...) But now it's like, the doctor told us it has very little chance whatsoever to be born alive, so well (...) And that's why I think – and this may sound weird – but this is the best news in the bad scenario we were imagining. (Mrs. 3 after being tested)

These experiences match with the providers' opinions, who also believe that in the decision about severe results less dilemmas are involved. In this respect, Down's syndrome

is in their view positioned between the two above described extremes of the 'black' results at one end, and the 'grey' results at the other end, because most dilemmas are involved there:

*There's Down on one side, and the other anomalies, which are incompatible with life, are sort of unique in a way, because, well, it's sort of predestined, they can't influence it. In case of Down's you can decide whether you'll accept it or not, but not in these cases because uhm, there's nothing to it. [Int: But isn't there still the decision to terminate or continue the pregnancy?] Yes, there is, but as far as the end result goes it doesn't make much difference. For those people it's a lost chance anyway. (...)
I always tell them, there are three types of results. The most frequent one is Down's. Then we have trisomy 13, 18 and the triploidies, which are less frequent; these are black. And then we have the results which are more awkward because the clinical picture can vary more - Turner's and Klinefelter's. And between these two opposites there's Down's which is serious enough uhm, yet compatible with life. (gynaecologist 2)*

The difference between more and less problematic results seems to be related to the degree to which the communication of the testing results, including the interpretation thereof, and the following decision are intertwined. Providers seemed to be aware of the idea that their communication of results and the decision based on that result are often interwoven:

*Yes, the patient has to decide, but of course, what you think and how you counsel them is also very important. (gynaecologist 2)
I don't feel responsible for the decision they make, but I'm also, uhm, I know that this decision is related to the way I 'm communicating this information – and you can act quite directive in that matter, and sometimes I think, well, it's just too awful to think what might happen. (clinical geneticist 1)*

Clients experience this interwoven character even more strongly. Being asked what a testing result means for them, they report that this depends for a great deal on what the providers would actually tell them about the result:

*And about the 'not okay' part, well, then I will go on asking, what exactly isn't okay? And then they will tell me, I suppose. (Mrs. 11 after being tested)
I think that if the result is okay, or not okay, that's the moment to ask what it means. (Mrs. 5 after being tested)
Well, any kind of, meaningful kind of... , well, of course the geneticists have to tell what is meaningful or not, but any chromosome abnormality that evokes discussion, is negative in my opinion, or in any case, belongs to the 'not okay' side. (Mrs. 2 after being tested)
There are some clear and some less clear results. And somewhere in between there's a moment of choice in which they will hopefully advise you well. (Mr. 2 after his wife being tested)*

However, while this kind of advice or direction regarding the interpretation of a result, or the decision following a result, may be somehow – implicitly – present in case of the ‘black’ results, these kinds of direction are less apparent in cases where the results are of mild or unknown clinical significance. Also for this reason the decision is experienced as a bigger dilemma in these cases.

IV. Clients' responsibility

Despite the providers being aware of the fact that the interpretation of the testing results may somehow be interwoven with the communication of the result and as such may be influencing the following decision, they still believe that in the end the clients are responsible for the decision to be made. The most important reason for this is that they consider the decision about termination or termination of pregnancy the clients' own personal affair.

Besides, I don't know the background of these people, I mean, which are important values for them and what else is important to them in life? At the beginning of my career I sometimes thought, it's so amazing what people decide (...) And in the beginning that bothered me, I thought like, how I put it makes a difference, but one day I left that perspective, like, it doesn't matter, it's part of these people, it has got to do with their frame of reference, with their experience of life, what they decide. (clinical geneticist 1)

Another reason why providers do not wish to interfere with the clients' decision about termination of pregnancy is the comparison they make with ‘social abortions’. Because in case of a ‘social abortion’ the client is also completely free to decide for herself about termination of pregnancy, some providers wonder why this should be any different in case of prenatal diagnosis:

We are also dealing with social abortions, and that's the other side of the coin (...) If somebody decides to terminate the pregnancy due to circumstances, that's an accepted situation, so that's why I think, why wouldn't it be an accepted situation to terminate the pregnancy in case of Turner's, uhm, a woman, a girl that will never be able to have children, or a Klinefelter's, with similar problems? I don't know if I would do this myself, but I don't think that's the gold standard to measure this. (gynaecologist 1)

Basically, the providers believe that ultimately, the decision about termination or continuation of pregnancy is the clients' responsibility:

As a matter of fact, when I put it simply, then the situation is such that when I've told my story and the message is out there, then their responsibility starts to act on this. Actually that's it. Of course it's not like, that I tell my story in a visit, and then say, 'well bye, do with it whatever you like', but yes the mechanism does actually

work like this. (clinical geneticist 1)

In the end you don't do anything more than shoving the problem onto the patient. You try to describe it the best you can, you explain the range of possibilities and then this man and woman may decide for themselves. That's what's happening after all. (gynaecologist 4)

The perception of the clients' responsibility regarding the decision about continuation or termination of pregnancy, is strongly influenced by the former mentioned predetermined context of choice. Because of this context, information about an abnormal testing result, communicated in the setting of prenatal diagnosis, seems to imply some responsibility, accountability or even blame for the future child's suffering, related to the detected chromosome aberration, if the pregnancy were continued. The aspect of accountability for the future child's suffering is most relevant in case of the problematic testing results of mild or unknown clinical significance, when continuation of pregnancy is considered a likely option:

Well, in case of Turner's or Klinefelter it's a very difficult decision indeed for parents to take, because all parents naturally wish for a healthy child, and uhm, well, are you willing to accept a child with Turner's or Klinefelter's syndrome, uhm, that's a very brave decision, because you know beforehand there will be all kinds of dysfunctional behaviours and maladjustments. (gynaecologist 2)
Such a child, a Turner's or Klinefelter's, where you can expect fertility problems, I always discuss this with these clients, but it depends on them, it's their responsibility to give birth to these children, to say like, okay, I think I'll be able to handle this and will be able in accounting for this to them. (clinical geneticist 1)

The clients also talked about the accountability for the future child's suffering in relation to the way they perceived their responsibility regarding their decision to continue or terminate the pregnancy. One client compared the choice not to terminate a pregnancy while knowing about the fetus' possible defects, with the situation where the fetus would be born with the same defects, but without her knowing this beforehand. The former situation would be the most heavy burden in her eyes, because in this situation the decision *not* to terminate the pregnancy would in her view equate to opting for having a child with some defects, for which therefore one might be held responsible:

However, that's a quite severe choice I think, if you opt for this. You see, if you don't know it and then it comes, well, then it doesn't matter, if the child is born you'll love it anyway, whether it's okay or not. But if you do know, well, then I don't think it's very sensible to opt for that, in that way. (Mrs. 13 after being tested)

The line of thought where the possible decision to continue the pregnancy automatically leads to the clients' feeling of responsibility and even guilt for the future child's suffering was also expressed by the Turkish couple in the case presented at the beginning

of this paper, who heard about the Klinefelter result. The son, who acted as interpreter in the interview, expressed his mother's feelings regarding this matter in the following way:

Again and again you will be faced with it of course, every time you play with that boy, when you look at him, you know in the back of your head that he won't have children, and you still have to tell him, and maybe he'll blame you for that, maybe it's someone who really likes children, and then, you know, he might put the blame on my mother. (son of Mrs. 2, after having received an abnormal testing result)

Discussion

This qualitative study of the providers' and clients' experiences in daily practice adds to the little knowledge we have about problematic findings in prenatal diagnosis. Such testing results first of all exist because providers wish to avoid underreporting. They therefore tend to inform the clients about all detected chromosome abnormalities, including the ones where they have doubts about the clinical significance. However, this may not be clear to clients, who might interpret any testing result told to them as significant, due to the simple fact that it is communicated. Consequently, in the context of prenatal diagnosis, which only provides a choice of either continuing or terminating the pregnancy, the communication of results of minor clinical significance will still lead to a process of decision making regarding those two choices. Additionally, compared to the more common chromosome abnormalities of severe and/or known clinical significance, decision making will be perceived as a bigger dilemma. Because ultimately, this decision is considered the clients' responsibility, the decision burden for clients is relatively large in these cases.

A limitation of our study might be that not all prenatal diagnosis providers recognize the emotional intensity of the clients' opinions presented here. This may be because, for reasons of clarity, we included text fragments which illustrated the problems of prenatal diagnosis in the most pronounced way, like in the case of the Turkish people. Because we interviewed the clients who had received a negative testing result just after they had heard the bad news, their reports may reflect a rather intense emotional state, which may have diminished in the following days and weeks. Still, as long as these statements were informative in relation to our research question, we decided to report these because they contributed to a high catalytic validity, i.e. the potential to influence practice and research.¹¹ In other words, we considered these results useful, because of their significance for the discussion about the question of whether targeted testing would be the obvious way to deal with problematic findings. Moreover, although we did not primarily aim for a high external validity of this study, several relevant themes found in our research were also presented in other recent papers on the providers' opinions about prenatal screening.^{12;13}

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Targeted testing the evident solution?

In various ways, targeted testing can provide a solution for the above-mentioned, interrelated problems. To fulfil this promise, targeted testing would need to exclude the results about which providers doubt whether they are clinically significant or not. Besides, it would need to exclude the results that are not meaningful in the context of prenatal diagnosis, i.e. which would not legitimately lead to the choice of continuing or terminating the pregnancy. Finally, it would need to exclude the results for which the dilemmas for the client are considered too large.

Thus, a scenario of targeted testing aimed for instance at the detection of trisomy 21, 18 and 13 could be an evident way to deal with problematic findings, simply because most problematic findings would be excluded from prenatal diagnosis. Although this kind of targeted testing scenario might still lead to some findings of mild or unknown clinical significance, e.g. mosaics trisomy 21, 18 and 13, far less problematic findings would be detected than in the conventional, full karyotyping scenario.

However, one might wonder, is the radical solution of targeted testing, which excludes most problematic results beforehand, really necessary? Wouldn't it be possible to find some less drastic solution to deal with problematic findings? For instance, when targeted testing would not be chosen, to accompany the communication of testing results by an explicit explanation about the context in which the reported information should be interpreted as meaningful.¹⁴ In case of the detection of for instance the SCAs, the clients could be explicitly told that this information is not significant for the decision about termination of pregnancy, but only for the future child's medical record. However, individual providers would then have to decide, and tell the clients, in which specific cases they do not consider the testing result significant for the decision about termination of pregnancy. Since this would require a kind of behaviour that diametrically opposes the widely accepted practice of non-directive counseling in prenatal diagnosis, the feasibility of this solution may be doubted. Another alternative solution in the current way of testing might be to aim for a more complete counseling to prepare clients for dilemmas that may be too big for them to handle. However, since current pre test counseling does often not enclose complete information about the range of chromosome abnormalities that can be detected^{15;16}, the aim of pre test counseling enclosing information about the dilemmas of all possible testing results might be hard to achieve.

In conclusion, compared to alternative solutions applied within the current scenario of testing, the radical solution of targeted testing seems indeed the most evident way of dealing with problematic findings in prenatal diagnosis, simply because it would exclude most problematic findings beforehand. Therefore, the decision burden for clients faced with results of mild or unknown clinical significance, would be substantially diminished in a scenario of targeted testing.

An important hindrance against implementation of targeted testing is the fact that this new way of testing is inextricably bound up with the necessity to answer the question of which testing results should be excluded from prenatal diagnosis. It is yet unclear if providers would be willing to make such an explicit statement. Previous experiences have

shown “how deep the disagreement can be about the wisdom of ‘drawing lines’ in this context”.^{13:17}

Because of the moral character of this question, it might be considered most natural to let the clients decide about the content of targeted testing, as was the suggestion in one of our focus groups, and in some literature as well.^{18:19} Although it is still unclear if individual clients or clients’ organizations would have to decide this, it is also doubted if this would be a change for the better. After all, in this approach clients would be given even more responsibility than in the current practice, where the clients’ responsibility is one of the aspects contributing to the high decision burden in case of the problematic results.

However, instead of passing the moral question of which testing results should be excluded from prenatal diagnosis, on to their clients, providers might also accept it as a challenge to answer this difficult question themselves. As such, the option of targeted testing could be the perfect practical excuse to discuss some fundamental, yet unanswered, questions in prenatal diagnosis. In the current practice of prenatal diagnosis, important ethical issues are mainly dealt with in the individual provider-client relationship. Because professional guidelines about how to deal with problematic findings are often lacking, targeted testing might cause a major change in this respect. When providers would be prepared to help answering the morally laden question of which testing results should be excluded from prenatal diagnosis, targeted testing would indeed be the evident way to deal with problematic findings in prenatal diagnosis. Moreover, as the implementation of targeted testing would necessarily be accompanied by the drawing up of professional guidelines, this new scenario might lead to a substantial improvement in the quality of the practice of prenatal diagnosis.

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Chapter 6

Targeted testing or full karyotyping in prenatal diagnosis? A focus group study.

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Submitted for publication

6

Abstract

Objective

The fact that some prenatal testing results would be missed in targeted testing can be perceived as both an advantage and disadvantage. This paper examines these and other arguments relevant for the discussion about targeted testing.

Methods

Three focus groups were held with Dutch professionals discussing the problems of unexpected findings in prenatal diagnosis, and future scenarios of prenatal testing. Transcripts of these discussions were analyzed and categorized in relevant themes related to arguments for and against targeted testing.

Results

Arguments about targeted testing were mainly related to different ideas about the objective of prenatal diagnosis. Targeted testing was supported when prenatal diagnosis was seen as connected with a specific indication. It was rejected when the objective was taken to be to detect as many abnormalities as possible.

Conclusion

The decisive issue in the discussion about targeted testing, both in our study and in the literature, is the objective of prenatal diagnosis. Once this objective includes the detection of abnormalities other than the one(s) sought because of the referral indication, the discussion needs to address the ethical question of which information should and should not be provided to parents, given the fact they have to decide about termination or continuation of pregnancy.

Introduction

Should rapid aneuploidy testing replace traditional karyotyping in prenatal diagnosis? This question was raised by Mann et al in 2001, and the discussion recently culminated in Leung's comment on Caine et al. in the *Lancet*.^{1,3} The discussion on targeted testing started after the clinical implementation of interphase fluorescence in situ hybridisation (I-FISH) in prenatal diagnosis^{4,7}, but has recently intensified with the introduction of quantitative fluorescence polymerase chain reaction (QF-PCR)⁸, mainly because QF-PCR is amenable to automation, so ideal for high throughput.³ At present, it is agreed upon that the scenario of targeted testing would be particularly applicable for women participating in screening programmes for Down's syndrome, if only because such a scenario would be more cost-effective than full karyotyping.³

Apart from the advantages of cost-effectiveness and rapidity, the discussion focuses on the fact that some of the results detected by full karyotyping would be missed in a scenario of targeted testing. Leung agrees with Caine et al, who report that about 1% of all invasive prenatal samples will have an undetected chromosomal abnormality and a third of these might have a significant risk of serious phenotypic consequences if QF-PCR is used alone. However, contrary to Caine et al, Leung still considers targeted testing a reasonable option.^{2,3}

Leung and others support the idea that targeted testing would be a way to dispose of the problems of some prenatal testing results.^{1,6,9,10} Problematic results of unknown and mild clinical significance, such as translocations, marker chromosomes, mosaics, and sex chromosome anomalies, are considered to put parents before a difficult choice.^{6,11} Targeted testing could be a solution for these problems because it would alleviate counseling difficulties¹⁰, and reduce unnecessary anxiety and potentially unnecessary terminations of pregnancy.⁶

However, in their 2004 review, Nicolini et al refer to the opposite view when they state that "there is a general consensus among cytogeneticists and physicians that the extra knowledge provided by full karyotype is beneficial", and that "it is generally thought that it would be gross misconduct not to pursue the opportunity to make such diagnoses".¹²

To encourage discussion, Leung et al call for an ethical study on the pros and cons of targeted testing¹¹. As a first step, all relevant "pro and con" arguments need to be listed. As a part of a larger study on unexpected findings in prenatal diagnosis, we have arranged a focus group setting where professionals could freely talk about their opinions before or against targeted testing. After comparing the arguments mentioned by the focus group participants with arguments from the literature, we will suggest which subjects should at least be included in the discussion about targeted testing in prenatal diagnosis.

Methods

Data collection

Focus group discussions took place in May 2003 in the Academic Medical Center in Amsterdam. Participants were providers from all eight specialized Clinical Genetics Departments in the Netherlands, and a few other Dutch professionals specialized in the field of prenatal diagnosis: two cytogeneticists, three clinical geneticists, three gynaecologists, one ultrasound specialist, one medical ethicist, one general practitioner, three midwives, four social workers, three health politicians and one health researcher (n=22). Discussions took place in two groups of seven and one group of eight participants, each group moderated by one of the three authors. Discussions in these three groups were followed by a plenary discussion about the same questions.

In the focus groups, professionals were asked for their opinion about the preferred future scenario for prenatal diagnosis, i.e. global or targeted.

Sub group discussions as well as the plenary session were audio-taped onto mini disc and transcribed verbatim. Additionally, an executive report of the plenary session was written and sent to all participants, who have all agreed on the content of the report.

Data analysis

Focus group verbatims and the executive report were imported in MAXqda, a software programme to assist in analysing qualitative data.¹³ Analysis was done through a cross-sectional code and retrieve method.¹⁴ In a framework approach, the first phase of coding started deductively from three main codes (general features of prenatal diagnosis; specific features of unexpected findings; discussion about targeted testing), and continued more inductively to add sub codes.¹⁵ Initially, the material was searched for arguments for and against targeted testing. In successive coding rounds, the selected material was analysed in a crystallisation style¹⁶, to discern different themes to which these arguments were related. Finally, a matrix was created to organise all the different themes in arguments for and against targeted testing.¹⁷

The data presented in the indirect speech originate from the executive report, and the data presented as citations are extracted from the verbatims. The cited participants are referred to in abbreviations (CCG=Clinical Cytogeneticist; CG=Clinical Geneticist; Eth=Ethicist; GP=General Practitioner; Gyn=Gynaecologist; MW=Midwife; SW=Social Worker). The numbers 1, 2 and 3 refer to the focus group in which they participated.

Findings

The arguments for and against targeted testing mentioned by the focus group participants could be distinguished into four different themes of an increasingly fundamental nature.

I. Providers

Some arguments against targeted testing were related to the attitude and role of the providers. One of the clinical cytogeneticists believed that it would take a huge effort to change the professionals' attitude, because professionals always focus on what they would miss, and especially the more experienced ones would still want to include everything. A consequence of targeted testing was mentioned which would be negative for the providers:

"But there is of course also another problem in switching to PCR, and that is that our colleagues, the cytogeneticists, would then be unemployed." (Gyn1)

II. Technical features

Several technical features of prenatal diagnosis were referred to. A participant presented the following argument in favour of targeted testing:

"I'm a cytogeneticist, so I know exactly what I would miss with targeted testing. But I also know I don't want to know a lot of these things, because it's so much trouble once you've detected these. Now, take mosaicism: how many of these are really clinically relevant?! Only a few. (...) I think we create more mosaics in the lab than actually exist..." (CCG1).

Other technical aspects were used as an argument against targeted testing, for instance that the technique of prenatal diagnosis would make the idea to exclude all problematic findings unrealistic:

"It's inevitable that every technique involves its own unclarity, so then you also have to tell your patients: 'Well, we've found something, but we don't exactly know what it means....'" (CCG2)

III. Miscarriage risk

The fact that prenatal diagnosis always involves a miscarriage risk was consistently used as an argument against targeted testing.

"The rapid tests don't answer all our questions, so they deviate from the gold standard in this respect. In my opinion this would be hard to sell, because we would offer less detection for the same price of risk." (CG3)

Apart from postulating a moral duty to deliver maximum information because of the miscarriage risk, it was noticed that insurance companies use this argument for efficiency reasons as well, when a patient undergoing prenatal DNA diagnostics is automatically eligible for chromosome analysis.

IV. Objective of prenatal diagnosis

Finally, arguments about targeted testing were related to different ideas about the objective of prenatal diagnosis. Targeted testing was seen as a reasonable option in case prenatal diagnosis was conceived as a medical diagnosis following a specific indication:

“This is what we do in most health care situations: a specific suspicion or expectation leads to a specific diagnosis. So then it’s not a matter of detecting every possible aberration – to put it boldly – but it’s a matter of delivering specific answers to people who have come up with specific questions.” (Eth3)

In this context, the need for differentiation, depending on the kind of indication, was also discussed:

“Patients who are referred after the nuchal translucency measurement might be offered an extensive range of analyses, because in this case much more can be found than with a patient referred after a second trimester triple test, which only focuses on Down’s syndrome. So you might use amnio-PCR after an aberrant triple test result, but use a chip or micro-array after a thickened nuchal translucency.” (Gyn2)

However, the practical consequences of this differentiation were not exactly clear:

“So this would mean a better selection of the population to whom we offer it, and then continue with a global examination.” (CCG2) “Okay, but then you should also consider that this global examination will become only more global in the future...” (GP2)

As an argument against targeted testing, it was suggested that the objective of prenatal diagnosis is to detect as many abnormalities as possible:

“Suppose, of all these pregnancies we are now examining, of which we have the material, and of which you know beforehand that, of all these 12,000 patients a year we are seeing, twelve [nb: corrected by another participant as three] of these have CF, and you are already examining this material: don’t you think we should check this as well?” (CG2).

Others considered the detection of as many aberrations as possible not a purpose in itself, but as necessary for providing parents with all opportunities to decide about their pregnancy:

“It is not eugenics in the sense that we like to breed out all abnormalities. (...) We like to offer parents the option of choice because we saw the other situation where patients didn’t have a choice too often, and we’ve witnessed the impact this had on people’s lives; that’s what we’d like to prevent...” (Gyn3)

Finally, some participants were against targeted testing because prenatal diagnosis should meet the parents' expectations, which were considered to be global:

"They come to check if everything's okay. For them, prenatal diagnosis is just a natural part of the check up routine; it's not about trying to get specific answers"
(MW-Re3)

However, reacting on the remark that most parents "just want to have a healthy child" someone said:

"But you shouldn't support them in the illusion this is possible!" (Gyn2)

Additionally, some participants suggested a specific variant of targeted testing in which the individual patient would be offered a 'menu' of testing possibilities:

"But why don't we give parents the choice and ask them: what do you prefer: the whole picture or do you want us to focus on Down's only?" (SW1).

The practical objection to this option was that providers such as midwives and general practitioners are not equipped for the high quality counseling required in this scenario. An ethical objection was made as well:

"But even for professionals it's such a hard choice what to test and what not to, so would it be ethically justified to confront people – who are no experts in this matter – with such dilemmas and choices that could never be well informed?"
(MW1)

Discussion

The providers' preference, found in our study, to keep things in prenatal diagnosis as they are, is also reflected in the literature.^{3,12} Additionally, the assumed unwillingness of patients to give up the diagnostic completeness of a full karyotype is mentioned.¹⁸ However, recent research showed that the majority of both providers and patients would be willing to consider molecular testing only.¹⁹

The miscarriage risk, as an intrinsic characteristic of prenatal diagnosis, is frequently referred to in the literature as argument against targeted testing as well.^{6,11,18} This argument may lose its relevance in the future, when examination of fetal DNA isolated from maternal blood would become a realistic opportunity in prenatal diagnosis.²⁰

The objective of prenatal diagnosis can vary from detecting only those abnormalities which are specifically searched for because of the indication, to detecting as many abnormalities as possible. The first possibility is supported by Nicolini et al, who typify the other extreme as a 'holistic' and outdated view of prenatal diagnosis.¹² The variant

suggested in the focus groups to differentiate testing scenarios according to indication, e.g. to search for Down's syndrome only if the increased risk is established in the regular maternal serum screening, and to extend this search to the full karyotype if the increased risk is based on nuchal translucency measurement, is suggested in the literature as well.^{11;21}

However, if such a differentiation procedure were applied, the choice of the screening instrument would become increasingly important. As such, this raises the question of whether the actual objective of screening programmes for Down's syndrome is to detect Down's syndrome, or to select women with increased risk for Down's syndrome, but then still try to detect as many abnormalities as possible. It is revealing in this respect that the assumption that screening programmes for Down's syndrome are only concerned with the prenatal detection of Down's syndrome, was openly criticized.³

The other possible objective – detecting as many abnormalities as possible, as an objective in itself – seems to be supported by Caine et al, who oppose targeted testing because it would result in a substantial number of live born children with hitherto preventable handicaps³. Still, following the remark of one of the participants that global testing will only get more global in the future, using microarray or multiplex-ligation-dependent probe amplification (MLPA)^{22;23}, it might also be questioned why full karyotyping would be the preferred technique anyway.^{5;11;12}

Some of our respondents argued that parents should have all possible opportunities to decide about continuation or termination of pregnancy, and that targeted testing is therefore not a wise option. On the other hand, the fact that prenatal diagnosis involves the parents' decision about termination or continuation of pregnancy is exactly the reason why some authors wish that prenatal diagnosis would not provide all possible testing results, because in case of some problematic findings this decision is considered too difficult.^{1;9;10;24}

All focus group participants considered the parents' expectations to be global, while the literature states that most parents are primarily concerned about Down's syndrome and are unaware of the possibility of other chromosome abnormalities.⁶ We have indications from our interviews that both statements can be true, i.e. that parents expect a global reassurance while at the same time they have Down's syndrome in mind as the particular chromosome abnormality that is being looked for. In any case, the role of pre test counseling will only increase in importance when targeted testing would be applied.⁷

The option suggested in the focus groups to give patients a more central role in deciding which tests are performed and which aren't, can also be found in the literature.^{12;18} However, both practical and ethical objections were raised by the focus group participants to the idea of offering individual patients a 'menu' of testing possibilities. Moreover, because women participating in screening programmes are approached systematically as a target group, which means they had no individual reason to seek assistance, an individualised choice would not match with the basic assumptions of screening.²⁵

Our study has the limitation that focus group discussions were held in only one country, with a limited, albeit varied number of professionals. Still, we believe that this study adds to our understanding of the discussion about targeted testing.

We conclude that the most decisive issue in this discussion is the objective of prenatal diagnosis. Regarding screening programmes for Down's syndrome it needs to be decided whether the objective of these programmes is to detect Down's syndrome only, or whether this objective is determined only after a specific high risk - depending on the kind of screening instrument used - is established. If the objective is to detect more than Down's syndrome, the discussion about targeted testing naturally involves the question of which information should be provided to parents - and which tests should consequently be performed. Because this question requires distinguishing between information that should and should not serve as input for the parents' decision about termination of pregnancy, this is an ethical issue. Therefore, the agenda for the discussion about targeted testing should first and foremost address the question, 'What is the objective of prenatal diagnosis?'

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Chapter 7

General discussion



This research project provided insight into the category of ‘grey testing results’ of prenatal diagnosis.

We showed that the usual term ‘unexpected findings’ is not the most appropriate way of “lumping” grey findings together, as unexpectedness is not the main characteristic of this category of testing results. Instead, unexpected findings are actually problematic findings, i.e. testing results of mild or unclear clinical significance leading to counseling problems and major dilemmas for the clients. At the same time, we have argued that problematic findings can only be distinguished *gradually* from standard abnormal testing results.

From the way providers deal with grey testing results before they communicate these to their clients, we have learnt that providers perceive a prenatal testing result not as some neutral data, but as information they themselves consider relevant for the parents’ decision about termination or continuation of pregnancy. Our observations therefore showed that the technical work of producing a result (usually attributed to the providers) and the moral decisionmaking about continuation or termination of pregnancy (usually attributed to the client) are sometimes more intermingled than is generally assumed. In the case of grey results appearing as indefinite results needing further clarification, providers sometimes include their clients in the decision about how to proceed with the testing process. At the same time, clients need to start their moral decisionmaking while the testing result is not yet definitive. As such, the clients’ moral decision-making may get intertwined with the technical aspects of the testing process, which may not be the most ideal application of shared decision-making.

Our research also led to a more profound understanding of the potential impact of targeted testing. Apart from delivering testing results more quickly, targeted testing could also be a way of restricting the range of chromosome anomalies detected in prenatal diagnosis. As such, it might be an alternative way of dealing with grey, or problematic, findings, because in targeted testing these problematic findings would not be detected. However, our analysis of the recent discussions about the pros and cons of targeted testing illustrates that the opposite opinions about targeted testing are inextricably bound up with conflicting opinions about the target of testing, i.e. the goal to be achieved in prenatal diagnosis. Targeted testing is definitely rejected when the objective of prenatal diagnosis is considered to be to detect as many chromosome abnormalities as possible.

Although targeted testing may still lead to some problematic results, we have shown that targeted testing could exclude most problematic results from prenatal diagnosis. Compared to other solutions applied within the conventional testing strategy, it would therefore relieve the decision burden for clients faced with a problematic finding the most. However, when targeted testing is implemented, the difficult moral question of which testing results should be included and excluded from prenatal diagnosis remains to be answered. It also remains to be determined who should be responsible for answering this moral question: clients, providers, or other parties, such as policy makers?

Who decides about the target?

The question of who should decide about which testing results should be included and excluded from prenatal diagnosis was introduced as a quite open question in Chapter 2. In the following chapters several elements were presented that contribute to the answer of this question.

First of all we urged caution about the apparently natural inclination to give individual clients a more central role in deciding about the content of the target - a tendency we met in the literature¹⁻³ as well as in our own empirical research. We presented several objections to the viewpoint that individual clients themselves should decide which testing results should be included in prenatal diagnosis. In Chapter 4 we warned of a situation where clients need to make decisions in an area where they are not necessarily the experts. We pointed out in Chapter 5 that, if the main reason for the implementation of targeted testing is to diminish the clients' decision burden, a targeted testing scenario where the clients' responsibility would increase, can not be considered an improvement. In Chapter 6 we cited the practical and ethical objections mentioned by our research participants to offer individual patients a 'menu' of testing possibilities. These participants seriously doubted that midwives and GPs are equipped for the high quality pre test counseling required in a scenario where clients are given such a central decision role. Besides, they considered it unethical to confront clients with a question that most providers considered too difficult to answer themselves. Also, we argued that giving women participating in screening programmes for Down's syndrome an individualised choice about what to test, would not match with the basic assumptions of screening.

Secondly, we argued in Chapter 3 that it is part of the providers' professional responsibility to participate in the discussion about which tests should and should not be offered, as this would correspond with our observations of the providers' involvement in daily practice, where the construction of testing results sometimes holds a moral dimension. Additionally, we suggested in Chapter 5 that providers, instead of passing these moral decisions on to their clients, could accept it as a challenge to answer the question of which testing results should be included in prenatal diagnosis themselves.

So, we do not support the seemingly self-evident option of giving individual clients of prenatal diagnosis *full* responsibility regarding the content of the target. Instead, providers should at least feel responsible for this matter in some degree as well. Whereas in conventional testing problematic findings are dealt with in each individual provider-client relationship, targeted testing deals with these same problematic findings much earlier, i.e. *before* these results even become available. Therefore, in a scenario of targeted testing, dealing with problematic findings could be replaced from the individual level to the organizational level. Preferably, both clients' and providers' organizations would be involved in answering the question of which testing results should be included in prenatal diagnosis. Other parties could participate in this decision process as well. After all, the question of which testing results should be included in prenatal diagnosis touches upon the question of what should be the goal of prenatal diagnosis and may therefore concern other social parties as well. However, since clients' and providers' organizations are

composed rather heterogeneously, it might not be easy to define how these organizations would be represented best. In case of the clients' organizations it might for instance be doubted if the (national umbrella body of) genetic support groups that are usually asked to advise in these matters actually represent the average woman participating in the screening programmes for Down's syndrome.

Reflections on the study

Obviously, this study encompassed some subjective elements. As in any qualitative study, human qualities like listening, observing, empathic understanding etc were purposely deployed by the researcher, aiming for a better understanding of the object of research. Still, this does not mean this study can be disposed of as a subjective undertaking. An appropriate way of assessing the scientific quality of qualitative research is to evaluate whether the research succeeded in doing justice to the object of research on the one hand, and to avoid the distortion of it on the other.^{4,5} Although several alternative concepts are suggested to specifically evaluate qualitative research, the common terms "reliability" and "validity" can be perfectly helpful for this purpose.⁶

Throughout the successive phases of this research we tried to conform to the well acknowledged quality criteria for scientific qualitative research.⁷ The use of several methods of data collection, as a way of triangulation⁸⁻¹⁰, contributed to the internal reliability of this study, as did several forms of member's check, described in the Chapters 3 and 4.

The external validity of this study was discussed in Chapter 5. In the following section we will focus on the internal validity, which will include the question regarding external reliability, of whether a replication of our study would lead to similar findings. Concerning the internal validity, the relevant question is whether you were investigating what you claimed to have been investigating. The researcher herself is a primary source of distortion, as in qualitative research the researcher is her own research instrument. Hence, the critical reader may, correctly, ask, 'What were the researcher's motives, background, perspectives, and preliminary hypotheses? And how have all these aspects influenced this research?' According to the quality instrument of reflexivity^{10,11}, the following will elucidate some relevant aspects of my role as researcher.

Science or prejudice?

I did not enter this research field without any theoretical ideas or opinions about the topic of research. For many years, I had been interested in the impact of medical technology on individual decision-making, and have written for instance about infertility and assisted reproductive technologies. Overall, I was fascinated by the idea that female clients, confronted with modern technology encompassing the need to take reproductive decisions, were often given the role of 'moral pioneers'¹². Personally I doubted whether personal feelings of discomfort, expressed by individual women who felt uneasy about having to make drastic decisions about for example preventive mastectomy in case of

hereditary breast cancer, could be captured in the conceptual framework used in psychosocial counseling.¹³ With regard to the field of prenatal diagnosis, I agreed with Berkel and Van der Weele, who suggested that a psychosocial approach does not necessarily touch upon moral questions, or may define them as emotional issues, which is at least partly beside the point.¹⁴ Moreover, I endorsed the philosophical viewpoint that the general significance attributed to the concept of individual autonomy does not necessarily represent respect for the individual client, because this significance could also *contribute* to the systematic negligence of the feelings, dilemmas and doubts that individuals are facing.^{15;16}

So I started this research in prenatal diagnosis being somewhat concerned about individual clients needing to bear an unfairly high (moral) responsibility, and I fully subscribed to Salmon and Young's recent call, who suggested that, "The latent research challenge is to look beyond choice and information as ends in themselves, to ask what the functions of being offered each might be for the patient."¹⁷

The sceptical reader might conclude, this is quite a potential source of distortion. However, since my theoretical drive for this research project was acknowledged from the outset, this drive could be well monitored, by myself, as well as my supervisors, to see if it would indeed distort the data collection or analysis in any way. Since I was clearly influenced by the theoretical inspiration described above, our main worry was of course that, as a researcher, I would be too eager to find and interpret data that would only confirm my concerns regarding the client's responsibility, while proper attention for the providers' perspective was lacking. Evidently, the fieldwork study design already prevented an extremely distorted view of the researcher. After all, which professional researcher would wish to finally come up with a report where only one side of the coin was represented, if it were only out of politeness for *all* the research subjects that had so courteously welcomed her in their daily practice? However, apart from this common-sense motivation to aim for a representation which *most* research subjects, and not only a few, would recognize as the practice they were involved in, there was of course also the reason of scientific rigour to carefully watch myself in the role of qualitative researcher.

Memos

In the observation and interview periods I made reflexive memos about two to three times a week, depending on the intensity of the observation process. These memos were written and stored in separate documents, apart from the observation protocols, interview transcripts, theoretical and methodical memos.¹⁸ Reading and re-reading these reflexive memos, and occasionally discussing these with my supervisors, contributed to the internal validity of this study. It helped me to monitor whether my experiences in my role as researcher would lead to unnecessary distortions in the object of research. Analysis of these reflexive memos led to the conclusion that, during this research, I was amply enabled to focus on the providers' perspective, in such a way that my own inclination towards the patients' perspective was well counterbalanced. To illustrate this, I will discuss three relevant memos in some detail.

The first two memos considered finding a balance between the role of observer and participant. The first one was written on the very first day of the formal observation period, on 11 July 2001. After a period of some months where I had mainly been observing to learn about the practical and technical aspects of the daily practice, we had agreed in which cases I would be informed about detected chromosome anomalies (the exact procedure is described in Chapter 3). In these cases I would observe the professional meetings related to that specific anomaly. On July 11th I wrote about a situation where a cytogeneticist had asked me to inform the clinical geneticist, whom I was going to see next, about a detail which she had just changed in the patient's file. This request made me well aware of the fact that I would be in a unique position during my observation period, since I would be the only person present at *all* professional meetings. Although I had realized before that as a researcher I would somehow become involved in daily practice, I had intended to make sure that this involvement would not be detrimental to my own focus of observing the setting that I had become part of.¹⁹ I kept monitoring this balance between these two roles throughout the observation period and about a month later I decided to change my strategy a little. After some weeks of observing, I had become intrigued by the way professionals communicated with each other, especially by their regularly checking of all kind of details. I wondered if this detail checking had any special function. Therefore, I decided (and I wrote down this decision in a memo on 16 August 2001) to allow myself a more active role in the information chain, with the intention to try to understand this phenomenon 'from within'. Thus, I purposely chose for a more participatory way of observing, where I could identify more with the professionals I was observing.

These two memos illustrate that I had an eye for the providers' perspective, and that I was well prepared to learn about their drives and motivations throughout the whole project. A third memo illustrates that the shift from the patients' towards the professionals' perspective sometimes even caught me by surprise. On 18 November 2002, almost two years after I had started this project, I wrote the following memo:

In my observation of X's intake, I watched 10 patients, who had all come because of their age. At the ninth patient, while X was doing the ultrasound, which looked good, I thought: 'well, now I'd like to see something special!' Having caught myself in this thought I felt terribly embarrassed. I realized that I was watching with a medical-technical eye myself! Instead of caring for the half naked woman, lying there on the bench, I was only interested in the ultrasound screen, as an abstract image that I had separated from that woman. An image about which I thought, after having seen nine similar images, 'well, let's come up with something special now, I'd like to see something spectacular!' (...) Suddenly I sympathized with the doctors, lab technicians, clinical geneticists and cytogeneticists, who are seeing all these same, normal pictures throughout the whole day, and naturally become sort of excited when they're faced with 'something special'.

Many other reflexive memos showed that the fieldwork offered many opportunities

for me as a researcher to identify with the professionals' point of view. Analysis of all reflexive memos proved that the professionals' perspective was as well represented in this project as the clients' perspective. To conclude, it reassured me in the belief that my theoretical drive had functioned more as an inspiration than as an obstacle for doing solid scientific research.

Added value of this research

The combination of my own theoretical drive and the fieldwork study design facilitating a thorough understanding of daily practice, led to a new perspective on the object of this research. So far, the literature on targeted testing had been dominated by clinicians who are themselves interested parties in the topic concerned. This study, performed from a more distant perspective, brought some more fundamental issues to the fore. Illustrative in this respect is the reaction of a cytogeneticist who said, after having read the first draft of the literature review (presented in its definite form in Chapter 2): "Well, that's interesting, I'm familiar with all the publications included in this review, but yet, your results are kind of refreshing, because you're discussing these papers from a whole different angle."

The most fundamental issue presented in this study is the idea that the discussion about targeted testing inherently bears an ethical component. Calls for an ethical study on the pros and cons of targeted testing²⁰ seem based on the theoretical idea that an ethical discussion only starts with the explicit call for this. In line with this way of thinking, one might also consider it possible to purposively *exclude* moral dilemmas from medical technical studies on prenatal testing.²¹ However, such theoretical ideas reflect an out-moded view on ethics, that considers discussions to be 'ethical' only when clearly recognized ethical or moral concepts are used. Instead, this study reflects a contemporary approach to ethical research, in which we examined all kinds of professional meetings and consultations where one is concerned with the good organisation of daily practice, not only the kind of practices where ethics is explicitly referred to.²² Moreover, with regard to the topic of research – chromosome analysis in prenatal diagnosis – we did not distinguish between the technology of testing itself and the use of it, as both are intertwined.²³ Overall, our study could be well understood as a form of ethical-empirical research, aiming to make the implicit normativeness, imbedded in the (use of) technology, more explicit, as this is supposed to improve the quality of public discussions.²⁴

Most of the previous chapters were focused on, or at least related to, the topic of targeted testing. Through this focus we have shed light on several normative aspects embedded in the daily practice of prenatal diagnosis. In the next section we will explain which implicit normative aspects of prenatal diagnosis will become manifest in the discussion on targeted testing.

Prenatal diagnosis reconsidered

The discussion on targeted testing inevitably includes the discussion on what actually *is* the target, or the goal to be achieved, in prenatal diagnosis. Apparently, considering the recent discussions on targeted testing as described in Chapter 6, there is no clear definition of the goal of prenatal diagnosis available that leads to a straightforward answer to the question, 'Should targeted testing be implemented in prenatal diagnosis or not, and if so, how?'. The definition in Milunsky's globally used handbook is not of much help here: "The fundamental philosophy of prenatal genetic diagnosis is to provide reassurance to couples at risk that they may selectively have unaffected children even if their procreative risk for having defective offspring is unacceptably high."²⁵ This definition seems to be applicable more for prospective parents at high risk for a specific familial condition than for women participating in screening programmes for Down's syndrome. In the changing field of prenatal diagnosis, additional definitions are therefore required. Serving as a pretext, the discussion on targeted testing may contribute to establishing a more accurate definition of the goal of prenatal diagnosis.

The actual discussion on targeted testing could contribute to build such a definition if, for a start, both parties for and against the implementation would be requested to explicitly define their supposed objective of prenatal diagnosis. In the current discussion these definitions are not yet clear. What would the supporters wishing to introduce targeted testing to alleviate counseling difficulties and parental anxiety²⁶, and to avoid the possibility of unnecessary terminations of pregnancy²⁷, believe to be the goal of prenatal diagnosis? From the arguments presented in the literature, it seems that their goal includes the ethical principle of *primum non nocere* (first do no harm). However, an explicit reference to the presumed goal of prenatal diagnosis is not presented. Readers can therefore not be sure if these authors indeed wish to protect their clients from the harm of being faced with dilemmas that are considered too big to handle, or if other arguments are (also) at stake here. Clarity is also lacking on the side of the opponents of targeted testing. What can for example be concluded from the counter-argument that, because women making a decision about undergoing invasive testing, probably factor into their expectation that, after undertaking the risk of amniocentesis, their reward will be 100% diagnostic accuracy?²⁸ And which goal of prenatal diagnosis lies behind the counter-argument that replacement of full karyotyping with rapid testing for trisomies 13, 18 and 21 after a positive screen for Down's syndrome will result in substantial numbers of live born children with hitherto preventable mental or physical disabilities?²⁸ Is the assumed goal here to detect as many chromosome abnormalities as possible for the sake of prevention on the societal level? Probably not, since traditionally in prenatal diagnosis the concern for the individual client is considered more important than the needs of society.²⁵

Next, assuming that targeted testing would be implemented, the discussion on the exact content of the target requires an explicit definition of the goal of prenatal diagnosis as well. How self-evident is it for instance to include trisomy 13 and 18 in the invasive testing

offer for women participating in screening programmes for Down's syndrome? Is severity the main criterion here? If that is the case, then why would only the severe *chromosome* abnormalities be included, and not the severe *genetic* abnormalities? With the rapid development of the molecular diagnostic techniques, it will only be a matter of years before all kinds of genetic diseases can be detected through these new testing procedures. And what about the X and Y chromosomes? Should sex chromosome testing only be applied to pregnancies referred with ultrasound characteristics suggestive of 45,X (Turner's syndrome)?²⁶ Is the criterion of severity applied here as well? The argument used in the literature ("Some obstetricians, clinical geneticists and genetic counsellors are uneasy about testing and reporting the sex chromosome status for all pregnancies."²⁹) may hint in this direction, but it certainly does not give a definite clue about the assumed goal of prenatal diagnosis.

Explicit mention of the goal of prenatal diagnosis is also required in the discussion about whether clients should be given a more central role in deciding which testing results to detect. Would women participating in the screening programmes for Down's syndrome be allowed only to restrict the content of a 'basic' target of e.g. the chromosomes 21, 18, 13, X and Y, or would individual requests to *extend* the target be granted as well? If so, would any individual request be honoured in that case, even when an objectively established increased risk is lacking? Apart from the decision about the content of testing, it has been suggested that clients need to be given a stronger choice about *entering* prenatal screening programmes. In most Western countries, apart from the Netherlands³⁰, routine screening uses an increasing refinement of objective risk estimations based on a combination of age, biochemical and ultrasonographic variables.³¹ However, an alternative approach, challenged by the idea of targeted testing, is that, rather than using objective criteria, clients make estimations themselves about their risk of having or not having an abnormal fetus, and about their personal perception of how relevant this estimation is and how serious the possible unwanted outcome (whether the loss of healthy fetus or the birth of an affected child) is.¹ An alternative approach like this definitely poses the question of which kind of goal of prenatal diagnosis is assumed here?

Accurate definition of prenatal diagnosis required

As explained above, the arguments in current discussion about targeted testing do not explicitly refer to the goal of prenatal diagnosis. Moreover, the absence of an accurate definition of prenatal diagnosis does not improve the quality of the discussion on targeted testing much. Meanwhile, the discussion, reflecting strong differences of opinion, continues.^{32,33} To constructively proceed here, more clarity with regard to the goal of prenatal diagnosis is now required.

For this purpose, the following definition might be taken as a starting point:

Prenatal cytogenetic diagnosis informs pregnant women about the presence or absence of severe chromosome abnormalities in their fetus, to enable them to decide about termination or continuation of pregnancy.

The following elements in this definition would need to be established more precisely:

Pregnant women: Which pregnant women are offered prenatal diagnosis? Who decides about this? Should objective (screening) criteria, established by health professionals, be used for this, or should prenatal diagnosis be offered to any individual pregnant woman requesting this for her own subjective reasons?

Severe: Which exact criteria are used to determine the severity of an abnormality?

Chromosome abnormality: When exactly is a chromosome aberration considered a phenotypical 'abnormality'? Which uncertainties regarding cytogenetic laboratory procedures and regarding the clinical prognosis are considered acceptable in this respect?

Informs (...) to enable them to decide: Is enabling the pregnant women to decide about termination or continuation of pregnancy in case of a detected abnormality, the main intention of informing them? In which cases can prenatal diagnosis also serve as reassurance, or as an opportunity to anticipate a detected abnormality? Or does informing the pregnant women mainly serve the public health goal of prevention?

Resuming, a more precise definition of the goal of prenatal diagnosis should at least be specific about (I) the category of pregnant women the test is meant for, (II) the criteria used to determine which chromosome abnormalities are detected, and (III) the ultimate reason to provide women with the information. In doing so, questions with regard to the content of the target and the role of the clients will naturally be answered.

Depending on different opinions about these three aspects of prenatal diagnosis, several variations of this definition are conceivable.

I. Variations of the first aspect may for instance lead to the following definitions:
Prenatal cytogenetic diagnosis informs

◆ *all pregnant women, OR*

◆ *pregnant women with an objectively established increased risk for Down's syndrome about the presence or absence of trisomy 21 in their fetus to enable them to decide about termination or continuation of pregnancy.*

II. Variations of the second aspect may for instance lead to the following definitions: Prenatal cytogenetic diagnosis informs pregnant women about the presence or absence of

- ◆ *trisomy 21 in their fetus, OR*
- ◆ *any chromosome abnormality in their fetus, OR*
- ◆ *severe chromosome abnormalities in their fetus,*

to enable them to decide about termination or continuation of pregnancy.

III. And finally, variations of the third aspect may for instance lead to the following definitions:

Prenatal cytogenetic diagnosis informs pregnant women about the presence or absence of any possible congenital abnormality in their fetus,

- ◆ *to enable them to decide about termination or continuation of pregnancy, OR*
- ◆ *to enable them to anticipate the detected abnormality, OR*
- ◆ *enabling secondary prevention of live born children with mental or physical disability.*

Evidently, many more variations of the definition of prenatal diagnosis can be made. What is most important to understand here is that the more specific this definition will be, the more constructively the discussion on targeted testing can proceed.

Final conclusion

Apart from the potential practical benefits that the introduction of targeted testing might bring about in prenatal diagnosis – a decrease of problematic findings –, the major impact of targeted testing lies in its requirement of a discussion about the target of testing. To facilitate such a discussion, we recommend that *any* concrete suggestion regarding the implementation of targeted testing (e.g. Which testing results should be included? To whom should targeted testing be offered? What should be the role of individual clients? Etc) explicitly refers to a clear description of the goal to be achieved in prenatal diagnosis. If this is done consistently, the option of targeted testing can be optimally benefited from. Serving as a catalyst, the discussion on targeted testing may then lead to more precise and differentiated definitions of the goal(s) of prenatal diagnosis. Once a more precise definition, or definitions, of the goal of prenatal diagnosis is applied, the appropriate name for the category of unexpected or problematic findings will naturally reveal itself, e.g. ‘unclear results’, or ‘additional results’.

The Netherlands may be the natural country to start such discussions. Our country has a very accurate registration of the practice of prenatal diagnosis, and Dutch providers are well represented in the national Working Party Prenatal Diagnosis and Fetal Therapy. Besides, this research has shown that these providers are highly concerned with, and willing to openly discuss the topic of problematic findings in prenatal diagnosis. We believe these are all ideal conditions for a constructive discussion about the goal of prenatal diagnosis and the advisability of targeted testing.

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Summary

Prenatal diagnosis may result in findings that were not specifically sought. Although providers are more or less familiar with this phenomenon, professional guidelines for dealing with 'unexpected findings' in prenatal diagnosis are lacking. Consequently, individual providers need to decide in each case of an unexpected finding what is the best way to handle this situation. The replacement of this *ad hoc* approach by a more structural strategy of dealing with unexpected findings could lead to an improvement in the quality of prenatal diagnosis practice. This thesis searches for the best way to deal with unexpected findings in prenatal diagnosis.

Chapter 1, The Introduction, describes that this thesis particularly focuses on amniocentesis and chorionic villi sampling performed because of the pregnant woman's increased age or her established high risk in a screening programme for Down's syndrome. It is explained that in about 50% of these cases, prenatal diagnosis provides an *other* chromosome abnormalities than trisomy 21 (leading to Down's syndrome). This chapter also presents a first introduction into the concept of unexpected findings, and mentions the aspects about this category that are still unclear. It is explained that while elucidating these unclaritys has been made part of the research project, these initial unclaritys have led to the use of different terms throughout the thesis, e.g. 'grey findings', 'indefinite findings' and 'problematic findings'.

Furthermore, the importance of new diagnostic techniques in a possible future scenario of 'targeted testing' is explained in this chapter. Prenatal tests applying for instance quantitative fluorescent polymerase chain reaction (QF-PCR) or multiplex-ligation-dependent probe amplification (MLPA) have the option to specifically focus the diagnostic process on the chromosome(s) suspected to be anomalous. In doing so, targeted testing would exclude all anomalies that were not sought from detection and would thus diminish the amount of unexpected findings in prenatal diagnosis. Because of this decrease, targeted testing is strongly advocated as well as opposed to.

Finally, this chapter explains how this research was set up. It started from the providers' question of how unexpected findings should be communicated in the daily practice of prenatal diagnosis. Because questions about communication lead to questioning the very existence of unexpected findings if targeted testing would indeed be introduced, this was rephrased of the broader question of how unexpected findings should be dealt with. An empirical ethical approach was chosen to answer this question, in the form of a case study consisting of qualitative research methods. Observations were made in the

daily practice of prenatal diagnosis. In-depth interviews were held with both providers and clients, and additional focus group discussions were held with providers only.

The **central research question** of this study was:

*How to deal with unexpected findings,
considering the potential role of targeted testing in this respect?*

In order to be able to answer this central research question, the following three **subquestions** were formulated:

1. What exactly *are* unexpected findings?
2. How do providers deal with unexpected testing results before they communicate these to their clients?
3. What might be the impact of targeted testing on the problem of unexpected findings in prenatal diagnosis?

Chapter 2 answers the first subquestion of what exactly are unexpected findings. The literature was systematically searched for publications on unexpected findings in prenatal diagnosis. On the selected articles a qualitative analysis was performed, using the methods of cross-case analysis and within-case analysis. Sixteen articles published between 1979 and 2003 were selected in this literature review. Analysis of these publications led to the classification of four problems of unexpected findings: 1. Unexpected for professionals; 2. Unexpected for clients; 3. Uncertainty; and 4. Other difficult counseling issues.

We conclude in this chapter that currently, the main problems of unexpected finding relate only slightly to their unexpected character. Instead, the main problems of unexpected findings relate to uncertainty and other aspects which create difficult counseling issues. Because these are problems that are only *more* apparent in case of the unexpected findings, unexpected findings can be distinguished only gradually from standard results. In establishing the potential significance of targeted testing for the problem of unexpected findings, it is important to establish the exact content of this category of findings. Because our literature review showed that the two main problems related to unexpected findings – uncertainty and difficult counseling issues – are quite dissimilar, the yet unanswered question is: ‘To which problems exactly would targeted testing be the solution?’ An important conclusion of this chapter is that before targeted testing can be applied, it is necessary to establish exact criteria in order to discern unexpected findings from standard testing results; this is done in Chapter 5.

Chapter 3 concerns the second subquestion of how providers deal with unexpected testing results before they communicate these to their clients. Beside normal (‘white’) and aberrant (‘black’) results, prenatal diagnosis can also lead to chromosome abnormalities of which it is still unclear if these will have phenotypical consequences. These indefinite

('grey') results need to be clarified. Entirely in agreement with the model of non-directive counseling that is applied within prenatal diagnosis, the usual strategy for dealing with grey results implies that the clarification process of such a result is a purely technical matter. This strategy implies that, as the individual client only enters the equation once the definitive result is communicated, it makes no difference *for whom* this technical process is performed. On the other hand it is difficult to deny that prenatal diagnosis is a form of diagnosis, which serves a certain purpose and it takes place within a certain framework, of which the client as a person is intrinsically part.

The research question of this chapter was: 'Is clarifying a grey result a strictly technical process, or is, during that process, the specific client kept in mind as well?' To examine this, observations were performed in the daily practice of the Clinical Genetics Department in the Academic Medical Center, to find out what professionals do to clarify grey results, i.e. to make them black or white.

A remarkable phenomenon was signalled in the observations of grey testing trajectories. In a number of trajectories clarifying the result was not considered the obvious next step in the process. In these cases, not only the patients, but professionals as well, were clearly embarrassed: there was an increase in professional contacts and in mutual consultations; cases were discussed at length at weekly meetings, etc. This embarrassment and the hesitation with respect to clarifying initial findings was not based on technical matters, e.g. because it was unclear which approach to apply. It rather seemed to stem from the question whether the current ambiguity actually *needed* clarification, a question which, in our view, introduced moral considerations into the seemingly amoral, technical phase of prenatal diagnosis.

The detailed descriptions of these trajectories show how professionals, while presently in the phase of constructing a testing result, anticipate the decision to terminate or continue the pregnancy. In testing trajectories in which the question of whether or not to clarify the grey result emerged, clarification of the preliminary findings was therefore related to the decision that was to be taken on the basis of that very result. Thus, these trajectories did not show the absolute non-involvement that defines the standard attitude of professionals concerning the decision about continuation of the pregnancy. In the clarification process of some grey results, the professionals were actually anticipating that "still pending" decision.

Based on our observations, it seems that professionals do not only generally view an aberrant result as information on chromosomes that is representative for the fetal genotype, and as information on chromosome aberrations with clinical consequences, but that they also generally view an aberrant result of prenatal diagnosis as information which is relevant for the decision on continuing or terminating the pregnancy. Whereas the assessments regarding the representativeness and phenotypical consequences of chromosomal information can be considered as purely (medical-)technical matters, the assessment regarding the relevance of chromosomal information for the decision about termination of pregnancy clearly has a moral dimension. Therefore, our observations challenge the general idea of a testing result as a strictly technical matter.

While the model of non-directive counseling is generally applied to prevent any

moral involvement in decisions *based* on the testing result, this chapter shows that moral involvement can also occur in the process of *making* testing results. Based on these observations, this chapter delineates the responsibilities of professionals regarding future scenarios of 'targeted testing' in which 'grey' testing results could be excluded.

As our observations have illustrated, professionals in prenatal diagnosis are definitely morally involved in their own practice. Providers should therefore not use the ideal of nondirectiveness as an argument to hold back from the discussion about which tests should and should not be offered in a scenario of targeted testing. Leaving the answering of this question to their clients would not be a proper interpretation of their professional responsibility, if only because this would not correspond with their observed involvement in the daily practice of prenatal diagnosis.

Chapter 4 also deals with the second subquestion, 'How do providers deal with unexpected testing results before they communicate these to their clients?' The same observation data were used as in Chapter 3. Whereas Chapter 3 discusses the moral involvement of professionals, in this chapter the communication is central. A secondary analysis was performed on the observation data of thirteen indefinite testing trajectories in which communication with clients had taken place *during* the testing procedure. While we had not included the provider-client communication in our original observation protocol, we had accidentally found out that such communication sometimes took place while the testing results were not yet definite. Thus, beside the familiar forms of pre test and post test counseling, we had witnessed a third form of communication taking place during the testing procedure. The aim of our secondary analysis was to explore the content of this intermediate communication. We found that, in the majority of cases, although the timing was different, the content of this communication, concerning medical-technical matters, was similar to that of pre test counseling. However, in four cases the content was different to that of pre test counseling, as more personal matters with regard to decision-making were discussed as well.

The conclusion of this chapter is that in case of a grey or indefinite testing result, clients could be involved in decision-making while the testing result is still being processed. However, due to some particular features of prenatal testing, e.g. uncertainty and the highly complex character of the testing procedures, we doubt whether clients should be involved in the diagnostic pathway of their own testing result. We recommend further research into the process of continuing decision-making to clarify how providers' and clients' responsibilities regarding the diagnostic process in prenatal diagnosis are distributed.

Chapter 5 deals with the third subquestion, 'What might be the impact of targeted testing on the problem of unexpected findings in prenatal diagnosis?' This chapter analyses the troublesome aspects of such findings, and examines in which way targeted testing may provide a solution to these problems.

Prenatal diagnosis may lead to the situation where parents have to decide about continuation or termination of their pregnancy. Testing results of mild or unknown clinical significance are considered problematic because the dilemmas for clients are larger and

more complicated than in case of the more common results of severe or known clinical significance. In a new method, targeted testing, prenatal diagnosis could focus on common results and exclude the more problematic results, such as unexpected findings. To assess if targeted testing is the evident way to deal with problematic findings in prenatal diagnosis, the problems associated with these findings were systematically examined in this chapter.

Providers from several disciplines were interviewed, individually and in focus group discussions, about their experiences with various testing results in general, and problematic results in particular. Clients were asked about their expectations and experiences regarding the same matter. Providers' and clients' experiences were analysed in comparison to search for themes related to problematic testing results.

This chapter shows that problematic results arise because providers, wishing to avoid underreporting, also report results of mild or unknown clinical significance. In a context where only two choices, i.e. continuing or terminating the pregnancy, are available, these results may lead to dilemmas. Because the decision about pregnancy is considered the clients' responsibility in the end, the decision burden for clients is relatively large in case of results of mild or unknown significance.

The conclusion of this chapter is that, compared to alternative solutions within the current scenario of testing, targeted testing can be considered the evident way to deal with problematic findings because it would diminish the decision burden for clients the most. Still, the implementation of targeted testing would require an explicit answer to the - morally laden - question of which testing results should be excluded from prenatal diagnosis. When providers are prepared to help answer this question, targeted testing may lead to an improvement in the quality of the prenatal diagnosis practice.

Chapter 6 also discusses the third subquestion. This chapter gives an overview of the discussion on targeted testing.

Because in the literature, so far, the discussion about targeted testing does not show a systematic reference to the arguments for and against targeted testing, this chapter aims to explore all used arguments and present these arguments systematically. For this, the results of focus group discussions were compared with the literature. Three focus groups were held with twenty two Dutch professionals of eight different health care disciplines involved in prenatal diagnosis. Professionals were asked for their opinions about the preferred future scenario for prenatal diagnosis, i.e. global or targeted. Transcripts of these discussions were analyzed and categorized in relevant themes related to arguments for and against targeted testing.

The arguments mentioned by the focus group participants could be distinguished into four different themes of an increasingly fundamental nature. Firstly, arguments against targeted testing were related to the attitude and role of the providers, like the fact that cytogeneticists would become unemployed once targeted testing were introduced. Secondly, several technical features of prenatal diagnosis were referred to. The fact that mosaicism would not occur anymore in targeted testing was presented as an advantage, but the idea that targeted testing would be able to solve all technical problems was on the other hand

believed to be an illusion. Thirdly, the argument that prenatal diagnosis always involves a miscarriage risk was used as an argument against targeted testing. Finally, arguments about targeted testing were related to the objective of prenatal diagnosis. Targeted testing was seen as a reasonable option in case prenatal diagnosis was conceived as a medical diagnosis following a specific indication. Contrarily, the option of targeted testing was rejected when the objective of prenatal diagnosis was taken to be to detect as many abnormalities as possible.

While some arguments of the focus group participants could be found in the literature, these discussions revealed some significant additional arguments as well. Systematic analysis of both the focus group discussion transcripts and the available literature made us conclude that the most decisive issue in the discussion about targeted testing is the question of what is considered the objective of prenatal diagnosis. When the objective is to detect the maximum range of chromosome abnormalities, targeted testing is obviously rejected.

For supporters of targeted testing, on the other hand, it is necessary to carefully think about the objective of prenatal diagnosis to determine the exact content of the target. The discussion about targeted testing therefore naturally involves the question of which information exactly should be provided to clients – and which tests should be performed as a consequence. Because this question requires distinguishing between information that should and should not serve as input for the clients' decision about termination of pregnancy, this can be considered an ethical issue. Therefore, the agenda for the discussion about targeted testing should first and foremost address the question, 'What actually is the objective of prenatal diagnosis?'

As a general discussion, **Chapter 7**, presents an answer to the central research question, 'How to deal with unexpected findings, considering the potential role of targeted testing in this respect?'

This chapter first of all presents the most relevant conclusions from the previous chapters, i.e. that 'unexpected' findings is not the most appropriate name for findings that are actually problematic; that the technical work of producing a testing result and the moral decision-making about continuation or termination of pregnancy are sometimes more intermingled than is generally assumed; that targeted testing is the evident way to deal with problematic findings; and, last but not least, that opposite opinions about targeted testing are inextricably bound up with conflicting opinions about the target of testing, i.e. the goal to be achieved in prenatal diagnosis.

Next, the question of who should decide about the target is addressed. We explain why we do not support the seemingly self-evident option to give individual clients of prenatal diagnosis full responsibility regarding the content of the target, for instance by giving them a 'menu' of testing possibilities, and why we believe that providers should at least feel responsible for this matter in some degree as well. Preferably, both providers' and clients' organizations would be involved in answering the question of which testing results should be included in future prenatal diagnosis. As this issue relates to the question of what should be the goal of prenatal diagnosis, this issue considers other social parties as well.

This chapter also presents an extensive reflection on the study, and with regard to the reliability and validity of the study, the role of the researcher is particularly discussed. The researcher's own initial ideas about the subject of research are presented, followed by a description of the process of writing memos, which is illustrated by two citations of the researcher's memos. This chapter thus shows that the researcher's theoretical drive had functioned more as an inspiration than as an obstacle for doing solid scientific research. It also explains the added value of this ethical-empirical research, which brought some fundamental issues to the fore, e.g. that the discussion about targeted testing inherently bears an ethical component.

Next, we explain in this chapter that the discussion on targeted testing inevitably includes the discussion on what actually *is* the target, or the goal to be achieved, in prenatal diagnosis. As there is no clear definition of the goal of prenatal diagnosis available, we conclude that more clarity with regard to the presumed goal of prenatal diagnosis is required.

For this purpose, we suggest that the following definition might be taken as a starting point:

Prenatal cytogenetic diagnosis informs pregnant women about the presence or absence of severe chromosome abnormalities in their fetus, to enable them to decide about termination or continuation of pregnancy.

Starting from this definition, a more precise definition of the goal of prenatal cytogenetic diagnosis should at least be specific about (I) the category of pregnant women the test is meant for (e.g. *all* or a *selected* group of pregnant women?), (II) the criteria used to determine which chromosome abnormalities are detected (e.g. *severe* or *all* chromosome abnormalities?), and (III) the ultimate function of providing women with the detected information (e.g. enabling women to decide about termination of pregnancy, or enabling them to get reassurance?). In trying to achieve this clarity, questions with regard to the content of the target and the role of the clients will naturally be answered.

The final conclusion of this thesis is that, apart from the potential practical benefits that the introduction of targeted testing might bring about in prenatal diagnosis – a decrease of problematic findings –, the major impact of targeted testing lies in its requirement of a discussion about the target of testing. To facilitate such a discussion, we recommend that any concrete suggestion regarding the implementation of targeted testing explicitly refers to a clear description of the goal to be achieved in prenatal diagnosis. If this is done consistently, the option of targeted testing can be optimally benefited from. Serving as a catalyst, the discussion on targeted testing may then lead to more precise and differentiated definitions of the goal(s) of prenatal diagnosis. Once a more precise definition, or definitions, of the goal of prenatal diagnosis is applied, the appropriate name for the category of unexpected or problematic findings will naturally reveal itself, e.g. 'unclear results', or 'additional results'.

For several reasons, the Netherlands may be the natural country to start the recommended discussions about the goal of prenatal diagnosis and the advisability of targeted testing.

Samenvatting

Prenatale diagnostiek kan uitslagen opleveren die niet speciaal werden gezocht. Hoewel zorgverleners min of meer bekend zijn met dit verschijnsel ontbreken er richtlijnen voor het omgaan met 'onverwachte uitslagen' in prenatale diagnostiek. Steeds wanneer zich zo'n onverwachte bevinding voordoet moeten individuele zorgverleners daarom zelf beslissen hoe met deze situatie om te gaan. Het vervangen van deze *ad hoc* benadering door een meer structurele aanpak zou tot een kwaliteitsverbetering in de prenatale diagnostiek kunnen leiden. Dit proefschrift doet verslag van een onderzoek naar de beste manier van omgaan met onverwachte bevindingen in de prenatale diagnostiek.

Hoofdstuk 1, de introductie, beschrijft allereerst dat dit proefschrift vooral gaat over de vlokcentest en vruchtwaterpunctie, uitgevoerd bij zwangere vrouwen vanwege hun hogere leeftijd, of een door screening vastgesteld verhoogd risico. Er wordt verteld dat in 50% van deze gevallen de test een *andere* uitslag oplevert dan trisomie 21 (dat leidt tot het syndroom van Down). Dit hoofdstuk biedt een eerste uitleg van het begrip 'onverwachte bevindingen' en bespreekt de aspecten hiervan die nog onduidelijk zijn. Ook het gebruik van de terminologie wordt hier toegelicht. Omdat opheldering van het begrip onderdeel van het onderzoek is worden door het proefschrift heen verschillende termen gebruikt, zoals 'grijze uitslagen', 'voorlopige uitslagen' en 'lastige uitslagen'.

In dit hoofdstuk wordt het belang van de toepassing van nieuwe diagnostische technieken in een mogelijk toekomstig scenario van 'targeted testing' (gerichte diagnostiek) toegelicht. Met de toepassing van testen als QF-PCR (quantitative fluorescent polymerase chain reaction) en MLPA (multiplex-ligation-dependent probe amplification) zou de prenatale diagnostiek alleen gericht kunnen worden op het chromosoom, of de chromosomen, waarbij men verwacht een afwijking te vinden. In een dergelijke gerichte vorm van diagnostiek zou het aantal onverwachte bevindingen dus afnemen, simpelweg omdat alle afwijkingen die niet speciaal worden gezocht ook niet meer worden opgespoord. Vanwege die afname van het aantal opgespoorde afwijkingen wordt de mogelijkheid van targeted testing zowel van harte ondersteund als hartgrondig afgewezen.

Tenslotte wordt in dit hoofdstuk de opzet van het onderzoek toegelicht. Startpunt voor dit onderzoek was de vraag van zorgverleners hoe zij onverwachte bevindingen in de dagelijkse praktijk met hun cliënten zouden moeten bespreken. Omdat een eventuele introductie van targeted testing consequenties heeft voor de mate waarin onverwachte

bevindingen überhaupt voorkomen, werd deze vraag breder geformuleerd als: hoe zou er met onverwachte bevindingen moeten worden *omgegaan*. In dit onderzoek werd gekozen voor een ethisch-empirische benadering, in de vorm van een gevalstudie waarbij meerdere kwalitatieve onderzoeksmethoden werden gebruikt. Naast observaties in de dagelijkse praktijk van prenatale diagnostiek werden er diepte-interviews gehouden met zorgverleners en cliënten. Met zorgverleners zijn daarnaast ook zogeheten focusgroep-discussies gehouden.

De **centrale onderzoeksvraag** luidde:

Hoe om te gaan met onverwachte bevindingen, gegeven de mogelijke rol van targeted testing?

Ter ondersteuning van de beantwoording van de centrale vraag werden de volgende **subvragen** geformuleerd:

1. Wat zijn precies onverwachte bevindingen?
2. Hoe gaan zorgverleners om met onverwachte bevindingen vóóordat zij deze met cliënten bespreken?
3. Wat is de mogelijke impact van targeted testing voor het probleem van lastige uitslagen in de prenatale diagnostiek?

Hoofdstuk 2 beantwoordt de eerste subvraag: Wat zijn nu eigenlijk onverwachte bevindingen? In de literatuur is systematisch gezocht naar publicaties over onverwachte bevindingen in de prenatale diagnostiek. De geselecteerde artikelen zijn vervolgens aan een kwalitatieve analyse onderworpen, waarbij de artikelen zowel één voor één als in onderlinge vergelijking zijn bestudeerd. Voor deze literatuurreview werden zestien artikelen geselecteerd die zijn verschenen tussen 1979 en 2001. In deze analyse konden vier soorten problemen van onverwachte bevindingen worden onderscheiden, te weten: 1. Onverwacht voor zorgverleners; 2. Onverwacht voor cliënten; 3. Onzekerheid; en 4. Overige lastige counselingskwesties.

De conclusie van dit hoofdstuk is dat de belangrijkste problemen van onverwachte bevindingen tegenwoordig niet zozeer te maken hebben met het onverwachte karakter van uitslagen, maar meer met onzekerheid en overige aspecten die tot lastige counselingskwesties leiden. Omdat dit problemen zijn die in het geval van onverwachte uitslagen slechts *nadrukkelijker* aanwezig zijn, kunnen onverwachte bevindingen niet in absolute, maar alleen in *graduele* zin van standaarduitslagen onderscheiden worden.

Om het mogelijk belang van targeted testing voor de problemen van de onverwachte bevindingen te kunnen bepalen moet allereerst worden vastgesteld wat nu precies onverwachte bevindingen zijn. Uit ons literatuuronderzoek blijkt echter dat de twee belangrijkste problemen – onzekerheid en overige lastige counselingskwestie – verschillend van aard zijn. De vraag die daarom onbeantwoord blijft is: Voor welke problemen beoogt targeted testing nu precies de oplossing te zijn? Een belangrijke conclusie van dit hoofdstuk luidt:

Alvorens targeted testing kan worden toegepast is het nodig precieze criteria op te stellen aan de hand waarvan onverwachte bevindingen van standaarduitslagen kunnen worden onderscheiden; dit is gedaan in hoofdstuk 5.

Hoofdstuk 3 gaat over de tweede subvraag: Hoe gaan zorgverleners om met onverwachte bevindingen vóórdat zij deze met hun cliënten bespreken? Naast normale ('witte') en afwijkende ('zwarte') uitslagen kan prenatale diagnostiek ook leiden tot chromosoomafwijkingen waarvan de fenotypische consequenties nog onduidelijk zijn. Deze voorlopige ('grijze') uitslagen moeten worden opgehelderd. In overeenstemming met het model van nondirectieve counseling gaat de gebruikelijke manier van omgaan met grijze uitslagen uit van het idee dat een dergelijk ophelderingsproces een strikt technische zaak is. Deze benadering houdt in feite in dat de individuele cliënt pas in beeld komt op het moment dat de definitieve uitslag wordt doorgegeven; daarom zou het ook geen verschil uitmaken voor *wie* dat technische ophelderingsproces wordt uitgevoerd. Tegelijkertijd kan echter moeilijk worden ontkend dat prenatale diagnostiek echt een vorm van diagnostiek is. En diagnostiek dient altijd een bepaald doel en vindt plaats binnen een bepaald referentiekader, waarvan de cliënt als persoon uiteraard deel uitmaakt.

De onderzoeksvraag van dit hoofdstuk was: Is het ophelderen van een grijze uitslag een strikt technisch proces of wordt in dit proces rekening gehouden met de individuele cliënt? Om dit te onderzoeken werden observaties uitgevoerd in de dagelijkse praktijk van de afdeling Klinische genetica van het Academisch Medisch Centrum. Daarbij werd bekeken wat zorgverleners doen om een grijze uitslag op te helderen, dat wil zeggen om een uitslag wit of zwart te maken.

Tijdens het observeren van de grijze uitslagtrajecten werd een opvallend verschijnsel waargenomen. In sommige trajecten werd het ophelderen van de uitslag niet als logische volgende stap beschouwd. In deze situaties vond een soort oponthoud plaats waarbij niet alleen de cliënten maar ook de zorgverleners zich duidelijk over de voortgang van het traject moesten beraden: er was sprake van een toename van professioneel overleg en van onderlinge consultatie, casussen werden uitgebreid besproken op de wekelijkse besprekingen etc. Dit oponthoud en de twijfel over hoe de uitslag verder opgehelderd zou moeten worden betrof echter niet de technische kant van de zaak. De aarzeling kwam daarentegen voort uit de vraag of opheldering wel *nodig* was, een vraag die naar ons idee morele overwegingen binnenbracht in de zogenaamde amorele, technische fase van prenatale diagnostiek. De gedetailleerde beschrijving van deze trajecten laat zien hoe zorgverleners, tijdens de fase van het maken van uitslagen, rekening houden met de beslissing over het afbreken of continueren van de zwangerschap. In uitslagtrajecten waarbij de vraag speelt of het wel nodig is een grijze uitslag op te helderen, was het proces van ophelderen van een voorlopige uitslag dus gerelateerd aan de beslissing die op grond van diezelfde uitslag genomen moet worden. In deze trajecten was dan ook geen sprake van de nagestreefde distantie van zorgverleners ten opzichte van de beslissing over de voortgang van de zwangerschap. In het ophelderingsproces van sommige grijze uitslagen liepen zorgverleners juist vooruit op die - nog te nemen - beslissing.

Uit onze observaties blijkt dat zorgverleners een afwijkende uitslag van prenatale diagnostiek niet alleen zien als informatie over de chromosomen die representatief is voor het genotype van de foetus, of als informatie over chromosoomafwijkingen met klinische consequenties. Zorgverleners zien een afwijkende uitslag van prenatale diagnostiek tevens als informatie die relevant is voor de beslissing over het afbreken of continueren van de zwangerschap. Echter, terwijl hun inschatting over de mate waarin de informatie over de chromosomen representatief is voor de foetus, en met betrekking tot de fenotypische consequenties, nog als een puur (medisch-)technische zaak kan worden beschouwd, is dat voor die laatste inschatting niet het geval. De inschatting of de informatie van de chromosomen relevant is met het oog op de beslissing over het afbreken van de zwangerschap heeft immers een *morele* dimensie. Op grond van onze observaties zijn daarom vraagtekens te plaatsen bij het idee dat het maken, dan wel ophelderen, van een testuitslag een strikt technische aangelegenheid zou zijn.

Normaal gesproken wordt het model van nodirectieve counseling gebruikt om zorgverleners te weerhouden van een morele inmenging in beslissingen die genomen worden *op grond van* een testuitslag. Dit hoofdstuk laat echter zien dat er ook al *tijdens het maken* van uitslagen van morele inmenging sprake kan zijn. Om deze reden worden in dit hoofdstuk de verantwoordelijkheden besproken die zorgverleners hebben ten aanzien van toekomstige scenario's van targeted testing (gerichte diagnostiek) waarbij grijze uitslagen kunnen worden uitgesloten. Zoals we hebben laten zien, zijn zorgverleners moreel betrokken bij hun eigen praktijk. Om die reden zouden ze zich daarom niet, onder het mom van nondirectiviteit, afzijdig dienen te houden van de discussie over de vraag welke testen wel en niet in een scenario van targeted testing aangeboden zouden moeten worden. Het zou een gemiste kans zijn de beantwoording van deze vraag geheel aan hun cliënten over te laten; behalve dat ze op deze manier hun professionele verantwoordelijkheid slechts een beperkte invulling zouden geven, zou dit bovendien niet overeenkomen met de mate waarin ze, blijkens onze observaties, in de dagelijkse praktijk betrokken zijn.

Hoofdstuk 4 gaat ook over de tweede subvraag: Hoe gaan zorgverleners om met onverwachte bevindingen vóórdat zij deze met hun cliënten bespreken? In dit hoofdstuk zijn dezelfde observatiegegevens gebruikt als in hoofdstuk 3, maar terwijl hoofdstuk 3 de morele betrokkenheid van zorgverleners als onderwerp had, staat hier de communicatie centraal. Er is een secundaire analyse uitgevoerd op de gegevens van dertien voorlopige uitslagtrajecten waarbij er tijdens het maken van de uitslag met cliënten is gecommuniceerd. In het oorspronkelijke onderzoeksdesign was de communicatie met cliënten niet opgenomen. Binnen dit design hadden we dan ook slechts bij toeval gezien dat er soms met cliënten werd gecommuniceerd nog voordat de uitslag definitief was. Naast de bekende vormen van 'pre test counseling' en 'post test counseling' signaleerden wij dus een vorm van counseling *tijdens het maken van de uitslag*. Middels een secundaire analyse wilden we de precieze inhoud van deze tussentijdse counseling onderzoeken.

In het merendeel van de geanalyseerde uitslagtrajecten bleek de timing van deze counseling weliswaar afwijkend, maar was de inhoud toch min of meer gelijk aan de

counseling voorafgaand aan de test, waarin vooral medisch-technische zaken besproken worden. In vier gevallen was de inhoud wel anders, omdat hier persoonlijke overwegingen met betrekking tot de besluitvorming werden besproken.

De conclusie van dit hoofdstuk luidt dat cliënten bij grijze, of voorlopige, uitslagtrajecten bij besluitvorming betrokken kunnen worden terwijl het uitslagtraject nog gaande is. Vanwege bepaalde karakteristieken van prenatale diagnostiek, zoals onzekerheid en de technische complexiteit van het testproces, kan echter worden betwijfeld of cliënten wel betrokken zouden moeten worden bij het diagnostisch traject van hun eigen uitslag. Verder onderzoek naar dit proces van doorlopende besluitvorming in de prenatale diagnostiek zou meer inzicht kunnen geven in de wijze waarop verantwoordelijkheden van cliënten en zorgverleners in dit opzicht verdeeld zijn.

Hoofdstuk 5 gaat over de derde subvraag: Wat is de mogelijke impact van targeted testing voor het probleem van lastige uitslagen in de prenatale diagnostiek? Dit hoofdstuk onderzoekt wat nu precies de lastige aspecten van deze uitslagen zijn, en op welke manier targeted testing hier een oplossing voor kan bieden.

Prenatale diagnostiek kan leiden tot de situatie waarin ouders moeten beslissen over het al dan niet afbreken van de zwangerschap. Uitslagen waarbij de klinische consequenties minder ernstig of onduidelijk zijn, worden als lastig beschouwd omdat de dilemma's voor de cliënten in deze gevallen groter zijn dan bij 'standaard'-uitslagen met bekende, ernstige consequenties. Met targeted testing, een nieuwe, gerichte vorm van diagnostiek, zou prenatale diagnostiek alleen op standaarduitslagen gericht kunnen zijn en zouden de lastige uitslagen kunnen worden uitgesloten. In dit hoofdstuk is onderzocht of targeted testing de meest voor de hand liggende manier is om met lastige uitslagen om te gaan. Met dit doel voor ogen werden alle verschillende aspecten van lastige uitslagen systematisch onderzocht.

Zorgverleners uit verschillende disciplines zijn geïnterviewd, zowel individueel als in focusgroepen, over hun ervaringen met verschillende uitslagen in het algemeen, en lastige uitslagen in het bijzonder. Cliënten zijn over hun verwachtingen en ervaringen met betrekking tot hetzelfde onderwerp bevestigd. De gegevens van zorgverleners en cliënten zijn vervolgens vergeleken om te zoeken naar thema's die specifiek zijn voor lastige uitslagen.

Dit hoofdstuk beschrijft dat lastige uitslagen ontstaan omdat zorgverleners, in een poging om te voorkomen dat zij onterecht informatie voor hun cliënten achterhouden, ook uitslagen doorgeven waarvan de consequenties minder ernstig of onbekend zijn. In een context waarin voor cliënten slechts twee keuzen beschikbaar zijn – afbreken van de zwangerschap of daarmee doorgaan – kunnen dit soort uitslagen tot dilemma's leiden. Omdat de verantwoordelijkheid voor de beslissing over de voortgang van de zwangerschap uiteindelijk bij de cliënten ligt, worden cliënten in geval van een uitslag waarin de consequenties minder ernstig of onbekend zijn, belast met een relatief grote verantwoordelijkheid.

De conclusie van dit hoofdstuk is dat, in vergelijking met andere mogelijke oplossingen, targeted testing een voor de hand liggende manier is om met lastige uitslagen om te gaan omdat hiermee de besluitvormingslast voor cliënten het meest zou worden beperkt. De implementatie van targeted testing vereist echter nog steeds een expliciet antwoord op de - moreel beladen- vraag welke uitslagen van prenatale diagnostiek zouden moeten worden uitgesloten. Wanneer zorgverleners bereid zijn bij te dragen aan de beantwoording van die vraag, zou targeted testing tot een kwaliteitsverbetering in de prenatale diagnostiek kunnen leiden.

Hoofdstuk 6 gaat ook over de derde subvraag en geeft een overzicht van de discussie over targeted testing. In de literatuur over targeted testing ontbreekt een systematisch overzicht van alle gebruikte voor- en tegenargumenten. In dit hoofdstuk worden alle argumenten uit de discussie over targeted testing op een rijtje gezet. Hiertoe zijn de resultaten van een focusgroep-discussie vergeleken met de literatuur. We hebben drie focusgroep-discussies gehouden met tweeëntwintig Nederlandse zorgverleners afkomstig uit acht verschillende disciplines in de gezondheidszorg. Al deze zorgverleners is gevraagd of zij als toekomstscenario in de prenatale diagnostiek een voorkeur hadden voor een globale of gerichte vorm van testen. De transcripten van deze discussies werden geanalyseerd. De gebruikte argumenten voor en tegen targeted testing konden worden gecategoriseerd in vier thema's met een oplopend fundamenteel karakter. Allereerst werden argumenten genoemd die te maken hebben met de rol en houding van zorgverleners, zoals de signalering dat cytogenetici door de introductie van targeted testing mogelijk zonder werk komen te zitten. Ten tweede werden diverse technische aspecten besproken, bijvoorbeeld het voordeel dat mozaïcisme bij targeted testing niet meer voor zou komen. Tegelijkertijd werd het idee dat targeted testing alle technische problemen op zou kunnen lossen als illusie van de hand gedaan. Als derde werd het argument tegen targeted testing genoemd dat prenatale diagnostiek altijd met een miskraamrisico gepaard gaat. Tenslotte werden diverse argumenten, zowel voor als tegen targeted testing, genoemd die te maken hadden met het doel van prenatale diagnostiek. In het geval prenatale diagnostiek beschouwd wordt als een vorm van medische diagnostiek die volgt op een specifieke indicatie, werd targeted testing als een redelijke optie gezien. Targeted testing werd echter verworpen wanneer men aanneemt dat het doel van prenatale diagnostiek eruit bestaat zoveel mogelijk chromosoomafwijkingen op te sporen.

Hoewel sommige argumenten ook in de literatuur zijn terug te vinden leverden de focusgroep-discussies een aantal interessante nieuwe argumenten op. Onze analyse van deze discussies in vergelijking met de literatuur bracht ons tot de conclusie dat het meest beslissende onderwerp van de discussie over targeted testing de vraag betreft wat nu precies als het doel van prenatale diagnostiek wordt beschouwd. Als het doel is zoveel mogelijk chromosoomafwijkingen op te sporen is targeted testing uiteraard geen voor de hand liggende optie. Voor voorstanders van targeted testing is het belangrijk goed na te denken over het doel van prenatale diagnostiek omdat zij op grond hiervan de inhoud van de testen kunnen bepalen. De discussie over targeted testing gaat namelijk vanzelfsprekend

over de vraag welke informatie wel en niet voor cliënten beschikbaar zou moeten komen – en welke testen dus wel en niet aangeboden zouden moeten worden. Met deze vraag is ook een ethische kwestie gemeoid. Deze vraag gaat in feite namelijk over de vraag welke informatie voor cliënten wel of niet als aanleiding zou moeten dienen voor hun beslissing over het afbreken van de zwangerschap. Het belangrijkste agendapunt voor de discussie over targeted testing is dan ook de vraag: Wat is precies het doel (de ‘target’) van prenatale diagnostiek?

De algemene discussie in **Hoofdstuk 7** beantwoordt de centrale onderzoeksvraag van dit proefschrift: Hoe om te gaan met onverwachte bevindingen, gegeven de mogelijke rol van targeted testing?

Dit hoofdstuk zet allereerst de belangrijkste conclusies van de voorgaande hoofdstukken op een rijtje, te weten: ‘Onverwachte bevindingen’ is niet de meest geschikte benaming voor uitslagen die in feite lastig zijn; De technische kant van het maken van een uitslag en de morele kant van de beslissing over het afbreken van de zwangerschap zijn soms meer met elkaar verweven dan algemeen wordt aangenomen; Targeted testing is een voor de hand liggende manier om met lastige uitslagen om te gaan; en De verdeelde meningen over targeted testing zijn onlosmakelijk verbonden met tegengestelde opvattingen over het doel van prenatale diagnostiek.

In dit hoofdstuk wordt ook besproken wie over de inhoud van de test zou moeten beslissen in geval targeted testing wordt ingevoerd. We leggen uit waarom we geen voorstander zijn van de kennelijk voor de hand liggende optie om die inhoud door individuele cliënten te laten bepalen, bijvoorbeeld in de vorm van een keuzemenu. We beargumenteren waarom zorgverleners zich hier tenminste medeverantwoordelijk voor zouden moeten voelen. Bij voorkeur zouden zowel cliëntorganisaties als beroepsorganisaties zich moeten buigen over de vraag welke soorten uitslagen de toekomstige prenatale diagnostiek op zou moeten leveren. Omdat hier ook een ethische vraag mee gemeoid is, zou het tevens goed zijn hier andere maatschappelijke organisaties bij te betrekken.

In dit hoofdstuk wordt ook verslag gedaan van de reflectie op dit onderzoek. Met het oog op de betrouwbaarheid en validiteit is daarbij de rol van de onderzoeker speciaal onder de loep genomen. De oorspronkelijke eigen ideeën van de onderzoeker worden besproken, en aan de hand van twee letterlijke citaten wordt het proces van het schrijven van memo’s toegelicht. Aldus wordt beschreven dat de theoretische achtergrond van de onderzoeker vooral als inspiratiebron heeft gediend, en niet als obstakel voor het doen van degelijk wetenschappelijk onderzoek. Dit hoofdstuk beschrijft tevens de toegevoegde waarde van een ethisch-empirische aanpak, die in dit onderzoek een aantal fundamentele aspecten naar voren heeft gebracht, zoals het feit dat de discussie over targeted testing tevens ethisch van aard is.

In dit hoofdstuk leggen we uit dat de discussie over targeted testing onvermijdelijk ook de vraag betreft wat nu eigenlijk het doel ('target') is waarop prenatale diagnostiek zich richt. Omdat er geen duidelijke definitie van het doel van prenatale diagnostiek beschikbaar is concluderen wij dat er in dit opzicht meer helderheid is vereist. We doen een eerste poging in de vorm van de volgende definitie:

Prenatale cytogenetische diagnostiek informeert zwangere vrouwen over de mogelijke aanwezigheid van ernstige chromosoomafwijkingen in de foetus, om hen in staat te stellen een beslissing te nemen over het afbreken of doorgaan van de zwangerschap.

Uitgaand van deze definitie kunnen we stellen dat een definitie van prenatale diagnostiek tenminste nauwkeurig zou moeten zijn over (I) de categorie zwangere vrouwen waarvoor de test is bedoeld (bijv. *alle* of een *geselecteerde* groep zwangere vrouwen?), (II) de criteria die worden gebruikt om te bepalen welke chromosoomafwijkingen worden opgespoord (bijv. *ernstige* of *alle* chromosoomafwijkingen?), en het uiteindelijke doel van het informeren van vrouwen over mogelijk bij de foetus aanwezige chromosoomafwijkingen (bijv. hen in staat stellen te beslissen over het afbreken van de zwangerschap, of hen in staat stellen gerustgesteld te worden?). In het streven naar meer duidelijkheid over het doel van prenatale diagnostiek, zullen de vragen met betrekking tot de inhoud van targeted testing en de rol van cliënten gaandeweg beantwoord worden.

De uiteindelijke conclusie van dit proefschrift luidt dat het belangrijkste voordeel van targeted testing is dat het, los van de mogelijke praktische voordelen, een discussie op gang brengt over het doel van prenatale diagnostiek. Om deze discussie te stimuleren stellen wij voor dat in *elke* aanbeveling met betrekking tot targeted testing expliciet genoemd wordt van welk doel van prenatale diagnostiek wordt uitgegaan. Wanneer dit consequent gebeurt kunnen de mogelijkheden van targeted testing optimaal worden benut. De discussie over targeted testing kan zodoende als katalysator dienen om een meer precieze en gedifferentieerde definitie van het doel, of doelen, van prenatale diagnostiek te kunnen formuleren. Zodra er sprake is van de beoogde duidelijkere definitie(s), zal er vanzelf meer duidelijkheid ontstaan over de juiste naam voor onverwachte of lastige uitslagen, bijvoorbeeld 'onduidelijke uitslagen' of 'bijkomende bevindingen'. Om verschillende redenen is Nederland het aangewezen land om te starten met de door ons aanbevolen discussie over het doel van prenatale diagnostiek en de wenselijkheid van targeted testing.

Dankwoord

De periode van het uitvoeren van een promotieonderzoek en het verslag daarvan doen in de vorm van een proefschrift is goed te vergelijken met wat zich afspeelt in een snelkookpan. In een relatief korte, samengeperste tijdspanne wordt de promovendus klaargestoomd om zijn of haar weg in de academische wereld voortaan zelfstandig te kunnen vervolgen. De weg naar die zo vurig verlangde zelfstandigheid wordt echter allerm minst in eenzaamheid afgelegd. Vele mensen hielden mij de afgelopen jaren in mijn promotiesnelkookpan gezelschap en waren getuige van de wijze waarop ook ik voor mijn zelfstandige academische beroepsuitoefening werd klaar- (en soms gaar-) gestoomd. Van de goede gewoonte om al die mensen langs deze weg te bedanken maak ik graag gebruik.

Allereerst zijn daar natuurlijk Dick Willems en Nico Leschot die mij als mijn promotoren al die jaren zo trouw terzijde hebben gestaan. Samen hadden zij gewerkt aan het plan voor dit onderzoek, al lang voordat ik als onderzoeker in beeld was. Juist daarom was het prettig dat zij mij zo ruim baan gaven dit promotieproject mede aan de hand van mijn eigen wensen en inzichten in te vullen. Nico Leschot wil ik heel hartelijk bedanken voor het vertrouwen dat hij al die tijd in mij heeft gesteld door mij als onderzoeker onvoorwaardelijk in 'zijn' praktijk toe te laten en voor zijn open geest waarmee hij mijn - soms kritische - buitenstaandersperspectief altijd welwillend aanhoorde. Door de vanzelfsprekendheid waarmee dat gebeurde vergat ik soms wel eens hoe bijzonder dat eigenlijk was, maar een empirisch-ethisch onderzoek als dit kan alleen maar slagen wanneer je als onderzoeker de mogelijkheid krijgt vrijelijk in de praktijk rond te kijken. Nico gaf mij die gelegenheid en daarvoor ben ik hem zeer dankbaar. Dick Willems heeft de speciale eigenschap als filosoof de zaken ook altijd praktisch en concreet voor te willen stellen. Hierdoor stimuleerde hij me in dit onderzoek steeds heel precies te formuleren – ook wanneer mij dat minder goed uit kwam. Met hem als sparringpartner kregen de definitieve teksten daardoor vaak net dat stukje meer dan wat er in eerste opzet in leek te zitten. Voor deze taak, die hij met verve op zich nam, wil ik hem alsnog hartelijk en nadrukkelijk bedanken, juist omdat mijn dankbaarheid het op die kritieke momenten niet altijd won van mijn frustratie over de noodzaak nogmaals die extra slag te moeten maken.

Op de afdeling Klinische Genetica van het AMC werd ik als onderzoeker zo hartelijk ontvangen dat ik gedurende de observatieperiodes het rijke gevoel had naast mijn eigen afdeling Huisartsgeneeskunde ook van deze afdeling deel uit te maken. Lia Knecht was mijn vaste aanspreekpunt waarbij ik met al mijn vragen terecht kon. Wilma Poelma wijdde mij

in het laboratoriumleven in en legde mij met eindeloos geduld uit welke kweekstoffen, pipetten, trechters en reageerbuisjes er allemaal door de handen van de analisten gaan alvorens er van een uitslag gesproken kan worden. Alle analisten wil ik bedanken voor hun enthousiaste medewerking aan onze afgesproken telefonische inseinprocedure (samen-gevat in de memo: "iets gevonden: Myra bellen"), die moest garanderen dat ik het overleg rondom elke gevonden (vermoede) afwijkende uitslag met eigen ogen en oren kon komen waarnemen. Ook alle cytogenetici, klinisch genetici en psychosociaal medewerkers van de afdeling wil ik hartelijk danken voor hun medewerking aan het onderzoek.

Ook vanuit de afdeling gynaecologie kreeg ik alle medewerking voor het onderzoek. Katia Bilardo was hier het vaste aanspreekpunt en mijn vrijgeleide naar haar collega's die hun medewerking zonder enige terughoudendheid toezegden. Graag wil ik iedereen bedanken die mij toestemming gaf op zijn of haar spreekuren mee te kijken en die bereid was in het kader van ons onderzoek patiënten om medewerking te vragen. Alle medewerksters van de poli prenatale diagnostiek wil ik graag van harte bedanken voor hun inspanningen om dit ook in organisatorisch opzicht mogelijk te maken. De medewerkers van alle verschillende afdelingen die vertegenwoordigd zijn in de Werkgroep Antenatale Diagnostiek wil ik tenslotte bedanken voor de toestemming die mij werd verleend dit wekelijks overleg gedurende de looptijd van het onderzoek bij te mogen wonen.

Alle professionals die zich in het kader van dit onderzoek door mij hebben willen laten interviewen, observeren en/of informeel bevragen kan ik vanwege de privacy uiteraard niet bij naam noemen, maar wil ik langs deze weg nogmaals heel hartelijk bedanken. De waardevolle input van al deze professionals, van zowel binnen als buiten het AMC, heeft dit onderzoek gemaakt tot wat het is en ik hoop daarom oprecht dat niemand zijn vertrouwen beschaamd zal zien in de wijze waarop zijn woorden in dit proefschrift - direct of indirect - zijn weergegeven.

Mijn meest nadrukkelijke dank wil ik uiteraard richten tot alle cliënten, de zwangere vrouwen en hun partners, die hun medewerking aan dit onderzoek hebben verleend. In een periode waarin zij genoeg aan hun eigen hoofd hadden wilden zij mij toch te woord staan. Vaak spraken ze daarbij de hoop uit dat andere vrouwen hiermee geholpen zouden zijn. Voor hun ruimhartige medewerking wil ik alle vrouwen en hun partners die ik heb mogen spreken direct nadat zij een vlokcentest of vruchtwaterpunctie hadden ondergaan of hiervan een slechte uitslag hadden ontvangen, nogmaals heel hartelijk bedanken.

Prof. Otto Bleker, prof. Ben Hamel, prof. Theresa Marteau, prof. Gerard de Vries, prof. Guido de Wert en dr. Marcel Mannens wil ik hartelijk danken voor hun bereidheid zitting te nemen in de manuscriptcommissie.

Buiten het AMC vond ik aansluiting bij collega's waarmee ik mijn 'work in progress' kon bespreken. De onderzoekers van het NWO-programma 'Sociale cohesie', Klasien Horstman, Marianne Boenink, Ruth Benschop, Gerard de Vries, Ine van Hoyweghen en Rein Vos wil ik bedanken voor de inspirerende bijeenkomsten waarin mijn werk van opbouwend commentaar werd voorzien. In een tweetal genetica-workshops van de onderzoekerschool

Wetenschap, Technologie en Moderne Cultuur (WTMC) kreeg ik de gelegenheid de theoretische uitgangspunten van mijn onderzoek aan een kritisch gehoor voor te leggen. In een meer informele context vond ik uitstekende gesprekspartners in Marianne Boenink, Amâde M'Charek en Annemiek Nelis. Omdat ik de enige van ons 'gamma'-eetclubje was die het promoveren nog voor de boeg had was er, in wisselende restaurants, steeds ruim aandacht voor mijn voortschrijdend inzicht op dit terrein, zowel in inhoudelijke als procesmatige zin, waarvan ik dankbaar gebruik heb gemaakt.

Los van het interessante onderzoek dat de reden was geweest van mijn sollicitatie, bleek mijn aanstelling in het AMC bij de afdeling Huisartsgeneeskunde nog vele andere positieve aspecten te behelzen die het werken aan mijn promotieonderzoek zonder meer hebben veraangenaamd.

Inhoudelijk vond ik in eerste instantie een klankbord bij het onderzoeksdeelprogramma (ODP) van Huisartsgeneeskunde. Na de oprichting van het nieuwe ODP Communicatie, Recht en Ethiek kon ik de voortgang van mijn werk daarnaast bespreken met collega's van de afdelingen Sociale Geneeskunde en Medische Psychologie. Ellen Smets wil ik met name bedanken voor de commentaren die zij mij gaf op grond van haar expertise op het gebied van de medische communicatie in het algemeen, en de genetische counseling in het bijzonder.

Op onze eigen afdeling groeide het Filosofie van de Zorg-overleg gestaag. Het groepje dat met Dick Willems, Jet Isarin en Ger Palmboom begonnen was, breidde zich gaandeweg uit met Susanne de Kort, Debby Keuken, Jean-Philippe de Jong en Jeannette Pols. Amâde M'Charek leverde versterking 'van buitenaf', en naast de besprekingen op het AMC werden ook de huiselijke soepmaaltijden ingevoerd, dit alles ter versteviging van het filosofisch gehalte van de ethiek-onderzoekers.

Het Netwerk Kwalitatief Onderzoek bood een mooie plek om de methodologische kant van mijn onderzoek verder te versterken. Thomas Ploch wil ik bedanken voor onze samenwerking hierin en de drijvende kracht die hij van het begin af aan voor het Netwerk is geweest.

Op de afdeling Huisartsgeneeskunde, die uit meerdere subafdelingen bestaat, voelde ik me al snel thuis. Als hoofd van de afdeling, en bindende factor, speelde Bert Schadé hierin een belangrijke rol. Of ik de 'publication game' inderdaad ga winnen valt nog te bezien, maar hopelijk kan ik me de komende jaren op vele andere vlakken nuttig voor de afdeling en divisie maken. Het hoofd van de opleiding Huisartsgeneeskunde, Margreet Wieringa-De Waard, gaf me alle ruimte mijn nieuwe werk zodanig in te plannen dat mijn promotieonderzoek niet zou stagneren. Nu ik na een kort intermezzo mijn twee banen opnieuw vanuit dezelfde werkkamer kan combineren blijven alle collega's die het werken op de afdeling Huisartsgeneeskunde zo aangenaam maken, gelukkig ook na mijn promotie mijn collega's.

Juist in een zo intensieve periode als een promotietraject spelen kamergenoten een belangrijke rol. Bij Jet Isarin herkende ik de persoonlijke drive van waaruit je onderzoek kan doen, en zag hoe dit een onderzoek zoveel meer diepte kan geven. Ongeveer halverwege sleepte Jet me bovendien door het schrijven van mijn 'sleutelartikel' heen. Als 'jonge onderzoekers in de herfst van hun carrière' stimuleerden Paul van Dijk en

Wouter Hoogervorst me mijn onderzoek een duidelijke maatschappelijke inbedding te geven. Ook hun gevraagde én ongevraagde mening over diverse onderwerpen stelde ik altijd zeer op prijs, maar voor de goede sfeer op de kamer hielp het wat mij betreft natuurlijk vooral dat zij altijd weer bereid bleken hartelijk om mijn grapjes te lachen!

In de loop der tijd leverden diverse mensen een heel concrete bijdrage aan mijn proefschrift. Liesbeth Litjens en Kim Kuzee wil ik bedanken voor hun bijdrage in het kader van hun wetenschappelijke stage tijdens hun studie geneeskunde. Beide eindverslagen kwamen na afloop nog meermaals als naslagwerk van pas, en los van de inhoudelijke samenwerking kon ik me ook verheugen in de leuke persoonlijke omgang die hieruit voortvloeide. Marjan Verheul deed haar bedrijfsnaam eer aan toe zij als een heuse 'Tiktijger' de resterende interviewopnames omzette in leesbare transcripten toen ik daar zelf allang de puf niet meer voor had. Evelien Philippa zorgde er met haar prachtige, eigen stijl voor dat het proefschrift niet zomaar 'een boekje' werd, maar een mooi vormgegeven boek dat ik met trots in de boekenkast kan zetten.

Robert Glover corrigeerde alle Engelse teksten. I would like to thank him for that, particularly for his spirit of enthusiasm in doing so. Moreover, I would definitely support his own suggestion of writing the book, entitled, *Herewith, moreover and whereas. A guide to Old English in modern Dutch medical research*, and am sure that many of my colleagues would be interested in reading it!

Tenslotte zijn er uiteraard diverse mensen uit mijn privéleven die - soms tegen wil en dank – het snelkookpanproces van mijn promotie van dichtbij hebben meegekregen.

Allereerst wil ik de zwangere vriendinnen en familieleden bedanken die mij gedurende mijn onderzoek met vragen bestookten. Met hun concrete vragen over prenatale diagnostiek maakten zij me duidelijk dat mijn onderzoek echt ergens over ging - en confronteerden me daarmee elk op hun eigen wijze met de complexiteit van de materie.

Huub en Wien boden een warme thuishaven in Amsterdam toen ik feitelijk nog in Nijmegen woonde en door de week alleen in Amsterdam verbleef.

De leden van het bestuur van de Muktinath Foundation International (MFI), Geert, Myra, André en Linda, konden alleen maar met lede ogen toezien hoe ik mijn taak als secretaris op minimale kracht uitvoerde. Als er één activiteit is die het meest onder de proefschriftdruk geleden heeft, dan is het wel mijn bestuurswerk voor de MFI en ik beloof dan ook plechtig dat mijn inspanningen na eind juni weer een secretaris waardig zullen zijn.

Lama Wangyal, de abt van de boeddhistische nonnen van Muktinath in Nepal, en zijn familie kwamen eind 1999 op wonderlijke wijze in ons leven. Mede vanwege dit tijdstip raakten zij onlosmakelijk verbonden met het schrijven van dit proefschrift. In dank voor de vele verschillende wijzen waarop zij mijn leven verrijken, draag ik dit proefschrift graag aan hen op.

Mijn moeder, als trouwe verzamelaar van mijn gepubliceerde werk, zal ongetwijfeld in haar sas met deze nieuwste aanwinst zijn. Ik op mijn beurt ben onzettend dankbaar dat zij er op mijn promotie bij zal zijn.

Franca, Hans, Silmass, Hans en de kinderen wil ik bedanken voor hun oprechte interesse waarmee ze bleven informeren naar de voortgang van mijn proefschrift. Niet alleen hun warme belangstelling deed me goed, maar vooral het feit dat zij mij er door hun gezelschap doorlopend aan herinnerden dat er inderdaad niemand is die op zijn sterfbed verzucht: "I wish I'd spent more time at the office!"

Mijn paranimfen had ik al lang geleden uitgekozen. Esther werd van collega langzamerhand vriendin, waar ik erg van genoot en nog lang van hoop te genieten. In de laatste maanden gingen we precies gelijk op in het promotietraject. Esther, ik zal straks zeker gebruik maken van jouw ervaring vier dagen voor mijn eigen plechtigheid - sowieso is het fantastisch dat ik straks een gepromoveerde paranimf naast me heb staan! Met Helmke, studiegenoot bij Cultuurpsychologie in Nijmegen, werd ik in Amsterdam gelukkig weer herenigd. Helmke, je weet dat ik altijd blij word van jouw sprankelende energie. Ik wilde je graag als mijn paranimf, niet alleen omdat je van het begin af aan echt geïnteresseerd was in mijn onderzoek, maar ook vanwege je consequente, niet aflatende belangstelling voor mijn nieuwste kledingaankopen. Zoals je weet was die interesse van levensbelang in drukbezette tijden waarin dat – gelukkig! - een welkome afleiding is gebleven.

Tenslotte wil ik André bedanken, al zo lang mijn man, maatje en nog zoveel meer. Natuurlijk, je stond zelf aan de basis van dit wilde plan ('Zeg Myra, jij wilde toch altijd nog eens promoveren?') en je hebt het ook steeds van harte ondersteund, zowel materieel als emotioneel, ook als de boel over dreigde te koken. Inmiddels ben ik het echter helemaal met je eens; er moet nu maar eens een eind komen aan deze periode waarin ik noodgedwongen in een nogal eendimensionale stand heb moeten functioneren. Maar gelukkig, de beloning is zoet en ik verheug me net als jij op al onze toekomstige gezamenlijke projecten!

Curriculum Vitae

Myra van Zwieten (1964, Utrecht) rondde in 1990 in Nijmegen haar studie cultuurpsychologie af, een studie naar de invloed van cultuur op individueel menselijk gedrag. Na een oriëntatie in het bedrijfsleven was zij enkele jaren werkzaam als docent sociale wetenschappen bij een hogere beroepsopleiding Maatschappelijk Werk en Dienstverlening. Dit combineerde ze met free-lance schrijven, onder meer over de wijze waarop individuele keuzeprocessen door medische technologie worden beïnvloed.

In 1997 beëindigde zij haar docentschap om zich full time met academisch onderzoek bezig te kunnen houden. In eerste instantie deed ze dit in Nijmegen, bij de vakgroep Ethiek, Filosofie en Geschiedenis van de geneeskunde, waar ze zich richtte op het onderwerp 'genetisering', het proces waarbij steeds meer verschijnselen in het menselijk bestaan binnen de invloedssfeer van de genetica worden gebracht. Samen met de onderzoeksjournalist André Kalden maakte zij vanuit dit perspectief het op een algemeen publiek gerichte boek *Ons gescreende lichaam: kansen en risico's van de genetica*.

In 1999 hield Myra met haar man een sabbatical in Nepal en India. Deze reis leidde onder meer tot de oprichting van de Muktinath Foundation International, een stichting die zich inzet voor boeddhistische nonnen in de Nepalese Himalaya, waar ze sindsdien secretaris van is. Na een werkbezoek aan het ethisch onderzoekscentrum The Hastings Center in New York en een dienstverband bij het International Forum for Biophilosophy te Leuven, startte zij in 2001 met het onderzoek in het AMC waarover in dit proefschrift verslag wordt gedaan.

Als universitair docent medische ethiek, verbonden aan de afdeling Huisartsgeneeskunde van het AMC, verzorgt Myra van Zwieten onderwijs in het basiscurriculum geneeskunde en begeleidt ze onderzoek op aanverwante terreinen. Vanuit het Netwerk Kwalitatief Onderzoek organiseert ze diverse activiteiten om het in het AMC uitgevoerd kwalitatief onderzoek verder te professionaliseren. Haar eigen onderzoeksinteresse, het raakvlak tussen ethiek en communicatie, wordt gevoed vanuit haar andere baan. Als docent bij de Huisartsopleiding van het AMC, verzorgt ze onder meer onderwijs op het gebied van arts-patiënt communicatie.

List of publications

Targeted testing: the evident way to deal with problematic findings in prenatal diagnosis?

Myra van Zwieten, Dick Willems, Nico Leschot. (submitted)

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The **target** of testing

Dealing with **‘unexpected’** findings in prenatal diagnosis

Prenatal diagnosis may detect other chromosome abnormalities than the one specifically sought. In most cases, chorionic villi sampling or amniocentesis is performed to search for trisomy 21 (leading to Down's syndrome). However, milder sex chromosome abnormalities like Turner's syndrome and Klinefelter's syndrome, or structural aberrations with unknown phenotypical consequences are also regularly found. Although providers are familiar with this phenomenon, professional guidelines for dealing with these so-called unexpected findings are still lacking.

This study aimed to find out what is the best way to deal with unexpected findings in prenatal diagnosis. The significance of new molecular techniques like quantitative fluorescent polymerase chain reaction (QF-PCR) and multiplex-ligation-dependent probe amplification (MLPA) was specifically examined in this respect.

Unexpected findings are actually problematic findings of mild or unclear clinical significance. These testing results require intensive counseling as it is more difficult in these cases to support clients needing to decide about termination or continuation of pregnancy. The application of new molecular techniques like QF-PCR or MLPA in a scenario of targeted testing would make it possible to exclude some, or all, problematic findings from prenatal diagnosis.

Among prenatal diagnosis providers, the desirability of targeted testing is disputed. For advocates, the possible exclusion of problematic findings is a major advantage. Opponents reject the option of targeted testing because they believe that prenatal diagnosis should detect as many chromosome abnormalities as possible. Therefore, the discussion about targeted testing relates to different views on the target, i.e. the goal to be achieved, in prenatal diagnosis.