CHAPTER 5.

CHANGING TO NIPT AS A FIRST-TIER SCREENING TEST AND FUTURE PERSPECTIVES: OPINIONS OF HEALTH PROFESSIONALS

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ABSTRACT

Objective The aim of this study was to investigate health professionals’ opinions toward offering noninvasive prenatal testing (NIPT) as first-tier screening test regardless of pregnant women’s risk, and toward a potential broader range of disorders.

Methods A questionnaire completed by obstetric health professionals (n = 240) after an in-service NIPT training in the West and North of the Netherlands.

Results The majority (72%) of respondents favored replacing first-trimester combined test (FCT) by NIPT, although 43% preferred to maintain nuchal translucency measurement. Many respondents believed that replacing FCT by NIPT would only have advantages (57%), would lead to more pregnant women opting for prenatal testing (69%), and would simplify counseling (47%). Differences in attitudes toward counseling between health professionals were observed. When considering NIPT to screen for broader range of disorders, the majority (92%) thought that this should include disorders characterized by neonatal death, whereas 52% of the respondents favored testing for fetomaternal risk factors. Overall, 46% thought screening should be offered as a fixed list of disorders.

Conclusion Most health professionals favor NIPT instead of FCT but prefer to maintain nuchal translucency measurement. If NIPT becomes available as a first-tier screening test, attention remains necessary to ensure that pregnant women make well-informed decisions in line with the aim of prenatal screening.
INTRODUCTION
The introduction of noninvasive prenatal testing (NIPT) has significantly changed the field of prenatal screening. With NIPT, circulating cell-free fetal DNA (of placental origin) can be detected in maternal plasma.\(^1\) NIPT is an accurate screening test for trisomy 21, 18, and 13 in both high-risk and low-risk pregnancies,\(^2;3\) with a sensitivity of \(>99\%\) and a false positive rate of \(<0.1.\)\(^4;5\) These test characteristics are far superior to those of the first-trimester combined test (FCT).\(^6;7\) Moreover, NIPT can be performed from 10 weeks of gestation onwards and carries no miscarriage risk. In affected families, NIPT can also be used to determine paternally inherited conditions, fetal sex for sex-linked disorders, and single-gene disorders such as achondroplasia.\(^4\) In commercial settings, NIPT is offered to detect chromosomal deletions and/or duplications and fetal sex determination for non-medical reasons.\(^8;9\) Initially, in accordance with international guidelines,\(^10;11\) NIPT was introduced as a test for women at ‘high risk’ of having a child with trisomy 21, 18, or 13. However, recently, the International Society for Prenatal Diagnosis considered it appropriate to offer cell-free DNA testing as a primary test to all pregnant women.\(^12\) To exclude false positives, a positive NIPT result should always be confirmed with amniocentesis or chorionic villus sampling, signifying that NIPT-based testing remains a two-step procedure.\(^12;13\) Therefore, NIPT is increasingly called cell-free DNA (cfDNA) screening.

An important prerequisite for responsible implementation of NIPT is health professional support. Should NIPT be implemented as a first-tier screening test, health professionals need to be aware of the mechanisms, test characteristics, and clinical utility of NIPT to offer accurate pretest counseling in order to facilitate pregnant women’s informed choice. In the USA, attitudes of health professionals toward offering NIPT as a first-tier screening test are generally favorable.\(^10;11\) A survey study among 222 members of the American College of Obstetrics and Gynecology has shown that 79% believe that NIPT should be offered as a first-tier screening test.\(^14\) Another study among 101 US obstetricians shows similar results.\(^15\) However, offering NIPT to all pregnant women raises the concern that NIPT is being presented and regarded as a routine procedure. This ‘routinization’ would be at odds with the notion that prenatal screening for fetal anomalies is offered to facilitate autonomous reproductive decision-making.\(^16;17\) Moreover, the trade-offs involved in prenatal testing may differ for health professionals and pregnant women: the first tend to place most value on the accuracy of a test, whereas pregnant women consider safety of the test to be the most important feature.\(^18-20\)

Because the entire fetal genome is represented in maternal plasma,\(^21;22\) the scope of NIPT is expected to broaden in the near future. Extending NIPT to screen for severe genetic disorders is supported by health professionals.\(^14;20;23\) Screening for phenotypically mild disorders and adult-onset disorders received less support, possibly
because of the controversy regarding testing for conditions that causes less or no harm and requires little to no medical care.(14;20;23)

If NIPT becomes available for a broader range of disorders, discussion is needed on the implementation in prenatal care. A focus group study in the Netherlands showed differences between stakeholders regarding preferences on broader prenatal testing.(24) Pregnant women preferred to choose individually from a wide range of possible test options, whereas most health professionals opted for a test limited to a number of severe conditions.(23)

In the Netherlands, all pregnant women are informed on prenatal aneuploidy screening since 2007. More than 80% of pregnant women receive counseling for prenatal screening from primary care midwives.(25) The overall uptake rate of FCT based prenatal screening for trisomy 21, 13, and 18 is around 27%, (26) but regional differences do exist. (27) Since April 2014, NIPT is offered as a second-tier test after FCT as part of a national implementation study (TRIDENT study, trial by Dutch laboratories for Evaluation of Noninvasive prenatal Testing).(28)

The aim of this study was to evaluate the opinion of health professionals regarding: 1) the position of NIPT in the prenatal screening program, 2) the potential replacement of FCT by NIPT and possible consequences for counseling, and 3) the range of disorders for which NIPT should be made available and ‘how to offer’ NIPT for a broader range of disorders. Differences between health professionals with different professional backgrounds were also assessed.

METHODS
A quantitative survey using a questionnaire was conducted. Ethical approval was granted by the Medical Ethical Committee of the VU University Medical Center (VUMC) in Amsterdam (grant no: 2012/106).

Respondents and procedures
A survey was performed among health professionals (midwives, gynecologists, and sonographers) working in two regions in the Netherlands: the West (Amsterdam) and the North (Groningen) (Table 1). Questionnaires were distributed after an in-service training for NIPT organized by the Regional Centers for Prenatal Screening in Amsterdam and Groningen in November 2013 and March 2014, respectively. Thus, the questionnaires were distributed before or right at the time NIPT was first introduced in the Netherlands. Additionally, health professionals were recruited from the departments of Obstetrics and Gynecology at the two University Medical Centers in Amsterdam (VUMC and Academic Medical Center). In Groningen, health professionals could also fill in an online version of the survey during the month of July 2014.
Survey instrument
The questionnaire was designed by an interdisciplinary group consisting of an ethicist, a health scientist, a psychologist and a gynecologist. The questionnaire was distributed simultaneously with international discrete choice experiment,(19) which will be published elsewhere. First, a brief description of NIPT as a screening test for common aneuploidies, including test characteristics, was given. The opinion of health professionals on the position of NIPT in the prenatal screening program was assessed (5 answers; Figure 1).

Specific questions assessed the attitudes of respondents toward replacement of FCT by NIPT and the possible consequences for counseling (9 statements; Table 2). A 5-point Likert scale was used to categorize respondents’ answers (1 = completely disagree to 5 = completely agree).

Health professionals were asked to rank information about NIPT in order of importance to pregnant women (6 options, 1 = most important to 6 = least important; Figure 2).

Two questions concerned NIPT screening for a broader range of disorders, based on the study by Van Schendel et al.,(29) assessing pregnant women’s attitudes toward NIPT based screening (and beyond). The first question evaluated the preferred scope of NIPT. The second question examined how to offer NIPT when screening for a broader range of disorders. Three options were listed: 1) ‘closed offer’ (i.e. a fixed list of disorders); having NIPT means having the fetus tested for all disorders included in the offer; 2) ‘optional packages’: the offer of disorders is divided into categories, containing disorders similar in type and severity; the woman can choose for which category or categories she wants to have testing; and 3) ‘free choice’: the woman can choose herself which disorders in the offer the fetus is and is not tested for (i.e. choice from a list of disorders). The final section included demographic questions about age, gender, profession, years in profession, and work region.

Data analysis
Descriptive analyses were used to describe the characteristics of the respondents. The 5-point Likert scale used to measure agreement on the attitudes statements was compressed into a 3-point scale in order to avoid small cell sizes: 1) completely disagree or disagree; 2) neither disagree nor agree; and 3) agree or completely agree. Multinomial logistic regression analyses were used to investigate differences between attitudes of health professionals with different professional backgrounds from Amsterdam and Groningen on the position of NIPT in the prenatal screening program. Those attitudes included the following subjects: 1) the position of NIPT in the prenatal screening program, 2) the potential replacement of FCT by NIPT and possible consequences for counseling, and 3) the range of disorders for which NIPT should be made available and how to offer NIPT for a broader range of disorders. Ordinal logistic
regression analyses were used to rank the information about NIPT that would be the most important for pregnant women according to health professionals. All analyses were adjusted for age and years of experience. Gender could not be included in the analyses as only 12 males participated. To account for multiple testing, a p-value of <0.01 was used to indicate statistical significance. A Chi-squared test was used to compare the attitudes of health professionals and pregnant women. Statistical analysis was performed using SPSS20.0 (IBM Statistics for Windows, IBM, NY, USA). When significant differences between the responses of health professionals based upon different professional backgrounds or work region were observed, we reported these differences.

RESULTS
Demographic characteristics
In total, 200 surveys were distributed in Amsterdam and 300 in Groningen. Because these are estimated values, and online participation was allowed, it was not possible to measure an exact response rate. A total of 241 health professionals returned the questionnaire (Table 1). One respondent who did not fully complete the questionnaire was excluded from the analysis, resulting in an inclusion of 240 respondents. The mean age was 40.2 years (SD 11.1, range 20–65 years). The majority were female (94%), and more than half of the respondents were midwives (58%). The mean years of working experience was 12.9 (SD 10.6, range 0–55 years). The majority of the respondents worked in the region of Amsterdam (63%, n=151). The majority of the Northern respondents were midwives (75%) compared with 48% midwives in the Western region.
Table 1. Demographic characteristics of respondents (n=240)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (% )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
</tr>
<tr>
<td>20-30</td>
<td>55 (23 )</td>
</tr>
<tr>
<td>31-40</td>
<td>85 (35 )</td>
</tr>
<tr>
<td>41-50</td>
<td>41 (17 )</td>
</tr>
<tr>
<td>51-60</td>
<td>49 (20 )</td>
</tr>
<tr>
<td>≥ 61</td>
<td>8 (3)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>226 (94)</td>
</tr>
<tr>
<td>Male</td>
<td>12 (5)</td>
</tr>
<tr>
<td><strong>Profession</strong></td>
<td></td>
</tr>
<tr>
<td>Midwife(^a)</td>
<td>140 (58)</td>
</tr>
<tr>
<td>Midwife &amp; sonographer</td>
<td>19 (8)</td>
</tr>
<tr>
<td>Sonographer</td>
<td>25 (10)</td>
</tr>
<tr>
<td>Gynecologist(^b)</td>
<td>44 (18)</td>
</tr>
<tr>
<td>Other(^c)</td>
<td>9 (4)</td>
</tr>
<tr>
<td><strong>Years in profession</strong></td>
<td></td>
</tr>
<tr>
<td>≤ 5</td>
<td>68 (28)</td>
</tr>
<tr>
<td>6-15</td>
<td>97 (40)</td>
</tr>
<tr>
<td>16-25</td>
<td>40 (17)</td>
</tr>
<tr>
<td>26-35</td>
<td>23 (10)</td>
</tr>
<tr>
<td>≥ 36</td>
<td>8 (3)</td>
</tr>
<tr>
<td><strong>Work region</strong></td>
<td></td>
</tr>
<tr>
<td>Amsterdam</td>
<td>151 (63)</td>
</tr>
<tr>
<td>Groningen</td>
<td>89 (37)</td>
</tr>
</tbody>
</table>

Totals may not add to 100% due to missing values and rounding.
\(^a\) Included midwives in training (n=5).
\(^b\) Included gynecologists in training (n=2).
\(^c\) Other professions included: genetic counselors (n=2), nurses (n=2), administrative workers in prenatal screening (n=2), teacher (n=1), fertility doctor (n=1), physician assistant (n=1).

**Positioning NIPT in the prenatal screening program**

Most respondents (72%, n = 171) thought that NIPT should replace FCT, but 43% (n = 102) preferred maintenance of NT measurement (Figure 1). A minority (22%, n = 53) thought that FCT should be maintained and NIPT should be offered as a follow-up test after a high risk at FCT. The probability of being in favor of full replacement of FCT by NIPT versus NIPT while preserving NT was significantly lower for sonographers (9% vs 48%) than for midwives (34% vs 42%) (OR = 0.181, p = 0.010).
Attitudes on replacement of FCT by NIPT

Many respondents (57%) thought that replacement of FCT by NIPT only has advantages, would make explaining test procedures easier (64%), and would simplify counseling (47%) (Table 2). Most health professionals (69%) believed that NIPT would lead to more pregnant women deciding to choose prenatal testing, and almost half (49%) believed that this would lead to pregnant women agreeing with screening without fully thinking through this decision. The majority (84%) disagreed with the statement that it would be unnecessary to give an explanation about invasive testing because few pregnant women would need follow-up testing. Moreover, 74% of respondents disagreed that pregnant women should be given less time to decide for or against testing, and only 25% believed that counseling for NIPT and sampling of maternal blood should take place on the same day. Significantly more gynecologists (46%, n = 20/44) (OR = 0.155, p = 0.000) and sonographers (37%, n = 16/43) (OR = 0.220, p = 0.001) compared with midwives (15%, n=21/138) favored this last statement.
Health professionals were asked to indicate what information about NIPT would be the most important according to pregnant women (Figure 2). Accuracy (1.64, SD 0.79) followed by safety (2.03, SD 1.1) of the test were considered to be the most important. The least important was costs (4.62, SD 1.2) and information about test procedure (4.74, SD 1.3).

Table 2. Attitudes of health professionals toward replacement of first trimester combined test by noninvasive prenatal test and considerations for counseling

<table>
<thead>
<tr>
<th>The replacement of FCT by NIPT...</th>
<th>(Completely) disagree</th>
<th>Neither disagree nor agree</th>
<th>(Completely) agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>...has only advantages</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>...will simplify the counseling</td>
<td>74 (32)</td>
<td>26 (11)</td>
<td>135 (57)</td>
</tr>
<tr>
<td>...will lead to more pregnant women deciding to do the test</td>
<td>91 (39)</td>
<td>35 (15)</td>
<td>110 (47)</td>
</tr>
<tr>
<td>...will lead to pregnant women agreeing with screening without fully thinking through this decision</td>
<td>30 (13)</td>
<td>43 (18)</td>
<td>163 (69)</td>
</tr>
<tr>
<td>...will lead to pregnant women agreeing with screening without fully thinking through this decision</td>
<td>65 (28)</td>
<td>54 (23)</td>
<td>115 (49)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>When counseling for NIPT in comparison to counseling for FCT...</th>
<th>(Completely) disagree</th>
<th>Neither disagree nor agree</th>
<th>(Completely) agree</th>
</tr>
</thead>
<tbody>
<tr>
<td>...the procedure of the test is easier to explain</td>
<td>46 (20)</td>
<td>39 (17)</td>
<td>151 (64)</td>
</tr>
<tr>
<td>...there is more time to give information about the disorders that will be tested</td>
<td>70 (30)</td>
<td>74 (31)</td>
<td>92 (39)</td>
</tr>
<tr>
<td>...it is unnecessary to give an explanation about invasive testing because only a few pregnant women will need this follow-up test</td>
<td>199 (84)</td>
<td>15 (6)</td>
<td>22 (9)</td>
</tr>
<tr>
<td>...less time for consideration can be given to pregnant women to do the test or not</td>
<td>175 (74)</td>
<td>38 (16)</td>
<td>23 (10)</td>
</tr>
<tr>
<td>...the counseling and procedure of the test (sampling of maternal blood) can take place the same day</td>
<td>140 (59)</td>
<td>36 (15)</td>
<td>60 (25)</td>
</tr>
</tbody>
</table>

Totals may not add up to 100% due to missing values and rounding. FCT= first trimester combined test. NIPT= non-invasive prenatal test.
Figure 2. Ranking of important features of noninvasive prenatal testing for pregnant women according to health professionals (mean values, 1=most important, 6=least important)

Offering NIPT for a broader potential: ‘what to offer’ and ‘how to offer’?

The attitudes of health professionals toward NIPT-based screening for a broader range of disorders are shown in Figure 3. The majority thought that NIPT should be used for disorders characterized by neonatal death or death within the first year of life (92%) or disorders for which children would need medical care throughout their lives (71%). A little more than half of the respondents (52%) agreed that screening for fetomaternal risk factors that have a negative influence on pregnancy outcome should be offered.

The attitudes of health professionals from our study versus those of pregnant women (based on the results of the study of Van Schendel et al(29) are shown in Figure 4. Overall, 46% (n = 111) of the health professionals thought that if NIPT-based screening is introduced for a broader range of disorders, this should be made available as a closed offer (i.e. fixed list of disorders), which was significantly less preferred by pregnant women (31%, n = 118/381) (p<0.001). Fewer health professionals (25%, n = 61) believed that pregnant women should have a free choice, compared with pregnant women (41%, n = 157/381) (p<0.001).
Disorders characterized by neonatal death or death within the first year of life
Disorders for which children will need medical care throughout their lives
Risk factors which can have a negative effect on the progress of pregnancy (e.g. preeclampsia or preterm birth)
Adult onset disorders
Disorders for which children will need little medical care throughout their lives
Other *

*Other included: Disorders for which the parents wish to do testing (n=3), not expanding the scope (n=2), only in the case of a familiar disease (n=2), severe disorders (n=2).

Figure 3. Opinion of health professionals toward non-invasive prenatal testing for a broader range of disorders
DISCUSSION

Positioning NIPT in the prenatal screening program

This study shows that the majority (72%) of Dutch obstetric health professionals are in favor of replacing FCT by NIPT, which is in line with previous reported studies among obstetric health providers from the USA. (14;15) However, 43% of the respondents in our study do state that when replacing FCT, NT measurement should be preserved. This corresponds with a survey among 278 US maternal fetal-medicine specialists concerning the clinical implementation of NIPT, where 71% of the respondents did not agree with NIPT replacing NT measurement. (30) Only a minority of the sonographers in our study preferred a full replacement of FCT by NIPT. It may be that because of their daily practice they see an additional value in a first-trimester scan, including NT measurement. There are concerns that important information about fetal conditions or fetomaternal risk factors (other than trisomy 21, 13, or 18) currently detected by an ultrasound scan at 12 to 13 weeks will be overlooked. (2;13) However, regarding other chromosomal anomalies, a recent retrospective cohort study suggested that only very few fetuses with a chromosomal abnormality other than trisomy 21, 13, or 18 would have been missed when using NIPT instead of FCT. (31) An approach could be to...
perform an ultrasound scan at 12 to 13 weeks with NT measurement alongside NIPT, or alternatively postponing NIPT after this scan, although evidence on its clinical utility is still under investigation.\(^{(12;13)}\) This last option would save costs in the case of intra-uterine demise occurring early in pregnancy and select fetuses with very enlarged NT, eligible for a broader genetic work-up than NIPT.\(^{(32)}\) Still, as first-trimester screening in the Netherlands aims exclusively to detect trisomy 21, 18, or 13, broadening the scope of screening should be preceded by a redefinition of the screening target.\(^{(33)}\)

**Attitudes toward replacement of FCT by NIPT**

Most respondents in our study believed that NIPT is an easier test to explain, which will simplify counseling. Although, half of the health professionals in this study stated that pregnant women might agree with screening without fully thinking about this decision. In addition, the majority of the respondents disagreed that counseling and sampling of maternal blood should take place on the same day. These results may illustrate possible concerns that the assumed benefits of NIPT, such as rapid, simple, and efficient testing, could threaten informed decision-making. These possible concerns should be taken seriously when NIPT is considered as a first-tier screening test. It is known that separating the test offer from the test procedure gives time for reflection, yet there is no empirical evidence that counseling and testing the same day will necessarily lead to an uninformed decision to accept the test.\(^{(17)}\) A way to optimize autonomous reproductive choice may be to make use of (online) decision aids prior to pre-test counseling for NIPT. A randomized controlled trial among 701 US pregnant women showed that an interactive decision-support guide about prenatal testing resulted in more informed choices.\(^{(34)}\)

In the Netherlands, counseling high-risk pregnant women about NIPT is currently performed by trained health professionals (mainly gynecologists) in the eight University Medical Centers. If NIPT were to be offered to all pregnant women, this would shift pre-test counseling to mainly primary care midwives who, up till now, have limited clinical experience with NIPT. Educational programs as well as proper guidelines for professionals are needed to maintain a high standard of care and to ensure that couples are able to make a well-informed decision. While it has already been shown that health professionals themselves consider accuracy of the test to be the most important feature of a prenatal test,\(^{(18-20)}\) this study showed that health professionals believe that pregnant women share this opinion, while in fact pregnant women place most value on the safety of a test.\(^{(18-20)}\)

**Attitudes toward offering NIPT for a broader scope**

As to previously published data,\(^{(14;20;23)}\) the majority of health professionals in our study were in favor of offering NIPT for severe genetic disorders. Surprisingly, only a little over half of the health professionals (52%) favored testing for fetomaternal risk
factors, which can have a negative effect on the course of pregnancy, such as preeclampsia or preterm birth. The questionnaire study of van Schendel et al. (29) among 381 pregnant women showed that 65% of the respondents were in favor of offering NIPT for these risk factors. It remains unclear why Dutch health professionals and pregnant women are not quite convinced to screen for these risk factors. Perhaps, health professionals think that NIPT is not valid for predicting outcome, such as for preeclampsia, or they find the efficacy of therapies for risk factors during pregnancy debatable.

A minority of respondents of our study supported the use of NIPT for adult-onset disorders or disorders for which children will need little medical care throughout their lives. This would rarely lead to termination of pregnancy, making the informational interests of the future child a topic to consider. In this connection, it has been argued that the future child has a ‘right to an open future’, including the right to decide later in life whether ‘to know’ or ‘not to know’. (13) Only 25% of health professionals in our study favored offering NIPT as a free choice from a list of disorders when broadening the scope of NIPT. The previously mentioned study among Dutch pregnant women showed that the largest group (41%) preferred to have a free choice. (29) Health professionals might raise objections to this because of practical considerations, as counseling would become a complicated and time-consuming task. (24) The discrepancy in attitudes may also reflect different views about how the aim of enabling reproductive choice can best be served. (24) Whereas on the one hand, one might argue that an individualized choice requires providing prospective parents with the option to be informed about whatever they want to know about the health of the future child, it has also been pointed out that an unlimited choice will lead to information overload, which may paradoxically undermine reproductive autonomy rather than serve it. (35) Many women are, in principle, in favor of ‘having a free choice’, but also acknowledge that the decision-making process might become complex and possibly overburden pregnant women. (24)

**Strengths and limitations**

One of the strengths of this study is the relatively large sample size and the different professional backgrounds represented. No information on non-respondents has been collected, and the study may have attracted more respondents that were interested in NIPT. Also, this study only observed the opinion of health professionals in the West and North of the Netherlands and cannot be generalized to other professionals in the Netherlands. In comparison to other countries, there is a relatively low uptake of prenatal screening in the Netherlands. Therefore, the interpretation of the results must be performed with caution, as these might not be generalizable to countries with a higher uptake. Noteworthy, this survey study was performed before, and for some right at the time NIPT was first introduced in the Netherlands. The attitudes of the majority of
health professionals were thus based only on information about NIPT rather than on their own clinical experience with the test.

CONCLUSION
Dutch health professionals have a positive attitude toward offering NIPT as a first-tier screening test to all pregnant women. The additional value of NT measurement if NIPT fully replaces FCT needs to be further investigated, as many professionals preferred to preserve the NT measurement. If NIPT was to be offered as a first-tier screening test, this would lead to a significant change in the organization of the counseling in the Netherlands, as it would then be primarily performed by primary care midwives. Most respondents in our study believe that NIPT is an easier test to explain, thereby simplifying counseling. Attention should be paid to ensure that patients make well-informed decisions, especially in the light of concerns about a possible routinization effect that would be at odds with the aim of prenatal screening. The prospect that, in the future, NIPT might be used for a broader range of disorders makes it imperative to consider how prenatal screening should then be offered and for which conditions.
REFERENCES


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