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ORIGINAL ARTICLE

NIPT-based screening for Down syndrome and beyond: what do pregnant women think?

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ABSTRACT

Objective The aim of the study is to study pregnant women's views on noninvasive prenatal testing (NIPT) for Down syndrome and the potential to test for a broader range of conditions.

Methods An online questionnaire available on the Dutch pregnancy fair website was completed by 381 pregnant women.

Results Of the women, 51% expressed interest in having NIPT, including 33% of women who had declined first-trimester screening. The majority (73%) thought that the uptake of screening would increase with NIPT. Most women agreed that testing for life-threatening (89%), severe physical (79%), or severe mental (76%) disorders should be offered. A minority (29%) felt that prenatal screening should also be offered for late-onset disorders. Most (41%) preferred to have a free choice from a list of disorders, 31% preferred a 'closed offer', and 26% preferred choosing between packages of disorders. Although most women (76%) thought that screening for a broad range of conditions would avoid much suffering, 39% feared that it would confront couples with choices, the implications of which would be difficult to grasp.

Conclusion The results suggest that the uptake of screening will increase with NIPT. If NIPT will be offered for a broad range of conditions, it is crucial to find a way that facilitates rather than undermines well-informed decision-making.
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Conflicts of interest: None declared

INTRODUCTION

Over the last few years, a vast amount of research and opinion papers have been published on the introduction and evaluation of noninvasive prenatal testing (NIPT) for fetal aneuploidies. With NIPT, a blood sample of the mother is drawn to determine whether a normal or abnormal quantity of fetal DNA from chromosome 21, 18, or 13 is present in the maternal plasma.[1] NIPT has a high sensitivity and specificity, can be performed from 7 weeks of gestation onwards, and poses no miscarriage risk. Studies performed among pregnant women and their partners have shown that these benefits make NIPT a preferred alternative to risky and stressful invasive procedures and to the less accurate first-trimester screening.[2–6] Although NIPT offers clear advantages over conventional prenatal tests, women have also expressed uneasiness about its use. Concerns that prenatal testing could become routinized and women might feel pressured to accept NIPT because it is uncomplicated and free of risk were raised.[5,6] Moreover, worries were conveyed about potential stigmatization of children and adults with a disability.[5,6] The latter concern is fundamental as NIPT is an emerging technology already expanding its use to test for more disorders than just fetal aneuploidies. At present, NIPT is applied to determine fetal sex in order to identify X-linked disorders and to determine fetal Rhesus D genotype in Rhesus D negative mothers.[7] However, NIPT has even more potential as it has been demonstrated that the entire fetal genome is represented in the maternal plasma,[8,9] making it possible to diagnose an increasing number of disorders. NIPT for several single-gene disorders is already feasible, especially in conditions where a

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single mutation accounts for the majority of cases, such as achondroplasia.[10] Moreover, an increasing number of commercial companies are expanding their NIPT offer to include (optional) screening for microdeletion syndromes and large duplications, although some commentators have called for caution.[11]

In the long run, it is expected that NIPT will also be deployed to detect fetomaternal risk factors (i.e. markers for preeclampsia or preterm birth), thus enabling adapted monitoring of a pregnancy.[12]

In the light of these developments, the question arises as to what the scope of NIPT-based prenatal screening should be. Should it include all conditions that can be tested for, or should it consist of a more limited offer? A recent study showed that most women with an increased risk for aneuploidies choose a follow-up test that offers the most information about their child (i.e. a high-resolution genomic array including genetic variants associated with susceptibility of disease).[13] Moreover, hypothetical interest in testing for several conditions (e.g. cancer susceptibility and childhood-onset and adult-onset disorders) among pregnant women increased when NIPT could be used instead of invasive diagnostic procedures.[14] On the one hand, it seems that widening the scope of NIPT is in line with the aim of prenatal screening, namely facilitating autonomous reproductive choices, whereas setting limits would raise the specter of paternalism. On the other hand, pretest information about the specifics of all conditions included in broad-scope screening may lead to information overload and thus undermine reproductive decision-making.[15]

Although something is known about pregnant women's interest in testing for broader range of conditions,[13–15] less is known about women's views on the preferred scope of NIPT-based screening and how it should be offered. This study therefore aims to identify pregnant women's attitudes toward NIPT both for common autosomal aneuploidies and for a potentially much broader range of conditions. The study will focus on understanding pregnant women's views on the following: (1) NIPT-based Down syndrome screening and its implications, (2) conditions for which NIPT-based screening should be available and possible consequences, and (3) who should decide for which conditions NIPT becomes available and, once determined, if it should be offered as a closed offer, in packages, or as a free choice.

This study was performed in the Netherlands, where the uptake of the first-trimester combined test is around 27%.[16] During the period of the study, NIPT was not yet available in the Netherlands. Shortly after our data were collected, NIPT became available for women at high risk (≥1 : 200) based on the first-trimester screening, as part of a national implementation research study (Trial by Dutch laboratories for Evaluation of Non-Invasive Prenatal Testing (TRIDENT) study).[17]

METHODS

A quantitative study, using an online questionnaire, was conducted between January 2014 and March 2014. Ethical approval was granted by the Medical Ethical Committee of the VU University Medical Center Amsterdam (2012.106).

Participants and procedure

A banner with a link to the questionnaire was placed on the website of the Dutch 'Nine Months Fair'. This is the biggest pregnancy fair in the Netherlands, which is held once a year and has around 52 000 annual visitors. Website visitors were invited to complete the questionnaire about 'a new prenatal test during pregnancy', which took about 10 min to complete. Being pregnant was the only criterion to take part in the study. Women who participated had a chance of winning a €25 gift voucher.

Survey instrument

The questionnaire was specifically developed for this study. In the first section, respondents were given a description of the prenatal screening program in the Netherlands (i.e. first-trimester screening, possibly followed by chorionic villus sampling or amniocentesis), followed by a question delineating whether the respondent had had any of the available tests in a previous or the current pregnancy or was planning to do so. A brief explanation was given about NIPT: test procedure (blood sample of mother), conditions included (trisomies 21, 13, and 18), test accuracy (>99% for trisomy 21), timing (>9 weeks), and need for follow-up testing to confirm positive NIPT result. Moreover, it was mentioned that NIPT will likely replace the current first-trimester screening test. Intention to have NIPT was measured with a single item: 'If NIPT was available in the Netherlands, would you choose this test in this or a next pregnancy?' (answer options: 'most certainly yes'; 'probably yes'; 'maybe yes, maybe not'; 'probably not'; 'most certainly not'). Women were also asked what they were willing to pay for NIPT [answer options: 'nothing'; 'the same as for the first-trimester screening (€150)'; '€250'; '€350'; '€450'; '€550 or more'].

Specific questions assessed respondents' views on NIPT-based screening for Down syndrome and beyond: *pregnant women's views on the implications of an NIPT-based Down syndrome screening* (six statements; see Table 1), *categories of disorders for which pregnant women think NIPT-based screening should become available in the future* (seven categories; see Figure 1), and *pregnant women's views on the implications of NIPT for a broader range of conditions* (six statements; see Table 2). Respondents were asked to indicate the extent to which they agreed with each statement or category on a 5-point Likert scale (1 = completely disagree, 2 = disagree, 3 = neither disagree, nor agree, 4 = agree, and 5 = completely agree).

To evaluate who should decide about the scope of NIPT, respondents were asked to answer the question: 'According to you, who should make the decision for which conditions NIPT becomes available?' (answer options: 'pregnant women and their partners'; 'healthcare professionals'; 'the government; patient or consumer organizations'; 'a special committee with a representative of all groups mentioned earlier'). Women were also asked by which method a broad range of conditions should be offered. Three options were listed: (1) 'closed offer': 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

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Table 1 **Attitudes of pregnant women toward noninvasive prenatal testing-based Down syndrome screening**

Implementation of NIPT for Down syndrome leads to…	(Completely) disagree *n* (%)	Neither disagree nor agree *n* (%)	(Completely) agree *n* (%)
…more pregnant women choosing to test for Down syndrome than with the current screening test	44 (12)	60 (16)	277 (73)
…pregnant women thinking less comprehensively about participation in prenatal screening than with the current screening test	131 (34)	96 (25)	154 (40)
…more pregnant women feeling obliged to participate in prenatal screening than with the current screening test	204 (54)	92 (24)	85 (22)
…fewer children with Down syndrome being born than with the current screening test	95 (25)	132 (35)	154 (40)
…prenatal screening being more useful for those who just want to prepare for having a child with Down syndrome	36 (9)	87 (23)	258 (68)

NIPT, noninvasive prenatal testing.

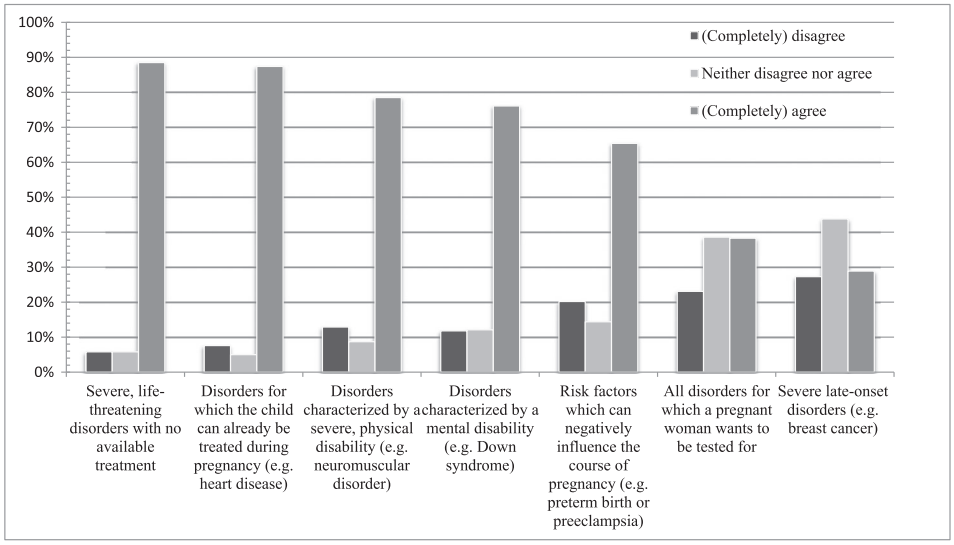

Figure 1 **Level of agreement of pregnant women on testing for different categories of conditions with noninvasive prenatal testing**

Table 2 **Attitudes of pregnant women toward noninvasive prenatal testing for a broad range of conditions**

Testing with NIPT for a broad range of conditions…	(Completely) disagree *n* (%)	Neither disagree nor agree *n* (%)	(Completely) agree *n* (%)
…is a good idea because it will avoid much suffering	39 (10)	53 (14)	289 (76)
…will lead to less acceptance of giving birth to an affected child	157 (41)	86 (23)	138 (36)
…will lead to less attention and care for people with a disorder	236 (62)	85 (22)	60 (16)
…should only be possible for disorders, so not for gender	73 (19)	102 (54)	206 (27)
…should also be possible for nonmedical cosmetic traits (e.g. eye or hair color)	333 (87)	29 (8)	19 (5)
…will confront couples with choices, the implications of which would be difficult for them to grasp	107 (28)	126 (33)	148 (39)

NIPT, noninvasive prenatal testing.

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.

Finally, the questionnaire contained questions on socio-demographics, including age, level of education, ethnicity, religion, gestational age, and having children.

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Data analysis

Descriptive analyses were used to describe the characteristics of the respondents. To define pregnant women's interest in having NIPT, 'most certainly yes' and 'probably yes' were combined as well as 'most certainly not' and 'probably not'. The 5-point Likert scale used to measure agreement on the items shown in Tables 1 and 2 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. Data were analyzed using SPSS 20.0 (IBM SPSS Statistics for Windows).

RESULTS

Sample characteristics

In total, 491 women participated in the online questionnaire; 24 women were not pregnant and therefore excluded. Women who did not complete the questions about NIPT ($n = 58$) or sociodemographic status ($n = 28$) were also excluded from analysis. Consequently, 381 questionnaires were included in the analysis. Respondents' characteristics are presented in Table 3.

Overall, the sample consisted of mostly highly educated women (57%). The mean age was 28.8 years ($SD = 4.3$, range: 18–40 years), and the mean gestational age was 18.7 weeks ($SD = 8.6$, range: 5–42 weeks). Of the women, 27% reported that they had had first-trimester screening in the current or a previous pregnancy, and 10% mentioned that they were planning to do so.

Views on NIPT-based Down syndrome screening

Of the 381 respondents, the majority (61%) had already heard of NIPT. Half of the respondents (51%) indicated that they would want to have NIPT in this or their next pregnancy if NIPT was available, 23% were unsure, and 26% did not want to have NIPT. Of the women who did not want to have NIPT, 70% mentioned that this was because they would never consider terminating their pregnancy. Of the women who reported having declined first-trimester screening (63%, $n = 240$), 33% said that they would choose for NIPT. Most women (56%) were willing to pay €150, 30% were willing to pay nothing, and 14% were willing to pay more than €250.

Women's attitudes toward NIPT for Down syndrome are shown in Table 1. The majority of women (73%) agreed with the statement that implementation of NIPT as a replacement of the current first-trimester screening test would lead to a higher uptake of prenatal screening for Down syndrome. Of all respondents, 40% worried about 'routinization' of screening as they agreed that, with NIPT, women would think less comprehensively about participation in prenatal screening. An equal number of women (40%) thought that because of NIPT, fewer children with Down syndrome would be born. On the other hand, 54% of women did not think that NIPT would lead to more women feeling obliged to participate in prenatal screening. The majority (68%) of women thought that prenatal screening would become more meaningful as an option for couples who just want to be able to prepare themselves in case of a child with Down syndrome.

Table 3 Characteristics of respondents

Characteristics	$N = 381$ n (%)
Age (years)	
≤ 25	82 (22)
26–35	275 (72)
≥ 36	24 (6)
Level of education[a]	
Low/intermediate	164 (43)
High	217 (57)
Ethnicity[b]	
Dutch	320 (84)
Other Western	22 (6)
Non-Western	36 (9)
Missing	3 (1)
Religion[c]	
None	223 (59)
Christian	137 (36)
Muslim	14 (4)
Other	7 (2)
Level of religiousness	
(Somewhat) active	84 (22)
Not active/not religious	297 (78)
Weeks of gestation	
≤ 13	121 (32)
14–27	200 (53)
28–42	60 (16)
Experience with first-trimester screening[d]	
No	274 (72)
Yes	107 (27)
Having children	
No	254 (67)
Yes	127 (33)

[a]Low: elementary school, lower level of secondary school, and lower vocational training; intermediate: higher level of secondary school and intermediate vocational training; high: high vocational training and university.[33]
[b]Ethnicity was categorized as Dutch, Other Western, or Non-Western by the following algorithm: Dutch if both parents were born in the Netherlands; Other Western if at least one of their parents was born in Europe (excluding Turkey), North America, Oceania, Indonesia, or Japan; and non-Western if at least one of their parents was born in Africa, Latin America, Asia (excluding Indonesia and Japan), and Turkey. If both parents were born abroad, then ethnicity was determined by the country of birth of the mother.[33]
[c]Christian: Calvinism, Protestantism, Roman Catholic, Reformed, and Baptism. Other: for example, Hinduism, Buddhism, and Paganism.
[d]Nine respondents (also) had experience with invasive testing (chorionic villus sampling or amniocentesis).

Views on a broader scope NIPT and its possible consequences

Women were asked to indicate for which conditions NIPT-based screening should be made available (Figure 1). The

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majority of women agreed that this screening should test for life-threatening disorders (89%), disorders characterized by severe physical disability (e.g. neuromuscular disorder) (79%), and disorders characterized by severe mental disability (e.g. Down syndrome) (76%). Moreover, 87% of women agreed that testing for fetal disorders treatable during pregnancy should be offered. Of the women, 65% stated that screening should be made available to identify risk factors with a negative influence on the course of pregnancy, such as preeclampsia or preterm birth, while only 29% of the women agreed that screening for late-onset disorders, such as hereditary breast cancer, should be made available. Of the respondents, 38% agreed that NIPT-based screening should be made available for any disorders a woman wants to test for, although an equal percentage of women neither agreed nor disagreed with this.

The attitudes of women toward screening for a broad range of conditions with NIPT are shown in Table 2. The majority of women (76%) agreed that testing for a broad range of conditions is a good idea as it could avoid much suffering, and 62% did not think that this would lead to less attention and care being given to people with a disorder. In contrast, 36% thought that it would lead to less acceptance of giving birth to an affected child. Moreover, 39% of the women thought that screening for a broad range of conditions would confront couples with choices, the implications of which are difficult for them to comprehend. The statement that screening should be made available for nonmedical cosmetic traits, like eye or hair color, was rejected by the vast majority of women (87%). Regarding testing for gender, however, most women (54%) neither agreed nor disagreed, while only 19% agreed that it should be made available.

A broader scope for NIPT: deciding what becomes available and how it is offered

Of the women, 40% felt that the decision for what kind of conditions NIPT-based screening may be offered should be made by pregnant women (and their partners), while 31% felt that this should be the responsibility of a special commission including delegates from the government, healthcare professionals, patient organizations, and pregnant women. Of the women, 23% stated that the decision should be made by healthcare professionals, and only 2% of the women felt that the government or the patient–consumer organizations should be making this decision.

The largest group of respondents (41%) thought that testing for a broad range of conditions should be offered as a 'free choice'. About a third (31%) felt that it should be offered as a 'closed offer', and a slightly lower percentage (26%) felt that it should be offered in 'optional packages'.

DISCUSSION

Half of the women in this study expressed interest in having NIPT, including a third of women who reported having declined first-trimester screening. The majority of women thought that the uptake of screening would increase with NIPT. Testing for a broader range of conditions could avoid much suffering, according to women. A considerable number of women thought that choices should be individualized with regard to the disorders for which the fetus gets tested. Nonetheless, 39% of the women feared that if NIPT is offered for a broader range of conditions, couples will be faced with choices, the implications of which are difficult for them to comprehend.

Views on NIPT-based Down syndrome screening

A relatively large percentage of respondents in this study had already heard of NIPT even though the test was not yet available. This can most likely be attributed to a widespread media coverage following a year of debate about NIPT and the government's announcement that it was going to be available soon. The majority of the women thought that with NIPT, the uptake of prenatal screening would increase. Earlier studies among pregnant women (and partners) in the UK[4] and the Netherlands[4,18] also concluded that implementing NIPT may result in a higher uptake of screening. However, interest in having NIPT in our study (51%) was not nearly as high as found in other studies, where hypothetical interest reached 72%[3] and even 88%.[4] Interestingly, now that NIPT is actually being offered to women, the uptake of NIPT seems to be lower,[19,20] although this could partly be due to the fact that it is still an expensive test that is not always reimbursed. Most women were willing to pay €150 for NIPT (the same amount as for the first-trimester screening), similar as to what was found by another Dutch study.[2]

The majority of respondents felt that with NIPT, prenatal screening would become more useful for those who just want to be informed in order to prepare themselves in case of Down syndrome. This is in line with studies by Lewis *et al.*[4] and Verweij *et al.*,[18] who found that a significant group who reported to choose for NIPT would not terminate their pregnancy. Moreover, a study in the UK concluded that although women had a positive attitude toward prenatal testing for most of the genetic conditions presented, their attitudes toward termination of pregnancy for these conditions were much less positive.[21] These findings suggest that the expected higher uptake of NIPT need not result in a corresponding increase in termination of pregnancies.

A large percentage of women in this study worried that women might feel a reduced need to reflect on the pros and cons of prenatal screening with NIPT. This concern about a possible 'routinization' of prenatal screening as a result of the ease and safety of NIPT was also expressed by pregnant women in our previous qualitative study.[6] Similar concerns are raised in the literature with regard to professional attitudes about the need for providing more than rudimentary pretest information about NIPT.[22]

Views on a broader scope NIPT and its possible consequences

Most women agreed that testing for life-threatening, severe physical, or severe mental disorders should be offered. Fewer women (65%) felt that screening should include testing for risk factors that can negatively influence the course of pregnancy, such as preeclampsia or preterm birth. This is remarkable, as one would expect more women to agree with this, because it could benefit the health of both the woman and her child.[12]

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The reason why fewer women in this study support this type of screening is not clear, but it could be that respondents did not fully understand this concept, as this kind of testing is not yet performed in the current practice and limited information was given.

Almost a third of respondents agreed to testing for severe late-onset disorders, like hereditary breast cancer. Testing for late-onset disorders in pregnancy is much debated mostly because, in the case of a continuing pregnancy, the child will be born with possibly 'undesirable' information, depriving him or her of the 'right not to know' and potentially leading to psychosocial harm.[23–25] Another type of controversial testing, namely testing for nonmedical cosmetic traits or gender, was also seen as unacceptable to most of the women in this study. This is in line with earlier studies on women's attitudes[6,26] and also corresponds to the view of many professionals that sex selection for nonmedical reasons is to be rejected.[27]

Although most women thought that NIPT-based screening for a broad range of conditions would avoid much suffering and would not lead to less care for people with a disorder, a considerable number feared that it would lead to less acceptance of giving birth to an affected child. The latter is in line with findings from a UK study among the general public, showing fear for a societal quest for 'perfection' and a lack of tolerance for people with a disability when the use of NIPT gets expanded.[28]

A broader scope NIPT: deciding what becomes available and how it is offered

In this study, a significant number of women thought that NIPT should be allowed for any disorder a woman wants to test for. Moreover, when being offered NIPT, a slight majority of women wanted the option to have a 'free choice' from a list of disorders, instead of a 'closed offer' or an offer in 'optional packages'. In this study, we thus found some support for the notion that when offered NIPT-based prenatal screening, women or couples should be allowed to make an individualized choice with regard to the range of conditions for which they would want to have the fetus tested. However, respondents seemed aware that testing for a broad range of conditions may complicate the decision-making process beyond what most couples are able to comprehend. This was also found in a study by De Jong *et al.*,[15] where participants favored an individualized choice about the scope of the test but realized this would be so complex that it could overburden women. These worries are conceivable, as offering a broader scope test would require more elaborate and detailed information about the specifics of all conditions included in the offer, complicating the counseling process.[29] Hewison *et al.*[30] show that women hold different opinions about the conditions that to them merit prenatal testing, and it was argued that individual views should be respected in order to achieve informed consent. They also acknowledged, though, that this is particularly difficult when offering a test for a broad range of conditions because of the risk of 'information overload'.[30] Interestingly, the 'optional packages' approach that is proposed in the literature as a way to solve this problem while allowing couples to make their own reproductive decisions as much as possible[31] received the least support in our study.

Strengths and limitations

One of the strengths of this study was the relatively large sample size and the fact that we included both women who already had experience with prenatal screening and women who had not. Our sample was also representative of the general population of pregnant women in the Netherlands regarding the average age at which they had their first child and uptake of Down syndrome screening.[16] However, the sample consisted of mostly highly educated, Dutch Caucasian women, which makes it less generalizable. Also, the survey measured intention to have NIPT, which is known to not always correspond well with the actual uptake of screening, as we have seen with the first-trimester screening test.[32] Finally, this study only addresses public attitudes in the Netherlands, which is a country with a relatively low uptake of prenatal screening. Therefore, results cannot be seen as being representative of other countries, but many similarities are evident.

CONCLUSION

The findings of this study suggest that the introduction of NIPT as a first screening test will result in an increase in the uptake of prenatal screening in the Netherlands. When, in the future, NIPT-based prenatal screening can be offered for a broader range of conditions, it is important to further investigate how to offer such a test in a way that strikes a careful balance between imposing unjustified limits to individualized choice, on the one hand, and overburdening women's capacities for autonomous decision-making on the other hand.

ACKNOWLEDGEMENTS

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WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- Studies have shown positive attitudes toward noninvasive prenatal testing (NIPT), although some concerns have been expressed about its use.

WHAT DOES THIS STUDY ADD?

- Most women believe that a broad-range NIPT-based screening would prevent suffering and should include life-threatening, severe physical, and severe mental disorders. A minority supports screening for nonmedical traits, gender, and late-onset disorders.
- Support for individualized choice, as well as fear that a broad-range NIPT-based screening would confront couples with choices, the implications of which would be difficult to grasp, was found.

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