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COMMENTARY

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First-trimester screening strategies: A balance between costs, efficiency and diagnostic yield

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Key points

What's already known about this topic?

- An early scan at 11–13 + 6 weeks offers the ideal opportunity for a first detailed anatomical assessment of the fetus.
- Non-invasive prenatal testing (NIPT) is superior to the combined test to screen for common trisomies, especially trisomy 21, in both singleton and twin pregnancies.

What does this study add?

- In first-trimester screening strategies based on NIPT and ultrasound, many factors must be considered when choosing how to combine the two methods. We propose four screening strategies with different pro- and contra arguments.
- The article may help choose the strategy that best fits local needs and health economic considerations.

1 | INTRODUCTION

The introduction of non-invasive prenatal testing (NIPT) by cell-free DNA (cfDNA) has reshaped the way first-trimester screening (FTS) is performed. In several countries NIPT is offered as second line screening, after the combined test (CT) including nuchal translucency (NT) measurement and maternal serum biochemistry (free beta-HCG and PAPP-A).[1] However, there is an increasing tendency to completely replace the CT with NIPT.[2,3] It is undisputed that, in a direct comparison with the CT, NIPT is a superior screening method for common trisomies, especially trisomy 21, in both singleton and twin pregnancies.[4–6] The performance diminishes when micro-deletions are also tested or a genome-wide approach is offered.[7] In fact, the screen-positive rate increases, the positive predictive value decreases and counseling couples to ensure informed consent becomes more challenging.[8–10] The additional value of these expanded menus needs to be balanced against this background. Replacing the CT with NIPT may result in a loss of the opportunity for a first detailed anatomical assessment of the fetus, which is highly valued by women.[11,12] It is known that about 30%–50% of fetal abnormalities can always be detected in the first trimester and that while some are strongly associated with chromosomal aberrations, others are isolated.[13,14] Notably, their prevalence exceeds that of genetic anomalies, especially in younger women who constitute the majority of the reproductive population.[15] Although there is still an ongoing debate, it seems reasonable that screening for structural anomalies should have its own place, next to NIPT, in the current FTS paradigm.[14,16–20] The primary aim of this commentary is to present four different screening strategies combining NIPT and ultrasound in the first trimester (NIPT after CT, NIPT after a 12–13 weeks anatomical assessment, NIPT without a 12–13 weeks anatomical assessment and NIPT followed by a 12–13-week anatomical assessment) with their pro and contra arguments. We are aware that the ultimate decision on which strategy to offer will be nationally determined by cost-effectiveness arguments, availability of local resources, and health policy priorities. We recognize that some pro- and contra-arguments

listed under one strategy may also apply to the others, but for the sake of conciseness, we avoid repeating them.

2 | FIRST TRIMESTER SCREENING STRATEGIES

2.1 | Strategy 1: NIPT as second tier screening after the CT

This screening strategy is chosen in many countries.[21] First-trimester combined screening is the first line test, followed by NIPT offered to pregnancies with an intermediate risk. The thresholds vary greatly per country. If the CT risk is above a certain threshold or if the subsequent NIPT result is abnormal, invasive testing is offered. In case of a low CT risk, no further examinations are recommended. With this strategy, test performance in screening for Trisomy 21 is optimized by using NIPT for those women who will benefit most, while keeping the number of NIPT tests as low as possible and maintaining all the other benefits of the CT.

Miltoft et al. investigated this two-stage approach with thresholds of 1:100 and 1:1000. This model was compared with the use of combined screening alone with the usual threshold of 1:300. All pregnancies affected by a trisomy 21 were detected by both screening policies. However, the false positive rate of the 2-stage model was 1.2% while it was 3.0% with the classical approach.[22] In another retrospective study by Prodan et al. with 2255 euploid pregnancies and 163 fetuses with trisomy 21, the CT and NIPT were carried out in all cases. An inconclusive NIPT result was classified as high risk. The aim was to compare the 2-stage screening approach (NIPT in the intermediate risk group only) with an NIPT-for-all approach. The detection rate for trisomy 21 was similar, at 98%–100%.[23] Gil et al. offered cfDNA screening to women with an intermediate FTS risk between 1:101 and 1:2500. Women in the high-risk group (risk of >1:100) were asked to choose between a diagnostic and a cfDNA test. The approach resulted in a real detection rate of 91.5% for trisomy 21, with only 38% of women with a risk above 1:100 opting for a diagnostic test. In the intermediate risk group (1:101-1:2500), 91.5% of pregnant women opted for cfDNA testing. Overall, amniocentesis or a chorionic villous sampling was performed in 2.7% of cases.[2]

2.1.1 | Pro-arguments

His model has the main advantage of not requiring any No change with respect to the current traditional screening policy of universal CT. NIPT is offered only to the intermediate risk group with an increase in detection of trisomy 21 cases, but at lower cost than in a NIPT for all policy.[24,25] This strategy is less challenging and time consuming than a sequential screening based on measuring the new additional ultrasound markers nasal bone, ductus venosus, or tricuspid flow in the intermediate group.[23,26] Also, the opportunity of globally assessing fetal anatomy during the nuchal scan can indirectly be considered as a screening test for chromosomal abnormalities with high detection rates for trisomy 18, 13, Triploidy and Turner syndrome.[13]

2.1.2 | Contra arguments

Contingent screening policies depend on the quality of the first line screening test. As the CT is more operator-dependent than NIPT, the overall test performance will be affected by the expertise of the ultrasound workforce.[27] Furthermore, the detection rate of Trisomy 21 will be lower than when NIPT is carried out in all pregnant women as the CT has lower sensitivity than NIPT even in expert centers.[28] Also, the two-stage screening process will result in a longer time to diagnosis compared to a direct "NIPT for all approach", which may cause psychological distress and/or limit access to terminate pregnancy.

2.2 | Strategy 2: NIPT after a 12–13-week anatomical assessment

The screening starts with a first-trimester anomaly scan offered before NIPT to identify pregnancies where immediate referral to a fetal medicine unit should be considered. Due to the strong association between fetal defects and major chromosomal abnormalities, it is recommended to perform invasive testing when a structural anomaly is diagnosed.[20]

2.2.1 | Pro-arguments

There is evidence that a first-trimester anomaly scan prior to NIPT allows for better candidate selection and avoids false reassurance of parents in pregnancies with unidentified major fetal anomalies.[29] A pre-NIPT ultrasound scan has the potential to change clinical management by showing structural abnormalities in about 2% of women.[30] In a randomized controlled trial, the ultrasound + NIPT approach was compared to the CT only strategy. In case of fetal anomalies or an increased NT >3.5 mm, invasive testing was carried out directly instead of NIPT or serum marker analysis. This accounted for 2% of pregnancies in which structural and genetic defects would have been missed by a NIPT-only strategy. However, in the remaining study population, NIPT reduced the overall invasive testing rate throughout the pregnancy to 0.3% in comparison to 1.7% in the CT group.[31]

A very important argument in favor of this strategy is a recent cost-effectiveness analysis showing that, although adding a formal anatomical assessment prior to NIPT may be financially more costly, this strategy is in the end more cost-effective that NIPT without an ultrasound scan.[32] In this study, the authors created a theoretical cohort of 400,000 pregnancies by developing a decision analysis model based on sensitivity rates reported in the literature. Then they reported cost-effectiveness by calculating incremental cost-

effectiveness ratio (ICER = the cost per 1 additional quality adjusted life years gained with one strategy compared to the other) and net monetary benefit. In their decision analysis model, the authors allocated each pregnant woman to one of two screening protocols: ultrasound before cfDNA screening or cfDNA screening alone. The results showed that a strategy involving routine first-trimester ultrasound before NIPT is more cost-effective than a strategy offering cfDNA without a preceding scan. Indeed, a NIPT-only screening approach would result in 38 more procedure-related losses, 87 more live births with aneuploidy, 35 more live births with a fetal structural anomaly, four more stillbirths and 93 fewer pregnancy terminations.[32] Although sensitivity analysis shows good potential for the generalization of the results to the general population, the authors acknowledge that country-specific differences may apply depending on the costs of the screening tests.

2.2.2 | Contra-arguments

The introduction of a systematic first-trimester anatomical assessment requires supplementary financial resources for additional training of sonographers, better ultrasound equipment, greater uptake of transvaginal scanning, and longer scanning time. A concern could be that a systematic search for anomalies could increase false-positive rates and cause maternal anxiety. However, recent studies from our group do not substantiate these concerns.[11,19]

Why the first-trimester scan matters and how to perform it

In order to maximize detection, it is important that this scan is performed beyond 11 weeks as at such an early stage 56% of major structural anomalies, which should always be detectable in the first trimester, may remain undiagnosed.[33] In two meta-analyses from Karim et al., the detection rates of a detailed anatomical examination at 11–13 weeks for non-cardiac and cardiac defects were 46.1% and 55.8%, respectively.[17,34] The latter can further be increased if the assessment of the ductus venosus flow is added to the scanning protocol. Some research groups observed detection rates of up to 60% in the first trimester.[35,36] In comparison, a recent Scandinavian study shows that the detection rate of a detailed anomaly scan in the second trimester, considered as the gold standard for the diagnosis of fetal defects, is also only about 50%. For cardiac defects the reported detection rate was as low as 13%.[37] A large body of literature has advocated the importance of using a systematic scanning protocol to examine early fetal anatomy.[14,19,34] This has been shown to be the strongest predictor of improved detection rates in the first trimester. In a prospective study from our group where a systematic protocol was implemented, we detected almost 50% of fetal anomalies in the first trimester.[19] The simple principle of "you can only find what you are looking for" can also be applied to first-trimester anatomical screening. In fact, all international guidelines, including the recently published ISUOG guidelines, recommend the use of a systematic and organ-specific protocol to investigate fetal anatomy between 11 and 14 weeks of gestation.[38] The extensiveness of the protocol may be adjusted depending on the time, resources, ultrasound equipment and experience of the operator. Importantly, due to the strong association between fetal defects and major chromosomal abnormalities, it is recommended to perform invasive testing when a structural anomaly is diagnosed.[39] Thus, a detailed anatomical examination in the late first trimester has the potential to further increase the detection rates of chromosomal abnormalities, including some that are not detectable by NIPT alone.[40,41]

2.3 | Strategy 3: NIPT as first tier screening without an early anatomical assessment

This screening strategy offers NIPT at 10 weeks of gestation in combination with a second-trimester anomaly scan at 18–22 weeks. In this scenario, a systematic first-trimester anatomical assessment is not offered.

2.3.1 | Pro-arguments

This approach may be preferred for several reasons.

First, many health authorities still consider screening for trisomy 21 and, to a lesser extent, for trisomy 18 and 13 as the main objective of the FTS. The test performance of NIPT is clearly superior to that of the CT and therefore it seems logical to opt for NIPT. *Second*, for financial, ethical, or health economic reasons, screening strategies in most countries only include one anomaly scan, usually carried out at about 20 weeks. Pregnant women are well-aware of the existence of this scan and obstetricians/sonographers are trained to identify anomalies at this gestational age when the fetus is bigger and anatomical assessment is easier and more comprehensive, including additional 30% of structural anomalies that cannot be identified during the first trimester.[14,21]

In settings where screening policies can only offer one ultrasound investigation during pregnancy, it appears plausible to choose a second-trimester scan.

2.3.2 | Contra-arguments

Foregone detection of conditions associated with an increased nuchal translucency measurement

Fetal NT can only be correctly evaluated at 11–14 weeks of gestation and a large NT accidentally noticed below 11 weeks is difficult to interpret as normality curves or established management protocols are still missing.[42,43] Increased NT is associated with an increased risk of genetic and structural anomalies and overall poor pregnancy outcome.[44–46] The consequence of losing the NT measurement is highlighted by the study of Miranda et al.[39] The authors examined 226 pregnancies with an NT of 3.5 mm or higher at 11–13 weeks, including 84 fetuses with genetic abnormalities. NIPT would have only detected about 80% of the genetic aberrations. In a larger

population-based study, the frequency of atypical chromosome abnormalities (other than T21,18,13 or SCA) was 4.1% for those with an NT of 3.5 mm above.[47] For this reason, several scientific societies recommend invasive testing instead of NIPT if the NT thickness is above a threshold of 3.0 mm or 3.5 mm.[48,49] Even a genome-wide NIPT does not cover the large spectrum of genetic anomalies potentially related to an increased NT.[50] In a Dutch study of almost 2000 fetuses with an NT measurement above the 95th percentile (p95), the authors observed that 5% of fetuses had other genetic aberrations, 2% had single-gene disorders and a further 2% had submicroscopic chromosomal anomalies detected by chromosomal microarray alongside the common trisomies (trisomy 21, 18 and 13) and isolated structural anomalies, in 24% and 9% of cases respectively.[51] If women had only offered cfDNA instead of the CT, 36% of all congenital anomalies detectable in the first trimester would have remained undetected.

Loss of combined serum markers information

The possible implications of the disappearance of serum screening analysis as part of the CT are illustrated by two Danish studies.[52,53] Petersen et al. retrospectively examined almost 200,000 pregnancies investigated by the CT, including 1122 with an abnormal fetal karyotype. Of those, 23.4% would have been missed by NIPT alone. Abnormal PAPP-A or free beta-hCG levels were present in 3% of women, and the prevalence of atypical abnormal karyotypes in this high-risk cohort was 1.6%. In the cohort where free beta-hCG level was 0.2 or ≥5.0 MoM, 10.9% of the fetuses were found to be chromosomally abnormal and 21.1% of these were labeled as atypical. In another study of 877 pregnancies with available CT and microarray results, the risk of chromosomal abnormalities other than the common trisomies increased by 2.6 times for a beta-hCG concentration of less than 0.37 MoM.[53] Other studies have also highlighted that an increased CT risk not only identifies common trisomies but also genetic anomalies that can only be diagnosed by microavrray analysis.[54] Almost 5% of the fetuses with a combined risk of 1:10 or more had an atypical chromosomal abnormality.[28] However, it should be noted that so far, no studies have proven that first-trimester serum markers alone or in the CT risk assessment result in a higher detection rate of genetic anomalies compared to an approach with NIPT and a subsequent mid-trimester ultrasound examination. Furthermore, to precisely assess the yield of serum markers, screen-positive cases with increased NT should be excluded from the analysis.

Loss of anatomical assessment

A recent retrospective Dutch study has analyzed the effect on timing of detection of structural anomalies after NIPT replaced the CT in the Netherlands. A hypothetical maximum of 60% of the anomalies detected during the second-trimester scan could have potentially been recognized earlier. Of these, 13% were major anomalies that should always be detected in the first trimester. The absence of a first-trimester anomaly scan inevitably delays the time when anomalies are detected. If women opt for termination of pregnancy, this will be carried out later in pregnancy. This is unfortunate, as it has been shown that termination of pregnancy in the first trimester is safer and associated with better maternal psychological outcomes.[55,56]

Women's preference for early screening

Women favor early screening and a first-trimester anomaly scan does not negatively affect their psychological status. As expected, a confirmation of the normal fetal development at the 11–13 weeks scan decreases anxiety levels and increases well-being. In women with false positive results, well-being and anxiety levels temporarily increased following false-positive results at the early scan but normalized again after the abnormality was not confirmed.[11]

2.4 | Strategy 4: NIPT followed by a 12–13-week anatomical assessment

This strategy combines NIPT at 10 weeks of gestation followed by a first-trimester anomaly scan at 12–13 weeks and by a second-trimester anomaly scan at 18–22 weeks. When NIPT shows an abnormal result, women are referred to a fetal medicine unit for advanced ultrasonography and genetic testing.

2.4.1 | Pro-arguments

An argument in favor of this screening paradigm might be the timely reassurance of women on the risk of trisomy 21, 18 and 13. For this reason, and because in most patients (98%) with favorable results screening is completed before 14 weeks of gestation, this strategy has been suggested as patient friendly.[57] Also, like strategy 3, strategy 4 offers a high detection rate for common trisomies at the earliest gestational ages, but unlike strategy 3, information from individual CT markers, such as the NT, is not lost. Finally, in this approach the CT could be used as a back-up option in women with inconclusive NIPT results not wishing to undergo invasive testing, while keeping in mind that low fetal fraction is suggestive of higher risk for chromosomal anomalies like trisomy 13, 18 and Triploidy.[58] Indeed, it is generally recommended to offer invasive testing if NIPT is inconclusive after due to low fetal fraction.[59]

2.4.2 | Contra-arguments

First, NIPT would have been performed in cases where, a posteriori, a better genetic test would have been indicated. If the NT is increased and/or structural anomalies are found, an invasive test including a microarray analysis or whole-exome sequencing is more appropriate than NIPT.[60] Performing NIPT before the NT measurement does not allow for the correct identification of these cases and may lead to false reassurance of couples based on the normality of the NIPT results.[61,62] In a study where women with a normal NIPT (for Trisomy

TABLE 1 Summary of the three screening strategies with pro and contra arguments.

First trimester screening strategy	Most relevant pro arguments	Most relevant contra arguments
Strategy 1: *NIPT as second tier screening for patients in the intermediate risk group after the CT*	Higher detection rate of common trisomies than with CT only Lees invasive procedures needed in the intermediate group Opportunity of assessing fetal anatomy globally during the nuchal scan Simpler form of sequential screening than by measuring additional ultrasound markers in the intermediate group	Inferior performance than a NIPT-for-all strategy Loss of diagnostic power in the intermediate group when NIPT replaces chromosomal microarrays in screen positive women Delay in obtaining a definitive diagnosis after a positive NIPT in the intermediate-risk group
Strategy 2: *NIPT after a 12–13-week anatomical assessment*	Highest detection rate in screening for common trisomies Correct allocation of pregnancies to invasive testing and NIPT First trimester detection of major defects Individual CT markers are available in screening for other complications Cost effective	Later reassurance Invasive testing as backup option for inconclusive NIPT results
Strategy 3: *NIPT as first tier screening without an early anatomical assessment*	Highest detection rate in screening for common trisomies One mid-trimester anomaly scan less costly than two anomaly scans in the first and second trimester Second trimester anomaly scan is well established and easier to perform compared to a first-trimester anomaly scan	Low detection rates for fetal defects with the second-trimester scan could be improved by adding the first-trimester anomaly scan Individual components of CT are associated with other pregnancy complications and would be missed Late diagnosis of major defects causes psychological burden and delay the option of termination of pregnancy
Strategy 4: *NIPT followed by a 12–13-week anatomical assessment*	Highest detection rate in screening for common trisomies First trimester detection of major defects Timely reassurance of most patients Individual CT markers are available in screening for other complications CT as backup option for inconclusive NIPT results	NIPT would be performed even in pregnancies where invasive testing is more appropriate (increased NT/anomalies) or where there was a missed miscarriage Increased costs due to the unnecessary double testing for those with an ultrasound abnormality at 12–13 weeks (NIPT + invasive testing) Psychological burden due to changed management after early apparent reassurance

Abbreviations: CT, combined test; NIPT, non-invasive prenatal testing.

21, 18 and 13) were also offered a first-trimester scan, an unexpected finding was observed in 3.5% of pregnancies with normal NIPT.[63] These aspects should be discussed during prenatal counseling by clearly explaining the characteristics of each individual test.[64]

Second, while the costs of cfDNA have been decreasing, a screening policy where (genome wide) NIPT is universally offered to all women prior to any ultrasound investigation could potentially result in higher costs. An even further increase in the overall costs would be caused by the higher proportion of NIPTs with an inconclusive result requiring another draw for NIPT.

Third, when NIPT shows a screen-positive result as early as 10 weeks, pregnant women need to wait longer before the abnormal screening test can be further evaluated by an invasive test. This may lead to parental psychological distress and in some cases even to the decision to terminate the pregnancy, even before an invasive test can be performed.

A summary of the four strategies with corresponding pro- and contra-arguments is given in Table 1.

3 | CONCLUSION

While the combination of ultrasound as screening for structural anomalies and NIPT as screening for chromosomal anomalies is the accepted strategy for effective FTS, many factors must be considered when choosing how to combine the two methods in a screening strategy. The time of diagnosis, costs, financial resources, healthcare priorities and preference of women are important factors. Also, the consequences deriving from abandoning the CT and the diagnostic power of a more advanced genetic investigation (microarrays/WES) in screen-positive cases must be factored in. These aspects should be discussed during prenatal counseling to increase individual reproductive choices while ultimately being placed in the context of the

financial resources and the screening priorities of country-specific health policies.

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CONFLICT OF INTEREST STATEMENT

All authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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