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COMMENTARY

Controversies in implementing non-invasive prenatal testing in a public antenatal care program

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Abstract

Women's autonomy and an inclusive society for all individuals are highly valued in Norway. The Norwegian Biotechnology Act changed in 2020 allowing first-trimester screening and cell-free DNA for common trisomies to all pregnant women. However, implementing non-invasive prenatal testing (NIPT) in a public antenatal care program is difficult, because many patients, politicians, and medical professionals do not consider trisomy 21 a severe medical disease. Screening for trisomies at an early gestation might inevitably lead to an increase in pregnancy terminations and making cost–benefit calculations is ethically challenging. Moreover, offering NIPT to all pregnant women is debatable because of the lower prevalence of fetal trisomies in younger women. Therefore, appropriate genetic pre-test counseling is essential. Furthermore, organizing the service between private institutions and public hospitals poses another debate and challenges both quality and equal access to health services for women across the country.

KEYWORDS
cell-free DNA screening, non-invasive prenatal testing, Norway, prenatal screening, public antenatal care

Norway was ranked the most prosperous country in the world based on happiness and financial health in 2015.[1] We are "stone rich" with a robust public healthcare system. High-quality pregnancy care is provided free of charge to all women, resulting in one of the lowest rates of perinatal morbidity and mortality worldwide. However, prenatal genetic testing has, until recently, not been available to all Norwegian women. The restricted use has been a consequence of regulations in a conservative Norwegian Biotechnology Act.

In Norway, all pregnant women were offered one mid-trimester scan, whereas additional scans were performed only on clinical indications. For reasons unknown, the Norwegian Biotechnology Act defined a mid-trimester scan as routine antenatal care, whereas first-trimester screening was considered prenatal genetic diagnostics to be performed at a fetal medicine center approved by the Directorate of Health. Despite this, women could pay for prenatal ultrasound at private institutions in Norway or abroad. A survey from Oslo performed in 2019 found that 86% of women paid for a private ultrasound examination early in pregnancy.[2]

In March 2017, the government introduced non-invasive prenatal testing (NIPT) into the public antenatal care program. Cell-free DNA screening was allowed as a second-tier test for women older than 38 years who had high risk of trisomy following the first-trimester

Abbreviation: NIPT, non-invasive prenatal testing

combined serum screening. Women with an individual risk of trisomy 21 greater than 1:250 or risk of trisomy 18/13 greater than 1:150 were offered cell-free DNA or invasive procedures. The argument for introducing NIPT was that cell-free DNA screening could replace invasive procedures and reduce the risk of procedure-related spontaneous abortions.

The strict regulations in the Norwegian Biotechnology Act resulted in widespread "reproductive medicine tourism". Indeed, one-third of pregnant women from the Oslo area traveled abroad to undergo ultrasound and NIPT in private clinics in Sweden and Denmark.[2] As a result of the travel restrictions caused by the coronavirus disease 2019 pandemic in 2020, closed borders created an additional problem.

In May 2020, the Norwegian parliament made major improvements to the Biotechnology Act, after a process driven by the opposition parties. It was decided that all women would gain access to routine ultrasound in the first and second trimesters and that women older than 35 years and those with increased risk for fetal malformations/aneuploidy, would be offered cell-free DNA screening through the public antenatal care program.

1 | THE CURRENT SITUATION IN NORWAY

Although the Biotechnology Act was changed "overnight", implementing the changes into medical practice has been slow. Today, 1.5 years later, first-trimester ultrasound and cell-free DNA are not fully implemented in the public antenatal care program. Women older than 35 years have been offered ultrasound and NIPT since January 1, 2022. Younger women will be offered their routine first-trimester ultrasound as part of the public antenatal care program at some point during 2022, but they will not be offered NIPT free of charge if the scan is normal.

Institutions offering prenatal testing in Norway must be approved by the Directorate of Health as prenatal testing is still under the Biotechnology Act. Only five fetal medicine centers have had approval until 2021. However, the new Biotechnology Act has opened the way for approval of NIPT testing in local hospitals and private institutions under specific conditions. This has opened a lucrative private market. Pregnant women less than 35 years of age pay 750–1000 euros for a consultation consisting of an ultrasound scan for pregnancy dating and cell-free DNA screening for trisomies. In some cases, sex chromosomal aneuploidies and copy number variations are also reported, even if such testing is not allowed by regulation. The actual cost of cell-free DNA screening in Norway is estimated to be around 200–450 euros, depending on test sample volumes, implying a rather large profit for private institutions.

Recently we have experienced a "brain drain" from Norwegian hospitals when trained midwives and doctors choose to work in private institutions, earning more compared with working in public hospitals. Consequently, it has become more difficult for the public health system to organize the new service for all pregnant women.

Key message

Fetal medicine and prenatal testing are crossroads between medicine, technology, politics, and ethics. Introducing cell-free DNA screening in a public antenatal care program is controversial.

In our opinion, the delay in implementing first-trimester screening in Norway is a result of political polemics. The Norwegian Parliament in 2020 made major revisions in the Biotechnology Act against the government parties' votes; as a result, the amendments were not followed by the political will to implement the changes.

In addition, the government has given directives regarding the organization of the service, which in our opinion are unwise. It was decided that private institutions and public hospitals should both provide an NIPT service instead of organizing the service as a public screening program directed to all women. Furthermore, private providers are unevenly distributed around Norway, resulting in less availability to women living outside the cities. This is problematic in a country with large distances and sparsely populated regions. We believe that splitting the service between private and public clinics is problematic for several reasons. First, the laboratory services depend on large-scale sample volumes to ensure cost-efficient analysis. Second, all women with positive NIPT results are referred to public fetal medicine centers offering genetic counseling and confirmatory invasive procedures. Therefore, we argue that performing all cell-free DNA tests in public laboratories would ensure the quality of pre-test counseling and simplify logistics, saving both patients and staff money and time.

After the election in September 2021, a new government has taken over. Whether the new government will facilitate the organization of first-trimester screening is yet to be seen.

2 | HOW SHOULD WE IMPLEMENT NIPT IN THE PUBLIC ANTENATAL CARE PROGRAM?

Cell-free DNA has proven its superiority as a screening test for fetal trisomies compared with combined first-trimester screening.[3] The use of cell-free DNA screening for all pregnant women regardless of maternal age or background risk of chromosomal abnormality has been endorsed by several professional societies.[4] Moreover, screening for rare or atypical chromosomal aberrations could be plausible also in the younger population, as maternal age does not increase the risk of fetal copy number variation, other than trisomy caused by meiotic non-disjunction.

If screening is performed by public hospitals with competence of delivering proper pre-test and post-test counseling, one might argue that the public antenatal screening program could also include other

rare, albeit clinically significant, chromosomal aberrations that, with a high level of certainty, will give rise to either fetal demise or severe disease in the newborn. However, screening for sex chromosomes or recurrent microdeletions and duplications should be refrained from, because sex chromosome aberrations and many copy number variations are associated with a wide spectrum of phenotypes. Such screening imposes stringent requirements regarding genetic counseling, demands that seem hard to fulfill through a national screening program.

Overall, the sensitivity and specificity of cell-free DNA screening for common fetal trisomies are high, with a low failure rate, and acceptable false results.[3] Nevertheless, placental mosaicism and "vanishing twin" pregnancies can cause false-positive results. Consequently, all positive NIPT results should be confirmed by invasive testing. Fetal DNA sampling before considering termination of pregnancy is particularly important when a fetal anomaly scan is normal.

According to a recent survey, 25%–50% of pregnant women in the Netherlands, Italy, Austria, and Spain, and over 75% of Belgian women, are tested with cell-free DNA for trisomies.[5] In Scandinavia, France, the Netherlands, and Belgium women are partially or fully reimbursed by the national healthcare system. In Belgium, pregnant women are charged 8 euros but in the Netherlands the individual cost for NIPT is 175 euros. In most other European countries, women have to pay themselves.[5] In the Netherlands, women can also choose screening for other rare chromosomal aberrations through a nationwide implementation study on NIPT.[6] Denmark has decided to keep the combined first-trimester screening as a first-tier test because the test is widely adopted within the Danish population. In Sweden, there are mixed strategies according to in which *län* the woman lives. In Norway, the fetal medicine network has suggested a national strategy for implementing first-trimester ultrasound and cell-free DNA in local hospitals and fetal medicine units according to the new regulations (Figure 1). This algorithm should be evaluated by an implementation study regarding women's preferences and clinical outcome data.

3 | WHY NOT OFFER NIPT TO ALL PREGNANT WOMEN?

The principles of autonomy in decision-making and the right to be informed about one's own health has a high standing in most European countries. Nonetheless, there is a conflict between women's autonomy and fetal existential value, inevitably linking prenatal testing to termination of pregnancy,

Cell-free DNA testing for trisomies has high sensitivity (95%–100%) and specificity (99.6%). The positive predictive value for cell-free DNA for women aged 35 years or older is high (for trisomy 21, 97%; for trisomy 18, 88%; and for trisomy 13, 67%), but this is not the case for younger women. Indeed, for women aged 20–29 years, NIPT has lower positive predictive values (for trisomy 21, 73%; for trisomy 18, 51%; and for trisomy 13, 28%).[7]

For example, a 29-year-old woman has an age-related risk for trisomy 21 of 1:1000. If the first-trimester scan is normal, her risk is reduced (1:2000), because ultrasound alone can detect 50% of cases of trisomy 21. As the positive predictive value of cell-free DNA in young women is 28%–73%, the universal screening will result in false-positive results. As a result, cell-free DNA screening in young women is not straightforward from a medical perspective.

Introducing new technology or new medical treatment into a national healthcare system should undergo economic evaluation. Most countries have some sort of regulatory agency weighing benefits against costs (eg, 5-year survival or quality-adjusted life-years against costs). However, cost–benefit analysis is not straightforward regarding universal cell-free DNA screening for fetal trisomies. Given that the "benefit" of NIPT is termination of pregnancy, it is ethically challenging to calculate saved costs for avoiding the birth of a baby with Down syndrome in a country ranking on top of the prosperity index because of the freedom it offers its citizens, the quality of its healthcare system and social bonds between its people. Can we make these calculations in a society "with room for all"? And—in the end—should preparing for a disabled child also count as an important "benefit" of screening, bringing valuable information to the parents to be?

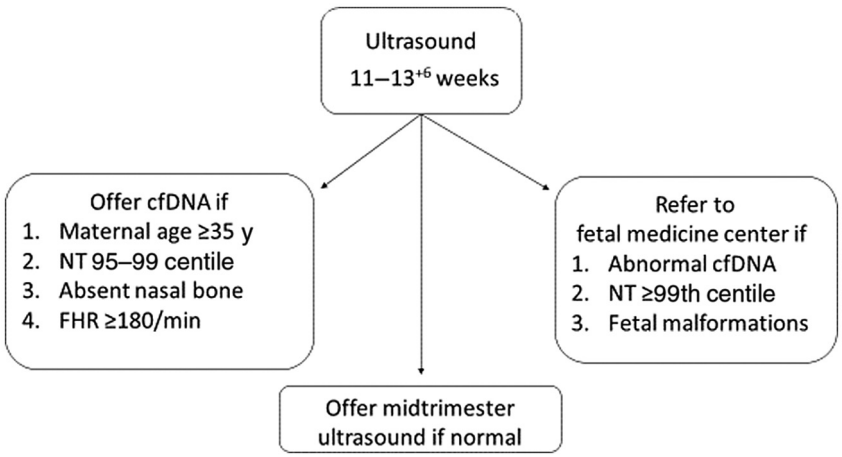

FIGURE 1 Algorithm for first-trimester ultrasound and cell-free DNA to be implemented in clinical practice in Norway from January 1, 2022. Abbreviations: cfDNA, cell-free DNA; FHR, fetal heart rate; NT, nuchal translucency

4 | CONCLUSIONS

We should consider first-trimester ultrasound and cell-free DNA screening for all women regardless of age. One could argue that including clinically significant rare "atypical" chromosomal aberrations in a public screening program might be beneficial following proper parental counseling and informed consent. In case of structural fetal malformations or genetic predisposition, invasive testing should be the first choice. We argue strongly against the current Norwegian directives regarding the organization of the service. All women will eventually be offered a first-trimester scan in the public hospitals, but young women should be able to make a co-payment if they opt for cell-free DNA as well.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

AUTHOR CONTRIBUTIONS

VS had the idea, KÅBS wrote the first draft, and all authors commented and accepted the final manuscript.

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