Social and medical need for whole genome high resolution NIPT

Malgorzata I. Srebniak1 | Maarten F. C. M. Knapen2 | Lutgarde C. P. Govaerts1 | Marike Polak3 | Marieke Joosten1 | Karin E. M. Diderich1 | Laura J. C. M. van Zutven1 | Krista A. K. E. Prinsen2 | Sam Riedijk1 | Attie T. J. I. Go2 | Robert-Jan H. Galjaard1 | Lies H. Hoefsloot1 | Diane Van Opstal1

1Department of Clinical Genetics, Erasmus MC, Rotterdam, the Netherlands
2Department of Obstetrics and Fetal Medicine, Erasmus MC, Rotterdam, the Netherlands
3Institute of Psychology, Erasmus University Rotterdam, Rotterdam, the Netherlands

Correspondence
Malgorzata I. Srebniak, Department of Clinical Genetics, Erasmus MC, Rotterdam, the Netherlands.
Email: m.srebniak@erasmusmc.nl

Abstract

Background: Two technological innovations in the last decade significantly influenced the diagnostic yield of prenatal cytogenetic testing: genomic microarray allowing high resolution analysis and noninvasive prenatal testing (NIPT) focusing on aneuploidy. To anticipate future trends in prenatal screening and diagnosis, we evaluated the number of invasive tests in our center and the number of aberrant cases diagnosed in the last decade.

Methods: We retrospectively analyzed fetal chromosomal aberrations diagnosed in 2009–2018 in 8,608 pregnancies without ultrasound anomalies.

Results: The introduction of NIPT as the first-tier test led to a substantial decrease in the number of invasive tests and a substantially increased diagnostic yield of aneuploidies in the first trimester. However, we have also noted a decreased detection of submicroscopic aberrations, since the number of invasive tests substantially decreased. We have observed that pregnant women were interested in broader scope of prenatal screening and diagnosis than detection of common trisomies.

Conclusion: Since the frequency of syndromic disorders caused by microdeletions/microduplications is substantial and current routine NIPT and ultrasound investigations are not able to detect them, we suggest that a noninvasive test with resolution comparable to microarrays should be developed, which will also meet patient’s needs.

KEYWORDS
diagnostic yield, microarray, NIPT, patients preferences, prenatal diagnosis

Technological innovations in the last decade significantly influenced the diagnostic yield of prenatal cytogenetic testing. This impact mostly depends on the testing resolution (Srebniak et al., 2017). In fetuses without ultrasound anomalies at the time of sampling (referred due to advanced maternal age [AMA], abnormal first trimester combined test [ftCT] results [with nuchal translucency, NT <3.5 mm], recurrence risk for chromosome aberrations), we, as others, previously showed that the replacement of karyotyping by microarray (in our clinic in 2012) led to a higher yield of pathogenic chromosome aberrations (Srebniak et al., 2017; Van Opstal et al., 2015; Vogel et al., 2018; Wapner et al., 2012). Moreover, our group showed that the majority of pregnant women opted for maximal information when applying for invasive testing.
SREBNIKA ET AL. (Srebniak et al., 2011; van der Steen et al., 2015). In 2014, the introduction of genome-wide noninvasive prenatal testing (NIPT) in the Netherlands as an alternative for invasive testing in a high risk population (abnormal ftCT >1:200, previous child with trisomy), led to a decreased diagnostic yield in the test population in our region (Srebniak et al., 2017). This decrease was mostly caused by an inherent prenatal under-detection of submicroscopic aberrations, since the vast majority of pregnant women preferred NIPT (with limited resolution of ~15–20 Mb) over invasive diagnostic testing (resolution ~500 kb) (Van Opstal et al., 2015). Concerns on this under-detection of chromosome aberrations were also noted by Evans, Andriole, et al., (2018) and Evans, Evans, Bennett, & Wapner, (2018).

We have seen that the noninvasive character of NIPT has a tremendous psychological impact on pregnant women. More patients with high risk results after ftCT were willing to undergo follow-up investigations after NIPT was introduced than when only invasive testing was available. Because after introduction of NIPT in high risk pregnancies (with abnormal ftCT results) a decrease of diagnostic yield was noticed, we have previously concluded that NIPT should not be offered as second-tier screening test (Srebniak et al., 2017). Since 2017, NIPT as a first-tier screening test is available for every pregnant women in the Netherlands in the TRIDENT2 study (van der Meij et al., 2019). Following our previous study (Srebniak et al., 2017), we also wanted to investigate the effect of this major change in the national screening program on the overall diagnostic yield in our region, where we routinely offer microarray for cytogenetic investigations of chorionic villi and amniotic fluid. To achieve that, we analyzed the frequency of fetal chromosomal aberrations diagnosed in our laboratory in the time period 2009–2018 in 8,608 pregnancies. These were pregnancies without fetal ultrasound anomalies at the time of sampling, that were referred for invasive prenatal microarray testing due to AMA, abnormal ftCT (with NT <3.5 mm), recurrence risk for chromosome aberrations or abnormal NIPT results. We evaluated not only the number of aberrant cases, but also the number of invasive tests in our center. Such evaluations are indispensable to anticipate future trends in prenatal screening and diagnosis. The retrospective analysis method and exclusion criteria were used as described before (Srebniak et al., 2017).

Evaluation of the influence of NIPT as a first-tier screening test and future perspectives: The introduction of NIPT as the first-tier test in our region led to the following.

1. A substantial decrease of the number of invasive tests in pregnant women without fetal ultrasound anomalies: from 1,176 in 2009 (AMA >35 year or abnormal ftCT), to 846 (2015, after introduction of NIPT as a second tier test and after abolishment of AMA as indication for prenatal diagnosis) and further down to 363 in 2018 (after introduction of NIPT as a first tier screening) (Figure 1).

2. In contrast to the previous study (Srebniak et al., 2017), a substantially increased diagnostic yield of pathogenic fetal chromosomal aberrations (Figures 1 and 2) in the first trimester was noted. The observed increase mainly involved the common aneuploidies (Figure 2).

3. However, it was noted that the total number of trisomy 21 cases diagnosed per year in all tested pregnancies (with or without ultrasound anomalies) still did not notably change, most probably due to the fact that uptake for

![FIGURE 1](image-url)
prenatal screening/testing did not increase with the introduction of NIPT.

4. We have noted a further decreased detection of submicroscopic aberrations (Figure 2), since the number of invasive tests substantially decreased and current NIPT resolution in our laboratory is still limited to ~15–20 Mb, enabling the detection of microscopically visible chromosome aberrations, but missing the submicroscopic ones. Moreover, detection is limited to autosomal chromosome aberrations.

From this study, we may conclude that the current prenatal screening program in the Netherlands is effective for common trisomies in our region, because it reduces the number of invasive testing, increases the efficiency of invasive prenatal testing and maintains the diagnostic yield of Down syndrome cases. Unfortunately due to limited NIPT resolution, it also shows that microdeletions/microduplications to a large extent will remain undiagnosed prenatally, and we previously showed that these disorders are unlikely to be detected by ultrasound examination (Srebniak et al., 2018). It is concerning as their incidence is rather high: 1:270, which is much higher than the prevalence of Down syndrome in younger women (Srebniak et al., 2018).

Our research data also showed that pregnant women are highly interested in more than screening for common aneuploidies, but are not willing to opt for invasive testing due to the risk for a miscarriage (van der Steen, 2019). This is also supported by the Dutch TRIDENT 2 study that showed that the majority (ca. 80%) of pregnant couples chooses whole genome testing instead of targeted testing of the common trisomies (van der Meij et al., 2019).

In conclusion, since the frequency of syndromic disorders caused by microdeletions/microduplications is substantial and because current prenatal screening protocols with NIPT focusing on aneuploidies and ultrasound investigations are not able to detect them, we suggest that a noninvasive test (either cfDNA [Fiorentino et al., 2017] or cell-based [Vossaert et al., 2018]) with resolution comparable to microarrays should be developed, which will also meet patient’s needs.

CONFLICT OF INTEREST
All authors declare no conflict of interests.

ORCID
Malgorzata I. Srebniak https://orcid.org/0000-0003-3429-6156

REFERENCES
Evans, M. I., Andriole, S., Curtis, J., Evans, S. M., Kessler, A. A., & Rubenstein, A. F. (2018). The epidemic of abnormal copy number variant cases missed because of reliance upon noninvasive prenatal screening. *Prenatal Diagnosis*, 38(10), 730–734. https://doi.org/10.1002/pd.5275
Evans, M. I., Evans, S. M., Bennett, T. A., & Wapner, R. J. (2018). The price of abandoning diagnostic testing for cell-free fetal DNA screening. *Prenatal Diagnosis*, 38(4), 243–245. https://doi.org/10.1002/pd.5226
Fiorentino, F., Bono, S., Pizzuti, F., Duca, S., Polverari, A., Faieta, M., … Spinella, F. (2017). The clinical utility of genome-wide non invasive prenatal screening. *Prenatal Diagnosis*, 37(6), 593–601. https://doi.org/10.1002/pd.5053
Srebniak, M., Boter, M., OudeEluijs, G., Joosten, M., Govaerts, L., Van Opstal, D., & Galjaard, R.-J. H. (2011). Application of SNP array for rapid prenatal diagnosis: Implementation, genetic counselling
Srebniak, M. I., Joosten, M., Knapen, M., Arends, L. R., Polak, M., van Veen, S., … Van Opstal, D. (2018). Frequency of submicroscopic chromosomal aberrations in pregnancies without increased risk for structural chromosomal aberrations: Systematic review and meta-analysis. *Ultrasound in Obstetrics and Gynecology, 51*(4), 445–452. https://doi.org/10.1002/uog.17533

Srebniak, M. I., Knapen, M., Polak, M., Joosten, M., Diderich, K. E. M., Govaerts, L. C. P., … Van Opstal, D. (2017). The influence of SNP-based chromosomal microarray and NIPT on the diagnostic yield in 10,000 fetuses with and without fetal ultrasound anomalies. *Human Mutation, 38*(7), 880–888. https://doi.org/10.1002/humu.23232

van der Meij, K. R. M., Sistermans, E. A., Macville, M. V. E., Stevens, S. J. C., Bax, C. J., Bekker, M. N., … Weiss, M. M. (2019). TRIDENT-2: National implementation of genome-wide non-invasive prenatal testing as a first-tier screening test in the Netherlands. *The American Journal of Human Genetics*. [Epub ahead of print]. https://doi.org/10.1016/j.ajhg.2019.10.005

van der Steen, S. L. (2019). *The New Era of Prenatal Genetic Testing Considerations regarding the scope, psychological consequences and pregnant couples’ preferences* [Internet]. Rotterdam: Erasmus University Rotterdam. Retrieved from: http://hdl.handle.net/1765/114728

van der Steen, S. L., Diderich, K. E., Riedijk, S. R., Verhagen-Visser, J., Govaerts, L. P., Joosten, M., … Galjaard, R. J. (2015). Pregnant couples at increased risk for common aneuploidies choose maximal information from invasive genetic testing. *Clinical Genetics, 88*(1), 25–31. https://doi.org/10.1111/cge.12479

Van Opstal, D., de Vries, F., Govaerts, L., Boter, M., Lont, D., van Veen, S., … Srebniak, M. I. (2015). Benefits and burdens of using a SNP array in pregnancies at increased risk for the common aneuploidies. *Human Mutation, 36*(3), 319–326. https://doi.org/10.1002/humu.22742

Vogel, I., Petersen, O. B., Christensen, R., Hjett, J., Lou, S., & Vestergaard, E. M. (2018). Chromosomal microarray as primary diagnostic genomic tool for pregnancies at increased risk within a population-based combined first-trimester screening program. *Ultrasound in Obstetrics and Gynecology, 51*(4), 480–486. https://doi.org/10.1002/uog.17548

Vossaert, L., Wang, Q., Salman, R., Zhuo, X., Qu, C., Henke, D., … Beaudet, A. (2018). Reliable detection of subchromosomal deletions and duplications using cell-based noninvasive prenatal testing. *Prenatal Diagnosis, 38*(13), 1069–1078. https://doi.org/10.1002/pd.5377

Wapner, R. J., Martin, C. L., Levy, B., Ballif, B. C., Eng, C. M., Zachary, J. M., … Jackson, L. (2012). Chromosomal microarray versus karyotyping for prenatal diagnosis. *New England Journal of Medicine, 367*(23), 2175–2184. https://doi.org/10.1056/NEJMoa1203382

**How to cite this article:** Srebniak MI, Knapen MFCM, Govaerts LCP, et al. Social and medical need for whole genome high resolution NIPT. *Mol Genet Genomic Med.* 2020;8:e1062. https://doi.org/10.1002/mgg3.1062