REVIEW

Recent advances in prenatal genetic screening and testing

[version 1; peer review: 3 approved]

Ignatia B. Van den Veyver

Department of Obstetrics and Gynecology and Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas, 77030, USA

V1 First published: 28 Oct 2016, 5(F1000 Faculty Rev):2591
<https://doi.org/10.12688/f1000research.9215.1>

Latest published: 28 Oct 2016, 5(F1000 Faculty Rev):2591
<https://doi.org/10.12688/f1000research.9215.1>

Abstract

The introduction of new technologies has dramatically changed the current practice of prenatal screening and testing for genetic abnormalities in the fetus. Expanded carrier screening panels and non-invasive cell-free fetal DNA-based screening for aneuploidy and single-gene disorders, and more recently for subchromosomal abnormalities, have been introduced into prenatal care. More recently introduced technologies such as chromosomal microarray analysis and whole-exome sequencing can diagnose more genetic conditions on samples obtained through amniocentesis or chorionic villus sampling, including many disorders that cannot be screened for non-invasively. All of these options have benefits and limitations, and genetic counseling has become increasingly complex for providers who are responsible for guiding patients in their decisions about screening and testing before and during pregnancy.

Keywords

prenatal screening, genetic abnormalities, pregnancy, risk

Open Peer Review

Approval Status

	1	2	3
version 1 28 Oct 2016			

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

1. **Steven Warsof**, Eastern Virginia Medical School, Norfolk, USA
2. **Neeta Vora**, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, USA
3. **Peter Benn**, University of Connecticut Health Center, Farmington, USA

Any comments on the article can be found at the end of the article.

Corresponding author: Ignatia B. Van den Veyver (iveyver@bcm.edu)

Competing interests: The author declares that they have no competing interests.

Grant information: The author(s) declared that no grants were involved in supporting this work.

Copyright: © 2016 Van den Veyver IB. This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Van den Veyver IB. **Recent advances in prenatal genetic screening and testing [version 1; peer review: 3 approved]** F1000Research 2016, 5(F1000 Faculty Rev):2591 <https://doi.org/10.12688/f1000research.9215.1>

First published: 28 Oct 2016, 5(F1000 Faculty Rev):2591 <https://doi.org/10.12688/f1000research.9215.1>

Introduction

For more than 30 years, identifying women at increased risk for pregnancies with Down syndrome has been the focus of prenatal screening programs that combine maternal age, levels of specific analytes in maternal serum, and ultrasound findings in the first or second trimester to derive a risk estimate for Down syndrome and secondarily for trisomy 18. These programs now reach a detection rate of up to 88–96% for Down syndrome and up to 85–95% for trisomy 18^{1,2}, depending on whether screening is performed in the first or second trimester of pregnancy, or both. In parallel, programs for universal parental carrier screening for autosomal recessive disorders, such as cystic fibrosis, as well as ethnicity-based carrier screening, such as for conditions more prevalent in the Ashkenazi Jewish population, were developed to identify parents at 25% risk of having an affected child with these disorders³. Identified carrier couples can then choose preimplantation genetic diagnosis to avoid affected pregnancies, or prenatal diagnosis, allowing them to consider termination of affected pregnancies or be prepared for the birth of an affected child.

With recent technological advances in methods to identify numerical and structural chromosome abnormalities and point mutations, such as array-based copy-number analysis, also known as chromosomal microarray analysis (CMA), and next-generation sequencing (NGS), the screening for and diagnosis of genetic abnormalities in the fetus is undergoing an unprecedented rapid evolution^{4–13}. In parallel, CMA and NGS have also accelerated the discovery of causes of intellectual disability, birth defects, and many rare genetic and genomic disorders^{14–17}. This has motivated the development of expansive carrier screens for hundreds of genetic disorders at once as well as the development of non-invasive cell-free fetal DNA (cffDNA)-based screens for fetal chromosomal aneuploidy, subchromosomal abnormalities, and single-gene disorders. The availability of CMA- and NGS-based methods, such as targeted gene-panel sequencing and, recently, whole-exome sequencing (WES), has also resulted in the ability to diagnose more fetal genetic conditions from samples obtained through amniocentesis or chorionic villus sampling (CVS).

All of these new tests have created new, exciting opportunities for comprehensive prenatal diagnosis and screening, but they are accompanied by important challenges. Healthcare providers must consider the consequences of their rapid introduction into the clinic because of the still-limited knowledge about the test performance of some assays in routine clinical practice, concerns related to cost-conscious implementation of optimized screening and testing strategies, equal access, and appropriate selection of who will benefit most. The ever-increasing amount of genetic information that can be obtained preconceptionally and prenatally also brings about ethical and genetic counseling challenges^{9,18–21}.

The introduction of chromosomal microarray analysis into prenatal diagnosis

The early goal of prenatal genetic screening was to identify women at increased risk for having a pregnancy with Down syndrome, resulting from an extra chromosome 21 (trisomy 21), the most common aneuploidy in liveborns, and, secondarily, Edwards syndrome (trisomy 18) and Patau syndrome (trisomy 13), so that a diagnostic

amniocentesis (withdrawing amniotic fluid from inside the uterus that contains fetal cells) or CVS (obtaining a small sample from the placenta) can be offered to those at increased risk. For many years, the standard test on cultured cells from prenatally obtained amniotic fluid or CVS has been a karyotype (chromosome analysis) that can detect chromosomal aneuploidy (extra or missing chromosomes) and structural abnormalities larger than 5–10 megabases (Mb) in size. This is sometimes supplemented by fluorescence *in situ* hybridization (FISH) to rapidly test for a few common aneuploidies if an expedited diagnosis is desired. FISH with locus-specific probes was also the method of choice to test for smaller structural chromosomal abnormalities but requires knowledge about which locus might be of interest, and only a few loci can be investigated in a single assay.

This dramatically changed when CMA became available, in which fluorescently labeled DNA is hybridized to a slide that carries thousands of probes spread across the genome. Higher or lower fluorescence intensity coming from DNA hybridized to specific probes identifies regions that have extra or missing copies of DNA, respectively. CMA has a much higher resolution than karyotyping, spanning from entire chromosomes (aneuploidy), to deletions and duplications of just several kilobases (kb) or even single exons. It also does not require cell culture, thus results can be available faster. CMA is now the first-tier genetic diagnostic test for children and adults with multiple congenital anomalies, genetic syndromes, and intellectual and developmental disabilities, where its diagnostic yield is 15 to 20%²². Widespread use of CMA for prenatal diagnosis lagged behind until results from a landmark multicenter trial sponsored by the National Institutes of Health, confirmed by other studies, demonstrated that CMA detects a clinically significant and potentially clinically significant copy number change in 1.7% of pregnancies with a normal karyotype and no observable fetal abnormalities; others have found a rate of 1% for clinically significant copy number variations (CNVs)²³. However, CMA also detects CNVs of uncertain clinical significance and that predispose to later-onset disorders in about 1% of cases (up to approximately 2%, depending on the study). This increases to 6% when there are congenital anomalies in the fetus^{5,23}. CMA also performs better than a karyotype for the analysis of stillbirth samples²⁴. The American College of Obstetrics and Gynecology now recommends that CMA is offered as the first-line test when fetal abnormalities are present and for stillbirth samples²⁵. CMA is also better than karyotyping for genetic studies of early miscarriages. Although about 50% of miscarriages are aneuploid, some have subchromosomal abnormalities and standard karyotyping is compromised in 40% owing to culture failure or maternal-cell contamination²⁶.

The significantly higher detection rate of chromosomal abnormalities with CMA, along with recommendations that amniocentesis should be made available to all women²⁷, led to predictions that more women would accept the small risk of amniocentesis or CVS for this benefit, which in a recent meta-analysis was found to be 0.11% or 1:909 and 0.22% or 1:454, respectively²⁸, and not elevated compared to background in another recent study²⁹. However, new developments in cffDNA-based non-invasive screening of maternal plasma or fetal aneuploidy reversed this expected trend, with a dramatic decrease in the number of diagnostic procedures performed³⁰.

Contributing to this decrease are a combination of assertive marketing of the new cfDNA-based tests by industry, incomplete understanding about the clinical performance and screening nature of cfDNA analysis, and a desire by women to avoid any potential risk to their pregnancies.

How cell-free fetal DNA analysis has changed the approach to prenatal diagnosis of genetic and chromosomal abnormalities

An ideal prenatal genetic diagnostic test would be both non-invasive and comprehensive, capable of simultaneously detecting chromosomal aneuploidy, structural chromosomal abnormalities, and single-gene mutations. Early efforts in the 1990's focused on isolating fetal cells and analyzing them for chromosomal aneuploidy, but the success rate was no better than standard maternal serum screening³¹. This was primarily because these circulating fetal cells are rare and difficult to purify and the diagnostic tools, mostly single-cell FISH, were limited. When Lo *et al.* discovered in 1997 that male fetal DNA could be amplified by PCR from maternal plasma³², attention shifted to the analysis of cfDNA from maternal plasma. Initially, PCR-based assays to identify fetal gender³³, fetal Rhesus genotype^{34–39}, and mutations that cause paternally inherited or *de novo* single-gene disorders were developed, which is an ongoing field of active investigation^{40–44}. In 2008, two groups reported that shotgun NGS of cell-free DNA (cfDNA) from maternal plasma, of which about 10% originates from the placenta and represents the fetal genome, can be used to determine if there is fetal aneuploidy by counting sequence tags mapped to each chromosome^{45,46}. Following this, a number of technical and clinical validation studies collectively showed high sensitivity and specificity for the detection of Down syndrome and other common aneuploidies in pregnant women at increased risk for fetal aneuploidy^{47–56}. Different technologies, one based on massively multiplexed PCR and another based on selection and sequencing of specific tags from chromosomes of interest, have also been developed and have similar performance^{57–65}. Overall, cfDNA-based tests have a detection rate and false positive rate of 99.4% and 0.16%, respectively, for Down syndrome, 96.6% and 0.05% for trisomy 18, 86.4% and 0.09% for trisomy 13, and 89.5% and 0.20% for monosomy X¹. Those numbers were mostly obtained from studies in a high-risk population⁶⁶, where the positive predictive value (PPV) for common aneuploidies, such as trisomy 21, is high and does not take into account the small numbers of samples where no result was obtained. As a reminder, PPV indicates how often a positive test result reflects a true positive and depends on the prevalence of the condition in the population studied. The PPVs of cfDNA screening are lower in low-risk or average-risk populations^{52,56,59,62,65,67–69} but still significantly better than those of the standard multiple marker serum screening algorithms¹. Together with reports from cytogenetic laboratories of relatively low confirmation rates in fetal samples studied because of positive cfDNA screening results^{70,71}, this has raised concern that non-invasive cfDNA testing for aneuploidy is less accurate when applied in clinical practice than was expected based on the published validation studies, which is an issue that has not yet been completely resolved and is to some degree also platform dependent. This underscores the need for objective genetic counseling with emphasis on the screening nature and limitations on the accuracy of these tests. Some companies also offer cfDNA screening for

twin pregnancies, but test performance is lower, in part because the cfDNA is a mixture of DNA from two fetuses⁷². One study has shown that this also influences results when a twin pregnancy has very early loss of one fetus or “vanishing twin” and that cfDNA from the trophoblast of the demised twin can be found up to 8 weeks after the demise⁷³.

As experience with cfDNA screening grows, other unknowns and caveats have emerged that complicate pre- and post-test genetic counseling. Because circulating cfDNA derives from the trophoblast, confined placental mosaicism for a tested chromosomal abnormality, known from CVS studies to be present in about 1%⁷⁴, may result in a positive cfDNA test, but the fetus is unaffected^{72,75–77} when follow-up diagnostic testing on amniotic fluid samples (preferred over CVS in these situations) is performed. Since cfDNA is admixed with a large excess of maternal cfDNA fragments, maternal mosaicism for the detected chromosomal abnormality in the mother⁷² may also cause a positive cfDNA screening result. For example, low-level germline or acquired mosaicism for monosomy X has been well described^{78,79}. Depending on which platform is used, <1 to 5% of the tests may fail, which has also been found to be associated with a higher risk for fetal aneuploidy⁸⁰. One cause of this could be low fetal fraction (i.e. the proportion of all the cfDNA in maternal plasma that is fetal) owing to placental abnormalities in some aneuploidies^{72,81}. However, other more common causes for low fetal fraction are a high maternal body mass index or early gestational age^{72,82,83}, the reason that cfDNA screening is not recommended before 10 weeks' gestation. Bianchi *et al.* first reported that rarely false positive cfDNA-screening results, particularly those suggestive of multiple aneuploidies or aneuploidy incompatible with embryonic or fetal development, may be associated with maternal malignancy, with the chromosomally abnormal cfDNA originating from tumor cells^{84–86}. While this is of potential high clinical impact, it is not currently established what the optimal follow-up for such women should be. Other maternal reasons for abnormal cfDNA-screening results can be the presence of fibroids⁸⁷ or, in rare cases, transplanted organs.

After initial demonstration that microdeletions can be detected in cfDNA^{88–92}, some providers now offer the option to add screening for selected clinically significant microdeletions and also rarer aneuploidies (trisomy 9, 16, and 22)^{93–99}. One provider in the United States recently began offering genome-wide cfDNA screening for deletions and duplications of >7 Mb^{100,101}. Rigorous clinical validation of these expanded cfDNA tests is problematic^{102,103} because these additional genetic conditions are each very rare and there is significant concern for high cumulative false positive and false negative rates.

To date, guidance offered by professional societies on cfDNA analysis state that they are screening tests and do not replace diagnostic testing^{1,2,104–108}. Most, but not all^{105,108}, also recommend offering it only to women at increased risk for aneuploidy, but all state that cfDNA screening for microdeletions has not yet been sufficiently clinically validated. Despite this, and likely because of intense marketing, many women are being offered cfDNA screening, irrespective of *a priori* risk, and the number of diagnostic procedures performed has dramatically declined. Many have voiced concern that this will result in failure to detect

significant chromosomal abnormalities currently only detectable by karyotyping and CMA. In addition, when diagnostic testing is performed after positive standard first trimester combined screening, 17–30% of chromosomal abnormalities identified in the fetus are not those for which the screen was positive^{109,110} and would not be detectable by currently offered cfDNA screening tests. Although it has recently been argued that this is less frequently a concern¹¹¹, data from a study in which common aneuploidy-specific qfPCR as follow-up testing on amniotic fluid samples for an abnormal serum screening result was compared to karyotype analysis¹¹², and another retrospective analysis also indicated that other chromosomal abnormalities that would be missed by cfDNA screening can be responsible for abnormal maternal serum screening results¹¹³, although at reported variable frequencies. Finally, reports that are not easy to confirm are also emerging that women have foregone confirmatory testing and made reproductive decisions based on cfDNA screening results alone^{114,115}.

The emergence of expanded carrier screening

Another recent development is in the area of carrier screening. For autosomal recessive genetic conditions to manifest, both copies (alleles) of a disease gene have to carry a deleterious mutation and carriers with only one mutant copy are unaffected. However, carriers for a deleterious mutation in the same gene have a 25% (1/4) risk with each pregnancy to have an affected child. Professional societies recommend reproductive carrier screening for a limited number of conditions, some of which pan-ethnically (e.g. spinal muscular atrophy) and some based on ethnicity (e.g. thalassemia, sickle cell disease, and conditions prevalent in the Ashkenazi Jewish population)^{116–120}. These recommendations are based on consensus among experts that take into account disease severity, age of onset and prevalence, cost effectiveness, and the availability of therapies or other management options for affected individuals (including preimplantation or prenatal genetic diagnosis). Important limitations of this strategy for reproductive carrier screening include that many individuals do not have accurate knowledge of their ancestry, the increasing admixture in populations, and the focus of screening on more prevalent disorders, while other rarer but potentially equally or more severe conditions are not included¹²¹.

To overcome such limitations, newer high-throughput mutation screening or sequencing methods have been developed that combine testing of multiple known disease genes in single “expanded” carrier tests and are beginning to be offered to women and their partners, irrespective of their ethnic background. Different companies are now offering such pan-ethnic expanded carrier screening panels, but there is variation in the number and identity of disorders screened for between different panels. Some also include copy number analysis for specific conditions and carrier screening of women for X-linked disorders with 50% risk of transmission to affected sons or to carrier daughters. These expanded carrier tests are a significant improvement compared to the smaller panels, but current cost and reimbursement policies limit universal access. In addition, as the number of genes included on these panels increases, 25%¹²² or more^{123,124} of those screened will be identified as carriers, yet the chance that both reproductive partners carry mutations in the same gene remains low. The need for genetic counseling about

these aspects and residual risks after testing puts significant strain on available genetic counseling services^{120,121,125}.

Prenatal whole-exome sequencing will change our ability to identify causes of fetal birth defects

The most recent development in prenatal and reproductive testing is fetal diagnostic WES. When fetal congenital abnormalities are identified on prenatal ultrasound, karyotype and CMA reveal a diagnosis in up to 20–30%^{7,23}, depending on the type of structural defect. For the remainder, single-gene tests or gene panels, such as testing for Noonan syndrome when there is an increased nuchal translucency in a fetus with a normal karyotype^{126,127}, may be useful, but very recent data suggest that diagnostic WES can provide answers in a substantial proportion of the remaining cases⁷. For WES, the majority of coding exons, which represent only 2% of the genome but contain 85% of disease-causing mutations, are sequenced. In the pediatric population, WES yields a molecular diagnosis in at least 25% of patients with a suspected genetic disorder and prior negative genetic testing^{128,129}. Several recent case reports or small series^{128–133} (some embedded in larger reports) that describe diagnostic WES for fetuses or newborns with prenatally detected congenital abnormalities are now appearing^{10,134}. Carss *et al.* report on their experience with WES on 30 prenatally or neonatally obtained samples from fetuses with congenital abnormalities but negative results on standard genetic testing. They found a genetic diagnosis in three (10%) and sequence variants of potential significance in five (17%)⁸. More recently, Alamillo *et al.* reported relevant mutations in four of seven prenatal cases¹³⁵, and Drury *et al.* found a 25% total detection rate in 24 fetuses with abnormal ultrasound findings, including a definitive diagnosis in five and plausible diagnosis in one¹¹. Our early results also indicate that the detection rate of a significant genetic abnormality with prenatal exome sequencing for fetuses with single or multiple congenital anomalies is at least 30%^{18,128}.

These combined data are very encouraging and indicate that prenatal diagnostic WES has the potential to double the number of pregnancies complicated by fetal congenital abnormalities for which a genetic etiology can be identified prenatally, but further larger studies are required.

Concluding remarks and forecasts for the future of prenatal and reproductive genetics

The recent rapid introduction of non-invasive prenatal screening for chromosomal abnormalities has changed the practice of prenatal genetic diagnosis and screening. Although both sensitivity and specificity of cfDNA screening for fetal Down syndrome and other common aneuploidies are very high, this technique does not have the same resolution or coverage as a karyotype or CMA nor does it replace the diagnostic capability or accuracy of amniocentesis or CVS. Although laboratories have begun to add screening for other aneuploidies, such as microdeletions and duplications, there is significant concern as more rare conditions are included about adequate clinical validation, high cumulative false positive rates, resulting in unnecessary diagnostic procedures, and high false negative rates resulting in missed genetic diagnoses. Awareness of these issues by providers and patients is incomplete and marketing

of cffDNA screening is highly focused on avoidance of the risk of diagnostic procedures. This may result in some patients electing for cffDNA screening when diagnostic testing is more optimal, such as in the work-up for fetal abnormalities even though prenatal CMA detects clinically significant chromosomal abnormalities in 1 to 1.7% in pregnancies without fetal anomalies and in 6% of pregnancies complicated by fetal anomalies, in addition to those chromosomal abnormalities detected by karyotyping. Thus, until non-invasive tests become more accurate and comprehensive, the growing trend of replacing diagnostic testing with cffDNA screening comes at a cost of missed prenatal genetic diagnoses. Furthermore, it is predicted that diagnostic WES to search for single-gene disorders has the potential to double the number of identified genetic causes of fetal abnormalities. Women should be counseled about the limitations of cffDNA screening in view of results from a recent meta-analysis that indicates a lower risk of diagnostic procedures than previously considered (about 1:909 for amniocentesis and 1:600 for CVS). Finally, although proof-of-principle studies have shown that it is technically feasible to non-invasively sequence the entire fetal genome, this is not currently achievable in a time- and cost-effective manner^{136,137}. Thus, until non-invasive analysis of fetal DNA improves to the point that it will have the same accuracy as that of karyotyping and CMA on amniotic fluid or CVS samples, genetic counseling should objectively present the limitations and benefits of all currently available approaches in the context of the individual woman's *a priori* risk, her desire for genetic knowledge about her pregnancy, and personalized risk-benefit considerations.

Since cffDNA is admixed with maternal cfDNA, it is unclear if diagnostic-level accuracy from this fetal DNA source will ever be achievable. This has sparked renewed interest by several groups in the isolation and analysis of intact fetal cells from maternal

blood^{138–145}, which contain a pure unmixed fetal genome, with a theoretical ability for similar diagnostic accuracy as that obtained through invasive diagnostic procedures. There is strong evidence that fetal cells can be recovered and analyzed, but the approach is currently labor intensive and costly and has not yet been proven to be robustly successful and adaptable to a high-throughput, relatively low-cost diagnostic testing option.

In conclusion, the advances of genomic medicine are impacting prenatal diagnosis, just like any other medical field. While these innovations offer exciting new opportunities and can empower families with increased knowledge about their reproductive risks and with decision-making autonomy, they have to be carefully introduced in an evidence-based and ethically responsible manner and monitored after implementation. Considering that many of these innovations are driven by for-profit companies, professional societies will play an increasingly important role in providing objective guidance to patients and providers.

Abbreviations

cffDNA, cell-free fetal DNA; cfDNA, cell-free DNA; CMA, chromosomal microarray analysis; CVS, chorionic villus sampling; FISH, fluorescence *in situ* hybridization; Mb, megabase; NGS, next-generation sequencing; PPV, positive predictive value; WES, whole-exome sequencing.

Competing interests

The author declares that they have no competing interests.

Grant information

The author(s) declared that no grants were involved in supporting this work.

References

- Benn P, Borrelli A, Chiu RW, *et al.*: **Position statement from the Chromosome Abnormality Screening Committee on behalf of the Board of the International Society for Prenatal Diagnosis.** *Prenat Diagn.* 2015; **35**(8): 725–34.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Practice Bulletin No. 163 Summary: Screening for Fetal Aneuploidy. *Obstet Gynecol.* 2016; **127**(5): 979–81.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Grody WW, Thompson BH, Gregg AR, *et al.*: **ACMG position statement on prenatal/preconception expanded carrier screening.** *Genet Med.* 2013; **15**(6): 482–3.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Van den Veyver IB, Patel A, Shaw CA, *et al.*: **Clinical use of array comparative genomic hybridization (aCGH) for prenatal diagnosis in 300 cases.** *Prenat Diagn.* 2009; **29**(1): 29–39.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Breman A, Pursley AN, Hixson P, *et al.*: **Prenatal chromosomal microarray analysis in a diagnostic laboratory: experience with >1000 cases and review of the literature.** *Prenat Diagn.* 2012; **32**(4): 351–61.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Wapner RJ, Martin CL, Levy B, *et al.*: **Chromosomal microarray versus karyotyping for prenatal diagnosis.** *N Engl J Med.* 2012; **367**(23): 2175–84.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- Van den Veyver IB, Eng CM: **Genome-Wide Sequencing for Prenatal Detection of Fetal Single-Gene Disorders.** *Cold Spring Harb Perspect Med.* 2015; **5**(10): pii: a023077.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Carss KJ, Hillman SC, Parthiban V, *et al.*: **Exome sequencing improves genetic diagnosis of structural fetal abnormalities revealed by ultrasound.** *Hum Mol Genet.* 2014; **23**(12): 3269–77.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- Hillman SC, Williams D, Carss KJ, *et al.*: **Prenatal exome sequencing for fetuses with structural abnormalities: the next step.** *Ultrasound Obstet Gynecol.* 2015; **45**(1): 4–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Talkowski ME, Ordulu Z, Pillalamarri V, *et al.*: **Clinical diagnosis by whole-genome sequencing of a prenatal sample.** *N Engl J Med.* 2012; **367**(23): 2226–32.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Drury S, Williams H, Trump N, *et al.*: **Exome sequencing for prenatal diagnosis of fetuses with sonographic abnormalities.** *Prenat Diagn.* 2015; **35**(10): 1010–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Ellard S, Kivuva E, Turmpenny P, *et al.*: **An exome sequencing strategy to diagnose lethal autosomal recessive disorders.** *Eur J Hum Genet.* 2015; **23**(3): 401–4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Filges I, Friedman JM: **Exome sequencing for gene discovery in lethal fetal**

- disorders—harnessing the value of extreme phenotypes. *Prenat Diagn*. 2015; 35(10): 1005–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
14. Stankiewicz P, Beaudet AL: Use of array CGH in the evaluation of dysmorphology, malformations, developmental delay, and idiopathic mental retardation. *Curr Opin Genet Dev*. 2007; 17(3): 182–92.
[PubMed Abstract](#) | [Publisher Full Text](#)
 15. Lee H, Deignan JL, Dorrani N, *et al.*: Clinical exome sequencing for genetic identification of rare Mendelian disorders. *JAMA*. 2014; 312(18): 1880–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 16. Gilissen C, Hehir-Kwa JY, Thung DT, *et al.*: Genome sequencing identifies major causes of severe intellectual disability. *Nature*. 2014; 511(7509): 344–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 17. Beaulieu CL, Majewski J, Schwartzentruber J, *et al.*: FORGE Canada Consortium: outcomes of a 2-year national rare-disease gene-discovery project. *Am J Hum Genet*. 2014; 94(6): 809–17.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 18. Westerfield LE, Stover SR, Mathur VS, *et al.*: Reproductive genetic counseling challenges associated with diagnostic exome sequencing in a large academic private reproductive genetic counseling practice. *Prenat Diagn*. 2015; 35(10): 1022–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 19. Hui L, Bianchi DW: Recent advances in the prenatal interrogation of the human fetal genome. *Trends Genet*. 2013; 29(2): 84–91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 20. McGillivray G, Rosenfeld JA, McKinlay Gardner RJ, *et al.*: Genetic counselling and ethical issues with chromosome microarray analysis in prenatal testing. *Prenat Diagn*. 2012; 32(4): 389–95.
[PubMed Abstract](#) | [Publisher Full Text](#)
 21. Dondorp W, Sikkema-Raddatz B, de Die-Smulders C, *et al.*: Arrays in postnatal and prenatal diagnosis: An exploration of the ethics of consent. *Hum Mutat*. 2012; 33(6): 916–22.
[PubMed Abstract](#) | [Publisher Full Text](#)
 22. Miller DT, Adam MP, Aradhya S, *et al.*: Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet*. 2010; 86(5): 749–64.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 23. Hillman SC, McMullan DJ, Hall G, *et al.*: Use of prenatal chromosomal microarray: prospective cohort study and systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2013; 41(6): 610–20.
[PubMed Abstract](#) | [Publisher Full Text](#)
 24. Reddy UM, Page GP, Saade GR, *et al.*: Karyotype versus microarray testing for genetic abnormalities after stillbirth. *N Engl J Med*. 2012; 367(23): 2185–93.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 25. American College of Obstetricians and Gynecologists Committee on Genetics: Committee Opinion No. 581: the use of chromosomal microarray analysis in prenatal diagnosis. *Obstet Gynecol*. 2013; 122(6): 1374–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 26. Dhillon RK, Hillman SC, Morris RK, *et al.*: Additional information from chromosomal microarray analysis (CMA) over conventional karyotyping when diagnosing chromosomal abnormalities in miscarriage: a systematic review and meta-analysis. *BJOG*. 2014; 121(1): 11–21.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 27. American College of Obstetricians and Gynecologists: ACOG Practice Bulletin No. 88, December 2007. Invasive prenatal testing for aneuploidy. *Obstet Gynecol*. 2007; 110(6): 1459–67.
[PubMed Abstract](#) | [Publisher Full Text](#)
 28. Akolekar R, Beta J, Picciarelli G, *et al.*: Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2015; 45(1): 16–26.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 29. Wulff CB, Gerds TA, Rode L, *et al.*: Risk of fetal loss associated with invasive testing following combined first-trimester screening for Down syndrome: a national cohort of 147,987 singleton pregnancies. *Ultrasound Obstet Gynecol*. 2016; 47(1): 38–44.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 30. Rose NC, Lagrave D, Hafen B, *et al.*: The impact of utilization of early aneuploidy screening on amniocenteses available for training in obstetrics and fetal medicine. *Prenat Diagn*. 2013; 33(3): 242–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
 31. Bianchi DW, Simpson JL, Jackson LG, *et al.*: Fetal cells in maternal blood: NIFTY clinical trial interim analysis. DM-STAT. NICHD fetal cell study (NIFTY) group. *Prenat Diagn*. 1999; 19(10): 994–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
 32. Lo YM, Corbetta N, Chamberlain PF, *et al.*: Presence of fetal DNA in maternal plasma and serum. *Lancet*. 1997; 350(9076): 485–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 33. Costa JM, Benachi A, Gautier E: New strategy for prenatal diagnosis of X-linked disorders. *N Engl J Med*. 2002; 346(19): 1502.
[PubMed Abstract](#) | [Publisher Full Text](#)
 34. Lo YM, Hjelm NM, Fidler C, *et al.*: Prenatal diagnosis of fetal RhD status by molecular analysis of maternal plasma. *N Engl J Med*. 1998; 339(24): 1734–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 35. Bianchi DW, Avent ND, Costa JM, *et al.*: Noninvasive prenatal diagnosis of fetal Rhesus D: ready for Prime(r) Time. *Obstet Gynecol*. 2005; 106(4): 841–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
 36. Geifman-Holtzman O, Grotgut CA, Gaughan JP: Diagnostic accuracy of noninvasive fetal Rh genotyping from maternal blood—a meta-analysis. *Am J Obstet Gynecol*. 2006; 195(4): 1163–73.
[PubMed Abstract](#) | [Publisher Full Text](#)
 37. Daniels G, Finning K, Martin P, *et al.*: Noninvasive prenatal diagnosis of fetal blood group phenotypes: current practice and future prospects. *Prenat Diagn*. 2009; 29(2): 101–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 38. Moise KJ Jr, Boring NH, O'Shaughnessy R, *et al.*: Circulating cell-free fetal DNA for the detection of RHD status and sex using reflex fetal identifiers. *Prenat Diagn*. 2013; 33(1): 95–101.
[PubMed Abstract](#) | [Publisher Full Text](#)
 39. Grande M, Ordoñez E, Cirigliano V, *et al.*: Clinical application of midtrimester non-invasive fetal RHD genotyping and identification of RHD variants in a mixed-ethnic population. *Prenat Diagn*. 2013; 33(2): 173–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 40. González-González MC, García-Hoyos M, Trujillo MJ, *et al.*: Prenatal detection of a cystic fibrosis mutation in fetal DNA from maternal plasma. *Prenat Diagn*. 2002; 22(10): 946–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 41. Chitty LS, Khalil A, Barrett AN, *et al.*: Safe, accurate, prenatal diagnosis of thanatophoric dysplasia using ultrasound and free fetal DNA. *Prenat Diagn*. 2013; 33(5): 416–23.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 42. Chitty LS, Mason S, Barrett AN, *et al.*: Non-invasive prenatal diagnosis of achondroplasia and thanatophoric dysplasia: next-generation sequencing allows for a safer, more accurate, and comprehensive approach. *Prenat Diagn*. 2015; 35(7): 656–62.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 43. Xiong L, Barrett AN, Hua R, *et al.*: Non-invasive prenatal diagnostic testing for β -thalassaemia using cell-free fetal DNA and next generation sequencing. *Prenat Diagn*. 2015; 35(3): 258–65.
[PubMed Abstract](#) | [Publisher Full Text](#)
 44. Hill M, Twiss P, Verhoef TI, *et al.*: Non-invasive prenatal diagnosis for cystic fibrosis: detection of paternal mutations, exploration of patient preferences and cost analysis. *Prenat Diagn*. 2015; 35(10): 950–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 45. Fan HC, Blumenfeld YJ, Chitkara U, *et al.*: Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood. *Proc Natl Acad Sci U S A*. 2008; 105(42): 16266–71.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 46. Chiu RW, Chan KC, Gao Y, *et al.*: Noninvasive prenatal diagnosis of fetal chromosomal aneuploidy by massively parallel genomic sequencing of DNA in maternal plasma. *Proc Natl Acad Sci U S A*. 2008; 105(51): 20458–63.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 47. Chiu RW, Akolekar R, Zheng YW, *et al.*: Non-invasive prenatal assessment of trisomy 21 by multiplexed maternal plasma DNA sequencing: large scale validity study. *BMJ*. 2011; 342: c7401.
[PubMed Abstract](#) | [Publisher Full Text](#)
 48. Palomaki GE, Kloza EM, Lambert-Messerlian GM, *et al.*: DNA sequencing of maternal plasma to detect Down syndrome: an international clinical validation study. *Genet Med*. 2011; 13(11): 913–20.
[PubMed Abstract](#) | [Publisher Full Text](#)
 49. Palomaki GE, Deciu C, Kloza EM, *et al.*: DNA sequencing of maternal plasma reliably identifies trisomy 18 and trisomy 13 as well as Down syndrome: an international collaborative study. *Genet Med*. 2012; 14(3): 296–305.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 50. Bianchi DW, Platt LD, Goldberg JD, *et al.*: Genome-wide fetal aneuploidy detection by maternal plasma DNA sequencing. *Obstet Gynecol*. 2012; 119(5): 890–901.
[PubMed Abstract](#) | [Publisher Full Text](#)
 51. Liang D, Lv W, Wang H, *et al.*: Non-invasive prenatal testing of fetal whole chromosome aneuploidy by massively parallel sequencing. *Prenat Diagn*. 2013; 33(5): 409–15.
[PubMed Abstract](#) | [Publisher Full Text](#)
 52. Song Y, Liu C, Qi H, *et al.*: Noninvasive prenatal testing of fetal aneuploidies by massively parallel sequencing in a prospective Chinese population. *Prenat Diagn*. 2013; 33(7): 700–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
 53. Mazloom AR, Dzakula Z, Oeth P, *et al.*: Noninvasive prenatal detection of sex chromosomal aneuploidies by sequencing circulating cell-free DNA from maternal plasma. *Prenat Diagn*. 2013; 33(6): 591–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 54. Stumm M, Entezami M, Haug K, *et al.*: Diagnostic accuracy of random massively parallel sequencing for non-invasive prenatal detection of common autosomal aneuploidies: a collaborative study in Europe. *Prenat Diagn*. 2014; 34(2): 185–91.
[PubMed Abstract](#) | [Publisher Full Text](#)
 55. Grati FR, Ferreira JC, Bajaj K: Noninvasive prenatal screening for fetal trisomies

- 21, 18, 13 and the common sex chromosome aneuploidies from maternal blood using massively parallel genomic sequencing of DNA. *Am J Obstet Gynecol.* 2014; 211(6): 711–2.
[PubMed Abstract](#) | [Publisher Full Text](#)
56. **F** Bianchi DW, Parker RL, Wentworth J, *et al.*: DNA sequencing versus standard prenatal aneuploidy screening. *N Engl J Med.* 2014; 370(9): 799–808.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 57. Zimmermann B, Hill M, Gemelos G, *et al.*: Noninvasive prenatal aneuploidy testing of chromosomes 13, 18, 21, X, and Y, using targeted sequencing of polymorphic loci. *Prenat Diagn.* 2012; 32(13): 1233–41.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 58. Ashoor G, Syngelaki A, Wagner M, *et al.*: Chromosome-selective sequencing of maternal plasma cell-free DNA for first-trimester detection of trisomy 21 and trisomy 18. *Am J Obstet Gynecol.* 2012; 206(4): 322.e1–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
 59. **F** Nicolaides KH, Syngelaki A, Ashoor G, *et al.*: Noninvasive prenatal testing for fetal trisomies in a routinely screened first-trimester population. *Am J Obstet Gynecol.* 2012; 207(5): 374.e1–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 60. Ashoor G, Syngelaki A, Wang E, *et al.*: Trisomy 13 detection in the first trimester of pregnancy using a chromosome-selective cell-free DNA analysis method. *Ultrasound Obstet Gynecol.* 2013; 41(1): 21–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
 61. Nicolaides KH, Syngelaki A, Gil M, *et al.*: Validation of targeted sequencing of single-nucleotide polymorphisms for non-invasive prenatal detection of aneuploidy of chromosomes 13, 18, 21, X, and Y. *Prenat Diagn.* 2013; 33(6): 575–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 62. Pergament E, Cuckle H, Zimmermann B, *et al.*: Single-nucleotide polymorphism-based noninvasive prenatal screening in a high-risk and low-risk cohort. *Obstet Gynecol.* 2014; 124(2 Pt 1): 210–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 63. Verweij EJ, Jacobsson B, van Schellema PA, *et al.*: European non-invasive trisomy evaluation (EU-NITE) study: a multicenter prospective cohort study for non-invasive fetal trisomy 21 testing. *Prenat Diagn.* 2013; 33(10): 996–1001.
[PubMed Abstract](#) | [Publisher Full Text](#)
 64. Nicolaides KH, Musci TJ, Struble CA, *et al.*: Assessment of fetal sex chromosome aneuploidy using directed cell-free DNA analysis. *Fetal Diagn Ther.* 2014; 35(1): 1–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
 65. Norton ME, Jacobsson B, Swamy GK, *et al.*: Cell-free DNA analysis for noninvasive examination of trisomy. *N Engl J Med.* 2015; 372(17): 1589–97.
[PubMed Abstract](#) | [Publisher Full Text](#)
 66. del Mar Gil M, Quezada MS, Bregant B, *et al.*: Cell-free DNA analysis for trisomy risk assessment in first-trimester twin pregnancies. *Fetal Diagn Ther.* 2014; 35(3): 204–11.
[PubMed Abstract](#) | [Publisher Full Text](#)
 67. Dan S, Wang W, Ren J, *et al.*: Clinical application of massively parallel sequencing-based prenatal noninvasive fetal trisomy test for trisomies 21 and 18 in 11,105 pregnancies with mixed risk factors. *Prenat Diagn.* 2012; 32(13): 1225–32.
[PubMed Abstract](#) | [Publisher Full Text](#)
 68. **F** Dar P, Curnow KJ, Gross SJ, *et al.*: Clinical experience and follow-up with large scale single-nucleotide polymorphism-based noninvasive prenatal aneuploidy testing. *Am J Obstet Gynecol.* 2014; 211(5): 527.e1–527.e17.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 69. **F** Zhang H, Gao Y, Jiang F, *et al.*: Non-invasive prenatal testing for trisomies 21, 18 and 13: clinical experience from 146,958 pregnancies. *Ultrasound Obstet Gynecol.* 2015; 45(5): 530–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 70. Wang J, Sahoo T, Schonberg S, *et al.*: Discordant noninvasive prenatal testing and cytogenetic results: a study of 109 consecutive cases. *Genet Med.* 2015; 17(3): 234–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
 71. Cheung SW, Patel A, Leung TY: Accurate description of DNA-based noninvasive prenatal screening. *N Engl J Med.* 2015; 372(17): 1675–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 72. Bianchi DW, Wilkins-Haug L: Integration of noninvasive DNA testing for aneuploidy into prenatal care: what has happened since the rubber met the road? *Clin Chem.* 2014; 60(1): 78–87.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 73. **F** Curnow KJ, Wilkins-Haug L, Ryan A, *et al.*: Detection of triploid, molar, and vanishing twin pregnancies by a single-nucleotide polymorphism-based noninvasive prenatal test. *Am J Obstet Gynecol.* 2015; 212(1): 79.e1–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 74. Grati FR, Malvestiti F, Ferreira JC, *et al.*: Fetoplacental mosaicism: potential implications for false-positive and false-negative noninvasive prenatal screening results. *Genet Med.* 2014; 16(8): 620–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
 75. Hall AL, Drendel HM, Verbrugge JL, *et al.*: Positive cell-free fetal DNA testing for trisomy 13 reveals confined placental mosaicism. *Genet Med.* 2013; 15(9): 729–32.
[PubMed Abstract](#) | [Publisher Full Text](#)
 76. Choi H, Lau TK, Jiang FM, *et al.*: Fetal aneuploidy screening by maternal plasma DNA sequencing: 'false positive' due to confined placental mosaicism. *Prenat Diagn.* 2013; 33(2): 198–200.
[PubMed Abstract](#) | [Publisher Full Text](#)
 77. Taglauer ES, Wilkins-Haug L, Bianchi DW: Review: cell-free fetal DNA in the maternal circulation as an indication of placental health and disease. *Placenta.* 2014; 35(Suppl): S64–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 78. Russell LM, Strike P, Browne CE, *et al.*: X chromosome loss and ageing. *Cytogenet Genome Res.* 2007; 116(3): 181–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
 79. Bianchi DW, Parsa S, Bhatt S, *et al.*: Fetal sex chromosome testing by maternal plasma DNA sequencing: clinical laboratory experience and biology. *Obstet Gynecol.* 2015; 125(2): 375–82.
[PubMed Abstract](#) | [Publisher Full Text](#)
 80. Palomaki GE, Kloza EM, Lambert-Messerlian GM, *et al.*: Circulating cell free DNA testing: are some test failures informative? *Prenat Diagn.* 2015; 35(3): 289–93.
[PubMed Abstract](#) | [Publisher Full Text](#)
 81. Rava RP, Srinivasan A, Sehnert AJ, *et al.*: Circulating fetal cell-free DNA fractions differ in autosomal aneuploidies and monosomy X. *Clin Chem.* 2014; 60(1): 243–50.
[PubMed Abstract](#) | [Publisher Full Text](#)
 82. Canick JA, Palomaki GE, Kloza EM, *et al.*: The impact of maternal plasma DNA fraction on next generation sequencing tests for common fetal aneuploidies. *Prenat Diagn.* 2013; 33(7): 667–74.
[PubMed Abstract](#) | [Publisher Full Text](#)
 83. Ashoor G, Syngelaki A, Poon LC, *et al.*: Fetal fraction in maternal plasma cell-free DNA at 11–13 weeks' gestation: relation to maternal and fetal characteristics. *Ultrasound Obstet Gynecol.* 2013; 41(1): 26–32.
[PubMed Abstract](#) | [Publisher Full Text](#)
 84. Osborne CM, Hardisty E, Devers P, *et al.*: Discordant noninvasive prenatal testing results in a patient subsequently diagnosed with metastatic disease. *Prenat Diagn.* 2013; 33(6): 609–11.
[PubMed Abstract](#) | [Publisher Full Text](#)
 85. **F** Bianchi DW, Chudova D, Sehnert AJ, *et al.*: Noninvasive Prenatal Testing and Incidental Detection of Occult Maternal Malignancies. *JAMA.* 2015; 314(2): 162–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 86. **F** Snyder HL, Curnow KJ, Bhatt S, *et al.*: Follow-up of multiple aneuploidies and single monosomies detected by noninvasive prenatal testing: implications for management and counseling. *Prenat Diagn.* 2016; 36(3): 203–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 87. McCullough RM, Almasri EA, Guan X, *et al.*: Non-invasive prenatal chromosomal aneuploidy testing—clinical experience: 100,000 clinical samples. *PLoS One.* 2014; 9(10): e109173.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 88. **F** Peters D, Chu T, Yatsenko SA, *et al.*: Noninvasive prenatal diagnosis of a fetal microdeletion syndrome. *N Engl J Med.* 2011; 365(19): 1847–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 89. Jensen TJ, Dzakula Z, Deciu C, *et al.*: Detection of microdeletion 22q11.2 in a fetus by next-generation sequencing of maternal plasma. *Clin Chem.* 2012; 58(7): 1148–51.
[PubMed Abstract](#) | [Publisher Full Text](#)
 90. Chen S, Lau TK, Zhang C, *et al.*: A method for noninvasive detection of fetal large deletions/duplications by low coverage massively parallel sequencing. *Prenat Diagn.* 2013; 33(6): 584–90.
[PubMed Abstract](#) | [Publisher Full Text](#)
 91. **F** Srinivasan A, Bianchi DW, Huang H, *et al.*: Noninvasive detection of fetal subchromosome abnormalities via deep sequencing of maternal plasma. *Am J Hum Genet.* 2013; 92(2): 167–76.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 92. Yu SC, Jiang P, Choy KW, *et al.*: Noninvasive prenatal molecular karyotyping from maternal plasma. *PLoS One.* 2013; 8(4): e60968.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 93. Vora NL, O'Brien BM: Noninvasive prenatal testing for microdeletion syndromes and expanded trisomies: proceed with caution. *Obstet Gynecol.* 2014; 123(5): 1097–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 94. Gregg AR, Van den Veyver IB, Gross SJ, *et al.*: Noninvasive prenatal screening by next-generation sequencing. *Annu Rev Genomics Hum Genet.* 2014; 15: 327–47.
[PubMed Abstract](#) | [Publisher Full Text](#)
 95. Gross SJ, Ryan A, Benn P: Noninvasive prenatal testing for 22q11.2 deletion syndrome: deeper sequencing increases the positive predictive value. *Am J Obstet Gynecol.* 2015; 213(2): 254–5.
[PubMed Abstract](#) | [Publisher Full Text](#)

96. Wapner RJ, Babiarz JE, Levy B, *et al.*: **Expanding the scope of noninvasive prenatal testing: detection of fetal microdeletion syndromes.** *Am J Obstet Gynecol.* 2015; **212**(3): 332.e1–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
97. Yaron Y, Jani J, Schmid M, *et al.*: **Current Status of Testing for Microdeletion Syndromes and Rare Autosomal Trisomies Using Cell-Free DNA Technology.** *Obstet Gynecol.* 2015; **126**(5): 1095–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
98. Helgeson J, Wardrop J, Boomer T, *et al.*: **Clinical outcome of subchromosomal events detected by whole-genome noninvasive prenatal testing.** *Prenat Diagn.* 2015; **35**(10): 999–1004.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
99. Benn P: **Posttest risk calculation following positive noninvasive prenatal screening using cell-free DNA in maternal plasma.** *Am J Obstet Gynecol.* 2016; **214**(6): 676.e1–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
100. Zhao C, Tynan J, Ehrich M, *et al.*: **Detection of fetal subchromosomal abnormalities by sequencing circulating cell-free DNA from maternal plasma.** *Clin Chem.* 2015; **61**(4): 608–16.
[PubMed Abstract](#) | [Publisher Full Text](#)
101. Lefkowitz RB, Tynan JA, Liu T, *et al.*: **Clinical validation of a noninvasive prenatal test for genome-wide detection of fetal copy number variants.** *Am J Obstet Gynecol.* 2016; **215**(2): 227.e1–227.e16.
[PubMed Abstract](#) | [Publisher Full Text](#)
102. Yatsenko SA, Peters DG, Saller DN, *et al.*: **Maternal cell-free DNA-based screening for fetal microdeletion and the importance of careful diagnostic follow-up.** *Genet Med.* 2015; **17**(10): 836–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
103. Sahoo T, Hovanes K, Strecker MN, *et al.*: **Expanding noninvasive prenatal testing to include microdeletions and segmental aneuploidy: cause for concern?** *Genet Med.* 2016; **18**(3): 275–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
104. Wilson KL, Czerwinski JL, Hoskovec JM, *et al.*: **NSGC practice guideline: prenatal screening and diagnostic testing options for chromosome aneuploidy.** *J Genet Couns.* 2013; **22**(1): 4–15.
[PubMed Abstract](#) | [Publisher Full Text](#)
105. Gregg AR, Gross SJ, Best RG, *et al.*: **ACMG statement on noninvasive prenatal screening for fetal aneuploidy.** *Genet Med.* 2013; **15**(5): 395–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
106. **F** Committee Opinion No. 640: Cell-Free DNA Screening For Fetal Aneuploidy. *Obstet Gynecol.* 2015; **126**(3): e31–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
107. **F** Dondorp W, de Wert G, Bombard Y, *et al.*: **Non-invasive prenatal testing for aneuploidy and beyond: challenges of responsible innovation in prenatal screening.** *Eur J Hum Genet.* 2015; **23**(11): 1438–50.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
108. **F** Gregg AR, Skotko BG, Benkendorf JL, *et al.*: **Noninvasive prenatal screening for fetal aneuploidy, 2016 update: a position statement of the American College of Medical Genetics and Genomics.** *Genet Med.* 2016; **18**(10): 1056–65.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
109. Alamillo CM, Krantz D, Evans M, *et al.*: **Nearly a third of abnormalities found after first-trimester screening are different than expected: 10-year experience from a single center.** *Prenat Diagn.* 2013; **33**(3): 251–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
110. Norton ME, Jelliffe-Pawlowski LL, Currier RJ: **Chromosome abnormalities detected by current prenatal screening and noninvasive prenatal testing.** *Obstet Gynecol.* 2014; **124**(5): 979–86.
[PubMed Abstract](#) | [Publisher Full Text](#)
111. Benn P, Norwitz ER, Pergament E: **Cell-free DNA vs sequential screening for the detection of fetal chromosomal abnormalities.** *Am J Obstet Gynecol.* 2016; **215**(2): 252–3.
[PubMed Abstract](#) | [Publisher Full Text](#)
112. Caine A, Maltby AE, Parkin CA, *et al.*: **Prenatal detection of Down's syndrome by rapid aneuploidy testing for chromosomes 13, 18, and 21 by FISH or PCR without a full karyotype: a cytogenetic risk assessment.** *Lancet.* 2005; **366**(9480): 123–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
113. **F** Petersen OB, Vogel I, Ekelund C, *et al.*: **Potential diagnostic consequences of applying non-invasive prenatal testing: population-based study from a country with existing first-trimester screening.** *Ultrasound Obstet Gynecol.* 2014; **43**(3): 265–71.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
114. Singh ON: **Clinical experience and follow-up with large-scale single-nucleotide polymorphism-based noninvasive prenatal aneuploidy testing.** *Am J Obstet Gynecol.* 2015; **213**(2): 253.
[PubMed Abstract](#) | [Publisher Full Text](#)
115. Dar P, Gross SJ, Benn P: **Reply: To PMID 25111587.** *Am J Obstet Gynecol.* 2015; **213**(2): 253–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
116. American College of Obstetricians and Gynecologists Committee on Genetics: **ACOG Committee Opinion No. 469: Carrier screening for fragile X syndrome.** *Obstet Gynecol.* 2010; **116**(4): 1008–10.
[PubMed Abstract](#) | [Publisher Full Text](#)
117. American College of Obstetricians and Gynecologists Committee on Genetics: **ACOG Committee Opinion No. 486: Update on carrier screening for cystic fibrosis.** *Obstet Gynecol.* 2011; **117**(4): 1028–31.
[PubMed Abstract](#) | [Publisher Full Text](#)
118. Prior TW, Professional Practice and Guidelines Committee: **Carrier screening for spinal muscular atrophy.** *Genet Med.* 2008; **10**(11): 840–2.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
119. Gross SJ, Pletcher BA, Monaghan KG: **Carrier screening in individuals of Ashkenazi Jewish descent.** *Genet Med.* 2008; **10**(1): 54–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
120. Edwards JG, Feldman G, Goldberg J, *et al.*: **Expanded carrier screening in reproductive medicine—points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine.** *Obstet Gynecol.* 2015; **125**(3): 653–62.
[PubMed Abstract](#) | [Publisher Full Text](#)
121. Langlois S, Benn P, Wilkins-Haug L: **Current controversies in prenatal diagnosis 4: pre-conception expanded carrier screening should replace all current prenatal screening for specific single gene disorders.** *Prenat Diagn.* 2015; **35**(1): 23–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
122. Lazarin GA, Haque IS, Nazareth S, *et al.*: **An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals.** *Genet Med.* 2013; **15**(3): 178–86.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
123. **F** Bell CJ, Dinwiddie DL, Miller NA, *et al.*: **Carrier testing for severe childhood recessive diseases by next-generation sequencing.** *Sci Transl Med.* 2011; **3**(65): 65ra4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
124. Martin J, Asan, Yi Y, *et al.*: **Comprehensive carrier genetic test using next-generation deoxyribonucleic acid sequencing in infertile couples wishing to conceive through assisted reproductive technology.** *Fertil Steril.* 2015; **104**(5): 1286–93.
[PubMed Abstract](#) | [Publisher Full Text](#)
125. Lazarin GA, Goldberg JD: **Current controversies in traditional and expanded carrier screening.** *Curr Opin Obstet Gynecol.* 2016; **28**(2): 136–41.
[PubMed Abstract](#) | [Publisher Full Text](#)
126. Pergament E, Alamillo C, Sak K, *et al.*: **Genetic assessment following increased nuchal translucency and normal karyotype.** *Prenat Diagn.* 2011; **31**(3): 307–10.
[PubMed Abstract](#) | [Publisher Full Text](#)
127. Alamillo CM, Fiddler M, Pergament E: **Increased nuchal translucency in the presence of normal chromosomes: what's next?** *Curr Opin Obstet Gynecol.* 2012; **24**(2): 102–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
128. **F** Yang Y, Muzny DM, Xia F, *et al.*: **Molecular findings among patients referred for clinical whole-exome sequencing.** *JAMA.* 2014; **312**(18): 1870–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
129. **F** Yang Y, Muzny DM, Reid JG, *et al.*: **Clinical whole-exome sequencing for the diagnosis of mendelian disorders.** *N Engl J Med.* 2013; **369**(16): 1502–11.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
130. Ravenscroft G, Nolent F, Rajagopalan S, *et al.*: **Mutations of GPR126 are responsible for severe arthrogryposis multiplex congenita.** *Am J Hum Genet.* 2015; **96**(6): 955–61.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
131. Slavotinek A, Kaylor J, Pierce H, *et al.*: **CRB2 mutations produce a phenotype resembling congenital nephrosis, Finnish type, with cerebral ventriculomegaly and raised alpha-fetoprotein.** *Am J Hum Genet.* 2015; **96**(1): 162–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
132. Mejlachowicz D, Nolent F, Maluenda J, *et al.*: **Truncating Mutations of MAGEL2, a Gene within the Prader-Willi Locus, Are Responsible for Severe Arthrogryposis.** *Am J Hum Genet.* 2015; **97**(4): 616–20.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
133. Poirier K, Martinovic J, Laquerrière A, *et al.*: **Rare ACTG1 variants in fetal microencephaly.** *Eur J Med Genet.* 2015; **58**(8): 416–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
134. Filges I, Nosova E, Bruder E, *et al.*: **Exome sequencing identifies mutations in KIF14 as a novel cause of an autosomal recessive lethal fetal ciliopathy phenotype.** *Clin Genet.* 2014; **86**(3): 220–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
135. Alamillo CL, Powis Z, Farwell K, *et al.*: **Exome sequencing positively identified relevant alterations in more than half of cases with an indication of prenatal ultrasound anomalies.** *Prenat Diagn.* 2015; **35**(11): 1073–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
136. Fan HC, Gu W, Wang J, *et al.*: **Non-invasive prenatal measurement of the fetal**

- genome. *Nature*. 2012; **487**(7407): 320–4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
137. Kitzman JO, Snyder MW, Ventura M, *et al.*: **Noninvasive whole-genome sequencing of a human fetus.** *Sci Transl Med*. 2012; **4**(137): 137ra76.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 138. Mouawia H, Saker A, Jais JP, *et al.*: **Circulating trophoblastic cells provide genetic diagnosis in 63 fetuses at risk for cystic fibrosis or spinal muscular atrophy.** *Reprod Biomed Online*. 2012; **25**(5): 508–20.
[PubMed Abstract](#) | [Publisher Full Text](#)
 139. Hatt L, Brinch M, Singh R, *et al.*: **Characterization of fetal cells from the maternal circulation by microarray gene expression analysis—could the extravillous trophoblasts be a target for future cell-based non-invasive prenatal diagnosis?** *Fetal Diagn Ther*. 2014; **35**(3): 218–27.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 140. Beaudet AL: **Using fetal cells for prenatal diagnosis: History and recent progress.** *Am J Med Genet C Semin Med Genet*. 2016; **172**(2): 123–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 141. Bi W, Breman A, Shaw CA, *et al.*: **Detection of ≥1Mb microdeletions and microduplications in a single cell using custom oligonucleotide arrays.** *Prenat Diagn*. 2012; **32**(1): 10–20.
[PubMed Abstract](#) | [Publisher Full Text](#)
 142. Hatt L, Brinch M, Singh R, *et al.*: **A new marker set that identifies fetal cells in maternal circulation with high specificity.** *Prenat Diagn*. 2014; **34**(11): 1066–72.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 143. Schlütter JM, Kirkegaard I, Petersen OB, *et al.*: **Fetal gender and several cytokines are associated with the number of fetal cells in maternal blood—an observational study.** *PLoS One*. 2014; **9**(9): e106934.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 144. Emad A, Bouchard EF, Lamoureux J, *et al.*: **Validation of automatic scanning of microscope slides in recovering rare cellular events: application for detection of fetal cells in maternal blood.** *Prenat Diagn*. 2014; **34**(6): 538–46.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 145. Emad A, Drouin R: **Evaluation of the impact of density gradient centrifugation on fetal cell loss during enrichment from maternal peripheral blood.** *Prenat Diagn*. 2014; **34**(9): 878–85.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)

Open Peer Review

Current Peer Review Status:

Editorial Note on the Review Process

Faculty Reviews are review articles written by the prestigious Members of **Faculty Opinions**. The articles are commissioned and peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

The reviewers who approved this article are:

Version 1

- Peter Benn**
University of Connecticut Health Center, Farmington, CT, USA
Competing Interests: No competing interests were disclosed.
- Neeta Vora**
Department of Obstetrics and Gynecology, University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC, USA
Competing Interests: No competing interests were disclosed.
- Steven Warsof**
Eastern Virginia Medical School, Norfolk, VA, USA
Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research