Washington State Health Care Authority

FINAL Key Questions and Background

Cell-free DNA prenatal screening for chromosomal aneuploidies

Updated: August 26, 2019

Background

Technology of Interest

Cell-free fetal DNA (cfDNA) screening is a form of noninvasive prenatal screening (NIPS, or noninvasive prenatal testing [NIPT]) used to determine the risk of a fetus having certain genetic abnormalities.[1] cfDNA testing analyzes fragments of fetal DNA that are present in maternal blood[1] and is considered noninvasive compared with traditional testing methods such as amniocentesis or chorionic villus sampling. The cfDNA in a sample of a woman's blood can be screened for trisomy 21 (Down syndrome), trisomy 13 (Patau syndrome), trisomy 18 (Edwards syndrome), and problems with the number of sex chromosomes such as Klinefelter syndrome and Turner syndrome.[2] Screening using cfDNA can also be used to assess the risk of other chromosomal abnormalities, such as microdeletions. Results of maternal blood screening tests for fetal aneuploidy are reported as the level of risk that the disorder might be present:

- A positive screening test result for aneuploidy means that the fetus is at higher risk of having the disorder compared with the general population. It does not mean that the fetus definitely has the disorder.[2]
- A negative result means that the fetus is at lower risk of having the disorder compared with the general population. It does not completely rule out the possibility that the fetus has the disorder.[2]

Clinical Need and Target Population

The use of cfDNA screening has mainly been evaluated in people who are already known to be at a higher risk of pregnancies with a chromosomal abnormality.[2,3] The evidence for people at low or unknown risk is more limited.[3] The American College of Obstetricians and Gynecologists (ACOG) has stated that the positive predictive value of cfDNA screening is better for individuals with an increased risk of having a child with a chromosomal disorder.[2] ACOG recommends "All women be offered the option of aneuploidy screening or diagnostic testing for fetal genetic disorders, regardless of maternal age."[2] ACOG does not recommend any particular test or screening strategy because all available tests have advantages and disadvantages that may make them more or less appropriate for a particular woman, given her needs and preferences.[2] Therefore, ACOG recommends that obstetric care providers should be prepared to discuss the benefits, risks, and limitations of all types of screening tests,[2] including cfDNA screening tests available in the U.S. (Table 1).

Table 1. Cell-free DNA Screening Tests Available in the United States

Cell-free DNA Screening Test Name	Manufacturer
ClariTest (aneuploidy screening)	GenPath Diagnostics
Harmony Prenatal Test	Roche
informaSeq	Integrated Genetics
MaterniT21 PLUS (Core and ESS)	Integrated Genetics
Panorama	Natera
Prequel Prenatal Screen	Myriad Genetics
QNatal Advanced	Quest Diagnostics
Veracity	NIPD Genetics
Verifi and Verifi Plus Prenatal Test	Illumina
VisibiliT	Sequenom

In the U.S., cfDNA screening for individuals with a high risk of fetal aneuploidy is covered by most commercial and public insurance plans.[4] Some insurance companies, including Anthem Blue Cross Blue Shield and Cigna, now cover cfDNA for all pregnancies.[4] However, clinical practice guideline authors vary in their recommendations, citing challenges with cost and the positioning of cfDNA in the screening and diagnostic pathways.[5,6] Therefore, questions remain as to whether cfDNA tests should be used universally in the general obstetric population, or only in cases of increased risk of aneuploidy (e.g., increased maternal age, family history of a particular genetic disorder).

Policy Context

cfDNA testing is used for prenatal screening for common chromosome abnormalities. There is uncertainty about the appropriateness of cfDNA screening for some populations, including those at low risk for common fetal genetic abnormalities. This topic was selected for a health technology assessment because of medium concerns for the safety and efficacy of cfDNA screening in the general population and high concern for cost.

This evidence review will help to inform Washington's independent Health Technology Clinical Committee as the committee determines coverage regarding cfDNA screening for pregnant individuals not known to be at high risk for chromosomal abnormalities.

Key Questions

1. What is the evidence on the efficacy and effectiveness of using cfDNA in pregnant individuals not known to be at high risk for chromosomal abnormalities:
    a. For trisomies 21, 18, and 13, compared to active screening approaches, including standard screening with serum biomarkers and ultrasound, screening with another cfDNA screening test, question-based screening, or invasive diagnostic testing?

   b. For common sex chromosome aneuploidies, any active screening approach, screening with another cfDNA screening test, no screening, or invasive diagnostic testing?

2. What direct harms are associated with screening using cfDNA in pregnant individuals not known to be at high risk for chromosomal abnormalities:
   a. For trisomies 21, 18, and 13, compared to active screening approaches, including standard screening with serum biomarkers and ultrasound, screening with another cfDNA screening test, question-based screening, or invasive diagnostic testing?
   b. For common sex chromosome aneuploidies, any active screening approach, screening with another cfDNA screening test, no screening, or invasive diagnostic testing?
3. Do important efficacy/effectiveness outcomes or direct harms of screening for trisomies 21, 18, and 13 and for common sex chromosome aneuploidies using cfDNA vary for the mother and fetus or infant by:
   a. Maternal characteristics (e.g., age)
   b. Singleton or multifetal pregnancy
   c. Timing of screening (e.g., gestational age)
4. What are the cost-effectiveness and other economic outcomes of screening for trisomies 21, 18, and 13 and for common sex chromosome aneuploidies using cfDNA in pregnant individuals not known to be at high risk for chromosomal abnormalities?

Contextual questions will not be systematically reviewed and are not shown in the analytic framework. To address contextual questions, we will rely on recent systematic reviews and/or a subset of the largest, most relevant recent primary research articles identified through our search.

Contextual Question 1. What are the benefits and harms of screening for trisomies 21, 18, and 13 and for common sex chromosome aneuploidies using cfDNA in pregnant individuals known to be at high risk for chromosomal abnormalities?

Scope

Study Component	Inclusion	Exclusion
Populations	Pregnant individuals of any age, ethnicity, and gestational age with a singleton or multifetal (monochorionic and dichorionic) pregnancy, who are not known as being at high risk for the target fetal conditions (i.e., an unselected population that is representative of the general population) We will also include studies of mixed-risk populations, where outcomes are reported by the level of risk	• Studies including only pregnant individuals known to be at high-risk (e.g., past history or identified as high risk through prenatal screening) • Studies in which the population risk is undetermined • Studies including only patients undergoing preimplantation testing of embryos for IVF

Study Component	Inclusion	Exclusion
Interventions	Screening for trisomies 21, 18, and 13 and for common sex chromosome aneuploidies using cfDNA	• Screening with cfDNA or other NIPT technologies for other chromosomal abnormalities or genetic conditions • Studies with an outdated cfDNA screening test or a cfDNA screening test that is not available in the U.S.
Comparators	• For trisomies, active screening approaches, including standard screening with serum biomarkers and ultrasound, screening with another cfDNA screening test, or question-based screening • For common sex chromosome aneuploidies, any active screening approach, screening with another cfDNA screening test, or no screening • Invasive diagnostic testing (e.g., amniocentesis)	• Studies without a comparator intervention • Studies with indirect comparisons • Studies with an outdated comparator or a comparator intervention that is not available in the U.S.
Outcomes	• Primary outcomes: pregnancy outcomes; use of cfDNA results for clinical management (e.g., further diagnostic testing, counseling) • Secondary outcomes: uptake of cfDNA screening; maternal/parental/family quality of life, including satisfaction (measured with validated instruments) • Safety: harms directly related to screening for trisomies 21, 18, and 13 and for common sex chromosome aneuploidies using cfDNA tests (e.g., misclassification, psychosocial harms) • Indirect outcomes: measures of cfDNA screening test performance • Economic: cost-effectiveness outcomes (e.g., cost per improved outcome) or cost-utility outcomes (e.g., cost per quality-adjusted life-year [QALY], incremental cost-effectiveness ratio [ICER])	• Other outcomes • Cost of testing from studies performed in non-U.S. countries • Cost of testing from studies performed in the U.S. that are older than 5 years
Setting	• Any outpatient or inpatient clinical setting in countries categorized as very high on the UN Human Development Index7	• Nonclinical settings (e.g., studies conducted using libraries of plasma samples) • Countries categorized other than very high on the UN Human Development Index7

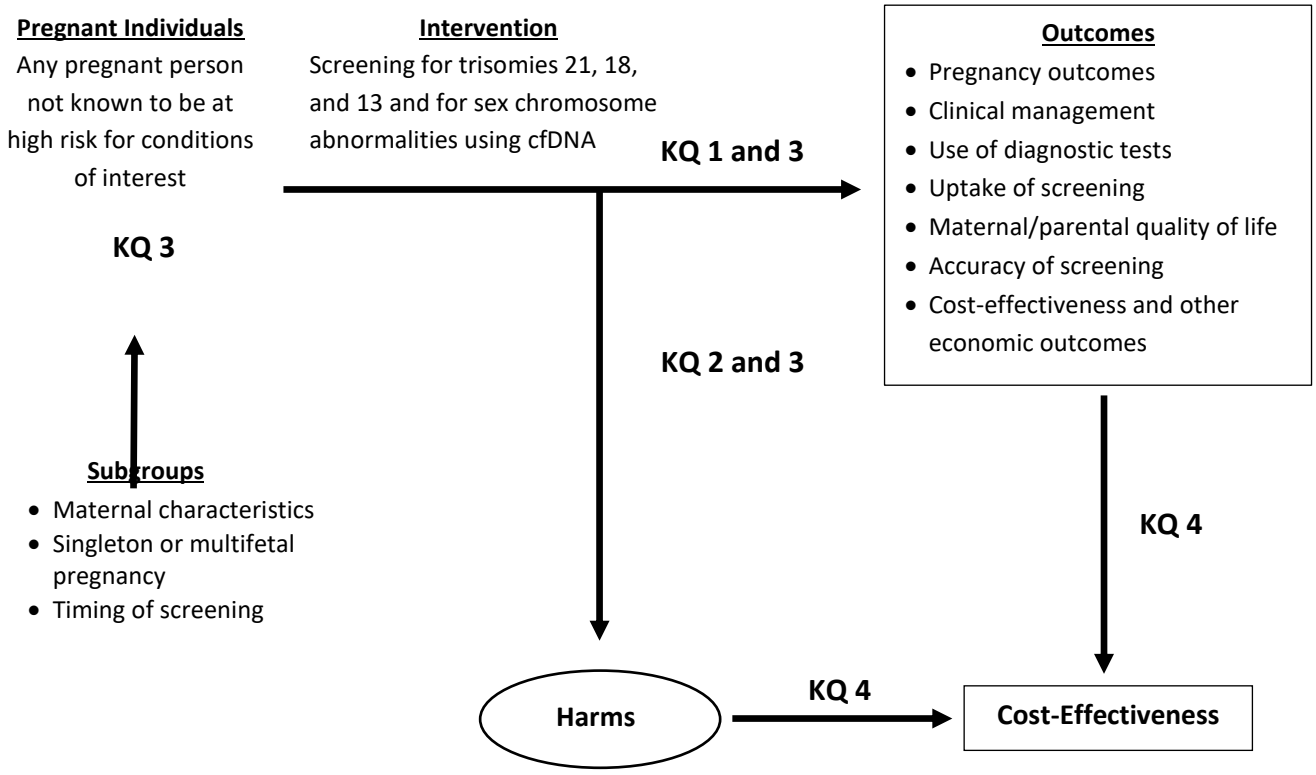
Study design	• Key Questions 1–4
	  ○ Randomized controlled trials
	  ○ Systematic reviews of randomized controlled trials
	  ○ Nonrandomized, comparative studies
	• Additional studies/data for Key Questions 2 and 3 (harms)
		• Abstracts, conference proceedings, posters, editorials, letters
		• Case reports and case series with fewer than 10 subjects (for harms only)
		• Proof-of-principle studies (e.g., algorithm modification)

Final - Updated

Study Component	Inclusion	Exclusion
	○ Nonrandomized studies without a comparator and with 10 or more participants • Additional studies/data for Key Question 4 ○ Cost-effectiveness studies and other formal comparative economic evaluations ○ Systematic reviews of cost-effectiveness studies and other formal comparative economic evaluations	• Studies with harms outcomes for a test that is not included in Key Question 1 • Systematic reviews that are superseded by a more comprehensive or high-quality systematic review
Publication	• Studies in peer-reviewed journals, technology assessments, or publicly available FDA or other government reports • Published in English • Published from 2007 through July 2019	• Studies whose abstracts do not allow study characteristics to be determined • Studies that cannot be located • Duplicate publications of the same study that do not report different outcomes or follow-up times, or single site reports from published multicenter studies • Studies in languages other than English • Studies published prior to 2007

Analytic Framework

The analytic framework below will guide the selection, synthesis, and interpretation of available evidence.



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References

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Public comment and response

All comments submitted on the draft key questions received a response in a separate document titled ***Draft key questions: comment and response***.