Topic Brief: Non-invasive Prenatal Cell-free DNA Screening

Date: 10/04/2022
Nomination Number: 0998

Purpose: This document summarizes the information addressing a nomination submitted on June 2, 2022 (https://effectivehealthcare.ahrq.gov/get-involved/nominated-topics/dna-screening) through the Effective Health Care Website. This information was used to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

Issue:
The clinical utility of expanding cell-free DNA testing of maternal blood to include panels of microdeletions and microduplications and genome-wide assessment of large chromosomal imbalances has not been established and has not been FDA-approved, but the testing is currently being used and use is expected to grow. A systematic review could contribute to the establishment of guidelines and influence payer practices.

Findings:
The scope of this topic met all EHC Program selection criteria and was considered for a systematic review. However, it was not selected.

Background

Chromosomal abnormalities such as microdeletions and microduplications (MMs) are a type of genetic copy number variant which are defined as either the addition or loss of a stretch of DNA compared to the standard human genome. Chromosomal MMs have long been associated with intellectual disability and developmental delay, and are known to cause various syndromes (e.g., Prader-Willi, Angelman, Smith-Magenis, and Williams-Beuren).[1] The most common microdeletion syndrome, 22q11.2 DiGeorge syndrome, occurs in live births at an estimated rate of 1 in 4,000 to 6,000; related symptoms may include cardiac anomalies and immune deficiencies.[2] The 1q21.1 microduplication, which is associated with developmental delay and intellectual disability, occurs in about 3 in 10,000 people.[3]

Prenatal cell-free DNA (cfDNA) screening, also called non-invasive prenatal screening/testing (NIPS), is a type of blood sampling test performed on pregnant people to determine whether the unborn child is more likely to have certain trisomy disorders such as trisomy 21 (Down syndrome).[4] Some companies now also offer NIPS testing for chromosomal MMs.[5] Health care providers widely use NIPS tests for MMs. NIPS tests are offered as laboratory developed tests (LDT), and FDA has had a general policy of enforcement discretion for most LDTs and does not generally enforce regulatory requirements for most laboratory developed tests. In a recent safety communication, the FDA warned of the possibility of false results and against claims of reliability and accuracy by the laboratories developing them.[6]

Scope

What is the diagnostic performance, effectiveness, and harms of DNA screening (NIPS) for detection of microdeletions/microduplications?

Table 1. Questions and PICOs (population, intervention, comparator, outcome)

Questions	NIPS for detection of MMs
Population	Individuals with first- and second-trimester singleton pregnancy or multiple pregnancies undergoing prenatal screening
Interventions	NIPS using analysis of cell-free fetal DNA via analyses such as whole genome sequencing, single-nucleotide polymorphism-based, semiconductor sequencing platform, Hidden Markov model, for detection of fetal MMs in addition to ultrasound
Comparators	The reference standard test is pre- or post-natal diagnostic test, namely CMA or FISH performed on cells obtained from chorionic villi and amniotic fluid as early as 8-12 weeks
Outcomes	Positive predictive value of NIPS for MM syndromes, Infant health outcomes/incidences of genetic abnormalities associated with conditions such as Microdeletion syndromes: 22q11.2 (DiGeorge syndrome) 1p36 deletion syndrome 4p16.3 (Wolf-Hirschhorn syndrome) 5p15.2 (Cri Du Chat syndrome) 15q11-13 MATERNAL DELETION SYNDROME (ANGELMAN SYNDROME) 15q11-13 PATERNAL DELETION SYNDROME (PRADER-WILLI SYNDROME) Microduplication syndromes: 1q21.1 DUPLICATION SYNDROME 2q31 DUPLICATION SYNDROME 2q23.1 DUPLICATION SYNDROME 3q29 DUPLICATION SYNDROME 5q35 MICRODUPLICATION SYNDROME Harms (e.g., psychological harms of inaccurate results, fetal injury or loss associated with some invasive tests or NIPS results)

Abbreviations: CMA= chromosomal microarray; FISH=fluorescence in situ hybridization; MM=microdeletions/microduplications; NIPS=non-invasive prenatal screening/testing.

Assessment Methods

See Appendix A.

Summary of Literature Findings

We did not find any recent systematic reviews that fit the scope of the nomination. We did find 26 primary studies addressing the key question. Of these, 16[7-22] explicitly reported the positive predictive value of NIPS for detection of microdeletions and/or microduplications. The remaining 10[23-32] studies reported similar metrics for the determination of test accuracy, including sensitivity/specificity and detection rate.

Table 2. Literature identified for each Key Question

Question	Systematic reviews (11/2019-11/2022)	Primary studies (11/2017-11/2022)
NIPS for detection of MMs	Total: 0	Total: 26 • Observational: 26[7-32] Clinicaltrials.gov • Recruiting: 0

Abbreviations: MM=microdeletions/microduplications; NIPS=non-invasive prenatal screening/testing.

See Appendix B for detailed assessments of all EPC selection criteria.

Summary of Selection Criteria Assessment

Despite the lack of proven clinical utility and the lack of FDA approval, NIPS for MMs are widely marketed and used. A systematic review could contribute to the development of guidelines and reassess coverage by insurance. A search of the literature for studies on the diagnostic performance, effectiveness, and harms of NIPS screening for detection of microdeletions/microduplications revealed 26 observational studies, 16 of which explicitly reported the positive predictive value of the NIPS testing. A systematic review could update guidance and assessment of coverage decisions.

Please see Appendix B for detailed assessments of individual EPC Program selection criteria.

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Author
Emily Gean
Robin Paynter
Lisa Winterbottom
Charli Armstrong

Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Acknowledgements
Christine Chang

This report was developed by the Scientific Resource Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA 290-2017-00003C). The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. No statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality or of the U.S. Department of Health and Human Services.

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Appendix A: Methods

We assessed nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Absence of Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years November 14, 2019 - November 14, 2022, on the questions of the nomination from these sources:

- AHRQ: Evidence reports and technology assessments
  - AHRQ Evidence Reports https://www.ahrq.gov/research/findings/evidence-based-reports/index.html
  - EHC Program https://effectivehealthcare.ahrq.gov/
  - US Preventive Services Task Force https://www.uspreventiveservicestaskforce.org/
  - AHRQ Technology Assessment Program https://www.ahrq.gov/research/findings/ta/index.html
- US Department of Veterans Affairs Products publications
  - Evidence Synthesis Program https://www.hsrd.research.va.gov/publications/esp/
  - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program https://www.healthquality.va.gov/
- Cochrane Systematic Reviews https://www.cochranelibrary.com/
- PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/
- PubMed https://www.ncbi.nlm.nih.gov/pubmed/
- Joanna Briggs Institute http://joannabriggs.org/
- Epistemonikos Epistemonikos

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a limited literature search in PubMed for the last five years November 14, 2017-November 14, 2022. We reviewed all studies identified titles and abstracts for inclusion. We classified identified studies by question and study design to estimate the size and scope of a potential evidence review.

Search strategy
MEDLINE ALL (Ovid) <1946 to November 14, 2022>
Date searched: November 15, 2022

1 Noninvasive Prenatal Testing/ or Pregnancy Trimester, First/ or Pregnancy Trimester, Second/ (31182)
2 (CFDNA or CFFDNA or NIPS or NIPT or (("cell-free" or noninvasive$3 or non-invasive$3) and (embryo$1 or fetal or fetus$2 or foetal or foetus$2 or antenatal$3 or ante-natal$3 or pregnant or prenatal$2 or pre-natal$2 or "first trimester" or "1st trimester" or "trimester 1" or "trimester one" or "second trimester" or "2nd trimester trimester 2" or "trimester two") and (analysis or analyses or diagnos* or DNA or Markov or screen* or sequencing or "single nucleotide" or test* or ultrasound or "whole genome"))).ti,ab,kf. (12012)
3 or/1-2 (42158)
4 Angelman Syndrome/ or Cri-du-Chat Syndrome/ or Chromosome Deletion/ or Chromosome Duplication/ or Chromosomes, Human, Pair 1/ or Chromosomes, Human, Pair 2/ or Chromosomes, Human, Pair 3/ or Chromosomes, Human, Pair 4/ or Chromosomes, Human, Pair 5/ or Chromosomes, Human, Pair 15/ or DiGeorge Syndrome/ or Prader-Willi Syndrome/ or Retinoblastoma/ or Wolf-Hirschhorn Syndrome/ (61047)
5 ((chromosom$4 adj3 (delet$4 or duplicat$4)) or "contiguous gene syndrome" or microdelet$4 or micro-delet$4 or microduplicat$4 or micro-duplicat$4 or submicroscopic or sub-microscopic or Angelman or "Cri-du-Chat " or DiGeorge or "Prader-Willi" or Retinoblastoma or "Wolf-Hirschhorn" or (chromosom$2 adj2 ("1" or one or "2" or two or "3" or three or "4" or four or "5" or five or "13" or thirteen or "15" or fifteen or "22" or twenty-two)) or "BP1-BP2" or "1q21.1" or "1p36" or "2q31" or "2q23.1" or "3q29" or "4p16.3" or "5p15.2" or "5q35" or "13q14" or "15q11.2" or "15q11" or "15q12" or "15q13" or "15q13.3" or "22q11.2").ti,ab,kf. (54126)
6 or/4-5 (92847)
7 and/3,6 (480)
8 7 not ((exp Animals/ not Humans/) or (animal or bovine or canine or cat or cats or dog or dogs or mice or mouse or rat or rats or rattus or rodentia or zebrafish).ti. or case report.pt.) (478)
9 limit 8 to english language (434)
10 remove duplicates from 9 (433)
11 limit 10 to yr="2019 -Current" (187)
12 11 and ((meta-analysis or systematic review).pt. or (metaanal* or meta-anal* or ((evidence or scoping or systematic or umbrella) adj3 (review or synthesis))).ti.) (4)
13 limit 10 to yr="2017 -Current" (241)
14 13 not 12 (237)
15 14 and ((controlled clinical trial or randomized controlled trial).pt. or (control* or placebo* or random* or trial).ti,ab,kf.) (12)
16 14 not 15 (225)
17 16 and (("comparative study" or "observational study").pt. or (Case-Control Studies or Cohort Studies or Controlled Before-After Studies or Follow-up Studies or Historically Controlled Study or Interrupted Time Series Analysis or Longitudinal Studies or Prospective Studies or Retrospective Studies or Retrospective Studies).sh. or (case-control or cohort$1 or "controlled before-after" or follow-up or "historically controlled" or "interrupted time series" or longitudinal$2 or prospective$2 or retrospective$2).ti,ab,kf.) (80)
18 16 not 17 (145)

Cochrane Central Register of Controlled Trials (Ovid EBM Reviews) October 2022
Date searched: November 15, 2022
1 Noninvasive Prenatal Testing/ or Pregnancy Trimester, First/ or Pregnancy Trimester, Second/ (1291)
2 (CFDNA or CFFDNA or NIPS or NIPT or (("cell-free" or noninvasive$3 or non-invasive$3) and (embryo$1 or fetal or fetus$2 or foetal or foetus$2 or antenatal$3 or ante-natal$3 or pregnant or prenatal$2 or pre-natal$2 or "first trimester" or "1st trimester" or "trimester 1" or "trimester

one" or "second trimester" or "2nd trimester trimester 2" or "trimester two") and (analysis or analyses or diagnos* or DNA or Markov or screen* or sequencing or "single nucleotide" or test* or ultrasound or "whole genome"))).ti,ab. (895)
3 or/1-2 (2173)
4 Angelman Syndrome/ or Cri-du-Chat Syndrome/ or Chromosome Deletion/ or Chromosome Duplication/ or Chromosomes, Human, Pair 1/ or Chromosomes, Human, Pair 2/ or Chromosomes, Human, Pair 3/ or Chromosomes, Human, Pair 4/ or Chromosomes, Human, Pair 5/ or Chromosomes, Human, Pair 15/ or DiGeorge Syndrome/ or Prader-Willi Syndrome/ or Retinoblastoma/ or Wolf-Hirschhorn Syndrome/- (320)
5 ((chromosom$4 adj3 (delet$4 or duplicat$4)) or "contiguous gene syndrome" or microdelet$4 or micro-delet$4 or microduplicat$4 or micro-duplicat$4 or submicroscopic or sub-microscopic or Angelman or "Cri-du-Chat " or DiGeorge or "Prader-Willi" or Retinoblastoma or "Wolf-Hirschhorn" or (chromosom$2 adj2 ("1" or one or "2" or two or "3" or three or "4" or four or "5" or five or "13" or thirteen or "15" or fifteen or "22 or twenty-two")) or "BP1-BP2" or "1q21.1" or "1p36" or "2q31" or "2q23.1" or "3q29" or "4p16.3" or "5p15.2" or "5q35" or "13q14" or "15q11.2" or "15q11" or "15q12" or "15q13" or "15q13.3" or "22q11.2").ti,ab. (627)
6 or/4-5 (736)
7 and/3,6 (3)
8 limit 7 to yr="2017 -Current" (2)

EPISTEMONIKOS
Date searched: November 15, 2022
(title:((title:(CFDNA OR CFFDNA OR NIPS OR NIPT OR (("cell-free" OR noninvasive* OR non-invasive*) AND (embryo* OR fetal OR fetus* OR foetal OR foetus* OR antenatal* OR ante-natal* OR pregnant OR pregnanc* OR prenatal* OR pre-natal* OR "first trimester" OR "1st trimester" OR "trimester 1" OR "trimester one" OR "second trimester" OR "2nd trimester trimester 2" OR "trimester two") AND (analysis OR analyses OR diagnos* OR DNA OR Markov OR screen* OR sequencing OR "single nucleotide" OR test* OR ultrasound OR "whole genome"))) OR abstract:(CFDNA OR CFFDNA OR NIPS OR NIPT OR (("cell-free" OR noninvasive* OR non-invasive*) AND (embryo* OR fetal OR fetus* OR foetal OR foetus* OR antenatal* OR ante-natal* OR pregnant OR pregnanc* OR prenatal* OR pre-natal* OR "first trimester" OR "1st trimester" OR "trimester 1" OR "trimester one" OR "second trimester" OR "2nd trimester trimester 2" OR "trimester two") AND (analysis OR analyses OR diagnos* OR DNA OR Markov OR screen* OR sequencing OR "single nucleotide" OR test* OR ultrasound OR "whole genome")))) AND (title:((chromosom* AND (delet* OR duplicat*)) OR "contiguous gene syndrome" OR microdelet* OR micro-delet* OR microduplicat* OR micro-duplicat* OR submicroscopic OR sub-microscopic OR Angelman OR "Cri-du-Chat" OR DiGeorge OR "Prader-Willi" OR Retinoblastoma OR "Wolf-Hirschhorn" OR "chromosome 1" OR "chromosome one" OR "chromosome 2" OR "chromosome two" OR "chromosome 3" OR "chromosome three" OR "chromosome 4" OR "chromosome four" OR "chromosome 5" OR "chromosome five" OR "chromosome 13" OR "chromosome thirteen" OR "chromosome 15" OR "chromosome fifteen" OR "chromosome 22" OR "chromosome twenty-two" OR "BP1-BP2" OR "1q21.1" OR "1p36" OR "2q31" OR "2q23.1" OR "3q29" OR "4p16.3" OR "5p15.2" OR "5q35" OR "13q14" OR "15q11.2" OR "15q11" OR "15q12" OR "15q13" OR "15q13.3" OR "22q11.2") OR abstract:((chromosom* AND (delet* OR duplicat*)) OR "contiguous gene syndrome" OR microdelet* OR micro-delet* OR microduplicat* OR micro-duplicat* OR submicroscopic OR sub-microscopic OR Angelman OR "Cri-du-Chat" OR DiGeorge OR "Prader-Willi" OR Retinoblastoma OR "Wolf-Hirschhorn" OR "chromosome 1" OR "chromosome one" OR "chromosome 2" OR "chromosome two" OR "chromosome 3" OR "chromosome three" OR "chromosome 4" OR "chromosome four" OR "chromosome 5" OR "chromosome five" OR

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PROSPERO

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ClinicalTrials.gov

Value

We assessed the nomination for value. We considered whether or not the clinical, consumer, or policymaking context had the potential to respond with evidence-based change, if a partner organization would use this evidence review to influence practice, and if the topic supports a priority area of AHRQ or the Department of Health and Human Services.

Appendix B. Selection Criteria Assessment

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the United States?	Yes
1b. Is the nomination a request for an evidence report?	Yes
1c. Is the focus on effectiveness or comparative effectiveness?	Yes
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	NIPS testing for MMs is commonly used and its use is expected to grow.
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the United States population or for a vulnerable population	Yes. The pregnant population seeking testing is vulnerable to the effects of potential inaccurate NIPS results.
2c. Incorporates issues around both clinical benefits and potential clinical harms	Yes.
2d. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes. Genetic testing costs can range from under $100 to more than $2,000.[33] Additional unnecessary costs result from false positive NIPS results.
3. Desirability of a New Evidence Review/Absence of Duplication	
3. A recent high-quality systematic review or other evidence review is not available on this topic	Yes. We did not find a recent systematic review that adequately addressed the nomination.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes. The FDA has not approved NIPS for MMs.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes. NIPS for MMs are used despite lack of FDA approval and cautions from the FDA.
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	Size/scope of review: 26 primary studies, for an estimated small systematic review.
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change and supports a priority of AHRQ or Department of Health and Human Services	Yes. A systematic review could influence the degree to which NIPS in MMs are used in practice, recommended/approved, and covered by payers.
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	Yes. The nominator represents a large health care system with intention to influence guideline development.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; FDA=United States Food and Drug Administration; MM=microdeletions/microduplications; NIPS=non-invasive prenatal screening/testing.