03-59000-18

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Reviewed: 09/28/23

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Subject: Noninvasive Prenatal Screening for Fetal Aneuploidies, Twin Zygosity, and Microdeletions Using Cell-Free Fetal DNA

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

National guidelines recommend that all pregnant individuals be offered screening for fetal chromosomal abnormalities, most of which are aneuploidies, an abnormal number of chromosomes. Trisomy syndromes are aneuploidies involving 3 copies of 1 chromosome. Trisomies 21, 18, and 13 are the most common forms of fetal aneuploidy that survive to birth. There are numerous limitations to standard screening for these disorders using maternal serum and fetal ultrasound. Noninvasive prenatal screening (NIPS) analyzing cell-free fetal DNA in maternal serum is a potential complement or alternative to conventional serum screening. NIPS using cell-free fetal DNA has also been proposed to screen for microdeletions. Prenatal testing for twin zygosity using cell-free fetal DNA has been proposed to inform decisions about early surveillance for twin-twin transfusion syndrome and other monochorionic twin-related abnormalties.

The technology for noninvasive, sequencing-based testing of maternal serum for fetal trisomy syndromes involves detection of cell-free fetal DNA fragments present in the plasma of pregnant individuals. As early as 8 to 10 weeks of gestation, these fetal DNA fragments comprise 6% to 10% or more of the total cell-free fetal DNA in a maternal plasma sample. The tests are unable to provide a result if the fetal fraction is too low (ie, <4%). Fetal fraction can be affected by maternal and fetal characteristics.

A newer approach to cell free DNA testing called the Vanadis NIPT does not involve polymerase chain reaction (PCR) amplification or sequencing. The procedure consists of digestion of cell-free DNA (cfDNA) using a restriction enzyme. The digested cfDNA is then hybridized and ligated to chromosome specific

DNA probes forming a circular DNA. All non-circular DNA is removed by exonuclease treatment. Finally, the circular DNA containing the cfDNA is amplified with rolling circle amplification to form rolling circle products that are labeled with chromosome- specific fluorescently labeled DNA probes. The fluorescently labeled rolling circle productss are imaged and counted with an automated microscopy scanner. The microscope takes multiple images from each well with different spectral filters, i.e each wavelength range presents a specific chromosome. With image analysis algorithms, the fluorescently labeled rolling circle products are counted for each sample. The ratio between the number of chromosome-specific rolling circle products is then transferred to risk calculation software to calculate the likelihood of a trisomy. Currently, Vanadis NIPT provides results for trisomy 21, trisomy 18 and trisomy 13, and fetal sex determination.

Single-gene disorders (also known as monogenic disorders) are caused by a variation in a single gene. Individually, single-gene disordersare rare, but collectively are present in approximately 1% of births. The Vistara Single-Gene Disorder Test panel screens for 25 conditions that result from variants across 30 genes. These include Noonan syndrome and other Noonan spectrum disorders, skeletal disorders (e.g., Osteogenesis Imperfecta, achondroplasia), craniosynostosis syndromes,Cornelia de Lange syndrome, Alagille syndrome, tuberous sclerosis, epileptic encephalopathy,SYNGAP1-related intellectual disability,CHARGE syndrome, Sotos syndrome, and Rett syndrome. The clinical presentation and severity of these disorders can vary widely.Some, but not all, can be detected by prenatal ultrasound examination.

POSITION STATEMENT:

NOTE: Coverage for genetic testing, screening, and counseling are applicable only under those contracts that include benefits for genetic testing, preventive health services, screening services, and medical counseling.

Nucleic acid sequencing-based testing of maternal plasma to screen for trisomy 21, 18, 13 **meets the definition of medical necessity** in members with singleton or twin pregnancies.

Nucleic acid sequencing-based testing of maternal plasma, other than in the situation specified above, is considered **experimental or investigational**. There is insufficient clinical evidence to permit conclusions on net health outcomes.

Nucleic acid sequencing-based testing of maternal plasma is considered **experimental or investigational** for the following indications:

- fetal sex chromosome aneuploidies
- microdeletions.

The evidence is insufficient to determine the effects of the technology on health outcomes.

Vanadis® NIPT of maternal plasma to screen for trisomy 21, 18 and 13 is considered **experimental or investigational** in all situations. The evidence is insufficient to determine the effects of the technology on health outcomes.

Vistara™ NIPT of maternal plasma to screen for single-gene disorders is considered **experimental or investigational** in all situations. The evidence is insufficient to determine the effects of the technology on health outcomes.

BILLING/CODING INFORMATION:

CPT Coding:

81420	Fetal chromosomal aneuploidy (eg, trisomy 21, monosomy X) genomic sequence analysis panel, circulating cell-free fetal DNA in maternal blood, must include analysis of chromosomes 13, 18, and 21
81422	Fetal chromosomal microdeletion(s) genomic sequence analysis (eg, DiGeorge syndrome, Cri-du-chat syndrome), circulating cell-free fetal DNA in maternal blood **(Investigational)**
81507	Fetal aneuploidy (trisomy 21, 18, and 13) DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy (Harmony™ Prenatal Test)
0060U	Twin zygosity, genomic targeted sequence analysis of chromosome 2, using circulating cell-free fetal DNA in maternal blood (**Investigational**)

CPT Code 88271 and unlisted codes 81599 and 81479 may also be used to report nucleic acid sequencing–based tests.

ICD-10 Diagnosis Codes That Support Medical Necessity:

O09.511	Supervision of elderly primigravida, first trimester
O09.512	Supervision of elderly primigravida, second trimester
O09.521	Supervision of elderly multigravida, first trimester
O09.522	Supervision of elderly multigravida, second trimester
O30.001 – O30.099	Twin pregnancy
Z31.430 – Z31.438	Encounter for genetic testing of female for procreative management
Z34.00 – Z34.93	Encounter for supervision of normal pregnancy
Z36.0 – Z36.9	Encounter for antenatal screening of mother

REIMBURSEMENT INFORMATION:

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline reviewed date.

DEFINITIONS:

No guideline specific definitions apply.

RELATED GUIDELINES:

Genetic Testing, 05-82000-28

OTHER:

Other names used to describe nucleic acid sequencing-based testing of maternal plasma:

Note: The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

- Harmony™ (T21, T18, T13)
- InformaSeq℠ (T21, T18, T13 with optional testing for select sex chromosome abnormalities)
- MaterniT21™ PLUS (core test: T21, T18, T13, and fetal sex aneuploidies; enhanced sequencing series includes T16, T22, and microdeletions)
- Panorama™ (T21, T18, T13 and select sex chromosome abnormalities; extended panel includes microdeletions)
- Prequel™ Prenatal Screen (T21, T18, T13)
- Qnatal™ (T21, T18, T13)
- Verifi® (T21, T18, T13)
- Vanadis® NIPT Solution (T21, T18, T13)
- Veracity Prenatal (T21, T18, T13, sex chromosome aneuploidies, and microdeletions)
- VisibiliT (T21 and T18).

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy and Coverage Committee on 09/28/23.

GUIDELINE UPDATE INFORMATION:

03/15/13	New Medical Coverae Guideline.
07/01/13	Quarterly HCPCS updates. Added code 0005M. Revised Program Exception section.
10/15/13	Revision; position statements and guideline title updated; formatting changes.
01/01/14	Annual HCPCS update. Added code 81507; deleted code 0005M.
03/15/14	Annual review; position statements maintained and references updated.
01/01/15	Annual HCPCS/CPT update. Added code 81420.
04/15/15	Annual review; position statements and references updated; formatting changes.
09/15/15	Revision; update position statement and references; formatting changes.
11/15/15	Revision; coding section updated.
12/15/16	Revision; title, description, position statements, and references updated; formatting changes.
01/01/17	Annual CPT/HCPCS update. Added 81422.
07/01/18	Quarterly CPT/HCPCS update. Added code 0060U.
08/01/18	Revision; ICD10 codes added.
10/15/18	Revision; coverage statement, description, coding, and references updated.
01/01/20	Annual CPT/HCPCS coding update. Deleted code 0009M.

04/01/20	Quarterly CPT/HCPCS update. Added code 0168U.
11/15/20	Review; Position statements and references updated.
10/01/21	Quarterly CPT/HCPCS update. Deleted code 0168U.
11/15/21	Review: Position statements maintained and references updated.
02/15/23	Review: Position statements, description, coding, and references updated.
10/15/23	Review: Coverage position statement, coding, and references updated.