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Reviewed: 09/26/24

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

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 fetal cell-free DNA (cfDNA) in maternal serum is a potential complement or alternative to conventional serum screening. NIPS using fetal cfDNA has also been proposed to screen for microdeletions. Prenatal testing for twin zygosity using fetalcfDNA 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 fetal cfDNA 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 fetal cfDNA 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.

Summary and Analysis of Evidence: Individuals with singleton or twin pregnancy who receive NIPS for T21, T18, and T13 using fetal cfDNA, the evidence includes observational studies and systematic reviews. Published studies on available tests and meta-analyses of these studies have consistently demonstrated very high sensitivity and specificity for detecting Down syndrome (T21) in singleton pregnancies. Most studies included only individuals at high-risk of T21, but several studies have reported similar levels of diagnostic accuracy in average-risk individuals. Compared with standard serum screening, both the sensitivity and specificity of fetal cfDNA screening are considerably higher. As a result, screening with fetal cfDNA for T21 will result in fewer missed cases of Down syndrome, fewer invasive procedures, and fewer cases of pregnancy loss following invasive procedures. Screening for T18 and T13 along with T21 may allow for preparation for fetal demise or termination of the pregnancy prior to fetal loss. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. The evidence for NIPS for sex chromosome aneuploidies using fetal cfDNA includes observational studies, mainly in high-risk pregnancies, and systematic reviews. Meta-analyses of available data have suggested high sensitivities and specificities, but the small number of cases makes definitive conclusions difficult. In addition, the clinical utility of identifying sex chromosome aneuploidies during pregnancy is uncertain. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. NIPS for T21, T18, and T13 using Vanadis NIPT, the evidence includes 2 industry sponsored studies. The available studies on clinical validity have limitations, and the added benefit of Vanadis NIPT compared with current approaches is unclear. Moreover, the clinical utility of Vanadis NIPT remains unclear and has not been evaluated in published studies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. The evidence for NIPS for single-gene disorders includes validation studies and a case study. There is insufficient evidence on clinical validity and data demonstrating improvement are unavailable. The American College of Obstetricians and Gynecologists (ACOG) Practice Advisory Cell-free DNA to Screen for Single-Gene Disorders (2019, reaffirmed 2023) concluded, “Although this technology is available

clinically and marketed as a single-gene disorder prenatal screening option for obstetric care providers to consider in their practice, often in presence of advanced paternal age, there has not been sufficient data to provide information regarding accuracy and positive and negative predictive value in the general population. For this reason, single-gene cell-free DNA screening is not currently recommended in pregnancy." The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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.

Noninvasive prenatal testing (NIPT) of maternal plasma to screen for single-gene disorders (e.g. Vistara™ NIPT) 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**)
0327U	Fetal aneuploidy (trisomy 13, 18, and 21), DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy, includes sex reporting, if performed
0341U	Fetal aneuploidy DNA sequencing comparative analysis, fetal DNA from products of conception, reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplication, mosaicism, and segmental aneuploid (**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:

None applicable.

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy and Coverage Committee on 09/26/24.

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.
10/15/24	Review: NIPT for single gene disorders position statement updated; description and references updated.