Genetic Testing for Reproductive Planning and Prenatal Testing

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INSTRUCTIONS FOR USE: Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Company reserves the right to determine the application of medical policies and make revisions to medical policies at any time. The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement. Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

SCOPE: Providence Health Plan, Providence Health Assurance, and Providence Plan Partners as applicable (referred to individually as "Company" and collectively as "Companies").

PLAN PRODUCT AND BENEFIT APPLICATION

☒ **Commercial** ☐ **Medicaid/OHP*** ☐ **Medicare****

*Medicaid/OHP Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

Diagnostic services needed to establish a diagnosis are covered regardless of where the ultimate diagnosis appears. Once the diagnosis is determined, coverage of further treatment is reimbursed if the service appears funded by the OHA for that condition. Medicaid members must also meet the genetic testing criteria governed by the Oregon Health Plan (OHP) Prioritized List Guideline Notes D1 and D17.

**Medicare Members

This *Company* policy may be applied to Medicare Plan members only when directed by a separate *Medicare* policy. Note that investigational services are considered **"not medically necessary"** for Medicare members.

COVERAGE CRITERIA

Notes:

- This policy does not address the following, which may be considered medically necessary:
  - *GJB2* and *GJB6* genes for hereditary hearing loss
  - Invasive prenatal diagnosis, including but not limited to *SMN1* and *SMN2* testing
  - Noninvasive Prenatal Screening (without microdeletions)
- The tests addressed in this policy only apply to biological parents.
- This policy addresses the following types of genetic testing and associated services:
  - Carrier Screening
  - Genetic testing of asymptomatic prospective biologic parents before or during pregnancy to determine the risk of having a child with a single gene disorder. Conditions addressed in this section include:
    - Cystic Fibrosis (CF)
    - Spinal Muscular Atrophy (SMA)
    - Fragile X Syndrome
    - Hemoglobinopathies and Thalassemias
    - Genetic Conditions in Individuals of Ashkenazi Jewish (Eastern and Central European) Descent
    - Other Single-Gene Genetic Conditions

- Expanded Genetic Panel Testing for Carrier Screening

- Noninvasive Prenatal Screening
  Noninvasive prenatal screening (NIPS), also known as noninvasive prenatal testing (NIPT), is genetic testing of cell-free fetal DNA from maternal blood to screen for an increased risk of chromosomal abnormalities in the fetus.
- Pregnancy Loss
  Genetic testing of parental DNA and/or fetal tissue after stillbirth or recurrent pregnancy loss to determine causative abnormalities.
- Genetic Panel Testing
  All components of a panel test must be medically necessary in order to the test to be covered.

Carrier Screening for Genetic Conditions

Note: Carrier screening testing has limits. See Billing Guidelines below.

Cystic Fibrosis (CF)

I. Carrier screening for CF using the American College of Obstetricians and Gynecologists/ American College of Medical Genetics and Genomics (ACOG/ACMG) recommended standard mutation panel* (panels may include 23-25 mutations listed below in the Policy Guidelines section) may be considered **medically necessary** when Genetic Counseling general criteria have been met and **either** of the following criteria (A. or B.) are met:

   A. A woman is considering pregnancy or is currently pregnant; **or**
   B. A woman's reproductive partner meets **any one** of the following criteria (1.-4.):
      1. The partner has a family history of CF; **or**
      2. The partner is either affected with CF or is a known carrier of a common CF-causing mutation; **or**
      3. The partner is affected with congenital absence of the vas deferens.
      4. The test is positive for the women considering pregnancy or currently pregnant

II. Carrier screening for CF using an expanded CF mutation panel (>25 mutations) may be considered **medically necessary** when the individual meets criterion I. above and the standard mutation panel for CF is negative.

III. Carrier screening for CF by complete *CFTR* gene sequencing may be considered **medically necessary** when the individual meets criterion I. above, and the standard or expanded mutation panel (criterion II.) for CF is negative.

IV. Carrier screening for CF by targeted sequencing of a single mutation may be considered **medically necessary** when the individual meets criterion I. above and when **either** of the following criteria (A. or B.) are met:

   A. The known familial mutation is not included in the standard or expanded CF mutation panels; **or**

B. Their partner is a known carrier of a CF-causing mutation not in the standard or expanded CF mutation panels.

V. Carrier screening for CF is considered **not medically necessary** in all other situations, including but not limited to:

A. When any of the criteria (I.-IV.) above are not met.
B. For standard population-based screening.
C. When a family member has been tested for mutations and received a result of variant of uncertain significance (VUS).

Fragile X Syndrome

VI. Carrier screening for Fragile X syndrome (*FMR1* gene) for a woman who is considering pregnancy or is currently pregnant may be considered **medically necessary** when Genetic Counseling general criteria have been met and **either** of the following criteria (A. or B.) are met:

A. There is a family history of fragile X-related disorders (including fragile X syndrome, fragile X-associated tremor/ataxia syndrome, and/or FMR1-related primary ovarian insufficiency) or intellectual disability suggestive of fragile X syndrome; **or**
B. Documentation of unexplained ovarian insufficiency or failure **or** an elevated follicle-stimulating hormone level before 40 years of age.

VII. Carrier screening for Fragile X syndrome (FMR1) is considered **not medically necessary** when criterion VI., above is not met, including, but not limited to testing for standard population-based screening.

Hemoglobinopathies and Thalassemias

VIII. Carrier screening for hemoglobinopathies and thalassemias (including but not limited to: Sickle Cell Anemia [*HBB* gene], Alpha Thalassemia [*HBA1*/*HBA2* genes] and Beta Thalassemia [HBB gene]) in individuals considering pregnancy (a woman and/or her reproductive partner) or a woman who is currently pregnant, may be considered **medically necessary** when Genetic Counseling general criteria have been met and any **one** of the following criteria are met:

A. Family history of a hemoglobinopathy; **or**
B. Affected or carrier first- or second-degree family member with a known pathogenic mutation. (First-degree relatives are parents, siblings, and children; and second-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings); **or**
C. Suspicion of hemoglobinopathy based on results of a complete blood count (CBC) and hemoglobin analysis (by electrophoresis, high performance liquid chromatography [HPLC] or isoelectric focusing).

IX. Carrier screening for hemoglobinopathies and thalassemias is considered **not medically necessary** when criterion VIII., above is not met, including, but not limited to testing for standard population-based screening.

Spinal Muscular Atrophy (SMA)

X. Carrier screening for SMA by genetic testing of the *SMN1* and *SMN2* genes may be considered **medically necessary** when Genetic Counseling general criteria have been met and **either** of the following criteria (A. or B.) are met:
   A. A woman is considering pregnancy or is currently pregnant; **or**
   B. A woman's reproductive partner meets either of the following criteria (1. or 2.):
      1. The partner has a family history of SMA; **or**
      2. The partner is affected with SMA or is a known carrier of a SMA-causing mutation.

XI. Carrier screening for SMA is considered **not medically necessary** in all other situations, including, but not limited to:

   A. When criterion X. above is not met.
   B. For standard population-based screening.
   C. When a family member has been tested for mutations and received a result of VUS (variant of uncertain significance).

Genetic Conditions Associated with Ashkenazi Jewish (Eastern and Central European) Descent

XII. Carrier screening for individuals (a woman and/or her reproductive partner) of Ashkenazi Jewish descent who are considering pregnancy, or for a woman of Ashkenazi Jewish descent who is currently pregnant may be **medically necessary** when Genetic Counseling general criteria have been met and for **any one or more** of the following conditions:

Note: Testing may be ordered as a single gene test or a multi-gene panel test. All genes included in the panel test must be specific to the condition being tested and must have established clinical utility. (See Policy Guidelines below)

   A. Bloom syndrome (*BLM* gene)
   B. Canavan disease (*ASPA* gene)
   C. Cystic Fibrosis (*CFTR* gene)
   D. Familial dysautonomia (*IKBKAP* gene)
   E. Familial hyperinsulinism (*ABCC8* gene)
   F. Fanconi anemia group C (*FANCC* gene)
   G. Gaucher disease type 1 (*GBA* gene)
   H. Glycogen storage disease type Ia (also known as von Gierke disease)(*G6PC* gene)
   I. Joubert syndrome (*TMEM216* gene)
   J. Maple syrup urine disease (*BCKDHA, BCKDHB*, and/or *DBT* genes)
   K. Mucolipidosis type IV (*MCOLN1* gene)
   L. Niemann–Pick disease type A (*SMPD1* gene)
   M. Spinal Muscular Atrophy (*SMN1* and *SMN2* genes)
   N. Tay-Sacks Disease (*HEXA* gene)

O. Usher syndrome type 1 (*PCDH15* gene)

XIII. Carrier screening for an individual (**either** a woman or her reproductive partner) whose reproductive partner is of Ashkenazi Jewish descent **and** is a confirmed carrier for any of the above listed conditions in criterion XII. may be considered **medically necessary** for that condition when Genetic Counseling general criteria have also been met.

XIV. Carrier screening for the conditions listed above for those who are not of Ashkenazi Jewish (Eastern and Central European) descent is considered **not medically necessary.**

Other Genetic Conditions Not Listed Above

XV. Carrier screening for single-gene conditions not listed above for couples who are considering pregnancy (a woman and/or her reproductive partner), or for a woman who is currently pregnant may be considered **medically necessary** when Genetic Counseling general criteria have been met and **either** of the following criteria (A. or B.) are met:

A. Testing is for a known pathogenic mutation confirmed in an affected first- or second-degree blood relative. (First-degree relatives are parents, siblings, and children; and second-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings); **or**
B. Targeted mutation analysis or gene sequencing when **either** of the following criteria (1. **or** 2.) are met:
    1. An individual's reproductive partner is a known carrier of a disease-causing mutation in a recessively inherited condition; **or**
    2. A genetic condition has been confirmed in an individual's affected first- or second-degree blood relative **and** the affected relative has not had genetic testing and is unavailable for testing.

XVI. Carrier screening for other genetic conditions not listed above is considered **not medically necessary** when criterion XV., above, is not met.

Expanded Genetic Panel Testing for Carrier Screening

XVII. Carrier screening using multi-gene panels (also known as expanded carrier screening) may be considered **medically necessary** when Genetic Counseling general criteria have been met if the individual meets medical necessity criteria applicable for the genes/conditions addressed above (criteria I.-XVI.).

XVIII. Carrier screening using multi-gene panels is considered **not medically necessary** when medical necessity criteria above are not met.

Noninvasive Prenatal Screening (NIPS/NIPT)

XIX. Noninvasive prenatal screening using cell-free DNA may be considered **medically necessary** for screening of trisomy 13, 18 and 21 in a viable, single gestation pregnancy ≥ 10 weeks gestation.

XX. Noninvasive prenatal screening using cell-free DNA is considered **not medically necessary** for the following indications:

A. Fetal sex determination.
B. History of miscarriage without a history of aneuploidy.
C. Twin zygosity (i.e., differentiating between identical and fraternal twins).

XXI. Noninvasive prenatal screening using cell-free DNA is considered **not medically necessary** in all other situations, including but not limited to:

A. When above criterion (XXIII.) is not met.
B. Multiple-gestation pregnancies.
C. Screening for single-gene disorders, including X-linked disorders such as Duchenne muscular dystrophy.
D. Presence of a vanishing twin or empty second gestational sac.
E. Aneuploidies of other autosomes (e.g., 7, 9, 16, 22).
F. Sex chromosome aneuploidies (X and/or Y).
G. Microdeletions.
H. Whole genome DNA screening (e.g., MaterniT® GENOME).
I. Screening of non-pregnant individuals.

Pregnancy Loss

XXII. Evaluation of chromosomal abnormalities for pregnancy loss may be considered **medically necessary** when Genetic Counseling general criteria have been met and when using either fluorescence in situ hybridization (FISH), karyotype analysis, or chromosomal microarray analysis in **either** (A. or B.) of the following situations:

A. For the evaluation of recurrent pregnancy loss (defined as a history of two or more consecutive failed pregnancies) via **one or both** of the following methods:
   1. Analysis of peripheral blood of one or both of the biological parents; **or**
   2. Analysis of fetal tissue (e.g., amniotic fluid, placenta or products of conception) when there is a maternal history of recurrent miscarriage; or
B. Analysis of fetal tissue when pregnancy loss occurs at 20 weeks or later of gestation (stillbirth).

XXIII. Evaluation of chromosomal abnormalities for pregnancy loss is considered **not medically necessary** when the above criteria are not met.

XXIV. Genetic testing to evaluate pregnancy loss using sequencing-based tests (e.g., single mutation or single gene testing, or multi-gene panel testing) is considered **not medically necessary.**

Genetic Panel Testing

XXV. Genetic panel testing for reproductive planning and prenatal testing is considered **not medically necessary** if any component of the panel is considered investigational.

XXVI. Repeat testing of the same germline genetic content, for the same genetic information, is considered **not medically necessary.**

Link to Evidence Summary

POLICY CROSS REFERENCES

- Genetic Counseling, MP316
- Whole Exome, Whole Genome, and Proteogenomic Sequencing and Genetic Testing for Mitochondrial Disorders, MP219
- Direct-to-Consumer and Over-the-Counter Testing, MP73

The full Company portfolio of current Medical Policies is available online and can be accessed here.

POLICY GUIDELINES

Standard CFTR Mutation Panel

The following 25 mutations are the most common CF-causing mutations according to the American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics and Genomics (ACMG):[1]

- ΔF508
- ΔI507
- G542X
- G551D
- W1282X
- N1303K
- R553X
- 621+1G>T
- R117H
- 1717-1G>A
- A455E
- R560T
- R1162X
- G85E
- R334W
- R347P
- 711+1G>T
- 1898+1G>A
- 2184delA
- 3849+10kbC>T
- 2789+5G>A
- 3569delC
- 3120+1G>A
- I148delT
- 1078delT

Genetic Conditions in Individuals of Ashkenazi Jewish (Eastern and Central European) Descent

The list conditions and causal genes which may meet medical necessity criteria above for carrier testing for individuals of Ashkenazi Jewish descent have been endorsed by a number of guidance documents published by the American College of Obstetrician and Gynecologists and the American College of Medical Genetics.[2-5]

In the context of this policy, *clinical utility* is defined as the likelihood that a genetic test will lead to improved health outcomes, specifically: aiding in current and future reproductive decision-making as well as pregnancy management decisions (e.g. the need for additional testing, fetal monitoring, mode of

delivery, in utero treatment options, management recommendations, including fetal surveillance, and referral to other specialists).

DOCUMENTATION REQUIREMENTS

In order to determine the clinical utility of a genetic test, the following documentation must be provided at the time of the request. Failure to submit complete documentation may affect the outcome of the review.

- Specific gene, trade or proprietary name of the test, or if a custom-built test, include every gene(s) and/or component of the test
- Name of laboratory where the testing is being conducted or was conducted
- Clinical notes to include the following:
  - Documentation of genetic counseling as required in the policy criteria below which includes how test results will impact clinical decision making
  - Reason (indication) for performing test, including the suspected condition
  - Existing signs and/or symptoms related to reason for current test request
  - Prior test/laboratory results related to reason for current test request
  - Family history, if applicable
  - How results from current test request will impact clinical decision making
- All relevant CPT/HCPCS codes billed
- Please refer to the medical policy "Genetic Counseling (All Lines of Business Except Medicare)" for additional information.

BACKGROUND

Genetic Counseling

The National Society of Genetic Counselors (NSGC) defines genetic counseling as the following:[6]

> "The process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates the following: Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence. Education about inheritance, testing, management, prevention, resources and research. Counseling to promote informed choices and adaptation to the risk or condition."

Carrier Screening

Carrier screening is genetic testing performed on an asymptomatic individual to determine whether that person has a mutation in a gene that is associated with a particular inherited disorder. Carrier screening can be performed for one specific condition or for multiple disorders and traditionally has been based on family history and ethnic background. Ethnic-specific, pan-ethnic, and expanded carrier screening are acceptable strategies for pre-pregnancy and prenatal carrier screening. Expanded carrier screening panels offered by laboratories may include options to screen for a focused subset of conditions (five-ten) to as many as several hundred conditions.[3]

Noninvasive Prenatal Screening

Noninvasive prenatal screening (NIPS; also referred to as noninvasive prenatal testing [NIPT]) was developed as an advanced screening test designed to detect the most common fetal aneuploidies in a noninvasive manner. These assays involve the analysis of cell-free fetal DNA (cfDNA, in some cases, also referred to as cfDNA) that is present in a mother's blood during pregnancy in order to detect chromosomal aneuploidies. They use recently developed ("next-generation") molecular techniques, such as massively parallel sequencing (MPS; i.e., the sequence analysis of millions of DNA fragments at the same time), that allow for an evaluation of fetal DNA in the cell-free component of the mother's blood (i.e., plasma). Although each NIPT assay is different with respect to its exact methodology and algorithms for data analysis, they are all considered roughly equal in terms of detection and false-positive rates.

Pregnancy Loss

Recurrent pregnancy loss (RPL) is a distinct disorder defined by two or more failed clinical pregnancies. There is a very high frequency of sporadic karyotypic abnormalities in products of conception while the incidence of karyotypic abnormalities in the parents is low. However, parents with unknown chromosomal abnormalities have a high risk of passing it on to their children. Of the examined products of conception, approximately 60% of early pregnancy losses are associated with sporadic chromosomal anomalies, primarily trisomies that are, in part, age related. However, in recurrent pregnancy loss, the risk of aneuploidy is just as high, but is less likely to be influenced by maternal age.[7]
Stillbirth, also known as intrauterine fetal demise, is defined as fetal death at 20 weeks or greater of gestation. An abnormal karyotype can be found in approximately 8–13% of stillbirths. The rate of karyotypic abnormalities exceeds 20% in fetuses with anatomic abnormalities or in those with growth restriction, but the rate of chromosomal anomalies found in normally formed fetuses is approximately 5%.[8]

CLINICAL EVIDENCE AND LITERATURE REVIEW

EVIDENCE REVIEW

This policy is based on the most current clinical practice guidelines published by the following U.S.-based professional associations: American College of Obstetricians and Gynecologists (ACOG), American College of Medical Genetics (ACMG), American Society of Reproductive Medicine (ASRM) and the Society of Maternal Fetal Medicine (SMFM). Please refer to the Clinical Practice Guidelines Section below for more details.

Since many of the genetic tests listed in the Policy Criteria section above are now considered standard of care by way of accepted practice guidelines from major medical societies; the evidence summary described below will focus on the indications for which genetic testing for reproductive planning and in the prenatal setting are still considered not medically necessary. A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted and below is a review of evidence identified through April 2026.

Carrier Screening for Genetic Conditions

Carrier screening for genetic disease in the general population lacks support from both evidence- and consensus-based clinical practice guidelines from major medical societies. In addition, there is no direct

evidence of clinical utility of carrier screening in the general population, as the published studies have reported prevalence, and not whether the results from the screening test impact reproductive decision-making.

Testing for screening or diagnostic purposes for a genetic disease when a family member has been found to have a variant of uncertain significance (VUS) is not considered to have clinical utility for any indication. No studies were identified for any genetic condition that reported on how testing for a VUS impacted clinical, medical management, or reproductive decisions; or how the results of these tests improved health outcomes.

Noninvasive Prenatal Screening (NIPS)

The use of noninvasive prenatal screening has been clinically validated for the common trisomies. However, testing labs are now offering NIPS testing for a number of indications that have not been validated in the clinic or through studies published in peer-reviewed journals. The use of NIPS to screen for aneuploidies of chromosomes (other than 13/18/21), including sex chromosomes, as well as for microdeletion syndromes and for testing of multi-gestational pregnancies has been reported in many studies over the past decade.[9] However, aneuploidies other than 13/81/21 as well as microdeletions are so rare that meaningful conclusions regarding test performance difficult to be drawn from many of the individual studies.

Common Trisomies: Low-Risk and General Obstetric Populations only

Several studies have been published on the clinical validity of NIPT tests. These studies are described below. Of note, the two largest cohort studies published recently by Zhang et al.[10] and Norton et al.[11] have been included in the two systematic reviews below,[12,13] but the individual studies are described in detail below.

In 2016, Taylor-Phillips et al. published the results of a systematic review which assessed the accuracy of NIPT testing for detection of trisomies 13, 18 and 21, including case-control and cohort studies that recruited women who had been given NIPT and a reference standard.[13] The review reported test performance statistics for both high-risk population and the general obstetrics populations. Pooled sensitivity, calculated by from bivariate random-effects regression, was applied to populations of pregnant women taking the test to estimate the positive predictive values for each population. In the high-risk population, the positive predictive values were 91%, 84% and 87% for Down, Edwards, and Patau syndromes, respectively. ln the general obstetric population, the positive predictive values were 82%, 37% and 49% for Down, Edwards, and Patau syndromes, respectively. The reviewers reported significant heterogeneity between included studies and most studies had a high risk of bias.

In 2017, Iwarsson et al. published a systematic review which assessed NIPT assays for detection of trisomy 21, 18 and 13 in a general pregnant population and in a high risk population.[12] The reviewers reported that in a general pregnant population (six studies, 62,201 patients), the pooled sensitivity for trisomy 21 was 99.3% (95% CI 95.5-99.9%) and specificity was 99.9% (95% CI 99.8-99.9%). Pooled sensitivity and specificity for T13 and T18 was not calculated in the general pregnant population due to the low number of studies. In a high-risk pregnant population, the pooled sensitivities for T21 and T18 were 99.8% (95% CI 98.1-99.9%) and 97.7% (95% CI 95.8-98.7%) respectively, and the pooled sensitivity for T13 is 97.5 (95% CI 81.9-99.7%), although there was limited quality of evidence for trisomy 13.

In 2023, and updated in 2024, Hayes published a review which evaluated the clinical utility for use NIPT screening for fetal trisomy 21, 18, and 13 in low-risk women with singleton or multiple gestation pregnancies, including 15 studies (five observational and 10 health economic modelling studies).[14] The review reported that, based on the results published by 10 modelling studies, that universal cfDNA screening in singleton pregnancies detects more cases of trisomy 21, 18, and 13 with fewer procedure-related miscarriages compared with conventional screening. However the body of evidence for clinical utility in general was found to be of very-low to low quality and the health economic modelling studies included in the review are not direct clinical utility studies. No studies were found that directly compared clinical outcomes for cfDNA screening with routine screening strategies in this population. As such the included studies have several limitations including variability in fetal abnormalities considered, heterogeneity in the conventional screen evaluated for comparison, assumptions that all patients with positive cfDNA screening would elect diagnostic testing, and treatment of cfDNA test failures. In addition, there was insufficient evidence to draw conclusions regarding cfDNA screening for trisomy 21, 18, and 13 in multiple gestation pregnancies. The review concluded that additional larger directly comparing clinical outcomes of cfDNA screening with those of routine screening strategies for low-risk or general obstetric patients are needed.

In 2019, the Washington State Health Care Authority published a systematic review addressing the clinical utility of cell-free DNA prenatal screening for chromosomal aneuploidies.[15] On the basis of results from 1 RCT, 9 test accuracy studies and 8 economic studies, investigators concluded that universal screening with cfDNA appears to be more accurate than conventional screening for the common trisomies (T21, T18, and T13) in the general obstetric population.

In 2021, Familiari et al. completed a systematic review of cell-free DNA analysis of maternal blood in prenatal screening for chromosomal microdeletions and microduplications.[16] A total of 42 publications were reviewed for a total of 474,189 pregnancies and 210 cases of microdeletion and microduplication syndromes. Diagnostic verification of positive cases was available in 71.7% of the cases (486 of 678). The weighted pooled screen positive rate (SPR), false positive rate (FPR) and positive predictive value (PPV) was 0.19% and 44.1. The authors also urge for parent notification that “among cases with a positive test, the proportion of fetuses that are confirmed to be affected after diagnostic testing is on average 40%, but this is likely to be lower in cases with no ultrasound anomalies.” Due to no confirmatory analysis being completed for the vast majority of cases with a negative test, the detection rate and the negative predictive value cannot be determined. A negative test report does not modify the risk for the examined microdeletion and microduplication syndromes and therefore the test result should express the result as “unchanged risk”, because the detection rate is essentially unknown.

Nonrandomized Comparative Studies

In 2015 Norton et al. published the results form a blinded, prospective industry-sponsored study that compared standard first-trimester screening versus the Ariosa cell-free DNA test (Harmony) in a population of average risk, single gestation women who received routine obstetric care at centers in the USA, Canada and Europe.[11] The researchers assigned pregnant women presenting for aneuploidy screening at 10 to 14 weeks of gestation to undergo both standard screening (with measurement of nuchal translucency and the maternal serum screen including three analytes) and cell-free DNA testing. Participants received the results of standard screening, however; the results of cell-free DNA testing were blinded. Determination of the birth outcome was determined using diagnostic genetic testing or

newborn examination. A total of 18,955 individuals were enrolled in the study and 15,841 were available for analysis. Cell-free fetal DNA testing identified all 38 cases (100% [95% CI, 90.7 to 100]) of trisomy 21 identified in the study, while standard screening identified only 30 of these cases (78.9% CI, 62.7 to 90.4; p=0.008). False positive rates were 0.06% (95% CI, 0.03 to 0.11) in the cell-free DNA group versus 5.4% (95% CI, 5.1 to 5.8) in the standard-screening group (p<0.001). The positive predictive value of screening with cell-free DNA was 80.9% (66.7 to 90.9) versus 3.4 (2.3 to 4.8) for standard screening (p<0.001). Among the 11,994 women with low-risk pregnancies on the basis of a maternal age under 35 years, cfDNA testing identified 19 of 19 women with trisomy 21, with 6 false positive results. The positive predictive value for cfDNA testing was 76.0% (95% CI, 54.9 to 90.6) for women under the age of 35 years. Overall, cell-free DNA testing for trisomy 21 outperformed standard screening using nuchal translucency measurement plus maternal triple serum screen, regardless of maternal age.

Nonrandomized Non-Comparative Studies

In 2015, Zhang et al. published an industry-sponsored prospective study evaluating the clinical performance of an NGS-based NonInvasive Fetal TrisomY (NIFTY) test in detecting trisomies 21, 18 and 13 in over 147,000 Chinese samples and compared its performance in both, low-risk and high-risk pregnancies.[10] A patient was classified as high risk for aneuploidy if they met any one of the following criteria: advanced maternal age (> 35 years), a positive conventional Down syndrome screening test, abnormal sonographic markers, and family history of aneuploidy or a previous pregnancy with a trisomic fetus. Patients with none of the high-risk factors were defined as low risk for aneuploidy. Results from the NIPT test were confirmed using karyotyping or follow-up clinical analysis. Of the 146,958 samples tested, results were available in 112,669 (76.7%). Aneuploidy was confirmed in 720/781 of the cases with positive NIPT results for trisomy 21, 167/218 of the cases positive for trisomy 18 and 22/67 of the cases positive for trisomy 13. The sensitivity of NIPT was 99.17%, 98.24% and 100% for trisomies 21, 18 and 13, respectively. The specificity was 99.95%, 99.95% and 99.96% for trisomies 21, 18 and 13, respectively. There were no significant differences in test performance between the 72,382 high-risk participants and the 40,287 low-risk participants in terms of sensitivity (99.21% vs 98.97%; p=0.82) or specificity (99.95% vs 99.95%; p=0.98). A limitation of this study was the incomplete follow-up of NIPT results, which may have led to bias in terms of test performance. Thirty three percent of patients were lost to follow-up, with the majority of women being lost because they declined to provide clinical outcomes (17.9%) or they elected pregnancy termination (13.0%).

In 2016, Chitty et al. published the results of a prospective cohort study designed to assess the impact of offering NIPT testing as part of the United Kingdom (UK) National Health Services maternity care pathway.[17] Eight maternity units across the UK participated, and included all pregnant women with a current Down's syndrome risk on screening of at least 1/1000, including 3175 pregnant women (934 of which [29%] were considered high risk). The positive predictive value was 92% (81% to 97%) in the overall cohort, 94% (83% to 99%) in the high risk group and 82% (48% to 98%) in the intermediate risk group.

In 2017 Palomaki et al. published a prospective multi-center cohort study which assessed the clinical validity of the Panorama screening test (Natera, Inc.) in a general pregnancy population, including 2,691 women, 564 of which (21%) were 35 years or older.[18] Of the 2685 women who underwent the test, 314 (12%) were indicated to be high risk. Among 2,681 reports, 16 women (0.6%) were screen-positive for trisomy 21, 18, or 13. Twelve were confirmed (positive predictive value (PPV), 75%; 95% CI, 48–93%) and four were false-positives (0.15%). The size of the group tested did not allow for a confident estimate of

other test performance measures. Limitations is this study include the following: pregnancies reported as true-positive were not confirmed by karyotype, the percent of women electing diagnostic testing was not reported, inclusion criteria were not explicitly stated and test failures were excluded from the analysis.

Evidence Summary

Prior to 2015, there were a paucity of studies that assessed NIPT test performance and clinical validity in low- to average-risk populations. As a result, the positive predictive value (PPV) of NIPT published in the 2015 Hayes review for average-risk populations (reported at below 50% for all three common aneuploidies) was based on one 2014 study. In 2015, two large nonrandomized studies (n= 19,000 and 147,000) published test performance measures. One study reported PPVs of 81% and 76% for high-risk women and average-risk women (over the age of 35), respectively. The larger study did not publish PPVs, but reported the sensitivity to be 98-100% for all three common aneuploidies in over 40, 000 women with no risk factors. As United Kingdom and the U.S. have started implementing NIPT into standard maternal care pathways, studies have begun to emerge on clinical validity of NIPT in "general obstetric" populations, allowing for more generalizable results. These initial studies (n=2685 and 3175) have reported PPVs of 75-92%, but have also reported higher false positive rates. It is anticipated that as more regions implement NIPT testing into routine care, that additional studies will be published on the impact of NIPT testing in the general obstetric population.

Microdeletion Syndromes

In 2015, Wapner et al. reported on a large case series to determine if NIPS can be used to detect fetal microdeletion syndromes, including 496 samples tested with Natera's single nucleotide polymorphisms (SNP)-based NIPS test.[19] The study assessed detection rates of five microdeletion syndromes: 22q11.2, 1p36, cri du chat, Prader-Willi, and Angelman. The evaluation included six positive controls, 362 negative controls and 111 artificial DNA mixtures that mimicked the fetal fraction found in cfDNA from pregnant plasma and were enriched with microdeletions. The analytic detection rate was 97.8% for 22q11.2 deletions and 100% for each of the other microdeletions. False-positive rates were 0.76% for 22q11.2 deletion syndrome and 0.24% for cri-du-chat syndrome. No false positives occurred for Prader-Willi (0/428), Angelman (0/442), or 1p36 deletion syndromes (0/422). Limitations of this study include the fact that the population studied was not a clinical population and the samples tested were artificially constructed, the number of positive samples was very small, and not all negative controls received the standard test for microdeletions.

In 2022, Jacobssen and colleagues published a prospective trial assessing the performance of a single nucleotide polymorphism- based, prenatal cell-free DNA screening for detection of 22q11.2 deletion syndrome.[20] The primary outcome was sensitivity, specificity, positive predictive value, and negative predictive value of cell-free DNA screening for the detection of all deletions, including the classical deletion and nested deletions that are 500 kb, in the 22q11.2 low-copy repeat A-D region. Secondary outcomes included the prevalence of 22q11.2 deletion syndrome and performance of an updated cell-free DNA algorithm that was evaluated with blinding to the pregnancy outcome. Of the 20,887 women enrolled, a genetic outcome was available for 18,289 (87.6%). A total of 12 22q11.2 deletion syndrome cases were confirmed in the cohort, including 5 (41.7%) nested deletions, yielding a prevalence of 1 in 1524. In the total cohort, cell-free DNA screening identified 17,976 (98.3%) cases as low risk for 22q11.2

deletion syndrome and 38 (0.2%) cases as high risk; 275 (1.5%) cases were nonreportable. Overall, 9 of 12 cases of 22q11.2 were detected, yielding a sensitivity of 75.0%; specificity of 99.84% positive predictive value of 23.7%, and negative predictive value of 99.98%. None of the cases with a nonreportable result was diagnosed with 22q11.2 deletion syndrome. The updated algorithm detected 10 of 12 cases (83.3%) with a lower false positive rate and a positive predictive value of 52.6%.

In 2022, the American College of Medical Genetics and Genomics (ACMG) published a systematic evidence review assessing the application of noninvasive prenatal screening using cell-free DNA in general-risk pregnancies. [21] Medline (PubMed) and Embase were used to identify studies examining detection of Down syndrome (T21), trisomy 18 (T18), trisomy 13 (T13), sex chromosome aneuploidies, rare autosomal trisomies, copy number variants, and maternal conditions, as well as studies assessing the psychological impact of NIPS and the rate of subsequent diagnostic testing. Random-effects meta-analyses were used to calculate pooled estimates of NIPS performance ($P < .05$). Heterogeneity was investigated through subgroup analyses. Risk of bias was assessed. A total of 87 studies met inclusion criteria. Diagnostic odds ratios were significant ($P < .0001$) for T21, T18, and T13 for singleton and twin pregnancies. NIPS was accurate (≥99.78%) in detecting sex chromosome aneuploidies. Performance for rare autosomal trisomies and copy number variants was variable. Use of NIPS reduced diagnostic tests by 31% to 79%. Conclusions regarding psychosocial outcomes could not be drawn owing to lack of data. Identification of maternal conditions was rare. Authors concluded that the performance of these tests when targeting microdeletions other than the common trisomies was “poor” and called for additional outcome studies.

In 2024, Hayes conducted an evidence review assessing cell-free DNA (cfDNA) screening for fetal chromosomal copy number variants.[22] Authors wrote that evidence was “insufficient” to determine clinical utility. Results from 4 studies suggest that use of cfDNA screening for fetal CNVs in singleton pregnancies leads to confirmatory diagnostic testing in some women. However, a small number of women had pregnancies with confirmed fetal CNVs and used the final results for pregnancy management decisions. Among those who elected confirmatory diagnostic testing based on the CNV cfDNA screening results, many cases were false-positive. It is unknown if additional CNV evaluation will impact the confirmatory diagnostic testing rate reduction from cfDNA fetal screening for common aneuploidy. The published evidence is very low in quality and insufficient to support any conclusions regarding clinical utility.

Pregnancy Loss

The majority of the studies published on the genetics of pregnancy loss are moderate to large-sized association studies. However, the evidence review below will focus on studies reporting measures of clinical utility of genetic testing for recurrent pregnancy loss and stillbirth.

CLINICAL PRACTICE GUIDELINES

Due to the fast-paced nature of genetic testing for reproductive purposes and prenatal genetic testing, professional societies are updating guidelines at a rapid pace. Therefore, only the most recent clinical practice guideline for U.S.-based professional societies will be described below.

Carrier Screening for Genetic Conditions

American College of Obstetricians and Gynecologists (ACOG)

In 2025, the American College of Obstetricians and Gynecologists (ACOG) reaffirmed two Committee Opinions that were published in 2017 regarding carrier screening for genetic conditions.[3,23] These documents provided recommendations for a set of specific conditions, including cystic fibrosis, spinal muscular atrophy, fragile X syndrome and Tay-Sachs disease. In addition, recommendations were provided for ethnicity specific screening, other targeted screening and expanded screening (including expanded cystic fibrosis panels and multigene panels for complex disorders). Lastly, guidance regarding genetic counseling was provided.

Pregnancy Loss

American College of Obstetricians and Gynecologists (ACOG)

The Committee Opinion (#682) published by ACOG, described above, on the use of chromosomal microarray analysis (CMA) in obstetrics and gynecology, addressed the use of CMA to evaluate stillbirths.[24] The panel recommended the use of CMA of fetal tissue for the evaluation of stillbirth (defined as pregnancy loss at or after 20 weeks gestation). The panel concluded that CMA was superior to karyotyping for stillbirth evaluation because it had a better likelihood of obtaining results and yields improved detection of causative abnormalities.

This recommendation was based on a study published by the NICHD Stillbirth Collaborative Research Network in 2012 that reported an analysis of samples from 532 stillbirths.[25] In this series, microarray analysis yielded results more often than did karyotype analysis (87.4% vs. 70.5%, P<0.001) and provided better detection of genetic abnormalities (aneuploidy or pathogenic copy-number variants, 8.3% vs. 5.8%; P=0.007).

The guideline also stated that the routine use of whole-genome or whole-exome sequencing for prenatal diagnosis was not recommended outside of the context of clinical trials.

EVIDENCE SUMMARY

Carrier Screening

There is sufficient evidence that carrier testing, including testing for a known familial mutation, targeted mutation analysis, gene sequencing and deletion/duplication analysis in certain circumstances leads to improved health outcomes in selected individuals with risk of a genetic condition and allows prospective parents to make informed reproductive choices. In addition, clinical practice guidelines support carrier testing in select situations for certain well-defined conditions. However, for individuals that do not meet the medical necessity criteria outlined above, carrier screening for single-gene conditions is investigational due to insufficient evidence and lack of support from clinical practice guidelines.
There is sufficient evidence that carrier screening for certain disorders in individuals of Ashkenazi Jewish descent improves health outcomes in this population. It has been established that the disorders listed in the medical necessity criteria above occur with substantially greater frequency in Ashkenazi Jewish descendants compared to the general population. In addition, clinical practice guidelines support carrier

screening for these indications. There is insufficient evidence and lack of support from clinical practice guidelines for the genetic testing of any other conditions for Ashkenazi Jewish descendants.

Carrier screening of adult-onset conditions is not medically necessary as these conditions typically have a highly variable age of onset and the large majority have complex symptoms and are poorly understood. Current American College of Obstetricians and Gynecologists guidance recommends against screening for these conditions.
There is insufficient evidence that carrier screening impacts clinical decision-making or improves health outcomes when used for general population screening. In addition, there is a lack of support from clinical practice guidelines for carrier screening of the general population.

There is insufficient evidence of both clinical validity and clinical utility of multi-gene (also referred to as "expanded") carrier screens. It has not been demonstrated that expanded carrier screens result in reductions of the number of births with an inherited disorder or impacts family planning decisions. In addition, there is a lack of consensus from specialty associations identifying appropriate population to undergo screening using these tests or which genes should be included in the panels.

Preimplantation Testing

There is sufficient evidence to support the use of preimplantation genetic diagnostic (PGD) testing for individuals who are known carriers of specific pathogenic disease-causing mutations, as outlined in the medical policy criteria above. PGD testing for these individuals leads to an increased likelihood of successful live births of healthy unaffected newborns. There is also sufficient evidence to support the use of PGD testing for individuals who are known carriers of balanced chromosomal translocations, as PGD testing leads to decrease risk of spontaneous abortion and increased likelihood of achieving a live birth. In addition, clinical practice guidelines support the use of PGD in these clinical situations.
There is insufficient evidence to support the use of preimplantation genetic diagnostic testing (PGD) in other situations not identified in the medical necessity policy criteria above. It is unclear if PGD leads to improved health outcomes for these indications. In addition, there is a lack of support from clinical practice guidelines for the use of PGD in these clinical situations.

There is insufficient evidence that preimplantation genetic screening (PGS) improves live birth rates, regardless of the presence of risk factors. In fact, newer PGS methods such as microarray do not appear to improve health outcomes in women with risk factors such as advanced maternal age or history of failed in-vitro fertilization cycles. In addition, major medical association guidelines have indicated that there are no proposed indications for which PGS is recommended.

Pregnancy Loss

There is sufficient evidence that evaluation of chromosomal abnormalities for pregnancy loss in certain situations, through specific testing methodologies outlined in the criteria above, alters reproductive decision-making and changes diagnostic testing strategies for future pregnancies. While direct clinical utility for traditional techniques such as fluorescence in situ hybridization (FISH) and karyotype analysis has been established; for chromosomal microarray, the potential for clinical utility parallels that of traditional techniques as it is much more sensitive than its predecessors. Due to insufficient evidence of clinical utility and lack of support from clinical practice guidelines, genetic testing for pregnancy loss is

investigational, when individuals do not meet medical necessity criteria as outlined above, or when sequencing based tests are used.

HEALTH EQUITY CONSIDERATIONS

The Centers for Disease Control and Prevention (CDC) defines health equity as the state in which everyone has a fair and just opportunity to attain their highest level of health. Achieving health equity requires addressing health disparities and social determinants of health. A health disparity is the occurrence of diseases at greater levels among certain population groups more than among others. Health disparities are linked to social determinants of health which are non-medical factors that influence health outcomes such as the conditions in which people are born, grow, work, live, age, and the wider set of forces and systems shaping the conditions of daily life. Social determinants of health include unequal access to health care, lack of education, poverty, stigma, and racism.

The U.S. Department of Health and Human Services Office of Minority Health calls out unique areas where health disparities are noted based on race and ethnicity. Providence Health Plan (PHP) regularly reviews these areas of opportunity to see if any changes can be made to our medical or pharmacy policies to support our members obtaining their highest level of health. Upon review, PHP creates a Coverage Recommendation (CORE) form detailing which groups are impacted by the disparity, the research surrounding the disparity, and recommendations from professional organizations. PHP Health Equity COREs are updated regularly and can be found online here.

BILLING GUIDELINES AND CODING

Carrier Screening

Testing for carrier screening of asymptomatic parents is limited to once per each condition per lifetime.

If a request is received for testing for an individual gene variant for carrier screening purposes that is addressed by a specific code (such as CPT codes for Cystic Fibrosis), and receives a negative test result, this does not preclude a request from being approved for testing of other specific gene variants.

Testing fetal DNA for the purpose of diagnostic prenatal testing is limited to once per pregnancy to diagnosis the fetus.

CPT 81507 is a proprietary test that should only be billed for Harmony Prenatal Test (Ariosa Diagnostics). CPT 81420 should never be billed with CPT 81507.

When no specific CPT or HCPCS code exists for the panel, the provider is required to bill using an unlisted code. It is not appropriate for the provider to bill any of the tests in a panel separately as if they were performed individually. This is a misrepresentation of services performed and is not appropriate based on either CPT or CMS guidelines. In a “Healthcare Fraud Prevention Partnership” white paper published in May, 2018, CMS identified unbundling of lab panels as an example of fraudulent billing.

Codes

Genetic testing for reproductive planning and in the prenatal setting may include but is not limited to any of the CPT/HCPCS codes listed below. Additional codes may apply.

CODES*		
CPT	0009M	Fetal aneuploidy (trisomy 21, and 18) DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy
	0060U	Twin zygosity, genomic targeted sequence analysis of chromosome 2, using circulating cell-free fetal DNA in maternal blood
	0124U	Fetal congenital abnormalities, biochemical assays of 3 analytes (free beta-hCG, PAPP-A, AFP), time-resolved fluorescence immunoassay, maternal dried-blood spot, algorithm reported as risk scores for fetal trisomies 13/18 and 21
	0231U	CACNA1A (calcium voltage-gated channel subunit alpha 1A) (eg, spinocerebellar ataxia), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) gene expansions, mobile element insertions, and variants in non-uniquely mappable regions
	0232U	CSTB (cystatin B) (eg, progressive myoclonic epilepsy type 1A, Unverricht-Lundborg disease), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions
	0233U	FXN (frataxin) (eg, Friedreich ataxia), gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions
	0234U	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
	0236U	SMN1 (survival of motor neuron 1, telomeric) and SMN2 (survival of motor neuron 2, centromeric) (eg, spinal muscular atrophy) full gene analysis, including small sequence changes in exonic and intronic regions, duplications and deletions, and mobile element insertions
	0252U	Fetal aneuploidy short (tandem)
	0254U	Reproductive medicine (preimplantation genetic assessment), analysis of 24 chromosomes using embryonic DNA genomic sequence analysis for aneuploidy, and a mitochondrial DNA score in euploid embryos, results reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplications, mosaicism, and segmental aneuploidy, per embryo tested
	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
	0400U	Obstetrics (expanded carrier screening), 145 genes by next-generation sequencing, fragment analysis and multiplex ligationdependent probe amplification, DNA, reported as carrier positive or negative
	0449U	Carrier screening for severe inherited conditions (eg, cystic fibrosis, spinal muscular atrophy, beta hemoglobinopathies [including sickle cell disease], alpha thalassemia), regardless of race or self-identified ancestry, genomic sequence analysis panel, must include analysis of 5 genes (CFTR, SMN1, HBB, HBA1, HBA2)
	0469U	Rare diseases (constitutional/heritable disorders), whole genome sequence analysis for chromosomal abnormalities, copy number variants, duplications/deletions, inversions, unbalanced translocations, regions of homozygosity (ROH), inheritance pattern that indicate uniparental disomy (UPD), and aneuploidy, fetal sample (amniotic fluid, chorionic villus sample, or products of conception), identification and categorization of genetic variants, diagnostic report of fetal results based on phenotype with maternal sample and paternal sample, if performed, as comparators and/or maternal cell contamination
	0488U	Obstetrics (fetal antigen noninvasive prenatal test), cellfree DNA sequence analysis for detection of fetal presence or absence of 1 or more of the Rh, C, c, D, E, Duffy (Fya), or Kell (K) antigen in alloimmunized pregnancies, reported as selected antigen(s) detected or not detected
	0489U	Obstetrics (single-gene noninvasive prenatal test), cellfree DNA sequence analysis of 1 or more targets (eg, CFTR, SMN1, HBB, HBA1, HBA2) to identify paternally inherited pathogenic variants, and relative mutation-dosage analysis based on molecular counts to determine fetal inheritance of maternal mutation, algorithm reported as a fetal risk score for the condition (eg, cystic fibrosis, spinal muscular atrophy, beta hemoglobinopathies [including sickle cell disease], alpha thalassemia)
	0494U	Red blood cell antigen (fetal RhD gene analysis), next-generation sequencing of circulating cell-free DNA (cfDNA) of blood in pregnant individuals known to be RhD negative, reported as positive or negative
	0536U	Red blood cell antigen (fetal RhD), PCR analysis of exon 4 of RHD gene and housekeeping control gene GAPDH from whole blood in pregnant individuals at 10+ weeks gestation known to be RhD negative, reported as fetal RhD status
	0632U	Red blood cell antigen (fetal RhD gene analysis), multiplex polymerase chain reaction (PCR) and next-generation circulating cell-free DNA (cfDNA), plasma from pregnant individuals known to be RhD negative, reported as detected or not detected sequencing (NGS) of
	0633U	Obstetrics (single-gene noninvasive prenatal test), cell-free DNA (cfDNA), nextgeneration sequencing (NGS) analysis of 1 or more targets (eg, CFTR, SMN1, HBB, HBA1, HBA2) to identify paternally inherited pathogenic variants and to determine fetal inheritance of maternal mutation, using maternal blood sample, algorithm reported as a fetal risk score

	81161	DMD (dystrophin) (e.g., Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed)
	81171	AFF2 (ALF transcription elongation factor 2 [FMR2]) (eg, fragile X intellectual disability 2 [FRAXE]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
	81172	AFF2 (ALF transcription elongation factor 2 [FMR2]) (eg, fragile X intellectual disability 2 [FRAXE]) gene analysis; characterization of alleles (eg, expanded size and methylation status)
	81173	AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; full gene sequence
	81174	AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; known familial variant
	81177	ATN1 (atrophin 1) (eg, dentatorubral-pallidoluysian atrophy) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
	81178	ATXN1 (ataxin 1) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
	81179	ATXN2 (ataxin 2) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
	81180	ATXN3 (ataxin 3) (eg, spinocerebellar ataxia, Machado-Joseph disease) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
	81181	ATXN7 (ataxin 7) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
	81182	ATXN8OS (ATXN8 opposite strand [non-protein coding]) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
	81183	ATXN10 (ataxin 10) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
	81184	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (eg, spinocerebellar ataxia) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
	81185	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (eg, spinocerebellar ataxia) gene analysis; full gene sequence
	81186	CACNA1A (calcium voltage-gated channel subunit alpha1 A) (eg, spinocerebellar ataxia) gene analysis; known familial variant
	81187	CNBP (CCHC-type zinc finger nucleic acid binding protein) (eg, myotonic dystrophy type 2) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
	81188	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
	81189	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; full gene sequence
	81190	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; known familial variant(s)
	81200	ASPA (aspartoacylase) (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)
	81201	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence

	81202	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
	81203	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
	81204	AR (androgen receptor) (eg, spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; characterization of alleles (eg, expanded size or methylation status)
	81205	BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)
	81209	BLM (Bloom syndrome, RecQ helicase-like) (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant
	81220	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
	81221	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; known familial variants
	81222	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; duplication/deletion variants
	81223	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; full gene sequence
	81224	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; intron 8 poly-T analysis (eg, male infertility)
	81233	BTK (Bruton's tyrosine kinase) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, C481S, C481R, C481F)
	81234	DMPK (DM1 protein kinase) (eg, myotonic dystrophy type 1) gene analysis; evaluation to detect abnormal (expanded) alleles
	81236	EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, myelodysplastic syndrome, myeloproliferative neoplasms) gene analysis, full gene sequence
	81237	EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, diffuse large B-cell lymphoma) gene analysis, common variant(s) (eg, codon 646)
	81239	DMPK (DM1 protein kinase) (eg, myotonic dystrophy type 1) gene analysis; characterization of alleles (eg, expanded size)
	81242	FANCC (Fanconi anemia, complementation group C) (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T)
	81243	FMR1 (fragile X messenger ribonucleoprotein 1) (eg, fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
	81244	FMR1 (fragile X messenger ribonucleoprotein 1) (eg, fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; characterization of alleles (eg, expanded size and promoter methylation status)
	81250	G6PC (glucose-6-phosphatase, catalytic subunit) (eg, Glycogen storage disease, type 1a, von Gierke disease) gene analysis, common variants (eg, R83C, Q347X)
	81251	GBA (glucosidase, beta, acid) (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G>A)

	81252	GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence
	81253	GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; known familial variants
	81254	GJB6 (gap junction protein, beta 6, 30kDa, connexin 30) (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])
	81255	HEXA (hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G>C, G269S)
	81256	HFE (hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D)
	81257	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring)
	81258	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; known familial variant
	81259	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; full gene sequence
	81260	IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (eg, familial dysautonomia) gene analysis, common variants (eg, 2507+6T>C, R696P)
	81265	Comparative analysis using Short Tandem Repeat (STR) markers; patient and comparative specimen (eg, pre-transplant recipient and donor germline testing, post-transplant non-hematopoietic recipient germline [eg, buccal swab or other germline tissue sample] and donor testing, twin zygosity testing, or maternal cell contamination of fetal cells)
	81269	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; duplication/deletion variants
	81271	HTT (huntingtin) (eg, Huntington disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
	81274	HTT (huntingtin) (eg, Huntington disease) gene analysis; characterization of alleles (eg, expanded size)
	81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)
	81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)
	81284	FXN (frataxin) (eg, Friedreich ataxia) gene analysis; evaluation to detect abnormal (expanded) alleles
	81285	FXN (frataxin) (eg, Friedreich ataxia) gene analysis; characterization of alleles (eg, expanded size)
	81286	FXN (frataxin) (eg, Friedreich ataxia) gene analysis; full gene sequence
	81289	FXN (frataxin) (eg, Friedreich ataxia) gene analysis; known familial variant(s)

	81290	MCOLN1 (mucolipin 1) (eg, Mucolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb)
	81302	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; full sequence analysis
	81303	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; known familial variant
	81304	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; duplication/deletion variants
	81311	NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61)
	81312	PABPN1 (poly[A] binding protein nuclear 1) (eg, oculopharyngeal muscular dystrophy) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
	81324	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
	81325	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis
	81326	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant
	81329	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; dosage/deletion analysis (eg, carrier testing), includes SMN2 (survival of motor neuron 2, centromeric) analysis, if performed
	81330	SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)
	81331	SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis
	81332	SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z)
	81333	TGFBI (transforming growth factor beta-induced) (eg, corneal dystrophy) gene analysis, common variants (eg, R124H, R124C, R124L, R555W, R555Q)
	81336	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; full gene sequence
	81337	SMN1 (survival of motor neuron 1, telomeric) (eg, spinal muscular atrophy) gene analysis; known familial sequence variant(s)
	81343	PPP2R2B (protein phosphatase 2 regulatory subunit Bbeta) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles
	81344	TBP (TATA box binding protein) (eg, spinocerebellar ataxia) gene analysis, evaluation to detect abnormal (eg, expanded) alleles

	81345	TERT (telomerase reverse transcriptase) (eg, thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (eg, promoter region)
	81349	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and loss-of-heterozygosity variants, low-pass sequencing analysis
	81350	UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variants (eg, *28, *36, *37)
	81354	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of structural and copy number variants, optical genome mapping (OGM)
	81361	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); common variant(s) (eg, HbS, HbC, HbE)
	81362	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); known familial variant(s)
	81363	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); duplication/deletion variant(s)
	81364	HBB (hemoglobin, subunit beta) (eg, sickle cell anemia, beta thalassemia, hemoglobinopathy); full gene sequence
	81400	Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
	81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
	81402	Molecular pathology procedure, Level 3 (eg, >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])
	81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
	81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
	81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
	81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)
	81407	Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)

	81408	Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)
	81412	Ashkenazi Jewish associated disorders (eg, Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1
	81413	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A
	81414	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); duplication/deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ1
	81415	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
	81416	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (eg, parents, siblings) (List separately in addition to code for primary procedure)
	81417	Exome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (eg, updated knowledge or unrelated condition/syndrome)
	81422	Fetal chromosomal microdeletion(s) genomic sequence analysis (eg, DiGeorge syndrome, Cri-du-chat syndrome), circulating cell-free fetal DNA in maternal blood
	81425	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
	81426	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (eg, parents, siblings) (List separately in addition to code for primary procedure)
	81427	Genome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (eg, updated knowledge or unrelated condition/syndrome)
	81430	Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, must include sequencing of at least 60 genes, including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1
	81431	Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); duplication/deletion analysis panel, must include copy number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes
	81434	Hereditary retinal disorders (eg, retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy), genomic sequence analysis panel, must include sequencing of at least 15 genes, including ABCA4, CNGA1, CRB1, EYS,

		PDE6A, PDE6B, PRPF31, PRPH2, RDH12, RHO, RP1, RP2, RPE65, RPGR, and USH2A
	81439	Hereditary cardiomyopathy (eg, hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy), genomic sequence analysis panel, must include sequencing of at least 5 cardiomyopathy-related genes (eg, DSG2, MYBPC3, MYH7, PKP2, TTN)
	81440	Nuclear encoded mitochondrial genes (eg, neurologic or myopathic phenotypes), genomic sequence panel, must include analysis of at least 100 genes, including BCS1L, C10orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAZ, TK2, and TYMP
	81442	Noonan spectrum disorders (eg, Noonan syndrome, cardio-facio-cutaneous syndrome, Costello syndrome, LEOPARD syndrome, Noonan-like syndrome), genomic sequence analysis panel, must include sequencing of at least 12 genes, including BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, and SOS1
	81443	Genetic testing for severe inherited conditions (eg, cystic fibrosis, Ashkenazi Jewish-associated disorders [eg, Bloom syndrome, Canavan disease, Fanconi anemia type C, mucolipidosis type VI, Gaucher disease, Tay-Sachs disease], beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes (eg, ACADM, ARSA, ASPA, ATP7B, BCKDHA, BCKDHB, BLM, CFTR, DHCR7, FANCC, G6PC, GAA, GALT, GBA, GBE1, HBB, HEXA, IKBKAP, MCOLN1, PAH)
	81470	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); genomic sequence analysis panel, must include sequencing of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2
	81471	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); duplication/deletion gene analysis, must include analysis of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2
	81479	Unlisted molecular pathology procedure
	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
	81599	Unlisted multianalyte assay with algorithmic analysis
	88235	Tissue culture for non-neoplastic disorders; amniotic fluid or chorionic villus cells
	88261	Chromosome analysis; count 5 cells, l karyotype, with banding
	88262	Chromosome analysis; count 15-20 cells, 2 karyotypes, with banding
	88263	Chromosome analysis; count 45 cells for mosaicism, 2 Karyotypes, with banding
	88264	Chromosome analysis; analyze 20-25 cells
	88267	Chromosome analysis, amniotic fluid or chorionic villus, count 15 cells, 1 karyotype, with banding
	88269	Chromosome analysis, in situ for amniotic fluid cells, count cells from 6-12 colonies, 1 karyotype, with banding

	88271	Molecular cytogenetics; DNA probe, each (eg, FISH)
	88272	Molecular cytogenetics; chromosomal in situ hybridization, analyze 3-5 cells (eg, for derivatives and markers)
	88273	Molecular cytogenetics; chromosomal in situ hybridization, analyze 10-30 cells (eg, for microdeletions)
	88274	Molecular cytogenetics; interphase in situ hybridization, analyze 25-99 cells
	88275	Molecular cytogenetics; interphase in situ hybridization, analyze 100-300 cells
	88280	Chromosome analysis; additional karyotypes, each study
	88283	Chromosome analysis; additional specialized banding technique (eg, NOR, C-banding)
	88285	Chromosome analysis; additional cells counted, each study
	88289	Chromosome analysis; additional high resolution study
	88291	Cytogenetics and molecular cytogenetics, interpretation and report
	89290	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for pre-implantation genetic diagnosis); less than or equal to 5 embryos
	89291	Biopsy, oocyte polar body or embryo blastomere, microtechnique (for preimplantation genetic diagnosis); greater than 5 embryo(s)
	88299	Unlisted cytogenetic study
	89398	Unlisted reproductive medicine laboratory procedure
HCPCS	S3844	DNA analysis of the connexin 26 gene (GJB2) for susceptibility to congenital, profound deafness

***Coding Notes:**

- The above code list is provided as a courtesy and may not be all-inclusive. Inclusion or omission of a code from this policy neither implies nor guarantees reimbursement or coverage. Some codes may not require routine review for medical necessity, but they are subject to provider contracts, as well as member benefits, eligibility and potential utilization audit.
- All unlisted codes are reviewed for medical necessity, correct coding, and pricing at the claim level. If an unlisted code is submitted for non-covered services addressed in this policy then it will be **denied as not covered**. If an unlisted code is submitted for potentially covered services addressed in this policy, to avoid post-service denial, **prior authorization is recommended**.
- **See the non-covered and prior authorization lists on the Company Medical Policy, Reimbursement Policy, Pharmacy Policy and Provider Information website for additional information.**
- HCPCS/CPT code(s) may be subject to National Correct Coding Initiative (NCCI) procedure-to-procedure (PTP) bundling edits and daily maximum edits known as "medically unlikely edits" (MUEs) published by the Centers for Medicare and Medicaid Services (CMS). This policy does not take precedence over NCCI edits or MUEs. Please refer to the CMS website for coding guidelines and applicable code combinations.

REFERENCES

1. Watson MS, Cutting GR, Desnick RJ, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. *Genet Med.* 2004;6(5):387-391. https://www.ncbi.nlm.nih.gov/pubmed/15371902
2. Scott SA, Edelmann L, Liu L, Luo M, Desnick RJ, Kornreich R. Experience with carrier screening and prenatal diagnosis for 16 Ashkenazi Jewish genetic diseases. *Human mutation.* 2010;31(11):1240-1250.

3. Committee on G. Committee Opinion No. 690: Carrier Screening in the Age of Genomic Medicine. *Obstetrics and gynecology.* 2017;129(3):e35-e40. https://www.ncbi.nlm.nih.gov/pubmed/28225425
4. Gross SJ, Pletcher BA, Monaghan KG. Carrier screening in individuals of Ashkenazi Jewish descent. *Genet Med.* 2008;10(1):54-56.
5. ACOG Committee Opinion No. 442: Preconception and prenatal carrier screening for genetic diseases in individuals of Eastern European Jewish descent. *Obstetrics and gynecology.* 2009;114(4):950-953.
6. Resta R, Biesecker BB, Bennett RL, et al. A new definition of Genetic Counseling: National Society of Genetic Counselors' Task Force report. *Journal of genetic counseling.* 2006;15(2):77-83.
7. Practice Committee of the American Society for Reproductive M. Evaluation and treatment of recurrent pregnancy loss: a committee opinion. *Fertil Steril.* 2012;98(5):1103-1111. https://www.ncbi.nlm.nih.gov/pubmed/22835448
8. ACOG Practice Bulletin No. 102: management of stillbirth. *Obstetrics and gynecology.* 2009;113(3):748-761. https://www.ncbi.nlm.nih.gov/pubmed/19300347
9. American College of Obstetricians and Gynecologists. Practice Bulletin No. 163 Summary: Screening for Fetal Aneuploidy. *Obstetrics and gynecology.* 2016;127(5):979-981. https://www.ncbi.nlm.nih.gov/pubmed/27101120
10. 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 in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology.* 2015;45(5):530-538.
11. Norton ME, Jacobsson B, Swamy GK, et al. Cell-free DNA analysis for noninvasive examination of trisomy. *The New England journal of medicine.* 2015;372(17):1589-1597.
12. Iwarsson E, Jacobsson B, Dagerhamn J, Davidson T, Bernabe E, Heibert Arnlind M. Analysis of cell-free fetal DNA in maternal blood for detection of trisomy 21, 18 and 13 in a general pregnant population and in a high risk population - a systematic review and meta-analysis. *Acta obstetricia et gynecologica Scandinavica.* 2017;96(1):7-18.
13. Taylor-Phillips S, Freeman K, Geppert J, et al. Accuracy of non-invasive prenatal testing using cell-free DNA for detection of Down, Edwards and Patau syndromes: a systematic review and meta-analysis. *BMJ open.* 2016;6(1):e010002.
14. Hayes Inc. Cell-Free DNA (cfDNA) [Formerly NIPS, NIPT] Screening for Fetal Trisomy 21, 18, and 13 in Low-Risk Women. . https://evidence.hayesinc.com/report/gti.nips4037. Published 2024. Accessed 2/18/2025.
15. Washington State Health Care Authority. Cell-free DNA Prenatal Screening for Chromosomal Aneuploidies: Final Evidence Report. https://www.hca.wa.gov/assets/program/cfdna-final-report-20191213.pdf. Published 2019. Accessed 4/20/2026.
16. Familiari A, Boito S, Rembouskos G, et al. Cell-free DNA analysis of maternal blood in prenatal screening for chromosomal microdeletions and microduplications: a systematic review. *Prenat Diagn.* 2021;41(10):1324-1331.
17. Chitty LS, Wright D, Hill M, et al. Uptake, outcomes, and costs of implementing non-invasive prenatal testing for Down's syndrome into NHS maternity care: prospective cohort study in eight diverse maternity units. *BMJ (Clinical research ed).* 2016;354:i3426.
18. Palomaki GE, Kloza EM, O'Brien BM, Eklund EE, Lambert-Messerlian GM. The clinical utility of DNA-based screening for fetal aneuploidy by primary obstetrical care providers in the general pregnancy population. *Genet Med.* 2017;19(7):778-786. https://www.ncbi.nlm.nih.gov/pubmed/28079901

19. 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 e331-339. https://www.ncbi.nlm.nih.gov/pubmed/25479548
20. Jacobson B, Clifton R, Egbert M, et al. Cell-free DNA screening for prenatal detection of 22q11. 2 deletion syndrome. *American Journal of Obstetrics and Gynecology.* 2022.
21. Rose NC, Barrie ES, Malinowski J, et al. Systematic evidence-based review: The application of noninvasive prenatal screening using cell-free DNA in general-risk pregnancies. *Genetics in Medicine.* 2022;24(7):1379-1391.
22. Hayes Inc. Cell-Free DNA (cfDNA) (Formerly NIPS, NIPT) Screening for Fetal Chromosomal Copy Number Variants. https://evidence.hayesinc.com/report/gti.nipsmicro4046. Published 2025. Accessed 4/20/2026.
23. Committee on G. Committee Opinion No. 691: Carrier Screening for Genetic Conditions. *Obstetrics and gynecology.* 2017;129(3):e41-e55. https://www.ncbi.nlm.nih.gov/pubmed/28225426
24. Committee on G, the Society for Maternal-Fetal M. Committee Opinion No.682: Microarrays and Next-Generation Sequencing Technology: The Use of Advanced Genetic Diagnostic Tools in Obstetrics and Gynecology (Published 2013 & reaffirmed 2023). *Obstetrics and gynecology.* 2023;128(6):e262-e268. https://www.ncbi.nlm.nih.gov/pubmed/27875474
25. Reddy UM, Page GP, Saade GR, et al. Karyotype versus microarray testing for genetic abnormalities after stillbirth. *The New England journal of medicine.* 2012;367(23):2185-2193. https://www.ncbi.nlm.nih.gov/pubmed/23215556

POLICY REVISION HISTORY

DATE	REVISION SUMMARY
2/2023	Converted to new policy template.
4/2023	Interim update (code configuration change only).
7/2023	Annual review & Q3 2023 code set. Removed criteria for pre-implantation genetic diagnosis and screening (81228 & 81229). Not medically necessary criteria added for repeat testing. Removal of PA for HFE testing (81256) and S-code (S3844). Add 0400U (code set) as PA.
7/2023	Criterion expanded for CF testing for reproductive partner.
1/2024	Q1 2024 code set update. Revised code descriptions.
4/2024	Q2 2024 code set update.
6/2024	Annual update. No changes.
7/2024	Q3 2024 code set update.
2/2025	Removal of criteria for noninvasive prenatal screening/testing.
4/2025	Q2 2025 code set update. New code added.
6/2025	Annual update. No changes to criteria.
11/2025	Interim update. NIPT criteria added.
1/2026	Q1 2026 code set update.
6/2026	Annual update. No changes.
7/2026	Q3 2026 code set update. Add 2 codes.