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DESCRIPTION:

A genetic or genomic test involves an analysis of human chromosomes, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), or gene products (e.g., enzymes and other types of proteins) to detect heritable or somatic variants, genotypes, or phenotypes related to disease and health.

There are several different types of genetic tests available today, including:

- **Carrier testing:** Carrier testing is used to identify people who carry one copy of a gene mutation that, when present in two copies, causes a genetic disorder. This type of testing is offered to individuals who have a family history of a genetic disorder and to people in certain ethnic groups with an increased risk of specific genetic conditions. If both parents are tested, the test can provide information about a couple's risk of having a child with a genetic condition.
- **Diagnostic testing:** Diagnostic testing is used to identify or rule out a specific genetic or chromosomal condition. In many cases, genetic testing is used to confirm a diagnosis when a particular condition is suspected based on physical signs and symptoms. Diagnostic testing can be performed before birth or at any time during a person's life, but is not available for all genes or all genetic conditions.
- **Newborn screening:** Newborn screening is used just after birth to identify genetic disorders that can be treated early in life. Millions of babies are tested each year in the United States. All states currently test infants for phenylketonuria (a genetic disorder that causes intellectual disability if left untreated) and congenital hypothyroidism (a disorder of the thyroid gland). Most states also test for other genetic disorders.
- **Predictive and presymptomatic testing:** Predictive and presymptomatic types of testing are used to detect gene variants associated with disorders that appear after birth, often later in life. These tests can be helpful to people who have a family member with a genetic disorder, but

who have no features of the disorder themselves at the time of testing. Predictive testing can identify variants that increase a person's risk of developing disorders with a genetic basis, such as certain types of cancer. Presymptomatic testing can determine whether a person will develop a genetic disorder before any signs or symptoms appear.

- **Preimplantation testing:** Preimplantation testing, also called preimplantation genetic diagnosis (PGD), is a specialized technique that can reduce the risk of having a child with a particular genetic or chromosomal disorder. It is used to detect genetic changes in embryos that were created using assisted reproductive techniques such as in-vitro fertilization. To perform preimplantation testing, a small number of cells are taken from these embryos and tested for certain genetic changes.
- **Prenatal testing:** Prenatal testing is used to detect changes in a fetus's genes or chromosomes before birth. This type of testing is offered during pregnancy if there is an increased risk that the baby will have a genetic or chromosomal disorder. In some cases, prenatal testing can lessen a couple's uncertainty or help them make decisions about a pregnancy. However, it cannot identify all possible inherited disorders and birth defects.

Cytogenetics is a branch of genetics that is involved with heredity and the cellular components, particularly chromosomes, associated with heredity. Cytogenetic testing involves the determination of chromosome number and structure. Variations in either the chromosome number or structure can produce numerous abnormalities that may lead to cancer, syndromes, or birth defects.

Summary and Analysis of Evidence: Alzheimer disease (AD): Patients with a clinical diagnosis of mild cognitive impairment or mild dementia associated with AD who are considering initiation or discontinuation of an FDA-approved amyloid-beta targeting therapy who receive genetic testing, the evidence includes randomized clinical trials. The incidence of asymptomatic, symptomatic, and serious amyloid-related imaging abnormalities (ARIA) following treatment with the amyloid-beta targeting therapies significantly higher in APOE ε4 homozygotes compared to heterozygotes and noncarriers. The boxed warnings in the FDA labels for approved amyloid-beta targeting therapies states that testing for APOE ε4 status should be performed prior to initiation of treatment to inform the risk of developing ARIA. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. Patients who are asymptomatic and at risk for developing late-onset AD who receive genetic testing, the evidence includes studies on gene associations, test accuracy, and effects on health outcomes. Many genes, including APOE, CR1, BIN1, PICALM, and TREM2, are associated with late-onset AD. However, the sensitivity and specificity of genetic testing for indicating which individuals will progress to AD is low, and numerous other factors can affect progression. Overall, genetic testing has not been shown to add value to the diagnosis of AD made clinically. The current lack of effective methods to prevent the onset of AD limits the clinical benefit for genetic testing. Asymptomatic patients, at risk for developing early-onset, autosomal dominant AD, and have a known familial variant who receive targeted genetic testing, the evidence includes studies on gene associations and test accuracy. Variants in the PSEN1 and PSEN2 and APP genes are known to cause early-onset AD in an autosomal dominant pattern with almost complete penetrance. Outside the reproductive setting when used for prognosis or prediction, there is insufficient evidence to draw conclusions on the benefits of genetic testing for pathogenic variants. Asymptomatic patients, at risk for developing early-onset, autosomal dominant AD, and have no known familial variant who receive genetic testing, the evidence includes studies on gene associations and test accuracy. Variants in the PSEN1, PSEN2, and APP genes are known to cause early-onset AD in an autosomal dominant pattern with almost complete

penetrance. The clinical validity for autosomal dominant early-onset AD will be reasonably certain when a variant found in the database of pathogenic PSEN1, PSEN2, and APP variants are identified. There is insufficient evidence to draw conclusions on the benefits of genetic testing for pathogenic variants. Duchenne and Becker Muscular Dystrophy: Evidence for male patients who have signs and symptoms of a dystrophinopathy who receive genetic testing for Duchenne muscular dystrophy (DMD) gene variants to confirm diagnosis without biopsy includes case series and database entries describing screening and results of types of variants found in patients with clinical signs of DMD or Becker muscular dystrophy (BMD). Virtually all males with DMD or BMD have identifiable DMD disease-associated variants, indicating a high clinical sensitivity for genetic testing. The clinical utility of DMD gene testing can be established for the index case to confirm the diagnosis without a muscle biopsy, to initiate effective treatment, and to distinguish between DMD and the less severe BMD. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. For patients who are female and are a relative of a patient with a DMD-associated dystrophinopathy who receive targeted DMD testing for a known familial variant to determine carrier status, the evidence includes case series and database entries describing screening and results of types of variants found in patients with clinical signs of DMD or BMD. Published data for the clinical validity for testing for a known familial variant are lacking but validity is expected to be high. Direct evidence on the clinical utility of DMD gene testing in at-risk female relatives is lacking. However, the chain of evidence is strong, because determination of carrier status in a female for a DMD familial variant necessitates or eliminates the need for routine cardiac surveillance and can indicate the likelihood of an affected offspring in women considering children. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. Patients who are asymptomatic male offspring of a female DMD familial variant carrier or an asymptomatic male sibling of a patient with a DMD-associated dystrophinopathy who receive targeted DMD testing for a known familial variant to determine DMD status, the evidence includes case series and database entries. Published data for clinical validity of testing for a known familial variant are lacking, but validity is expected to be high. Direct evidence on the clinical utility of DMD gene testing in asymptomatic male offspring of a female DMD familial variant carrier or male sibling of a patient with a DMD-associated dystrophinopathy is also lacking. However, the chain of evidence is strong, because detection of the DMD familial variant necessitates or eliminates the need for increased medical surveillance or cardiac surveillance in an asymptomatic male offspring of a female carrier or the asymptomatic male sibling of a patient with a DMD-associated dystrophinopathy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. Carrier screening: Patients who are asymptomatic but at risk for having offspring with an inherited X-linked or autosomal recessive genetic disorder who receive targeted risk-based carrier screening, the evidence includes studies supporting clinical validity and clinical utility. Results of carrier testing can be used to inform reproductive decisions such as preimplantation genetic diagnosis, in vitro fertilization, not having a child, invasive prenatal testing, adoption, or pregnancy termination. American College of Obstetricians and Gynecologists (ACOG) (2017; reaffirmed 2023) made the following recommendations on expanded carrier screening: "Ethnic-specific, panethnic, and expanded carrier screening are acceptable strategies for prepregnancy and prenatal carrier screening". Based on consensus, ACOG recommended the following criteria: carrier frequency ≥1/100; well-defined phenotype; detrimental effect on the quality of life, cause cognitive or physical impairment, require surgical or medical intervention, or have an onset early in life; not be primarily associated with a disease of adult-onset. ACOG provided a detailed example of a panel that includes testing for 22 conditions that

meet these criteria:α-thalassemia, β-thalassemia, Bloom syndrome, Canavan disease, CF, familial dysautonomia, familial hyperinsulinism, Fanconi anemia C, fragile X syndrome, galactosemia, Gaucher disease, glycogen storage disease type 1A, Joubert syndrome, medium-chain acyl-CoA dehydrogenase deficiency, maple syrup urine disease types 1A and 1B, mucolipidosis IV, Niemann-Pick disease type A, phenylketonuria, sickle cell anemia, Smith-Lemli-Opitz syndrome, spinal muscular atrophy, and Tay-Sachs disease. For patients who are either at increased risk or population risk for having offspring with an inherited X-linked or autosomal recessive genetic disorder who receive a non-targeted carrier screening panel, the evidence includes studies supporting clinical validity and clinical utility. Studies have found that non-targeted carrier screening identifies more carriers and more potentially affected fetuses. Many of the genes in carrier screening panels do not meet the ACOG consensus-driven criteria of at least a 1% carrier rate for all ethnic groups. However, non-targeted testing can address the discrepancies between self-reported ethnicity and genetic ancestry in an ethnically mixed population. As panels become larger the likelihood of being identified as a carrier of a rare genetic disorder increases, leading to an at-risk couple rate of nearly 2% for having an offspring with a recessive or X-linked disorder. Many, though notably not all, of these rare genetic disorders are associated with severe or profound symptoms including shortened lifespan and intellectual or physical disability. With adequate genetic counseling, carrier screening panels can inform reproductive choices, and observational studies have shown that a majority of couples would consider intervention that depends on the severity of the condition. Therefore, non-targeted carrier screening panels for severe recessive and X-linked genetic disorders can have a significant clinical impact. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. Fanconi anemia (FA): Patients who signs or symptoms of FA who receive genetic testing for FA, the evidence includes small cohort studies and case series. Due to the rarity of clinical FA, there is limited published evidence to determine whether genetic testing for FA improves outcomes. The available evidence demonstrates that most patients with a clinical diagnosis of FA have identified pathogenic variants. This supports the use of genetic testing for the diagnosis when standard testing, including chromosomal breakage analysis, is inconclusive. Therefore, when signs and/or symptoms of FA are present, but the diagnosis cannot be made by standard testing, genetic testing will improve the ability to make a definitive diagnosis and direct care. The evidence is sufficient to determine that the technology results in an improvement in the net health outcomes. For patients who have a close relative with the diagnosis of FA who receive genetic testing for FA to determine future risk of the disease, the evidence consists of small cohort studies and case series. Relevant outcomes are test validity, other test performance measures, and changes in reproductive decision making. Genetic testing has clinical utility if there is a close relative with FA primarily first-degree relatives. This will primarily apply to young siblings of an affected individual and may help to direct early monitoring and treatment of bone marrow failure that may prevent or delay progression. Treatment of bone marrow failure with hematopoietic cell transplantation is considered more likely to be successful if initiated earlier in the course of the disease. The evidence is sufficient to determine that the technology results in an improvement in the net health outcomes. FMR1: Evidence for testing patients who have characteristics of Fragile X syndrome (FXS) or an FXS-associated disorder includes studies evaluating the clinical validity of fragile X mental retardation 1 gene (FMR1) variant testing. The evidence demonstrates that FMR1 variant testing can establish a definitive diagnosis of FXS and fragile X-related syndromes when the test is positive for a pathogenic variant. Following a definitive diagnosis, the treatment of comorbid conditions may be improved. At a minimum, providing a diagnosis eliminates the need for further diagnostic workup. A chain of evidence supports

improved outcomes following FMR1 variant testing. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. For patients who have a personal or family history of FXS who are seeking reproductive counseling, the evidence includes studies evaluating the clinical validity of FMR1 variant testing and the effect on reproductive decisions. Testing the repeat region of the FMR1 gene in the context of reproductive decision-making may include: individuals with either a family history of FXS or a family history of undiagnosed intellectual disability, fetuses of known carrier mothers, or affected individuals or their relatives who have had a positive cytogenetic fragile X test result who are seeking further counseling related to the risk of carrier status among themselves or their relatives. DNA testing would accurately identify premutation carriers and distinguish premutation from full mutation carrier women. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. FLT3, NPM1, and CEBPA: For patients who have cytogenetically normal acute myeloid leukemia (AML) who receive genetic testing for variants in FLT3, NPM1, and CEBPA to risk-stratify AML, the evidence includes RCTs, retrospective observational studies, and systematic reviews of these studies. FLT3 internal tandem duplication variants confer a poor prognosis, whereas NPM1 (without the FLT3 internal tandem duplication variant) and CEBPA variants (including biallelic mutations and single mutations in the basic leucine zipper region) confer a favorable prognosis. The prognostic effect of FLT3 tyrosine kinase domain variants is uncertain. Data have suggested an overall survival benefit with transplantation for patients with FLT3 internal tandem duplication, but do not clearly demonstrate an overall survival benefit of transplantation for patients with NPM1 and CEBPA variants. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. For patients who have AML with a genetic variant in FLT3, NPM1, or CEBPA, the evidence for measurable residual disease (MRD) monitoring of these genetic variants is limited to retrospective observational studies. Detection of MRD based on NPM1 variant presence is associated with higher risks for relapse and lower overall survival; prospective evaluations using MRD results to direct prognostic evaluation and treatment decisions are needed. For the use of genetic variants to detect MRD, the evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Hereditary hemochromatosis (HH): Patients who have abnormal iron indices or clinical signs of iron overload who receive genetic testing for human hemochromatosis (HFE), the evidence includes retrospective and prospective observational studies. Studies have demonstrated that current genetic testing detects the majority of the hereditary hemochromatosis (HH) disease, but that, among those with positive tests (HH homozygotes), clinical penetrance is low. There is no direct evidence of the clinical utility of genetic testing, but, along with prior knowledge of the effectiveness of treatment for clinical iron overload, there is a strong chain of evidence that supports the definitive genetic diagnosis of persons with early signs of HH. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. α-Thalassemia: Evidence for genetic testing of patients who have suspected α-thalassemia includes case reports and case series documenting the association between pathogenic variants and clinical syndromes. For the α-thalassemia syndromes that have clinical implications, diagnosis can be made based on biochemical testing without genetic testing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Evidence for patients who have biochemical evidence of α-thalassemia who are considering conception who receive genetic testing for α-thalassemia includes case reports and case series that correlate pathogenic variants with clinical disease. Preconception carrier testing is intended to avoid the most serious form of α-thalassemia, hemoglobin Bart's. This condition leads to intrauterine death or death shortly after birth and is

associated with increased obstetrical risks for the mother. Screening of populations at risk is first done by biochemical tests, including hemoglobin electrophoresis and complete blood count and peripheral smear, but these tests cannot reliably distinguish between the carrier and trait syndromes, and cannot determine which configuration of variants is present in α-thalassemia trait. Therefore, these tests cannot completely determine the risk of a pregnancy with hemoglobin Bart's and hydrops fetalis. Genetic testing can determine with certainty the number of abnormal genes present, and therefore can more precisely determine the risk of hydrops fetalis. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. For patients who have hemoglobin H disease (α-thalassemia intermedia) who receive genetic testing for α-thalassemia, the evidence includes case series that correlate specific variants with a prognosis of the disease. There is some evidence for a genotype-phenotype correlation with disease severity, but no current evidence indicates that patient management or outcomes would be altered by genetic testing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Pain management: For patients who receive pharmacogenetic testing to target therapy, the evidence includes a hybrid implementation-effectiveness randomized trial, a single-blind randomized trial, a prospective cohort study with historical controls that assessed genotype-guided management of postoperative pain, and a prospective non-randomized pragmatic trial that evaluated chronic pain control when treatment occurred via a CYP2D6-guided approach to opioid prescribing versus standard management. The hybrid randomized trial concluded that preemptive CYP2D6-guided opioid selection is feasible in an elective surgery setting and that this approach may decrease postoperative opioid utilization with similar pain control compared to usual care; however, these results were only exploratory in nature. The single-blind randomized trial similarly concluded that postoperative opioid prescription guided by genetic results may improve pain control and reduce opioid consumption compared to usual care. The prospective cohort study reported on the use of genetic panel test results to guide the selection of analgesics in a postoperative setting and reported statistically significant improvement in total scores of a composite endpoint that measured analgesia, patient satisfaction, and the impact of drug-associated side effects versus historical controls. However, methodologic limitations precluded assessment of the effects on outcomes. The prospective non-randomized pragmatic trial evaluated a CYP2D6-guided approach and found a statistically significant but modest improvement in chronic pain control in the intermediate and poor metabolizers. The effect of pharmacogenetic testing alone cannot be determined from this trial. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. For patients who receive pharmacogenetic testing to assess the risk of developing opioid use disorder (OUD), the evidence includes nonrandomized studies. One nonrandomized study has demonstrated the clinical validity of a pharmacogenetic test to assess the risk of developing OUD. However, the study had several limitations, including recall bias due to self-reported opioid use, selection bias due to the study's enrichment strategy, and a lack of diversity. One case-control study was identified that investigated the clinical utility of this technology. While the sample was ancestrally diverse, the study population was mostly male and, compared to the general population, was older and had higher rates of OUD and pain. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Mental health: The evidence for patients who are evaluated for diagnosis or risk of a mental illness who receive genetic testing for risk of that disorder, includes various observational studies (cohort, case-control, genome-wide association study). Most studies evaluated the association between genotype and mental health disorders or gene-drug interactions among individuals at risk for mental health conditions. No studies were identified that

evaluated whether testing for variants changed clinical management or affected health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. For patients with major depressive disorder (MDD) who receive GeneSight testing guided drug treatment, the evidence includes 4 randomized controlled trials (RCTs). The RCTs compared response (≥50% decrease in Hamilton Depression Rating Scale-17 [HAM-D17] or Patient Health Questionnaire-9 [PHQ-9]), remission (HAM-D17 ≤7 or PHQ-9 ≤5), and symptom improvement (mean % change in HAM-D17 or PHQ-9) with antidepressant therapy informed by GeneSight test results to antidepressant therapy selected without GeneSight test results (ie, standard of care [SOC]). The PRecision Medicine In MEntal Health Care (PRIME Care) trial did not find a statistically significant difference between GeneSight guided treatment and SOC in the primary outcome of remission at 24 weeks follow-up, but significant differences in the secondary outcome of symptom score improvement and treatment response were observed, favoring the GeneSight group. However, this trial had a high loss to follow-up (21%) and had inadequate participant recruitment based on a priori sample size estimation and power analysis. The GAPP-MDD trial, also comparing GeneSight guided treatment with SOC, found no statistically significant differences between groups in response, remission or symptom improvement at 8 weeks follow-up, although like the GUIDED trial, a high proportion (up to 69%) of randomized participants were excluded from outcome analysis and the study was not adequately powered to detect between-group differences. All of the trials have major limitations in design and conduct and in consistency and precision, thus none provided adequate evidence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. For patients with a mental illness other than depression who are undergoing drug treatment who receive genetic testing for genes associated with medication pharmacokinetics and pharmacodynamics, the evidence includes a systematic review and meta-analysis and RCTs evaluating associations between specific genes and outcomes of drug treatment. There was evidence of reporting bias and among the randomized moderate and severe anxiety patients with only anxiety, 25% in the experimental arm and 17% in the SOC arm were lost to follow-up over the 12-week period. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Rett syndrome (RTT): For patients who have signs or symptoms and receive genetic testing for RTT-associated genes, the evidence includes case series and prospective cohort studies. Methyl-CpG-binding protein 2 (MECP2) variants are found in most patients with RTT, particularly in those who present with classic clinical features of RTT. The diagnostic accuracy of genetic testing for RTT cannot be determined with absolute certainty given variable clinical presentations of typical versus atypical RTT, but testing appears to have high sensitivity and specificity. Genetic testing has clinical utility when signs and symptoms of RTT are present to establish a specific genetic diagnosis. Identification of a specific class or type of pathogenic variant may alter some aspects of management and may eliminate or necessitate surveillance for different clinical manifestations of the disease. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. For patients who are asymptomatic sisters of an individual with RTT who receive targeted genetic testing for a known familial RTT-associated variant, the evidence includes case series and prospective cohort studies. Targeted familial variant testing of asymptomatic sisters can eliminate or necessitate surveillance given the variability of clinical presentation in girls due to X-chromosome inactivation and clinical severity based on the type of pathogenic variant present. In sisters of reproductive age, determination of carrier status can eliminate or necessitate prenatal testing and inform reproductive decision making. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. For patients who are females with a child with RTT

who are considering future childbearing who receive targeted genetic testing for a known familial RTT-associated variant, the evidence includes cases series and prospective cohort studies. Targeted familial variant testing of a woman with a child with RTT to determine carrier status may inform prenatal testing and reproductive decision making. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. Prostate cancer: Evidence for patients who are being considered for an initial prostate biopsy who receive testing for genetic and protein biomarkers of prostate cancer (eg, kallikreins biomarkers and 4Kscore Test, proPSA and Prostate Health Index, TMPRSS fusion genes and MyProstateScore, SelectMDx for Prostate Cancer, ExoDx Prostate, Apifiny, PCA3 score, and PanGIA Prostate) includes systematic reviews, meta-analyses, and primarily observational studies. The evidence supporting clinical utility varies by the test but has not been directly shown for any biomarker test. Absent direct evidence of clinical utility, a chain of evidence might be constructed. However, the performance of biomarker testing for directing biopsy referrals is uncertain. While some studies have shown a reduction or delay in biopsy based on testing, a chain of evidence for clinical utility cannot be constructed due to limitations in clinical validity. Test validation populations have included men with a positive digital rectal exam (DRE), a prostate-specific antigen (PSA) level outside of the gray zone (between 3 or 4 ng/mL and 10 ng/mL), or older men for whom the information from test results are less likely to be informative. Many biomarker tests do not have standardized cutoffs to recommend a biopsy. In addition, comparative studies of the many biomarkers are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. For patients who are being considered for repeat biopsy who receive testing for genetic and protein biomarkers of prostate cancer (eg, PCA3 score, Gene Hypermethylation and ConfirmMDx test, Prostate Core Mitomics Test, MyProstate Score), the evidence includes systematic reviews and meta-analyses and primarily observational studies. The performance of biomarker testing for guiding rebiopsy decisions is lacking. The tests are associated with a diagnosis of prostate cancer and aggressive prostate cancer, but studies on clinical validity are limited and do not compare performance characteristics with standard risk prediction models. Direct evidence supporting clinical utility has not been shown. No data are currently available on the longer-term clinical outcomes of the use of genetic and protein biomarkers to decide on repeat prostate biopsy, The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Patients with localized prostate cancer treated with radical prostatectomy (RP) who receive ArteraAI Prostate Test, the evidence includes retrospective cohort studies of clinical validity using archived samples. Limitations of the studies include clinical heterogeneity of study populations, variability in data recording, and different conditions under which measurements occurred. No study reported management changes made in response to ArteraAI Prostate Test results. Overall, ArteraAI Prostate Test is validated for disease-specific outcomes for prostate cancer patients who underwent RP and can provide additional prognostic information that may guide postoperative management, but further studies are needed to determine if MMAI can be used to decide specific treatment regimens that improve health outcomes. PTEN hamartoma tumor syndrome (PHTS): PHTS is characterized by hamartomatous tumors and PTEN germline disease-associated variants. Clinically, PHTS includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome (PLS). For patients who have clinical signs or symptoms of PHTS or who are asymptomatic with a first-degree relative with a PHTS and a known familial variant who receive genetic testing for a PTEN familial variant, the evidence includes case series and a large prospective study on the frequency of a PTEN variants in individuals meeting clinical criteria for a PHTS, and studies of cancer risk estimates in individuals with a PTEN disease-associated

variant. The published clinical validity of testing for the PTEN gene is variable. The true clinical validity is difficult to ascertain because the syndrome is defined by the presence of a PTEN disease-associated variant. The sensitivity of tests for Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome has been reported to be up to 80% and 60%, respectively. Direct evidence of the clinical utility of genetic testing for PTEN is lacking; however, confirming a diagnosis in a patient with clinical signs of a PHTS will lead to changes in clinical management by increasing surveillance to detect cancers associated with PHTS at an early and treatable stage. Although most cases of a PHTS occur in individuals with no known family history of PHTS, testing of at-risk relatives will identify those who should also undergo increased cancer surveillance. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. Inherited peripheral neuropathies: Most inherited polyneuropathies were originally described clinically as variants of Charcot-Marie-Tooth (CMT) disease. The clinical phenotype of CMT is highly variable. CMT disease is genetically and clinically heterogeneous. Variants in more than 30 genes and more than 44 different genetic loci have been associated with inherited neuropathies. For patients with suspected inherited motor and sensory peripheral neuropathy who receive testing for genes associated with inherited peripheral neuropathies, the evidence includes case-control and genome-wide association studies. For the evaluation of hereditary motor and sensory peripheral neuropathies and hereditary neuropathy with liability to pressure palsies (HNPP), the diagnostic testing yield is likely to be high, particularly when sequential testing is used based on patient phenotype. However, the clinical utility of genetic testing to confirm a diagnosis in a patient with a clinical diagnosis of an inherited peripheral neuropathy is unknown. No direct evidence for improved outcomes with the use of genetic testing for hereditary motor and sensory peripheral neuropathies and HNPP was identified. However, a chain of evidence supports the use of genetic testing to establish a diagnosis in cases of suspected inherited motor or sensory neuropathy, when a diagnosis cannot be made by other methods, to initiate supportive therapies. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. Alpha1-antitrypsin deficiency (AATD): Evidence for patients who have suspected AATD who receive genetic testing for AATD, the evidence includes studies on clinical validity, and several controlled studies assessing potential clinical utility. Genetic testing can confirm a diagnosis of AATD suggested by serum testing by identifying the known genetic variants associated with the disease and identify AATD when a diagnosis is uncertain due to the suspicious clinical presentation that is not confirmed by serum testing. A chain of evidence suggests that making a diagnosis of AATD in individuals with suspected AATD can support clinical utility by allowing monitoring for multisystem complications and initiation of accepted therapies. Knowledge of AATD status may lead to behavior changes or changes in medical management that lead to improved health outcomes. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. Celiac disease: Evidence on the use of HLA-DQ2/HLA-DQ8 testing to rule out celiac disease in patients with discordant serologic and histologic findings or individuals with persistent symptoms despite negative serology and histology includes systematic reviews and comparative studies. An UpToDate 2023 article, Diagnosis of celiac disease in adults (Kelly) includes: “Discordant serology and biopsy results may be due to a false-positive tTG serology or a false-negative biopsy result as celiac disease may have a patchy distribution. The intestinal biopsy should be reviewed by a pathologist familiar with celiac disease to look for subtle abnormalities of celiac disease. In addition, we perform an alternate antibody test (EMA-IgA or DGP-IgA). If serology and histology remain discordant, we perform HLA-DQ2/DQ8 typing.” The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. Whole exome and whole genome: For children who are not

critically ill with multiple unexplained congenital anomalies or a neurodevelopmental disorder of unknown etiology following a standard workup who receive whole exome sequencing (WES) with trio testing when possible, the evidence includes large case series and within-subject comparisons. Patients who have multiple congenital anomalies or a developmental disorder with a suspected genetic etiology, but whose specific genetic alteration is unclear or unidentified by a standard clinical workup, may be left without a clinical diagnosis of their disorder, despite a lengthy diagnostic workup. For a substantial proportion of these patients, WES may return a likely pathogenic variant. Several large and smaller series have reported diagnostic yields of WES ranging from 25% to 60%, depending on the individual's age, phenotype, and previous workup. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. Children with a suspected genetic disorder other than multiple congenital anomalies or a neurodevelopmental disorder of unknown etiology following a standard workup who receive WES with trio testing when possible, the evidence includes small case series and prospective research studies. There is an increasing number of reports evaluating the use of WES to identify a molecular basis for disorders other than multiple congenital anomalies or neurodevelopmental disorders. The diagnostic yields in these studies range from as low as 3% to 60%. Some studies have reported on the use of a virtual gene panel with restricted analysis of disease-associated genes, and WES data allow reanalysis as new genes are linked to the patient phenotype. Overall, a limited number of patients have been studied for any specific disorder, and clinical use of WES for these disorders is at an early stage with uncertainty about changes in patient management. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. For patients who have previously received WES who receive repeat WES, including re-analysis of previous test results, the evidence includes nonrandomized studies and a systematic review. There is no direct evidence of clinical utility. In a meta-analysis of nonrandomized studies, re-analysis of WES data resulted in an 11% increase in diagnostic yield in individuals who were previously undiagnosed via WES. Three nonrandomized studies published after the meta-analysis had findings consistent with the meta-analysis. Conclusions were limited by heterogeneity across individual studies and a lack of detailed reporting on reasons for new diagnoses, changes in management based on new diagnoses, and the frequency of the identification of variants of uncertain significance (VUS). Additionally, the optimal timing of re-analysis has not been established, and there are no clear guidelines on what factors should prompt the decision to repeat testing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Children who are not critically ill with multiple unexplained congenital anomalies or a neurodevelopmental disorder of unknown etiology following a standard workup or WES who receive whole genome sequencing (WGS) with trio testing when possible, the evidence includes nonrandomized studies and a systematic review. In studies of children with congenital anomalies and developmental delays of unknown etiology following standard clinical workup, the yield of WGS has ranged between 20% and 40%. A majority of studies described methods for interpretation of WGS indicating that only pathogenic or likely pathogenic variants were included in the diagnostic yield and that VUS were frequently not reported. Although the diagnostic yield of WGS is at least as high as WES in individuals without a diagnosis following standard clinical workup, it is unclear if the additional yield results in actionable clinical management changes that improve health outcomes. Further, while reporting practices of VUS found on exome and genome sequencing vary across laboratories, WGS results in the identification of more VUS than WES. Higher yield and higher VUS from WGS currently have limited clinical utility. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Children who are suspected of having a genetic

disorder other than multiple unexplained congenital anomalies or a neurodevelopmental disorder of unknown etiology following a standard workup who receive WGS with trio testing when possible, the evidence includes case series. Whole genome sequencing has also been studied in other genetic conditions with yield ranging from 9% to 55%. Overall, a limited number of patients have been studied for any specific disorder, and clinical use of WGS as well as information regarding meaningful changes in management for these disorders is at an early stage. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. For critically ill infants with a suspected genetic disorder of unknown etiology following a standard workup who receive rapid WGS (rWGS) or rapid WES (rWES) with trio testing when possible, the evidence includes randomized controlled trials (RCTs) and case series. Several retrospective and prospective studies including more than 800 critically ill infants and children in total have reported on diagnostic yield for rWGS or rWES. These studies included phenotypically diverse but critically ill infants and had yields of between 30% and 60% for pathogenic or likely pathogenic variants. Studies have also reported associated changes in patient management for patients receiving a diagnosis from rWGS or rWES, including avoidance of invasive procedures, medication changes to reduce morbidity, discontinuation of or additional testing, and initiation of palliative care or reproductive planning. A chain of evidence linking meaningful improvements in diagnostic yield and changes in management expected to improve health outcomes supports the clinical value of rWGS or rWES. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. Mitochondrial disorders: Evidence for patients with signs or symptoms of a mitochondrial disease who receive genetic testing includes case series and cohort studies. There is some evidence on clinical validity that varies by the patient population and testing strategy. Studies reporting diagnostic yield for known pathogenic variants using next-generation sequencing (NGS) panels tend to report rates ranging from 15% to 25%. Clinical specificity is unknown, but population-based studies have indicated that the prevalence of certain variants exceeds the prevalence of clinical disease, suggesting that the variant will be found in some people without the clinical disease (false-positives). Clinical utility is relatively high for confirming the diagnosis of mitochondrial diseases in people who have signs and symptoms of the disease. In these patients, a positive result in genetic testing can avoid a muscle biopsy and eliminate the need for further clinical workup. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. For patients who are asymptomatic with a close relative with a mitochondrial disease and a known pathogenic variant and who receive targeted familial variant testing, the evidence includes case series and cohort studies. Clinical validity is expected to be high for targeted testing of a known familial variant, assuming sufficient analytic validity. Clinical utility can be demonstrated by testing at-risk family members who have a close relative with a pathogenic variant. When a specific mitochondrial disease is present in the family that is severe enough to cause impairment and/or disability, genetic testing may impact reproductive decision making. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. Chromosomal Microarray Analysis (CMA): For patients who have developmental delay/intellectual disability, autism spectrum disorder, or multiple congenital anomalies not specific to a well-delineated genetic syndrome who receive CMA testing, the evidence includes primarily case series. The available evidence supports test validity. Although systematic studies of the impact of CMA on patient outcomes are lacking, the improvement in diagnostic yield over karyotyping has been well-demonstrated. Direct evidence of improved outcomes with CMA compared with karyotyping is also lacking. However, for at least a subset of the disorders potentially diagnosed with CMA testing in this patient population, there are well-

defined and accepted management steps associated with positive test results. Further, there is evidence of changes in reproductive decision-making as a result of positive test results. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. For patients who have developmental delay/intellectual disability, autism spectrum disorder, or multiple congenital anomalies not specific to a well-delineated genetic syndrome who receive next-generation sequencing panel testing, the evidence includes primarily case series. Relevant outcomes are test validity, changes in reproductive decision-making, morbid events, and resource utilization. The testing yield and likelihood of an uncertain result are variable, based on the gene panel, gene tested, and patient population; additionally, there are risks of uninterpretable and incidental results. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Adolescent idiopathic scoliosis (AIS): Evidence for patients with AIS who receive clinical management with prognostic testing using an algorithm incorporating SNV-based testing, the evidence includes cross-sectional studies reporting on the clinical validity of the ScoliScore test, along with cross-sectional studies reporting on the association between SNVs in various genes and scoliosis progression. A study on the clinical validity for the ScoliScore AIS prognostic DNA-based test has reported a high negative predictive value for ruling out the possibility of progression to severe curvature in a population with a low baseline likelihood of progression. It is not clear if the increase in predictive accuracy provided by testing is statistically or clinically meaningful. Other genetic studies have not demonstrated significant associations between the SNVs used in the ScoliScore and scoliosis progression. The clinical validity of DNA-based testing (either through testing of individual SNVs or an algorithm incorporating SNV results) for predicting scoliosis progression in patients with AIS has not been established. The value of early identification and intervention(s) for people at risk for progression of the disease and whether laboratory testing improves disease identification beyond clinical evaluation are unknown. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Hereditary pancreatitis (HP): The evidence for patients who have chronic pancreatitis (CP) or acute recurrent pancreatitis (ARP) who receive testing for genes associated with HP includes cohort studies on variant detection rates and meta-analyses. There are studies on the detection rate of HP-associated genes in various populations. Few studies have enrolled patients with known HP; those doing so have reported detection rates for disease-associated variants between 52% and 62%. For other studies that tested patients with CP or ARP, disease-associated variant detection rates varied widely across studies. There is a lack of direct evidence that testing for HP improves health outcomes and insufficient indirect evidence that, in patients with CP or ARP, management would change after genetic testing in a manner likely to improve health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. For patients who are asymptomatic with family members with HP who receive testing for a known familial variant associated with HP, the evidence includes a very limited number of studies. No direct evidence was identified comparing outcomes in patients tested or not tested for a familial variant. It is possible that at-risk relatives who are identified as having a familial variant may alter lifestyle factors, and this might delay or prevent CP onset. However, studies evaluating behavioral changes and the impact on disease are lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Ovarian cancer: For patients without diagnosed epithelial ovarian cancer (EOC) and in a family at risk of developing EOC who receive germline genetic testing for genes associated with hereditary ovarian cancer (OC) (ie, BRIP1,RAD51C, and RAD51D), the evidence includes studies of clinical validity and studies of OC risk, including meta-analyses. Evidence supporting clinical validity was obtained from numerous studies

reporting relative risk (RR) or odds ratios (OR) and 4 studies provided penetrance estimates. Study designs included family-based case-control and population- or multicenter-based case-control. The number of pathogenic (P)/likely pathogenic (LP) variants identified in association studies ranged from 10 to 36, 11 to 44, and 8 to 13 for BRIP1, RAD51C, and RAD51D, respectively. Given the penetrance of BRIP1,RAD51C, and RAD51D variants, the outcomes following risk-reducing oophorectomy and RRSO examined in women with a family history consistent with hereditary OC (including BRCA1 and BRCA2 carriers) can be applied to women with BRIP1, RAD51C, and RAD51D variants, with the benefit-to-risk balance affected by penetrance. In women at high-risk of hereditary OC who would consider risk-reducing interventions, identifying a BRIP1, RAD51C, or RAD51D variant provides a more precise estimated risk of developing OC compared to family history alone and can offer women a more accurate understanding of benefits and potential harms of any intervention. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. For patients without diagnosed EOC and in a family at risk of developing EOC who receive germline genetic testing for NBN gene variants, the evidence includes studies of clinical validity and studies of OC risk, including a meta-analysis. NBN variants have been associated with a 2- to 3.5-fold increased risk of OC across studies. However, a significantly increased frequency of NBN mutations has not been consistently observed in cases versus controls and penetrance estimates have not been reported. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Patients without diagnosed EOC and in a family at risk of developing EOC who are considering prophylactic surgery who receive germline genetic testing of first- and/or second-degree relative(s) with a personal history of EOC for genes associated with hereditary OC to guide prophylactic decision-making or interpretation of test results in the undiagnosed, at-risk family member, the evidence on the use of preventative interventions is indirect, relying on studies of at-risk women and BRCA carriers. In women at risk of hereditary OC who are considering prophylactic surgery, genetic testing of first- and/or second-degree relative(s) with a personal history of EOC to identify a familial BRIP1, RAD51C, or RAD51D germline variant provides a more precise estimated risk of developing OC compared to family history alone, and reduces the incidence of uninformative negative test results or non-actionable variants of unknown significance (VUS). Testing a relative with early-onset disease, bilateral disease, or multiple primaries is recommended, as that individual has the highest likelihood of obtaining an informative, positive test result. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. Patients without diagnosed EOC and in a family at risk of developing EOC who are considering prophylactic surgery who receive germline genetic testing of first- and/or second-degree relative(s) with a personal history of EOC for NBN gene variants to guide prophylactic decision-making or interpretation of test results in the undiagnosed, at-risk family member, direct evidence is lacking. Given that the clinical validity of NBN germline variant testing has not been established, a chain of evidence cannot be constructed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. For patients with diagnosed OC who receive germline genetic testing for BRIP1, RAD51C, RAD51D, and NBN gene variants to guide treatment decisions in the individual with diagnosed EOC, the evidence includes studies of variant prevalence and studies of OC risk. Direct evidence for the clinical utility of genetic testing for BRIP1, RAD51C, RAD51D, and NBN variants in individuals with OC was not identified. In studies evaluating homologous recombination deficiency (HRD) assays in BRCA wild-type patients, an overlapping therapeutic benefit was found between deficient/high loss-of-heterozygosity and proficient/low loss-of-heterozygosity tumors and results were not stratified by non-BRCA HRD genes. The use of BRIP1,

RAD51C, RAD51D, and NBN variant status to guide maintenance and recurrence therapy continues to be elucidated in the clinical trial setting. In contrast to undiagnosed women at high familial risk of OC, women diagnosed with OC who undergo testing for BRIP1, RAD51C, RAD51D, and NBN variants do not yield clinically actionable results. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. High breast cancer risk: Evidence for patients with risk of hereditary breast cancer/ovarian cancer (HBOC) who receive genetic testing for a CHEK2 variant includes studies of variant prevalence and studies of breast cancer risk. The available studies on clinical validity have demonstrated that CHEK2 variants are of moderate penetrance, and confer a risk of breast cancer 2 to 4 times that of the general population. Direct evidence for the clinical utility of genetic testing for CHEK2 variants in individuals with risk of HBOC was not identified. It is unclear whether the relative risk (RR) associated with the moderate penetrance variants would increase risk enough beyond that already conferred by familial risk to change screening behavior. In contrast to high-penetrance variants, there is unlikely to be a similar benefit-to-risk calculus for risk-reducing mastectomy in women with a moderate penetrance variant such as CHEK2. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. For patients with risk of HBOC who receive genetic testing for an ATM variant, the evidence includes studies of variant prevalence and studies of breast cancer risk. The available studies on clinical validity have demonstrated that ATM variants are of moderate penetrance; moreover, ATM variants confer a risk of breast cancer 2 to 4 times that of the general population. Direct evidence for the clinical utility of genetic testing for ATM variants in individuals with risk of HBOC was not identified. It is unclear whether the RR associated with the moderate penetrance variants would increase risk enough beyond that already conferred by familial risk to change screening behavior. In contrast to high-penetrance variants, there is unlikely to be a similar benefit-to-risk calculus for preventive interventions in women with a moderate penetrance variant such as ATM. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. For patients with risk of HBOC who receive genetic testing for a BARD1 variant, the evidence includes studies of variant prevalence and studies of breast cancer risk. The available studies on clinical validity have demonstrated that BARD1 variants are of low to moderate penetrance; BARD1 variants confer a risk of breast cancer about 2 to 3 times that of the general population. Direct evidence for the clinical utility of genetic testing for BARD1 variants in individuals with a risk of HBOC was not identified. It is unclear whether the RR associated with the low to moderate penetrance variants would increase risk enough beyond that already conferred by familial risk to change screening behavior. In contrast to high-penetrance variants, there is unlikely to be a similar benefit-to-risk calculus for preventive interventions in women with a low to moderate penetrance variant such as BARD1. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Inflammatory bowel disease (IBD): A number of studies have examined the association between the serologic markers ASCA and ANCA and inflammatory bowel disease. Systematic reviews have found relatively low sensitivity and moderately high specificity. Moreover, the clinical utility of these assays has not been demonstrated. No studies demonstrated the use of these markers in lieu of a standard workup for IBD. The evidence is insufficient to determine the effects of the technology on health outcomes. Nonfamilial Breast Cancer: Patients who are asymptomatic and at average risk of breast cancer by clinical criteria who receive testing for common single nucleotide variants (SNVs) associated with a small increase in the risk of breast cancer, the evidence includes observational studies. Clinical genetic tests may improve the predictive accuracy of current clinical risk predictors. However, the magnitude of improvement is small, and clinical significance is uncertain. Whether the potential

harms of these tests due to false-negative and false-positive results are outweighed by the potential benefit associated with improved risk assessment is unknown. Evaluation of this technology is further complicated by the rapidly increasing numbers of SNVs associated with a small risk of breast cancer. Long-term prospective studies with large sample sizes are needed to determine the clinical validity and utility of SNV-based models for predicting breast cancer risk. The discriminatory ability offered by the genetic factors currently known is insufficient to inform clinical practice. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Macular Degeneration: For patients who are asymptomatic with risk of developing age-related macular degeneration who receive genetic testing for age-related macular degeneration, the evidence includes genetic association studies and risk-prediction models. The clinical validity of genetic testing appears to provide a small, incremental benefit to risk stratification based on nongenetic risk factors. The clinical utility of genetic testing for age-related macular degeneration is limited, in that there are currently no preventive measures that can be undertaken. No studies have shown improvements in health outcomes in patients identified as being at high risk based on genetic testing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Patients with age-related macular degeneration who receive genetic testing for age-related macular degeneration, the evidence includes genetic association studies and risk-prediction models. The clinical utility of genetic testing in patients who have age-related macular degeneration is limited, in that genetic testing has not been shown to be superior to clinical evaluation in determining the risk of progression of disease. In addition, there is no known association with specific genotypes and specific therapies. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Cytochrome P450 (CYP450): The cytochrome P450 (CYP450) family is involved in the metabolism of many currently administered drugs, and genetic variants in CYP450 are associated with altered metabolism of many drugs. Testing for CYP450 variants may assist in selecting and dosing drugs affected by these genetic variants. The FDA has included pharmacogenomics information in the physician prescribing information (drug labels) of multiple drugs. The FDA has given clear and specific directives on use of a specific dose for eliglustat, tetrabenazine, and siponimod. The FDA approved eliglustat for treatment of adults with Gaucher disease type 1 who are CYP2D6 extensive metabolizers (Ems), intermediate metabolizers, or poor metabolizers (PMs) as detected by an FDA-cleared test. The FDA approved tetrabenazine for the treatment of chorea associated with Huntington disease. According to the label, patients requiring doses above 50 mg per day should be genotyped for the drug-metabolizing enzyme CYP2D6 to determine if the patient is a PM or EM. The FDA approved siponimod for the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults. The recommended maintenance dosage is 2 mg. The recommended maintenance dosage in patients with a CYP2C9*1/*3 or *2/*3 genotype is 1 mg. Siponimod is contraindicated in patients with a CYP2C9*3/*3 genotype. For patients who need antiplatelet therapy who are undergoing or being considered for clopidogrel therapy who receive a cytochrome P450 (CYP) 2C19 guided treatment strategy includes randomized controlled trials (RCTs). RCTs have evaluated the role of genetic testing for CYP2C19 for selecting appropriate antiplatelet treatment and/or amplified dosing of clopidogrel using an intermediate outcome measure of platelet reactivity to predict CYP2C19 metabolic state. One RCT has shown there was no statistical difference in patients with "on-treatment high platelet reactivity" who received genotype-guided management or standard treatment with clopidogrel. Another RCT showed that carriers of loss of function alleles did not respond to augmented clopidogrel as well as they did to prasugrel, while physician-directed clopidogrel

was effective for most noncarriers. However, routine testing using platelet reactivity as an outcome measure to predict CYP2C19 metabolic state has not been shown to improve health outcomes. Results of TAILOR-PCI reported no statistically significant difference in a composite end point of cardiovascular death, myocardial infarction, stroke, stent thrombosis, and severe recurrent ischemia among patients with CYP2C19 loss-of-function alleles who underwent percutaneous coronary intervention (PCI), genotype-guided selection of an oral P2Y12 inhibitor compared with conventional clopidogrel therapy. In a trial comparing ticagrelor and clopidogrel use in individuals with stroke, results of the CHANCE-2 RCT reported a statistically significant decrease in risk of recurrent stroke in CYP2C19 loss-of-function carriers taking ticagrelor compared to clopidogrel in the first 90 days after presentation, without an increased risk of significant bleeding. Ticagrelor was associated with a higher number of total bleeding events compared to clopidogrel and the results are limited by the lack of inclusion of those with delayed presentation, receipt of thrombolysis, or cardioembolic stroke, and majority of patients genotyped as intermediate metabolizers, limiting generalizability. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Patients who are undergoing or being considered for treatment with highly active antiretroviral agents, immunosuppressant therapy for organ transplantation, beta-blockers, or antitubercular medications who receive a CYP450-guided treatment strategy, the evidence includes retrospective studies and underpowered RCTs. In general, most published CYP450 pharmacogenomic studies for these drugs consist of retrospective evaluations of CYP450 genotype associations, reporting intermediate outcomes (eg, circulating drug concentrations) or less often, final outcomes (eg, adverse events or efficacy). Many of these studies are small, underpowered, and hypothesis generating. Prospective intervention studies, including RCTs documenting the clinical usefulness of CYP450 genotyping to improve existing clinical decision making to guide dose or drug selection, which may then translate into improvement in patient outcomes, were not identified. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. There is insufficient evidence to support the use of the X-linked Intellectual Disability Panel for all indications. Although there are ongoing clinical studies, the current data are inadequate to permit scientific conclusions on net health outcomes.

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. Coverage may be governed by state or federal mandates.

GENETIC TESTING TO ESTABLISH A DIAGNOSIS OF INHERITABLE DISEASE

Genetic testing **meets the definition of medical necessity** when used to establish a molecular diagnosis of an inheritable disease when the following criteria are met:

- The member displays clinical features, or is at direct risk of inheriting the mutation in question (presymptomatic); **AND**
- The result of the test will directly impact the treatment being delivered to the member; **AND**
- After history, physical examination, pedigree analysis, genetic counseling, and completion of conventional diagnostic studies, a definitive diagnosis remains uncertain, and one of the diagnoses listed in the table below may be suspected (the list is not all-inclusive)

OR

- For assisted reproductive technology (also known as preimplantation genetic testing [PGT] or preimplantation genetic diagnosis [PGD]) cases (i.e. in vitro fertilization (IVF), gamete intrafallopian transfer (GIFT), artificial insemination) where either parent is known to have a chromosomal abnormality. Results of testing must impact reproductive treatment and planning. **NOTE:** applicable only under those contracts that include infertility benefits.

Diagnosis Table:

Albinism (albino)	Cystic Fibrosis (CF) **(see criteria below)**	Hemochromatosis (gene sequence analysis)	Retinoblastoma
Angelman Syndrome (see criteria below)	Duchenne Muscular Dystrophy (DMD) or Becker Muscular Dystrophy (BMD) **(see criteria below)**	Huntington's Chorea (see criteria below)	Sickle Cell Anemia
Canavan Disease	Fabry Disease	Myotonic Dystrophy (see criteria below)	Spinal Muscular Atrophy
Chromosome 22q11.2 Deletion Syndrome **(see criteria below)**	Fragile X Syndrome (see criteria below)	Niemann-Pick (enzyme or mutation analysis)	Tuberous Sclerosis (see criteria below)
Charcot-Marie-Tooth Disease	Gaucher Disease (see criteria below)	Prader-Willi Syndrome **(see criteria below)**	Von Hippel-Lindau Syndrome

The following test list includes, but is not limited to, specific indications for testing that may **meet the definition of medical necessity** and those for which testing is considered **experimental or investigational**.

Diagnosis	**Criteria**
Angelman Syndrome	Genetic testing for Angelman Syndrome **meets the definition of medical necessity** for **ONE** of the following: • Cytogenic deletion is suspected on chorionic villus sampling (CVS) or amniocentesis • Previous child diagnosed with Angelman Syndrome caused by a UBE3A mutation.
Carrier Screening for Genetic Diseases Targeted carrier screening is performed in individuals having an increased risk based on population carrier	Targeted carrier screening for X-linked and autosomal recessive genetic diseases (also called risk-based or ethnic-based testing) **meets the definition of medical necessity** for members who are pregnant or are considering pregnancy and are at increased risk of having offspring with

prevalence, or personal or family history.	an X-linked or autosomal recessive disease when one of the following criteria is met: • One or both individuals have a first- or second-degree relative who is affected **OR** • One individual is known to be a carrier **OR** • One or both individuals are members of a population known to have a carrier rate that exceeds a threshold considered appropriate for testing for a particular condition. (First-degree relatives include a biological parent, brother, sister, or child; second-degree relatives include biologic grandparent, aunt, uncle, niece, nephew, grandchildren, and half-sibling.) **AND ALL** of the following criteria are met: • The natural history of the disease is well understood and there is a reasonable likelihood that the disease is onewith high morbidity in the homozygous or compound heterozygous state • Alternative biochemical or other clinical tests to definitively diagnose carrier status are not available, or, if available, provide an indeterminate result or are individually less efficacious than genetic testing • The genetic test has adequate clinical validity to guide clinical decision making and residual risk is understood; • If targeted testing is performed by a panel, the panel meets the minimum number of recommended gene variants but does not exceed the maximum (see note below) • Previous carrier screening or individual targeted gene testing for the gene variant(s) of interest has not been performed; **AND** • An association of the marker with the disorder has been established. All targeted screening not meeting any of the above criteria **does not meet the definition of medical necessity**.
Non-targeted carrier screening involves screening individuals or couples for	Non-targeted carrier screening panels for autosomal recessive and X-linked genetic disorders **meets the definition of medical necessity** as an alternative to testing of individual genes (eg, SMN1 gene and CFTR gene) for members who are pregnant or are considering pregnancy

disorders in many genes by next-generation sequencing.	at any risk level including high risk and average risk when all of the following criteria are met: •The natural history of each disease is well understood and there is reasonable likelihood that the disease is one with high morbidity or early mortality in the homozygous or compound homozygous state; •Alternative biochemical or other clinical tests to definitively diagnose carrier status are not available, or, if available, provide an indeterminate result or are individually less efficacious than genetic testing; •The genetic test has adequate clinical validity to guide clinical decision-making and residual risk is understood; •An association of the markers with the disorders has been established; •If testing is performed by a panel, the panel meets the minimum number of recommended gene variants but does not exceed the maximum (see note below); **AND** •Previous carrier screening has not been performed. Non-targeted carrier screening panels are considered **experimental or investigational** in all other situations when above criteria are not met. There is insufficient clinical evidence to permit conclusions on net health outcomes. **Notes**: The statements above only apply if there are no separate position statements that outline specific criteria for carrier screening. If a separate position statement exists, then criteria for medical necessity in that position statement supersedes these statements. Targeted carrier screening for autosomal recessive or X-linked conditions is also called risk-based test or ethnic-based testing. If targeted testing is performed by a panel, the most appropriate panel code available should be used. The panel and the panel billing code should include CFTR and SMN1. If the carrier screening test is a panel less than 15 genes and does not include CFTR or SMN1, but would be 15 or more genes if including CFTR or SMN1, then it should be coded with 81443. Panels closely resembling 81443

	should be billed using 81443 rather than billing individually (ie, unbundling). Non-targeted carrier screening applies to persons of any risk including average risk. Any panel using 81443 for non-targeted carrier screening must include the CFTR and SMN1 genes. Non-targeted carrier screening panels should include the minimum number of genes but not exceed the maximum number of genes recommended by professional guidelines from the American College of Obstetricians and Gynecologists (ACOG; 2-22 conditions) or the American College of Medical Genetics and Genomics (ACMG; 113 genes). In 2021, the ACMG recommended that the phrase "expanded carrier screening" be replaced by "carrier screening" as expanded carrier screening is not well or precisely defined by professional organizations. Previously, ACMG defined expanded panels as those that use next-generation sequencing to screen for variants in many genes, as opposed to gene-by-gene screening (eg, ethnic-specific screening or panethnic testing for cystic fibrosis). The ACMG consensus group specified gene recommendations which include testing for 97 autosomal recessive genes and 16 X-linked genes, all of which associate with disorders of moderate, severe, or profound severity and are of 1/200 or greater carrier frequency. Non-targeted carrier screening panels that test for genes beyond this provide diminishingly small results, and pleiotropy, locus heterogeneity, variant interpretation, and poor genotype-phenotype correlation may disproportionately impact the ability to provide accurate prognostic information. (BCBSA 2.04.107 Carrier Screening for Genetic Diseases) Carrier screening should only be performed in adults.
Chromosomal Microarray Analysis (CMA) (Also referred to as genomic hybridization (CGH) or array comparative genomic hybridization (aCGH).)	Chromosome microarray (CMA) analysis **meets the definition of medical necessity** as an alternative to karyotyping in members who are undergoing invasive diagnostic prenatal (fetal) testing, [1]Chromosomal microarray analysis of fetal tissue **meets the definition of medical necessity** for the evaluation of pregnancy loss in cases of pregnancy loss at 20 weeks of gestation or earlier when there is a maternal history of

[1](Anora™ miscarriage test, CombiSNP™ Array for Pregnancy Loss, and CombiBAC™ Array)	recurrent miscarriage (defined as a history of 2 or more failed pregnancies); or in all cases of pregnancy loss after 20 weeks of gestation. Chromosomal microarray analysis of fetal tissue in cases of miscarriage or intrauterine fetal demise is considered **experimental or investigational** in all other situations. There is insufficient clinical evidence to permit conclusions on net health outcomes. The use of next generation sequencing in the setting of invasive prenatal testing is considered **experimental or investigational**. There is a lack of clinical data to permit conclusions on efficacy and net health outcomes.
Chromosome 22q11.2 Deletion Syndrome	Genetic testing for chromosome 22q11.2 deletion syndrome **meets the definition of medical necessity** in an at-risk fetus based on ultrasound findings or family history.
Cystic Fibrosis (CF)	Genetic carrier testing for cystic fibrosis **meets the definition of medical necessity** for **ONE** of the following: • Individuals with a positive family history of CF • Either parent has a diagnosis of CF • Fetal echogenic bowel has been identified on ultrasound • Couples currently planning a pregnancy or seeking prenatal testing.

Duchenne Muscular Dystrophy (DMD) and Becker Muscular Dystrophy (BMD)	Genetic testing for DMD gene variants **meets the definition of medical necessity** for the following conditions:
	• In a male with signs and symptoms of a dystrophinopathy in order to confirm the diagnosis and direct treatment.
	• For at-risk female* relatives:
	  ○ To confirm or exclude the need for cardiac surveillance
	  ○ For preconception testing to determine the likelihood of an affected offspring in a woman considering a pregnancy.
	• For at-risk male** offspring to confirm or exclude the need for medical and cardiac surveillance.

	*(At-risk female: first- and second-degree female relatives and include the proband's mother, female siblings of the proband, female offspring of the proband, the proband's maternal grandmother, maternal aunts, and their offspring). **(At-risk male: an asymptomatic male offspring of a female carrier or an asymptomatic male sibling of a patient with a DMD-associated dystrophinopathy). Genetic testing for DMD gene variants is considered **experimental or investigational** in all other situations. There is a lack of clinical data to permit conclusions on health outcomes.
FMR1 Variants (Including Fragile X Syndrome)	See below.
Gaucher Disease	Genetic testing for Gaucher Disease **meets the definition of medical necessity** for **ONE** of the following: • There is an affected family member who has an identified GBA mutation or Gaucher disease • Either parents or a previously affected sibling have an identified GBA mutation or Gaucher disease.
Huntington's Chorea	Genetic testing for Huntington's chorea **meets the definition of medical necessity** when there is a confirmed diagnosis of Huntington's chorea in the family.
Myotonic Dystrophy	Genetic testing for myotonic dystrophy (Types 1 or 2) **meets the definition of medical necessity** for **ONE** of the following: • At least one parent has a confirmed diagnosis of myotonic dystrophy • At least one parent has been diagnosed as a presymptomatic carrier of myotonic dystrophy.
Prader-Willi Syndrome	Genetic testing for Prader-Willi Syndrome **meets the definition of medical necessity** when **ONE** of the following: • Previous child diagnosed with Prader-Willi Syndrome • Cytogenic deletion is suspected on chorionic villus sampling (CVS) or amniocentesis.

Single-Gene Disorders	Invasive diagnostic prenatal (fetal) testing for molecular analysis for single-gene disorders **meets the definition of medical necessity** when a pregnancy has been identified as being at high risk for: 1. Autosomal dominant conditions, at least 1 of the parents has a known pathogenic variant. 2. Autosomal recessive conditions: • Both parents are suspected to be carriers or are known to be carriers, **OR** • One parent is clinically affected and the other parent is suspected to be or is a known carrier. 3. X-linked conditions: A parent is suspected to be or is a known carrier. **AND ALL** of the following are met: • The natural history of the disease is well understood, and there is a reasonable likelihood that the disease is one with high morbidity in the homozygous or compound heterozygous state • Any variants have a high penetrance • The genetic test has adequate sensitivity and specificity to guide clinical decision making and residual risk is understood, **AND** • An association of the marker with the disorder has been established. Invasive diagnostic prenatal (fetal) testing for molecular analysis for single-gene disorders is considered **experimental or investigational** if the above criteria are not met. There is insufficient clinical evidence to permit conclusions on net health outcomes.
Tuberous Sclerosis	Genetic testing for Tuberous Sclerosis **meets the definition of medical necessity** for **ONE** of the following: • Family history of Tuberous Sclerosis • A specific mutation in the TSC1 and TSC2 gene has been identified in an affected family member.
Whole Exome Sequencing **Whole Genome Sequencing**	Prenatal diagnosis, screening, or preimplantation testing of an embryo using whole exome or whole genome sequencing is considered **experimental or investigational**.

	There is insufficient clinical evidence to permit conclusions on net health outcomes.

Genetic testing for screening the general population, other than conditions noted above, is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes.

Genetic testing of children to predict adult-onset diseases **does not meet the definition of medical necessity** unless test results will guide current decisions concerning prevention and this benefit would be lost by waiting until the child has reached adulthood.

NEWBORN SCREENING

See U.S. Preventive Services Task Force (USPSTF) Recommendations at uspreventiveservicestaskforce.org.

POSTNATAL AND OTHER GENETIC TESTS

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.

To be considered genetic testing (vs. genetic screening) for indications other than to establish a diagnosis of inheritable disease, **ALL** of the following criteria must be met:

Diagnostic results from conventional testing and physical examination are inconclusive; **AND**

Results of molecular diagnostic testing are necessary to guide treatment decisions.

The following test list includes, but is not limited to, specific indications for testing that may **meet the definition of medical necessity** and those for which testing is considered **experimental or investigational**.

TEST	CRITERIA
Cytogenetically Normal Acute Myeloid Leukemia	Genetic testing for FLT3 internal tandem duplication (FLT3-ITD), NPM1, and CEBPA variants **meets the definition of medical necessity** in cytogenetically normal acute myeloid leukemia when testing will be used to guide management decisions in members who would receive treatment other than low-dose chemotherapy or best supportive care. Genetic testing for FLT3 internal tandem duplication (FLT3-ITD), NPM1, and CEBPA variants is considered **experimental or investigational** in all other situations. The

	evidence is insufficient to determine the effects of the technology on health outcomes. Genetic testing for FLT3 tyrosine kinase domain variants is considered **experimental or investigational** for all indications. The evidence is insufficient to determine the effects of the technology on health outcomes. Genetic testing for FLT3, NPM1, and CEBPA variants to detect minimal residual disease is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes.
Alzheimer Disease **Note:** Genetic testing for Alzheimer disease may be offered along with analysis of cerebral spinal fluid levels of the tau protein and amyloid-b peptide 1-42 (see MCG 05-86000-22). This group of tests may be collectively referred to as the Admark™ Profile, offered by Athena Diagnostics. Quest AD-Detect® Apolipoprotein E (APOE) (CPT code 82542)	Targeted genetic testing for a known familial variant in the presenilin genes (PSEN) or amyloid-beta precursor protein (APP) gene associated with autosomal dominant early-onset Alzheimer disease **meets the definition of medical necessity** in an asymptomatic member to determine future risk of disease when the following criteria are met: • The member has a close relative (ie, first- or second-degree relative) with a known familial variant associated with autosomal dominant early-onset Alzheimer disease **AND** • Results of testing will inform reproductive decision making. Genetic testing for variants in presenilin genes (PSEN) or amyloid-beta precursor protein (APP) gene associated with autosomal dominant early-onset Alzheimer disease **meets the definition of medical necessity** in an asymptomatic member to determine future risk of disease when the following criteria are met: • The member has a family history of dementia consistent with autosomal dominant Alzheimer disease for whom the genetic status of the affected family members is unavailable AND • Results of testing will inform reproductive decision making. Genetic testing for the apolipoprotein E (APOE) gene to guide initiation or management of a U.S. Food and Drug Administration-approved amyloid-beta targeting therapy **meets the definition of medical necessity** in members with

	mild cognitive impairment or mild dementia associated with Alzheimer disease. Genetic testing for the risk assessment of Alzheimer disease in asymptomatic members is considered **experimental or investigational** in all other situations. Genetic testing includes, but is not limited to, testing for the apolipoprotein E epsilon 4 allele (APOE ε4) or triggering receptor expressed on myeloid cells 2 (TREM2). There is insufficient clinical evidence to permit conclusions on health outcomes.
Assessment of Measurable Residual Disease (MRD)	Next-generation sequencing (eg. clonoSEQ) to detect MRD at a threshold of 10^{-4} as an alternative test in members with acute lymphoblastic leukemia or chronic lymphocytic leukemia **meets the definition of medical necessity**. Next-generation sequencing (eg. clonoSEQ) to detect MRD at a threshold of *less* than 10^{-4} in members with acute lymphoblastic leukemia or chronic lymphocytic leukemia is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes. Next-generation sequencing (eg. clonoSEQ) to detect MRD at a threshold of 10^{-5} as an alternative test in members with multiple myeloma **meets the definition of medical necessity**. Next-generation sequencing (eg. clonoSEQ) to detect MRD at a threshold of less than 10^{-5} in members with multiple myeloma is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes. Next-generation sequencing to detect MRD in members with diffuse large B-cell lymphoma or mantle cell lymphoma is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes. Next-generation sequencing to detect MRD in all other situations is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes.

A-Thalassemia	Preconception (carrier) testing for α-thalassemia in prospective parents **meets the definition of medical necessity** when both parents have evidence of possible α-thalassemia (including α-thalassemia minor, hemoglobin H disease [α-thalassemia intermedia], or α-thalassemia minima [silent carrier]) based on biochemical testing. Genetic testing to confirm a diagnosis of α-thalassemia **does not meet the definition of medical necessity**. The diagnosis of α-thalassemia can be made without genetic testing. Genetic testing of members with hemoglobin H disease (α-thalassemia intermedia) to determine prognosis is considered **experimental or investigational**. There is insufficient clinical evidence to permit conclusions on health outcomes. Genetic testing for α-thalassemia in other clinical situations is considered **experimental or investigational**. There is insufficient clinical evidence to permit conclusions on health outcomes. (Prenatal testing is not addressed in the position statements above.)
Biallelic RPE65 Inherited Retinal Dystrophies	Genetic testing to detect the presence of pathogenic variants in the RPE65 gene **meets the definition of medical necessity** to establish a diagnosis of inherited retinal dystrophy.
CADASIL Syndrome	Genetic testing for a NOTCH3 variant to confirm the diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) syndrome in a member **meets the definition of medical necessity** under the following conditions: • Clinical signs, symptoms, and imaging results are consistent with CADASIL, indicating that the pretest probability of CADSIL is at least in the moderate-to-high range (score of 14 or greater*); **AND** • The diagnosis of CADASIL is inconclusive following alternative methods of testing, including magnetic resonance imaging.

For individuals who are asymptomatic with a family member with a diagnosis of CADASIL syndrome:

- If there is a family member (first- and second-degree relative) with a known variant, targeted genetic testing of the known NOTCH3 familial variant **meets the definition of medical necessity.**
- If the family member's genetic status is unknown, genetic testing of NOTCH3 **meets the definition of medical necessity.**

Genetic testing for a NOTCH3 variant to confirm the diagnosis of CADASIL syndrome in all other situations is considered **experimental or investigational**. There is insufficient clinical evidence to permit conclusions on health outcomes.

***Screening Tool to Select Patients for NOTCH3 Gene:**

Features	No. With NOTCH3 Variant	Percent With NOTCH3 Variant	Points
Clinical:			
Migraine	239/463	52%	1
Migraine with aura	65/85	76%	3
Transient ischemic attack/stroke	380/526	72%	1 (2 if <50 y)
Psychiatric disturbance	106/380	28%	1
Cognitive decline	188/434	43%	3
Radiologic:			
LE	277/277	100%	3
LE extended to temporal pole	174/235	74%	1
LE extended to external capsule	228/303	75%	5
Subcortical infarcts	210/254	83%	2

Cardiovascular Disease or Aneurysm (9p21-EarlyMICheck™ Genotype Test, deCODE MI™)	The use of genotyping for 9p21 single nucleotide polymorphisms is considered **experimental or investigational**, including but not limited to, identification of members who may be at increased risk of cardiovascular disease or its manifestations (e.g., MI, ischemic stroke, peripheral arterial disease, coronary artery calcification), or identification of members who may be at increased risk for aneurysmal disease (abdominal aortic aneurysms, intracranial aneurysms, polypoidal choroidal vasculopathy). There is insufficient evidence regarding the clinical utility of this testing to permit conclusions on health outcomes.
Cardiovascular Risk and/or Effectiveness of Statin Therapy (Cardio IQ™ KIF6 Genotype, KIF6 StatinCheck™ Genotype)	KIF6 Genotyping is considered **experimental or investigational** for predicting cardiovascular risk and/or the effectiveness of statin therapy. There is insufficient evidence on the clinical validity of the testing to permit conclusions on health outcomes.
Celiac Disease (HLA Typing; PROMETHEUS® Celiac PLUS)	HLA-DQ2 and HLA-DQ8 testing **meets the definition of medical necessity** to rule out celiac disease in individuals with discordant serologic and histologic (biopsy) findings or individuals with persistent symptoms despite negative serology and histology. HLA-DQ2 and HLA-DQ8 testing for celiac disease is considered **experimental or investigational** in all other situations. There is insufficient clinical evidence to permit conclusions on net health outcomes.
Chromosomal Microarray Analysis (CMA) (Also referred to as genomic hybridization (CGH) or array comparative genomic hybridization (aCGH).) (Affymetrix CytoScan® Dx; FirstStepDx PLUS; Reveal® SNP Microarray Pediatric)	Chromosomal microarray analysis **meets the definition of medical necessity** as first line testing in the initial postnatal evaluation of members with any of the following: • Apparent nonsyndromic developmental delay/intellectual disability • Autism spectrum disorder **OR** • Multiple congenital anomalies not specific to a well-delineated genetic syndrome. Chromosomal microarray analysis is considered **experimental or investigational** for the evaluation of all other conditions of delayed development, including but not limited to idiopathic growth or language delay. The

	evidence is insufficient to determine the effects of the technology on health outcomes. Panel testing using next-generation sequencing (NGS) is considered **experimental or investigational** in all cases of suspected genetic abnormality in children with developmental delay/intellectual disability, autism spectrum disorder or congenital anomalies. The evidence is insufficient to permit conclusions whether NGS panel testing improves outcomes.
Cardiac Ion Channelopathies [Includes QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada syndrome (BrS), and short QT syndrome (SQTS)] (FAMILION® Test)	**Long QT Syndrome (LQTS)** Genetic testing to confirm a diagnosis of congenital LQTS **meets the definition of medical necessity** when signs and/or symptoms of LQTS are present but a definitive diagnosis cannot be made without genetic testing. This includes: • Members who do not meet the clinical criteria for LQTS (i.e., those with a Schwartz score less than 4), but who have a moderate-to-high pretest probability based on the Schwartz score and/or clinical criteria. Note: Determining the pretest probability of LQTS is not standardized. An example of a member with a moderate-to-high pretest probability of LQTS is a member with a Schwartz score of 2 – 3. Refer to Diagnostic Scoring System* for LQTS below. Genetic testing of asymptomatic members to determine future risk of LQTS **meets the definition of medical necessity** when at least one of the following criteria is met: • A close relative (ie, first-, second-, or third-degree relative) with a known LQTS mutation; **OR** • A close relative diagnosed with LQTS by clinical means whose genetic status is unavailable. Genetic testing for LQTS for all other situations not meeting criteria above, including but not limited to determining prognosis and/or directing therapy in members with known LQTS is considered **experimental or investigational**. There is insufficient clinical evidence to permit conclusions on net health outcomes.

	Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) Genetic testing to confirm a diagnosis of CPVT **meets the definition of medical necessity** when signs and/or symptoms of CPVT are present, but a definitive diagnosis cannot be made without genetic testing. Genetic testing of asymptomatic members to determine future risk of CPVT **meets the definition of medical necessity** when at least one of the following criteria is met: • A close relative (ie, first-, second-, or third-degree relative) with a known CPVT mutation; **OR** • A close relative diagnosed with CPVT by clinical means whose genetic status is unavailable. Genetic testing for CPVT for all other situations not meeting the criteria above is considered **experimental or investigational**. There is insufficient clinical evidence to permit conclusions on net health outcomes. **Brugada Syndrome (BrS)** Genetic testing to confirm a diagnosis of BrS **meets the definition of medical necessity** when signs and/or symptoms consistent with BrS are present but a definitive diagnosis cannot be made without genetic testing. Genetic testing of asymptomatic members to determine future risk of BrS **meets the definition of medical necessity** when members have a close relative (ie, first-, second-, or third-degree relative) with a known BrS mutation. Genetic testing for BrS for all other situations not meeting the criteria above is considered **experimental or investigational**. There is insufficient clinical evidence to permit conclusions on net health outcomes. **Short QT Syndrome (SQTS)** Genetic testing of asymptomatic members to determine future risk of SQTS **meets the definition of medical necessity** when members have a close relative (ie, first-, second-, or third-degree relative) with a known SQTS mutation. Genetic testing for SQTS for all other situations not meeting the criteria above is considered **experimental or**

	investigational. There is insufficient clinical evidence to permit conclusions on net health outcomes. **NOTE**: First-degree relatives: children, brothers, sisters and parents. Second-degree relatives: grandparents, aunts, uncles, nieces, nephews, half-siblings, and grandchildren. Third-degree relatives: great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins.
CHARGE Syndrome	Genetic testing for CHARGE syndrome **meets the definition of medical necessity** to confirm a diagnosis in a member with signs/symptoms of CHARGE syndrome when a definitive diagnosis cannot be made with clinical criteria. Genetic testing for CHARGE syndrome is considered **experimental or investigational** in all other situations. The evidence is insufficient to determine the effects of the technology on health outcomes.
Evaluation of Stable Ischemic Heart Disease	Gene expression testing in the evaluation of members with stable ischemic heart disease is considered **experimental or investigational** for all indications, including but not limited to prediction of coronary artery disease in stable, nondiabetic members. There is a lack of clinical data to permit conclusions on net health outcomes.
Cutaneous Malignant Melanoma (Melaris®)	Genetic testing for genes associated with familial cutaneous malignant melanoma or associated with susceptibility to cutaneous malignant melanoma is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes.
Cytochrome P450 Genotype-Guided Treatment Strategy	CYP2D6 genotyping to determine drug metabolizer status **meets the definition of medical necessity** for members with: • Gaucher disease being considered for treatment with eliglustat; **OR** • Huntington disease being considered for treatment with tetrabenazine in a dosage greater than 50 mg per day. CYP2C9 genotyping to determine drug metabolizer status **meets the definition of medical necessity** for members

	with relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, being considered for treatment with Siponimod. CYP450 genotyping for the purpose of aiding in the choice of drug or dose to increase efficacy and/or avoid toxicity for the following drugs is considered **experimental or investigational** (If a separate position statement exists, then criteria for medical necessity in that position statement supersedes this statement): • selection or dosage of codeine • dosing of efavirenz and other antiretroviral therapies for HIV infection • dosing of immunosuppressants for organ transplantation • selection or dosing of β-blockers (eg, metoprolol) • dosing and management of antitubercular medications. The evidence is insufficient to determine the effects of the technology on health outcomes. CYP450 genotyping for the purpose of aiding in the choice of clopidogrel vs alternative antiplatelet agents, or in decisions on the optimal dosing for clopidogrel, is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes. The use of genetic testing panels that include multiple CYP450 variants is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes.
Dilated Cardiomyopathy	Comprehensive genetic testing for members with signs or symptoms of dilated cardiomyopathy (ie, heart failure or arrhythmias, frequently presenting as dyspnea on exertion and peripheral edema) which is considered idiopathic after a negative workup for secondary causes **meets the definition of medical necessity**. Targeted genetic testing for asymptomatic members with a first-degree relative* who has dilated cardiomyopathy and

	a known familial variant **meets the definition of medical necessity**. *First-degree relative- child, brother, sister, parent. Genetic testing for dilated cardiomyopathy is considered **experimental or investigational** in all other situations. The evidence is insufficient to determine the effects of the technology on health outcomes.
Duchenne and Becker Muscular Dystrophy	Genetic testing for DMD gene **meets the definition of medical necessity** for the following conditions: • In a male with signs and symptoms of a dystrophinopathy in order to confirm the diagnosis and direct treatment. • For at-risk female relatives (first- and second-degree female relatives and include the proband's mother, female siblings of the proband, female offspring of the proband, the proband's maternal grandmother, maternal aunts, and their offspring): o To confirm or exclude the need for cardiac surveillance o For preconception testing to determine the likelihood of an affected offspring in a woman considering a pregnancy. • For at-risk male offspring (asymptomatic male offspring of a female carrier or an asymptomatic male sibling of a member with a DMD-associated dystrophinopathy) to confirm or exclude the need for medical and cardiac surveillance. Genetic testing for DMD gene variants is considered **experimental or investigational** in all other postnatal situations. There is a lack of clinical data to permit conclusions on health outcomes.
FMR1 Variants (Including Fragile X Syndrome)	Genetic testing for FMR1 variants **meets the definition of medical necessity** for the following member populations: Members who have a personal or family history of fragile X syndrome who are seeking reproductive counseling, including: • Prenatal testing of fetuses of known carrier mothers;

	• Affected members or relatives of affected members who have had a positive cytogenetic fragile X test result who are seeking information on carrier status; • Members who have a family history of fragile X syndrome or a family history of undiagnosed intellectual disability. Members with characteristics of fragile X syndrome or a fragile X–associated disorder, including: • Member with intellectual disability, developmental delay, or autism spectrum disorder; • Members with neurologic symptoms consistent with fragile X-associated tremor or ataxia syndrome; • Women with primary ovarian insufficiency under the age of 40 in whom fragile X-associated primary ovarian insufficiency is suspected. Genetic testing for FMR1 variants is considered **experimental or investigational** for all other uses. The evidence is insufficient to determine the effects of the technology on health outcomes.
Hereditary Pancreatitis	Genetic testing for hereditary pancreatitis **meets the definition of medical necessity** for members aged 18 years and younger with unexplained acute recurrent (greater than 1 episode) or chronic pancreatitis with documented elevated amylase or lipase levels. Genetic testing for hereditary pancreatitis is considered **experimental or investigational** in all other situations. The evidence is insufficient to determine the effects of the technology on health outcomes.
Germline Variants of the RET Proto-Oncogene in Medullary Carcinoma of the Thyroid	Genetic testing for RET proto-oncogene point variants **meets the definition of medical necessity** for the following indications: • Asymptomatic members of families with defined RET gene variants • Members of families known to be affected by inherited medullary thyroid cancer, but not previously evaluated for RET variants • Members with sporadic medullary thyroid cancer.

	Genetic testing for RET proto-oncogene point variants is considered **experimental or investigational**, as there is insufficient clinical evidence to support the use of genetic testing for screening the general population. There is a lack of clinical data to permit conclusions on efficacy and net health outcomes.
Mental Health Conditions (GeneSightRX®, PROOVE Drug Metabolism Profile, PHARMAchip, SureGene, MD Tox Expanded Comprehensive Profile; MD Tox Psychiatry & Risk Factors Profile; Idgenetix panels.)	Genetic testing for diagnosis and management of mental health disorders is considered **experimental or investigational** in all situations, including but not limited to: • To confirm a diagnosis of a mental health disorder in an individual with symptoms. • To predict future risk of a mental health disorder in an asymptomatic individual. • To inform the selection or dose of medications used to treat mental health disorders, including but not limited to the following medications: ○ selective serotonin reuptake inhibitors ○ selective norepinephrine reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors ○ tricyclic antidepressants ○ antipsychotic drugs. The evidence is insufficient to determine the effects of the technology on health outcomes. Genetic testing panels for mental health disorders, including but not limited to the Genecept Assay, STA^{2}R test, the GeneSight Psychotropic panel, the Proove Opioid Risk assay, and the Mental Health DNA Insight panel, are considered **experimental or investigational** for all indications. The evidence is insufficient to determine the effects of the technology on health outcomes.
Helicobacter pylori (H. pylori) Treatment (AmHPR H. pylori AB Resistance NGS Panel)	Genotyping to determine cytochrome p450 (CYP2C19) genetic polymorphisms is considered **experimental or investigational** for the purpose of managing the treatment of H. pylori infection. The evidence is insufficient to determine the effects of the technology on health outcomes.

Hereditary Cardiomyopathies	Genetic testing for predisposition to hypertrophic cardiomyopathy (HCM) **meets the definition of medical necessity** for individuals who are at risk for development of HCM, defined as having a first-degree relative with established HCM, when there is a known pathogenic gene variant present in that affected relative. Genetic testing for predisposition to HCM **does not meet the definition of medical necessity** for members with a family history of HCM in which a first-degree relative with established HCM has tested negative for pathogenic variants. Genetic testing for predisposition to HCM is considered **experimental or investigational** for all other member populations, including but not limited to individuals who have a first-degree relative with clinical HCM, but in whom genetic testing is unavailable. The evidence is insufficient to determine the effects of the technology on health outcomes. * (**First-degree relatives**: children, brothers, sisters and parents.) Genetic testing to determine the diagnosis or management of all other hereditary cardiomyopathies, including but not limited to, arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C), restrictive, and left ventricular noncompaction cardiomyopathies, is considered **experimental or investigational**. There is a lack of clinical data to permit conclusions on net health outcomes.
Inherited Peripheral Neuropathy	Genetic testing **meets the definition of medical necessity** when the diagnosis of an inherited peripheral motor or sensory neuropathy is suspected due to signs and/or symptoms but a definitive diagnosis cannot be made without genetic testing. Genetic testing for an inherited peripheral neuropathy is considered **experimental or investigational** for all other indications. The evidence is insufficient to determine the effects of the technology on health outcomes.
Inflammatory Bowel Disease	Determination of anti-neutrophil cytoplasmic antibody (ANCA), anti-Saccharomyces cerevisiae antibody (ASCA),

(Prometheus© IBD sgi Diagnostic™; Prometheus© Crohn's Prognostic; Prometheus© IBD Serology 7)	OmpC antibodies, and I2 antibodies is considered **experimental or investigational.** The evidence is insufficient to determine the effects of the technology on health outcomes.
Lactase Insufficiency (LactoType®)	The use of targeted MCM6 -13910C>T variant analysis for the prediction of lactase insufficiency is considered **experimental or investigational**. There is insufficient evidence that the testing would affect medical management or improve clinical outcomes.
Lipoprotein(a) Variant(s) as a Decision Aid for Aspirin Treatment (LPA-Aspirin Genetype)	The use of genetic testing for the LPArs3798220 allele (LPA-Aspirin Genotype) is considered **experimental or investigational** in members who are being considered for treatment with aspirin to reduce risk of cardiovascular events. There is insufficient evidence to permit conclusions on how this testing would change medical management and improve health outcomes.
Macular Degeneration (Macula Risk®; Macula Risk®PGx; RetnaGene™, Vita Risk®)	Genetic testing for macular degeneration is considered **experimental or investigational** for all indications. The evidence is insufficient to determine the effects of the technology on health outcomes.
Neurofibromatosis (NF)	Genetic testing for neurofibromatosis (NF1 or NF2) variants **meets the definition of medical necessity** when a diagnosis of neurofibromatosis is clinically suspected due to signs of disease, but a definitive diagnosis cannot be made without genetic testing. Genetic testing for neurofibromatosis (NF1 or NF2) variants in at-risk relatives with no signs of disease **meets the definition of medical necessity** when a definitive diagnosis cannot be made without genetic testing **AND** at least one of the following criteria is met: • A close relative (ie, first-, second-, or third-degree relative) has a known NF1 or NF2 variant; **or** • A close relative has been diagnosed with neurofibromatosis but whose genetic status is unavailable. Genetic testing for neurofibromatosis for all other situations not meeting the criteria outlined above is considered **experimental or investigational**. The evidence

	is insufficient to determine the effects of the technology on health outcomes.
Nonfamilial Breast Cancer (City of Hope Breast Cancer Susceptibility Assay, deCODE BreastCancer™, & deCODEme Complete Scan,)	Testing for one or more single nucleotide variants to predict an individual's risk of breast cancer is considered **experimental or investigational**. The GeneType® breast cancer risk test (previously known as BREVAGenplus) is considered **experimental or investigational** for all indications, including but not limited to use as a method of estimating individual member risk for developing breast cancer. The evidence is insufficient to determine the effects of the technology on health outcomes.
Molecular Testing for Germline Variants Associated with Ovarian Cancer	Testing for germline BRIP1, RAD51C, and RAD51D variants for ovarian cancer risk assessment in adults **meets the definition of medical necessity** when the following criteria are met (1 or 2): 1. The member has a diagnosis of epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer; AND • The member has not previously been tested for these gene variants; AND • The member is thought to be the most informative member of a family (proband) to have genetic testing; AND • The member has closely related (1st- or 2nd-degree*) relatives who are considering genetic testing for these gene variants to inform prophylactic decision-making or who have test results that cannot be fully interpreted without testing an affected relative. 2. The member has not been diagnosed with epithelial ovarian cancer; **AND** • The member has a blood relative* with a known pathogenic/likely pathogenic germline BRIP1, RAD51C, or RAD51D variant; **OR** • The member has a 1st- or 2nd-degree relative* diagnosed with ovarian cancer. Testing for BRIP1, RAD51C, and RAD51D variants for ovarian cancer risk assessment in adults who do not meet

	the criteria above is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes. Testing for germline NBN variants for ovarian cancer risk assessment is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes. Testing for germline BRIP1, RAD51C, RAD51D, and NBN variants in members diagnosed with epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer to guide treatment is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes. *(For familial assessment, 1st- and 2nd-degree relatives are blood relatives on the same side of the family (maternal or paternal): 1st-degree relatives: parents, siblings, and children 2nd-degree relatives: grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings.)
Pain Management (AvertD™, GeneSight Analgesic; Idgenetix Pain; MD Tox Comprehensive Profile; MD Tox Comprehensive & Risk Factors Profile; MD Tox Pain Profile; Pain Management Panel; PersonaGene Genetic; Proove® Narcotic Risk; Proove® Opioid Risk; Proove® Pain Perception; Pain Medication DNA Insight™; Millennium PGTSM; YouScript®.)	Genetic testing for pain management is considered **experimental or investigational** for all indications. The evidence is insufficient to determine the effects of the technology on health outcomes. Genetic testing for acute pain management to assess the risk of developing opioid use disorder is considered **experimental or investigational** for all indications. The evidence is insufficient to determine the effects of the technology on health outcomes.
Germline Genetic Testing for Gene Variants Associated With Breast Cancer in Individuals at High Breast Cancer Risk	Testing for CHEK2, BARD1, and ATM variants in the assessment of breast cancer risk is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes.
Prostate Cancer	The one-time use of Oncotype DX Prostate Score®, Decipher® tumor-based assays, or Prolaris® Biopsy Test to guide management of prostate cancer **meets the definition**

of medical necessity when all of the following criteria are met:

- Post biopsy and pathological examination shows localized adenocarcinoma of the prostate with no clinical evidence of metastasis or lymph node involvement; **and**
- Prostate cancer risk group* of very-low-risk, low-risk, favorable intermediate-risk, unfavorable intermediate-risk or high-risk prostate cancer; **and**
- Life expectancy greater than 10 years; **and**
- Member has not received treatment for prostate cancer and is a candidate for active surveillance or definitive therapy.

***NCCN Prostate Cancer Risk Groups (NCCN V2.2025)**

<table>
<tr><td>Very low</td><td colspan="3">Has all of the following:
cT1c
Grade Group 1
PSA <10 ng/mL
<3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core
PSA density <0.15 ng/mL/g</td></tr>
<tr><td>Low</td><td colspan="3">Has all of the following but does not qualify for very low risk:
cT1–cT2a
Grade Group 1
PSA <10 ng/mL</td></tr>
<tr><td rowspan="2">Intermediate</td><td rowspan="2">Has all of the following:
No high-risk group features
No very-high-risk
group features
Has one or more intermediate risk factors (IRFs):
cT2b–cT2c
Grade Group 2
or 3
PSA 10–20 ng/mL</td><td>Favorable intermediate</td><td>Has all of the following:
1IRF
Grade Group 1 or 2
<50% biopsy cores positive (eg <6 of 12 cores)</td></tr>
<tr><td>Unfavorable intermediate</td><td>Has one or more of the following:
2 or 3 IRFs
Grade Group 3
• ≥50% biopsy cores positive (eg ≥ 6 of 12 cores)</td></tr>
<tr><td>High</td><td colspan="3">Has one or more high-risk features, but does not meet criteria for very high risk:
cT3–cT4 • Grade Group 4 or Grade Group 5
• PSA >20 ng/mL</td></tr>
<tr><td>Very high</td><td colspan="3">Has at least two of the following:
cT3–cT4 • Grade Group 4 or 5 • PSA >40 ng/mL</td></tr>
</table>

	The use of Decipher® tumor-based assays, Oncotype DX Prostate Score®, or Prolaris® Biopsy Test for all other indications is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes. The use of all other gene expression analysis, protein biomarkers, and multimodal artificial intelligence (e.g. ArteraAI Prostate) to guide management of prostate cancer is considered **experimental or investigational**. The following genetic and protein biomarkers for the diagnosis of prostate cancer are considered **experimental or investigational:** • Autoantibodies ARF 6, NKX3-1, 5'-UTR-BMI1, CEP 164, 3'-UTR-Ropporin, Desmocollin, AURKAIP-1, CSNK2A2 (eg, Apinify®) • Candidate gene panels • Gene hypermethylation testing (e.g., ConfirmMDx®) • HOXC6 and DLX1 testing (e.g., SelectMDx®) • IsoPSA® • Kallikrein markers (e.g.,4Kscore™ Test) • Mitochondrial DNA variant testing (e.g., Prostate Core Mitomics Test™) • PCA3, ERG, and SPDEF RNA expression in exosomes (e.g., ExoDx™ Prostate IntelliScore) • PCA3 testing (e.g. Progensa® PCA3 Assay) • Prostate Health Index (phi) • TMPRSS:ERG fusion genes (e.g., MyProstateScore). The evidence is insufficient to determine the effects of the technology on health outcomes. Single nucleotide variant testing (e.g., 23and me, deCODE) for cancer risk assessment of prostate cancer is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes.

PTEN Hamartoma Tumor Syndrome (PHTS)	Genetic testing for PTEN **meets the definition of medical necessity** to confirm the diagnosis when a member has clinical signs of a PTEN hamartoma tumor syndrome. Targeted genetic testing for a PTEN familial variant **meets the definition of medical necessity** in a first-degree relative of a proband with a known PTEN pathogenic variant. Genetic testing for PTEN is considered **experimental or investigational** for all other indications. The evidence is insufficient to determine the effects of the technology on health outcomes.
Rett Syndrome	Genetic testing for Rett syndrome associated genes (eg, MECP2, FOXG1, or CDKL5) **meets the definition of medical necessity** to confirm a diagnosis of Rett syndrome in a child with developmental delay and signs/symptoms of Rett syndrome when a definitive diagnosis cannot be made without genetic testing. Targeted genetic testing for a known familial Rett syndrome associated variant **meets the definition of medical necessity** to determine carrier status of first-degree female relatives of an individual with Rett syndrome. All other indications for genetic testing for Rett syndrome associated genes, including routine carrier testing (prenatal or preconception) in members with negative family history, and testing of asymptomatic family members to determine future risk of disease, are considered **experimental or investigational**. The evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome.
ScoliScore™	DNA-based prognostic testing for adolescent idiopathic scoliosis is considered **experimental or investigational**. There is insufficient clinical evidence in peer-reviewed literature to permit conclusions on net health outcomes.
Statin-Induced Myopathy (Statin Induced Myopathy (SLCO1B1) Genotype, SLCO1B1 Variants)	Genetic testing for the presence of variants in the SLCO1B1 gene to identify members at risk of statin-induced myopathy is considered **experimental or investigational**. There is insufficient clinical evidence to permit conclusions on health outcomes.

Tamoxifen Treatment	Genotyping to determine cytochrome p450 (CYP2D6) genetic variants is considered **experimental or investigational** for the purpose of managing treatment with tamoxifen for members at high risk for or with breast cancer. The evidence is insufficient to determine the effects of the technology on health outcomes.
Warfarin Dosing (eQ-PCR™ LightCycle; eSensor® Warfarin Plus; eSensor® Warfarin Sensitivity; INFINITI 2C9-VKORC1 Multiplex Assay; Rapid Genotyping Assay; Verigence Warfarin Metabolism Nucleic Acid Test®)	Genotyping to determine cytochrome p450 2C9 (CYP2C9), P450 4F2 (CYP4F2), and vitamin K epoxide reductase subunit C1 (VKORC1) genetic variants is considered **experimental or investigational** for the purpose of managing the administration and dosing of warfarin, including use in guiding the initial warfarin dose to decrease time to stable INR and reduce the risk of serious bleeding. The evidence is insufficient to determine the effects of the technology on health outcomes.
Whole Exome Sequencing **Whole Genome Sequencing** (ExaCT-1, ExomeNext, ExomeNext-Rapid, TruGenome tests, XomeDx)	Standard whole exome sequencing, with trio testing (testing of child and both parents) when possible, **meets the definition of medical necessity** for the evaluation of unexplained congenital or neurodevelopmental disorder in children when **ALL** of the following criteria are met: • The member has been evaluated by a clinician with expertise in clinical genetics, including at minimum a family history and phenotype description, and counseled about the potential risks of genetic testing • There is potential for a change in management and clinical outcome for the member being tested • A genetic etiology is considered the most likely explanation for the phenotype despite previous genetic testing (eg, chromosomal microarray analysis and/or targeted single-gene testing), **OR** when previous genetic testing has failed to yield a diagnosis and the affected member is faced with invasive procedures or testing as the next diagnostic step (eg, muscle biopsy). Rapid whole exome sequencing or rapid whole genome sequencing, with trio testing when possible, **meets the definition of medical necessity** for the evaluation of critically ill infants in neonatal or pediatric intensive care

	with a suspected genetic disorder of unknown etiology when **both (1 & 2)** of the following criteria are met: 1. **At least one** of the following criteria is met: a. Multiple congenital anomalies (e.g. persistent seizures, abnormal ECG, hypotonia); b. An abnormal laboratory test or clinical features suggests a genetic disease or complex metabolic phenotype (e.g, abnormal newborn screen, hyperammonemia, lactic acidosis not due to poor perfusion); **or** c. An abnormal response to standard therapy for a major underlying condition. 2. **None** of the following criteria apply regarding the reason for admission to intensive care: a. An infection with normal response to therapy; b. Isolated prematurity; c. Isolated unconjugated hyperbilirubinemia; d. Hypoxic Ischemic Encephalopathy; e. Confirmed genetic diagnosis explains illness; f. Isolated Transient Neonatal Tachypnea; g. Nonviable neonates. Whole exome sequencing is considered **experimental or investigational** for the diagnosis of genetic disorders in all other situations. The evidence is insufficient to determine the effects of the technology on health outcomes. Whole genome sequencing is considered **experimental or investigational** for the diagnosis of genetic disorders in all other situations. The evidence is insufficient to determine the effects of the technology on health outcomes. Repeat whole exome sequencing for the diagnosis of genetic disorders, including re-analysis of previous test results, is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes. Whole exome sequencing and whole genome sequencing are considered **experimental or investigational** for screening for genetic disorders. The evidence is insufficient

	to determine the effects of the technology on health outcomes.
X Chromosome Abnormality Test (XCAT) for Turner Syndrome (XCAT-TS)	The use of the XCAT-TS test to detect Classic and Mosaic Turner Syndrome is considered **experimental or investigational** as there is insufficient clinical evidence in peer-reviewed literature to permit conclusions the test is as beneficial as the established alternatives and on net health outcomes

*Diagnostic Scoring System for LQTS

Criteria	Points
Electrocardiographic findings	
* QTc >480 msec	3
* QTc 460-470 msec	2
* QTc <450 msec	1
History of torsades de pointes	2
T-wave alternans	1
Notched T-waves in three leads	1
Low heart rate for age	0.5
Clinical history	
* Syncope brought on by stress	2
* Syncope without stress	1
* Congenital deafness	0.5
Family history	
* Family members with definite LQTS	1
* Unexplained sudden death in immediate family members younger than 30 years of age	0.5

Genetic Counseling: Genetic counseling is covered in accordance to the member's contract benefits for medical counseling. Pre and post genetic counseling **meets the definition of medical necessity** as an adjunct to the genetic test(s).

Genetic testing for screening the general population, other than conditions noted above, is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes.

Home testing (including self-testing home kits) is considered **experimental or investigational** as the clinical validity of the tests have not been established. The evidence is insufficient to determine the effects of the technology on health outcomes.

The following tests are considered **experimental or investigational**, as there is insufficient evidence to support the use of these tests for all indications. Although there are ongoing clinical studies the current data are inadequate to permit scientific conclusions on net health outcomes:

BRCAplus®

BreastNext™

+RNAinsight for BreastNext

BreastSentry

BROCA Cancer Risk Panel

CancerNext® xG, CancerNext-Expanded® xG+, +RNAinsight®

CardioPredict™

ColoNext™

+RNAinsight for ColoNext

ColoSeq™

Comprehensive Cancer Panel

Counsyl Reliant Cancer Screen

CustomNext®

+RNAinsight for CustomNext

DetoxiGenomic® Profile Test

epiSEEK™

GenArray™

Gene Trails Genotyping Panels

GeneSeq®:Cardio

Genoptix® MDS Molecular Profile

GYNPlus®

+RNAinsight for GYNPlusHCM Sequencing Panel

Heart Cholesterol Balance™

Heart HDL Map™

High/Moderate Risk Panel

MD Tox Cardiac & Risk Factors Profile

Mitochondrial Disorders Panel

MitoMED-Autism™

Monogenic Hypertension Evaluation Panel

MVL Vision Panel

myRisk®

Nemaline Myopathy Panel

nucSEEK™

OneOme RightMed Tests

OvaNext™

+RNAinsight for OvaNext

Pan Cardiomyopathy Panel

PancNext™

Panexia™

Periodic Fever Syndromes Panel

ProstateNext

+RNAinsight for ProstateNext

RenalNext™

TumorNext

X-linked Intellectual Disability Panel.

CYTOGENETIC STUDIES (CHROMOSOMAL STUDIES)

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

Cytogenetic studies **meet the definition of medical necessity** for the diagnosis and treatment of the following conditions (the list is not all-inclusive):

- Genetic disorders (e.g., Down's Syndrome) in a fetus
- Failure of sexual development
- Chronic myelogenous leukemia
- Acute leukemias lymphoid, acute leukemias myeloid
- Acute leukemias unclassified; **or**

- Myelodysplasia.

BILLING/CODING INFORMATION:

Note: Code list may not be all-inclusive.

CPT Coding:

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
81200	ASPA (aspartoacylase) (e.g. Canavan disease) gene analysis, common variants (e.g. E285A, Y231X)
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) (e.g. Maple syrup urine disease) gene analysis, common variants (e.g. R183P, G278S, E422X)
81209	BLM (Bloom syndrome, RecQ helicase-like) (e.g. Bloom syndrome) gene analysis, 2281del6ins7 variant
81218	CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid leukemia), gene analysis, full gene sequence
81220	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g. cystic fibrosis) gene analysis; common variants (e.g. ACMG/ACOG guidelines)
81221	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g. cystic fibrosis) gene analysis; known familial variants
81222	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g. cystic fibrosis) gene analysis; duplication/deletion variants
81223	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g. cystic fibrosis) gene analysis; full gene sequence
81224	CFTR (cystic fibrosis transmembrane conductance regulator) (e.g. cystic fibrosis) gene analysis; intron 8 poly-T analysis (e.g. male infertility)
81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (e.g. drug metabolism), gene analysis, common variants (e.g. *2, *3, *4, *8, *17) **(Investigational)**
81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g. drug metabolism), gene analysis, common variants (e.g. *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)

81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g. drug metabolism), gene analysis, common variants (e.g. *2, *3, *5, *6)
81228	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number variants, comparative genomic hybridization [CGH] microarray analysis
81229	Cytogenomic (genome-wide) analysis for constitutional chromosomal abnormalities; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants, comparative genomic hybridization (CGH) microarray analysis
81230	CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (eg, drug metabolism) gene analysis, common variant(s) (eg, *2, *22) **(Investigational)**
81231	CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (eg, drug metabolism) gene analysis, common variants (eg, *2, *3, *4, *5 *6, *7) **(Investigational)**
81242	FANCC (Fanconi anemia, complementation group C) (e.g. Fanconi anemia, type C) gene analysis, common variant (e.g. 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)
81245	FLT3 (fms-related tyrosine kinase 3) (e.g. acute myeloid leukemia), gene analysis, internal tandem duplication (ITD) variants (ie, exons 14, 15)
81246	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (eg, D835, I836) **(Investigational)**
81250	G6PC (glucose-6-phosphatase, catalytic subunit) (e.g. Glycogen storage disease, Type 1a, von Gierke disease) gene analysis, common variants (e.g. R83C, Q347X)
81251	GBA (glucosidase, beta, acid) (e.g. Gaucher disease) gene analysis, common variants (e.g. N370S, 84GG, L444P, IVS2+1G>A)
81255	HEXA (hexosaminidase A [alpha polypeptide]) (e.g. Tay-Sachs disease) gene analysis, common variants (e.g. 1278insTATC, 1421+1G>C, G269S)
81256	HFE (hemochromatosis) (e.g. hereditary hemochromatosis) gene analysis, common variants (e.g. C282Y, H63D)
81257	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g. alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for common deletions or variant (e.g. Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, 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) (e.g. familial dysautonomia) gene analysis, common variants (e.g. 2507+6T>C, R696P)

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
81277	Cytogenomic neoplasia (genome-wide) microarray analysis, interrogation of genomic regions for copy number and loss-of-heterozygosity variants for chromosomal abnormalities
81290	MCOLN1 (mucolipin 1) (e.g. Mucolipidosis, type IV) gene analysis, common variants (e.g. IVS3-2A>G, del6.4kb)
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (e.g. hereditary hypercoagulability) gene analysis, common variants (e.g. 677T, 1298C) **(Investigational)**
81302	MECP2 (methyl CpG binding protein 2) (e.g. Rett syndrome) gene analysis; full sequence analysis
81303	MECP2 (methyl CpG binding protein 2) (e.g. Rett syndrome) gene analysis; known familial variant
81304	MECP2 (methyl CpG binding protein 2) (e.g. Rett syndrome) gene analysis; duplication/deletion variants
81310	NPM1 (nucleophosmin) (e.g. acute myeloid leukemia) gene analysis, exon 12 variants
81313	PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer) **(Investigational)**
81321	PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
81322	PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
81323	PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant
81324	PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
81325	PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis
81326	PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant
81328	SLCO1B1 (solute carrier organic anion transporter family, member 1B1) (eg, adverse drug reaction) gene analysis, common variant(s) (eg, *5) **(Investigational)**
81331	SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (e.g. Prader-Willi syndrome and/or Angelman syndrome), methylation analysis
81332	SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (e.g. alpha-1-antitrypsin deficiency), gene analysis, common variants (e.g. *S and *Z)
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
81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (e.g. warfarin metabolism), gene analysis, common variants (e.g. -1639G>A, c.173+1000C>T) **(Investigational)**

81370	HLA Class I and II typing, low resolution (e.g. antigen equivalents); HLA-A, -B, -C, -DRB1/3/4/5, and DQB1
81371	HLA Class I and II typing, low resolution (e.g. antigen equivalents); HLA-A, -B, and DRB1 (e.g. verification typing)
81372	HLA Class I typing, low resolution (e.g. antigen equivalents); complete (ie, HLA-A, -B, and C)
81373	HLA Class I typing, low resolution (e.g. antigen equivalents); 1 locus (e.g. HLA-A, -B, or C), each
81374	HLA Class I typing, low resolution (e.g. antigen equivalents); 1 antigen equivalent (e.g. B*27), each
81375	HLA Class II typing, low resolution (e.g. antigen equivalents); HLA-DRB1/3/4/5 and DQB1
81376	HLA Class II typing, low resolution (e.g. antigen equivalents); 1 locus (e.g. HLA-DRB1, DRB3/4/5, -DQB1, -DQA1, -DPB1, or DPA1), each
81377	HLA Class II typing, low resolution (e.g. antigen equivalents); 1 antigen equivalent, each
81378	HLA Class I and II typing, high resolution (ie, alleles or allele groups), HLA-A, -B, -C, and DRB1
81379	HLA Class I typing, high resolution (ie, alleles or allele groups); complete (ie, HLA-A, -B, and C)
81380	HLA Class I typing, high resolution (ie, alleles or allele groups); 1 locus (e.g. HLA-A, -B, or C), each
81381	HLA Class I typing, high resolution (ie, alleles or allele groups); 1 allele or allele group (e.g. B*57:01P), each
81382	HLA Class II typing, high resolution (ie, alleles or allele groups); 1 locus (e.g. HLA-DRB1, -DRB3, -DRB4, -DRB5, -DQB1, -DQA1, -DPB1, or DPA1), each
81383	HLA Class II typing, high resolution (ie, alleles or allele groups); 1 allele or allele group (e.g. HLA-DQB1*06:02P), each
81400	MOLECULAR PATHOLOGY PROCEDURE LEVEL 1
81401	MOLECULAR PATHOLOGY PROCEDURE LEVEL 2
81402	MOLECULAR PATHOLOGY PROCEDURE LEVEL 3
81403	MOLECULAR PATHOLOGY PROCEDURE LEVEL 4
81404	MOLECULAR PATHOLOGY PROCEDURE LEVEL 5
81405	MOLECULAR PATHOLOGY PROCEDURE LEVEL 6
81406	MOLECULAR PATHOLOGY PROCEDURE LEVEL 7
81407	MOLECULAR PATHOLOGY PROCEDURE LEVEL 8
81408	MOLECULAR PATHOLOGY PROCEDURE LEVEL 9
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)
81418	Drug metabolism (eg, pharmacogenomics) genomic sequence analysis panel, must include testing of at least 6 genes, including CYP2C19, CYP2D6, and CYP2D6 duplication/deletion analysis (**Investigational**)
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)
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 **(Investigational)**
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)
81448	Hereditary peripheral neuropathies panel (eg, Charcot-Marie-Tooth, spastic paraplegia), genomic sequence analysis panel, must include sequencing of at least 5 peripheral neuropathy-related genes (eg, BSCL2, GJB1, MFN2, MPZ, REEP1, SPAST, SPG11, and SPTLC1) **(Investigational)**

81460	Whole mitochondrial genome (eg, Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged-red fibers [MERFF], neuropathy, ataxia, and retinitis pigmentosa [NARP], Leber hereditary optic neuropathy [LHON]), genomic sequence, must include sequence analysis of entire mitochondrial genome with heteroplasmy detection **(Investigational)**
81465	Whole mitochondrial genome large deletion analysis panel (eg, Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia), including heteroplasmy detection, if performed **(Investigational)**
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 **(Investigational)**
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 **(Investigational)**
81493	Coronary artery disease, mRNA, gene expression profiling by real-time RT-PCR of 23 genes, utilizing whole peripheral blood, algorithm reported as a risk score **(investigational**) [Test no longer available]
81539	Oncology (high-grade prostate cancer), biochemical assay of four proteins (Total PSA, Free PSA, Intact PSA, and human kallikrein-2 [hK2]), utilizing plasma or serum, prognostic algorithm reported as a probability score **(Investigational)**
81541	Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin embedded tissue, algorithm reported as a disease-specific mortality risk score
81542	Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score
81551	Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin embedded tissue, algorithm reported as a likelihood of prostate cancer detection on repeat biopsy **(Investigational)**
83080	Hemosiderin; b-Hexosaminidase, each assay
88230	Tissue culture for non-neoplastic disorders; lymphocyte
88233	Tissue culture for non-neoplastic disorders; skin or other solid tissue biopsy
88235	Tissue culture for non-neoplastic disorders; amniotic fluid or chorionic villus cells
88237	Tissue culture for neoplastic disorders; bone marrow, blood cells
88239	Tissue culture for neoplastic disorders; solid tumor
88240	Cryopreservation, freezing and storage of cells, each cell line
88241	Thawing and expansion of frozen cells, each aliquot
88245	Chromosome analysis for breakage syndromes; baseline Sister Chromatid Exchange (SCE), 20-25 cells
88248	Chromosome analysis for breakage syndromes; baseline breakage, score 50-100 cells, count 20 cells, 2 karyotypes (eg, for ataxia telangiectasia, Fanconi anemia, fragile X)

88249	Chromosome analysis for breakage syndromes; score 100 cells, clastogen stress (eg, diepoxybutane, mitomycin C, ionizing radiation, UV radiation)
88261	Chromosome analysis; count 5 cells, 1 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 (e.g., FISH-fluorescence in situ hybridization)
88272	Chromosomal in situ hybridization, analyze 3 – 5 cells (e.g., for derivatives and markers)
88273	Chromosomal in situ hybridization, analyze 10 – 30 cells (e.g., for microdeletions)
88274	Interphase in situ hybridization, analyze 25 – 99 cells
88275	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
96041	Medical genetics and genetic counseling services, each 30 minutes of total time provided by the genetic counselor on the date of the encounter
0004M	Scoliosis, DNA analysis of 53 single nucleotide polymorphisms (SNPs), using saliva, prognostic algorithm reported as a risk score **(Investigational)**
0005U	Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score **(Investigational)**
0008U	Helicobacter pylori detection and antibiotic resistance, DNA, 16S and 23S rRNA, gyrA, pbp1, rdxA and rpoB, next generation sequencing, formalin-fixed paraffin embedded or fresh tissue or fecal sample, predictive, reported as positive or negative for resistance to clarithromycin, fluoroquinolones, metronidazole, amoxicillin, tetracycline, and rifabutin **(Investigational)**
0011M	Oncology, prostate cancer, mRNA expression assay of 12 genes (10 content and 2 housekeeping), RT-PCR test utilizing blood plasma and/or urine, algorithms to predict high-grade prostate cancer risk **(Investigational)**
0021U	Oncology (prostate), detection of 8 autoantibodies (ARF 6, NKX3-1, 5'-UTR-BMI1, CEP 164, 3'-UTR-Ropporin, Desmocollin, AURKAIP-1, CSNK2A2), multiplexed immunoassay and flow cytometry serum, algorithm reported as risk score **(Investigational)**
0023U	Oncology (acute myelogenous leukemia), DNA, genotyping of internal tandem duplication, p.D835, p.I836, using mononuclear cells, reported as detection or non-detection of FLT3 mutation and indication for or against the use of midostaurin
0029U	Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (ie, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1 and rs12777823) **(Investigational)**

0030U	Drug metabolism (warfarin drug response), targeted sequence analysis (ie, CYP2C9, CYP4F2, VKORC1, rs12777823) **(Investigational)**
0031U	CYP1A2 (cytochrome P450 family 1, subfamily A, member 2)(eg, drug metabolism) gene analysis, common variants (ie, *1F, *1K, *6, *7) **(Investigational)**
0032U	COMT (catechol-O-methyltransferase)(drug metabolism) gene analysis, c.472G>A (rs4680) variant **(Investigational)**
0036U	Exome (ie, somatic mutations), paired formalin-fixed paraffin-embedded tumor tissue and normal specimen, sequence analyses
0046U	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia) internal tandem duplication (ITD) variants, quantitative **(Investigational)**
0047U	Oncology (prostate), mRNA, gene expression profiling by real-time RT-PCR of 17 genes (12 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a risk score
0049U	NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, quantitative
0050U	Targeted genomic sequence analysis panel, acute myelogenous leukemia, DNA analysis, 194 genes, interrogation for sequence variants, copy number variants or rearrangements **(Investigational)**
0053U	Oncology (prostate cancer), FISH analysis of 4 genes (ASAP1, HDAC9, CHD1 and PTEN), needle biopsy specimen, algorithm reported as probability of higher tumor grade **(Investigational)**
0063U	Neurology (autism), 32 amines by LC-MS/MS, using plasma, algorithm reported as metabolic signature associated with autism spectrum disorder **(Investigational)**
0070U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, common and select rare variants (ie, *2, *3, *4, *4N, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14A, *14B, *15, *17, *29, *35, *36, *41, *57, *61, *63, *68, *83, *xN) **(Investigational)**
0071U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, full gene sequence (List separately in addition to code for primary procedure) **(Investigational)**
0072U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D6-2D7 hybrid gene) (List separately in addition to code for primary procedure) **(Investigational)**
0073U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D7-2D6 hybrid gene) (List separately in addition to code for primary procedure) **(Investigational)**
0074U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, non-duplicated gene when duplication/multiplication is trans) (List separately in addition to code for primary procedure) **(Investigational)**
0075U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 5' gene duplication/multiplication) (List separately in addition to code for primary procedure) **(Investigational)**

0076U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 3' gene duplication/ multiplication) (List separately in addition to code for primary procedure) **(Investigational)**
0094U	Genome (eg, unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis
0101U	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated (15 genes [sequencing and deletion/duplication], EPCAM and GREM1 [deletion/duplication only]) **(Investigational)** [ColoNext]
0102U	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated [17 genes (sequencing and deletion/duplication)] **(Investigational)** [BreastNext]
0103U	Hereditary ovarian cancer (eg, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA and array CGH, with MRNA analytics to resolve variants of unknown significance when indicated [24 genes (sequencing and deletion/duplication); EPCAM (deletion/duplication only)] **(Investigational)** [OvaNext]
0113U	Oncology (prostate), measurement of PCA3 and TMPRSS2-ERG in urine and PSA in serum following prostatic massage, by RNA amplification and fluorescence-based detection, algorithm reported as risk score **(Investigational)**
0117U	Pain management, analysis of 11 endogenous analytes (methylmalonic acid, xanthurenic acid, homocysteine, pyroglutamic acid, vanilmandelate, 5-hydroxyindoleacetic acid, hydroxymethylglutarate, ethylmalonate, 3-hydroxypropyl mercapturic acid (3-HPMA), quinolinic acid, kynurenic acid), LC-MS/MS, urine, algorithm reported as a pain-index score with likelihood of atypical biochemical function associated with pain **(Investigational)**
0129U	Hereditary breast cancer–related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53) **(Investigational)** [BRCAplus]
0130U	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), targeted mRNA sequence analysis panel (APC, CDH1, CHEK2, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, and TP53) (List separately in addition to code for primary procedure) **(Investigational)** [+RNAinsight for ColoNext]
0133U	Hereditary prostate cancer–related disorders, targeted mRNA sequence analysis panel (11 genes) (List separately in addition to code for primary procedure) **(Investigational)** [+RNAinsight for ProstateNext]

0134U	Hereditary pan cancer (eg, hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (18 genes) (List separately in addition to code for primary procedure) **(Investigational)** [+RNAinsight for CancerNext]
0136U	ATM (ataxia telangiectasia mutated) (eg, ataxia telangiectasia) *mRNA sequence analysis* (List separately in addition to code for primary procedure) **(Investigational)**
0137U	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) *mRNA sequence analysis* (List separately in addition to code for primary procedure) **(Investigational)**
0138U	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) mRNA sequence analysis (List separately in addition to code for primary procedure) **(Investigational)**
0156U	Copy number (eg, intellectual disability, dysmorphology), sequence analysis (**Investigational**)
0157U	APC (APC regulator of WNT signaling pathway) (eg, familial adenomatosis polyposis [FAP]) mRNA sequence analysis (List separately in addition to code for primary procedure) (**Investigational**)
0158U	MLH1 (mutL homolog 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure) (**Investigational**)
0159U	MSH2 (mutS homolog 2) (eg, hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure) (**Investigational**)
0160U	MSH6 (mutS homolog 6) (eg, hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure) (**Investigational**)
0161U	PMS2 (PMS1 homolog 2, mismatch repair system component) (eg, hereditary nonpolyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure) (**Investigational**)
0162U	Hereditary colon cancer (Lynch syndrome), targeted mRNA sequence analysis panel (MLH1, MSH2, MSH6, PMS2) (List separately in addition to code for primary procedure) (**Investigational**)
0170U	Neurology (autism spectrum disorder [ASD]), RNA, next-generation sequencing, saliva, algorithmic analysis, and results reported as predictive probability of ASD diagnosis **(Investigational)**
0171U	Targeted genomic sequence analysis panel, acute myeloid leukemia, myelodysplastic syndrome, and myeloproliferative neoplasms, DNA analysis, 23 genes, interrogation for sequence variants, rearrangements and minimal residual disease, reported as presence/absence **(Investigational)**
0173U	Psychiatry (ie, depression, anxiety), genomic analysis panel, includes variant analysis of 14 genes (**Investigational**)
0175U	Psychiatry (eg, depression, anxiety); genomic analysis panel, variant analysis of 15 genes (**Investigational**)

0203U	Autoimmune (inflammatory bowel disease), mRNA, gene expression profiling by quantitative RT-PCR, 17 genes (15 target and 2 reference genes), whole blood, reported as a continuous risk score and classification of inflammatory bowel disease aggressiveness **(Investigational)**
0205U	Ophthalmology (age-related macular degeneration), analysis of 3 gene variants (2 CFH gene, 1 ARMS2 gene), using PCR and MALDI-TOF, buccal swab, reported as positive or negative for neovascular agerelated macular-degeneration risk associated with zinc supplements **(Investigational)**
0209U	Cytogenomic constitutional (genome-wide) analysis, interrogation of genomic regions for copy number, structural changes and areas of homozygosity for chromosomal abnormalities
0212U	Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband
0213U	Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes,deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator genome (eg, parent, sibling)
0214U	Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes,deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband
0215U	Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator exome (eg, parent, sibling)
0218U	Neurology (muscular dystrophy), DMD gene sequence analysis, including small sequence changes, deletions, duplications, and variants in non-uniquely mappable regions, blood or saliva, identification and characterization of genetic variants
0228U	Oncology (prostate), multianalyte molecular profile by photometric detection of macromolecules adsorbed on nanosponge array slides with machine learning, utilizing first morning voided urine, algorithm reported as likelihood of prostate cancer **(Investigational)**
0235U	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor 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

0237U	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia), genomic sequence analysis panel including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions
0265U	Rare constitutional and other heritable disorders, whole genome and mitochondrial DNA sequence analysis, blood, frozen and formalin-fixed paraffinembedded (FFPE) tissue, saliva, buccal swabs or cell lines, identification of single nucleotide and copy number variants
0290U	Pain management, mRNA, gene expression profiling by RNA sequencing of 36 genes, whole blood, algorithm reported as predictive risk score **(Investigational)**
0291U	Psychiatry (mood disorders), mRNA, gene expression profiling by RNA sequencing of 144 genes, whole blood, algorithm reported as predictive risk score **(Investigational)**
0292U	Psychiatry (stress disorders), mRNA, gene expression profiling by RNA sequencing of 72 genes, whole blood, algorithm reported as predictive risk score **(Investigational)**
0293U	Psychiatry (suicidal ideation), mRNA, gene expression profiling by RNA sequencing of 54 genes, whole blood, algorithm reported as predictive risk score **(Investigational)**
0297U	Oncology (pan tumor), whole genome sequencing of paired malignant and normal DNA specimens, fresh or formalinfixed paraffin-embedded (FFPE) tissue, blood or bone marrow, comparative sequence analyses and variant identification
0339U	Oncology (prostate), mRNA expression profiling of HOXC6 and DLX1, reverse transcription polymerase chain reaction (RT-PCR), first-void urine following digital rectal examination, algorithm reported as probability of high-grade cancer **(Investigational)**
0345U	Psychiatry (eg, depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6 **(Investigational)**
0347U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 16 gene report, with variant analysis and reported phenotypes (**Investigational**)
0348U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 25 gene report, with variant analysis and reported phenotypes (**Investigational**)
0349U	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis, including reported phenotypes and impacted gene-drug interactions (**Investigational**)
0350U	Infectious disease (bacterial or viral), biochemical assays, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), interferon gamma-induced protein-10 (IP-10), and C-reactive protein, serum, algorithm reported as likelihood of bacterial infection (**Investigational**)
0359U	Oncology (prostate cancer), analysis of all prostate-specific antigen (PSA) structural isoforms by phase separation and immunoassay, plasma, algorithm reports risk of cancer **(Investigational)**

0364U	Oncology (hematolymphoid neoplasm), genomic sequence analysis using multiplex (PCR) and next-generation sequencing with algorithm, quantification of dominant clonal sequence(s), reported as presence or absence of minimal residual disease (MRD) with quantitation of disease burden, when appropriate [clonoSEQ]
0376U	Oncology (prostate cancer), image analysis of at least 128 histologic features and clinical factors, prognostic algorithm determining the risk of distant metastases, and prostate cancer-specific mortality, includes predictive algorithm to androgen deprivation-therapy response, if appropriate **(Investigational)** [ArteraAI Prostate]
0392U	Drug metabolism (depression, anxiety, attention deficit hyperactivity disorder [ADHD]), gene-drug interactions, variant analysis of 16 genes, including deletion/duplication analysis of CYP2D6, reported as impact of gene-drug interaction for each drug (**Investigational**)
0400U	Obstetrics (expanded carrier screening), 145 genes by nextgeneration sequencing, fragment analysis and multiplex ligationdependent probe amplification, DNA, reported as carrier positive or negative
0403U	Oncology (prostate), mRNA, gene expression profiling of 18 genes, first-catch urine, algorithm reported as percentage of likelihood of detecting clinically significant prostate cancer (**Investigational**)
0411U	Psychiatry (eg, depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6 (**Investigational**)
0425U	Genome (eg, unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis, each comparator genome (eg, parents, siblings)
0426U	Genome (eg, unexplained constitutional or heritable disorder or syndrome), ultra-rapid sequence analysis
0434U	Drug metabolism (adverse drug reactions and drug response), genomic analysis panel, variant analysis of 25 genes with reported phenotypes (**Investigational**)
0437U	Psychiatry (anxiety disorders), mRNA, gene expression profiling by RNA sequencing of 15 biomarkers, whole blood, algorithm reported as predictive risk score (**Investigational**)
0438U	Drug metabolism (adverse drug reactions and drug response), buccal specimen, gene-drug interactions, variant analysis of 33 genes, including deletion/duplication analysis of CYP2D6, including reported phenotypes and impacted genedrug interactions (**Investigational**)
0449U	Carrier screening for severe inherited conditions (eg, cystic fibrosis, spinal muscular atrophy, beta hemoglobinopathies [including sickle cell disease], alpha thalassemias) regardless of race or self-identified ancestry, genomic sequence analysis of 5 genes (CFTR, SMN1, HBB, HBA1, HBA2)
0460U	Oncology, whole blood or buccal, DNA single nucleotide polymorphism (SNP) genotyping by real-time PCR of 24 genes, with variant analysis and reported phenotypes **(Investigational)**
0461U	Oncology, pharmacogenomic analysis of single-nucleotide polymorphism (SNP) genotyping by real-time PCR of 24 genes, whole blood or buccal swab, with variant analysis, including impacted gene-drug interactions and reported phenotypes **(Investigational)**

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
0475U	Hereditary prostate cancer, related disorders, genomic sequence analysis panel using next-generation sequencing (NGS), Sanger sequencing, multiplex ligation-dependent probe amplification (MLPA), and array comparative genomic hybridization (CGH), evaluation of 23 genes and duplications/deletions when indicated, pathologic mutations reported with a genetic risk score for prostate cancer **(Investigational)**
0476U	Drug metabolism, psychiatry (e.g., major depressive disorder, general anxiety disorder attention deficit hyperactivity disorder [ADHD], schizophrenia), whole blood, buccal swab, and pharmacogenomic genotyping of 14 genes and CYP2D6 copy number variant analysis and reported phenotypes (**Investigational**)
0477u	Drug metabolism, psychiatry (eg, major depressive disorder, general anxiety disorder, attention deficit hyperactivity disorder [ADHD], schizophrenia), whole blood, buccal swab, and pharmacogenomic genotyping of 14 genes and CYP2D6 copy number variant analysis, including impacted gene-drug interactions and reported phenotypes (**Investigational**)
0582U	Rare diseases (constitutional disease/hereditary disorders), rapid whole genome DNA sequencing for single nucleotide variants, insertions/deletions, copy number variations, blood, saliva, tissue sample, variants reported
0583U	Rare diseases (constitutional disease/hereditary disorders), rapid whole genome comparator DNA sequencing for single-nucleotide variants, insertions/deletions, copy number variations, blood, saliva, tissue sample, variants reported with proband results (List separately in addition to code for primary procedure)

HCPCS Coding:

G9143	Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s) **(Investigational)**
S0265	Genetic counseling, under physician supervision, each 15 minutes
S3841	Genetic testing for retinoblastoma
S3842	Genetic testing for Von Hippel-Lindau Disease
S3844	DNA analysis of the Connexin 26 Gene (GJB2) for susceptibility to congenital, profound, deafness
S3845	Genetic testing for Alpha-Thalassemia
S3846	Genetic testing for Hemoglobin E Beta-Thalassemia
S3849	Genetic testing for Niemann-Pick Disease
S3850	Genetic testing for sickle cell anemia
S3852	DNA analysis for APOE epsilon 4 allele for susceptibility to Alzheimer's disease
S3853	Genetic testing for myotonic muscular dystrophy

S3861	Genetic testing, sodium channel, voltage-gated, type V, alpha subunit (SCN5A) and variants for suspected Brugada Syndrome
S3865	Comprehensive gene sequence analysis for hypertrophic cardiomyopathy
S3866	Genetic analysis for a specific gene mutation for hypertrophic cardiomyopathy (HCM) in an individual with a known HCM mutation in the family
S3870	Comparative genomic hybridization (CGH) microarray testing for developmental delay, autism spectrum disorder and/or intellectual disability

REIMBURSEMENT INFORMATION:

Florida Blue has adopted the U.S. Preventive Services Task Force (USPSTF) Recommendations. In order to be covered, Services shall be provided in accordance with prevailing medical standards consistent with the USPSTF Recommendations.

Codes 83080, 88230, 88233, 88235, 88237, 88239, 88240, 88241, 88245, 88248, 88249, 88261, 88262, 88263, 88264, 88267, 88269 are limited to four (4) tests within a 12-month period.

Code 88291 is limited to twenty-five (25) of each test within a 12-month period.

Code 88271 is limited to forty-one (41) tests within a 12-month period.

Code 88280 is limited to two (2) tests within a 12-month period.

Codes 88272, 88273, 88274, 88283, 88285, 88289, S3841, S3842, S3844, S3845, S3846, S3849, S3850, S3853 and S3861 are limited to one (1) of each test within a 12-month period.

The following information is required for services subject to medical review, including services in excess of reimbursement limitations: documentation to support medical necessity: reason for test(s), previous lab results, how the results of the test will be utilized, how the results of the test will contribute to improved health outcomes, or alters patient's treatment and or management.

LOINC Codes:

Documentation Table	LOINC Codes	LOINC Time Frame Modifier Code	LOINC Time Frame Modifier Codes Narrative
Physician history and physical	28626-0	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim
Attending physician visit note	18733-6	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim.
Attending physician progress note	18741-9	18805-2	Include all data of the selected type that represents observations made six months or

			fewer before starting date of service for the claim.
Plan of treatment	18776-5	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim.
Laboratory studies	26436-6	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage products:

The following National Coverage Determinations (NCDs) were reviewed on the last guideline reviewed date and are located at cms.gov: Next Generation Sequencing (NGS) (90.2), Pharmacogenomic Testing for Warfarin Response (90.1) and Cytogenetic Studies (190.3).

The following were reviewed on the last guideline reviewed date: Molecular Diagnostic Services (MolDX) coverage determinations; located at cms.gov.

The following Local Coverage Determinations (LCDs) are located at fcso.com: Molecular Pathology Procedures (L34519), 4Kscore Test Algorithm (L37798), Pharmacogenomics Testing (L39073).

The following Local Coverage Determination (LCD) located at cms.gov was reviewed on the last guideline reviewed date: Prostate Cancer Detection with IsoPSA® (L39284).

The following Local Coverage Article is located at fcso.com: Billing and Coding: Molecular Pathology and Genetic Testing (A58918).

DEFINITIONS:

Carrier screening: Genetic testing that is performed on an individual who does not have any symptoms of a particular genetic disorder but may have one abnormal allele for the gene that is associated with the disorder. (ACOG Committee Opinion No. 690, 2017)

Compound Heterozygous: The presence of 2 different mutant alleles at a particular gene locus, one on each chromosome of a pair.

Expanded carrier screening: Disease screening that evaluates an individual's carrier state for multiple conditions at once and regardless of ethnicity. (ACOG Committee Opinion No. 690, 2017)

Homozygous: Having the same alleles at a particular gene locus on homologous chromosomes (chromosome pairs).

Panethnic screening: Individuals are screened regardless of their ethnic background. (ACOG Committee Opinion No. 690, 2017, reaffirmed 2023)

Penetrance: The proportion of individuals with a variant that causes a disorder who exhibit clinical symptoms of that disorder.

Residual Risk: The risk that an individual is a carrier of a disease, but testing for carrier status of the disease is negative (eg, if the individual carries a pathogenic variant not included in the test assay).

RELATED GUIDELINES:

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer, 05-86000-26

Genetic Testing for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers (BRCA1, BRCA2, PALB2), 05-82000-30

Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes, 05-82000-31

Tumor/Genetic Markers, 05-86000-22

OTHER:

None applicable.

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22. Blue Cross Blue Shield Association Evidence Positioning System®. 2.04.13 Genetic Testing for Alzheimer Disease, 11/24.
23. Blue Cross Blue Shield Association Evidence Positioning System® . 2.04.33 Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer, 12/24.
24. Blue Cross Blue Shield Association Evidence Positioning System®. 2.04.38 Cytochrome P450 Genotype-Guided Treatment Strategy, 07/25.
25. Blue Cross Blue Shield Association Evidence Positioning System®. 2.04.43 Genetic Testing for Cardiac Ion Channelopathies, 02/25.
26. Blue Cross Blue Shield Association Evidence Positioning System®. 2.04.44 Genetic Testing for Familial Cutaneous Malignant Melanoma, 04/25.
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31. Blue Cross Blue Shield Association Evidence Positioning System®. 2.04.75 Genetic Testing of CADASIL Syndrome, 05/25.
32. Blue Cross Blue Shield Association Evidence Positioning System®. 2.04.79 Genetic Testing for Alpha-1 Antitrypsin Deficiency, 02/25.
33. Blue Cross Blue Shield Association Evidence Positioning System®. 2.04.80 Genetic Testing for Hereditary Hemochromatosis, 06/25.
34. Blue Cross Blue Shield Association Evidence Positioning System®. 2.04.81 Genetic Testing for Rett Syndrome, 06/24.
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47. Blue Cross Blue Shield Association Evidence Positioning System®. 2.04.106 Genetic Testing for CHARGE Syndrome, 04/25.
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49. Blue Cross Blue Shield Association Evidence Positioning System®. 2.04.110 Genetic Testing for Diagnosis and Management of Mental Health Conditions, 08/25.
50. Blue Cross Blue Shield Association Evidence Positioning System® . 2.04.111 Gene Expression Profiling, Protein Biomarkers, and Multimodal Artificial Intelligence for Prostate Cancer Management, 05/25.
51. Blue Cross Blue Shield Association Evidence Positioning System®. 2.04.114 Genetic Testing for Idiopathic Dilated Cardiomyopathy, 03/25.
52. Blue Cross Blue Shield Association Evidence Positioning System®. 2.04.116 Invasive Prenatal (Fetal) Diagnostic Testing, 09/25.
53. Blue Cross Blue Shield Association Evidence Positioning System®. 2.04.117 Genetic Testing for Mitochondrial Disorders, 10/24.
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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy and Coverage Committee on 07/24/25.

GUIDELINE UPDATE INFORMATION:

11/15/03	Medical Coverage Guideline Annual review. Developed separate guideline for Genetic Testing For Miscellaneous Diagnoses. Developed separate genetic testing guidelines for the following: BRCA1 and BRCA2, colon cancer (FAP and HNPCC), and medullary carcinoma of the thyroid (RET proto-oncogene).
01/01/04	Annual HCPCS coding update: added S3853.
07/01/05	HCPCS update: added S0265.
12/15/05	Biennial review: coverage unchanged.

01/01/06	Annual HCPCS coding update: added 83900, 83907, 83908, 83909, 83914; revised 83898, 83901.
06/15/06	Revision to include new codes into limitation section.
01/01/07	Annual HCPCS coding update: added 96040; deleted 99401, 99402, 99403, and 99404.
07/15/07	Annual review, coverage statements maintained, guideline reformatted, references updated.
01/01/08	Annual HCPCS coding update: revised 83898, 83900, 83901, and 83908.
01/01/09	Annual HCPCS coding update: descriptor revised for codes 83890, 83891, 83892, 83893, 83894, 83897, 83900, 83903, 83907, 83909, and 83914.
10/15/09	Annual review: position statement, reimbursement section, guideline title and references updated.
12/15/10	Revision; description section, inheritable disease diagnosis table reimbursement and coding sections updated; prenatal test table and Other Genetic Tests section added.
07/15/10	Revision; Other Genetic Tests section updated.
10/01/11	Revision; formatting changes.
11/15/11	Revision; CPT code 88275 removed from the Reimbursement Information section.
01/01/12	Annual HCPCS update. Added codes 81200-81408.
02/15/12	Revision; Postnatal and Other Genetic Tests section, Billing/Coding Information section and references updated.
04/01/12	Quarterly HCPCS update. Deleted codes S3835, S3837, S3843, S3847, S3848, S3851, S3860, S3862.
08/15/12	Revision; Postnatal and Other Genetic Tests section updated.
10/15/12	Revision; Postnatal and Other Genetic Tests, Coding, and references updated.
01/01/13	Annual HCPCS update: added codes 81161, 81252-81254, 81321-81326; revised codes 81400-81408; deleted codes 83890-83914; updated reimbursement section. Prenatal & Postnatal Genetic Tests sections and references updated.
05/15/13	Revision; Genetic Testing to Establish a Diagnosis of Inheritable Disease and Postnatal and Other Genetic Tests sections updated; coding and references updated.
07/01/13	Quarterly HCPCS update. Added code 0004M; revised codes 81400-81408; Program Exceptions section updated.
08/15/13	Revision; Postnatal and Other Genetic Tests, Program Exceptions, and references updated.
09/15/13	Revision; experimental test list and references updated.
11/15/13	Revision; Postnatal and Other Genetic Tests section and references updated.
01/01/14	Annual HCPCS update. Added code 81287; revised codes 81371, 81376, & S3870.
02/15/14	Revision; position statement section updated.
07/01/14	Quarterly HCPCS update. Revised codes 81402 & 81404.
08/15/14	Revision; position statement section and references updated.
10/15/14	Revision; Position statement section and references updated.
01/01/15	Annual HCPCS/CPT update. Added codes 81246, 81313, 81410-81471;deleted code S3855.
03/15/15	Revision; position statement section, coding, and references updated.
07/01/15	Quarterly CPT/HCPCS update. Revised codes 81401 and 81406.

10/15/15	Revision; position statement section and references updated.
10/26/15	Revision; investigational test list updated.
11/15/15	Revision; coding section updated.
12/15/15	Revision; position statement section, coding, program exception, and references updated.
01/01/16	Annual HCPCS/CPT update; codes 81170, 81218, 81219, 81272, 81273, 81311, 81314, 81412, 81432-81434, 81437, 81438, 81442, 81493 added; codes 81355, 81401-81404, 81435, 81436, 81445-81455 revised; code S3721 deleted.
02/15/16	Revision; position statement section updated.
04/01/16	Quarterly HCPCS/CPT update; code 0010M revised.
05/15/16	Revision; Position statement section, coding, and references updated.
08/08/16	Revision; experimental test list updated.
08/31/16	Revision; Position Statement section; experimental test list updated.
11/08/16	Revision; deleted code 81311.
12/15/16	Revision; Position statement section and references updated.
01/01/17	Annual CPT/HCPCS update. Added 81413, 81414, 81439, 81539; revised 81400-81408; deleted 81280-81282, 0010M.
02/15/17	Revision; position statement section and references updated.
04/15/17	Revision; FMR1 Mutations, Acute Myeloid Leukemia, CHARGE Syndrome, Neurofibromatosis, PTEN Hamartoma Tumor Syndrome, and Cytogenetic Studies position statements added; Hereditary Pancreatitis and Inherited Peripheral Neuropathy position statements updated; description, coding, and references updated.
05/01/17	CPT Code update: code 0005U added.
06/15/17	Revision; Position statement section updated including CADASIL Syndrome position statements added and genetic testing for Alzheimer Disease position statement revised; references updated.
08/01/17	Coding Updates: Added codes 0007U, 0008U, 0010U, 0012U-0017U.
10/15/17	Revision; CMA investigational position statement added for the evaluation of all other conditions of delayed development; Diagnosis Table, coding, and references updated.
11/15/17	Revision to AML position statement section.
12/15/17	Revision; position statement section updated including testing for one or more single nucleotide polymorphisms (SNPs) and references updated.
01/01/18	Annual CPT/HCPCS update. Added codes 81230-81232, 81238, 81258-81269, 81328, 81334, 81335, 81346, 81448, 81541, 81551, 0011M, 0027U-0034U; revised codes 81257, 81432, 81439; deleted code 0015U. Investigational test list updated and code 0020U added.
02/15/18	Revision; position statements, test names, and references updated.
04/01/18	Quarterly HCPCS/CPT update. Added codes 0036U, 0037U, 0040U.
05/15/18	Revision; position statements, coding, program exception, and references updated.
05/16/18	Revision; RPE65 genetic testing position statement added and investigational test list updated.
07/01/18	Quarterly HCPCS/CPT update. Added codes 0046U-0050U, 0053U.
09/15/18	Revision; investigational status maintained but statements updated for genotype-guided warfarin dosing and testing for diagnosis/management of mental health conditions;

	position statements added for CYP450 genotype-guided treatment strategy; NCCN breast cancer risk criteria for PALB2 testing updated.
10/01/18	Quarterly HCPCS/CPT update. Added codes 0063U, 0069U-0076U, 0078U, 0079U; deleted 0028U.
10/15/18	Coding updated.
12/15/18	Revision; Next generation sequencing for measurable residual disease investigational statement added; genetic and protein biomarkers for the diagnosis of prostate cancer test list updated; coding and references updated.
01/01/19	Annual CPT/HCPCS coding update. Added codes 81171-81174, 81204, 81443, 0081U; revised codes 81244, 81287, 0008U; deleted code 0020U.
02/15/19	Revision; code 0081U deleted (refer to MCG 05-86000-22).
03/15/19	Revision; Position statements for FMR1 variants testing and FLT3, NPM1, and CEBPA variants testing updated; coding and references updated.
05/15/19	Revision; Position statements, including testing for dilated cardiomyopathy, and references updated.
07/01/19	Quarterly CPT/HCPCS update. Added codes 0094U, 0101U-0104U.
08/15/19	Revision; Genetic testing panels for mental health disorders & genetic testing for diagnosis and management of mental health disorders position statements maintained; testing for Rett syndrome position statements and references updated.
10/01/19	Quarterly CPT/HCPCS update. Added codes 0113U, 0117U, 0129U-0138U; deleted code 0104U. Deleted codes 81206-81208, 0016U.
10/24/19	Revision; PALB2 testing section updated.
01/01/20	Review; Assessment of MRD statements updated; statements for assays & gene expression profiling for diagnosis, cancer risk assessment, or management of prostate cancer maintained; coding & references updated. Annual CPT/HCPCS coding update. Added codes 81277, 81307, 81308, 81542, 0156U-0162U; revised code 81350.
04/01/20	Quarterly CPT/HCPCS update. Added codes 0170U & 0171U.
05/15/20	Revision; Whole exome and whole genome position statements updated; coding, and references updated.
07/01/20	Revision: CADASIL syndrome positon statements updated; gene expression analysis and protein biomarkers to guide management of prostate cancer reviewed and position statement maintained; references updated. Quarterly CPT/HCPCS update. Added codes 0173U and 0175U.
09/15/20	Revision; References updated; code 0069U removed (refer to policy 05-86000-28).
10/01/20	Quarterly CPT/HCPCS update. Added codes 0203U-0222U.
11/15/20	Revision; PALB2 position statements updated; Testing for BRIP1, RAD51C, and RAD51D variants position statements added; coding and references updated.
01/01/21	Annual CPT/HCPCS update. Codes 0228U, 0234U, 0235U, 0237U added; codes 81400-81400-81408 revised.
02/15/21	Review; Measurable residual disease (MRD) statements updated; gene expression analysis and protein biomarkers to guide management of prostate cancer maintained; prenatal whole exome/whole genome sequencing statement added; investigational test

	list, coding, and references updated. Codes 0007U & 0079U removed (refer to policy 05-86000-32).
06/15/21	Revision; Carrier screening position statements added; coding and references updated.
09/01/21	Revision: Breast cancer risk statements updated; coding and references updated
10/01/21	Quarterly CPT/HCPCS update. Code 0265U added.
11/15/21	Review: ExoDX Prostate IntelliScore test position statement maintained.
01/01/22	Annual CPT/HCPCS coding update. Codes 81349, 0290U- 0293U, 0297U added; 81228, 81229 revised.
02/15/22	Revision: Genetic testing to guide initiation or management FDA-approved amyloid-beta targeting therapy (aducanumab) investigational statement added; gene expression profiling and protein biomarkers for prostate cancer management position statement maintained; references updated.
05/15/22	Review: Gene expression analysis and protein biomarkers to guide management of prostate cancer position statement maintained; references updated.
07/15/22	Revision: Genetic testing for Rett syndrome associated genes position statement updated; references updated.
10/01/22	Quarterly CPT/HCPCS update. Codes 0339U and 0345U added.
11/15/22	Review: Cytochrome P450, carrier screening, gene variants associated with breast cancer risk and ovarian cancer position statements updated; coding and references updated.
01/01/23	Annual CPT/HCPCS coding update. Code 81418 added.
02/15/23	Revision: coding and references updated.
04/01/23	Quarterly CPT/HCPCS update. Code 0364U added.
06/15/23	IsoPSA test added to prostate cancer section; genetic cancer susceptibility panel testing statement removed, investigational test list and references updated.
07/01/23	Quarterly CPT/HCPCS update. Codes 0392U & 0400U added; code 0053U deleted. Coding section updated and note in position statement section updated.
10/01/23	Quarterly CPT/HCPCS update. Codes 0403U & 0411U added. References updated.
01/01/24	Position statements maintained. Annual CPT/HCPCS coding update. Codes 0425U, 0426U, 0434U, 0437U, 0438U added. Program exception and references updated.
04/01/24	Quarterly CPT/HCPCS coding update. Code 0449U added.
07/01/24	Quarterly CPT/HCPCS coding update. Codes 0460U, 0461U, 0469U, 0475U added.
08/15/24	Review: Position statements and investigational test list reviewed and updated; description, coding and references updated.
10/01/24	Quarterly CPT/HCPCS coding update. Codes 0476U,0477U added; code 0403U revised, code 0078U deleted.
12/15/24	Genetic testing for apolipoprotein E (APOE) gene in Alzheimer disease position statement revised. IsoPSA test reviewed; description, coding, and references updated.
01/01/25	Annual CPT/HCPCS coding update. Code 96041 added; code 96040 deleted.
07/01/25	References updated.
08/15/25	Annual review: Genetic testing for pain management to assess risk of developing opioid use disorders statement added; repeat whole exome sequencing statement added;

	testing for prostate cancer management section updated; investigational test list updated; all other statements maintained; description, coding, and references updated
10/01/25	Quarterly CPT/HCPCS coding update. Codes 0582U and 0583U added.
01/01/26	Annual CPT/HCPCS Coding Update. Codes 0033U, 0131U, 0132U, 0135U deleted. Codes 81232, 81346, S3722 removed.