2.04.92	General Approach to Evaluating the Utility of Genetic Panels		
Original Policy Date:	September 27, 2013	**Effective Date:**	April 1, 2023
Section:	2.04 Medicine	**Page:**	Page 1 of 28

Policy Statement

Note: Starting on July 1, 2022 (per CA law SB 535) for commercial plans regulated by the California Department of Managed Healthcare and California Department of Insurance (PPO and HMO), health care service plans and insurers shall not require prior authorization for biomarker testing, including biomarker testing for cancer progression and recurrence, if a member has stage 3 or 4 cancer. Health care service plans and insurers can still do a medical necessity review of a biomarker test and possibly deny coverage after biomarker testing has been completed and a claim is submitted (post service review).

I. Genetic panels that are limited in scope, use next-generation sequencing or chromosomal microarray analysis, that are not addressed in another policy more specific to the request (see Policy Guidelines and Rationale section), and meet all criteria (**as outlined in the Rationale section**) and are classified in one of the categories below, may be considered **medically necessary** when the individual is felt to be at high risk based on clinical information:
   - A. Panels for hereditary or genetic conditions
     1. Diagnostic testing of an individual's germline to benefit the individual
     2. Testing of an asymptomatic individual to determine future risk of disease
   - B. Cancer panels
     1. Testing of an asymptomatic individual to determine future risk of cancer
     2. Testing cancer cells from an individual to benefit the individual by identifying targeted treatment
   - C. Reproductive panels
     1. Preconception testing
        a. Carrier testing of the parent(s)
     2. Prenatal testing
        a. Carrier testing of the parent(s)
        b. In utero testing of a fetus, including testing for aneuploidy or familial variants
     3. Preimplantation genetic testing

II. Genetic panels that use next-generation sequencing or chromosomal microarray that do not meet the criteria for a specific category are considered **investigational,** including but not limited to general screening or large panels (unless clearly noted to be medically necessary in a policy more specific to the request).

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

There are many genetic tests addressed in other policies which may involve panels. This policy is intended for use when no other applicable policy exists.

The use of "code stacking" or submitting requests for multiple single genes (instead of using an appropriate panel code) will be considered an expanded or large panel and therefore treated as investigational. Individual genes that might otherwise be approved will not be covered when submitted in this fashion with multiple other CPT codes that indicate a panel is being used. Multiple single gene CPT code submission can be allowed on exception when a panel test is identified by name that is allowed in another policy and there is no reasonable panel CPT code that could be used instead (e.g., Guardant 360 or FoundationOne Liquid).

Testing related to hereditary breast and ovarian cancer, see Blue Shield of California Medical Policy: Genetic Testing for BRCA1 or BRCA2 for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers.

Testing related to hereditary colorectal cancer, see Blue Shield of California Medical Policy: Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes.

Panel testing related to non-small-cell lung cancer, see Blue Shield of California Medical Policy: Molecular Analysis for Targeted Therapy or Immunotherapy of Non-Small-Cell Lung Cancer.
Panel testing related to hereditary cancers other than breast, ovarian, colorectal, and non-small-cell lung cancer, see Blue Shield of California Medical Policy: Genetic Cancer Susceptibility Panels Using Next Generation Sequencing.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG-AMP) Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at-risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Coding

CPT codes 81410-81471 are specific for genomic sequencing procedures (or "next-generation sequencing" panels). The panel must meet the requirements in the code descriptor in order to use the code.

If the panel does not meet the requirements for the codes above and does not use an algorithmic analysis, for any specific analyte in the panel that is listed in the tier 1 (81200-81355) or tier 2 (81400-81408) codes, that CPT code would be reported for that specific analyte along with the unlisted code 81479 (1 unit) for any analytes on the panel not listed in the CPT codes. If none of the analytes on the panel are listed in the more specific CPT codes, unlisted code 81479 would be reported once for the whole test.

If the panel uses an algorithmic analysis of the results of the component tests to produce a numeric score or probability, it would be a multianalyte assay with algorithm analysis (MAAA) and reported with one of the specific codes in the 815XX section or appendix O in CPT. If there is no specific code listed, the unlisted MAAA code 81599 would be used.

The following CPT code represents RadTox™ cfDNA test, DiaCarta Clinical Lab, DiaCarta Inc. Per the manufacturer, this is an in vitro diagnostic device for the prediction of risk for toxicity in patients receiving radiation. The test measures cfDNA levels which proportionally increase after radiation. cfDNA is isolated from whole blood and subjected to nucleic acid probe hybridization analysis that uses branched DNA technology for measuring the ctDNA levels.

- **0285U:** Oncology, response to radiation, cell-free DNA, quantitative branched chain DNA amplification, plasma, reported as a radiation toxicity score

The following CPT code represents MindX Blood Test™ - Longevity, MindX Sciences™ Laboratory, MindX Sciences™ Inc. Per the manufacturer, this is a MAAA test that tracks longevity and predicts short and long-term risk for dying. It matches patients with possible medications and may be repeated to monitor response to treatment. It uses an algorithm reported as predictive risk score. This test may have been billed with 81599.

- **0294U:** Longevity and mortality risk, mRNA, gene expression profiling by RNA sequencing of 18 genes, whole blood, algorithm reported as predictive risk score

Description

Genetic panel testing offers potential advantages and disadvantages compared with direct sequence analysis. This conceptual framework outlines a structure for evaluating the utility of genetic panels, by classifying them into clinically relevant categories and developing criteria for evaluating panels in each category.

Related Policies

- General Approach to Genetic Testing
- Genetic Cancer Susceptibility Panels Using Next Generation Sequencing
- Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

An exhaustive list of commercially available panel tests is beyond the scope of this conceptual framework. For example, 1 laboratory offers 243 different genetic panels, of a total of 929 molecular genetics tests.[11]

Rationale

Background

This conceptual framework applies only if there is not a separate evidence review in the Medical Policy Reference Manual that outlines specific criteria for testing. If a separate evidence review does exist, then the criteria for medical necessity therein supersede the guidelines herein.

Context

The purpose of this conceptual framework is to provide a structure for evaluating the utility of genetic panels that use newer genetic testing methodologies. In providing a framework for evaluating genetic panels, this review will not attempt to determine the clinical utility of genetic testing for specific disorders per se. For most situations, this will mean that at least 1 mutation in the panel has already been determined to have clinical utility and that clinical indications for testing are established. Once the clinical utility for at least 1 of the mutations included in the panel has been established, then the focus is on whether use of a panel is a reasonable alternative to individual tests.

Genetic Panel Testing

A genetic panel will be defined as a test that simultaneously evaluates multiple genes, as opposed to sequential testing of individual genes. This includes panels performed by next-generation sequencing (NGS), massive parallel sequencing, and chromosomal microarray analysis (CMA) testing. The definition of a panel will not include panels that report on gene expression profiling, which generally do not directly evaluate genetic mutations.

New Sequencing Technologies

New genetic technology, such as NGS and chromosomal microarray, has led to the ability to examine many genes simultaneously.[1] This in turn has resulted in a proliferation of genetic panels. Panels using next-generation technology are currently widely available, covering a broad range of conditions related to inherited disorders, cancer, and reproductive testing.[2-4] These panels are intuitively attractive to use in clinical care because they can analyze multiple genes more quickly and may lead to greater efficiency in the workup of genetic disorders. It is also possible that newer technology can be performed more cheaply than direct sequencing, although this may not be true in all cases.

Newer sequencing techniques were initially associated with higher error rates than direct sequencing.[5] While there are limited published data directly comparing the accuracy of NGS with direct sequencing, several publications have reported that the concordance between NGS and Sanger sequencing is greater than 99% for cancer susceptibility testing,[6] inherited disorders,[7] and

hereditary hearing loss.[8] Another potential pitfall is the easy availability of a multitude of genetic information, much of which has uncertain clinical consequences. Variants of uncertain significance are found commonly and in greater numbers with NGS than with direct sequencing.[9,10]

The intended use for these panels is variable, for example, for the diagnosis of hereditary disorders, a clinical diagnosis may be already established, and genetic testing is performed to determine whether this is a hereditary condition, and/or to determine the specific variant present. In other cases, there is a clinical syndrome (phenotype) with a broad number of potential diagnoses, and genetic testing is used to make a specific diagnosis. For cancer panels, there are also different intended uses. Some panels may be intended to determine whether a known cancer is part of a hereditary cancer syndrome. Other panels may include somatic variants in a tumor biopsy specimen that may help identify a cancer type or subtype and/or help select the best treatment.

There is no standardization to the makeup of genetic panels. Panel composition is variable, and different commercial products for the same condition may test a different set of genes. The makeup of the panels is determined by the specific lab that developed the test. Also, the composition of any individual panel is likely to change over time, as new variants are discovered and added to existing panels.

Despite the variability in the intended use and composition of panels, there are a finite number of broad panel types that can be identified and categorized. Once categorized, specific criteria on the utility of the panel can be developed for each category. One difficulty with this approach is that the distinction between the different categories, and the distinction between the intended uses of the panels, may not be clear. Some panels will have features or intended uses that overlap among the different categories.

To determine the criteria used for evaluating panels, the evidence review will first classify panels into a number of clinically relevant categories, according to their intended use. Then, for each category, criteria will be proposed that can be applied to tests within that category. Because our goal is to outline a general approach to testing, we will not evaluate individual panels; rather, we will supply examples of genetic panels in each category to assist Plans in classifying the individual panels.

Literature Review

Types of Panel Testing

There are numerous types of panel testing, because in theory a panel may be substituted for individual variant testing in any situation where more than 1 gene is being examined. Commercially available panels fall largely into several categories, which we classify using the BCBSA categories of genetic testing (see Appendix Table 1).

We have classified genetic panels into 3 major categories: panels for genetic and hereditary conditions, cancer panels, and reproductive panels. Within these categories, we created subcategories by the intended use of the panels.

Panels for Genetic or Hereditary Conditions

Panels for genetic or hereditary conditions are generally single-gene disorders, which are inherited in Mendelian fashion. They are defined by a characteristic phenotype, which may characterize a specific disease or represent a syndrome that encompasses multiple underlying diseases.
The intended use of these panels may be for:

- Diagnostic testing of an individual's germline to benefit the individual. To confirm a suspected diagnosis in patients with signs and/or symptoms of the condition; or to identify a causative etiology for a clinical syndrome, for which there are multiple possible underlying conditions.
- Testing an asymptomatic individual to determine future risk of disease.

There are several variations of panels for use in diagnosis or risk assessment of genetic or hereditary conditions. For our purposes, panels will be divided into the following types:

- *Panels containing variants associated with a single condition*. These panels generally include all known pathogenic variants for a defined disease and do not include variants associated with other diseases. An example of such a panel would be one that includes pathogenic variants for hypertrophic cardiomyopathy but does not include variants associated with other cardiovascular disorders. These panels can be used for diagnostic or risk assessment purposes.
- *Panels containing variants associated with multiple related conditions*. These panels include all known pathogenic variants for a defined disease and variants associated with other related disorders. An example of such a panel would be a pan cardiomyopathy panel that includes pathogenic variants for hypertrophic cardiomyopathy and other types of cardiomyopathy (e.g., dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy). These panels can be used for diagnostic or risk assessment purposes.
- *Panels containing variants for clinical syndromes associated with multiple distinct conditions*. These panels include variants associated with multiple potential disease states that define a particular clinical syndrome. In general, a specific diagnosis cannot be made without genetic testing, and genetic testing can identify one among several underlying disease states that manifest as a clinical syndrome. An example of this type of panel is one for intellectual disability that includes variants associated with many potential underlying disease states. These panels are used for diagnostic purposes.

Cancer Panels

Genetic panels for cancer can be of several types and may test for either germline or somatic variants. Their intended purpose can be for:

- Testing an asymptomatic patient to determine future risk of cancer
- Therapeutic testing of cancer cells from an affected individual to benefit the individual by directing targeted treatment based on specific somatic variants.

There are variations of panels for use in risk assessment or for directing targeted treatment. For our purposes, panels will be divided into the following types:

- *Panels containing multiple variants indicating risk for a specific type of cancer or cancer syndrome (germline variants).* These panels contain multiple related variants that indicate susceptibility to one or more cancers. They include germline variants and will generally be used for risk assessment in asymptomatic individuals who are at-risk for variants based on family history or other clinical data. An example of this type of panel would be one testing for multiple *BRCA1* and *BRCA2* variants associated with hereditary breast and ovarian cancer syndrome.
- *Panels containing multiple variants associated with a wide variety of cancer types (somatic variants).* These panels are generally used to direct treatment with drugs that target specific variants. They test for somatic variants from tissue samples of existing cancers. Many of these somatic variants are found across a wide variety of solid tumors. An example is the CancerNext Panel (Ambry Genetics), which tests for a broad number of somatic variants that can direct treatment.

Reproductive Panels

Reproductive panels test for variants associated with heritable conditions and are intended either for:

- Carrier testing of parent(s) preconception
- Carrier testing of parent(s) prenatal
- Prenatal (in utero) testing

Preconception testing usually tests for variants that are autosomal recessive or X-linked or, in some cases, for autosomal dominant variants with late clinical onset. Preconception tests can be performed on parents at-risk for a variant based on family history or can be done as screening tests in parents without a family history suggestive of a variant. Prenatal testing refers to tests performed during pregnancy. At present, prenatal testing for genetic variants is performed on the fetus, using amniocentesis or chorionic villous sampling. Testing of maternal blood for chromosomal aneuploidy is currently available, and in the future, it may be possible to test for fetal variants using maternal blood.

There are variations of panels for use in preconception or prenatal testing. For our purposes, panels will be divided into the following types:

- *Panels containing variants associated with a single disorder.* These panels are generally performed in at-risk individuals with a family history of a heritable disorder. An example of this type of panel would be a cystic fibrosis gene panel intended for use in individuals with a family history of cystic fibrosis.
- *Panels containing variants associated with multiple disorders.* These panels are generally performed as screening tests for parents without a family history of a heritable disorder. They can also be used to evaluate individuals with a family history of a heritable disorder. An example of this type of panel is the Targeted Array Comparative Hybridization (aCGH) Panel.

Criteria for Evaluating Genetic Panels

The following are criteria that can be applied to evaluating genetic panels, with an explanation of the way the criteria are to be defined and applied. Not all criteria will apply to all panels. Appendix Table 2 and Appendix Figures 1 through 4 list the specific criteria that should be used for each category.

Test is Performed in a Clinical Laboratory Improvement Amendments–Licensed Lab

- Testing is performed in a laboratory licensed under Clinical Laboratory Improvement Amendments for high-complexity testing. This requires delivery of a reproducible set of called, quality-filtered variants from the sequencing platform.
- These calculations should occur before variant annotation, filtering, and manual interpretation for patient diagnosis.

Technical Reliability of Panels Approaches That of Direct Sequencing

- The technical reliability for detecting individual variants, compared with the criterion standard of conventional direct Sanger sequencing, is reported.
  - The testing methods are described, and the overall analytic validity for that type of testing is defined.
- Any decrease in analytic sensitivity and specificity is not large enough to result in a clinically meaningful difference in diagnostic accuracy (clinically valid).

All individual components of the panel have demonstrated they are clinically useful for the condition being evaluated OR the implications and consequences of test results that have not demonstrated clinical utility are clear, AND there is no potential for incidental findings to cause harm.

- For each panel, if each variant in the panel would be indicated for at least some patients with the condition, then this criterion is met.
  - If there are individual variants that do not have clinical utility, then the potential to cause harm might occur.
- For incidental findings, the potential for harm may be due to:
  - Incorrect diagnosis due to false-positive or false-negative results
    - False-positive: Unnecessary treatment that may have adverse events
    - False-negative: Effective treatment not provided
  - Incorrect risk assessment

        - Unnecessary surveillance tests may lead to further confirmatory tests that may be invasive
        - Effective surveillance or screening not provided to patients at-risk
        - Incorrect decision made on reproductive decision making
            - Alteration made in reproductive planning that would not have been made with correct information
            - No alteration made in reproductive planning, where alteration would have been made with correct information

Panel Testing Offers Substantial Improvement in Efficiency vs Sequential Analysis of Individual Genes

- The composition of the panel is sufficiently complex such that next-generation sequencing or chromosomal microarray analysis is expected to offer considerable advantages. The complexity of testing can be judged by:
    - The number of genes tested
    - The size of the genes tested
    - The heterogeneity of the genes tested

The Impact of Ancillary Information is Well-Defined

- If a panel contains both variants that are medically necessary and variants that are investigational (or not medically necessary), the impact of results for investigational (or not medically necessary) variants is considered, taking into account the following possibilities:
    - The information may be ignored (no further impact)
    - The information may result in further testing or changes in management:
        - Positive impact
        - Negative impact
- It is more likely that the results of tests that are not medically necessary cause a negative, rather than a positive, impact on the patient. This is because additional tests and management changes that follow are not evidence-based and because additional testing and treatment generally involve risks.

Decision Making Based on Genetic Results is Well-Defined

- Results of the genetic testing will lead to changes in diagnosis and/or treatment.
- The potential changes in treatment are defined prior to testing and accord with the current standard of care.
- Changes in diagnosis or management are associated with improvements in health outcomes.
- For prenatal and preconception testing:
    - Alterations in reproductive decision making are expected, depending on the results of testing.

Testing Yield is Acceptable for the Target Population

- The number of individuals who are found to have a pathogenic variant, in relation to the total number of individuals tested, is reasonable given the underlying prevalence and severity of the disorder, and the specific population that is being tested.
    - It is not possible to set an absolute threshold for acceptable yield across different clinical situations. Some guidance can be given from clinical precedence as follows:
        - For diagnosis of hereditary disorders, genetic testing is generally performed when signs and symptoms of the disease are present, including family history. The likelihood of a positive genetic test depends on the accuracy of the signs and symptoms (pretest probability of disorder), and the clinical sensitivity of genetic testing. For disorders such as testing for congenital long QT syndrome and Duchenne muscular dystrophy, the likelihood of a positive result in patients with signs and symptoms of the disease is greater than 10%.

    - For cancer susceptibility, testing is recommended for genetic abnormalities such as the *BRCA* gene and Lynch syndrome when the likelihood of a positive result is in the range of 2% to 10%.
    - For a clinical syndrome that has multiple underlying etiologies, such as developmental delay in children, chromosomal microarray analysis is recommended when the likelihood of a positive result is in the 5% to 20% range.
- There is an increase in yield over alternative methods of diagnosis, and this increase is clinically significant.

Other Issues to Consider

- Most tests will not, and possibly should not, be ordered by generalists.
    - Guidance for providers is appropriate on the expertise necessary to ensure that test ordering is done optimally.
- Many tests, particularly those for inherited disorders, should be accompanied by patient counseling, preferably by certified genetic counselors.
    - Counseling may be needed both before and after testing, depending on the specific condition being tested

Summary of Evidence

Genetic panels using next-generation technology or chromosomal microarray analysis are available for many clinical conditions. The major advantage of panels is the ability to analyze many genes simultaneously, potentially improving the breadth and efficiency of the genetic workup. A potential disadvantage of panels is that they provide a large of amount of ancillary information whose significance may be uncertain. Limited published evidence has reported that the analytic validity of panels approaches that of direct sequencing. The clinical validity and clinical utility of panels are condition-specific. The clinical validity of panels will reflect the clinical validity of the underlying individual variants. The clinical utility of panels will depend on the context in which they are used, ie, whether the advantages of panel testing outweigh the disadvantages for the specific condition under consideration.

Supplemental Information

Practice Guidelines and Position Statements

No guidelines or statements were identified.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in November 2017 did not identify any ongoing or unpublished trials that would likely influence this conceptual framework.

Appendix 1

Appendix Table 1. Categories of Genetic Testing

Category	Addressed
1. Testing of an affected individual's germline to benefit the individual	
1a. Diagnostic	
1b. Prognostic	
1c. Therapeutic	
2. Testing cancer cells from an affected individual to benefit the individual	

Category	Addressed
2a. Diagnostic	
2b. Prognostic	
2c. Therapeutic	
3. Testing an asymptomatic individual to determine future risk of disease	
4. Testing of an affected individual's germline to benefit family members	
5. Reproductive testing	
5a. Carrier testing: preconception	
5b. Carrier testing: prenatal	
5c. In utero testing: aneuploidy	
5d. In utero testing: familial variants	
5e. In utero testing: other	
5f. Preimplantation testing with in vitro fertilization	

Appendix Table 2. Criteria for Evaluating Panels by Type and Intent of Panel

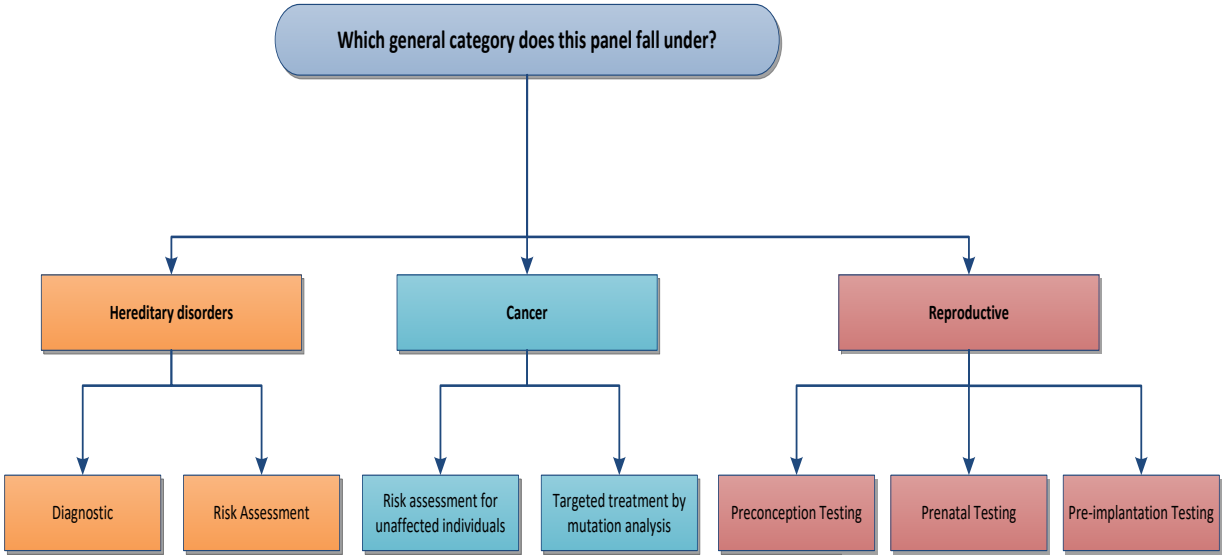
Panel Category	Examples of Disease Tests by Respective Panel	Criteria for Evaluating Utility of Panel
1. Diagnosis of hereditary, single-gene disorders		• All individual components of the panel have demonstrated clinical utility, OR test results that have not demonstrated clinical utility do not have a potential to cause harm • Testing is performed in a CLIA-approved lab • Analytic validity of panel approaches that of direct sequencing • Panel testing offers substantial advantages in efficiency compared with sequential analysis of individual genes
Category 1a – Diagnostic testing Panels that include variants for a single condition	• Retinitis Pigmentosa Panel • Leigh Disease Panel	• Includes all criteria for criterion 1 (Diagnosis of hereditary, single-gene disorders)
Category 1b – Diagnostic testing Panels that include variants for multiple conditions (indicated plus nonindicated conditions)	• Retinitis Pigmentosa/Leber Congenital Amaurosis Panel • Cardiology Disorders Panel • Ciliopathies Panel	• Includes all criteria for criterion 1 (Diagnosis of hereditary, single-gene disorders) PLUS • The impact of ancillary information is well-defined •
Category 1c – Diagnostic testing Panels that include variants for multiple conditions (clinical syndrome for which clinical diagnosis not possible)	• Intellectual Disabilities Panel • Aortopathies Panel • Epilepsy Panel	• Includes all criteria for criterion 1 (Diagnosis of hereditary, single-gene disorders) PLUS • The impact of ancillary information is well-defined • Yield of testing is acceptable for the target population
Category 1d – Risk Assessment Risk assessment panels for at-risk individuals	• Most panels for hereditary conditions can be used for this purpose when there is not a known variant in the family	• Includes all criteria for criterion 1 (Diagnosis of hereditary, single-gene disorders) PLUS • Yield of testing is acceptable for the target population
2. Cancer panels		• All individual components of the panel have demonstrated clinical utility, OR test results

Panel Category	Examples of Disease Tests by Respective Panel	Criteria for Evaluating Utility of Panel
		that have not demonstrated clinical utility do not have a potential to cause harm • Testing is performed in a CLIA-approved lab • Analytic validity of panel approaches that of direct sequencing • Panel testing offers substantial advantages in efficiency compared with sequential analysis of individual genes
Category 2a – Risk assessment Risk assessment panels for at-risk individuals	• Hereditary colon cancer syndromes panel • Breast Cancer Panel	• Includes all criteria for criterion 2 (Cancer panels) PLUS • Yield of testing is acceptable for the target population
Category 2b – Targeted treatment based on variant analysis • **Panels with multiple variants intended to direct treatment – all indicated tests** • **Effective targeted treatment based on variant analysis is available**	• Congenital Metabolic Disorders Panel • Newborn Screening Confirmation Panel	• Includes all criteria for criterion 2 (Cancer panels) PLUS • Yield of testing is acceptable for the target population
Category 2c – Targeted treatment based on variant analysis • **Panels with multiple variants intended to direct treatment (indicated plus nonindicated tests)** • **Effective targeted treatment based on variant analysis has not been established**	• Hereditary Cancers Panels, when there is an effective targeted treatment for the specific type of cancer	• Includes all criteria for criterion 2 (Cancer panels) PLUS • Impact of ancillary information is defined
Category 2d • **Panels with multiple variants intended to direct treatment – no indicated tests for that particular cancer** • **Effective targeted treatment based on variant analysis has not been established**	• Hereditary Cancers Panels, when there is no known effective treatment for the specific type of cancer	• Includes all criteria for criterion 2 (Cancer panels) PLUS • Decision making based on potential results is defined • Yield of testing is acceptable for the target population • Impact of ancillary information is defined • Probability that ancillary information leads to further testing or management changes
3. Reproductive panels		• All individual components of the panel have demonstrated clinical utility, OR test results that have not demonstrated

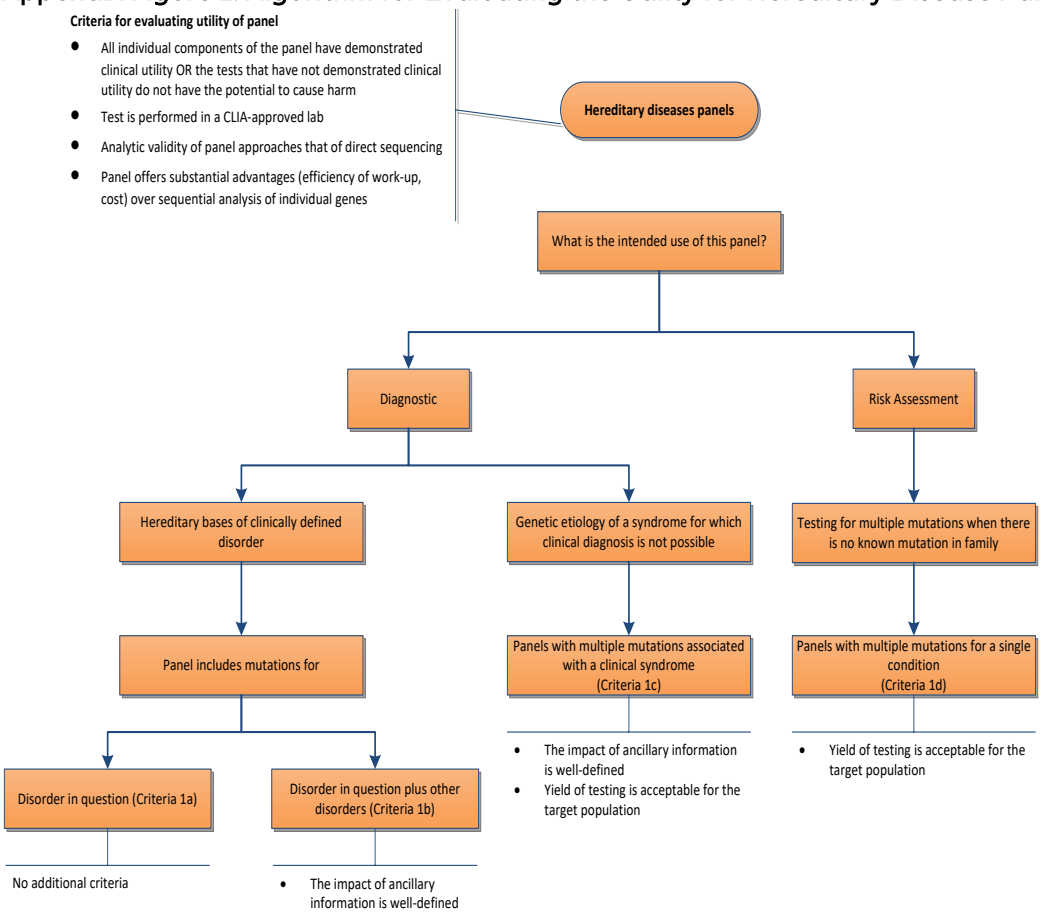
Panel Category	Examples of Disease Tests by Respective Panel	Criteria for Evaluating Utility of Panel
		clinical utility do not have a potential to cause harm • Testing is performed in a CLIA-approved lab • Analytic validity of panel approaches that of direct sequencing • Panel testing offers substantial advantages in efficiency compared with sequential analysis of individual genes
Category 3a – Preconception testing of at-risk individuals Panels that include only variants associated with increased risk	• Ashkenazi Jewish Carrier test Panel • ACMG or ACOG Guidelines Based Carrier Screening Panel	• Includes all criteria for criterion 3 (Reproductive panels) PLUS • Decision making based on genetic results is well-defined •
Category 3b - Preconception testing of at-risk individuals Panels that include variants associated with increased risk plus other variants	• Ethnicity Specific Panel • Pre-conception Based Panel	• Includes all criteria for criterion 3 (Reproductive panels) PLUS • Decision making based on genetic results is well-defined • Impact of ancillary information is defined
Category 3c – Preconception screening Panels intended for preconception testing – screening panels for different populations	• Preconception Screening Panel	• Includes all criteria for criterion 3 (Reproductive panels) PLUS • Yield of testing is acceptable for the target population • Decision making based on genetic results is well-defined
Category 3d – Prenatal screening Panels that include only variants associated with increased risk	• Targeted Array Comparative Hybridization (aCGH) Panel	• Includes all criteria for criterion 3 (Reproductive panels) PLUS • Decision making based on genetic results is well-defined
Category 3e - Prenatal screening Panels that include variants associated with increased risk plus other variants	• Targeted Array Comparative Hybridization (aCGH) Panel	• Includes all criteria for criterion 3 (Reproductive panels) PLUS • Yield of testing is acceptable for the target population • Decision making based on genetic results is well-defined
Category 3f – Preimplantation testing Panels that include only variants associated with increased risk	• Targeted Array Comparative Hybridization (aCGH) Panel	• Includes all criteria for criterion 3 (Reproductive panels) PLUS • Decision making based on genetic results is well-defined
Category 3g – Preimplantation testing Panels that include variants associated with increased risk plus other variants	• Targeted Array Comparative Hybridization (aCGH) Panel	• Includes all criteria for criterion 3 (Reproductive panels) PLUS • Yield of testing is acceptable for the target population • Decision making based on genetic results is well-defined

CLIA: Clinical Laboratory Improvement Amendments.

Appendix Figure 1. General Categories

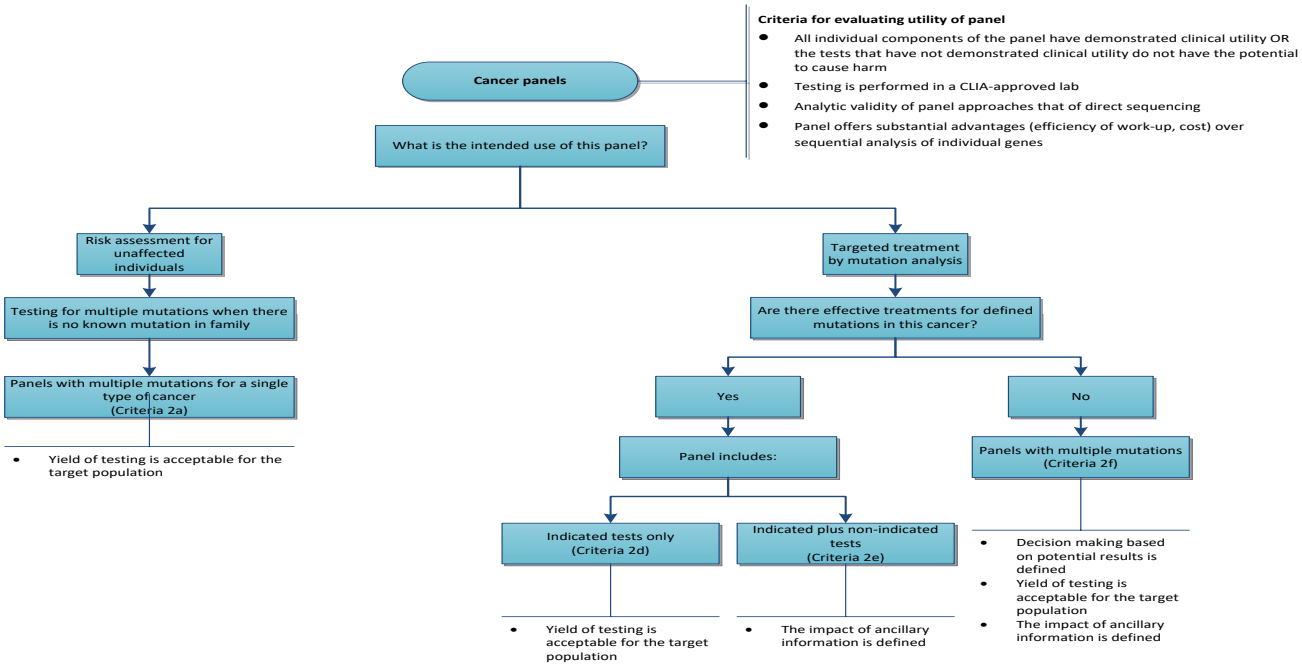


Appendix Figure 2. Algorithm for Evaluating the Utility for Hereditary Disease Panels



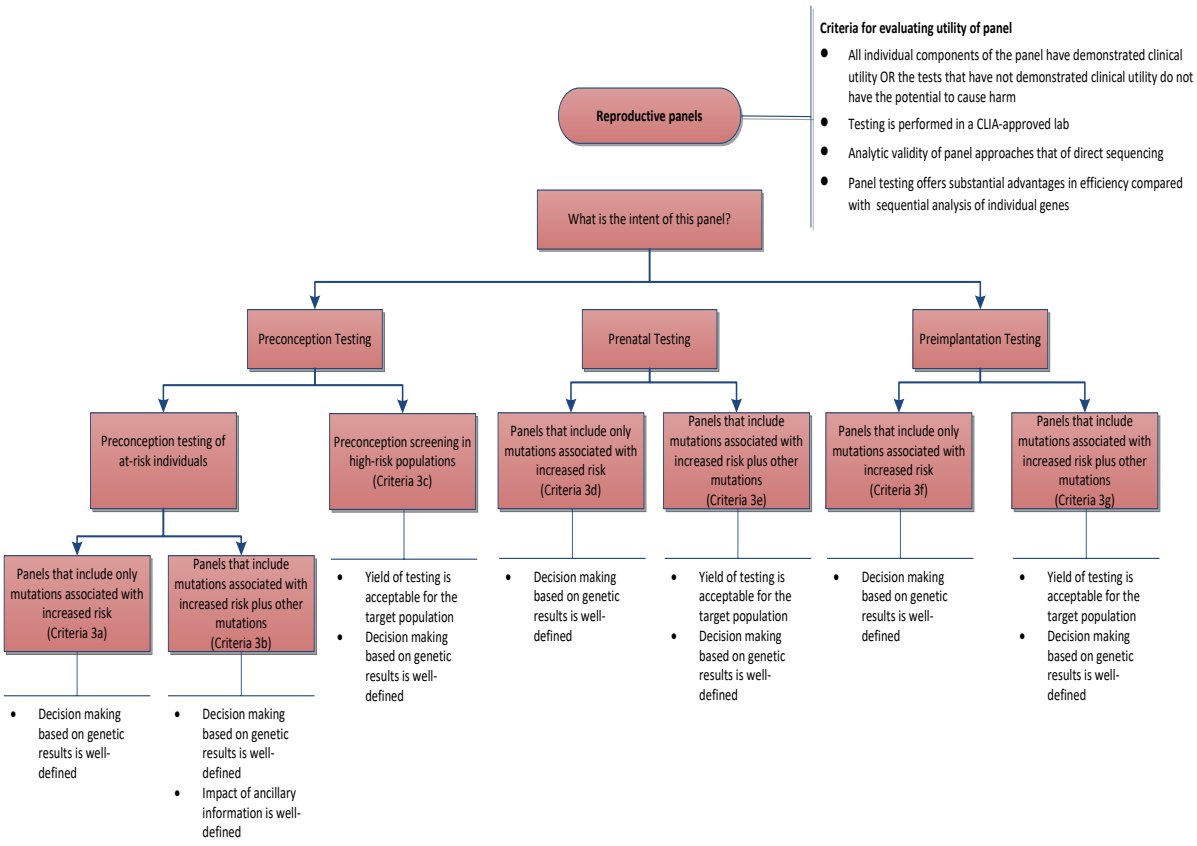
CLIA: Clinical Laboratory Improvement Amendments.

Appendix Figure 3. Algorithm for Evaluating the Utility of Cancer Panels



CLIA: Clinical Laboratory Improvement Amendments.

Appendix Figure 4. Algorithm for Evaluating Utility for Reproductive Panels



CLIA: Clinical Laboratory Improvement Amendments.

References

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
- Family history if applicable
- How test result will impact clinical decision making
- Reason for performing test
- Signs/symptoms/test results related to reason for genetic testing Cancer description, location and tumor staging if applicable
- Provider order for genetic test
- Name and description of genetic panel
- Name of laboratory performing the test
- Any available evidence supporting the analytic validity and clinical validity/utility of the specific genetic panel
- CPT codes to be billed for the particular genetic panel

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0268U	Hematology (atypical hemolytic uremic syndrome [aHUS]), genomic sequence analysis of 15 genes, blood, buccal swab, or amniotic fluid
	0285U	Oncology, response to radiation, cell-free DNA, quantitative branched chain DNA amplification, plasma, reported as a radiation toxicity score
	0294U	Longevity and mortality risk, mRNA, gene expression profiling by RNA sequencing of 18 genes, whole blood, algorithm reported as predictive risk score
	81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81165	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81166	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81167	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81200	ASPA (aspartoacylase) (e.g., Canavan disease) gene analysis, common variants (e.g., E285A, Y231X)
	81201	APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
	81202	APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
	81203	APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
	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)
	81206	BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative ***(Code revision effective 1/1/2023)***
	81207	BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative

Type	Code	Description
	81208	BCR/ABL1 (t(9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative ***(Code revision effective 1/1/2023)***
	81209	BLM (Bloom syndrome, RecQ helicase-like) (e.g., Bloom syndrome) gene analysis, 2281del6ins7 variant
	81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (e.g., colon cancer, melanoma), gene analysis, V600 variant(s)
	81212	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
	81215	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
	81216	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81217	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
	81218	CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (e.g., acute myeloid leukemia), gene analysis, full gene sequence
	81219	CALR (calreticulin) (e.g., myeloproliferative disorders), gene analysis, common variants in exon 9
	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)
	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
	81235	EGFR (epidermal growth factor receptor) (e.g., non-small cell lung cancer) gene analysis, common variants (e.g., exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
	81240	F2 (prothrombin, coagulation factor II) (e.g., hereditary hypercoagulability) gene analysis, 20210G>A variant
	81241	F5 (coagulation factor V) (e.g., hereditary hypercoagulability) gene analysis, Leiden variant

Type	Code	Description
	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 mental retardation 1) (e.g., fragile X mental retardation) gene analysis; evaluation to detect abnormal (e.g., expanded) alleles
	81244	FMR1 (fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; characterization of alleles (e.g., expanded size and methylation status)
	81245	FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (i.e., exons 14, 15)
	81246	FLT3 (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (e.g., D835, I836)
	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)
	81252	GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (e.g., nonsyndromic hearing loss) gene analysis; full gene sequence
	81253	GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (e.g., nonsyndromic hearing loss) gene analysis; known familial variants
	81254	GJB6 (gap junction protein, beta 6, 30kDa, connexin 30) (e.g., nonsyndromic hearing loss) gene analysis, common variants (e.g., 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])
	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; 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) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; known familial variant
	81259	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., 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)
	81261	IGH@ (Immunoglobulin heavy chain locus) (e.g., leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); amplified methodology (e.g., polymerase chain reaction)
	81262	IGH@ (Immunoglobulin heavy chain locus) (e.g., leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); direct probe methodology (e.g., Southern blot)
	81263	IGH@ (Immunoglobulin heavy chain locus) (e.g., leukemia and lymphoma, B-cell), variable region somatic mutation analysis
	81264	IGK@ (Immunoglobulin kappa light chain locus) (e.g., leukemia and lymphoma, B-cell), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)

Type	Code	Description
	81265	Comparative analysis using Short Tandem Repeat (STR) markers; patient and comparative specimen (e.g., pre-transplant recipient and donor germline testing, post-transplant non-hematopoietic recipient germline [e.g., buccal swab or other germline tissue sample] and donor testing, twin zygosity testing, or maternal cell contamination of fetal cells)
	81266	Comparative analysis using Short Tandem Repeat (STR) markers; each additional specimen (e.g., additional cord blood donor, additional fetal samples from different cultures, or additional zygosity in multiple birth pregnancies) (List separately in addition to code for primary procedure)
	81267	Chimerism (engraftment) analysis, post transplantation specimen (e.g., hematopoietic stem cell), includes comparison to previously performed baseline analyses; without cell selection
	81268	Chimerism (engraftment) analysis, post transplantation specimen (e.g., hematopoietic stem cell), includes comparison to previously performed baseline analyses; with cell selection (e.g., CD3, CD33), each cell type
	81269	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis; duplication/deletion variants
	81270	JAK2 (Janus kinase 2) (e.g., myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
	81272	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (e.g., gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (e.g., exons 8, 11, 13, 17, 18)
	81273	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (e.g., mastocytosis), gene analysis, D816 variant(s)
	81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; variants in exon 2 (e.g., codons 12 and 13)
	81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; additional variant(s) (e.g., codon 61, codon 146)
	81287	MGMT (O-6-methylguanine-DNA methyltransferase) (e.g., glioblastoma multiforme) promoter methylation analysis
	81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
	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)
	81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81293	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
	81294	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
	81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

Type	Code	Description
	81296	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
	81297	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
	81298	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81299	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
	81300	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
	81301	Microsatellite instability analysis (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (e.g., BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
	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
	81311	NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (e.g., colorectal carcinoma), gene analysis, variants in exon 2 (e.g., codons 12 and 13) and exon 3 (e.g., codon 61)
	81313	PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (e.g., prostate cancer)
	81314	PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) (e.g., gastrointestinal stromal tumor [GIST]), gene analysis, targeted sequence analysis (e.g., exons 12, 18)
	81315	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (e.g., promyelocytic leukemia) translocation analysis; common breakpoints (e.g., intron 3 and intron 6), qualitative or quantitative
	81316	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (e.g., promyelocytic leukemia) translocation analysis; single breakpoint (e.g., intron 3, intron 6 or exon 6), qualitative or quantitative
	81317	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81318	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
	81319	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
	81321	PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis

Type	Code	Description
	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
	81330	SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) (e.g., Niemann-Pick disease, Type A) gene analysis, common variants (e.g., R496L, L302P, fsP330)
	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)
	81340	TRB@ (T cell antigen receptor, beta) (e.g., leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using amplification methodology (e.g., polymerase chain reaction)
	81341	TRB@ (T cell antigen receptor, beta) (e.g., leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using direct probe methodology (e.g., Southern blot)
	81342	TRG@ (T cell antigen receptor, gamma) (e.g., leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
	81350	UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (e.g., drug metabolism, hereditary unconjugated hyperbilirubinemia [Gilbert syndrome]) gene analysis, common variants (e.g., *28, *36, *37)
	81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (e.g., warfarin metabolism), gene analysis, common variant(s) (e.g., -1639G>A, c.173+1000C>T)
	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
	81410	Aortic dysfunction or dilation (e.g., Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); genomic sequence analysis panel, must include sequencing of at least 9 genes, including FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK

Type	Code	Description
	81411	Aortic dysfunction or dilation (e.g., Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome); duplication/deletion analysis panel, must include analyses for TGFBR1, TGFBR2, MYH11, and COL3A1
	81412	Ashkenazi Jewish associated disorders (e.g., 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 (e.g., 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 (e.g., 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 (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
	81416	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (e.g., parents, siblings) (List separately in addition to code for primary procedure)
	81417	Exome (e.g., unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (e.g., updated knowledge or unrelated condition/syndrome)
	81420	Fetal chromosomal aneuploidy (e.g., trisomy 21, monosomy X) genomic sequence analysis panel, circulating cell-free fetal DNA in maternal blood, must include analysis of chromosomes 13, 18, and 21
	81425	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis
	81426	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (e.g., parents, siblings) (List separately in addition to code for primary procedure)
	81427	Genome (e.g., unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (e.g., updated knowledge or unrelated condition/syndrome)
	81430	Hearing loss (e.g., nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, must include sequencing of at least 60 genes, including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1
	81432	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53
	81433	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11

Type	Code	Description
	81434	Hereditary retinal disorders (e.g., retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy), genomic sequence analysis panel, must include sequencing of at least 15 genes, including ABCA4, CNGA1, CRB1, EYS, PDE6A, PDE6B, PRPF31, PRPH2, RDH12, RHO, RP1, RP2, RPE65, RPGR, and USH2A
	81435	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11
	81436	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11
	81437	Hereditary neuroendocrine tumor disorders (e.g., medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); genomic sequence analysis panel, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TMEM127, and VHL
	81438	Hereditary neuroendocrine tumor disorders (e.g., medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL
	81439	Hereditary cardiomyopathy (e.g., hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy), genomic sequence analysis panel, must include sequencing of at least 5 cardiomyopathy-related genes (e.g., DSG2, MYBPC3, MYH7, PKP2, TTN)
	81440	Nuclear encoded mitochondrial genes (e.g., neurologic or myopathic phenotypes), genomic sequence panel, must include analysis of at least 100 genes, including BCS1L, C10orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAZ, TK2, and TYMP
	81442	Noonan spectrum disorders (e.g., Noonan syndrome, cardio-facio-cutaneous syndrome, Costello syndrome, LEOPARD syndrome, Noonan-like syndrome), genomic sequence analysis panel, must include sequencing of at least 12 genes, including BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, and SOS1
	81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (e.g., ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
	81450	Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, and RNA analysis when performed, 5-50 genes (e.g., BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed
	81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (e.g., ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL,

Type	Code	Description
		NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
	81460	Whole mitochondrial genome (e.g., 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
	81465	Whole mitochondrial genome large deletion analysis panel (e.g., Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia), including heteroplasmy detection, if performed
	81470	X-linked intellectual disability (XLID) (e.g., syndromic and non-syndromic XLID); genomic sequence analysis panel, must include sequencing of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2
	81471	X-linked intellectual disability (XLID) (e.g., syndromic and non-syndromic XLID); duplication/deletion gene analysis, must include analysis of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2
	81479	Unlisted molecular pathology procedure
	81500	Oncology (ovarian), biochemical assays of two proteins (CA-125 and HE4), utilizing serum, with menopausal status, algorithm reported as a risk score
	81503	Oncology (ovarian), biochemical assays of five proteins (CA-125, apolipoprotein A1, beta-2 microglobulin, transferrin, and pre-albumin), utilizing serum, algorithm reported as a risk score
	81506	Endocrinology (type 2 diabetes), biochemical assays of seven analytes (glucose, HbA1c, insulin, hs-CRP, adiponectin, ferritin, interleukin 2-receptor alpha), utilizing serum or plasma, algorithm reporting a risk score
	81507	Fetal aneuploidy (trisomy 21, 18, and 13) DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy
	81508	Fetal congenital abnormalities, biochemical assays of two proteins (PAPP-A, hCG [any form]), utilizing maternal serum, algorithm reported as a risk score
	81509	Fetal congenital abnormalities, biochemical assays of three proteins (PAPP-A, hCG [any form], DIA), utilizing maternal serum, algorithm reported as a risk score
	81510	Fetal congenital abnormalities, biochemical assays of three analytes (AFP, uE3, hCG [any form]), utilizing maternal serum, algorithm reported as a risk score
	81511	Fetal congenital abnormalities, biochemical assays of four analytes (AFP, uE3, hCG [any form], DIA) utilizing maternal serum, algorithm reported as a risk score (may include additional results from previous biochemical testing)
	81512	Fetal congenital abnormalities, biochemical assays of five analytes (AFP, uE3, total hCG, hyperglycosylated hCG, DIA) utilizing maternal serum, algorithm reported as a risk score

Type	Code	Description
	81599	Unlisted multianalyte assay with algorithmic analysis
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
09/27/2013	BCBSA Medical Policy Adoption
01/30/2015	Coding Update
07/31/2015	Coding Update
02/01/2016	Coding Update Policy revision without position change
05/01/2016	Policy revision without position change
02/01/2017	Coding update
03/01/2017	Administrative Update (Laboratory clarification)
06/01/2017	Policy revision without position change
02/01/2018	Policy revision without position change Coding update
01/01/2019	Policy statement clarification Coding update
05/01/2019	Policy revision without position change
08/01/2019	Administrative Update
03/01/2020	Coding update
04/01/2020	Annual review. No change to policy statement.
01/01/2021	Coding update
04/01/2021	Annual review. No change to policy statement. Policy guidelines updated.
11/01/2021	Coding update
03/01/2022	Coding update
04/01/2022	Annual review. No change to policy statement.
10/01/2022	Administrative Update
03/01/2023	Coding update
04/01/2023	Annual review. No change to policy statement.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
General Approach to Evaluating the Utility of Genetic Panels 2.04.92 **Policy Statement:** **Note**: Starting on July 1, 2022 (per CA law SB 535) for commercial plans regulated by the California Department of Managed Healthcare and California Department of Insurance (PPO and HMO), health care service plans and insurers shall not require prior authorization for biomarker testing, including biomarker testing for cancer progression and recurrence, if a member has stage 3 or 4 cancer. Health care service plans and insurers can still do a medical necessity review of a biomarker test and possibly deny coverage after biomarker testing has been completed and a claim is submitted (post service review). I. Genetic panels that are limited in scope, use next-generation sequencing or chromosomal microarray analysis, that are not addressed in another policy more specific to the request (see Policy Guidelines and Rationale section), and meet all criteria (**as outlined in the Rationale section**) and are classified in one of the categories below, may be considered **medically necessary** when the individual is felt to be at high risk based on clinical information: A. Panels for hereditary or genetic conditions 1. Diagnostic testing of an individual's germline to benefit the individual 2. Testing of an asymptomatic individual to determine future risk of disease B. Cancer panels 1. Testing of an asymptomatic individual to determine future risk of cancer 2. Testing cancer cells from an individual to benefit the individual by identifying targeted treatment C. Reproductive panels 1. Preconception testing a. Carrier testing of the parent(s)	**General Approach to Evaluating the Utility of Genetic Panels 2.04.92** **Policy Statement:** **Note**: Starting on July 1, 2022 (per CA law SB 535) for commercial plans regulated by the California Department of Managed Healthcare and California Department of Insurance (PPO and HMO), health care service plans and insurers shall not require prior authorization for biomarker testing, including biomarker testing for cancer progression and recurrence, if a member has stage 3 or 4 cancer. Health care service plans and insurers can still do a medical necessity review of a biomarker test and possibly deny coverage after biomarker testing has been completed and a claim is submitted (post service review). I. Genetic panels that are limited in scope, use next-generation sequencing or chromosomal microarray analysis, that are not addressed in another policy more specific to the request (see Policy Guidelines and Rationale section), and meet all criteria (**as outlined in the Rationale section**) and are classified in one of the categories below, may be considered **medically necessary** when the individual is felt to be at high risk based on clinical information: A. Panels for hereditary or genetic conditions 1. Diagnostic testing of an individual's germline to benefit the individual 2. Testing of an asymptomatic individual to determine future risk of disease B. Cancer panels 1. Testing of an asymptomatic individual to determine future risk of cancer 2. Testing cancer cells from an individual to benefit the individual by identifying targeted treatment C. Reproductive panels 1. Preconception testing a. Carrier testing of the parent(s)

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
2. Prenatal testing a. Carrier testing of the parent(s) b. In utero testing of a fetus, including testing for aneuploidy or familial variants 3. Preimplantation genetic testing II. Genetic panels that use next-generation sequencing or chromosomal microarray that do not meet the criteria for a specific category are considered **investigational,** including but not limited to general screening or large panels (unless clearly noted to be medically necessary in a policy more specific to the request).	2. Prenatal testing a. Carrier testing of the parent(s) b. In utero testing of a fetus, including testing for aneuploidy or familial variants 3. Preimplantation genetic testing II. Genetic panels that use next-generation sequencing or chromosomal microarray that do not meet the criteria for a specific category are considered **investigational,** including but not limited to general screening or large panels (unless clearly noted to be medically necessary in a policy more specific to the request).