PHP_2.04.92	General Approach to Evaluating the Utility of Genetic Panels		
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Section:	2.0 Medicine	**Page:**	Page 1 of 24

State Guidelines

Applicable Medi-Cal guidelines as of the publication of this policy (this guideline supersedes the criteria in the Policy Statement section below):

I. Department of Managed Health Care (DMHC) All Plan Letter (APL) Guideline:
- N/A

II. Department of Health Care Services (DHCS) Provider Manual Guideline:
- TAR and Non-Standard Benefits List: Codes 80000 thru 89999 (tar and non cd8)
- Pathology: Molecular Pathology (path molec)

***Due to the broad range of testing/codes that can apply to this policy, please see above link(s) for the specific criteria related to the code(s) being billed.*

Below is an excerpt of the Molecular Pathology guideline language. Please refer to the specific Provider Manual in the link above for the complete guideline.

Biomarker and Pharmacogenetic Testing
Medi-Cal covers medically necessary biomarker and pharmacogenomic testing, as described in the manual section Proprietary Laboratory Analyses (PLA). Medi-Cal may not cover all CPT and HCPCS codes associated with a particular biomarker or pharmacogenomic test. As such, the particular biomarker or pharmacogenomic test code may be covered with an approved Treatment Authorization Request (TAR) if medical necessity is established, as described in the TAR and Non-Benefit: Introduction to List section of the Provider Manual.

Biomarker Testing
Biomarker testing is used to diagnose, treat, manage, or monitor a Medi-Cal member's disease or condition to guide treatment decisions. As defined by Section 14132.09 of the Welfare and Institutions Code, biomarker testing is the analysis of an individual's tissue, blood or other biospecimen for the presence of a biomarker. Biomarker testing includes, but is not limited to, single-analyte tests, multiplex panel tests and whole genome sequencing. Biomarkers are a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a specific therapeutic intervention. A biomarker includes, but is not limited to, gene mutations or protein expression. Medically necessary biomarker testing is subject to utilization controls and evidence-based clinical practice guidelines.

When testing for biomarkers, all Medi-Cal providers must ensure that they are provided in a manner that limits disruptions to care. As with all Medi-Cal benefits, restricted or denied use of biomarker testing for the purpose of diagnosis, treatment or ongoing monitoring of any medical condition is subject to Medi-Cal's grievance, appeal and State Fair Hearing processes, as well as any additional processes established specifically for Medi-Cal managed care plans.

Pharmacogenomic Testing
Pharmacogenomic testing is defined as a laboratory genetic testing that includes, but is not limited to, a panel test to identify how a person's genetics may impact the efficacy, toxicity and safety of medications. Medically necessary pharmacogenomic testing is covered subject to utilization controls and evidence-based clinical practice guidelines.

III. Department of Health Care Services (DHCS) All Plan Letter (APL) Guideline:
- APL 22-010 – Cancer Biomarker Testing

Below is an excerpt of the guideline language. Please refer to the specific All Plan Letter in the link above for the complete guideline.

For the purposes of this APL, "Biomarker test" is defined as a diagnostic test, single or multigene, of an individual's biospecimen, such as tissue, blood, or other bodily fluids, for DNA or RNA alterations, including phenotypic characteristics of a malignancy, to identify an individual with a subtype of cancer, in order to guide treatment. Biomarkers, also called tumor markers, are substances found in higher-than-normal levels in the cancer itself, or in blood, urine, or tissues of some individuals with cancer. Biomarkers can determine the likelihood some types of cancer will spread. They can also help doctors choose the best treatment.

Medi-Cal managed care health plans (MCPs) are required to cover medically necessary biomarker testing for members with:
- Advanced or metastatic stage 3 or 4 cancer.
- Cancer progression or recurrence in the member with advanced or metastatic stage 3 or 4 cancer.

MCPs are prohibited from imposing prior authorization requirements on biomarker testing that is associated with a federal Food and Drug Administration (FDA)-approved therapy for advanced or metastatic stage 3 or 4 cancer. If the biomarker test is not associated with an FDA-approved cancer therapy for advanced or metastatic stage 3 or 4 cancer, MCPs may still require prior authorization for such testing.

Policy Statement

Any criteria that are not specifically addressed in the above APL and Provider Manuals, please refer to the criteria below.

I. Genetic panels that use next-generation sequencing or chromosomal microarray analysis, and are classified in one of the categories below, may be considered **medically necessary** when all criteria are met for each category, as outlined in the Rationale section:
   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.**

Policy Guidelines

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. 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.

Coding
See the Codes table for details.

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.

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, i.e., whether the advantages of panel testing outweigh the disadvantages for the specific condition under consideration.

Panels can be classified into categories based on their intended use and composition. For each category of panels, specific criteria can be used to evaluate medical necessity. When all criteria for a given category are met, that panel may be considered medically necessary.

Related Policies

- Comprehensive Genomic Profiling for Selecting Targeted Cancer Therapies
- General Approach to Genetic Testing

Benefit Application

Blue Shield of California Promise Health Plan is contracted with L.A. Care Health Plan for Los Angeles County and the Department of Health Care Services for San Diego County to provide Medi-Cal health benefits to its Medi-Cal recipients. In order to provide the best health care services and practices, Blue Shield of California Promise Health Plan has an extensive network of Medi-Cal primary care providers and specialists. Recognizing the rich diversity of its membership, our providers are given training and educational materials to assist in understanding the health needs of their patients as it could be affected by a member's cultural heritage.

The benefit designs associated with the Blue Shield of California Promise Medi-Cal plans are described in the Member Handbook (also called Evidence of Coverage).

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments 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 impractical. For example, the EGL Genetics offers 243 different genetic panels, of a total of 929 molecular genetics tests.[11] Table 1 provides a sample of panels that use NGS or chromosomal microarray technologies.

Table 1. Panels Using Next-Generation Sequencing or Chromosomal Microarray Analysis (as of December 2017)

Test Name	Laboratory
Agammaglobulinemia Panel	ARUP Laboratories
Ashkenazi Jewish Diseases Panel	ARUP Laboratories
Mitochondrial Disorders Panel	ARUP Laboratories
Amyotrophic Lateral Sclerosis Panel	ARUP Laboratories
Aortopathy Panel	ARUP Laboratories
Autism Panel	ARUP Laboratories
Brugada Syndrome Panel	ARUP Laboratories
Vascular Malformation Syndromes	ARUP Laboratories
Retinitis Pigmentosa/Leber Congenital Amaurosis Panel	ARUP Laboratories
Cardiomyopathy and Arrhythmia Panel	ARUP Laboratories
Periodic Fever Syndromes Panel	ARUP Laboratories
Arrhythmias Sequencing Panel	EGL Genetics
Arrhythmias Deletion/Duplication Panel	EGL Genetics
Autism Spectrum Disorders	EGL Genetics
Cardiomyopathy Panel	EGL Genetics
Ciliopathies Panel	EGL Genetics
Congenital Glycosylation Disorders	EGL Genetics
ACOG/ACMG Carrier Screen Targeted Mutation Panel	EGL Genetics
Epilepsy	EGL Genetics
Eye Disorders	EGL Genetics
Neuromuscular Disorders	EGL Genetics
Noonan Syndrome and Related Disorders	EGL Genetics
Short Stature Panel	EGL Genetics
Sudden Cardiac Arrest Panel	EGL Genetics
X-linked Intellectual Disability	EGL Genetics
CancerNext™	Ambry Genetics
BreastNext™	Ambry Genetics
ColoNext™	Ambry Genetics
OvaNext™	Ambry Genetics
RhythmNext®	Ambry Genetics
X-linked Intellectual Disability	Ambry Genetics
TAADNext®	Ambry Genetics
Cobalamin Metabolism Comprehensive Panel	Baylor College of Medicine
Progressive External Ophthalmoplegia Panel	Baylor College of Medicine
CoQ10 Comprehensive Panel	Baylor College of Medicine
Usher Syndrome Panel	Baylor College of Medicine
Retinitis Pigmentosa Panel	Baylor College of Medicine

Test Name	Laboratory
Pyruvate Dehydrogenase Deficiency and Mitochondrial Respiratory Chain Complex V Deficiency Panel	Baylor College of Medicine
Myopathy/Rhabdomyolysis Panel	Baylor College of Medicine
Mitochondrial Disorders Panel	Baylor College of Medicine
Low Bone Mass Panel	Baylor College of Medicine
Glycogen Storage Disorders Panel	Baylor College of Medicine
Leigh Disease Panel	Medical Neurogenetics
Pan Cardiomyopathy Panel	Partners Healthcare
Isolated Non-syndromic Congenital Heart Defects Panel	Partners Healthcare
Noonan Spectrum Panel	Partners Healthcare
Usher Syndrome Panel	Partners Healthcare
Hereditary Colon Cancer Syndromes	Mayo Medical Laboratories
Hypertrophic Cardiomyopathy Panel	Mayo Medical Laboratories
Dilated Cardiomyopathy Panel	Mayo Medical Laboratories
Arrhythmogenic Right Ventricular Cardiomyopathy Panel	Mayo Medical Laboratories
Noonan Syndrome Panel	Mayo Medical Laboratories
Marfan Syndrome Panel	Mayo Medical Laboratories
Long QT Syndrome	Mayo Medical Laboratories
Brugada Syndrome	Mayo Medical Laboratories
Signature Prenatal Microarray	Signature Genomics
Counsyl™ Panel	Counsyl Genomics
GoodStart Select™	GoodStart Genetics

Health Equity Statement

Blue Shield of California Promise Health Plan's mission is to transform its health care delivery system into one that is worthy of families and friends. Blue Shield of California Promise Health Plan seeks to advance health equity in support of achieving Blue Shield of California Promise Health Plan's mission.

Blue Shield of California Promise Health Plan ensures all Covered Services are available and accessible to all members regardless of sex, race, color, religion, ancestry, national origin, ethnic group identification, age, mental disability, physical disability, medical condition, genetic information, marital status, gender, gender identity, or sexual orientation, or identification with any other persons or groups defined in Penal Code section 422.56, and that all Covered Services are provided in a culturally and linguistically appropriate manner.

Rationale

Background

This conceptual framework applies if there is not a separate evidence review 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 evidence review is to provide a framework 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 variant 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 one of the variants included in the panel has been established, then the focus is on whether the 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. The definition of a panel will not include panels that report on gene expression profiling, which generally do not directly evaluate genetic variants.

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.[2,3,4] 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 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 Signature Prenatal Microarray 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, i.e., 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	
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)

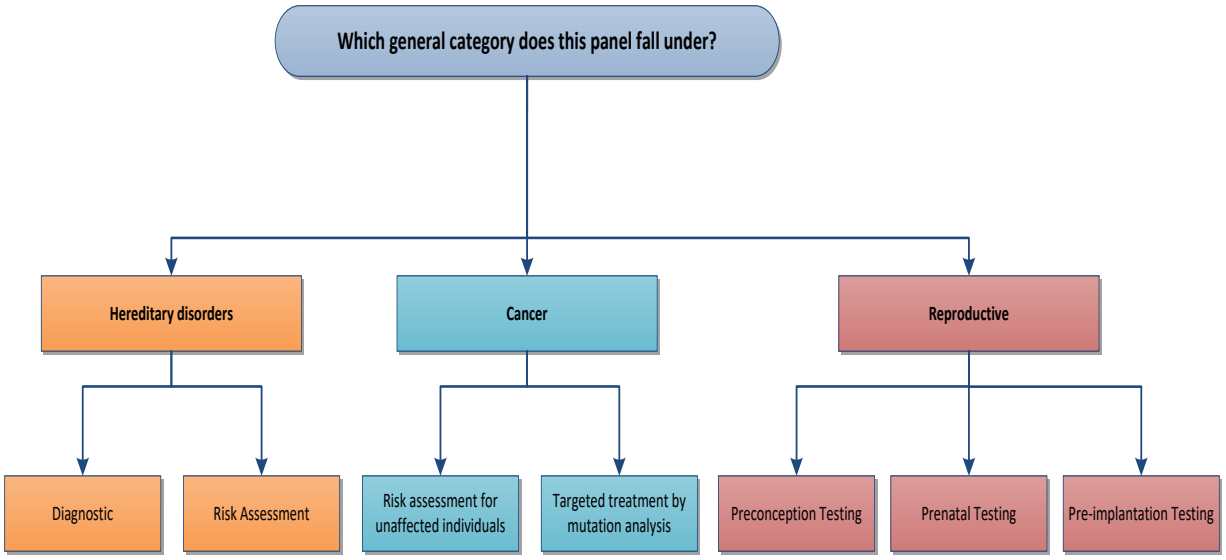
Panel Category	Examples of Disease Tests by Respective Panel	Criteria for Evaluating Utility of Panel
Category 1b – Diagnostic testing Panels that include variants for multiple conditions (indicated plus nonindicated conditions)	• Retinitis Pigmentosa/Leber Congenital Amaurosis Panel • Cardiology Disorders 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 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)	• 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

Panel Category	Examples of Disease Tests by Respective Panel	Criteria for Evaluating Utility of Panel
• Effective targeted treatment based on variant analysis has not been established		
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 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

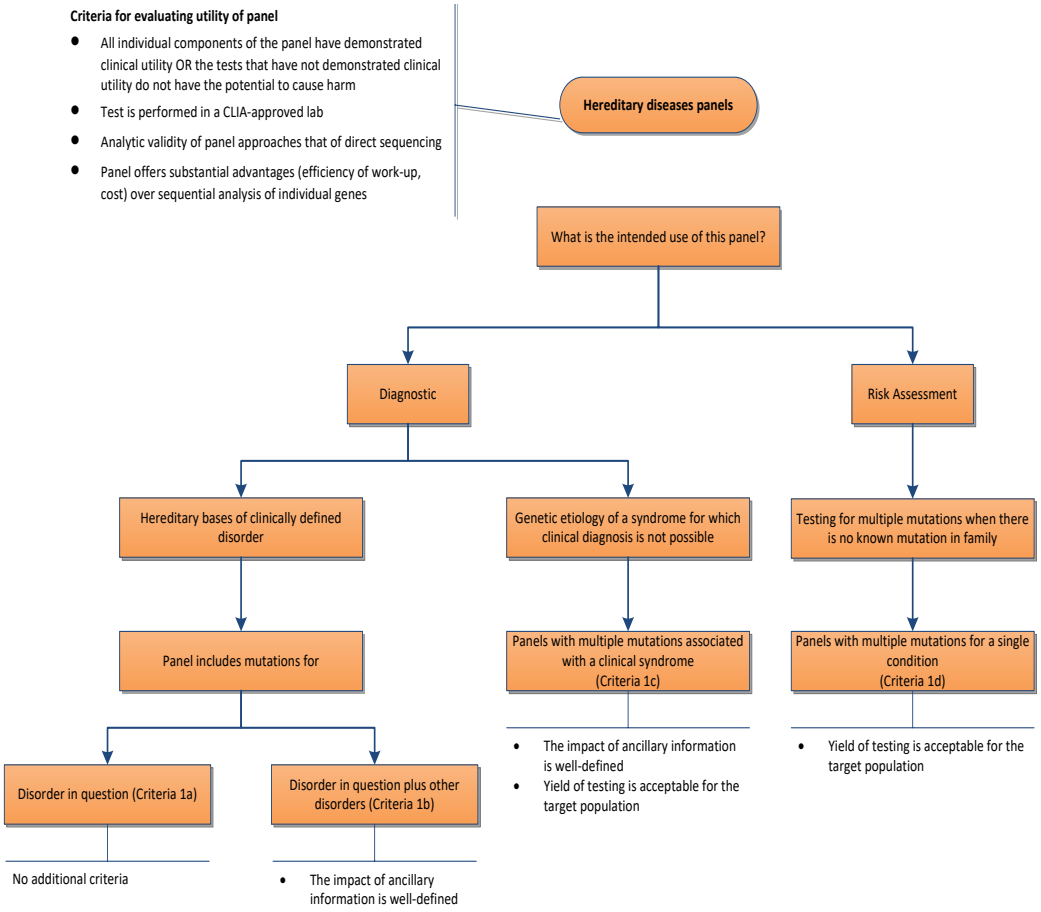
Panel Category	Examples of Disease Tests by Respective Panel	Criteria for Evaluating Utility of Panel
		• Decision making based on genetic results is well-defined
Category 3f – Preimplantation testing Panels that include only variants associated with increased risk	• Targeted Array Comparative Hybridization (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

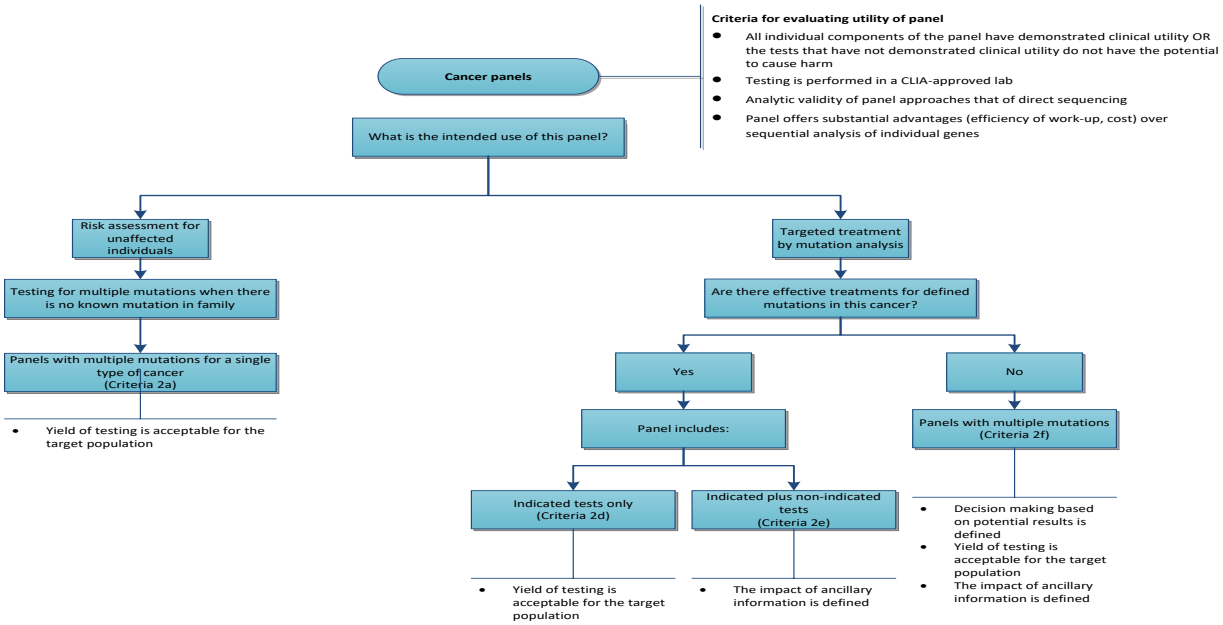


Appendix Figure 2. Algorithm for Evaluating the Utility for Hereditary Disease Panels



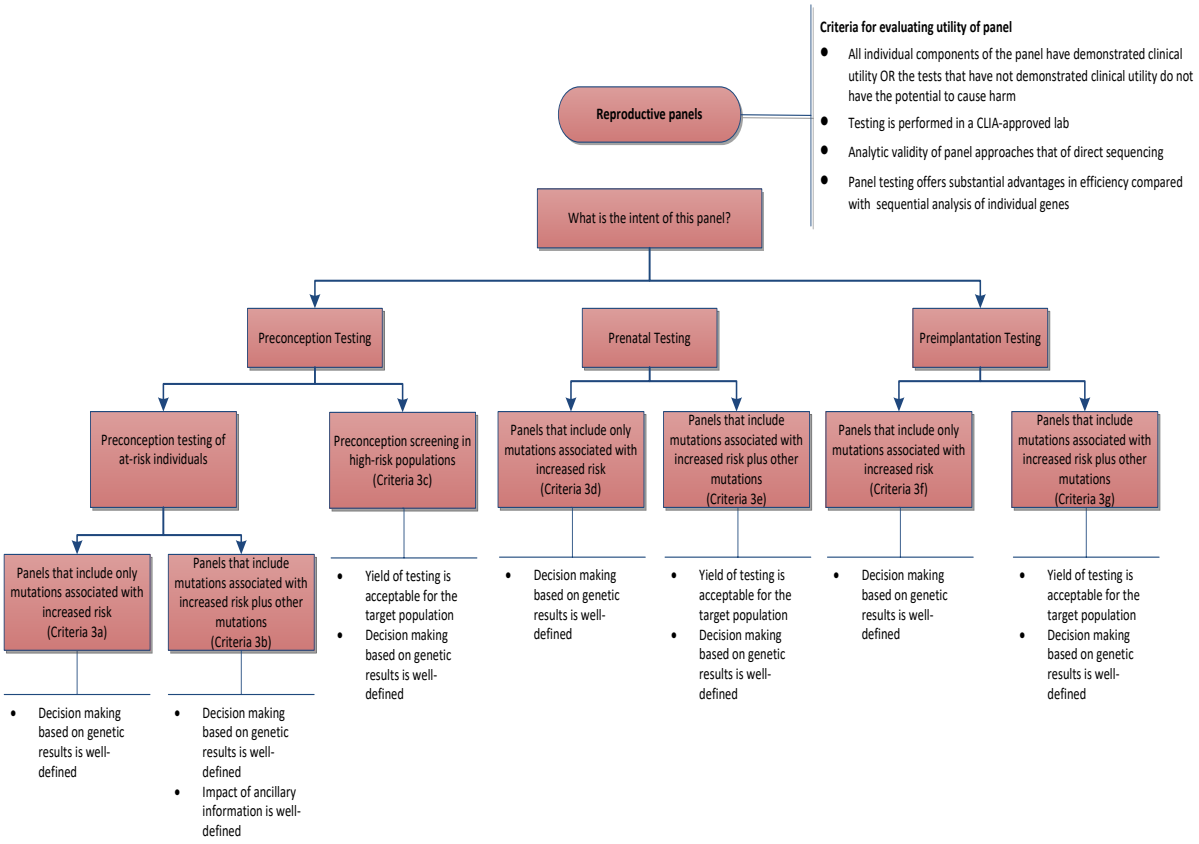
CLIA: Clinical Laboratory Improvement Amendments.

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.

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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

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	0315U	Oncology (cutaneous squamous cell carcinoma), mRNA gene expression profiling by RT-PCR of 40 genes (34 content and 6 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical risk result (i.e., Class 1, Class 2A, Class 2B) Includes DecisionDx®-SCC, Castle Biosciences, Inc, Castle Biosciences, Inc
	81200-81355	Tier 1 molecular pathology procedures for targeted germline or somatic genetic testing of specific genes with established clinical utility

Type	Code	Description
	81400	Molecular pathology procedure, Level 1 (e.g., identification of single germline variant [e.g., SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
	81401	Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
	81402	Molecular pathology procedure, Level 3 (e.g., >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])
	81403	Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
	81404	Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
	81405	Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
	81406	Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
	81407	Molecular pathology procedure, Level 8 (e.g., analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
	81408	Molecular pathology procedure, Level 9 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis)
	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
	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

Type	Code	Description
	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)
	81418	Drug metabolism (e.g., pharmacogenomics) genomic sequence analysis panel, must include testing of at least 6 genes, including CYP2C19, CYP2D6, and CYP2D6 duplication/deletion analysis
	81419	Epilepsy genomic sequence analysis panel, must include analyses for ALDH7A1, CACNA1A, CDKL5, CHD2, GABRG2, GRIN2A, KCNQ2, MECP2, PCDH19, POLG, PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, SLC2A1, SLC9A6, STXBP1, SYNGAP1, TCF4, TPP1, TSC1, TSC2, and ZEB2
	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
	81422	Fetal chromosomal microdeletion(s) genomic sequence analysis (e.g., DiGeorge syndrome, Cri-du-chat syndrome), circulating cell-free fetal DNA in maternal blood
	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
	81431	Hearing loss (e.g., nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); duplication/deletion analysis panel, must include copy number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes
	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
	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

Type	Code	Description
	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
	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
	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
	81441	Inherited bone marrow failure syndromes (IBMFS) (e.g., Fanconi anemia, dyskeratosis congenita, Diamond-Blackfan anemia, Shwachman-Diamond syndrome, GATA2 deficiency syndrome, congenital amegakaryocytic thrombocytopenia) sequence analysis panel, must include sequencing of at least 30 genes, including BRCA2, BRIP1, DKC1, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, GATA1, GATA2, MPL, NHP2, NOP10, PALB2, RAD51C, RPL11, RPL35A, RPL5, RPS10, RPS19, RPS24, RPS26, RPS7, SBDS, TERT, and TINF2
	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
	81443	Genetic testing for severe inherited conditions (e.g., 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 (e.g., ACADM, ARSA, ASPA, ATP7B, BCKDHA, BCKDHB, BLM, CFTR, DHCR7, FANCC, G6PC, GAA, GALT, GBA, GBE1, HBB, HEXA, IKBKAP, MCOLN1, PAH)
	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
	81449	Solid organ neoplasm, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; RNA analysis
	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,

Type	Code	Description
		KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed
	81451	Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
	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, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
	81456	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis
	81457	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, microsatellite instability
	81458	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, copy number variants and microsatellite instability
	81459	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements
	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
	81462	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (e.g., plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants and rearrangements
	81463	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (e.g., plasma), interrogation for sequence variants; DNA analysis, copy number variants, and microsatellite instability
	81464	Solid organ neoplasm, genomic sequence analysis panel, cell-free nucleic acid (e.g., plasma), interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements
	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

Type	Code	Description
	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
	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
03/01/2026	New policy.
06/01/2026	Administrative update. Definitions of Decision Determinations section updated.

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary or **Medical Necessity** means reasonable and necessary services to protect life, to prevent significant illness or significant disability, or alleviate severe pain through the diagnosis or treatment of disease, illness, or injury, as required under W&I section 14059.5(a) and 22 CCR section 51303(a). Medically Necessary services must include services necessary to achieve age-appropriate growth and development, and attain, maintain, or regain functional capacity.

For Members less than 21 years of age, a service is Medically Necessary if it meets the Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) standard of Medical Necessity set forth in 42 USC section 1396d(r)(5), as required by W&I sections 14059.5(b) and 14132(v). Without limitation, Medically Necessary services for Members less than 21 years of age include all services necessary to achieve or maintain age-appropriate growth and development, attain, regain or maintain functional capacity, or improve, support, or maintain the Member's current health condition. Contractor must determine Medical Necessity on a case-by-case basis, taking into account the individual needs of the Child.

Criteria Determining Experimental/Investigational Status

Below is an excerpt of the language taken from California Children's Services Numbered Letter 05-1020.*

*Department of Healthcare Services Numbered Letter 05-1020. Accessed April 21, 2026, from https://www.dhcs.ca.gov/services/ccs/Documents/CCS-NL-05-1020-Experimental-and-Investigational-Services.pdf

Policy

A. The California Children's Services (CCS) Program and the Genetically Handicapped Persons Program (GHPP) will not provide coverage for experimental services unless specifically authorized by law.
B. The CCS Program and GHPP may provide coverage for an investigational service if:
    1. It is approved by the FDA under any Investigational New Drug (IND) Application; or

2. It is authorized for use under the State of California's Right to Try Act; and
3. Its use is consistent with its FDA-approved IND Application or the State of California's Right to Try Act;

C. Additional criteria that will be considered in the adjudication process include:
1. Conventional therapy will not adequately treat the intended patient's condition;
2. Conventional therapy will not prevent progressive disability or premature death;
3. The provider of the proposed service has a record of safety and success with it or equivalent to that of other providers of the investigational services;
4. Other criteria (e.g., cost and availability) may be considered in the adjudication of a given request in cases in which more than one investigational service is available;
5. There is reasonable expectation that the investigational service will significantly prolong the patient's life or will maintain or restore a range of physical and social function suited to activities of daily living; and
6. The service is not being performed as part of a research study protocol. For a beneficiary with cancer who participates in a clinical trial for cancer, California Health and Safety Code (HSC) § 1370.6 requires that all routine patient care costs related to the clinical trial be covered if the beneficiary's CCS-paneled treating physician recommends participation in the clinical trial after determining that participation in the clinical trial has a meaningful potential to benefit the enrollee. The coverage does not include investigational services that have not been approved by the FDA and that are associated with the clinical trial.

Feedback

Blue Shield of California Promise Health Plan is 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 Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/en/bsp/providers.

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

Questions regarding the applicability of this policy should be directed to the Blue Shield of California Promise Health Plan Prior Authorization Department at (800) 468-9935, or the Complex Case Management Department at (855) 699-5557 (TTY 711) for San Diego County and (800) 605-2556 (TTY 711) for Los Angeles County or visit the provider portal at www.blueshieldca.com/en/bsp/providers.

Disclaimer: Blue Shield of California Promise Health Plan 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 member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield of California Promise Health Plan reserves the right to review and update policies as appropriate.