Medical Policy

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Title: General Approach to Evaluating the Utility of Genetic Panels

Related Policies:	▪ *General Approach to Genetic Testing* ▪ *Genetic Cancer Susceptibility Panels Using Next-Generation Sequencing*

Professional / Institutional
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Populations	Interventions	Comparators	Outcomes
Individuals: • Who are symptomatic with a suspected genetically associated disease	**Interventions of interest are:** • Genetic testing for a suspected genetically associated disorder	**Comparators of interest are:** • Standard clinical management without genetic testing	**Relevant outcomes include:** • Test accuracy • Test validity • Disease-specific survival • Overall survival • Change in disease status • Morbid events • Functional outcomes

Populations	Interventions	Comparators	Outcomes
			• Changes in reproductive decision making
Individuals: • Who are asymptomatic and have a close relative diagnosed with a genetically associated disease	**Interventions of interest are:** • Genetic testing for a genetically associated disorder	**Comparators of interest are:** • Standard clinical management without genetic testing	**Relevant outcomes include:** • Test accuracy • Test validity • Disease-specific survival • Overall survival • Change in disease status • Morbid events • Functional outcomes • Changes in reproductive decision making

DESCRIPTION

Panel testing offers potential advantages 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.

OBJECTIVE

The objective of this review is to outline the conceptual framework to assess the clinical utility of genetic panel tests.

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.

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 Pane	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

Test Name	Laboratory
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
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

Test Name	Laboratory
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

POLICY

A. Genetic panels that use next-generation sequencing or chromosomal microarray, 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:

   1. Panels for hereditary or genetic conditions
      a. Diagnostic testing of an individual's germline to benefit the individual
      b. Testing of an asymptomatic individual to determine future risk of disease

   2. Cancer panels
      a. Testing of an asymptomatic individual to determine future risk of cancer
      b. Testing cancer cells from an individual to benefit the individual by identifying targeted treatment

   3. Reproductive panels
      a. Carrier testing of the parent(s) – Preconception
      b. Carrier testing of the parent(s) – Prenatal (during pregnancy)
      c. In utero testing of a fetus

B. Genetic panels that use next-generation sequencing or chromosomal microarray that do not meet the criteria for a specific category are **experimental / investigational.**

POLICY GUIDELINES

Genetics Nomenclature Update

A. 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.

B. 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

Previous	Updated	Definition
	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

A. 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.

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.

RATIONALE

This conceptual framework has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through November 7, 2017.

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 (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 (eg, 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.

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.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. 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.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
Tier 1 Molecular Pathology Procedure Codes	
81200	ASPA (aspartoacylase) (eg, Canavan disease) gene analysis, common variants (eg, E285A, Y231X)
81201	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
81202	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
81203	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
81205	BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)
81206	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
81207	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative
81208	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative
81209	BLM (Bloom syndrome, RecQ helicase-like) (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant
81210	BRAF (BRAF proto-oncogene serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600E variant(s)
81211	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants in BRCA1 (i.e., exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon
81212	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
81213	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; uncommon duplication/deletion variants
81214	BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and common duplication/deletion variants (i.e., exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)

CPT/HCPCS	
81215	BRCA1 (breast cancer 1) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81216	BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81217	BRCA2 (breast cancer 2) (eg, hereditary breast and ovarian cancer) gene analysis; known familial variant
81218	CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid leukemia), gene analysis, full gene sequence)
81219	CALR (calreticulin) (EG, myeloproliferative disorders), gene analysis, common variants in exon 9
81220	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
81221	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; known familial variants
81222	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; duplication/deletion variants
81223	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; full gene sequence
81224	CFTR (cystic fibrosis transmembrane conductance regulator) (eg, cystic fibrosis) gene analysis; intron 8 poly-T analysis (eg, male infertility)
81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *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) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)
81228	Cytogenomic constitutional chromosomal abnormalities (genome-wide) constitutional chromosomal abnormalities analysis; interrogation of genomic regions for copy number variants (eg, Bacterial Artificial Chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)
81229	Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities
81235	EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
81240	F2 (prothrombin, coagulation factor II) (eg, hereditary hypercoagulability) gene analysis, 20210G>A variant
81241	F5 (coagulation Factor V) (eg, hereditary hypercoagulability) gene analysis, Leiden variant
81242	FANCC (Fanconi anemia, complementation group C) (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T)
81243	FMR1 (fragile X messenger ribonucleoprotein 1) (eg, fragile X syndrome, X-linked intellectual disability [XLID]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles

CPT/HCPCS	
81244	FMR1 (Fragile X messenger ribonucleoprotein 1) (eg, fragile X syndrome, X-linked intellectual disability [XLID])gene analysis; characterization of alleles (eg, expanded size and methylation status)
81245	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis, internal tandem duplication (ITD) variants (i.e., exons 14, 15)
81246	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (eg, D835, I836)
81250	G6PC (glucose-6-phosphatase, catalytic subunit) (eg, Glycogen storage disease, Type 1a, von Gierke disease) gene analysis, common variants (eg, R83C, Q347X)
81251	GBA (glucosidase, beta, acid) (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G>A)
81252	GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence
81253	GJB2 (gap junction protein, beta 2, 26kDa; connexin 26) (eg, nonsyndromic hearing loss) gene analysis; known familial variants
81254	GJB6 (gap junction protein, beta 6, 30kDa, connexin 30) (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])
81255	HEXA (hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G>C, G269S)
81256	HFE (hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D)
81257	HBA1/HBA2 (alpha globin 1 and alpha globin 2) (eg, alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for common deletions or variant (eg, Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring)
81260	IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex-associated protein) (eg, familial dysautonomia) gene analysis, common variants (eg, 2507+6T>C, R696P)
81261	IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); amplified methodology (eg, polymerase chain reaction)
81262	IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); direct probe methodology (eg, Southern blot)
81263	IGH@ (Immunoglobulin heavy chain locus) (eg, leukemia and lymphoma, B-cell), variable region somatic mutation analysis
81264	IGK@ (Immunoglobulin kappa light chain locus) (eg, leukemia and lymphoma, B-cell), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
81265	Comparative analysis using Short Tandem Repeat (STR) markers; patient and comparative specimen (eg, pre-transplant recipient and donor germline testing, post-transplant non-hematopoietic recipient germline [eg, buccal swab or other germline tissue sample] and donor testing, twin zygosity testing, or maternal cell contamination of fetal cells)

CPT/HCPCS	
81266	Comparative analysis using Short Tandem Repeat (STR) markers; each additional specimen (eg, 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 procedures)
81267	Chimerism (engraftment) analysis, post transplantation specimen (eg, hematopoietic stem cell), includes comparison to previously performed baseline analyses; without cell selection
81268	Chimerism (engraftment) analysis, post transplantation specimen (eg, hematopoietic stem cell), includes comparison to previously performed baseline analyses; with cell selection (eg, CD3, CD33), each cell type
81270	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
81272	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), gene analysis, D816 variant(s)
81273	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (eg, exons 8, 11, 13, 17, 18)
81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13
81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)
81287	MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme), methylation analysis
81288	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis
81290	MCOLN1 (mucolipin 1) (eg, Mucolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A>G, del6.4kb)
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)
81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81293	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81294	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81296	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81297	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81298	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

CPT/HCPCS	
81299	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81300	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81301	Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
81302	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; full sequence analysis
81303	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; known familial variant
81304	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; duplication/deletion variants
81310	NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants
81311	NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61)
81313	PCA3/KLK3 (prostate cancer antigen 3 [non-protein coding]/kallikrein-related peptidase 3 [prostate specific antigen]) ratio (eg, prostate cancer)
81314	PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) (eg, gastrointestinal stromal tumor [GIST]), gene analysis, targeted sequence analysis (eg, exons 12, 18)
81315	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative
81316	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; single breakpoint (eg, intron 3, intron 6 or exon 6), qualitative or quantitative
81317	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81318	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81319	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
81322	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
81323	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant
81324	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
81325	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis

CPT/HCPCS	
81326	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant
81330	SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)
81331	SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis
81332	SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z)
81340	TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using amplification methodology (eg, polymerase chain reaction)
81341	TRB@ (T cell antigen receptor, beta) (eg, leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s); using direct probe methodology (eg, Southern blot)
81342	TRG@ (T cell antigen receptor, gamma) (eg, leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)
81350	UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1) (eg, irinotecan metabolism), gene analysis, common variants (eg, *28, *36, *37)
81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variant(s) (eg, -1639G>A, c.173+1000C>T)
Tier 2 Molecular Pathology Procedure Codes	
81400	Molecular pathology procedure, Level 1(eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81402	Molecular pathology procedure, Level 3 (eg, >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])
81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)

CPT/HCPCS	
81407	Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
81408	Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)
81479	Unlisted molecular pathology procedure (Out of sequence)
Genomic Sequencing Procedures and Other Molecular Multianalyte Assay Codes	
81410	Aortic dysfunction or dilation (eg, 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 (eg, 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 (eg, Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease, genomic sequence analysis panel, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1
81413	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); genomic sequence analysis panel, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A
81414	Cardiac ion channelopathies (eg, Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia); duplication / deletion gene analysis panel, must include analysis of at least 2 genes, including KCNH2 and KCNQ1
81415	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
81416	Exome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis each comparator exome (eg, parents, siblings) (List separately in addition to code for primary procedure)
81417	Exome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence (eg, updated knowledge or unrelated condition/syndrome)
81420	Fetal chromosomal aneuploidy (eg, trisomy 21, monosomy X) genomic sequence analysis panel, circulating cell-free fetal DNA in maternal blood, must include analysis of chromosomes 13, 18, and 21
81425	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis
81426	Genome (eg, unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator genome (eg, parents, siblings) (List separately in addition to code for primary procedure)
81427	Genome (eg, unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained genome sequence (eg, updated knowledge or unrelated condition/syndrome)

CPT/HCPCS	
81430	Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, must include sequencing of at least 60 genes, including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1
81431	Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); duplication/deletion analysis panel, must include copy number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes
81432	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 14 genes, including ATM, BRCA1, BRCA2, BRIP1, CDH1, MLH1, MSH2, MSH6, NBN, PALB2, PTEN, RAD51C, STK11, and TP53
81433	Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analysis for BRCA1, BRCA2, MLH1, MSH2, and STK11
81434	Hereditary retinal disorders (eg, retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy), genomic sequence analysis panel, must include sequencing of at least 15 genes, including ABCA4, CNGA1, CRB1, EYS, PDE6A, PDE6B, PRPF31, PRPH2, RDH12, RHO, RP1, RP2, RPE65, RPGR, and USH2A
81435	Hereditary colon cancer disorders (eg, 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 (eg, 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 (eg, 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 (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma; duplication/deletion analysis panel, must include analysis for SDHB, SDHC, SDHD, and VHL
81439	Inherited cardiomyopathy (eg, hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy) genomic sequence analysis panel, must include sequencing of at least 5 genes, including DSG2, MYBPC3, MYH7, PKP2, and TTN
81440	Nuclear encoded mitochondrial genes (eg, neurologic or myopathic phenotypes), genomic sequence panel, must include analysis of at least 100 genes, including BCS1L, C10orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAZ, TK2, and TYMP
81442	Noonan spectrum disorders (eg, Noonan syndrome, cardio-facio-cutaneous syndrome, Costello syndrome, LEOPARD syndrome, Noonan-like syndrome), genomic sequence analysis panel, must include sequencing of at least 12 genes, including BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2 and SOS1

CPT/HCPCS	
81445	Solid organ neoplasm, genomic sequence analysis panel 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis
81450	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; DNA analysis or combined DNA and RNA analysis
81455	Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis
81460	Whole mitochondrial genome (eg, Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged-red fibers [MERFF], neuropathy, ataxia, and retinitis pigmentosa [NARP], Leber hereditary optic neuropathy [LHON]), genomic sequence, must include sequence analysis of entire mitochondrial genome with heteroplasmy detection
81465	Whole mitochondrial genome large deletion analysis panel (eg, Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia), including heteroplasmy detection, if performed
81470	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); genomic sequence analysis panel, must include sequencing of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2
81471	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic XLID); duplication/deletion gene analysis, must include analysis of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2

REVISIONS	
02-07-2014	Policy added to the bcbsks.com web site on 01-08-2014 for an effective date of 02-07-2014.
03-25-2016	Published 02-24-2016. Effective 03-25-2016.
	Description section updated
	In Policy section: ▪ In Item A 1 a removed "of heritable conditions" to read, "Diagnostic testing of an individual's germline to benefit the individual" ▪ In Item A 1 b removed "Risk assessment for" and added "Testing of an" and "to determine future risk of disease" to read "Testing of an asymptomatic individuals to determine future risk of disease" ▪ In A 2 a removed "Risk assessment for" and added "Testing of an" and "to determine future risk of cancer" to read "Testing of an asymptomatic individuals to determine future risk of cancer" ▪ In Item A 2 b removed "based on mutation analysis" and added "Testing cancer cells from an individual to benefit the individual by identifying" to read "Testing cancer cells from an individual to benefit the individual by identifying targeted treatment" ▪ In Item A 3 a removed "testing of at-risk individuals" and added "Carrier testing of the parent(s)" to read, "Carrier testing of the parent(s) – Preconception"

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	▪ In Item A 3 b removed "testing" and added "Carrier testing of the parent(s)" and "(during pregnancy)" to read, "Carrier testing of the parent(s) – Prenatal (during pregnancy)" ▪ In Item 3 added "In utero testing of a fetus" ▪ In Item 3 removed "Preconception screening"
	Rationale section updated
	In Coding section: ▪ Added CPT Codes: 81162, 81170, 81218, 81219, 81272, 81273, 81276, 81311, 81314, 81412, 81432, 81433, 81434, 81437, 81438, 81442, 81490, 81493, 81525, 81528, 81535, 81536, 81538, 81540, 81545, 81595, 0009M, 0010M (Effective January 1, 2016) ▪ Added CPT Codes: 81161, 81246, 81287, 81288, 81313, 81410, 81411, 81415, 81416, 81417, 81420, 81425, 81426, 81427, 81430, 81431, 81435, 81436, 81440, 81445, 81450, 81455, 81460, 81465, 81470, 81471, 81479, 81500, 81503, 81504, 81506, 81507, 81508, 81509, 81510, 81511, 81512, 81519, 81599, 0001M, 0002M, 0003M, 0004M, 0006M, 0007M, 0008M ▪ Revised CPT Codes: 81210, 81275, 81355 (Effective January 1, 2016) ▪ Updated Coding notations
	References updated
	Appendix section added
04-25-2016	In Coding section: ▪ CPT Coding nomenclature updated per AMA correction notification – 0010M
01-01-2017	In Coding section: ▪ Added CPT Codes: 81413, 81414, 81439, 81539 (Effective January 1, 2017) ▪ Removed CPT Codes: 81280, 81281, 81282, 0001M (Effective December 31, 2016)
10-01-2017	In Coding section: ▪ Added PLA Code: 0022U ▪ Deleted MAAA Administrative Code: 0010M (Effective 12-31-2016)
02-24-2021	Updated Description section
	Updated Rational section
	Updated Reference section
03-18-2021	In Coding section: • Removed CPT code 81545
01-03-2022	Updated Coding section Revised nomenclature 81228 "Constitutional" and "microarray" removed and "constitutional chromosomal abnormalities" added. Also some changes made to the examples
08-25-2022	Added Policy Guideline Section: Genetics Nomenclature Update A. 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. B. 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

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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

A. 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.

Updated Coding Section

- Removed CPT Codes 81161, 81162, 81170, 81490, 81493, 81500, 81503, 81504, 81506, 81507, 81508, 81509, 81510, 81511, 81512, 81519, 81525, 81528, 81535, 81536, 81538, 81539, 81540, 81595, 81599, 0002M, 0003M, 0004M, 0006M, 0007M, 0008M, 0009M, 0022U
- Removed Coding Bullets
  - CPT codes 81410-81471 are specific CPT codes 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 that are 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.

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	○ If the panel utilizes 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.
01-03-2023	Updated Coding Section ▪ Updated nomenclature for 81445, 81450, and 81455
01-01-2024	Updated Coding Section ▪ Updated nomenclature for 81445, 81450, 81455, 81243 and 81244 (eff. 01-01-2024) ▪ Removed ICD-10 Diagnoses Box

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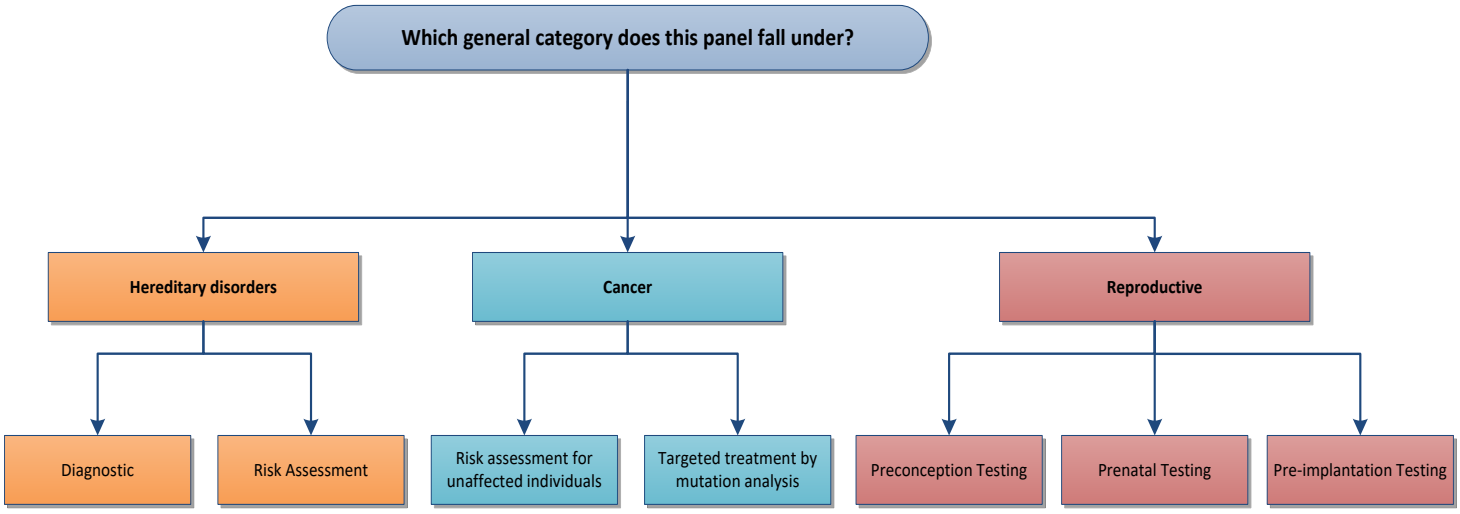
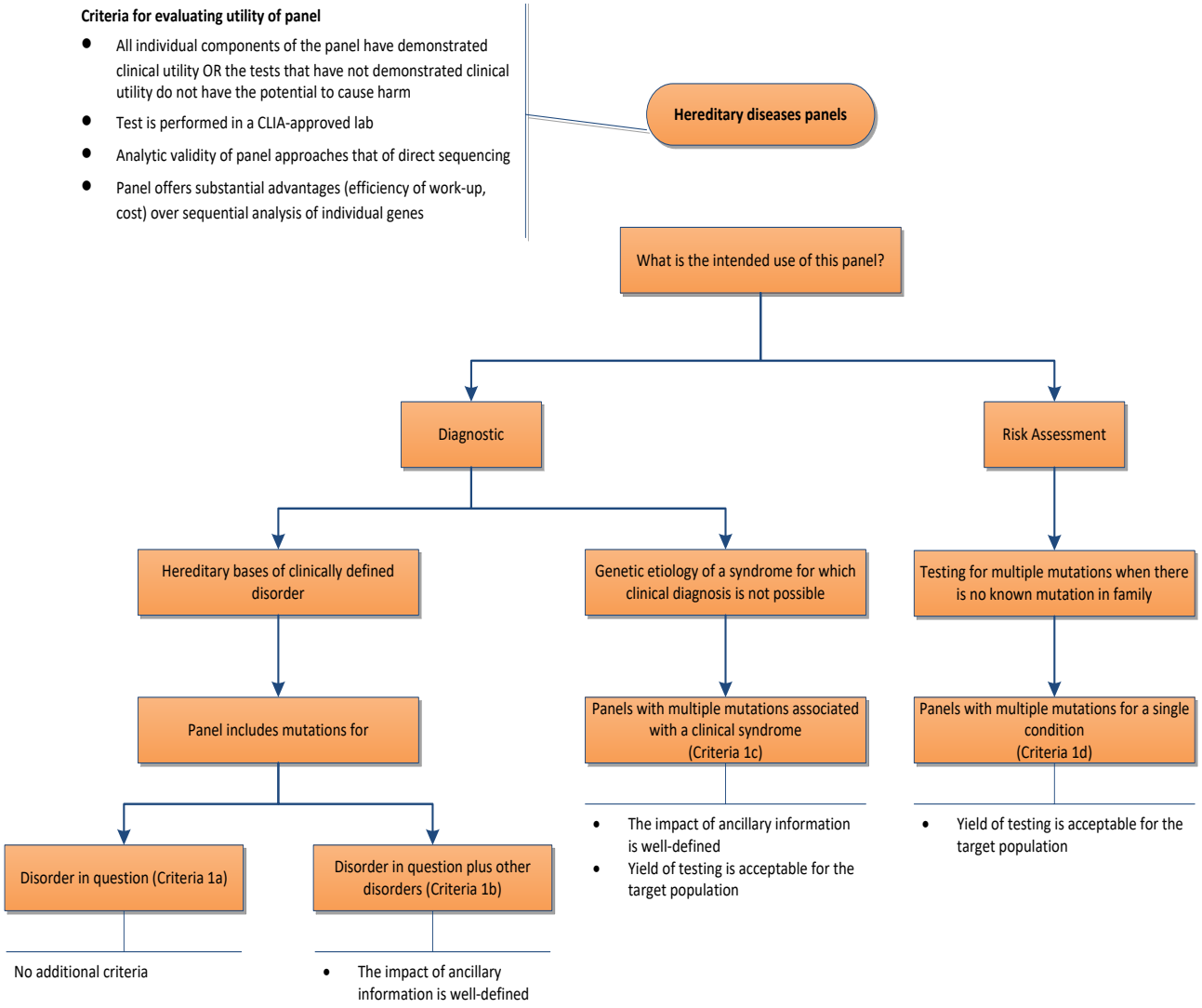
APPENDIX

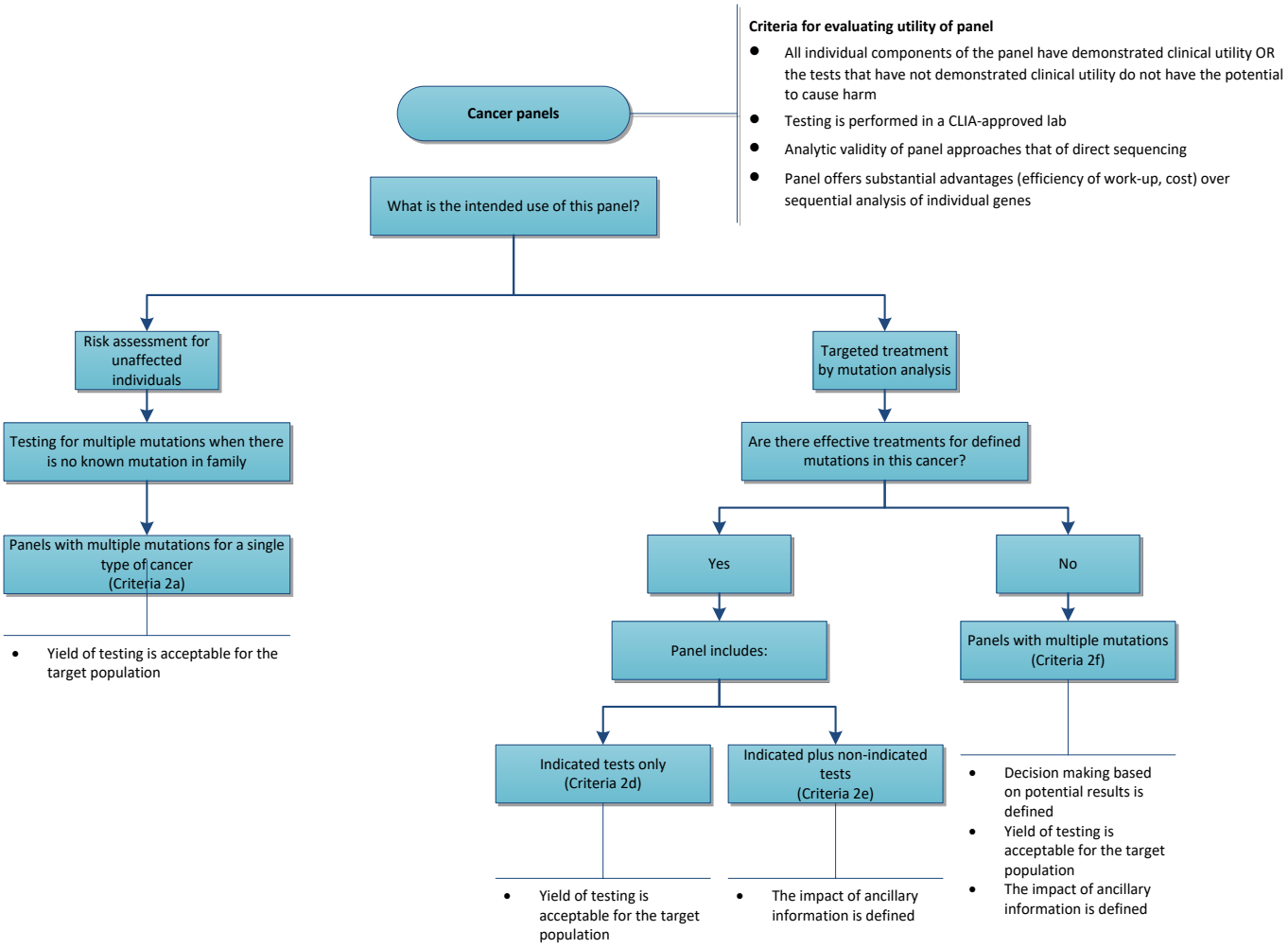
Appendix Figure 1. General Categories



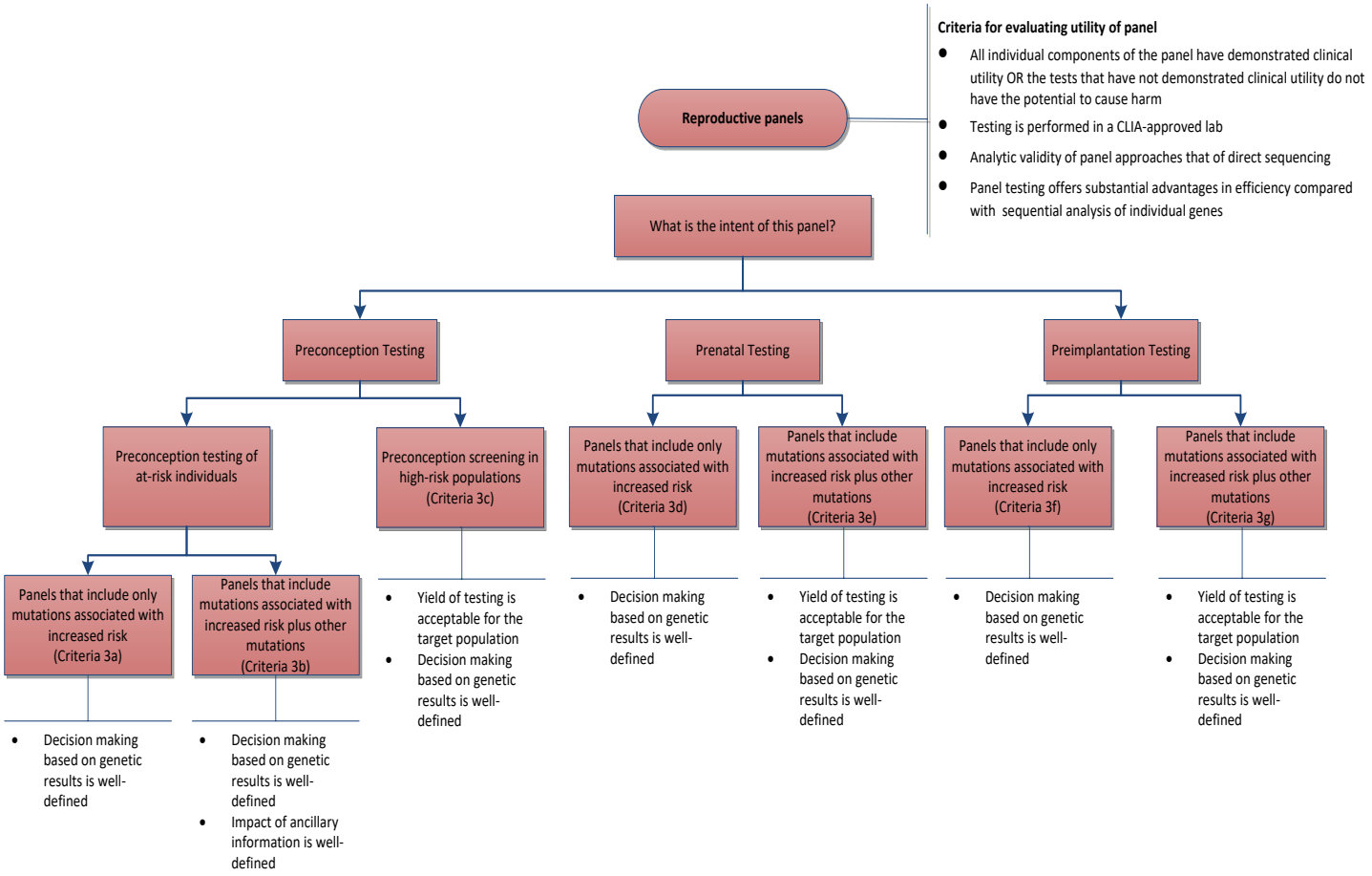
Appendix Figure 2. Algorithm for Evaluating the Utility for Hereditary Disease Panels



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



Appendix Figure 4. Algorithm for Evaluating Utility for Reproductive Panels



Appendix Table 1. Categories of Genetic Testing

Category	Addressed	
	Yes	**No**
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 patient 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: mutations		
5e. In utero testing: other		
5f. Preimplantation testing with IVF		

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

Panel Category	Examples of Panels	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 variant for a single condition	• Retinitis Pigmentosa Panel • Leigh Disease Panel	• Includes all criteria for 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 • Noonan Syndrome and Related Disorders Panel	• Includes all criteria for 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)	• X-linked Intellectual Disability Panel • Marfan, Aneurysm and Related Disorders Panel • Epilepsy Panel	• Includes all criteria for 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 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

Panel Category	Examples of Panels	Criteria for Evaluating Utility of Panel
		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 • BreastNext Panel	• Includes all criteria for 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	None identified	• Includes all criteria for 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	• CancerNext panels, when there is an effective targeted treatment for the specific type of cancer	• Includes all criteria for 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	• CancerNext panels, when there is no known effective treatment for the specific type of cancer	• Includes all criteria for 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 • GoodStart Panel (customized)	• Includes all criteria for 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	• GoodStart Panel (full panel, not customized)	• Includes all criteria for 3. Reproductive panels PLUS • Decision making based on genetic results is well-defined • Impact of ancillary information is defined

Panel Category	Examples of Panels	Criteria for Evaluating Utility of Panel
Category 3c – Preconception screening Panels intended for preconception testing – screening panels for different populations	• Counsyl Panel	• Includes all criteria for 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	• Signature prenatal microarray Panel (customized)	• Includes all criteria for 3. Reproductive panels PLUS • Decision making based on genetic results is well-defined
Category 3e - Prenatal screening Panels that include mutations associated with increased risk plus other variants	• Signature prenatal microarray Panel (full panel, not customized)	• Includes all criteria for 3. Reproductive panels PLUS • Yield of testing is acceptable for the target population • Decision making based on genetic results is well-defined
Category 3f – Pre-Implantation testing Panels that include only variants associated with increased risk	• Signature prenatal microarray Panel (customized)	• Includes all criteria for 3. Reproductive panels PLUS • Decision making based on genetic results is well-defined
Category 3g – Pre-Implantation testing Panels that include variants associated with increased risk plus other variants	• Signature prenatal microarray Panel (full panel, not customized)	• Includes all criteria for 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 Amendment.