Medical Policy

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Title: General Approach to Evaluating the Utility of Genetic Panels

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DESCRIPTION

There are an increasing number of commercially available genetic panels, coinciding with the evolution of genetic testing that allows simultaneous analysis of multiple genes. Panel testing offers potential advantages, as well as pitfalls, compared to direct sequence analysis. This concept policy outlines a framework for evaluating the utility of genetic panels, by classifying panels into clinically relevant categories and developing criteria that can be used for evaluating panels in each category.

Background

This policy applies only if there is not a separate medical policy that outlines specific criteria for testing. If a separate policy does exist, then the criteria for medical necessity in that policy supersede the guidelines in this policy.

Purpose

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 mutation in the panel has already been determined to have clinical utility and that clinical indications for testing are established. Once the clinical utility for at least one of the included mutations in the panel is established, then the focus is on whether the use of a panel is a reasonable alternative to individual tests.

Definition of a genetic panel

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 panels performed by microarray testing. The definition of a panel will not include panels that report on gene expression profiling, which generally do not directly evaluate genetic mutations.

Background

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 in the areas of inherited disorders, cancer, and reproductive testing.[2-4] These panels are intuitively attractive to use in clinical care because they can analyze multiple genes more quickly and may lead to greater efficiency in the work-up 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 a higher error rate than direct sequencing.[5] While there is limited published data directly comparing he accuracy of NGS with direct sequencing, several publications in 2015 report that the concordance between NGS and Sanger sequencing was 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 unknown significance are found commonly and in greater numbers with NGS compared 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 mutation that is 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 mutations in a tumor biopsy specimen that may help identify a cancer type or subtype and/or help select best treatment.

There is no standardization to the makeup of genetic panels. Composition of the panels is variable, and different commercial products for the same condition may test a different set of genes. The make-up of the panels is determined by the specific lab that has developed the test. In addition, the composition of any individual panel is likely to change over time, as new mutations are discovered and added to the 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 categorization is done, specific criteria regarding the utility of the panel can then 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 a clean one. Some panels will have features or intended uses that overlap among the different categories.

To determine the criteria that will be useful for evaluating panels, the evidence review will first classify panels into a number of clinically relevant categories, according to their intended use. Next, for each category, criteria will be proposed that can be applied to tests within that category. As this outlines a general approach to testing, the evidence review will not attempt to evaluate individual panels, but 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 (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of LDTs.

There has been a rapid proliferation of commercially available panel tests, and an exhaustive list is beyond the scope of this evidence review. For example, one laboratory (Emory Genetics Laboratory) offers 243 different genetic panels, of a total of 929 molecular genetics tests.[11] Table 1 provides a sample of some of the available panels that use NGS or chromosomal microarray technology.

Table 1. Panels Using Next-Generation Sequencing or Chromosomal Microarray Technology

Test Name	Laboratory
Agammaglobulinemia Panel	**ARUP Laboratories**
Amyotrophic Lateral Sclerosis Pane	
Aortopathy Panel	
Ashkenazi Jewish Diseases Panel	
Autism Panel	
Brugada Syndrome Panel	
Cardiomypathy and Arrhythmia Panel	
Mitochondrial Disorders Panel	
Periodic Fever Syndromes Panel	
Retinitis Pigmentosa/Leber Congenital Amaurosis Panel	
Vascular Malformation Syndromes	
ACOG/ACMG Carrier Screen Targeted Mutation Panel	**Emory Genetics Laboratory**
Arrhythmias Deletion/Duplication Panel	
Arrhythmias Sequencing Panel	
Autism Spectrum Disorders	
Cardiomyopathy Panel	
Ciliopathies Panel	
Congenital Glycosylation Disorders	
Epilepsy	
Eye Disorders	
Neuromuscular Disorders	
Noonan Syndrome and Related Disorders	
Short Stature Panel	
Sudden Cardiac Arrest Panel	
X-linked Intellectual Disability	
BreastNext™	**Ambry Genetics**
CancerNext™	
ColoNext™	
Marfan, Aneurysm and Related Disorders Panel	
OvaNext™	
Pan Cardio Panel	
X-linked Intellectual Disability	
Cobalamin Metabolism Comprehensive Panel	**Baylor College of Medicine**
CoQ10 Comprehensive Panel	
Glycogen Storage Disorders Panel	
Low Bone Mass Panel	
Mitochondrial Disorders Panel	
Myopathy/Rhabdomyolysis Panel	
Progressive External Ophthalmoplegia Panel	
Pyruvate Dehydrogenase Deficiency and Mitochondrial Respiratory Chain Complex V Deficiency Panel	
Retinitis Pigmentosa Panel	
Usher Syndrome Panel	
Leigh Disease Panel	**Medical Neurogenetics**
Isolated Non-syndromic Congenital Heart Defects Panel	**Partners Healthcare**
Noonan Spectrum Panel	
Pan Cardiomyopathy Panel	
Usher Syndrome Panel	

Test Name	Laboratory
Arrhythmogenic Right Ventricular Cardiomyopathy Panel	**Mayo Medical Laboratories**
Brugada Syndrome	
Dilated Cardiomyopathy Panel	
Hereditary Colon Cancer Syndromes	
Hypertrophic Cardiomyopathy Panel	
Long QT Syndrome	
Marfan Syndrome Panel	
Noonan Syndrome Panel	
Signature Prenatal Microarray	**Signature Genomics**
Counsyl™ Panel	**Counsyl Genomics**
GoodStart Select™	**GoodStart Genetics**

POLICY

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.

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.**

RATIONALE

This evidence review was updated with literature review. The most recent update covers the period through December 20, 2015.

Types of Panels

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

Genetic panels will be classified into 3 major categories: panels for genetic and hereditary conditions, cancer panels, and reproductive panels. Within these categories, subcategories will be created according to the intended use of the panels.

Panels for Genetic or Hereditary Conditions

These are generally single-gene disorders, which are inherited in Mendelian fashion. They are defined by a characteristic phenotype, which may be characteristic of a specific disease, or which may 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 the purposes of this review, panels will be divided into the following types:

- *Panels containing mutations associated with a single condition*. They generally include all of the known pathologic mutations for a defined disease and do not include mutations associated with other diseases. An example of such a panel would be one that includes pathologic mutations for hypertrophic cardiomyopathy and that does not include mutations associated with other cardiovascular disorders. These panels can be used for diagnostic or risk assessment purposes.
- *Panels containing mutations associated with multiple related conditions*. They include all of the known pathologic mutations for a defined disease, and also include mutations associated with other related disorders. An example of such a panel would be a pan cardiomyopathy panel that includes pathologic mutations for hypertrophic cardiomyopathy and other types of cardiomyopathy, such as dilated cardiomyopathy or arrhythmogenic right ventricular cardiomyopathy. These panels can be used for diagnostic or risk assessment purposes.
- *Panels containing mutations for clinical syndromes that are associated with multiple distinct conditions*. These panels include mutations that are 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 a number of underlying disease states that manifests as a clinical syndrome. An example of this type of panel is a panel for intellectual disability that includes mutations

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 mutations. The intended purpose of these panels 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 mutations.

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

- *Panels containing multiple mutations indicating risk for a specific type of cancer or cancer syndrome (germline mutations).* These panels contain multiple related mutations that indicate susceptibility to 1 or more cancers. They include germline mutations and will generally be used for risk assessment in asymptomatic individuals who are at risk for mutations based on family history or other clinical data. An example of this type of panel would be a panel testing for multiple *BRCA1* and *BRCA2* mutations associated with hereditary breast and ovarian cancer syndrome.
- *Panels containing multiple mutations that are associated with a wide variety of cancer types (somatic mutations).* These panels are generally used to direct treatment with drugs that target specific mutations. They test for somatic mutations from tissue samples of existing cancers. Many of these somatic mutations are found across a wide variety of solid tumors. An example of this type of panel is the CancerNext panel (Ambry Genetics) that tests for a broad number of somatic mutations that can direct treatment.

Reproductive Panels

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

- Carrier testing of parent(s) preconception
- Carrier testing of parent(s) postconception (during pregnancy)
- preimplantation testing
- prenatal (in utero) testing

Preconception testing usually tests for mutations that are autosomal recessive or X-linked, or in some cases, for autosomal dominant mutations with late clinical onset. Preconception tests can be performed on parents who are at risk for a mutation based on family history, or can be done as screening tests in parents who do not have a family history suggestive of a mutation. Prenatal testing refers to tests that are performed during a pregnancy. At the present time, prenatal testing for genetic mutations 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 mutations using maternal blood.

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

- *Panels containing mutations associated with a single disorder.* These panels are generally performed in at-risk individuals who have a family history of a heritable disorder. An example of this type of panel would be a cystic fibrosis gene panel that is intended for use in individuals with a family history of cystic fibrosis.

- *Panels containing mutations associated with multiple disorders.* These panels are generally performed as screening tests for parents who do not have a family history of a heritable disorder. They can also be used to evaluate individuals who have a family history of a heritable disorder. An example of this type of panel is the Signature Prenatal Microarray Panel.

Criteria to Be Used in Evaluating Genetic Panels

The following is a list of all the 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 1 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 Amendment–Licensed Lab

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

Analytic Validity of Panels Approaches That of Direct Sequencing

- The analytic validity for detecting individual mutations, compared with the criterion standard of conventional direct Sanger sequencing, is reported.
  - The testing methods are clearly 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 (clinical validity).

All individual components of the panel have demonstrated clinical utility for the condition being evaluated, OR the implications and consequences of test results that have not demonstrated clinical utility are clear, and there is not a potential for incidental findings to cause harm.

- For each panel, if each individual mutation in the panel would be indicated for at least some patients with the condition, then this criterion is met.
  - If there are individual mutations 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 effects
    - False negative: Effective treatment not provided
  - Incorrect risk assessment
    - Unnecessary surveillance tests that may lead to further confirmatory tests that may be invasive
    - Effective surveillance/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 Advantages in Efficiency Compared With Sequential Analysis of Individual Genes

- The composition of the panel is sufficiently complex such that next-generation sequencing, or chromosomal microarray, is expected to offer considerable advantages. 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 mutations that are medically necessary and mutations that are investigational (or not medically necessary), the impact of results for investigational (or not medically necessary) mutations 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 involves risks.

Decision Making Based on Genetic Results Is Well-Defined

- Results of genetic test will lead to changes in diagnosis and/or treatment.
- The potential changes in treatment are defined prior to testing and are in accordance with 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.

Yield of Testing Is Acceptable for the Target Population

- The number of individuals who are found to have a pathologic mutation, 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 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 disease is greater than 10%.

    - For cancer susceptibility, testing is recommended for genetic abnormalities such as *BRCA* 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 testing is recommended when the likelihood of a positive result is in the 5% to 20% range.
- There is Increase in yield over alternate 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 in optimal fashion.
- 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.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov on December 22, 2015, did not identify any ongoing or unpublished trials that would likely influence this review.

Summary of Evidence

Genetic panels using next-generation technology or chromosomal microarray are available for many clinical conditions. The major advantage of these genetic panels is the ability to analyze many genes simultaneously, potentially improving the breadth and efficiency of genetic work-up. Limited published evidence reports that the analytic validity of these panels approaches that of direct sequencing. Disadvantages of the panels are that their accuracy may be lower compared with direct sequencing and that the impact of a large of amount of ancillary information may be uncertain.

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

Practice Guidelines and Position Statements

No guidelines or statements were identified.

U.S. Preventive Services Task Force Recommendations

Not applicable.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. 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.

CPT/HCPCS

Tier 1 Molecular Pathology Procedure Codes

81161	DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed
81162	BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis
81170	ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain
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 (ie, 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 (ie, exon 13 del 3.835kb, exon 13 dup 6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)
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 (genome-wide) microarray 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 mental retardation 1) (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles
81244 FMR1 (Fragile X mental retardation 1) (eg, fragile X mental retardation) 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 (ie, exons 14, 15)
81246 FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (eg, D835, I836)

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)

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
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
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)
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)

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

81445 Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed

81450 Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA and RNA analysis when performed, 5-50 genes (eg, BRAF, CEBPA, DNMT3A, EZH2, FLT3, IDH1, IDH2, JAK2, KRAS, KIT, MLL, NRAS, NPM1, NOTCH1), interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed

81455 Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA and RNA analysis when performed, 51 or greater genes (eg, 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

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

Multianalyte Assays with Algorithmic Analyses Codes

81490 Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score

81493 Coronary arter disease mRNA, gene expression profiling by real-time RT-PCR of 23 genes, utilizing whole peripheral blood, algorithm reported as a risk score

81500 Oncology (ovarian), biochemical assays of two proteins (CA-125 and HE4), utilizing serum, with menopausal status, algorithm reported as a risk score

81503 Oncology (ovarian), biochemical assays of five proteins (CA-125, apolipoprotein A1, beta-2 microglobulin, transferrin, and pre-albumin), utilizing serum, algorithm reported as a risk score

81504 Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores

81506 Endocrinology (type 2 diabetes), biochemical assays of seven analytes (glucose, HbA1c, insulin, hs-CRP, adiponectin, ferritin, interleukin 2-receptor alpha), utilizing serum or plasma, algorithm reporting a risk score

81507 Fetal aneuploidy (trisomy 21, 18, and 13) DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy

81508 Fetal congenital abnormalities, biochemical assays of two proteins (PAPP-A, hCG [any form]), utilizing maternal serum, algorithm reported as a risk score

81509 Fetal congenital abnormalities, biochemical assays of three proteins (PAPP-A, hCG [any form], DIA), utilizing maternal serum, algorithm reported as a risk score

81510 Fetal congenital abnormalities, biochemical assays of three analytes (AFP, uE3, hCG [any form]), utilizing maternal serum, algorithm reported as a risk score

81511 Fetal congenital abnormalities, biochemical assays of four analytes (AFP, uE3, hCG [any form], DIA) utilizing maternal serum, algorithm reported as a risk score (may include additional results from previous biochemical testing)

81512 Fetal congenital abnormalities, biochemical assays of five analytes (AFP, uE3, total hCG, hyperglycosylated hCG, DIA) utilizing maternal serum, algorithm reported as a risk score

81519 Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score

81525 Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score

81528 Oncology (colorectal) screening, quantitative real-time target and signal amplification of 10 DNA markers (KRAS mutations, promoter methylation of NDRG4 and BMP3) and fecal hemoglobin, utilizing stool, algorithm reported as a positive or negative result

81535 Oncology (gynecological), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score; first single drug or drug combination

81536 Oncology (gynecological), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score; each additional single drug or drug combination (List separately in addition to code for primary procedure)

81538 Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival

81539 Oncology (high-grade prostate cancer), biochemical assay of four proteins (Total PSA, Free PSA, Intact PSA, and human kallikrein-2 [hK2]), utilizing plasma or serum, prognostic algorithm reported as a probability score

81540 Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a probability of a predicted main cancer type and subtype

81545 Oncology (thyroid), gene expression analysis of 142 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (eg, benign or suspicious)

81595 Cardiology (heart transplant), mRNA, gene expression profiling by real-time quantitative PCR of 20 genes (11 content and 9 housekeeping), utilizing subfraction of peripheral blood, algorithm reported as a rejection risk score

81599 Unlisted multianalyte assay with algorithmic analysis

0002M Liver disease, ten biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, haptoglobin, AST, glucose, total cholesterol and triglycerides) utilizing serum, prognostic algorithm reported as quantitative scores for fibrosis, steatosis and alcoholic steatohepatitis (ASH)

0003M Liver disease, ten biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, haptoglobin, AST, glucose, total cholesterol and triglycerides) utilizing serum, prognostic algorithm reported as quantitative scores for fibrosis, steatosis and nonalcoholic steatohepatitis (NASH)

0004M Scoliosis, DNA analysis of 53 single nucleotide polymorphisms (SNPs), using saliva, prognostic algorithm reported as a risk score

0006M Oncology (hepatic), mRNA expression levels of 161 genes, utilizing fresh hepatocellular carcinoma tumor tissue, with alpha-fetoprotein level, algorithm reported as a risk classifier

0007M Oncology (gastrointestinal neuroendocrine tumors), real-time PCR expression analysis of 51 genes, utilizing whole peripheral blood, algorithm reported as a nomogram of tumor disease index

0008M Oncology (breast), mRNA analysis of 58 genes using hybrid capture, on formalin-fixed paraffin-embedded (FFPE) tissue, prognostic algorithm reported as a risk score

0009M Fetal aneuploidy (trisomy 21, and 18) DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy

0022U Targeted genomic sequence analysis panel, non-small cell lung neoplasia, DNA and RNA analysis, 23 genes, interrogation for sequence variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider

- 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.
- 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.

Diagnoses

Diagnosis coding would depend on the condition for which the testing is being performed, if the test is being performed as screening or carrier testing, and any family history of the condition.

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" ▪ 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)

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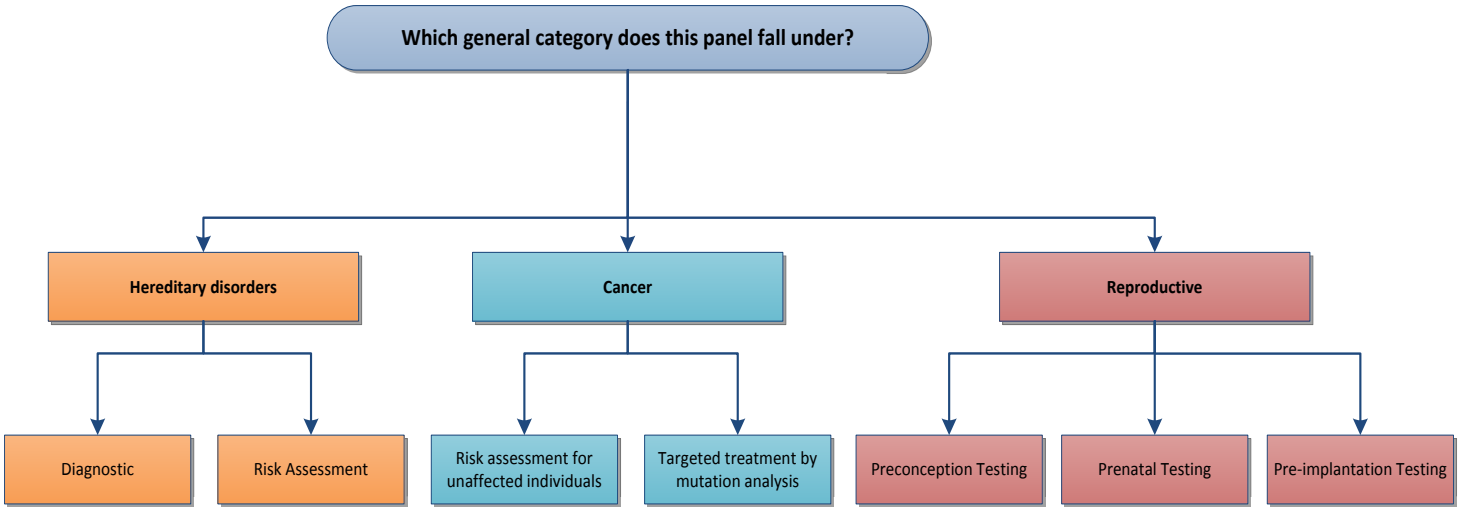
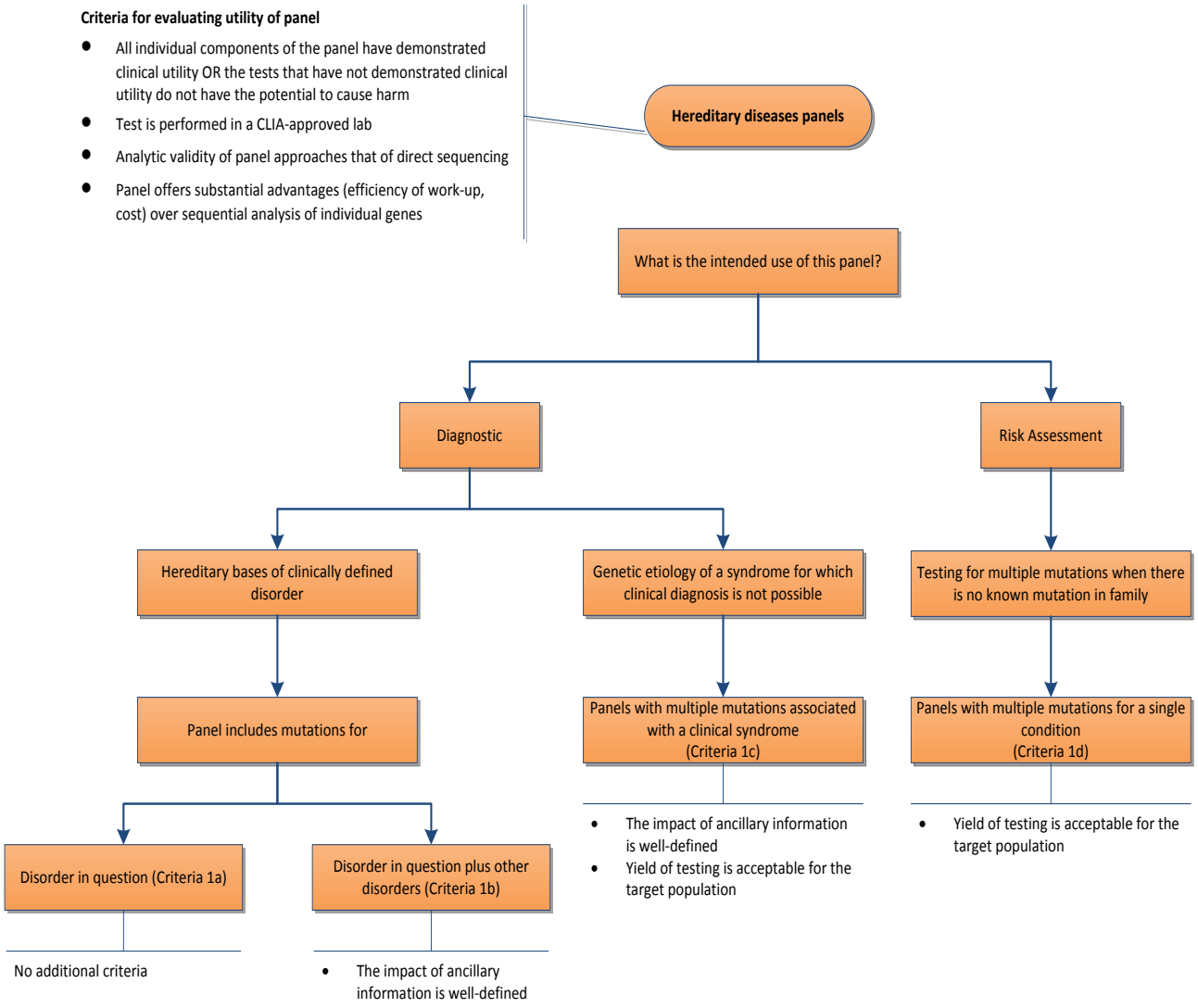
APPENDIX

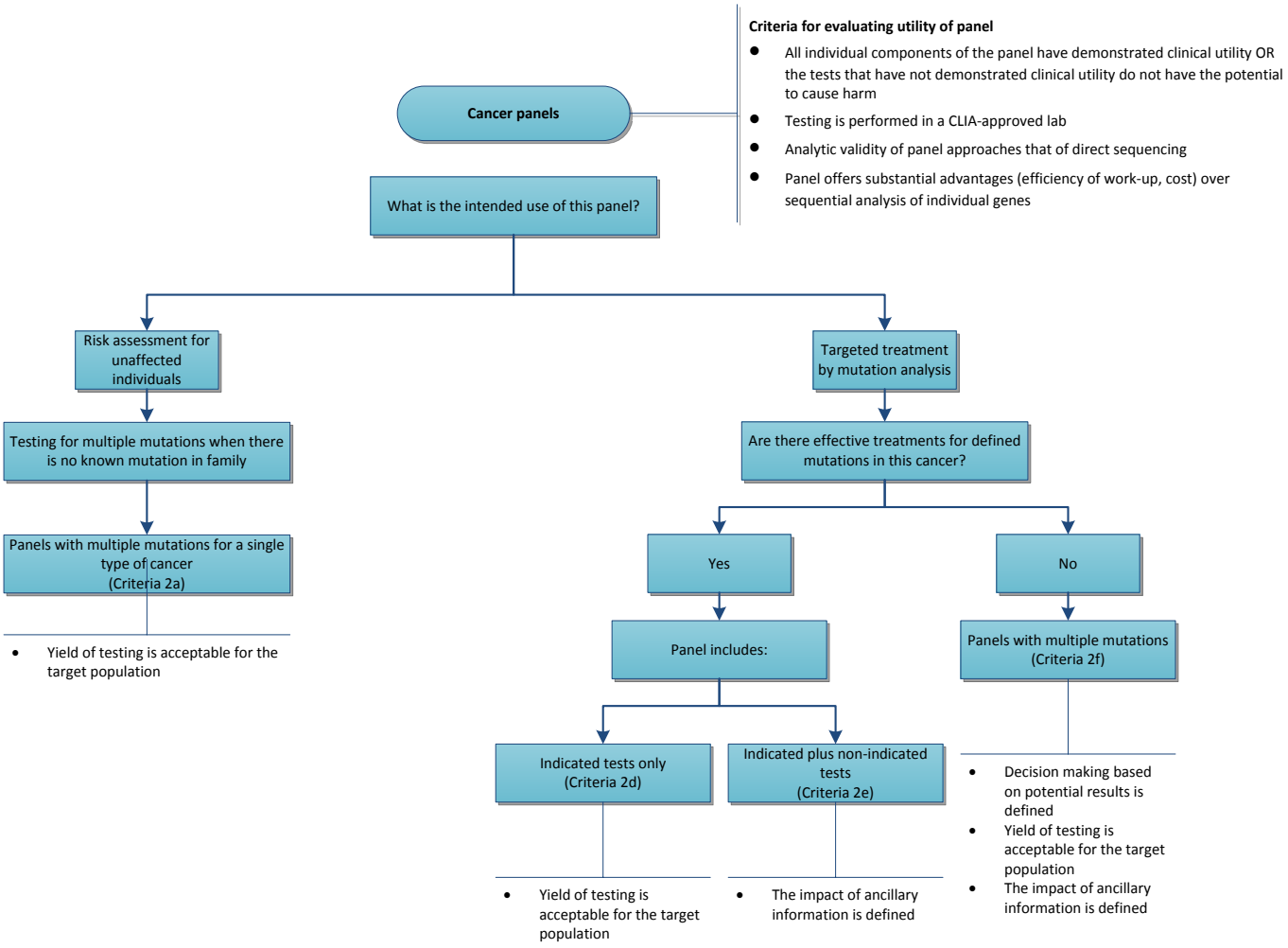
Appendix Figure 1. General Categories



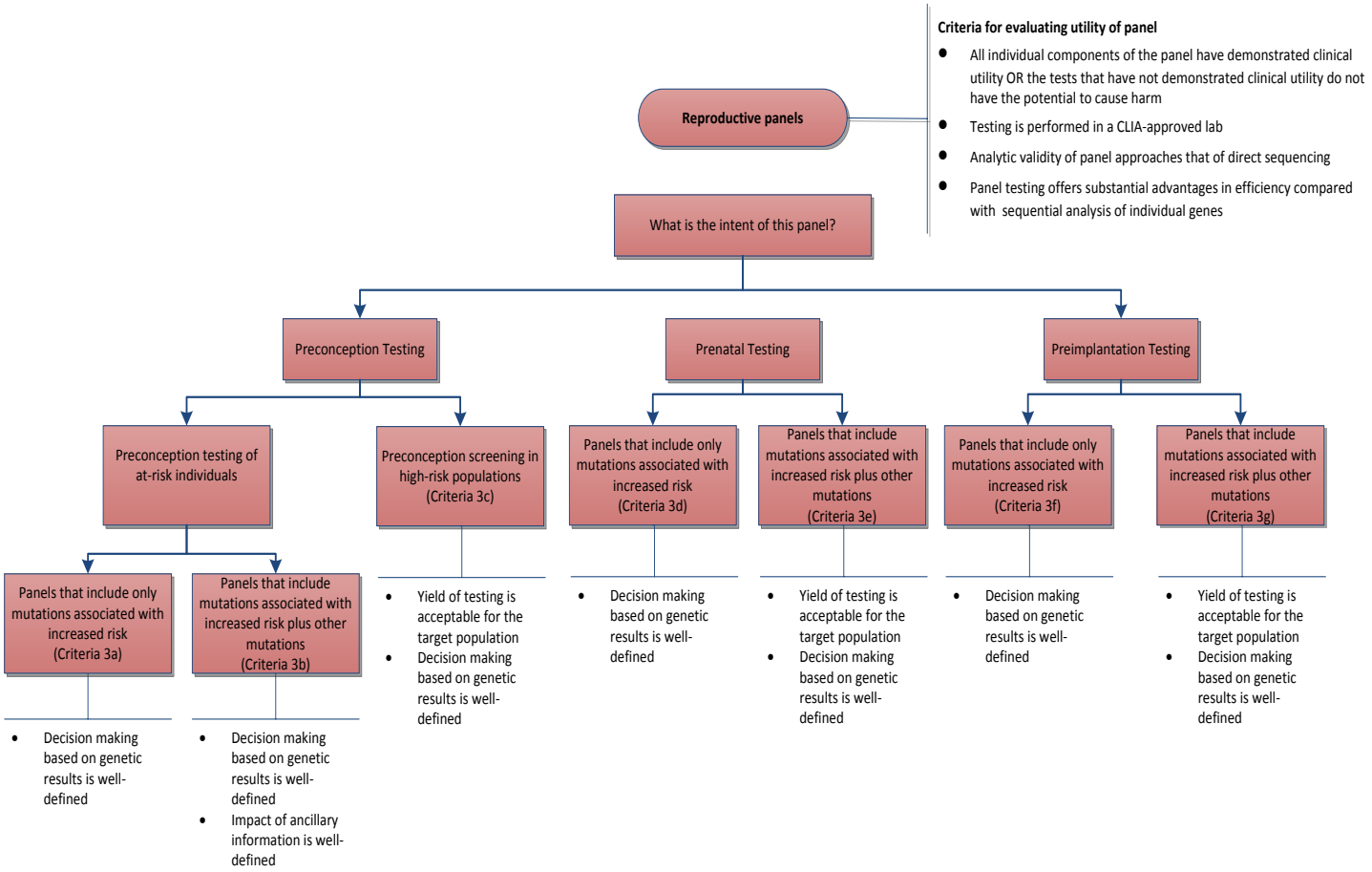
Appendix Figure 2. Algorithm for Evaluating the Utility for Hereditary Disease Panels



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 mutations 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 mutations for multiple conditions (indicated plus nonindicated conditions)	• Retinitis Pigmentosa/Leber Congenital Amaurosis Panel • Pan Cardio 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 mutations 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 mutation 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 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 mutation analysis • Panels with multiple mutations intended to direct treatment – all indicated tests • Effective targeted treatment based on mutation 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 mutation analysis • Panels with multiple mutations intended to direct treatment (indicated plus nonindicated tests)	• 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

Panel Category	Examples of Panels	Criteria for Evaluating Utility of Panel
• Effective targeted treatment based on mutation analysis has not been established		
Category 2d • Panels with multiple mutations intended to direct treatment – no indicated tests for that particular cancer • Effective targeted treatment based on mutation 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 mutations 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 mutations associated with increased risk plus other mutations	• 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
Category 3c – Preconception screening Panels intended for preconception testing – screening panels for different populations	• Counsyl Panel	• 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 mutations 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 mutations	• 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 mutations 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 mutations associated with increased risk plus other mutations	• 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.