Evaluating the Utility of Genetic Panels

Effective: October 1, 2017

Next Review: July 2018
Last Review: September 2017

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Genetic panel tests evaluate many genes simultaneously, and have been developed for numerous indications, including hereditary cancer risk assessment, pharmacogenetics, and diagnosis of congenital disorders. Many panel tests include genes that do not have demonstrated clinical utility for their testing.

MEDICAL POLICY CRITERIA

There is not enough research to demonstrate that all genes and/or gene variants included in the panels listed below may be used to manage treatment decisions and improve net health outcomes. If one of the panel components (gene or gene variant) is determined to be investigational, then the entire panel is investigational. Therefore, the following genetic panels are considered investigational:

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<td>Stickler Syndrome NGS Panel</td>
<td>Connective Tissue Gene Tests</td>
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<td>SureGene Test for Antipsychotic and Antidepressant Response® Gene Panel (STAR2)</td>
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<td>SymGene68™ Next Generation Sequencing Cancer Panel</td>
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<tr>
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<tr>
<td>YouScript® personalized prescribing system</td>
<td>Genelex Corporation</td>
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NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.
In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or mutation(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test, if available:
   - History and physical exam
   - Conventional testing and outcomes
   - Conservative treatment provided

CROSS REFERENCES

1. Medical Policy Manual: Genetic Testing Section Table of Contents

BACKGROUND

New genetic technology, such as next generation sequencing 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. The intended use for these panels is variable. For example, for the diagnosis of hereditary disorders, a clinical diagnosis may already be established, and genetic testing is performed to determine whether there 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.

Panels using next generation technology are currently available in the areas of cancer, cardiovascular disease, neurologic disease, psychiatric conditions, and for reproductive testing.\(^2-4\) These panels are intuitively attractive to use in clinical care because they can screen for numerous mutations within a single or multiple genes quickly, and may lead to greater efficiency in the work-up of genetic disorders. It is also possible that these “bundled” gene tests can be performed more cost effectively than direct sequencing, although this may not be true in all cases. However, panel testing also provides information on genetic variants that are of unclear clinical significance or which would not lead to changes in patient management.

One potential challenge of genetic panel testing is the availability of a large amount of ancillary genetic information, much of which has uncertain clinical consequences and management strategies. Identification of variants for which the clinical management is uncertain may lead to unnecessary follow-up testing and procedures, all of which have their own inherent risks.
Additionally, the design and composition of genetic panel tests have not been standardized. Composition of the panels is variable, and different commercial products for the same condition may test different sets of genes. The make-up of the panel 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.

**GENETIC COUNSELING**

Due to the complexity of interpreting genetic test results, patients should receive pre- and post-test genetic counseling from a qualified professional when testing is performed to diagnose or predict susceptibility for inherited diseases. The benefits and risks of genetic testing should be fully disclosed to individuals prior to testing, and counseling concerning the test results should be provided.

**REGULATORY STATUS**

The majority of genetic panel tests are laboratory derived tests that are not subject to U.S. Food and Drug Administration (FDA) approval. Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

**Note:** Separate Medical Policies may apply to some specific genetic tests and panels not addressed in the criteria below. See the [Genetic Testing Section](#) of the Medical Policy Manual Table of Contents for additional genetic testing policies.

**EVIDENCE SUMMARY**

Genetic cancer susceptibility panels utilizing next generation sequencing are best evaluated in the framework of a diagnostic test, as the test provides diagnostic information that assists in treatment decisions. The clinical utility of genetic panel testing refers to the likelihood that the panel will result in improved health outcomes.

For positive test results, the health benefits are related to interventions that reduce the risk of developing the disease, earlier or more intensive screening to detect and treat early disease symptoms, or interventions to improve quality of life.

- Alternatively, negative test results may prevent unnecessary intensive monitoring, invasive tests or procedures, or ineffective therapies.

For genetic panels that test for a broad number of variants, some components of the panel may be indicated based on the patient’s clinical presentation and/or family history, while other components may not be indicated. The impact of test results related to non-indicated mutations must be well-defined and take into account the possibility that the information may cause harm by leading to additional unnecessary interventions that would not otherwise be considered based on the patient’s clinical presentation and/or family history.

Therefore, the focus of the following review is on evidence from well-designed controlled trials or large cohort studies that demonstrate the clinical utility of each panel test, i.e., the ability of results from the comprehensive genetic panels to:
1. Guide decisions in the clinical setting related to either treatment, management, or prevention; and

2. Improve health outcomes as a result of those decisions.

A limited body of literature exists on the potential clinical utility of available next generation sequencing (NGS) panels.

NONRANDOMIZED STUDIES

Desmond (2015) reported on an observational study assessing whether testing of hereditary cancer gene mutations other than BRCA1/2 altered clinical management in a prospectively collected cohort of 1046 patients from three institutions who were negative for BRCA1/2.[5] Patients were tested with the 29-gene Hereditary Cancer Syndromes test (Invitae) or the 25-gene MyRisk test (Myriad Genetics). The investigators evaluated the likelihood of a post-test change in management considering gene-specific consensus management guidelines, gene-associated cancer risks, and personal and family history. Of this cohort, 40 patients (3.8%; 95% CI, 2.8%-5.2%) harbored deleterious mutations, most commonly in moderate-risk breast and ovarian cancer genes and Lynch syndrome genes. Among 63 mutation-positive patients, 20 were found to harbor mutations in high-risk genes associated with detailed NCCN management guidelines which would change the pretest recommendations for screening and/or preventive surgery. However, the most common mutations found were those in genes associated with low or moderately increased breast cancer risk (40 of 63 patients), where a change in management would be recommended for these patients in a minority of cases (10 of 40), involving either increased screening or preventive surgery. Since this study only reported anticipated changes in management, these mutation-positive patients were not provided with these post-test recommendations. The investigators conceded that the potential clinical effect reported in this cohort is likely to apply only to an appropriately ascertained cohort, thereby limiting the generalizability of the results.

Kurian (2014) evaluated the information from a NGS panel of 42 cancer associated genes in women who had been previously referred for clinical BRCA1/2 testing after clinical evaluation of hereditary breast and ovarian cancer from 2002 to 2012.[6] The authors aimed to assess concordance of the results of the panel with prior clinical sequencing, the prevalence of potentially clinically actionable results, and the downstream effects on cancer screening and risk reduction. Potentially actionable results were defined as pathogenic variants that cause recognized hereditary cancer syndromes or have a published association with a two-fold or greater relative risk of breast cancer compared to average risk women. In total, 198 women participated in the study. Of these, 174 had breast cancer and 57 carried 59 germline BRCA mutations. Testing with the panel confirmed 57 of 59 of the pathogenic BRCA mutations; of the two others, one was detected but reclassified as a VUS and the other was a large insertion that would not be picked up by NGS panel testing. Of the women who tested negative for BRCA mutations (n=141), 16 had pathogenic mutations in other genes (11.4%). The affected genes were ATM (n=2), BLM (n=1), CDH1 (n=1), CDKN2A (n=1), MLH1 (n=1), MUTYH (n=5), NBN (n=2), PRSS1 (n=1), and SLX4 (n=2). Eleven of these variants had been previously reported in the literature and five were novel. 80% of the women with pathogenic mutations in the non BRCA1/2 genes had a personal history of breast cancer. Overall, a total of 428 VUS were identified in 39 genes, among 175 patients.
Six women with mutations in *ATM*, *BLM*, *CDH1*, *NBN* and *SLX4* were advised to consider annual breast MRIs because of an estimated doubling of breast cancer risk, and six with mutations in *CDH1*, *MLH1* and *MUTYH* were advised to consider frequent colonoscopy and/or endoscopic gastroduodenoscopy (once every 1-2 years) due to estimated increases in gastrointestinal cancer risk. One patient with a *MLH1* mutation consistent with Lynch syndrome underwent risk-reducing salpingo-oophorectomy and early colonoscopy which identified a tubular adenoma that was excised (she had previously undergone hysterectomy for endometrial carcinoma).

Mauer (2014) reported a single academic center’s genetics program’s experience with NGS panels for cancer susceptibility.[7] The authors conducted a retrospective review of the outcomes and clinical indications for the ordering of Ambry’s next generation sequencing panels (BreastNext, OvaNext, ColoNext, and CancerNext) for patients seen for cancer genetics counseling from April 2012 to January 2013. Of 1,521 new patients seen for cancer genetics counseling, 1,233 (81.1%) had genetic testing. Sixty of these patients (4.9% of the total) had a next generation sequencing panel ordered, 54 of which were ordered as a second-tier test after single-gene testing was performed. Ten tests were cancelled due to out-of-pocket costs or previously identified mutations. Of the 50 tests obtained, five were found to have a deleterious result (10%; compared with 131 [10.6%] of the 1,233 single-gene tests ordered at the same center during the study time frame). The authors report that of the 50 completed tests, 30 (60%) did not affect management decisions, 15 (30%) introduced uncertainty regarding the patients’ cancer risks, and five (10%) directly influenced management decisions.

A number of other studies have evaluated the impact of panel testing on clinical management of a variety of conditions, including prostate cancer,[8] breast and/or ovarian cancer,[9-11] and non-specific hereditary cancers,[12] as well as genetic profiling of tumor tissue to guide cancer treatment.[13,14] While some of these studies noted specific changes in medical management resulting from the testing, none of them evaluated whether these changes led to improvements in patient outcomes.

**PRACTICE GUIDELINE SUMMARY**

**AMERICAN SOCIETY OF CLINICAL ONCOLOGY**

A 2015 update of a policy statement on genetic and genomic testing for cancer susceptibility from the American Society of Clinical Oncology (ASCO) addresses the application of next-generation sequencing.[15] According to this statement:

ASCO recognizes that concurrent multigene testing (i.e., panel testing) may be efficient in circumstances that require evaluation of multiple high-penetrance genes of established clinical utility as possible explanations for a patient’s personal or family history of cancer. Depending on the specific genes included on the panel employed, panel testing may also identify mutations in genes associated with moderate or low cancer risks and mutations in high-penetrance genes that would not have been evaluated on the basis of the presenting personal or family history. Multigene panel testing will also identify variants of uncertain significance (VUS) in a substantial proportion of patient cases. ASCO affirms that it is sufficient for cancer risk assessment to evaluate genes of established clinical utility that are suggested by the patient’s personal and/or family history. Because of the current uncertainties and knowledge
gaps, providers with particular expertise in cancer risk assessment should be involved in the ordering and interpretation of multigene panels that include genes of uncertain clinical utility and genes not suggested by the patient’s personal and/or family history.

This type of testing may be particularly useful in situations where there are multiple high-penetration genes associated with a specific cancer, the prevalence of actionable mutations in one of several genes is high, and it is difficult to predict which gene may be mutated on the basis of phenotype or family history.

So far, there is little consensus as to which genes should be included on panels offered for cancer susceptibility testing- this heterogeneity presents a number of challenges. All panels include high-penetration genes that are known to cause autosomal-dominant predisposition syndromes, but often include genes that are not necessarily linked to the disease for which the testing is being offered. There is uncertainty regarding the appropriate risk estimates and management strategies for families with unexpected mutations in high-penetration genes when there is no evidence of the associated syndrome. Clinical utility remains the fundamental issue with respect to testing for mutations in moderate penetrance genes. It is not yet clear whether clinical management should change based on the presence or absence of a mutation. There is insufficient evidence at the present time to conclusively demonstrate the clinical utility of testing for moderate-penetration mutations, and no guidelines exist to assist oncology providers. Early experience with panel-based testing indicates that a substantial proportion of tests identify a VUS in 1 or more genes, and VUSs are more common in broad-panel testing both because of the number of genes tested and because of the limited understanding of the range of normal variation in some of these genes.

NATIONAL COMPREHENSIVE CANCER NETWORK

The National Comprehensive Cancer Network (NCCN) guidelines on genetic/familial high-risk assessment for breast and ovarian cancer (v2.2017)\(^{[16]}\) state the following regarding multi-gene testing:

- Patients who have a personal or family history suggestive of a single inherited cancer syndrome are most appropriately managed by genetic testing for that specific syndrome. When more than one gene can explain an inherited cancer syndrome, then multi-gene testing may be more efficient and/or cost effective.
- There is also a role for multi-gene testing in individuals who have tested negative (indeterminate) for a single syndrome, but whose personal or family history remains strongly suggestive of an inherited susceptibility.
- As commercially available tests differ in the specific genes analyzed (as well as classification of variants and many other factors), choosing the specific laboratory and test panel is important.
- Multi-gene testing can include “intermediate” penetrant (moderate risk) genes. For many of these genes, there are limited data on the degree of cancer risk and there are no clear guidelines on risk management for carriers of mutations. Not all genes included on available multi-gene test are necessarily clinically actionable.
- As is the case with high-risk genes, it is possible that the risks associated with moderate-risk genes may not be entirely due to that gene alone, but may be influenced by gene/gene
or gene/environment interactions. Therefore, it may be difficult to use a known mutation alone to assign risk for relatives.

- In many cases, the information from testing for moderate penetrance genes does not change risk management compared to that based on family history alone.
- There is an increased likelihood of finding variants of unknown significance when testing for mutations in multiple genes.
- It is for these and other reasons that multi-gene testing is ideally offered in the context of professional genetic expertise for pre- and post-test counseling.

**SUMMARY**

Genetic test panels are available for many clinical conditions. Genetic panels may be focused to a few genes or may be broad and include a large number of genes. The advantage of genetic panels is the ability to analyze many genes simultaneously, potentially improving the breadth and efficiency of the genetic workup. A disadvantage of panel testing is that the results may provide information on genetic mutations that are of unclear clinical significance or which would not lead to changes in patient management. These results may potentially cause harm by leading to additional unnecessary interventions and anxiety that would not otherwise be considered based on the patient’s clinical presentation and/or family history. There is not enough research to show that the genetic panels listed in the policy criteria can lead to better health outcomes for patients. Therefore, these panel tests are considered investigational.

**REFERENCES**


**CODES**

There are few specific codes for molecular pathology testing by panels. If the specific analyte is listed with a CPT code, the specific CPT code should be reported. If the specific analyte is not listed with a specific CPT code, unlisted code 81479 should be reported. The unlisted code would be reported once to represent all of the unlisted analytes in the panel.

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<th>Codes</th>
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<tr>
<td>CPT</td>
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<td>Oncology (hepatic), mRNA expression levels of 161 genes, utilizing fresh hepatocellular carcinoma tumor tissue, with alpha-fetoprotein level, algorithm reported as a risk classifier</td>
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<td>Helicobacter pylori detection and antibiotic resistance, DNA, 16S and 23S rRNA, gyrA, ppb1, rdxA and rpoB, next generation sequencing, formalin-fixed paraffin embedded or fresh tissue, predictive, reported as positive or negative for resistance to clarithromycin, fluoroquinolones, metronidazole, amoxicillin, tetracycline and rifabutin</td>
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<td>Infectious disease (bacterial), strain typing by whole genome sequencing, phylogenetic-based report of strain relatedness, per submitted isolate</td>
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<td>Oncology, RNA, gene expression by whole transcriptome sequencing, formalin-fixed paraffin embedded tissue or fresh frozen tissue, predictive algorithm reported as potential targets for therapeutic agents</td>
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<td>BRCA1, BRCA2 (breast cancer 1 and 2) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis</td>
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<td>ASPA (aspartoacylase) (eg, Canavan disease) gene analysis, common variants</td>
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<td>BCKDHB (branched-chain keto acid dehydrogenase E1, beta polypeptide) (eg, Maple syrup urine disease) gene analysis, common variants (eg, R183P, G278S, E422X)</td>
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<td>;other breakpoint, qualitative or quantitative</td>
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<td>BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)</td>
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<td>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 8-9 del 7.1kb)</td>
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<td>full gene sequence</td>
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<td>intron 8 poly-T analysis (eg, male infertility)</td>
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<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants</td>
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<td>81229</td>
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<td>Interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities</td>
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<td>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)</td>
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<td>F5 (<em>coagulation factor V</em>) (eg, hereditary hypercoagulability) gene analysis, Leiden variant</td>
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<td>FANCC (<em>Fanconi anemia, complementation group C</em>) (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A&gt;T)</td>
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<td>FMR1 (<em>Fragile X mental retardation 1</em>) (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles</td>
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<td>characterization of alleles (eg, expanded size and methylation status)</td>
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<td>FLT3 (<em>fms-related tyrosine kinase 3</em>) (eg, acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (ie, exons 14, 15)</td>
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<td>tyrosine kinase domain (TKD) variants (eg, D835, I836)</td>
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<td>G6PC (glucose-6-phosphatase, catalytic subunit) (eg, Glycogen storage disease, Type 1a, von Gierke disease) gene analysis, common variants (eg, R83C, Q347X)</td>
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<td>GJB6</td>
<td>(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)])</td>
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<td>(hexosaminidase A [alpha polypeptide]) (eg, Tay-Sachs disease) gene analysis, common variants (eg, 1278insTATC, 1421+1G&gt;C, G269S)</td>
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<td>(hemochromatosis) (eg, hereditary hemochromatosis) gene analysis, common variants (eg, C282Y, H63D)</td>
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<td>HBA1/HBA2</td>
<td>(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)</td>
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<td>IKBKAP</td>
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<td>IGH@</td>
<td>(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)</td>
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<td>IGH@</td>
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<td>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)</td>
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<td>;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 procedure)</td>
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<td>Chimerism (engraftment) analysis, post transplantation specimen (eg, hematopoietic stem cell), includes comparison to previously performed baseline analyses; without cell selection</td>
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<tr>
<td>81268</td>
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<td>;with cell selection (eg, CD3, CD33), each cell type</td>
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<td>JAK2</td>
<td>(Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant</td>
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<td>KIT</td>
<td>(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)</td>
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<td>KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), gene analysis, D816 variant(s)</td>
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<td>KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)</td>
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<td>KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)</td>
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<td>Long QT syndrome gene analyses (eg, KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2); full sequence analysis (Deleted 1/1/2017)</td>
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<td>;duplication/deletion variants (Deleted 1/1/2017)</td>
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<td>MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme), methylation analysis</td>
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<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; promoter methylation analysis</td>
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<td>MCOLN1 (muco1ipin 1) (eg, Mucolipidosis, type IV) gene analysis, common variants (eg, IVS3-2A&gt;G, del6.4kb)</td>
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<td>MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)</td>
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<td>MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis</td>
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<td>NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants</td>
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<td>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)</td>
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<td>PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) (eg, gastrointestinal stromal tumor [GIST]), gene analysis, targeted sequence analysis (eg, exons 12, 18)</td>
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<td>PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis</td>
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<td>SEPT9 (Septin9) (eg, colorectal cancer) methylation analysis</td>
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<td>SMPD1(sphingomyelin phosphodiesterase 1, acid lysosomal) (eg, Niemann-Pick disease, Type A) gene analysis, common variants (eg, R496L, L302P, fsP330)</td>
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<td>SNRPN/UBE3A (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (eg, Prader-Willi syndrome and/or Angelman syndrome), methylation analysis</td>
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<td>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)</td>
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<td>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)</td>
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<td>;using direct probe methodology (eg, Southern blot)</td>
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<td>TRG@ (T cell antigen receptor, gamma) (eg, leukemia and lymphoma), gene rearrangement analysis, evaluation to detect abnormal clonal population(s)</td>
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<td>VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variant(s) (eg, -1639G&gt;A, c.173+1000C&gt;T)</td>
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<td>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</td>
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<td></td>
<td>81411</td>
<td>;duplication/deletion analysis panel, must include analyses for TGFBR1, TGFBR2, MYH11, and COL3A1</td>
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<td>81412</td>
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<td>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</td>
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<td>81413</td>
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<td>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</td>
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<td>81432</td>
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<td>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</td>
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<tr>
<td>81433</td>
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<td>Hereditary breast cancer-related disorders (eg, hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11</td>
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<tr>
<td>81434</td>
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<td>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</td>
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<td>81437</td>
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<td>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</td>
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<td>81438</td>
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<td>Hereditary neuroendocrine tumor disorders (eg, medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL</td>
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<tr>
<td>Codes</td>
<td>Number</td>
<td>Description</td>
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<td>81440</td>
<td>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</td>
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<td>81442</td>
<td>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</td>
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<tr>
<td>81445</td>
<td>Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, and RNA analysis when performed, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed</td>
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<tr>
<td>81450</td>
<td>Targeted genomic sequence analysis panel, hematolymphoid neoplasm or disorder, DNA analysis, 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</td>
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<tr>
<td>81455</td>
<td>Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, 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</td>
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<td>81460</td>
<td>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</td>
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<td>81465</td>
<td>Whole mitochondrial genome large deletion analysis panel (eg, Kearns-Sayre syndrome, chronic progressive external ophthalmoplegia), including heteroplasmy detection, if performed</td>
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<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
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<tr>
<td>81500</td>
<td>Oncology (ovarian), biochemical assays of two proteins (CA-125 and HE4), utilizing serum, with menopausal status, algorithm reported as a risk score</td>
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<tr>
<td>81503</td>
<td>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</td>
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<tr>
<td>81506</td>
<td>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</td>
<td></td>
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<tr>
<td>81508</td>
<td>Fetal congenital abnormalities, biochemical assays of two proteins (PAPP-A, hCG [any form]), utilizing maternal serum, algorithm reported as a risk score</td>
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<td>Codes</td>
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<td>81509</td>
<td>Fetal congenital abnormalities, biochemical assays of three proteins (PAPP-A, hCG [any form], DIA), utilizing maternal serum, algorithm reported as a risk score</td>
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<td></td>
<td>81510</td>
<td>Fetal congenital abnormalities, biochemical assays of three analytes (AFP, uE3, hCG [any form]), utilizing maternal serum, algorithm reported as a risk score</td>
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<tr>
<td></td>
<td>81511</td>
<td>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)</td>
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<tr>
<td></td>
<td>81512</td>
<td>Fetal congenital abnormalities, biochemical assays of five analytes (AFP, uE3, total hCG, hyperglycosylated hCG, DIA) utilizing maternal serum, algorithm reported as a risk score</td>
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<tr>
<td></td>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
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<tr>
<td></td>
<td>84311</td>
<td>Spectrophotometry, analyte not elsewhere specified</td>
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<tr>
<td></td>
<td>88299</td>
<td>Unlisted cytogenetic study</td>
</tr>
<tr>
<td></td>
<td>88380</td>
<td>Microdissection (ie, sample preparation of microscopically identified target); laser capture</td>
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<tr>
<td>HCPCS</td>
<td>S3854</td>
<td>Gene expression profiling panel for use in the management of breast cancer treatment</td>
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</table>

*Date of Origin: October 2013*