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Medical Policy Manual

Topic: Genetic Cancer Susceptibility Panels Using Next Generation Sequencing

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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 testing for cancer susceptibility may be approached by a focused method that involves testing for well-characterized mutations based on a clinical suspicion of which gene(s) may be the cause of the familial cancer. Panel testing involves testing for multiple mutations in multiple genes at one time.

Several companies, including Ambry Genetics and GeneDx, offer genetic testing panels that use next-generation sequencing methods for hereditary cancers. Next generation sequencing refers to one of several methods that use massively parallel platforms to allow the sequencing of large stretches of DNA. Panel testing is potentially associated with greater efficiencies in the evaluation of genetic diseases; however, it may provide information on genetic mutations that are of unclear clinical significance or which would not lead to changes in patient management. Currently available panels do not include all genes associated with hereditary cancer syndromes. In addition, these panels do not test for variants (i.e. single nucleotide polymorphisms [SNPs]), which may be associated with a low, but increased cancer risk.

Next Generation Sequencing Cancer Panels

A list of the genes that are included in these panels is given in Tables 1 and 2, followed by a brief description of each gene.

Table 1: Ambry Genetics Hereditary Cancer Panel Tests

Gene Tested	BRCAplus	GYNplus	BreastNext	OvaNext	ColoNext	PancNext	PGLNext	RenalNext	CancerNext
BRCA1	X	X	X	X		X			X
BRCA2	X	X	X	X		X			X
ATM			X	X		X			X
BARD1			X	X					X
BRIP1			X	X					X
MRE11A			X	X					X
NBN			X	X					X
RAD50			X	X					X
RAD51C			X	X					X
PALB2			X	X		X			X
STK11	X		X	X	X	X			X
CHEK2			X	X	X				X
PTEN	X	X	X	X	X			X	X
TP53	X	X	X	X	X	X		X	X
CDH1	X		X	X	X				X
MUTYH			X	X	X				X
MLH1		X		X	X	X		X	X
MSH2		X		X	X	X		X	X
MSH6		X		X	X	X		X	X
EPCAM		X		X	X	X		X	X
PMS2		X		X	X	X		X	X
APC					X	X			X
BMPR1A					X				X
SMAD4					X				X
NF1			X	X			X		X
RAD51D			X	X					X
CDK4									X
CDKN2A						X			X
RET							X		
SDHA							X	X	
SDHAF2							X		
SDHB							X	X	
SDHC							X	X	
SDHD							X	X	
TMEM127							X		
VHL							X	X	
FH								X	
FLCN								X	
MET								X	
MITF								X	
TSC1								X	
TSC2								X	

GeneDx offers a number of comprehensive cancer panels that use next generation sequencing, summarized in Table 2.

Table 2: GeneDx Hereditary Cancer Panel Tests

Gene Tested	Breast/Ovarian Cancer Panel	Breast Cancer High Risk Panel	Endometrial Cancer Panel	Lynch/ Colorectal Cancer High Risk Panel	Colorectal Cancer Panel	Pancreatic Cancer Panel	Comprehensive Cancer Panel
BRCA1	X	X	X			X	X
BRCA2	X	X	X			X	X
ATM	X				X	X	X
BARD1	X						X
BRIP1	X						X
MRE11A							
NBN	X						
RAD50							
RAD51C	X						X
PALB2	X		X			X	X
STK11	X	X			X	X	X
CHEK2	X		X		X		X
PTEN	X	X	X		X		X
TP53	X	X	X		X	X	X
CDH1	X	X			X		X
MUTYH			X	X	X		X
MLH1	X		X	X	X	X	X

MSH2	X		X	X	X	X	X
MSH6	X		X	X	X	X	X
EPCAM	X		X	X	X	X	X
PMS2	X		X	X	X	X	X
APC				X	X	X	
BMPR1A					X		X
SMAD4					X		X
RAD51D	X						X
CDK4						X	X
CDKN2A						X	X
VHL						X	X
XRCC2	X				X	X	X
FANCC							X
AXIN2					X		X

Mayo Clinic also offers a hereditary colon cancer multi-gene panel analysis, which includes the genes in the Ambry Genetics ColoNext, with the addition of two other low-risk genes (*MLH3* and *AXIN2*).

The University of Washington offers the BROCA Cancer Risk Panel, which is a next generation sequencing panel that includes the following mutations: *AKT1*, *APC*, *ATM*, *ATR*, *BAP1*, *BARD1*, *BMPR1A*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CDK4*, *CDKN2A*, *CHEK1*, *CHEK2*, *CTNNA1*, *FAM175A*, *GALNT12*, *GEN1*, *GREM1*, *HOXB13*, *MEN1*, *MLH1*, *MRE11A*, *MSH2* (+*EPCAM*), *MSH6*, *MUTYH*, *NBN*, *PALB2*, *PIK3CA*, *PPM1D*, *PMS2*, *POLD1*, *POLE*, *PRSS1*, *PTEN*, *RAD50*, *RAD51*, *RAD51C*, *RAD51D*, *RET*, *SDHB*, *SDHC*, *SDHD*, *SMAD4*, *STK11*, *TP53*, *TP53BP1*, *VHL*, and *XRCC2*.[1]

The University of Washington also offers the ColoSeq™ gene panel, which includes 19 genes associated with Lynch syndrome (hereditary non-polyposis colorectal cancer, HNPCC), familial adenomatous polyposis (FAP), MUTYH-associated polyposis (MAP), hereditary diffuse gastric cancer (HDGC), Cowden syndrome, Li-Fraumeni syndrome, Peutz-Jeghers syndrome, Muir-Torre syndrome, Turcot syndrome, and Juvenile Polyposis syndrome: *AKT1, APC, BMPR1A, CDH1, EPCAM, GALNT12, GREM1, MLH1, MSH2, MSH6, MUTYH, PIK3CA, PMS2, POLE, POLD1, PTEN, SMAD4, STK11*, and *TP53*.[2]

Myriad Genetics offers myRisk™ Hereditary Cancer Panel, a comprehensive 25-gene cancer panel, that encompasses the simultaneous analysis of a larger number of genes combined in a panel for the identification of mutations impacting inherited risks for eight cancers: breast, colorectal, ovarian, endometrial, gastric, pancreatic, melanoma and prostate. Myriad does not identify the specific mutations.

Regulatory Status

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. Ambry Genetics is CLIA licensed.

MEDICAL POLICY CRITERIA

The following genetic cancer panels that use next generation sequencing are considered **investigational** because the current scientific evidence is not yet sufficient to establish how test results from panels which include a broad number of genes may be used to direct treatment decisions and improve health

outcomes associated with all components of the panels:

Test Name	Laboratory
BRCAplus	Ambry Genetics™
Breast Cancer High Risk Panel	GeneDx
BreastNext™	Ambry Genetics™
Breast/Ovarian Cancer Panel	GeneDx
BROCA Cancer Risk Panel	University of Washington
CancerNext™	Ambry Genetics™
ColoNext™	Ambry Genetics™
Colorectal Cancer Panel	GeneDx
ColoSeq™	University of Washington
Comprehensive Cancer Panel	GeneDx
GYNplus	Ambry Genetics™
Endometrial Cancer Panel	GeneDx
Lynch/Colorectal Cancer High Risk Panel	GeneDx
myRisk™ Hereditary Cancer Panel	Myriad
OncoPlex Multiplexed Gene Sequencing Panel	University of Washington
OvaNext™	Ambry Genetics™
PancNext™	Ambry Genetics™
Pancreatic Cancer Panel	GeneDx
PGLNext™	Ambry Genetics™
RenalNext™	Ambry Genetics™

SCIENTIFIC EVIDENCE

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. Validation of the clinical use of any diagnostic test focuses on 3 main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

For genetic panels that test for a broad number of mutations, 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 the 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.

Analytic Validity

Nonrandomized Study

In order to determine whether next generation sequencing would enable accurate identification of inherited mutations for breast and ovarian cancer, Walsh and colleagues developed a genomic assay to capture, sequence, and detect all mutations in 21 genes, (which included 19 of the genes on the BreastNext and OvaNext panels).[3] Constitutional genomic DNA from individuals with known inherited mutations, was hybridized to custom oligonucleotides and then sequenced. The analysis was carried out blindly as to the mutation in each sample. All single nucleotide substitutions, small insertions and deletions, and large duplications and deletions were detected. There were no false positive results.

Clinical Validity

The published literature provides no guidance for the assessment of the clinical validity of panel testing for cancer susceptibility with next generation sequencing. Although it may be possible to evaluate the clinical validity of sequencing of individual genes found on these panels, the clinical validity of next generation sequencing for cancer susceptibility panels, which include mutations associated with an unknown or variable cancer risk, are of uncertain clinical validity.

Clinical Utility

Identifying an individual with a genetic mutation that confers a high risk of developing cancer could lead to changes in clinical management and improved health outcomes. There are well-defined clinical guidelines on the management of patients who are identified as having a high-risk hereditary cancer syndrome. Changes in clinical management could include modifications in cancer surveillance, specific risk-reducing measures (e.g., prophylactic surgery), and treatment guidance (e.g., avoidance of certain exposures). In addition, other at-risk family members could be identified.

On the other hand, identifying mutations that have intermediate or low penetrance is of limited clinical utility. Clinical management guidelines for patients found to have one of these mutations are not well-defined. In addition, there is a potential for harm, in that the diagnosis of an intermediate- or low-risk mutation may lead to undue psychological stress and unnecessary prophylactic surgical intervention.

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

Nonrandomized Studies

- In 2014, in an industry-sponsored study, Cragun et al. reported the prevalence of clinically significant mutations and variants of uncertain significance among patients who underwent ColoNext panel testing.[4] For the period included in the study (March 2012-March 2013), the ColoNext test included the *MLH1, MSH2, MSH6, PMS2*, *EPCAM*, *BMPR1*, *SMAD4*, *STK11*, *APC*, *MUTYH*, *CHEK2*, *TP53*, *PTEN*, and *CDH1* genes; alterations were classified as follows: (1) pathogenic mutation; (2) variant, likely pathogenic; (3) variant, unknown significance; (4) variant, likely benign; (5) benign. Data was analyzed for 586 patients whose ColoNext testing results and associated clinical data were maintained in a database by Ambry Genetics. Sixty-one patients (10.4%) had genetic alterations consistent with pathogenic mutations or likely pathogenic variants; after 8 patients with only *CHEK2* or one *MUTYH* mutation were removed, 42 patients (7.2%) were considered to have actionable mutations. One hundred eighteen patients (20.1%) had at least one variant of uncertain significance, including 14 patients who had at least

one variant of uncertain significance in addition to a pathologic mutation. Of the 42 patients with a pathologic mutation, most (30 patients, or 71%) clearly met National Comprehensive Cancer Network guidelines for syndrome-based testing, screening, or diagnosis, based on the available clinical and family history. The authors note that, "The reality remains that syndrome based testing would have been sufficient to identify the majority of patients with deleterious mutations. Consequently, the optimal and most cost-effective use of panel-based testing as a first-tier test *vs.* a second tier test (i.e. after syndrome-based testing is negative), remains to be determined."

- Mauer et al. reported a single academic center's genetics program's experience with next generation sequencing panels for cancer susceptibility.[5] 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, 5 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 5 (10%) directly influenced management decisions.

Conclusion

Genetic cancer susceptibility panels using next generation sequencing for breast cancer, ovarian cancer, colon cancer or multiple cancer types (e.g., BreastNext, OvaNext, ColoNext and CancerNext, respectively) include mutations associated with varying risk of developing cancer. Therefore, these panels are of limited utility in that they may identify a clinically actionable mutation/syndrome, but could also identify a mutation for which there are no well-established guidelines or actionable level of risk associated with it. In addition, high rates of variants of uncertain significance have been reported with the use of these panels.[6]

Clinical Practice Guidelines and Position Statements

American Society of Clinical Oncology (ASCO)

In a 2010 policy statement update on genetic and genomic testing for cancer susceptibility, ASCO stated that testing for high-penetrance mutations in appropriate populations has clinical utility in that they inform clinical decision making and facilitate the prevention or amelioration of adverse health outcomes, but that genetic testing for intermediate-penetrance mutations are of uncertain clinical utility because the cancer risk associated with the mutation is generally too small to form an appropriate basis for clinical decision making.[7] ASCO recommends that genetic tests with uncertain clinical utility (low-to-moderate penetrance mutations) be administered in the context of clinical trials.

National Comprehensive Cancer Network (NCCN)

NCCN guidelines on genetic/familial high-risk assessment for breast and ovarian cancer (v1.2014)[8] state that next generation sequencing gene panels for hereditary breast, ovarian and other cancers have limitations including an unknown percentage of variants of unknown significance, uncertainty of level

of risk associated with most of the genes on the panel, and lack clear guidelines on the risk management of carriers of some of the mutations on the panel. The guidelines also state, "Because of the complexity and limited data regarding their clinical utility, hereditary multigene cancer panels should only be ordered in consultation with a cancer genetics professional." The most recent NCCN guidelines on genetic/familial high risk assessment for colorectal cancer (v2.2014) does not address next generation sequencing gene panels.[9]

Summary

Genetic cancer panels that use next generation technology include mutations for a wide variety of cancers. The mutations included in these panels are associated with varying levels of risk of developing cancer, and only some of the mutations are associated with well-defined cancer syndromes which have established clinical management guidelines. The major advantage of these genetic panels is the ability to analyze many genes simultaneously, potentially improving the breadth and efficiency of genetic workup. Disadvantages of the panels are lower accuracy compared to direct sequencing, and the uncertain impact of a large amount of ancillary information related to non-indicated test results. Test results related to non-indicated mutations may potentially 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. Currently, there is insufficient evidence to establish the clinical utility of the genetic cancer panels listed in the Medical Policy Criteria; therefore, these tests are considered investigational. Additional research is needed to demonstrate the clinical utility of simultaneous testing for all components of each panel test.

REFERENCES

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9. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology™. Genetic/Familial High-Risk Assessment: Colorectal v.2.2014. [cited 07/23/2014]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf

CROSS REFERENCES

Genetic Testing for Hereditary Breast and/or Ovarian Cancer, Genetic Testing, Medical Policy No. 2

Genetic Testing for Inherited Susceptibility to Colon Cancer, Genetic Testing, Medical Policy No. 6

Evaluating the Utility of Genetic Panels, Genetic Testing, Medical Policy No. 64

CODES	NUMBER	DESCRIPTION
There are no specific codes for molecular pathology testing by panels. If the specific analyte is listed in CPT codes 81200-81355 or 81400-81408, the specific CPT code would be reported. If the specific analyte is not listed in the more specific CPT codes, unlisted code 81479 would be reported. The unlisted code would be reported once to represent all of the unlisted analytes in the panel.		
CPT	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	;known familial variants
	81203	;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	;minor breakpoint, qualitative or quantitative
	81208	;other breakpoint, qualitative or quantitative
	81209	*BLM (Bloom syndrome, RecQ helicase-like)* (eg, Bloom syndrome) gene analysis, 2281del6ins7 variant
	81210	*BRAF (v-raf murine sarcoma viral oncogene homolog B1)* (eg, colon cancer), gene analysis, V600E variant
	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

CODES	NUMBER	DESCRIPTION
		6kb, exon 14-20 del 26kb, exon 22 del 510bp, exon 8-9 del 7.1kb)
	81212	;185delAG, 5385insC, 6174delT variants
	81213	;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	;known familial variant
	81216	*BRCA2 (breast cancer 2)* (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81217	;known familial variant
	81220	*CFTR (cystic fibrosis transmembrane conductance regulator)* (eg, cystic fibrosis) gene analysis; common variants (eg, ACMG/ACOG guidelines)
	81221	;known familial variants
	81222	;duplication/deletion variants
	81223	;full gene sequence
	81224	;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	;interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities

CODES	NUMBER	DESCRIPTION
	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	;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)
	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	;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)

CODES	NUMBER	DESCRIPTION
	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	;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	;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)
	81267	Chimerism (engraftment) analysis, post transplantation specimen (eg, hematopoietic stem cell), includes comparison to previously performed baseline analyses; without cell selection
	81268	;with cell selection (eg, CD3, CD33), each cell type
	81270	*JAK2 (Janus kinase 2)* (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
	81275	*KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene)* (eg, carcinoma) gene analysis, variants in codons 12 and 13
	81280	Long QT syndrome gene analyses (eg, *KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, KCNJ2, CACNA1C, CAV3, SCN4B, AKAP, SNTA1, and ANK2*); full sequence analysis
	81281	;known familial sequence variant
	81282	;duplication/deletion variants

CODES	NUMBER	DESCRIPTION
	81287	*MGMT (O-6-methylguanine-DNA methyltransferase)* (eg, glioblastoma multiforme), 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	;known familial variants
	81294	;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	;known familial variants
	81297	;duplication/deletion variants
	81298	*MSH6 (mutS homolog 6 [E. coli])* (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81299	;known familial variants
	81300	;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	;known familial variant
	81304	;duplication/deletion variants
	81310	*NPM1 (nucleophosmin)* (eg, acute myeloid leukemia) gene analysis, exon 12 variants
	81315	*PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor*

CODES	NUMBER	DESCRIPTION
		alpha) (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative
	81316	;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	;known familial variants
	81319	;duplication/deletion variants
	81321	*PTEN (phosphatase and tensin homolog)* (eg, Cowden syndrome, *PTEN* hamartoma tumor syndrome) gene analysis; full sequence analysis
	81322	;known familial variant
	81323	;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	;full sequence analysis
	81326	;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	;using direct probe methodology (eg, Southern blot)
	81342	*TRG@ (T cell antigen receptor, gamma)* (eg, leukemia and lymphoma), gene

CODES	NUMBER	DESCRIPTION
		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 variants (eg, -1639/3673)
	81400	Molecular pathology procedure, Level 1
	81401	Molecular pathology procedure, Level 2
	81402	Molecular pathology procedure, Level 3
	81403	Molecular pathology procedure, Level 4
	81404	Molecular pathology procedure, Level 5
	81405	Molecular pathology procedure, Level 6
	81406	Molecular pathology procedure, Level 7
	81407	Molecular pathology procedure, Level 8
	81408	Molecular pathology procedure, Level 9
	81479	Unlisted molecular pathology procedure
HCPCS	None	