Clinical UM Guideline

Subject:	Gene Mutation Testing for Cancer Susceptibility and Management		
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Description

This document addresses gene mutation testing to determine whether an individual is at risk for the development of malignant tumors (including but not limited to breast, colon, lung, pancreatic and ovarian cancers) and to guide targeted cancer therapy in individuals with malignant conditions. This document also addresses the use of circulating tumor DNA testing to assess gene mutations.

Note(s):

- This document does **not** address gene panel testing (defined by five or more genes or gene variants tested on the same day on the same member by the same rendering provider). For information on these tests, please see the following:
  - GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling
  - GENE.00049 Circulating Tumor DNA Panel Testing (Liquid Biopsy)
- This document does **not** address circulating tumor cell (CTC) tests. For information on these tests, please see LAB.00015 Detection of Circulating Tumor Cells.
- This document does **not** provide coverage criteria for drugs including but not limited to chemotherapeutic agents or associated therapeutic products.
- For information on genetic testing for inherited diseases (including preconception or prenatal genetic testing and testing for germline genetic diseases), see CG-GENE-13 Genetic Testing for Inherited Diseases.
- When an individual genetic test is addressed in a separate medical policy or clinical utilization management guideline (CUMG), that policy or CUMG applies. For additional information, please see the following related documents:
  - CG-GENE-15 Genetic Testing for Lynch Syndrome, Familial Adenomatous Polyposis (FAP), Attenuated FAP and MYH-associated Polyposis
  - CG-GENE-16 BRCA Genetic Testing
  - CG-GENE-19 Measurable Residual Disease Assessment in Lymphoid Cancers Using Next Generation Sequencing
  - GENE.00025 Proteogenomic Testing for the Evaluation of Malignancies
  - GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling

Clinical Indications

Medically Necessary:

A. *Gene Mutation Testing for Cancer Susceptibility (See Table A below)*
Gene mutation testing for cancer susceptibility is considered **medically necessary** when all of the following criteria are met:

1. The genetic disorder is associated with a potentially significant cancer; **and**
2. The risk of the significant cancer associated with the genetic disorder cannot be identified through biochemical or other testing; **and**
3. A specific mutation, or set of mutations, has been established in the scientific literature to be reliably associated with the risk of developing malignancy; **and**
4. The results of the genetic test may impact the medical management (for example, surveillance; life-style) of the individual; **and**
5. Genetic counseling, which encompasses **all** of the following components, has been performed:
    a. Interpretation of family and medical histories to assess the probability of disease occurrence or recurrence; **and**
    b. Education about inheritance, genetic testing, disease management, prevention and resources; **and**
    c. Counseling to promote informed choices and adaptation to the risk or presence of a genetic condition; **and**
    d. Counseling for the psychological aspects of genetic testing.

B. *Gene Mutation Testing to Guide Targeted Cancer Therapy (See Table B below)*
Gene mutation testing to identify individuals who may benefit from the use of a targeted cancer therapy (associated therapeutic product [ATP]) is considered **medically necessary** when *all* of the following criteria are met:

1. The individual is a candidate for targeted therapy using an ATP (for example, pharmaceutical or biologic treatment) and the mutation status of a specific gene is required prior to initiating treatment with the ATP; **and**
2. A specific mutation, or set of mutations, has been established in the scientific literature to identify those most likely to respond to a targeted therapy or ATP.

C. *Circulating Tumor DNA (Liquid Biopsy) (See Table C below)*
Use of a circulating tumor DNA (ctDNA) test is considered **medically necessary** to guide targeted cancer therapies in individuals with solid tumors when the mutation(s) meets **criteria "B" above** and when formalin-fixed paraffin-embedded tumor tissue (FFPET) is inadequate in quality or quantity or is unavailable for testing.

Note: For information on circulating tumor DNA panel testing (defined by five or more genes or gene variants tested on the same day on the same member by the same rendering provider), see GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling or GENE.00049 Circulating Tumor DNA Panel Testing for Cancer (Liquid Biopsy).

Not Medically Necessary:

A. *Gene Mutation Testing for Cancer Susceptibility*
Gene mutation testing for cancer susceptibility is considered **not medically necessary** in individuals not meeting **all** of the Section A criteria above.

B. *Gene Mutation Testing to Guide Targeted Cancer Therapy*
Gene mutation testing to identify individuals who may benefit from the use of a targeted cancer therapy is considered **not medically necessary** when the medically necessary criteria in Section B above are not met.

C. *Circulating Tumor DNA (Liquid Biopsy)*
Use of a circulating tumor DNA (ctDNA) test is considered **not medically necessary** when the medically necessary criteria in Section C above is not met, including to detect the recurrence of a solid tumor, including colorectal cancer, and to test for solid tumor cancer susceptibility.

Coding

The following codes for treatments and procedures applicable to this guideline 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 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.

When services may be Medically Necessary when criteria are met:

CPT	
81120	*IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble)* (eg glioma), common variants (eg, R132H, R132C)
81121	*IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial)* (eg glioma), common variants (eg, R140W, R172M)
81170	*ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase)* (eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain
81175	*ASXL1 (additional sex combs like 1, transcriptional regulator)* (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence
81176	*ASXL1 (additional sex combs like 1, transcriptional regulator)* (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; targeted sequence analysis (eg, exon 12)
81191	*NTRK1 (neurotrophic receptor tyrosine kinase 1)* (eg, solid tumors) translocation analysis
81192	*NTRK2 (neurotrophic receptor tyrosine kinase 2)* (eg, solid tumors) translocation analysis

81193	*NTRK3 (neurotrophic receptor tyrosine kinase 3)* (eg, solid tumors) translocation analysis
81194	*NTRK (neurotrophic-tropomyosin receptor tyrosine kinase 1, 2, and 3)* (eg, solid tumors) translocation analysis
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
81210	*BRAF (B-Raf proto-oncogene, serine/threonine kinase)* (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
81218	*CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha)* (eg, acute myeloid leukemia), full gene sequence
81219	*CALR (calreticulin)* (eg, myeloproliferative disorders), gene analysis, common variants in exon 9
81233	*BTK (Bruton's tyrosine kinase)* (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, C481S, C481R, C481F)
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) [including but not limited to cobas® Mutation Test v2, OncoBEAM™ Lung1: EGFR, therascreen EGFR]
81236	*EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit)* (eg, myelodysplastic syndrome, myeloproliferative neoplasms) gene analysis, full gene sequence
81237	*EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit)* (eg, diffuse large B-cell lymphoma) gene analysis, common variant(s) (eg, codon 646)
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*)
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, gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (eg, exons 8, 11, 13, 17, 18)
81273	*KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog)* (eg, mastocytosis), gene analysis, D816 variant(s)
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)

81279	*JAK2 (Janus kinase 2)* (eg, myeloproliferative disorder) targeted sequence analysis (eg, exons 12 and 13)
81307	*PALB2 (partner and localizer of BRCA2)* (eg, breast and pancreatic cancer) gene analysis; full gene sequence
81308	*PALB2 (partner and localizer of BRCA2)* (eg, breast and pancreatic cancer) gene analysis; known familial variant
81309	*PIK3CA (phosphatidylinositol-4, 5-biphosphate 3-kinase, catalytic subunit alpha)* (eg, colorectal and breast cancer) gene analysis, targeted sequence analysis (eg, exons 7, 9, 20)
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)
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
81320	*PLCG2 (phospholipase C gamma 2)* (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, R665W, S707F, L845F)
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
81334	*RUNX1 (runt related transcription factor 1)* (eg, acute myeloid leukemia, familial platelet disorder with associated myeloid malignancy), gene analysis, targeted sequence analysis (eg, exons 3-8)
81338	*MPL (MPL proto-oncogene, thrombopoietin receptor)* (eg, myeloproliferative disorder) gene analysis; common variants (eg, W515A, W515K, W515L, W515R)
81339	*MPL (MPL proto-oncogene, thrombopoietin receptor)* (eg, myeloproliferative disorder) gene analysis; sequence analysis, exon 10
81347	*SF3B1 (splicing factor [3b] subunit B1)* (eg, myelodysplastic syndrome/acute myeloid leukemia) gene analysis, common variants (eg, A672T, E622D, L833F, R625C, R625L)
81348	*SRSF2 (serine and arginine-rich splicing factor 2)* (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, P95H, P95L)
81357	*U2AF1 (U2 small nuclear RNA auxiliary factor 1)* (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, S34F, S34Y, Q157R, Q157P)

81360	*ZRSR2 (zinc finger CCCH-type, RNA binding motif and serine/arginine-rich 2)* (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variant(s) (eg, E65fs, E122fs, R448fs)
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) [when specified as the following]: • *ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase)* (eg, acquired imatinib resistance), T315I variant • *CBFB/MYH11 (inv(16))* (eg, acute myeloid leukemia), qualitative, and quantitative, if performed • *EML4/ALK (inv(2))* (eg, non-small cell lung cancer), translocation or inversion analysis • *ETV6/RUNX1 (t(12;21))* (eg, acute lymphocytic leukemia), translocation analysis, qualitative, and quantitative, if performed • *MLL/MLLT3 (t(9;11))* (eg, acute myeloid leukemia), translocation analysis, qualitative, and quantitative, if performed • *RUNX1/RUNX1T1 (t(8;21))* (eg, acute myeloid leukemia) translocation analysis, qualitative, and quantitative, if performed
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) [when specified as the following]: • *DNMT3A (DNA [cytosine-5-]-methyltransferase 3 alpha)* (eg, acute myeloid leukemia), targeted sequence analysis (eg, exon 23) • *GNAQ (guanine nucleotide-binding protein G[q] subunit alpha)* (eg, uveal melanoma), common variants (eg, R183, Q209) • *VHL (von Hippel-Lindau tumor suppressor)* (eg, von Hippel-Lindau familial cancer syndrome), deletion/duplication analysis
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) [when specified as the following]: • *CDKN2A (cyclin-dependent kinase inhibitor 2A)* (eg, CDKN2A-related cutaneous malignant melanoma, familial atypical mole-malignant melanoma syndrome), full gene sequence • *FGFR2 (fibroblast growth factor receptor 2)* (eg, craniosynostosis, Apert syndrome, Crouzon syndrome), targeted sequence analysis (eg, exons 8, 10) • *FGFR3 (fibroblast growth factor receptor 3)* (eg, achondroplasia, hypochondroplasia), targeted sequence analysis (eg, exons 8, 11, 12, 13)

- *MEN1 (multiple endocrine neoplasia 1)* (eg, multiple endocrine neoplasia type 1, Wermer syndrome), duplication/deletion analysis
- *RET (ret proto-oncogene)* (eg, multiple endocrine neoplasia, type 2B and familial medullary thyroid carcinoma), common variants (eg, M918T, 2647_2648delinsTT, A883F)
- *SDHC (succinate dehydrogenase complex, subunit C, integral membrane protein, 15kDa)* (eg, hereditary paraganglioma-pheochromocytoma syndrome), duplication/deletion analysis
- *SDHD (succinate dehydrogenase complex, subunit D, integral membrane protein)* (eg, hereditary paraganglioma), full gene sequence
- *STK11 (serine/threonine kinase 11)* (eg, Peutz-Jeghers syndrome), duplication/deletion analysis
- *VHL (von Hippel-Lindau tumor suppressor)* (eg, von Hippel-Lindau familial cancer syndrome), full gene sequence

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) [when specified as the following]:

- *MEN1 (multiple endocrine neoplasia 1)* (eg, multiple endocrine neoplasia type 1, Wermer syndrome), full gene sequence
- *RET (ret proto-oncogene)* (eg, multiple endocrine neoplasia, type 2A and familial medullary thyroid carcinoma), targeted sequence analysis (eg, exons 10, 11, 13-16)
- *SMAD4 (SMAD family member 4)* (eg, hemorrhagic telangiectasia syndrome, juvenile polyposis), duplication/deletion analysis
- *SDHB (succinate dehydrogenase complex, subunit B, iron sulfur)* (eg, hereditary paraganglioma), full gene sequence
- *SDHC (succinate dehydrogenase complex, subunit C, integral membrane protein, 15kDa)* (eg, hereditary paraganglioma-pheochromocytoma syndrome), full gene sequence
- *STK11 (serine/threonine kinase 11)* (eg, Peutz-Jeghers syndrome), full gene sequence
- *WT1 (Wilms tumor 1)* (eg, Denys-Drash syndrome, familial Wilms tumor), full gene sequence

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) [when specified as the following]:

- *CDH1 (cadherin 1, type 1, E-cadherin [epithelial])* (eg, hereditary diffuse gastric cancer), full gene sequence
- *SMAD4 (SMAD family member 4)* (eg, hemorrhagic telangiectasia syndrome, juvenile polyposis), full gene sequence

81408 Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis) [when specified as the following]:

	• *ATM (ataxia telangiectasia mutated)* (eg, ataxia telangiectasia), full gene sequence • *NF1 (neurofibromin 1)* (eg, neurofibromatosis, type 1), full gene sequence
81479	Unlisted molecular pathology procedure [when specified as testing for the following genes: *ABL2, BAP1, BARD1, BCOR, BMPR1A, BRIP1, CALT, CBF, CBF2, CBL, CDK4, CDK12, CHEK1, CHEK2, CRLF2, CSF1R, DDX41, EPOR, FANCL, GATA2, IGHV, IL7R, JAK1, JAK3, KMT2A, MECOM (EVI1), MEN2, MET, MYC, MYH11, NBN, PDGFRG, PHF6, PPM1D, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L, RB1, ROS1, SDHAF2, SETBP1, SH2B3, STAG2, STAT3, TET2*]
0016U	Oncology (hematolymphoid neoplasia), RNA, *BCR/ABL1* major and minor breakpoint fusion transcripts, quantitative PCR amplification, blood or bone marrow, report of fusion not detected or detected with quantitation BCR-ABL1 major and minor breakpoint fusion transcripts, University of Iowa, Department of Pathology, Asuragen
0017U	Oncology (hematolymphoid neoplasia), *JAK2* mutation, DNA, PCR amplification of exons 12-14 and sequence analysis, blood or bone marrow, report of *JAK2* mutation not detected or detected *JAK2* Mutation, University of Iowa, Department of Pathology
0023U	Oncology (acute myelogenous leukemia), DNA, genotyping of internal tandem duplication, p.D835, p.I836, using mononuclear cells, reported as detection or nondetection of FLT3 mutation and indication for or against the use of midostaurin LeukoStrat® CDx FLT3 Mutation Assay, LabPMM LLC, an Invivoscribe Technologies, Inc company, Invivoscribe Technologies, Inc
0027U	*JAK2* (*Janus kinase 2*) (eg, myeloproliferative disorder) gene analysis, targeted sequence analysis exons 12-15 *JAK2* Exons 12 to 15 Sequencing, Mayo Clinic, Mayo Clinic
0040U	*BCR/ABL1 (t(9;22))* (eg, chronic myelogenous leukemia) translocation analysis, major breakpoint, quantitative MRDx BCR-ABL Test; MolecularMD
0046U	*FLT3 (fms-related tyrosine kinase 3)* (eg, acute myeloid leukemia) internal tandem duplication (ITD) variants, quantitative *FLT3* ITD MRD by NGS; LabPMM LLC, an Invivoscribe Technologies, Inc. Company
0049U	*NPM1 (nucleophosmin)* (eg, acute myeloid leukemia) gene analysis, quantitative NPM1 MRD by NGS; LabPMM LLC, an Invivoscribe Technologies, Inc. Company
0111U	Oncology (colon cancer), targeted KRAS (codons 12, 13, and 61) and NRAS (codons 12, 13, and 61) gene analysis utilizing formalin-fixed paraffin-embedded tissue Praxis™ Extended RAS Panel, Illumina, Illumina
0154U	Oncology (urothelial cancer), RNA, analysis by real-time RT-PCR of the *FGFR3 (fibroblast growth factor receptor 3)* gene analysis (ie, p.R248C [c.742C>T], p.S249C [c.746C>G], p.G370C [c.1108G>T], p.Y373C [c.1118A>G], FGFR3-TACC3v1, and FGFR3-TACC3v3), utilizing formalin-fixed paraffin-embedded urothelial cancer tumor

	tissue, reported as FGFR gene alteration status therascreen® FGFR RGQ RT-PCR Kit, QIAGEN, QIAGEN GmbH
0155U	Oncology (breast cancer), DNA, *PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha)* (eg, breast cancer) gene analysis (ie, p.C420R, p.E542K, p.E545A, p.E545D [g.1635G>T only], p.E545G, p.E545K, p.Q546E, p.Q546R, p.H1047L, p.H1047R, p.H1047Y), utilizing formalin-fixed paraffin-embedded breast tumor tissue, reported as *PIK3CA* gene mutation status therascreen® *PIK3CA* RGQ PCR Kit, QIAGEN, QIAGEN GmbH
0177U	Oncology (breast cancer), DNA, *PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha)* gene analysis of 11 gene variants utilizing plasma, reported as *PIK3CA* gene mutation status therascreen® *PIK3CA* RGQ PCR Kit, QIAGEN, QIAGEN GmbH
0235U	*PTEN (phosphatase and tensin homolog)* (eg, Cowden syndrome, PTEN hamartoma tumor syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions Genomic Unity® PTEN Analysis, Variantyx Inc, Variantyx Inc

HCPCS

S3840	DNA analysis for germline mutations of the RET proto-oncogene for susceptibility to multiple endocrine neoplasia type 2 [MEN 2]
S3841	Genetic testing for retinoblastoma
S3842	Genetic testing for von Hippel-Lindau disease

ICD-10 Diagnosis

	All malignancy-related diagnoses, including but not limited to
C00.0-C96.9	Malignant neoplasms
D45	Polycythemia vera
D47.01-D47.09	Mast cell neoplasms of uncertain behavior
D47.1	Chronic myeloproliferative disease [primary myelofibrosis]
D47.3	Essential (hemorrhagic) thrombocythemia
D47.4	Osteomyelofibrosis
E71.440	Ruvalcaba-Myhre-Smith syndrome
E88.89	Metabolic disorder, unspecified [Erdheim-Chester Disease]
Q85.8-Q85.9	Other/unspecified phakomatoses, not elsewhere classified [Peutz-Jeghers, von Hippel-Lindau syndromes, PTEN hamartoma syndrome]
Z15.01-Z15.09	Genetic susceptibility to malignant neoplasm
Z80.0-Z80.9	Family history of primary malignant neoplasm
Z85.00-Z85.9	Personal history of malignant neoplasm

When services are Not Medically Necessary:

For the procedure and diagnosis codes listed above when criteria are not met.

When services are also Not Medically Necessary:
For the following procedure codes, or when the code describes a procedure designated in the Clinical Indications section as not medically necessary.

CPT

81242	*FANCC (Fanconi anemia, complementation group C)* (eg, Fanconi anemia, type C) gene analysis, common variant (eg, IVS4+4A>T)
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) [when specified as the following]: • *HRAS (v-Ha-ras Harvey rat sarcoma viral oncogene homolog)* (eg, Costello syndrome), exon 2 sequence
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) [when specified as the following]: • *HRAS (v-Ha-ras Harvey rat sarcoma viral oncogene homolog)* (eg, Costello syndrome), full gene sequence
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) [when specified as the following]: • *BRAF (B-Raf proto-oncogene, serine/threonine kinase)* (eg, Noonan syndrome), full gene sequence
81479	Unlisted molecular pathology procedure [when specified as testing for the following genes]: • MRE11A • RAD50 • RECQL4 • RINT1 • SLX4 • SMARCA4 • XRCC2
0229U	*BCAT1 (Branched chain amino acid transaminase 1)* and *IKZF1 (IKAROS family zinc finger 1)* (eg, colorectal cancer) promoter methylation analysis Colvera®, Clinical Genomics Pathology Inc

ICD-10 Diagnosis

All malignancy-related diagnoses, including but not limited to

C00.0-C96.9	Malignant neoplasms
Z15.01-Z15.09	Genetic susceptibility to malignant neoplasm
Z80.0-Z80.9	Family history of primary malignant neoplasm
Z85.00-Z85.9	Personal history of malignant neoplasm

Discussion/General Information

A. Gene Mutation Testing for Cancer Susceptibility in Individuals with Cancer *(See Table A below)*

Genetic testing for cancer susceptibility is used to predict an individual's risk of cancer development in the future and to identify carriers (individuals who do not have the cancer but have a copy of a genetic variant which has been associated with the development of cancer). It has been estimated that approximately 5-10% of all cancers are considered to be hereditary (the result of inherited genetic susceptibility).

Genetic testing for cancer susceptibility (a form of predictive genetic testing) is generally carried out in asymptomatic individuals who are considered to be at high risk for developing cancer due to a strong family medical history of the disease, or other factors. Predictive genetic testing can be further divided into two categories: presymptomatic and predispositional. Presymptomatic predictive genetic testing confirms or denies the development of the disease in those at risk as the condition's genetic variant is highly penetrant and there is little or no variable expression. Predispositional predictive genetic tests provide information about an individual's risk of developing a specific disorder in the future. Predispositional predictive genetic testing is generally carried out for incompletely penetrant conditions and the results are not indicative of the inevitable occurrence of a condition or disease, nor are they a guarantee that a disease will not develop in the future.

One of the limitations of predictive genetic testing is the challenge in interpreting positive test results. Some individuals who test positive for a disease-associated variant may never develop the disease. In order to be useful in the clinical setting, the results of predictive genetic testing should have a high positive predictive value (PPV) and evidence should demonstrate that such results improve either disease prevention or management, as compared with care without genetic testing. Please refer to CG-GENE-13 Genetic Testing for Inherited Diseases for more information on the specific types of genetic tests, including but not limited to predictive genetic testing.

A position statement published by the American Society of Clinical Oncology (ASCO) indicates that genetic testing for cancer susceptibility is appropriate when the:

> 1) Individual has personal or family history features suggestive of a genetic cancer susceptibility condition, 2) the genetic test can be adequately interpreted, and 3) the test results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer (ASCO, 2003).

ASCO also recommends that genetic testing only be provided in the setting of pre- and post-test counseling, which should include a discussion of the risks and benefits of cancer early detection and prevention modalities (ASCO, 2003).

In assessing the value of a specific genetic test for susceptibility to a particular malignant condition, consideration should be given to the peer-reviewed, published literature addressing the analytical validity, clinical validity, and clinical utility of the test. Each genetic test must be carefully evaluated to determine whether or not the identified variant reliably identifies a specific type of cancer, and that the results of the genetic test, whether affirmative or negative, will impact the clinical management of the individual (for example, guide treatment decisions, surveillance recommendations or preventive strategies). The results of genetic testing are also expected to improve net health outcomes, (that is, the anticipated health benefits of the interventions outweigh any harmful effects [medical or psychological] of the intervention).

The National Comprehensive Cancer Networks (NCCN) guidelines do not contain recommendations for the general strategy of testing a tumor for a wide range of biomarkers. However, the guidelines do contain recommendations for specific genetic testing for individual cancers, when there is a known drug-biomarker combination that has demonstrated benefits for that particular type of tumor, such as non-small cell lung cancer (NCCN NSCLC).

Multiple Endocrine Neoplasia Type 2 (MEN 2) and Thyroid Cancer

Thyroid cancer (carcinoma) is relatively uncommon. In the United States, the lifetime risk of being diagnosed with thyroid cancer is approximately 1%. An estimated 44,280 cases of newly diagnosed thyroid cancer are expected in the United States in 2021 (National Cancer Institute [NCI]).

Multiple endocrine neoplasia type 2 (MEN 2) is a genetic condition which can be passed from generation to generation in a family. The gene associated with MEN 2 is called RET (RET proto-oncogene). A mutation in the RET gene increases an individual's risk of developing medullary thyroid cancer and other tumors associated with MEN 2.

Three major types of tumors are associated with MEN 2: medullary thyroid cancer, parathyroid tumors, and pheochromocytoma. MEN 2 is classified into three subtypes based on clinical features: MEN 2A, which affects 60% to 90% of MEN 2 families; MEN 2B, which affects 5% of MEN 2 families; and FMTC, which affects 5% to 35% of MEN 2 families (ASCO, 2013). The most common sign of multiple endocrine neoplasia type 2 is medullary thyroid cancer.

Based on histological findings, thyroid cancer includes the following categories: (1) differentiated (follicular, papillary and Hurthle); (2) medullary; and (3) anaplastic (aggressive undifferentiated tumor). Medullary thyroid cancer (MTC) develops from the "C" or parafollicular cells of the thyroid gland which produce calcitonin. Approximately 80% of the cases of MTC are sporadic. The remaining inherited syndromes include multiple endocrine neoplasia (MEN) type 2A (also known as MEN 2A), MEN 2B and familial MTC (FMTC). All three

of these subtypes, MEN 2A, MEN 2B and FMTC are inherited in an autosomal dominant pattern and involve an elevated risk for the development of medullary carcinoma of the thyroid. MEN 2A and MEN 2B have an increased risk for the development of pheochromocytoma. MEN 2A has an elevated risk for parathyroid adenoma or hyperplasia. Additional features in MEN 2B include distinctive facies with enlarged lips, mucosal neuromas of the lips and tongue and ganglioneuromatosis of the gastrointestinal tract. MTC generally occurs in early childhood in MEN 2B, early adulthood in MEN 2A, and middle age in FMTC (Moline, 2013).

Mutations in the RET proto-oncogene are found in at least 95% of individuals with MEN 2A and 88% of FMTC. Mutations associated with MEN 2A and familial MTC have been most frequently identified in several codons of the extracellular domains of exon 10, 11 and 13, while MEN 2B and some FMTC mutation have been identified within the intracellular exons 14 to 16. Somatic mutations in exons 11, 13 and 16 have also been identified in at least 25% of sporadic MTC tumors. Approximately 6% of individuals with clinical sporadic MTC are carriers of a RET germline mutation (National Comprehensive Cancer Network® [NCCN], 2021).

The management of MEN 2 depends on the type of MEN 2 diagnosed and whether the condition was identified prior to clinical signs and symptoms. If treated prior to regional lymph node metastases, MEN2 can usually be cured surgically. However, the majority of individuals (up to 75%) have lymph node involvement at the time of diagnosis. Because the development of invasive MTC is usually preceded by C-cell hyperplasia and can be detected by the oversecretion of calcitonin in response to a chemical challenge, annual surveillance employing biochemical testing has been used to monitor those with inherited disease before it progresses beyond the earliest stages. Genetic assays for RET mutations may be utilized as an alternative to annual biochemical testing for C-cell hyperplasia in individuals with a known family history of MEN 2A, 2B, or FMTC. Annual biochemical screening can be discontinued in those individuals who test negative for RET mutations. Individuals who test positive for RET mutations may elect to undergo immediate thyroidectomy or defer thyroidectomy until biochemical tests suggest the development of MTC. Genetic assays for RET oncogene mutations have also been used to determine if new cases of MTC without a known family history are truly sporadic in origin. Positive test results in this setting may prompt the evaluation of family members or initiate screening for pheochromocytoma.

The American Thyroid Association (ATA) developed four MTC risk levels based on correlations between RET genotype and MEN 2 phenotype, and made specific recommendations regarding the ideal timing for prophylactic thyroidectomy (ATA, 2015). For individuals with RET variants associated with MEN 2B, who have the highest risk for early-onset MTC, thyroidectomy is recommended within the first year of life. For individuals at the next highest risk level (i.e., those with variants involving RET codon 634), thyroidectomy is recommended in the first 5 years of life. For individuals with genotypes at the third highest level of risk, thyroidectomy should be considered prior to the age of 5 years, but may be delayed if stringent clinical criteria are met. For individuals with genotypes in the lowest risk category, thyroidectomy may be delayed after age 5 in the context of normal screening results and a family history consistent with less aggressive MTC.

According to the recommendations set forth in the guidelines by the NCCN (NCCN, 2021), genetic testing for RET-proto-oncogene mutations is recommended for all newly diagnosed individuals with clinically apparent sporadic MTC, and for screening children and adults in known relatives with inherited forms of MTC.

In summary, there is adequate data to show that genetic tests for point mutation in the RET gene can identify those with an inherited susceptibility for MTC prior to the onset of clinical manifestations. Test results affect individual management by prompting age-appropriate prophylactic thyroidectomy, the early diagnosis and treatment of pheochromocytoma and/or hyperparathyroidism, continued biochemical monitoring in affected individuals, and by prompting discontinuation of monitoring in individuals who test negative.

PTEN Hamartoma Tumor Syndrome

Germline mutations in PTEN have been identified in a variety of rare syndromic manifestations that are collectively known as PTEN hamartoma tumor syndrome (PHTS). The defining clinical feature of PHTS is the presence of hamartomatous tumors, benign tumors resulting from an overgrowth of normal tissue. The phenotypic spectrum of PHTS includes Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), and adult Lhermitte-Dulcos disease (ALDD). Notably, germline mutations in PTEN are also associated with adult Lhermitte-Dulcos disease, autism spectrum disorders with macrocephaly, and possibly intellectual disability/developmental delay with macrocephaly. The estimated penetrance of PTEN mutation is approximately 80%, although risk estimates vary.

CS is characterized by multiple hamartomas and/or an increased risk of developing cancerous lesions in various tissues and organs, including the skin, mucous membranes, breast, thyroid, endometrium and brain. Other cancers associated with CS include colorectal cancer, kidney cancer, and possibly melanoma. Additional conditions associated with CS include macrocephaly and Lhermitte-Duclos disease. A small percentage of affected individuals have delayed development or intellectual disability. The features of CS overlap with those of BRRS.

The BRRS variant of Cowden syndrome/PHTS is characterized by the presence of macrocephaly, gastrointestinal hamartomatous polyps, multiple lipomas, hemangiomas, developmental delay, and in males, pigmented macules of the glans penis. The signs of BRRS that may be present at birth include macrocephaly and macrosomia. Developmental delays may present in early childhood. Other signs associated with BRRS include pectus excavatum, hypotonia, hyperextensibility of joints, thyroid disorders, seizures and scoliosis.

Adult Lhermitte-Dulcos disease (ALDD, also known as dysplastic gangliocytoma of the cerebellum) is characterized by the development of slow-growing, benign hamartomatous outgrowths of the cerebellum. The lesions typically arise in the cerebellar hemispheres, most frequently in the left hemisphere. This condition is most frequently seen in adults, with the average age at diagnosis of 34 years. Developmental abnormalities including macrocephaly and intellectual developmental disorder are common. A presumptive diagnosis of PHTS may be made based on clinical findings; however, a definitive diagnosis of PHTS is made when genetic testing identifies a germline mutation.

The diagnostic criteria for CS are multifaceted. The NCCN guidelines include testing criteria and clinical diagnostic criteria for CS. According to the NCCN guidelines, the CS/PHTS testing algorithm was established to assist in determining which individuals are candidates for testing for PTEN pathogenic or likely pathogenic variants and can be used to evaluate the need for further risk assessment and genetic testing. The revised clinical diagnostic criteria can be used to identify clinical features associated with CS/PHTS. Individuals who meet the revised clinical diagnostic criteria for CS/PHTS are candidates for testing for PTEN pathogenic or likely pathogenic variants (NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, 2022).

According to the NCCN guidelines, the testing criteria for CS/PHTS are divided into three categories *(see criteria below)*. An individual is considered for testing for PTEN pathogenic or likely pathogenic variants based on whether he or she meets specific criteria or combinations of criteria from these three categories.

1. The first category includes any individual with a personal history of BRRS, adult LDD, autism spectrum disorder with macrocephaly, or two or more biopsy-proven trichilemmomas. Additionally, individuals with a family history positive for the presence of a known PTEN pathogenic or likely pathogenic variant.
2. The next category represents "major" features which have been associated with CS/PHTS. An individual exhibiting at least two of the major criteria where one of these is macrocephaly meets the threshold for genetic testing. Similarly, an individual exhibiting three or more of the major criteria without macrocephaly or an individual who meets one of the major criteria and three or more of the minor criteria, would also meet the genetic testing threshold. If an individual has two or more major criteria but does not have macrocephaly, then one of the major criteria may be included as one of the three minor criteria in order to meet the testing threshold. Lastly, an individual with a first-degree relative diagnosed with CS/PHTS or BRRS for whom testing has not been performed would also fulfill the threshold for PTEN testing if the individual meets at least one major criterion and two or more minor criteria. With respect to the presence of mucocutaneous lesions, the panel did not consider the published evidence sufficient to specify an exact number or extent of these lesions required for the condition to be defined as a major criterion for Cowden syndrome. The NCCN panel also felt that evidence from the literature was not sufficient to include fibrocystic breast disease, uterine fibroids or fibromas as part of the testing criteria.
3. The final category of criteria includes features with a "minor" association with CS/PHTS. In order to fulfill the genetic testing criteria in this category, an individual would need to meet at least four or more of the minor criteria or three or more minor criteria and one of the major criteria.

   It is also worth noting that an individual with a first-degree relative diagnosed with CS or BRRS for whom testing has not been completed would also meet the PTEN gene mutation testing criteria provided the individual meets at least one of the major criteria and two or more of the minor criteria (NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, 2022).

The testing criteria below provides a summary of NCCN's testing criteria for CS/PHTS as well as the major and minor criteria.

- Individual has a family history of a known PTEN pathogenic or likely pathogenic variant:
  OR
- Individual meets the clinical *diagnostic criteria* for CS/PHTS as evidenced by Any of the following:
  - Personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS); **or**
  - Personal history of Adult Lhermitte-Duclos disease; **or**
  - Personal history of autism spectrum disorder AND macrocephaly; **or**
  - Personal history of two or more biopsy-proven trichilemmomas:

  OR
- Individual has ANY of the following combinations of the "Major*****" criteria (features) associated with CS/PHTS:
  - Personal history of two or more major criteria (one of which is macrocephaly); **or**
  - Personal history of three or more major criteria without macrocephaly; **or**
  - Personal history of one major criterion and three or more minor criteria; **or**
  - If an individual has two or more major criteria but does not have macrocephaly, then one of the major criteria can be included as one of the three minor criteria to fulfill the testing threshold.

  OR
- Individual has ANY of the following combinations of the "Minor^{+}" criteria (features) associated with CS/PHTS:
  - Personal history of four or more minor criteria: **or**
  - As mentioned above, individual has a personal history of three or more minor criteria and one of the major criteria.

  OR
- Individual has a first-degree relative who has a clinical diagnosis of CS, PHTS or BRRS for who testing to confirm the diagnosis of CS/PHTS has not been performed, provided the individual meets at least one of the major criteria or two or more of the minor criteria.

***Major Criteria (Features)**	**$^{+}$Minor Criteria (Features)**

• Breast cancer
• Endometrial cancer
• Follicular thyroid cancer
• Multiple GI hamartomas or ganglioneuromas
• Macrocephaly (megalocephaly) (that is, ≥ 97%, 58 cm in adult female, 60 cm in adult male)
• Macular pigmentation of glans penis
• Mucocutaneous lesions
  o One biopsy-proven trichilemmoma
  o Multiple palmoplantar keratoses
  o Multifocal or extensive oral mucosal papillomatosis
	• Autism spectrum disorder
	• Colon cancer
	• ≥ 3 esophageal glycogenic acanthoses
	• Lipomas
	• Intellectual disability (that is, IQ < 75)
	• Papillary or follicular variant of papillary thyroid cancer
	• Thyroid structural lesions (that is, adenoma, nodule[s], goiter)
	• Renal cell carcinoma
	• Single GI hamartomas or ganglioneuroma

○ Multiple cutaneous facial papules (often verrucous)	• Testicular lipomatosis • Vascular anomalies (including multiple intracranial developmental venous anomalies)

TABLE A: Testing for conditions listed in the table below without a "Yes" in the column for "Clinical Utility of Gene Mutation Testing for Cancer Susceptibility Demonstrated" have not been shown to be useful in making determinations regarding cancer susceptibility. In many cases, this is because knowledge of the genetic status does not change management. The following table lists commonly requested gene testing targets along with an assessment of whether or not they have been shown to be useful in determining if an individual is at increased risk for the development of a specific type of malignancy or in guiding clinical management in an at-risk individual (for example, increased cancer surveillance).

TABLE A Gene Mutation Testing for Cancer Susceptibility

(Return to Clinical Indications) – (Return to Discussion/General Information)

Gene	Condition	Clinical Utility of Gene Mutation Testing for Cancer Susceptibility Demonstrated
APC	Colorectal cancer	CG-GENE-15 Genetic Testing for Lynch Syndrome, Familial Adenomatous Polyposis (FAP), Attenuated FAP and MYH-associated Polyposis
ATM	Breast cancer	CG-GENE-16 BRCA Genetic Testing GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling RAD.00036 MRI of the Breast
BAP1	Melanoma	Yes
BARD1	Breast cancer	CG-GENE-16 BRCA Genetic Testing GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling
	Ovarian cancer	No
BMPR1A	Familial Juvenile Polyposis	Yes
BRCA1	Breast cancer	CG-GENE-16 BRCA Genetic Testing

		GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling
BRCA2	Breast cancer	CG-GENE-16 BRCA Genetic Testing GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling
BRIP1	Ovarian cancer	Yes
CDH1	Breast cancer	RAD.00036 MRI of the Breast
	Hereditary diffuse gastric cancer	RAD.00036 MRI of the Breast
	Ovarian cancer	No
CDKN2A	Melanoma	Yes
CDK4	Melanoma	Yes
CHEK2	Breast cancer	CG-GENE-16 BRCA Genetic Testing GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling RAD.00036 MRI of the Breast
EPCAM	Lynch-related tumors (cancers) including: colorectal, gastric, small bowel, endometrial, ovarian, pancreas, ureter, renal pelvis, biliary tract, brain, sebaceous gland adenomas and keratocanthomas	CG-GENE-15 Genetic Testing for Lynch Syndrome, Familial Adenomatous Polyposis (FAP), Attenuated FAP and MYH-associated Polyposis
FANCC	Breast cancer	No
	Ovarian cancer	No
MEN1	Multiple endocrine neoplasia type 1 (MEN1)	Yes
MEN2	Multiple endocrine neoplasia type 2 (MEN2)	Yes
	Thyroid cancer	Yes
MET	Non-small cell lung cancer	Yes
MLH1	Lynch-related tumors (cancers) including colorectal, gastric, small bowel, endometrial, ovarian, pancreas, ureter, renal pelvis, biliary tract, brain, sebaceous gland adenomas and keratocanthomas	CG-GENE-15 Genetic Testing for Lynch Syndrome, Familial Adenomatous Polyposis (FAP), Attenuated FAP and MYH-associated Polyposis
MRE11A	Breast cancer	No
	Ovarian cancer	No

MSH2	Lynch-related tumors (cancers) including colorectal, gastric, small bowel, endometrial, ovarian, pancreas, ureter, renal pelvis, biliary tract, brain, sebaceous gland adenomas and keratocanthomas	CG-GENE-15 Genetic Testing for Lynch Syndrome, Familial Adenomatous Polyposis (FAP), Attenuated FAP and MYH-associated Polyposis
MSH6	Lynch-related tumors (cancers) including colorectal, gastric, small bowel, endometrial, ovarian, pancreas, ureter, renal pelvis, biliary tract, brain, sebaceous gland adenomas and keratocanthomas	CG-GENE-15 Genetic Testing for Lynch Syndrome, Familial Adenomatous Polyposis (FAP), Attenuated FAP and MYH-associated Polyposis
MUTYH (MYH)	Colorectal cancer	CG-GENE-15 Genetic Testing for Lynch Syndrome, Familial Adenomatous Polyposis (FAP), Attenuated FAP and MYH-associated Polyposis
NBN	Breast cancer	Yes
NF1	Breast Cancer	Yes
PALB2	Breast cancer	CG-GENE-16 BRCA Genetic Testing GENE.00052 RAD.00036 MRI of the Breast
	Gastric cancer	No
PMS2	Lynch-related tumors (cancers) including colorectal, gastric, small bowel, endometrial, ovarian, pancreas, ureter, renal pelvis, biliary tract, brain, sebaceous gland adenomas and keratocanthomas	CG-GENE-15 Genetic Testing for Lynch Syndrome, Familial Adenomatous Polyposis (FAP), Attenuated FAP and MYH-associated Polyposis
PTEN	Ovarian cancer	No
	PTEN hamartoma tumor syndrome, Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS) and Adult Lhermitte-Duclos disease (ALDD)	Yes; see Discussion section
RAD50	Breast cancer	No
	Ovarian cancer	No
RAD51C	Breast cancer	CG-GENE-16 BRCA Genetic Testing GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling
	Ovarian cancer	Yes
RAD51D	Breast cancer	CG-GENE-16 BRCA Genetic Testing

		GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling
	Ovarian cancer	Yes
RB1	Retinoblastoma	Yes
RECQL4	Breast cancer	No
	Ovarian cancer	No
RET	Adrenal tumors	Yes
	Multiple endocrine neoplasia type 2 (MEN2)	Yes
	Medullary thyroid carcinoma	Yes
	Neuroendocrine tumors	Yes
	Paraganglioma	Yes
	Pheochromocytoma	Yes
	Thyroid carcinoma	Yes
RINT1	Breast cancer	No
	Ovarian cancer	No
SDHAF2	Hereditary paraganglioma-pheochromocytoma syndrome	Yes
SDHB	Hereditary paraganglioma-pheochromocytoma syndrome	Yes
SDHC	Hereditary paraganglioma-pheochromocytoma syndrome	Yes
SDHD	Hereditary paraganglioma-pheochromocytoma syndrome	Yes
SLX4	Breast cancer	No
	Ovarian cancer	No
SMAD4	Colorectal cancer	Yes
	Juvenile polyposis syndrome	Yes
SMARCA4	Breast cancer	No
	Ovarian cancer	No
STK11	Breast cancer	RAD.00036 MRI of the Breast
	Colorectal cancer	Yes
	Peutz-Jegher syndrome	Yes
TP53	Breast cancer	CG-GENE-18 Genetic Testing for TP53 Mutations
	Li-Fraumeni syndrome	CG-GENE-18 Genetic Testing for TP53 Mutations
VHL	Von Hippel-Lindau Syndrome	Yes
WT1	Wilms tumor	Yes
XRCC2	Breast cancer	No

	Ovarian cancer	No

B. Gene Mutation Testing to Guide Targeted Therapy in Individuals with a Malignant Condition (See Table B below)

Increased understanding of the human genome has made it possible to identify genomic variation in both normal and malignant tissues. Newer therapies may be targeted to specific variants ("targeted biologic therapy") and may not have been evaluated in individuals without the specific variant or be considered unlikely to benefit individuals without the specific variant.

Examples of targeted therapies include those that:

- Block specific enzymes and growth factor receptors involved in cancer cell proliferation. These drugs are also called signal transduction inhibitors.
- Modify the function of proteins that regulate gene expression and other cellular functions.
- Induce cancer cells to undergo apoptosis.
- Block the growth of blood vessels and blood supply to tumors.
- Help the immune system to destroy cancer cells.

The Food and Drug Administration (FDA) has approved numerous companion diagnostic devices to detect variants in specific genes for the targeted treatment of cancer. Methodologies include, but are not necessarily limited to: immunohistochemistry (IHC), real-time or multiplex polymerase chain reaction (PCR), fluorescence in situ hybridization (FISH), and next generation sequencing (NGS). As an example of a targeted cancer therapy, in 2017, the FDA approved IDHIFA® (enasidenib) for the treatment of relapsed or refractory acute myeloid leukemia (AML). However, the FDA drug label also stipulated that IDHIFA should only be used in individuals with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA approved test.

In some cases, genetic testing, also called molecular characterization, is recommended for risk stratification and treatment planning, which affects choice of chemotherapeutic regimen, surveillance considerations, and minimal (measurable) disease detection.

Targeted Therapy and Treatment Planning for Leukemias

Leukemia, which is sometimes referred to as a blood cancer, is a type of cancer that affects the blood and bone marrow. The disease occurs when blood cells produced in the bone marrow grow out of control Frequently, leukemia starts the white blood cells, but some leukemias start in other blood cell types. There are various forms of leukemia, which are generally categorized based on whether the leukemia is acute (fast growing) or chronic (slower growing), and whether it starts in myeloid cells or lymphoid cells. As an example, acute lymphoblastic leukemia (AML) and chronic myeloid leukemia (CML) are both blood and bone marrow cancers that affect the same types of white blood cells. While the onset of AML occurs suddenly as very immature cells

quickly crowd out normal cells in the bone marrow, CML has a delayed onset, with the CML cells slowly growing out of control. Targeted therapy may be used for the treatment of various types of leukemias.

Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (also known lymphoblastic lymphoma [ALL/LBL] and acute lymphocytic leukemia) refers to blood malignancies of lymphoid precursor cells. These entities are described as ALL/LBL because in this setting, leukemia and lymphoma display overlapping clinical presentations of the same disease; the systems for classification and diagnosis do not distinguish between leukemia and lymphoma. Broadly, ALL/LBL is divided into tumors of B cell and T cell descent; tumors of natural killer (NK) cell lineage are also recognized but occur less frequently. Because the various subtypes are morphologically indistinguishable, immunophenotyping is required to determine the lineage.

Most cases of ALL/LBL have molecular and/or cytogenetic abnormalities that are associated with unique phenotypes, prognostic features, and/or influence the choice of treatment. The World Health Organization (WHO) classification system uses immunophenotype and cytogenetic/molecular features to delineate specific categories of ALL/LBL.

With regards to gene mutation testing in individuals suspected of having ALL/LBL, the NCCN recommends:

> The Ph-like phenotype is associated with recurrent gene fusions and mutations that activate tyrosine kinase pathways and includes gene fusions involving ABL1, ABL2, CRLF2, CSFIR, EPOR, JAK2, and PDGFRD and mutations involving FLT3, IL7R, SH2B3, JAK1, JAK3, and JAK2 (in combination with CRLF2 gene fusions). Testing for these abnormalities at diagnosis may aid in risk stratification. The safety and efficacy of targeted agents in this population is an area of active research… In cases of hypodiploid ALL where germline TP53 mutations are common, testing should be considered (NCCN ALL, 2021).

Acute Myeloid Leukemia

Acute myeloid leukemia (AML) refers to a group of leukemias that arise from a myeloid precursor in the bone marrow. Although AML is fairly rare overall, accounting for only about 1% of all cancers it is still one of the most common types of leukemia in adults. Cytogenetically normal AML is the largest defined subclass of AML and accounts for approximately 45% of all AML cases. In spite of the lack of cytogenetic abnormalities, these cases frequently have genetic variants that influence outcomes. The incidence of AML increases with age, with a median age at diagnosis of 68 years. Clinical signs and symptoms include but are not limited to, anemia, neutropenia, and thrombocytopenia. AML is also known as acute myelocytic leukemia, acute myelogenous leukemia, acute granulocytic leukemia, acute non-lymphocytic leukemia) (ACS, 2022).

Management of individuals with AML relies on the results of genetic testing to inform diagnosis, prognosis, and predict response to therapy. Abnormalities in specific genes, such as mutations in ASXL1, BCR-ABL, c-KIT, FLT3-ITD, FLT3-TKD, NPM1, CEBPA (biallelic), IDH1, IDH2, PML-RARA, RUNX1, and TP53 confer prognostic significance in adults with AML. In addition to prognostic implications, some gene may impact medical decision making or have therapeutic significance in AML (NCCN AML 2022).

The revised 2008 World Health Organization (WHO) AML classification scheme emphasizes the importance of genetic testing in AML Similarly, NCCN recommends that all individuals suspected of having AML be tested for specific gene mutations. Because numerous mutations are associated with AML, testing using multiplex gene panels and comprehensive next-generation sequencing (NGS) analysis may be used for the ongoing management of AML and various phases of treatment (NCCN AML 2022; Swerdlow, 2008). For information on gene panel testing in MDS, please refer GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling.

AML is vigorously treated upon detection with chemotherapy and stem cell transplantation.

Acute Promyelocytic Leukemia

Acute promyelocytic leukemia (APL) is a biologically and clinically distinct variation of AML. In particular, individuals with APL typically present with symptoms related to complications of anemia, neutropenia, and thrombocytopenia. Other signs and symptoms include combinations of weakness and easy fatigability, infections of variable severity, and/or hemorrhagic findings such as gingival bleeding, ecchymoses, menorrhagia or epistaxis. Unique to APL is a presentation with bleeding caused by disseminated intravascular coagulation. Frequently, by the time that individual seeks medical care, the situation has become a life-threatening emergency because of the risk of catastrophic bleeding. Often, at diagnosis, the marrow is nearly 100 percent replaced by malignant promyelocytes, which results in severe anemia, thrombocytopenia, and neutropenia.

APL represents a medical emergency with a high rate of mortality due to hemorrhage. Treatment of the bleeding disorder is usually initiated as soon as the diagnosis is suspected based on cytologic criteria, and even before definitive cytogenetic or molecular confirmation of the diagnosis has been made. Gene mutation testing is not required to diagnose or treat APL. Diagnosis of APL may be made based on an evaluation of the clinical presentation, cell morphology, immunophenotyping, identification of PML/RARα rearrangements using karyotyping, real-time polymerase chain reaction (RT-PCR), or fluorescence in situ hybridization (FISH), and immunofluorescence with anti-PML monoclonal antibodies.

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is one of the chronic lymphoid neoplasms (lymphoproliferative disorders) that is characterized by a progressive accumulation of functionally incompetent lymphocytes, which are usually of monoclonal origin. CLL is considered identical (that is, one disease with different manifestations) to small lymphocytic lymphoma (SLL). The term CLL is used when the disease manifests predominately in the blood, whereas the term SLL is used when involvement is predominately nodal.

The evaluation of suspected cases of CLL varies according to the presentation. The diagnosis of CLL is generally suspected in asymptomatic individuals when a routine blood count reveals an absolute lymphocytosis. Evaluation of such individuals would usually include a complete blood count with differential and peripheral blood immunophenotyping using flow cytometry. Tests to identify genetic changes that occur in CLL might include but are not necessarily limited to FISH and PCR to identify chromosomal deletions, 13 [del(13q)], and trisomy 12.

The NCCN guidelines on Chronic Lymphocytic Leukemia indicate that TP53 mutation status is associated with low response rates to chemoimmunotherapy and recommends that TP53 mutation testing be done to inform prognosis and/or therapy determination.

> Del(17p), which reflects the loss of the TP53 gene and is frequently associated with mutations in the remaining TP53 allele, is associated with short treatment-free interval, short median survival (32 months), and poor response to chemotherapy. TP53 abnormalities can occur in the absence of del(17p) and TP53 mutations have been identified as predictors of resistance to fludarabine-based or bedamustine-based regimens and poor survival, independent of 17p chromosome status (NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, 2022).

Additionally, the NCCN also recommends that IGHV mutation status be determined prior to initiating treatment for CLL:

> The choice of first-line treatment for CLL/SLL should be based on the disease stage, presence or absence of del(17p) or TP53 mutation, IGHV mutation status (if considering chemoimmunotherapy), patient's age, performance status, comorbid conditions, and the agent's toxicity profile. (NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, 2022).

The mutation status of at least two other genes have been identified as playing an important role in the selection of targeted therapies for the treatment of CLL. In individuals with CLL/SLL who do not have del(17p)/TP53 mutation, the NCCN states "testing for BTK and PLCG2 mutations may be useful in patients with disease progression or no response while on BTK inhibitor therapy. BTK and PLCG2 mutation status alone is not an indication to change treatment" (NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, 2022).

CLL is an extremely diverse disease with certain subsets of individuals having survival rates without treatment that are similar to the normal population. With the possible exception of allogeneic hematopoietic cell transplantation (HCT), there currently is no treatment option that can cure CLL. According to the NCCN: "Long-term results from several prospective studies have shown that allogeneic hematopoietic cell transplant (HCT) can provide long-term disease control and also overcome the poor prognosis associated with del(17p) and TP53 mutations" (NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, 2022).

Chronic Myeloid Leukemia

Chronic myeloid leukemia (CML), also known as chronic myelogenous, chronic myelocytic or chronic granulocytic leukemia) is a myeloproliferative neoplasm in which the bone marrow makes too many myeloid cells. These blood cells are abnormal and can build up in the blood and bone marrow so there is less room for the healthy white blood cells. CML is a relatively uncommon disease, primarily affecting older adults at an average age of 64 years. CML it is not an inherited disease. Instead, the DNA mutations associated with CML occur over an individual's lifetime, rather than being present from birth.

CML is associated with the BCR-ABL mutation that is formed by the combining of two genes: BCR (on chromosome 22) and ABL1 (on chromosome 9), resulting in the BCR-ABL1 fusion gene (also known as the Philadelphia chromosome). The presence of the BCR-ABL1 fusion gene confirms the diagnosis of CML. CML patients who have the Philadelphia chromosome (Ph+ CML) have a more favorable prognosis than those without the Philadelphia chromosome (Ph- CML). Testing for the BCR-ABL abnormality can be done using cytogenetics (chromosome analysis or karyotyping), FISH and RT-PCR (to detect and measure the BCR-ABL1 RNA transcripts in leukemic cell). DNA sequencing methods may be used to identify secondary mutations within BCR-ABL1 that are known to cause resistance to therapy.

Prior to the availability of protein tyrosine kinase inhibitors (TKIs), the only curative option for CML was high-dose chemotherapy with hematopoietic stem cell transplantation (HSCT). but with the emergence of BCR-ABL-targeted TKIs, the role of HSCT has become less clear. Protein TKIs are typically utilized in the treatment of CML. Point mutations in the BCR-ABL1 kinase domain are a frequent mechanism of secondary resistance to TKI therapy and are associated with poor prognosis and higher risk of disease progression.

Several drugs in the protein TKI class have now been approved by the United States Food and Drug Administration for the treatment of CML Most individuals have a good response to this first-line of therapy. However, some individuals develop secondary (acquired) resistance to the first-line therapeutic agent, which may be due to secondary mutations of the BCR-ABL gene. BCR-ABL1 kinase domain (KD) mutation status can be used to guide selection of alternative TKIs for CML patients who experience resistance to or intolerance to initial TKI therapy. The NCCN recommends that in individuals who present with advanced phase CML, the selection of TKI should be based on prior therapy and/or BCR-ABL1 mutation profile.

Additionally, according to the NCCN, "NGS allows for the detection of low-level BCR-ABL1 kinase domain mutations as well as resistance mutations in genes other than BCR-ABL1 that may confer resistance to TKIs or portend disease progression" and "NGS with myeloid mutation panel should be considered for patients with no identifiable BCR-ABL1 mutations" (NCCN Chronic Myeloid Leukemia, V1 2023).

The NCCN also recommends gene mutational analysis when allogeneic hematopoietic cell transplantation is being considered for patients with advanced phase CML.

Hairy Cell Leukemia

Hairy cell leukemia (HCL) is a relatively uncommon chronic B cell lymphoproliferative disorder (lymphoid neoplasm) characterized by the build-up of small mature B cell lymphoid cells with abundant cytoplasm and "hairy" projections inside the peripheral blood, bone marrow, and splenic red pulp. This typically causes splenomegaly and a variable decline in the production of normal red blood cells, platelets, mature granulocytes, and monocytes. The amplified production of malignant cells, along with a decrease in these mature elements, results in a variety of systemic consequences, including, but not limited to, anemia, splenomegaly, bleeding, and an increased risk of infection.

The etiology of HCL is not completely understood. Most cases of HCL are believed to arise from a late, activated memory B cell somatic BRAF V600E gene mutation. The resultant abnormal activation of the RAF-MEK-ERK signaling pathway leads to a distinct phenotype and prolonged cell survival.

Exposures to environmental hazards such as ionizing radiation and pesticides have been mentioned as possible causes. Exposure to cigarette smoke, alcohol consumption, solvents and obesity do not appear to be risk factors for the development of HCL.

The diagnosis of HCL is generally made based on the results of bone marrow biopsy and aspirate in conjunction with immunophenotyping by flow cytometry. The aberrant ("hairy") cells exhibit expression of pan-B cell antigens (for example, CD19, CD20, CD22) along with CD103, CD11c, and CD25. Gene mutation testing is typically not required to make the diagnosis of HCL.

Because this malignancy progresses very slowly and sometimes doesn't progress at all, it is not always necessary to begin treatment for HCL immediately after the diagnosis is confirmed.

Systemic Mastocytosis

Systemic mastocytosis is a rare disorder characterized by the expansion and focal accumulation of neoplastic mast cells (MC) in various organs, including the skin, spleen, liver, bone marrow and gastrointestinal tract. The World Health Organization (WHO) categorizes mastocytosis into cutaneous

mastocytosis (CM), systemic mastocytosis (SM) and mast cell sarcoma (MCS). WHO also further delineates SM into additional categories based on disease-specific features:

1. Indolent SM (ISM)
2. Smoldering SM (SSM)
3. Aggressive SM (ASM)
4. SM with an associated hematopoietic neoplasm (SM-AHN) and
5. MC leukemia (MCL).

MCS is a rare, localized, aggressive MC tumor that typically progresses to MCL within a short time. Advanced SM (ASM, SM-AHN, MCL) and MCS have unfavorable prognoses. Without successful therapy, the estimated median survival time in these individuals is less than 3 years. Once the diagnosis of SM has been made, the subtype (variant) of disease must be identified, as treatment and prognosis differ for each disorder\ (Valent, 2021).

Systemic mastocytosis is frequently diagnosed after affected individuals seek medical care for symptoms caused by the disorder. Symptoms of systemic mastocytosis may include cutaneous lesions, flushing, itching, hives, abdominal pain, diarrhea, nausea or vomiting, bone or muscle pain, anemia, bleeding disorders, splenomegaly, lymphadenopathy, depression, mood changes and problems concentrating.

A somatic mutation in the KIT gene is the most common genetic alteration found in systemic mastocytosis. The KIT gene encodes a protein that helps regulate cell growth and division. When the KIT gene is mutated, it can cause uncontrolled production of MCs which then accumulate in various organs of the body.

With regards to gene mutation testing for individuals suspected of having systemic mastocytosis, the NCCN recommends that:

> If a diagnosis of SM is suspected, molecular testing for KIT D816V using an assay with high sensitivity (eg, ASO-qPCR or digital droplet PCT) can first be undertaken on the peripheral blood, in combination with measurement of the serum tryptase level and evaluation of clinical signs and/or symptoms suggestive of SM-related organ involvement.
>
> Following a positive test of peripheral blood, KIT mutational analysis may also be performed on the bone marrow aspirate. Fresh bone marrow is aspirate is preferable but formalin-fixed paraffin-embedded tissue can also be used. Decalcified tissue typically interferes with DNA/RNA assays, and thus, decalcified BM should not be used for mutational analysis. If initial screening of the peripheral blood fails to detect the KIT D816V mutation in a patient with suspected SM, testing of the bone marrow should be undertaken with a highly sensitive assay (eg, ASO-qPCR or digital droplet PCR).

Additionally, the NCCN recommends:

> Myeloid mutation panel testing should be performed on the bone marrow, but can be performed on the peripheral blood in the presence of an AHN and/or circulating mast cells. Myeloid mutation panels alone are not recommended for the detection of KIT D816V. Next-generation sequencing (NGS) assays can exhibit low sensitivity and higher-sensitivity assays should always be performed (NCCN Systemic Mastocytosis, 2021).

Currently, there is no treatment of systemic mastocytosis. Treatment is targeted at relieving the effects of MC overgrowth and avoiding environmental and dietary triggers.

Targeted Therapy and Treatment Planning for Myelodysplastic Syndromes

The myelodysplastic syndromes (MDS) consist of a group of blood malignancies characterized by clonal hematopoiesis, one or more cytopenias (ie, anemia, neutropenia, and/or thrombocytopenia), and atypical cellular maturation. MDS shares some pathologic and clinical features with AML, but MDS has a lower percentage of blasts in bone marrow and peripheral blood (by definition, < 20 percent). Individuals with MDS are at risk for symptomatic anemia, infection, bleeding, and transformation to AML. Because the clinical presentation of MDS in individuals varies significantly, diagnosis and disease stratification are based on multiple factors including clinical data, morphology of peripheral blood and bone marrow, cytogenetics, fluorescence in situ hybridization (FISH), flow cytometry and next-generational sequencing myeloid mutations studies. The primary clinical challenge in these disorders are morbidities caused by cytopenias and the potential for MDS to evolve into acute myeloid leukemia (AML). Additionally, there are complications that may arise as a result of chronic transfusions, treatment toxicity and in some cases systemic inflammatory conditions (NCCN Myelodysplastic Syndromes, 2022).

Genetic frequently somatically mutated in MDS include: ASXL1, BCOR, CALR, CBL, DDX41, DNMT3A, ETV6, EZH2, FLT3, GATA2, IDH1, IDH2, JAK2, MPL, NF1, NPM1, NRAS, PHF6, PPM1D, RUNX1, SETBP1, SF3B1, SRSF2, STAG2, STAT3, TET2, TP53, U2AF1, WT1, ZRSR2. However, it is important to note that several MDS-associated genes, (including but not limited to DNMT3A, EZH2, NRAS, SF3B1, TP53 and TET2) can occur in non-disease states and no single gene mutation is diagnostic of MDS. Additionally, mutations in several genes can occur in neoplasms other than MDS including malignancies of lymphoid origin such as acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL). Therefore, mutations should not be considered presumptive evidence of MDS when the diagnostic criteria for MDS have not been met. Instead, gene mutation testing may be used to inform the diagnosis of MDS (NCCN Myelodysplastic Syndromes, 2022). For information on gene panel testing in MDS, please refer GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling.

Mutations in several genes have prognostic value. As an example, mutations of ASXL1, ETV6, EZH2, RUNX1 and TP53 have been associated with decreased overall survival, while only mutations in SF3B1 have been

associated with a more favorable prognosis in several, but not all studies NCCN Myelodysplastic Syndromes, 2022).

Therapeutic options for individuals with MDS include supportive care, low-intensity therapy, high-intensity therapy (including allogeneic HCT) and participation in clinical trials.

Targeted Therapy and Treatment Planning for Myeloproliferative Neoplasms (MPNs)/Myeloproliferative Disorders (MPDs)

The MPDs/MPNs are a large group of relatively rare pathogenetically related diseases arising in the bone marrow and characterized by the proliferation of one or more myeloid cell lines in the bone marrow resulting in increased numbers of relatively mature neoplastic cells in the peripheral blood. According to the World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissue, MPNs include chronic myelogenous leukemia (BCR-ABL1 positive [CML]), PV, PMF and ET. However, CML is unique in that it is the only one of these conditions that is positive for the BCR-ABL1 translocation. The others, PV, MF and ET are considered part of the operational sub-category of BCR-ABL1 negative conditions (Swerdlow, 2017).

MPNs are characterized by a complex collection of symptoms. The symptoms vary within and between each MPN subtype, but typically include constitutional symptoms such as fatigue, weight loss, pruritus, symptoms associated with splenomegaly, and a variety of laboratory abnormalities, including leukocytosis, thrombocytosis and erythrocytosis. And while there are a number of shared clinical features across the conditions, each of the three BCR-ABL–negative MPNs is considered a distinct clinical entity. ET is characterized by elevation in platelet count and megakaryocyte proliferation in the bone marrow. PV is distinguished by an increase in red blood cell production, with resulting increases in RBC mass and hemoglobin and hematocrit levels. Frequently, platelet and white blood cell count are also elevated. PMF is characterized by anemia, progressive splenomegaly and bone marrow fibrosis, and multi-organ extramedullary hematopoiesis. Most of these features, however, are not diagnostically specific, and secondary causes of erythrocytosis, thrombocytosis and bone marrow fibrosis must be excluded.

The BCR-ABL1–negative MPNs are genetically characterized by the overlapping presence of mutations in three driver genes—JAK2, CALR, and MPL. Mutations in either of these driver genes results in increased activity in the JAK/STAT signal transduction pathway.

The diagnosis and monitoring of individuals with BCR-ABL–negative MPN can be challenging because several of the clinical and laboratory features of the classic forms of these diseases-PV, ET, or PMF-can be mimicked by other conditions such as myeloid fibrosis. Additionally, these diseases cannot always be identified with certainty on morphologic bone marrow exam, and diagnosis can be complicated by altering disease patterns. As an example, PV and ET can undergo a leukemic transformation or evolve into PMF.

The 2017 WHO guidelines on the Classification of Tumours of Haematopoietic and Lymphoid Tissue were revised in 2017 to reflect the recent discovery of genetic abnormalities involved in the pathogenesis of BCR-ABL1 negative MPN. The WHO diagnostic criteria include a combination of clinical, laboratory cytogenetic, and molecular testing. The diagnosis of PMF requires the individual to meet 3 major and 2 minor criteria. The diagnosis of PV requires meeting both major criteria and one minor criterion or the presence of the first major criterion together with two minor criteria, whereas the diagnosis of ET requires meeting all 4 criteria The 2017 WHO criteria recommends that JAK2V617F and other clonal markers be tested in individuals suspected of having ET and PMF. WHO also recommends that testing for JAK2V617F and JAK2 exon 12 variants be conducted in individuals suspected of having PV. These guidelines also provide the following information regarding JAK2 mutation testing:

> JAK2 mutations are not specific for any single clinical or morphologic MPN phenotype, and are also reported in some cases of myelodysplastic syndromes (MDS), myelodysplastic/myeloproliferative neoplasms (MDS/MPN) and acute myeloid leukaemia (AML). Thus, an integrated, multidisciplinary approach is necessary for the classification of myeloid neoplasms (Swerdlow, 2017).

The National Comprehensive Cancer Network (NCCN) guidelines on Myeloproliferative Neoplasms recommends that molecular testing for JAK2V617F mutations be performed in all individuals suspected of having ET, MF or PV. For individuals suspected of having PV, when JAK2V617F mutation testing is negative, molecular testing for the JAK2 exon 12 mutation should also be conducted. These NCCN guidelines include MPL mutation testing in the initial workup of all individuals suspected of having an MPN. The NCCN recommends that when JAK2 V617F mutation testing is negative, molecular testing for MPL and CALR mutations should be performed for individuals with MF and ET (NCCN, 2021).

Table B below contains a list of targeted cancer therapies, the associated cancer and the genetic variant that may be tested in order to direct targeted cancer therapy, including to guide recommended treatment planning. This information may be used to determine the appropriateness of a requested genetic test when considering the medical necessity criteria in the section above labeled: **Gene Mutation Testing to Guide Targeted Cancer Therapy.** Table B is current as of the publish date of this document. FDA approvals after the publish date (for example new drugs or new indications for existing drugs), will not be reflected in Table B until the next publish date. Reviewers should not rely solely on the absence of a drug/gene combination in Table B when determining whether a particular gene test meets the medical necessity criteria. For additional information and periodic updates on drug and companion diagnostic device approvals/clearances, visit the FDA websites at: https://labels.fda.gov/ and https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools.

TABLE B Gene Mutation Testing to Guide Targeted Cancer Therapy
(Return to Clinical Indications) – (Return to Discussion/General Information)

Gene Mutation Status Tested	Condition	Cancer Treatment Considerations	Related Anthem Document
ABL1	Acute lymphoblastic leukemia (ALL)	Treatment planning (NCCN)	GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling
ABL2	Acute lymphoblastic leukemia (ALL)	Treatment planning (NCCN)	GENE.00052
ALK	Inflammatory myofibroblastic tumor	Xalkori (crizotinib)	GENE.00052
	Non-small cell lung cancer (NSCLC)	Alecensa (alectinib)	GENE.00052
		Alunbrig (brigatinib)	GENE.00052
		Keytruda (pembrolizumab) Gene mutation testing required to exclude individuals with EGFR or ALK genomic tumor abberations	GENE.00052
		Libtayo (cemiplimab-rwlc) Gene mutation testing required to exclude individuals with EGFR, ALK or ROS1 genomic tumor abberations	
		Lorbrena (lorlatinib)	GENE.00052
		Opdivo (nivolumab)	GENE.00052

		Tecentriq (atezolizumab)	GENE.00052
		Xalkori (crizotinib)	GENE.00052
		Yervoy (ipilimumab)	GENE.00052
		Zykadia (ceritinib)	GENE.00052
ASXL1	Acute myeloid leukemia (AML)	Treatment planning (NCCN)	GENE.00052
	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
	Myeloproliferative neoplasm (MPN)	Treatment planning (NCCN)	GENE.00052
ATM	Prostate cancer	Poly (ADP-ribose) polymerase (PARP) inhibitor	GENE.00052
BARD1	Prostate cancer	Poly (ADP-ribose) polymerase (PARP) inhibitor	GENE.00052
BCOR	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
BCR-ABL	Acute lymphoblastic leukemia (ALL)	Treatment planning Gleevec (imatinib) – per FDA label Iclusig (ponatinib) – per FDA label Sprycel (dasatinib) – per FDA label	

	Acute myeloid leukemia (AML)	Treatment planning (NCCN)	GENE.00052
	Chronic myeloid (myelogenous) leukemia	Treatment planning (NCCN)	
		Bosulif (bosutinib)	
		Gleevec (imatinib)	
		Iclusig (ponatinib)	
		Scemblix (asciminib)	
		Sprycel (dasatinib)	
		Tasigna (nilotinib)	
BRAF	Central nervous system tumor(s)	FDA-approved BRAF inhibitor	
	Gastrointestinal stromal tumor (GIST)	Treatment planning (NCCN)	
	Hairy cell leukemia		
	Hepatobiliary cancer	Tafinlar (dabrafenib)	
	Non-small cell lung cancer (NSCLC)	Opdivo (nivolumab)	GENE.00052
		Yervoy (ipilimumab)	
BRAF fusion	Pilocytic astrocytoma	Koselugo (selumetinib) (NCCN)	
BRAF V600	Erdheim-Chester Disease	Zelboraf (vemurafenib)	
	Melanoma	Braftovi (encorafenib)	
		Cotellic (cobimetinib)	

		Mekinist (trametinib)	
		MEKTOVI (binimetinib)	
		Tafinlar (dabrafenib)	
	Melanoma	Tecentriq (atezolizumab)	
BRAF V600E	Anaplastic thyroid cancer	Mekinist (trametinib)	
		Tafinlar (dabrafenib)	
	Colorectal cancer	Braftovi (encorafenib	
		Erbitux (cetuximab)	
		Vectibix (panitumumab)	
	Hepatobiliary cancer	Mekinist (trametinib) (NCCN)	
	Melanoma	Braftovi (encorafenib	
		Cotellic (cobimetinib)	
		Mekinist (trametinib)	
		MEKTOVI (binimetinib)	
		Tafinlar (dabrafenib)	
		Zelboraf (vemurafenib)	
	Non-small cell lung cancer (NSCLC)	Erbitux (cetuximab)	GENE.00052
		Mekinist (trametinib)	
		Tafinlar (dabrafenib)	

	Pediatric diffuse high-grade gliomas, unresectable or metastatic solid tumors	Mekinist (trametinib) Tafinlar (dabrafenib)	
	Pilocytic astrocytoma	Koselugo (selumetinib) (NCCN)	
BRAF V600K	Melanoma	Braftovi (encorafenib	
		Cotellic (cobimetinib)	
		Mekinist (trametinib)	
		MEKTOVI (binimetinib)	
		Tafinlar (dabrafenib)	
	Pediatric diffuse high-grade gliomas, unresectable or metastatic solid tumors	Mekinist (trametinib) Tafinlar (dabrafenib)	
	Pilocytic astrocytoma	Koselugo (selumetinib)	
BRCA	Breast cancer	Lynparza (olaparib)	GENE.00052 CG-GENE-16 BRCA Testing for Breast and/or Ovarian Cancer Syndrome
		Talzenna (talazoparib)	
		Zejula (niraparib)	
	Ovarian cancer	Lynparza (olaparib)	
	Ovarian cancer (epithelial ovarian, fallopian tube, or primary peritoneal cancer)	Rubraca (rucaparib)	
	Pancreatic cancer	Lynparza (olaparib)	
	Prostate cancer	Lynparza (olaparib)	GENE.00052

BRCA1	Pancreatic adenocarcinoma	Lynparza (olaparib)	CG-GENE-16
	Prostate cancer	Poly (ADP-ribose) polymerase (PARP) inhibitor	GENE.00052 CG-GENE-16
BRCA2	Pancreatic adenocarcinoma	Lynparza (olaparib)	CG-GENE_16
	Prostate cancer	Poly (ADP-ribose) polymerase (PARP) inhibitor	GENE.00052 CG-GENE-16
BRIP1	Prostate cancer	Poly (ADP-ribose) polymerase (PARP) inhibitor	GENE.00052
BTK	Chronic lymphocytic leukemia/Small lymphocytic lymphoma	Treatment planning (NCCN)	
c-KIT	Acute myeloid leukemia (AML)	Treatment planning (NCCN)	GENE.00052
CALR	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
	Myeloproliferative neoplasm (MPN)	Treatment planning (NCCN)	GENE.00052
CALT Type 1/ Type 1-like	Myeloproliferative neoplasm (MPN)	Treatment planning (NCCN)	
CBF	Acute myeloid leukemia (AML)	Treatment planning (NCCN)	GENE.00052
CBF-MYH11	Acute myeloid leukemia (AML)	Treatment planning (NCCN)	GENE.00052
CBF2	Acute myeloid leukemia (AML)	Treatment planning (NCCN)	GENE.00052

CBL	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
CDK12	Prostate cancer	Poly (ADP-ribose) polymerase (PARP) inhibitor	GENE.00052
CEBPA	Acute myeloid leukemia (AML)	Treatment planning (NCCN)	GENE.00052
CHEK1	Prostate cancer	Poly (ADP-ribose) polymerase (PARP) inhibitor	GENE.00052
CHEK2	Prostate cancer	Poly (ADP-ribose) polymerase (PARP) inhibitor	GENE.00052
CRLF2	Acute lymphocytic leukemia/lymphoblastic lymphoma (ALL/LBL)	Treatment planning (NCCN)	GENE.00052
CSFIR	Acute lymphocytic leukemia/lymphoblastic lymphoma (ALL/LBL)	Treatment planning (NCCN)	GENE.00052
DDX41	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
DNMT3A	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
EGFR	Non-small cell lung cancer (NSCLC)	Gilotrif (afatinib)	GENE.00052
		Keytruda (pembrolizumab) Gene mutation testing required to exclude individuals with EGFR or ALK genomic tumor abberations	GENE.00052

		Libtayo (cemiplimab-rwlc) Gene mutation testing required to exclude individuals with EGFR, ALK or ROS1 genomic tumor abberations	
		Opdivo (nivolumab)	GENE.00052
		Tecentriq (atezolizumab)	GENE.00052
		Yervoy (ipilimumab)	GENE.00052
EGFR exon 19 deletions	Non-small cell lung cancer (NSCLC)	Iressa (gefitinib)	GENE.00052
		Tagrisso (osimertinib)	
		Tarceva (erlotinib)	
		Vizimpro (dacomitinib)	
EGFR exon 20	Non-small cell lung cancer (NSCLC)	Rybrevant (amivantamab)	GENE.00052
EGFR exon 20f	Non-small cell lung cancer (NSCLC)	Exkivity (mobocertinib)	GENE.00052
EGFR exon 21 (L858R) mutation	Non-small cell lung cancer (NSCLC)	Tagrisso (osimertinib)	GENE.00052
EGFR exon 21 (L858R) substitution	Non-small cell lung cancer (NSCLC)	Iressa (gefitinib)	GENE.00052
		Tarceva (erlotinib)	
EGFR T790M mutation	Non-small cell lung cancer (NSCLC)	Tagrisso (osimertinib)	GENE.00052
EPOR	Acute lymphocytic leukemia/lymphoblastic lymphoma (ALL/LBL)	Treatment planning (NCCN)	GENE.00052

ETV6	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
EZH2	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
	Myeloproliferative neoplasm (MPN)	Treatment planning (NCCN)	
FANCL	Prostate cancer	Poly (ADP-ribose) polymerase (PARP) inhibitor	GENE.00052
FGFR	Gastrointestinal stromal tumor (GIST)	Treatment planning (NCCN)	
FGFR2	Urothelial cancer	Balversa (erdafitinib)	
FGFR2 fusion or non-fusion rearrangement	Cholangiocarcinoma	Lytgobi (futibatinib	
		Truseltiq (infigratinib)	
FGFR3	Urothelial cancer	Balversa (erdafitinib)	
FLT3	Acute lymphocytic leukemia/lymphoblastic lymphoma (ALL/LBL)	Treatment planning (NCCN)	GENE.00052
	Acute myeloid leukemia (AML)	Rydapt (midostaurin)	GENE.00052
		Xospata (gilterinib)	
	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
FLT3-ITD	Acute myeloid leukemia (AML)	Treatment planning (NCCN)	GENE.00052
FLT3-TKD	Acute myeloid leukemia (AML)	Treatment planning (NCCN)	GENE.00052

GATA2	Acute myeloid leukemia (AML)	Treatment planning (NCCN)	GENE.00052
	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
Homologous recombination repair (HRR) gene alterations (for example: ATM, BARD1, BRIP1, BRCA1, BRCA2, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54L).	Prostate cancer	Poly (ADP-ribose) polymerase (PARP) inhibitor	GENE.00052
IDH1	Acute myeloid leukemia (AML)	Tibsovo (ivosidenib)	GENE.00052
	Cholangiocarcinoma	Tibsovo (ivosidenib)	
	Chondrosarcoma	Tibsovo (ivosidenib)	
	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
IDH2	Acute myeloid leukemia (AML)	Idhifa (enasidenib)	GENE.00052
	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
IGHV	Chronic lymphocytic leukemia/Small lymphocytic lymphoma (CLL/SLL)	Treatment planning (NCCN)	GENE.00052
IL7R	Acute lymphocytic leukemia/lymphoblastic lymphoma (ALL/LBL)	Treatment planning (NCCN)	GENE.00052

ITD	Acute myeloid leukemia (AML)	Treatment planning (NCCN)	GENE.00052
JAK1	Acute lymphocytic leukemia/lymphoblastic lymphoma (ALL/LBL)	Treatment planning (NCCN)	GENE.00052
JAK2	Acute lymphocytic leukemia/lymphoblastic lymphoma (ALL/LBL)	Treatment planning (NCCN)	GENE.00052
	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
	Myeloproliferative neoplasm (MPN)	Treatment planning (NCCN)	GENE.00052
JAK3	Acute lymphocytic leukemia/lymphoblastic lymphoma (ALL/LBL)	Treatment planning (NCCN)	GENE.00052
KIT	Gastrointestinal stromal tumor (GIST)	Gleevec (imatinib mesylate)	
	Melanoma	Treatment planning (NCCN)	
KIT D816V	Systemic mastocytosis	Treatment planning (NCCN)	
KMT2A	Acute myeloid leukemia (AML)	Treatment planning (NCCN)	GENE.00052
KRAS	Colorectal cancer	Erbitux (cetuximab)	
		Vectibix (panitumumab)	
KRAS G12C	Non-small cell lung cancer (NSCLC)	Lumakras (sotorasib	GENE.00052
MECOM (EVI1)	Acute myeloid leukemia (AML)	Treatment planning (NCCN)	GENE.00052

MET	Non-small cell lung cancer (NSCLC)	Tabrecta (capmatinib)	GENE.00052
		Tepmetko (tepotinib)	
		Xalkori (crizotinib)	
MLLT3	Acute myeloid leukemia (AML)	Treatment planning (NCCN)	GENE.00052
MPL	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
	Myeloproliferative neoplasm (MPN) (MPL and MPL W515l/K)	Treatment planning (NCCN)	
	Acute myeloid leukemia (ALL) (MPL-RARA)	Treatment planning (NCCN)	
MYC and BCL2 and/or BCL6	High grade B-cell lymphomas translocations	Levoleucovorin (levoleucovorin)	
MYH11	Acute myeloid leukemia (AML)	Treatment planning (NCCN)	GENE.00052
NF1	Gastrointestinal stromal tumor (GIST)	Treatment planning (NCCN)	
	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
NPM1	Acute myeloid leukemia (AML)	Treatment planning (NCCN)	GENE.00052
	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
NRAS	Colorectal cancer	Erbitux (cetuximab)	
		Vectibix (panitumumab)	

	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
NTRK	Gastrointestinal stromal tumor (GIST)	Treatment planning (NCCN)	
	Unresectable or metastatic solid tumors	Vitrakvi (larotrectinib)	
PALB2	Pancreatic adenocarcinoma	Lynparza (olaparib)	
	Prostate cancer	Poly (ADP-ribose) polymerase (PARP) inhibitor	GENE.00052
PDGFRA	Gastrointestinal stromal tumor (PDGFRA D842V)	Gleevec (imatinib mesylate)	
	Unresectable or metastatic gastrointestinal stromal tumor (GIST) (PDGFRA D842V)	Ayvakit (avapritinib)	
	Unresectable or metastatic gastrointestinal stromal tumor (GIST) (PDGFRA exon 18)	Ayvakit (avapritinib)	
PDGFRD	Acute lymphocytic leukemia/lymphoblastic lymphoma	Treatment planning (NCCN)	GENE.00052
PHF6	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
Philadelphia chromosome (BCR-ABL)	Acute lymphoblastic leukemia (ALL)	Gleevec (imatinib mesylate)	
	Chronic myeloid leukemia (CML)	Tasigna (nilotinib)	
PIK3CA	Breast cancer	Piqray (alpelisib)	

PLCG2	Chronic lymphocytic leukemia/Small lymphocytic lymphoma	Treatment planning (NCCN)	
PML-RARA	Acute myeloid leukemia	Treatment planning (NCCN)	GENE.00052
PPM1D	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
PPP2R2A	Prostate cancer	Poly (ADP-ribose) polymerase (PARP) inhibitor	GENE.00052
RAD51B	Prostate cancer	Poly (ADP-ribose) polymerase (PARP) inhibitor	GENE.00052
RAD51C	Prostate cancer	Poly (ADP-ribose) polymerase (PARP) inhibitor	GENE.00052
RAD51D	Prostate cancer	Poly (ADP-ribose) polymerase (PARP) inhibitor	GENE.00052
RAD54L	Prostate cancer	Poly (ADP-ribose) polymerase (PARP) inhibitor	GENE.00052
RAS	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	
	Myeloproliferative neoplasm (MPN)	Treatment planning (NCCN)	
ROS1	Non-small cell lung cancer (NSCLC)	Libtayo (cemiplimab-rwlc) Gene mutation testing required to exclude	

		individuals with EGFR, ALK or ROS1 genomic tumor abberations	
		Opdivo (nivolumab)	GENE.00052
		Xalkori (crizotinib)	GENE.00052
		Yervoy (ipilimumab)	GENE.00052
RUNX1	Acute myeloid leukemia (AML)	Treatment planning (NCCN)	GENE.00052
	Myelodysplastic syndromes (MDS)	Treatment planning (NCCN)	GENE.00052
RUNX1T1	Acute myeloid leukemia (AML)	Treatment planning (NCCN)	
SDH	Gastrointestinal stromal tumor (GIST)	Treatment planning Stivarga (regorafenib) (NCCN)	
SETBP1	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
SF3B1	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
SH2B3	Acute lymphocytic leukemia/lymphoblastic lymphoma (ALL/LBL)	Treatment planning (NCCN)	GENE.00052
SRSF2	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
STAG2	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052

STAT3	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
TET2	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
TKD	Acute myeloid leukemia (AML)	Treatment planning (NCCN)	GENE.00052
TP53	Acute lymphocytic leukemia/lymphoblastic lymphoma (ALL/LBL)	Treatment planning (NCCN)	GENE.00052
	Acute myeloid leukemia (AML)	Treatment planning (NCCN) Venclexta (venetoclax)	GENE.00052
	Chronic lymphocytic leukemia (CLL)	Treatment planning (NCCN)	
	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
	Small lymphocytic lymphoma (SLL)	Treatment planning (NCCN)	GENE.00052
U2AF1	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052
VHL	Von Hippel-Lindau (VHL) associated renal cell carcinoma, central nervous system (CVS) hemangioblastoma, or pancreatic neuroendocrine tumors	Welireg (belzutifan) Votrient (pazopanib)	
WT1	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052

ZRSR2	Myelodysplastic syndrome (MDS)	Treatment planning (NCCN)	GENE.00052

C. Circulating Tumor DNA (Liquid Biopsy)

Cancer develops from genetic alterations in DNA that affect the way cells grow and divide. A tissue biopsy is the gold standard for detecting DNA alterations that can be used to identify cancer, determine treatment options, or evaluate responsiveness to treatment. Tissue biopsies have several disadvantages: the biopsy procedure may be painful, such as the insertion of a long needle or a surgical procedure; the retrieved tissue may be too small for analysis; or an individual may not be able to physically tolerate the procedure. In addition, because tissue biopsies only represent cellular samples from parts of a tumor, important diagnostic data could be missed.

Circulating tumor DNA (ctDNA), also known as liquid biopsy, is proposed as a less-invasive method for cancer identification, surveillance, and treatment guidance. The National Cancer Institute (NCI) defines liquid biopsy as "A test done on a sample of blood to look for cancer cells from a tumor that are circulating in the blood or for pieces of DNA from tumor cells that are in the blood." Tests of ctDNA detect small fragments of mutated DNA that are released from tumors into blood, presumably by apoptosis and/or necrosis. These tests are being explored as a less-invasive diagnostic alternative to tissue biopsies to improve the selection of targeted therapeutic agents for late-stage cancers and for post-cancer monitoring.

There are several limitations of liquid biopsies. Regarding cancer management, many cancers do not have specific DNA variants that can be identified and, when present, can be different in individuals with the same cancer. The DNA found in the fluid sample may not fully represent the tumor and mislead treatment decisions. The genetic variants found may not be "driver" variants and may not provide useful information about the cancer. Regarding cancer detection, liquid biopsies can test positive for cancer when no cancer is present (false-positive) or test negative when cancer is present (false-negative). Because cancer cells release more mutated DNA fragments in later cancer stages, the test may not identify early cancer. Likewise, a liquid biopsy can detect cancerous cells that may never actually cause harm, leading to overtreatment (NCI, 2018). While liquid biopsies are promising, a great deal of research is still needed to determine when these tests improve outcomes for individuals with cancer. Nonetheless, in circumstances when tumor tissue is inadequate in quality or quantity or is unavailable for testing, and the presence or absence of a variant is likely to guide drug treatment, it is reasonable to test for ctDNA given that no alternative exists.

Liquid biopsies are regulated by the Clinical Laboratory Improvement Amendments (CLIA) program, which oversees and certifies the laboratories conducting FDA-approved and non-FDA approved tests. The FDA approval or clearance does not necessarily imply that the test improves clinical outcomes or should be used for clinical management. Testing for ctDNA performed in CLIA-certified laboratories also do not require evidence of clinical utility; only analytical and clinical validity of the test must be demonstrated prior to clinical use.

This document does not address ctDNA panel testing (defined by five or more genes or gene variants tested on the same day on the same member by the same rendering provider). For information on ctDNA panel testing, see GENE.00049 Circulating Tumor DNA Panel Testing for Cancer (Liquid Biopsy).

EGFR Mutation Testing to Select Targeted Therapy in Individuals with Non-small Cell Lung Cancer

Liquid biopsy tests for ctDNA are targeted for specific gene variants. For example, in the instance of NSCLC, a targeted liquid biopsy may be used to identify the presence of the epidermal growth factor receptor (EGFR) variant and determine if individuals may benefit from kinase inhibitor medication.

The College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology released a joint guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors (TKI) (Lindeman, 2018). This document has a strong recommendation stating, "In lung adenocarcinoma patients who harbor sensitizing EGFR mutations and have progressed after treatment with an EGFR-targeted TKI, physicians must use EGFR T790M mutational testing when selecting patients for third-generation EGFR-targeted therapy." Regarding circulating tumor cell testing (also referred to as circulating plasma cfDNA, plasma cfDNA and cfDNA), they state the following:

- There is currently insufficient evidence to support the use of circulating plasma cfDNA molecular methods for establishing a primary diagnosis of lung adenocarcinoma (no recommendation; insufficient evidence, confidence, or agreement to provide a recommendation).
- In some clinical settings in which tissue is limited and/or insufficient for molecular testing, physicians may use a cfDNA assay to identify EGFR mutations (recommendation; some limitations in quality of evidence).
- Physicians may use plasma cfDNA methods to identify EGFR T790M mutations in lung adenocarcinoma patients with progression or secondary clinical resistance to EGFR-targeted TKIs; testing of the tumor sample is recommended if the plasma result is negative (expert consensus opinion; serious limitations in quality of evidence).

The NCCN has the following category 2A recommendation regarding ctDNA testing to identify the EGFR variant in individuals with NSCLC: "If there is insufficient tissue to allow testing for all of EGFR, ALK, ROS1 and BRAF, repeat biopsy and/or plasma testing should be done." (NCCN NSCLC V2.2021).

The FDA has approved at least two tests for detecting the EGFR variant in individuals with NSCLC. For example:

- cobas EGFR Mutation Test v2 (Roche Molecular Systems Inc., Pleasanton, CA, USA)
  - Solid tumor tissue testing:
    On June 1, 2016, the FDA in PMA (P150047) expanded the approval of the cobas® Mutation Test v2 (Roche Molecular Diagnostics, Pleasanton, CA), a tissue biopsy test, to be used as a real-time polymerase chain reaction (PCR) blood plasma test that detects defined mutations of the epidermal growth factor receptor (EGFR) gene in individuals with non-small cell lung cancer (NSCLC). The test

is indicated as a companion diagnostic to identify individuals who have exon 19 deletions or L858R mutations and would benefit from treatment with Tarceva® (erlotinib), a kinase inhibitor. According to the FDA, individuals who test negative with the cobas plasma test should undergo a tissue biopsy for confirmation (FDA 2016[b]).

- ctDNA testing:
  On September 28, 2016, the FDA approved the cobas plasma test for detecting the EGFR T790M mutation for individuals who would benefit from treatment with Tagrisso (osimertinib), a kinase inhibitor recommended after progression of NSCLC during first-line treatment (P150044). The FDA states that the efficacy of the plasma test for targeting Tagrisso is limited, and plasma specimens should only be used when a tissue biopsy is not possible (FDA 2016[c]).

In addition to the FDA-approved companion diagnostic tests, some commercially available tests (performed at a CLIA certified laboratories) are available which detect EGFR variants in individuals with non-small cell lung cancer are also available. As an example, OncoBEAM™ (Sysmex Inostics, Mundelein, IL) has developed the Lung1 EGFR ctDNA test which may be used to identify individuals with non-small cell lung cancer who may benefit from treatment with an EGFR-targeted tyrosine kinase inhibitor.

PIK3CA Mutation Testing to Select Targeted Therapy in Individuals with Breast Cancer

Mutations in the phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA) gene have been implicated in the pathogenesis of several cancers, including but not limited to colon, gastric, breast, endometrial, and lung cancer. Researchers are exploring the role of PIK3CA mutations in the initiation, progression and management of various cancers.

Mutations in the PIK3CA gene can also lead to the development of a group of rare, non-malignant disorders collectively known as PIK3CA-related overgrowth spectrum (PROS). PROS disorders include fibroadipose hyperplasia, CLOVES syndrome, megalencephaly-capillary malformation (MCAP) syndrome, hemihyperplasia-multiple lipomatosis (HHML) syndrome, hemimegalencephaly and facial infiltrating lipomatosis. This document does not address PROS.

Other names for PIK3CA include but are not limited to:

- catalytic subunit alpha polypeptide gene
- PI3K
- PI3KCA
- PI3K-alpha
- PI3-kinase p110 subunit alpha.

The FDA approved the companion diagnostic test *therascreen* PIK3CA RGQ PCR Kit (QIAGEN Germantown, MD) to detect the PIK3CA variants in both, a breast tumor tissue specimen and a plasma specimen (ctDNA). According to the FDA, individuals who are negative by the *therascreen* test using the ctDNA should undergo tumor biopsy for PIK3CA variant testing. Use of the ctDNA test has not been evaluated in a prospective

clinical study; approval was based on a retrospective secondary analysis of participants enrolled in the SOLAR-1 clinical trial. The SOLAR-1 trial evaluated alpelisib on the basis of tumor-tissue PIK3CA mutation status.

The May 24, 2019 FDA Summary and Effectiveness Data (SSED) includes a discussion of the concordance of the PIK3CA variant results of the *therascreen* PIK3CA RGQ PCR Kit (P190004) which uses plasma samples and the *therascreen* PIK3CA RGQ PCR Kit, which uses tissue samples (P190001). Of the 328 PIK3CA tissue positive subjects, only 179 were plasma PIK3CA positive. Of the 215 PIK3CA tissue negative subjects, 209 were plasma PIK3CA negative. The negative percent agreement (NPA) was 97.2% while the positive percent agreement (PPA) was only 54.6%. It was noted that five PIK3CA variants (H1047Y, Q546R, Q546E, E545D and E545A) were not identified by the *therascreen* PIK3CA RGQ PCR Kit using plasma clinical samples. FDA approval of the PIK3CA RGQ PCR Kit is contingent upon additional post market accuracy studies of those variants. Because of the high false negative rate (the plasma test failed to discover approximately 46% of the variants identified in the tumor tissue test), reflex testing of plasma mutation negative samples using tissue specimens is required.

The NCCN Clinical Practice Guidelines on Breast Cancer (V2.2022) recommends that in individuals with HR-positive/HER2-negative breast cancer, PIK3CA mutation testing using tumor tissue or ctDNA in peripheral blood (liquid biopsy) be conducted in order to identify candidates for alpelisib plus fulvestrant, (category 1 rating). If liquid biopsy results are negative, tumor tissue testing is recommended.

With regard to treatment regimens for men with breast cancer, the NCCN indicates the following:

> Management of advanced breast cancer in males is similar to that in females; however, it is preferred that when an aromatase inhibitor is used, a GnRH analog should be given concurrently. Available data suggest single-agent fulvestrant has similar efficacy in males as in females. Newer agents such as CDK4/6 inhibitors in combination with an aromatase inhibitor or fulvestrant, mTOR inhibitors, and PIK3CA inhibitors have not been systematically evaluated in clinical trials in males with breast cancer. However available real-world data suggest comparable efficacy and safety profiles and it is reasonable to recommend these agents to males based on extrapolation of data from studies comprised largely of female participants with advanced breast cancer.

Testing to Detect the Recurrence of Colorectal Cancer

Colvera™ (Clinical Genomics Pathology, Bridgewater, NJ) has been explored as a liquid biopsy test to detect the recurrence of colorectal cancer (CRC). In 2017, Murray and colleagues investigated the analytical and clinical validity of the Colvera plasma test for the detection of methylated BCAT1 and IKZF1 in individuals with CRC. The researchers randomized 264 plasma samples and 120 buffer samples, divided the samples into 8 batches of 48, and processed the samples over 8 days using 2 equipment lines. Clinical validity was analyzed by using Colvera on 222 archived plasma samples (n=26 with known CRC) from individuals who were scheduled for colonoscopy as part of a previous trial (Pedersen, 2015). The researchers found that the limit of

detection (LOD) was 12.6 pg/ml (95% confidence interval [CI], 8.6 to 23.9), the equivalent of 2 diploid genomes/ml of plasma. Colvera tested positive for 19/26 known cancer cases for an agreement of 73% (95% CI, 52% to 88%). For the 196 nonneoplastic subjects, Colvera had an agreement of 89% (95% CI, 84% to 93%). Total agreement was 87% (194/222; 95% CI, 82% to 91%). Limitations of the study included a small sample size.

In 2020, Musher and colleagues published a cross-sectional study evaluating the diagnostic accuracy of the Colvera test compared with carcinoembryonic antigen (CEA) for identifying recurrence of CRC. The study enrolled 537 adults who were undergoing surveillance after treatment for stage II or III CRC. Blood samples were collected at a single time point, within 6 months of surveillance radiological imaging, and evaluated using the Colvera test and CEA. A total of 322 (60%) individuals were included in the final analysis; 20 (3.7%) were excluded because they did not meet eligibility criteria and 195 (36.3%) were excluded for insufficient information. Among the evaluable participants, CRC recurrence occurred in 27 (8.4%) of individuals. The sensitivity of the Colvera test for detecting CRC recurrence (63%) was significantly higher than CEA testing (48.1%), p=0.046. However, the specificity of CEA testing (96.3%) was significantly higher than Colvera testing (91.5%), p=0.012. While the Colvera test appears to be a promising diagnostic tool to predict the recurrence of CRC, the study has several limitations which prevent drawing conclusions regarding its diagnostic accuracy. For example, as discussed above, a substantial proportion (40%) of study participants were excluded from the analysis. Additionally, the authors acknowledge that although this study demonstrated that the specificity of CEA in the 295 subjects without cancer recurrence was higher than that of Colvera, the significance of a false positive result in this study is uncertain due to the relatively short follow-up period. Because the Colvera and CEA results were correlated with only one imaging test, it is possible that some individuals thought to be without recurrence might later prove to have recurrent disease after further imaging. Additional well-designed prospective, randomized controlled trials with longer follow-up are needed to determine whether, Colvera, when compared to CEA facilitates earlier diagnosis of CRC recurrence and, in turn, improves cancer-related outcomes.

TABLE C Circulating Tumor DNA Testing to Guide Targeted Cancer Therapy in Individuals with Solid Tumor(s) (when Criteria B in the Clinical Indications section are met). (Return to Clinical Indications)

Drug Being Considered for Targeted Cancer Therapy	Gene Mutation Status Tested	Condition	Related Anthem Document
Gilotrif (Afatinib)	EGFR	Non-small cell lung cancer	
Iressa (Gefitinib)	EGFR exon 19 deletions	Non-small cell lung cancer	

	or EGFR exon 21 (L858R) substitution		
PIQRAY (alpelisib)	PIK3CA	Breast cancer	
Tarceva (Erlotinib)	EGFR exon 19 deletions or EGFR exon 21 (L858R) substitution	Non-small cell lung cancer	
Tagrisso (Osimertinib)	EGFR) exon 19 deletions or EGFR exon 21 (L858R) mutations or EGFR T790M mutation	Non-small cell lung cancer	
Vizimpro (Dacomitinib)	EGFR exon 19 deletions or EGFR exon 21 L858R substitution	Non-small cell lung cancer	

Note: This document does not address ctDNA panel testing (defined by five or more genes or gene variants tested on the same day on the same member by the same rendering provider. For information on ctDNA panel testing for indications other than selecting targeted therapy agents in individuals with cancer, see:

- GENE.00049 Circulating Tumor DNA Panel Testing for Cancer (Liquid Biopsy).

Definitions

Associated Therapeutic Product (ATP): The therapeutic, preventive, and prophylactic drugs and biological products approved in association with an IVD (FDA, 2016).

Biallelic Mutation: A mutation in both copies of a particular gene that affects the function of both copies.

Bone marrow: The inner, soft part of certain bones, where new blood cells are made.

Circulating tumor DNA (ctDNA): Also known as a liquid biopsy, this test detects small fragments of mutated DNA that are released from tumors into blood, presumably by apoptosis and/or necrosis.

Cytogenetics: The branch of genetics that examines the structure of DNA within the cell nucleus, (the number and morphology of chromosomes).

Epidermal growth factor receptor (EGFR): A cell receptor that is associated with regulation of cell growth.

First-degree relative: Any relative who is a parent, sibling, or offspring of an individual.
The National Human Genome Research Institute of the National Institutes of Health (NIH) defines the following terms in the context of potential transmission of inherited conditions associated with genetic mutations as follows:

- First-degree relative: Any relative who shares approximately 50% of an individual's genetic material, such as an individual's parent (father or mother), full sibling (brother or sister), or offspring.
- Second-degree relative: Any relative who shares approximately 25% of an individual's genetic material, such as an individual's grandparent, grandchild, uncle, aunt, niece, nephew, or half-sibling.
- Third-degree relative: Any relative who shares approximately 12.5% of an individual's genetic material, such as an individual's first cousin, great grandparent, great grandchild, great uncle, great aunt, half-uncle, half-aunt, half-niece, or half-nephew.

Genome: The total genetic composition of an organism.

In Vitro Companion Diagnostic Devices (IVD): An in vitro device or an imaging tool that provides information essential for the safe and effective use of a corresponding therapeutic product. The use of an IVD companion diagnostic device with a particular therapeutic product is stipulated in the instructions for use in the FDA labeling of both the diagnostic device and the corresponding therapeutic product, as well as in the FDA labeling of any generic equivalents and biosimilar equivalents of the therapeutic product (FDA, 2016).

Lymphoid cells: Cells derived from the lymphatic system, including lymphocytes, lymphoblasts, and plasma cells.

Lymphoid tissue: Relating to the tissue responsible for producing antibodies and lymphocytes. Examples of lymphoid tissue includes but is not limited to the lymph nodes, thymus, tonsils, and spleen.

Mast cells: Immune cells of the myeloid lineage that are present in connective tissues. Mast cells are also known as mastocytes.

Mast cell sarcoma: A particularly aggressive form of sarcoma.

Myeloid cells: A subgroup of lymphocytes (white blood cells) derived from the bone marrow, and which play a major role in innate immunity. Myeloid cells include granulocytes, monocytes, macrophages, and dendritic cells.

Next-generation sequencing (NGS): Any of the technologies that allow rapid sequencing of large numbers of segments of DNA, up to and including entire genomes.

Point mutation: A change within a gene that results in one base pair in the DNA sequence being altered

Sarcoma: A tumor that is mad of connective tissue cell.

Targeted cancer therapy: Targeted cancer therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules ("molecular targets") that are involved in the growth, progression, and spread of cancer. They recognize a specific feature of the cancer cell, attach to it, and destroy it. Targeted cancer therapies are sometimes called "molecularly targeted drugs," "molecularly targeted therapies," "precision medicines," or similar names (NCI, 2014).

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The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
Reviewed	11/10/2022	Medical Policy & Technology Assessment Committee (MPTAC) review. Folded content of CG-GENE-07 BCR-ABL Mutation Analysis and CG-GENE-17 RET Proto-oncogene Testing for Endocrine Gland Cancer Susceptibility into this document. Updated the Discussion/General Information (including Table A and Table B), References and Index sections. Updated Coding section to add 81170, S3840 and genes to Tier 2 codes previously addressed in CG-GENE-07, CG-GENE-13 and CG-GENE-17; added additional genes to NOC code.
	06/29/2022	Updated Coding section with 07/01/2022 CPT changes; revised descriptor for CPT 0229U.
Revised	02/17/2022	Medical Policy & Technology Assessment Committee (MPTAC) review. Expanded scope of document to address solid and non-solid tumors (removed

		"solid tumors" from title). Updated Table A and Table B. Folded content of CG-GENE-01 Janus Kinase 2, CALR and MPL Gene Mutation Assays and CG-GENE-08 Genetic Testing for PTEN Hamartoma Tumor Syndrome into this document. Updated Discussion and General Information, Definitions, References, and Index sections. Updated Coding section; added 0017U, 0027U, 81219, 81270, 81279, 81338, 81339 previously addressed in CG-GENE-01; added 0235U, 81321, 81322, 81323 previously addressed in CG-GENE-08; added 81175, 81176, 81206, 81207, 81208, 81218, 81233, 81236, 81237, 81273, 81310, 81315, 81316, 81320, 81334, 81347, 81348, 81357, 81360, 0016U, 0040U, 0049U and genes to Tier 2 codes; expanded diagnosis codes to include non-solid tumors where applicable.
	04/14/2021	Corrected Coding section to add HCPCS code S3841 missing from document.
Revised	02/11/2021	MPTAC review. Moved content on circulating tumor DNA to guide targeted cancer therapy in individuals with solid tumor(s) and to detect the recurrence of colorectal cancer (fewer than 5 genes or gene variants tested on the same day on the same member by the same rendering provider) from GENE.00049 to this document. Content formerly addressed in CG-GENE-02 Analysis of RAS Status, CG-GENE-03 BRAF Mutation Analysis, CG-GENE-12 PIK3CA Mutation Testing for Malignant Condition and CG-GENE-20 Epidermal Growth Factor Receptor [EGFR] Testing), folded into this document. Table B (formerly Appendix A) updated. Removed cross-references to CG-GENE-03, CG-GENE-12, CG-GENE-20. Document reformatted. Updated Description/Scope, Discussion/General Information, Definitions, References and Websites for Additional Information, and Index sections. Reformatted and updated Coding section.
	11/12/2020	In Appendix A, updated the information on Lynparza (olaparib) to include BRCA mutation testing in individuals with pancreatic or prostate cancer and homologous recombination repair (HRR) genes alteration testing in individuals with prostate cancer. In the Description section, added cross-reference to GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling. Updated Coding section with 01/01/2021 CPT changes; added 81191, 81192, 81193, 81194 replacing Tier 2 code.
Reviewed	05/14/2020	MPTAC review. Updated the Clinical Utility table in the Discussion and General Information section. Also updated the References, Websites for Additional Information and Appendix A. Updated Coding section; added 81120, 81121, 81245, 81246, 81272, 81314, 0023U, 0046U, 0154U, S3842, 81401 and genes added to Tier 2 and unlisted CPT codes.
New	11/07/2019	MPTAC review. Initial document development. Moved content related to whole genome, whole exome and gene panel testing from GENE.00001 Genetic Testing for Cancer Susceptibility to GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling. Moved

	remaining content of GENE.00001 Genetic Testing for Cancer Susceptibility to new clinical utilization management guideline with new title (CG-GENE-14 Gene Mutation Testing for Solid Tumor Cancer Susceptibility and Management) which addresses gene mutation testing to determine cancer susceptibility and guide targeted cancer therapy in individuals with solid tumors. Updated the Coding section to add CPT codes 81242, 81307, 81308, 81403, 81408.