Clinical UM Guideline

Subject:	Gene Mutation Testing for Solid Tumor Cancer Susceptibility and Management		
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Description

This document addresses gene mutation testing:
1) To determine whether an individual is at risk for the development of solid malignant tumors (including but not limited to breast, colon, lung, pancreatic and ovarian cancers); and
2) To guide targeted cancer therapy in individuals with solid malignant tumors.

This document also addresses the use of circulating tumor testing to assess solid malignant tumor 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.
- 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-08 Genetic Testing for PTEN Hamartoma Tumor Syndrome
  - 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-17 RET Proto-oncogene Testing for Endocrine Gland Cancer Susceptibility
  - GENE.00025 Proteogenomic Testing for the Evaluation of Malignancies

Clinical Indications

Medically Necessary:

A. *Gene Mutation Testing for Solid Tumor Cancer Susceptibility (See Table A below)*
Gene mutation testing for solid tumor 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 in Individuals with Solid Tumors (See Table B below)*
Gene mutation testing of a solid tumor 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 Solid Tumor Cancer Susceptibility*
Gene mutation testing for solid tumor 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 in Individuals with Solid Tumors*
Gene mutation testing of a solid tumor 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)
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
81210	*BRAF (B-Raf proto-oncogene, serine/threonine kinase)* (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
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]

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*)
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)
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)
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)
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)
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]: • *EML4/ALK (inv(2))* (eg, non-small cell lung cancer), translocation or inversion analysis
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]: • *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]: • *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
- *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
- *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 [considered medically necessary for breast cancer]

81479	Unlisted molecular pathology procedure [when specified as testing for the following genes: *BMPR1A, BRIP1, CHEK2, MET, NBN, RAD51C, RAD51D, RB1, ROS1, SDHAF2*]
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
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
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

HCPCS

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
E88.89	Metabolic disorder, unspecified [Erdheim-Chester Disease]
Q85.8	Other phakomatoses, not elsewhere classified [Peutz-Jeghers, von Hippel-Lindau syndromes]

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]: • BARD1 • MRE11A • RAD50 • RECQL4 • RINT1 • SLX4 • SMARCA4 • XRCC2

0229U	*BCAT1 (Branched chain amino acid transaminase 1)* or *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 Solid Tumor(s) (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 (NSCLC).

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 solid tumor cancer susceptibility or in making decisions in the clinical management of an individual with a solid cancer. In many cases, this is because knowledge of the genetic status does not change management of the condition. 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 malignant solid tumor or in guiding clinical management (for example, increased cancer surveillance).

TABLE A Gene Mutation Testing for Cancer Susceptibility in Individuals with Solid Tumors(s)
(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
ATM	Breast cancer	RAD.00036
BARD1	Breast cancer	No
	Ovarian cancer	No
BMPR1A	Familial Juvenile Polyposis	Yes
BRCA1	Breast cancer	CG-GENE-16
BRCA2	Breast cancer	CG-GENE-16
BRIP1	Ovarian cancer	Yes
CDH1	Breast cancer	RAD.00036
	Hereditary diffuse gastric cancer	RAD.00036
	Ovarian cancer	No
CHEK2	Breast cancer	RAD.00036
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
FANCC	Breast cancer	No
	Ovarian cancer	No
MEN1	Multiple endocrine neoplasia type 1 (MEN1)	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
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
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
MUTYH (MYH)	Colorectal cancer	CG-GENE-15
NBN	Breast cancer	Yes

NF1	Breast Cancer	Yes
PALB2	Breast cancer	RAD.00036
	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
PTEN	Breast cancer	CG-GENE-08
	Ovarian cancer	No
	PTEN hamartoma tumor syndrome, Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS) and Adult Lhermitte-Duclos disease (ALDD)	CG-GENE-08
RAD50	Breast cancer	No
	Ovarian cancer	No
RAD51C	Breast cancer	No
	Ovarian cancer	Yes
RAD51D	Breast cancer	No
	Ovarian cancer	Yes
RB1	Retinoblastoma	Yes
RECQL4	Breast cancer	No
	Ovarian cancer	No
RET	Multiple endocrine neoplasia type 2 (MEN2)	CG-GENE-17
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
	Colorectal cancer	Yes
	Peutz-Jegher syndrome	Yes
TP53	Breast cancer	CG-GENE-18
	Li-Fraumeni syndrome	CG-GENE-18
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 Solid Tumor(s) (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.

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. 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 in Individuals with Solid Tumors**. 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 in Individuals with Solid Tumors(s)
(Return to Clinical Indications) – (Return to Discussion/General Information)

Drug Being Considered for Targeted Cancer Therapy	Gene Mutation Status Tested	Condition	Related Anthem Document
Alecensa (alectinib)	ALK	Non-small cell lung cancer	
Alunbrig (brigatinib)	ALK	Non-small cell lung cancer	
Ayvakit (avapritinib)	PDGFRA exon 18, PDGFRA D842V	Unresectable or metastatic gastrointestinal stromal tumor (GIST)	
Balversa (erdafitinib)	FGFR2	Urothelial cancer	
	FGFR3	Urothelial cancer	
Braftovi (encorafenib)	BRAF V600	Melanoma	
	BRAF V600E	Colorectal cancer	
	BRAF V600E	Melanoma	
	BRAF V600K	Melanoma	
Cotellic (cobimetinib)	BRAF V600	Melanoma	
	BRAF V600E	Melanoma	
	BRAF V600K	Melanoma	
Erbitux (cetuximab)	KRAS	Colorectal cancer	
	NRAS	Colorectal cancer	
FDA-approved BRAF inhibitor	BRAF	Central nervous system tumor(s)	
	BRAF	Hairy-cell leukemia	
Gilotrif (afatinib)	EGFR	Non-small cell lung cancer	
Gleevec (imatinib mesylate)	PDGFRA D842V	Gastrointestinal stromal tumor	
	Philadelphia chromosome	Acute lymphoblastic leukemia (ALL)	CG-GENE-07 BCR-ABL Mutation Analysis
	KIT	Gastrointestinal stromal tumor	

	Philadelphia chromosome	Chronic myeloid leukemia (CML)	CG-GENE-07 BCR-ABL Mutation Analysis
Idhifa (enasidenib)	IDH2	Acute myeloid leukemia (AML)	
Iressa (gefitinib)	EGFR exon 19 deletions or EGFR exon 21 (L858R) substitution	Non-small cell lung cancer	
Keytruda (pembrolizumab) Gene mutation testing required to exclude individuals with EGFR or ALK genomic tumor abberations	ALK	Non-small cell lung cancer	
	EGFR	Non-small cell lung cancer	
Lorbrena (lorlatinib)	ALK	Non-small cell lung cancer	
Lynparza (olaparib)	BRCA	Breast cancer	CG-GENE-16 BRCA Testing for Breast and/or Ovarian Cancer Syndrome
	BRCA	Ovarian cancer	CG-GENE-16 BRCA Testing for Breast and/or Ovarian Cancer Syndrome
	BRCA	Pancreatic cancer	CG-GENE-16 BRCA Testing for Breast and/or Ovarian Cancer Syndrome
	Homologous recombination repair (HRR) genes	Prostate cancer	GENE.00052 Whole Genome Sequencing, Whole Exome Sequencing, Gene Panels, and Molecular Profiling
Mekinist (trametinib)	BRAF V600	Melanoma	
	BRAF V600E	Anaplastic thyroid cancer	
	BRAF V600E	Melanoma	
	BRAF V600K	Melanoma	
	BRAF V600E	Non-small cell lung cancer	
MEKTOVI (binimetinib)	BRAF V600	Melanoma	
	BRAF V600KE	Melanoma	
	BRAF V600K	Melanoma	
Opdivo (nivolumab)	ALK	Non-small cell lung cancer	
	BRAF	Non-small cell lung cancer	

	EGFR	Non-small cell lung cancer	
	ROS1	Non-small cell lung cancer	
Piqray (alpelisib)	PIK3CA	Breast cancer	
Rubraca (rucaparib)	BRCA	Ovarian cancer (epithelial ovarian, fallopian tube, or primary peritoneal cancer)	CG-GENE-16 BRCA Testing for Breast and/or Ovarian Cancer Syndrome
Rydapt (midostaurin)	FLT3	Acute myeloid leukemia	
Tabrecta (capmatinib)	MET	Non-small cell lung cancer	
Tafinlar (dabrafenib)	BRAF V600	Melanoma	
	BRAF V600E	Anaplastic thyroid cancer	
	BRAF V600E	Melanoma	
	BRAF V600E	Non-small cell lung cancer	
	BRAF V600K	Melanoma	
Tagrisso (osimertinib)	EGFR exon 19 deletions or EGFR exon 21 (L858R) mutation or EGFR T790M mutation	Non-small cell lung cancer	
Talzenna (talazoparib)	BRCA	Breast cancer	CG-GENE-16 BRCA Testing for Breast and/or Ovarian Cancer Syndrome
Tarceva (erlotinib)	EGFR exon 19 deletions or EGFR exon 21 (L858R) substitution	Non-small cell lung cancer	
Tasigna (nilotinib)	Philadelphia chromosome	Chronic myeloid leukemia	CG-GENE-07 BCR-ABL Mutation Analysis
Tecentriq (atezolizumab)	ALK	Non-small cell lung cancer	
	EGFR	Non-small cell lung cancer	
Tepmetko (tepotinib)	MET	Non-small cell lung cancer	
Tibsovo (ivosidenib)	IDH1	Acute myeloid leukemia	
Vectibix (panitumumab)	KRAS	Colorectal cancer	
	NRAS	Colorectal cancer	
Vitrakvi (larotrectinib)	NTRK	Unresectable or metastatic solid tumors	
Vizimpro (dacomitinib)	EGFR exon 19 deletions or EGFR exon 21 L858R substitution	Non-small cell lung cancer	

Xalkori (crizotinib)	ALK MET ROS1	Non-small cell lung cancer	
Xospata (gilterinib)	FLT3	Acute myeloid leukemia	
Yervoy (ipilimumab)	ALK	Non-small cell lung cancer	
	BRAF	Non-small cell lung cancer	
	EGFR	Non-small cell lung cancer	
	ROS1	Non-small cell lung cancer	
Zejula (niraparib)	BRCA	Breast cancer	CG-GENE-16 BRCA Testing for Breast and/or Ovarian Cancer Syndrome
Zelboraf (vemurafenib)	BRAF V600	Erdheim-Chester Disease	
	BRAF V600	Erdheim-Chester Disease	
	BRAF V600E	Melanoma	
	BRAF V600E	Melanoma	
Zykadia (ceritinib)	ALK	Non-small cell lung cancer	

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" variantss 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 variantss 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 (V6.2020) 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 men is similar to that in women; 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 men as in women. 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 men with breast cancer. However available real-world data suggest comparable efficacy and safety profiles and it is reasonable to recommend these agents to men 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 or EGFR exon 21 (L858R) substitution	Non-small cell lung cancer	
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 solid tumors, 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).

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.

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

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).

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.

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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Tarceva
Targeted therapy
Therascreen EGFR
THxID BRAF assay
Tyrosine Kinase
Vizimpro
Zelboraf® (vemurafenib)

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
	04/14/2021	Corrected Coding section to add HCPCS code S3841 missing from document.
Revised	02/11/2021	Medical Policy & Technology Assessment Committee (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.