Healthy Blue

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).

References

Peer Reviewed Publications:

1. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med. 2015; 373(2):123-135.

2. Gerber DE, Minna JD. ALK inhibition for non-small cell lung cancer: from discovery to therapy in record time. Cancer Cell. 2010; 18(6):548-551.
3. Kalia M. Personalized oncology: recent advances and future challenges. Metabolism. 2013; 62(Suppl 1): S11-S14.
4. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med. 2010; 363(18):1693-1703.
5. Li Y, Ye X, Liu J, et al. Evaluation of EML4-ALK fusion proteins in non-small cell lung cancer using small molecule inhibitors. Neoplasia. 2011; 13(1):1-11.
6. Philip R, Carrington L, Chan M. US FDA perspective on challenges in co-developing in vitro companion diagnostics and targeted cancer therapeutics. Bioanalysis. 2011; 3(4):383-389.
7. Shaw AT, Solomon B. Targeting anaplastic lymphoma kinase in lung cancer. Clin Cancer Res. 2011; 17(8):2081-2086.
8. Stricker T, Catenacci DV, Seiwert TY. Molecular profiling of cancer--the future of personalized cancer medicine: a primer on cancer biology and the tools necessary to bring molecular testing to the clinic. Semin Oncol. 2011; 38(2):173-185.
9. Vincent MD, Kuruvilla MS, Leighl NB, Kamel-Reid S. Biomarkers that currently affect clinical practice: EGFR, ALK, MET, KRAS. Curr Oncol. 2012: 19(Suppl 1): S33-S44.

BRAF Mutation Analysis

1. Aguilera D, Janss A, Mazewski C, et al. Successful retreatment of a child with a refractory brainstem ganglioglioma with vemurafenib. Pediatr Blood Cancer. 2016; 63(3):541-543.
2. Andrulis M, Penzel R, Weichert W, et al. Application of a BRAF V600E mutation-specific antibody for the diagnosis of hairy cell leukemia. Am J Surg Pathol. 2012; 36(12):1796-1800.
3. Arcaini L, Zibellini S, Boveri E, et al. The BRAF V600E mutation in hairy cell leukemia and other mature B-cell neoplasms. Blood. 2012; 119(1):1888-1891.
4. Arkenau HT, Kefford R, Long GV. Targeting BRAF for patients with melanoma. Br J Cancer. 2011; 104(3):392-398.
5. Balch CM, Soong SJ, Gershenwald JE, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. J Clin Oncol. 2001; 19(16):3622-3634.
6. Bautista F, Paci A, Minard-Colin V, et al. Vemurafenib in pediatric patients with BRAFV600E mutated high-grade gliomas. Pediatr Blood Cancer. 2014; 61(6):1101-1103.
7. Bokemeyer C, Bondarenko I, Hartmann JT, et al. Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. Ann Oncol. 2011; 22(7):1535-1546.
8. Bokemeyer C, Cutsem EV, Rougier P, et al. Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: pooled analysis of the CRYSTAL and OPUS randomised clinical trials. Eur J Cancer. 2012; 48(10):1466-1475.
9. Bokemeyer C, Kohne C, Rougier P, et al. Cetuximab with chemotherapy (CT) as first-line treatment for metastatic colorectal cancer (mCRC): analysis of the CRYSTAL and OPUS studies according to KRAS and BRAF mutation status. J Clin Oncol 2010; 28:15s. (Abstr 3506).
10. Boyd EM, Bench AJ, van 't Veer MB, et al. High resolution melting analysis for detection of BRAF exon 15 mutations in hairy cell leukaemia and other lymphoid malignancies. Br J Haematol. 2011; 155(5):609-612.
11. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011; 364(26):2507-2516.

12. Davies H, Bignell GR, Cox C, Stephens P, et al. Mutations of the BRAF gene in human cancer. Nature. 2002; 417(6892):949-954.
13. De Roock W, Claes B, Bernasconi D, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. Lancet Oncol 2010; 11(8):753-762.
14. Diamond EL, Subbiah V, Lockhart AC, et al. Vemurafenib for BRAF V600-mutant Erdheim-Chester disease and Langerhans cell histiocytosis: analysis of data from the histology-independent, Phase 2, open-label VE-BASKET study. JAMA Oncol. 2019; 5(1):122.
15. Dietrich S, Glimm H, Andrulis M, et al. BRAF inhibition in refractory hairy-cell leukemia. N Engl J Med. 2012; 366(21):2038-2040.
16. Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol. 2008; 26(35):5705-5712.
17. Flaherty KT, Puzanov I, Kim KB, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. N Engl J Med. 2010; 363(9):809-819.
18. Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med. 2012; 367(2):107-114.
19. Follows GA, Sims H, Bloxham DM, et al. Rapid response of biallelic BRAF V600E mutated hairy cell leukaemia to low dose vemurafenib. Br J Haematol. 2013; 161(1):150-153.
20. Gautschi, O, Pauli, C, Strobel, K, et al. A patient with BRAF V600E lung adenocarcinoma responding to vemurafenib. J Thorac Oncol. 2012; 7(10): e23-24.
21. Haroche J, Cohen-Aubart F, Emile JF, et al. Dramatic efficacy of vemurafenib in both multisystemic and refractory Erdheim-Chester disease and Langerhans cell histiocytosis harboring the BRAF V600E mutation. Blood. 2013; 121(9):1495-1500.
22. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012; 380(9839):358-365.
23. Héritier S, Emile JF, Barkaoui MA, et al. BRAF mutation correlates with high-risk Langerhans cell histiocytosis and increased resistance to first-line therapy. J Clin Oncol. 2016; 34(25):3023-3030.
24. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. N Engl J Med. 2015; 373(8):726-736.
25. Kaley T, Touat M, Subbiah V, et al. BRAF inhibition in BRAFV600-mutant gliomas: results from the VE-BASKET study. J Clin Oncol. 2018; 36(35):3477-3484.
26. Khan MA, Andrews S, Ismail-Khan R, et al. Overall and progression-free survival in metastatic melanoma: analysis of a single-institution database. Cancer Control. 2006; 13(3):211-217.
27. Laurent-Puig P, Cayre A, Manceau G, et al. Analysis of PTEN, BRAF, and EGFR status in determining benefit from cetuximab therapy in wild-type KRAS metastatic colon cancer. J Clin Oncol. 2009; 27(35):5924-5930.
28. Li J, Sasane M, Zhang J, et al. Is time to progression associated with post-progression survival in previously treated metastatic non-small cell lung cancer with BRAF V600E mutation? A secondary analysis of phase II clinical trial data. BMJ Open. 2018; 8(8):e021642.
29. Lin JS, Webber EM, Senger CA, et al. Systematic review of pharmacogenetic testing for predicting clinical benefit to anti-EGFR therapy in metastatic colorectal cancer. Am J Cancer Res 2011; 1(5):650-662.
30. Long GV, Hauschild A, Santinami M, et al. Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. N Engl J Med. 2017; 377(19):1813-1823.
31. López-Rubio M, Garcia-Marco JA. Current and emerging treatment options for hairy cell leukemia. Onco Targets Ther. 2015; 8:2147-2156.

32. Mao C, Liao RY, Qiu LX, et al. BRAF V600E mutation and resistance to anti-EGFR monoclonal antibodies in patients with metastatic colorectal cancer: a meta-analysis. Mol Biol Rep 2011; 38(4):2219-2223.
33. Marks AM, Bindra RS, DiLuna ML, et al. Response to the BRAF/MEK inhibitors dabrafenib/trametinib in an adolescent with a BRAF V600E mutated anaplastic ganglioglioma intolerant to vemurafenib. Pediatr Blood Cancer. 2018; 65(5):e26969.
34. McClain KL, Picarsic J, Chakraborty R, et al. CNS Langerhans cell histiocytosis: Common hematopoietic origin for LCH-associated neurodegeneration and mass lesions. Cancer. 2018; 124(12):2607-2620.
35. Ogino S, Shima K, Meyerhardt JA, et al. Predictive and prognostic roles of BRAF mutation in stage III colon cancer: results from intergroup trial CALGB 89803. Clin Cancer Res. 2012; 18(3):890-900.
36. Peters S, Michielin O, Zimmermann S. Dramatic response induced by vemurafenib in a BRAF V600E-mutated lung adenocarcinoma. J Clin Oncol. 2013; 31(20):e341-344.
37. Peyrade F, Re D, Ginet C, et al. Low-dose vemurafenib induces complete remission in a case of hairy-cell leukemia with a V600E mutation. Haematologica. 2013; 98(2):e20-22.
38. Pietrantonio F, Petrelli F, Coinu A, et al. Predictive role of BRAF mutations in patients with advanced colorectal cancer receiving cetuximab and panitumumab: a meta-analysis. Eur J Cancer. 2015; 51(5):587-594.
39. Planchard D, Besse B, Groen HJM, et al. An open-label phase 2 trial of dabrafenib plus trametinib in patients with previously treated BRAF V600E-mutant metastatic non-small cell lung cancer. Lancet Oncol. 2016; 17(7):984-993.
40. Oneal PA, Kwitkowski V, Luo L, et al. FDA approval summary: Vemurafenib for the treatment of patients with Erdheim-Chester Disease with the BRAFV600 Mutation. Oncologist. 2018; 23(12):1520-1524.
41. Richman SD, Seymour MT, Chambers P, et al. KRAS and BRAF mutations in advanced colorectal cancer are associated with poor prognosis but do not preclude benefit from oxaliplatin or irinotecan: results from the MRC FOCUS trial. J Clin Oncol. 2009; 27(35):5931-5937.
42. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2015; 372(1):30-39.
43. Robinson SD, O'Shaughnessy JA, Cowey CL, et al. BRAF V600E-mutated lung adenocarcinoma with metastases to the brain responding to treatment with vemurafenib. Lung Cancer. 2014; 85(2):326-330.
44. Rowland A, Dias MM, Wiese MD, et al. Meta-analysis of BRAF mutation as a predictive biomarker of benefit from anti-EGFR monoclonal antibody therapy for RAS wild-type metastatic colorectal cancer. Br J Cancer. 2015; 112(12):1888-1894.
45. Rush S, Foreman N, Liu A. Brainstem ganglioglioma successfully treated with vemurafenib. J Clin Oncol. 2013; 31(10):e159-e160.
46. Seymour MT, Brown SR, Richman S, et al. Addition of panitumumab to irinotecan: results of PICCOLO, a randomized controlled trial in advanced colorectal cancer (aCRC) [abstract]. ASCO Meeting Abstracts 2011; 29:3523.
47. Shahabi V, Whitney G, Hamid O, et al. Assessment of association between BRAF-V600E mutation status in melanomas and clinical response to ipilimumab. Cancer Immunol Immunother. 2012; 61(5):733-737.
48. Shao H, Calvo K, Gronborg M, et al. Distinguishing hairy cell leukemia variant from hairy cell leukemia: development and validation of diagnostic criteria. Leuk Res 2013; 37(4):401-409.
49. Sharma SG, Gulley ML. BRAF mutation testing in colorectal cancer. Arch Pathol Lab Med. 2010; 134(8):1225-1228.
50. Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. N Engl J Med. 2012; 366(8):707-714.
51. Subbiah V, Kreitman RJ, Wainberg ZA, et al. Dabrafenib and Trametinib treatment in patients with locally advanced or metastatic BRAF V600-mutant anaplastic thyroid cancer. J Clin Oncol. 2018; 36(1):7-13.

52. Tiacci E, Trifonov V, Schiavoni G, et al. BRAF mutations in hairy-cell leukemia. N Engl J Med. 2011; 364(24):2305-2315.
53. Van Cutsem E, Kohne CH, Lang I, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol. 2011; 29(15):2011-2019.
54. Vasen HF, Moslein G, Alonso A, et al. Guidelines for the clinical management of Lynch syndrome (hereditary non-polyposis cancer). J Med Genet. 2007; 44(6):353-362.
55. Vultur A, Villanueva J, Herlyn M. BRAF inhibitor unveils its potential against advanced melanoma. Cancer Cell. 2010; 18(4):301-302.
56. Wilson PM, Labonte MJ, Lenz HJ. Molecular markers in the treatment of metastatic colorectal cancer. Cancer J. 2010; 16(3):262-272.
57. Xi L, Arons E, Navarro W, et al. Both variant and IGHV4-34-expressing hairy cell leukemia lack the BRAF V600E mutation. Blood. 2012; 119(14):3330-3332.

Circulating Tumor DNA
1. Karlovich C, Goldman JW, Sun JM, et al. Assessment of EGFR Mutation Status in Matched Plasma and Tumor Tissue of NSCLC Patients from a Phase I Study of Rociletinib (CO-1686). Clin Cancer Res. 2016; 22(10):2386-2395.
2. Murray DH, Rohan TB, Gaur S, et al. Validation of a circulating tumor-derived DNA blood test for detection of methylated BCAT1 and IKZF1 DNA. J Appl Lab Med. 2017; 2(2)165-175.
3. Musher BL, Melson JE, Amato G et al. Evaluation of circulating tumor DNA for methylated BCAT1 and IKZF1 to detect recurrence of stage II/stage III colorectal cancer (CRC). Cancer Epidemiol Biomarkers Prev. 2020 Sep 21. Epub ahead of print.
4. Perakis S and Speicher MR. Emerging concepts in liquid biopsies. BMC Med. 2017; 15(1):75.
5. Ramalingam SS, Yang JC, Lee CK, et al. Osimertinib as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer. J Clin Oncol. 2018; 36(9):841-849.
6. Thress KS, Brant R, Carr TH, et al. EGFR mutation detection in ctDNA from NSCLC patient plasma: A cross-platform comparison of leading technologies to support the clinical development of AZD9291. Lung Cancer. 2015; 90(3):509-515.

EGFR Mutation Analysis
1. An N, Zhang Y, Niu H, et al. EGFR-TKIs versus taxanes agents in therapy for nonsmall-cell lung cancer patients: a PRISMA-compliant systematic review with meta-analysis and meta-regression. Medicine (Baltimore). 2016; 95(50):e5601.
2. Asahina H, Yamazaki K, Kinoshita I, et al. A phase II trial of gefitinib as first-line therapy for advanced non-small cell lung cancer with epidermal growth factor receptor mutations. Br J Cancer. 2006; 95(8):998-1004.
3. Bell DW, Lynch TJ, Haserlat SM, et al. Epidermal growth factor receptor mutations and gene amplification in non-small-cell lung cancer: molecular analysis of the IDEAL/INTACT gefitinib trials. J Clin Oncol. 2005; 23(31):8081-8092.
4. Brugger W, Triller N, Blasinska-Morawiec M, et al. Prospective molecular marker analyses of EGFR and KRAS from a randomized, placebo-controlled study of erlotinib maintenance therapy in advanced non-small-cell lung cancer. J Clin Oncol. 2011; 29(31):4113-4120.
5. Cappuzzo F, Hirsch FR, Rossi E, et al. Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer. J Natl Cancer Inst. 2005; 97(9):643-655.

6. Cappuzzo F, Ligorio C, Jänne PA, et al. Prospective study of gefitinib in epidermal growth factor receptor fluorescence in situ hybridization-positive/phospho-Akt-positive or never smoker patients with advanced non-small-cell lung cancer: the ONCOBELL trial. J Clin Oncol. 2007a; 25(16):2248-2255.
7. Cappuzzo F, Ligorio C, Toschi L, et al. EGFR and HER2 gene copy number and response to first-line chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). J Thorac Oncol. 2007b: 2(5):423-429.
8. Cascinu S, Berardi R, Salvagni S, et al. A combination of gefitinib and FOLFOX-4 as first-line treatment in advanced colorectal cancer patients. A GISCAD multicentre phase II study including a biological analysis of EGFR overexpression, amplification and NF-kB activation. Br J Cancer. 2008; 98(1):71-76.
9. Clark GM, Zborowski DM, Culbertson JL, et al. Clinical utility of epidermal growth factor receptor expression for selecting patients with advanced non-small cell lung cancer for treatment with erlotinib. J Thorac Oncol. 2006; 1(8):837-846. da Cunha Santos G, Dhani N, Tu D, et al. Molecular predictors of outcome in a phase 3 study of gemcitabine and erlotinib therapy in patients with advanced pancreatic cancer: National Cancer Institute of Canada Clinical Trials Group Study PA.3. Cancer. 2010; 116(24):5599-5607.
10. Dacic S, Flanagan M, Cieply K, et al. Significance of EGFR protein expression and gene amplification in non-small cell lung carcinoma. Am J Clin Pathol. 2006; 125(6):860-865.
11. D'Angelo SP, Pietanza, MC, Johnson ML, et al. Incidence of EGFR exon 19 deletions and L858R in tumor specimens from men and cigarette smokers with lung adenocarcinomas. J Clin Oncol. 2011; 29(15):2066-2070.
12. Douillard JY, Pirker R, O'Byrne KJ, et al. Relationship between EGFR expression, EGFR mutation status, and the efficacy of chemotherapy plus cetuximab in FLEX study patients with advanced non-small-cell lung cancer. J Thorac Oncol. 2014; 9(5):717-724.
13. Douillard JY, Shepherd FA, Hirsh V, et al. Molecular predictors of outcome with gefitinib and docetaxel in previously treated non-small-cell lung cancer: data from the randomized phase III INTEREST trial. J Clin Oncol. 2010; 28(5):744-752.
14. Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small cell lung cancer treated chemotherapy alone and in combination with erlotinib. J Clin Oncol. 2005; 23(25):5900-5909.
15. Feld R, Sridhar SS, Shepherd FA, et al. Use of the epidermal growth factor receptor inhibitors gefitinib and erlotinib in the treatment of non-small cell lung cancer: a systematic review. J Thorac Oncol. 2006; 1(4):367-376.
16. Franek J, Cappelleri JC, Larkin-Kaiser KA, et al. Systematic review and network meta-analysis of first-line therapy for advanced EGFR-positive non-small-cell lung cancer. Future Oncol. 2019; 15(24):2857-2871.
17. Fukuoka M, Wu YL, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). J Clin Oncol. 2011; 29(21):2866-2874.
18. Geyer JR, Stewart CF, Kocak M, et al. A phase I and biology study of gefitinib and radiation in children with newly diagnosed brain stem gliomas or supratentorial malignant gliomas. Eur J Cancer. 2010; 46(18):3287-3293.
19. Han SW, Kim TY, Hwang PG, et al. Predictive and prognostic impact of epidermal growth factor receptor mutation in non-small-cell lung cancer patients treated with gefitinib. J Clin Oncol. 2005; 23(11):2493-2501.
20. Helman E, Nguyen M, Karlovich CA, et al. Cell-free DNA next-generation sequencing prediction of response and resistance to third-generation EGFR inhibitor. Clin Lung Cancer. 2018; 19(6):518-530.
21. Hirsch FR, Varella-Garcia M, Cappuzzo F, et al. Combination of EGFR gene copy number and protein expression predicts outcome for advanced non-small-cell lung cancer patients treated with gefitinib. Ann Oncol. 2007; 18(4):752-760.

22. Hirsch FR, Varella-Garcia M, McCoy J, et al. Increased epidermal growth factor receptor gene copy number detected by fluorescence in situ hybridization associates with increased sensitivity to gefitinib in patients with bronchioloalveolar carcinoma subtypes: A Southwest Oncology Group Study. J Clin Oncol. 2005; 23(28):6838-6845.
23. Huang SF, Liu HP, Li LH, et al. High frequency of epidermal growth factor receptor mutations with complex patterns in non-small cell lung cancers related to gefitinib responsiveness in Taiwan. Clin Cancer Res. 2004; 10(24):8195-8203.
24. Inoue A, Suzuki T, Fukuhara T, et al. Prospective phase II study of gefitinib for chemotherapy-naive patients with advanced non-small-cell lung cancer with epidermal growth factor receptor gene mutations. J Clin Oncol. 2006; 24(21):3340-3346.
25. Janne PA, Yang JC, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N Engl J Med. 2015; 372(18):1689-1699.
26. Jenkins S, Yang JC, Ramalingam SS, et al. Plasma ctDNA analysis for detection of the EGFR T790M mutation in patients with advanced non-small cell lung cancer. J Thorac Oncol. 2017; 12(7):1061-1070.
27. John T, Akamatsu H, Delmonte A, et al. EGFR mutation analysis for prospective patient selection in AURA3 phase III trial of osimertinib versus platinum-pemetrexed in patients with EGFR T790M-positive advanced non-small-cell lung cancer. Lung Cancer. 2018; 126:133-138.
28. Karlovich C, Goldman JW, Sun JM, et al. Assessment of EGFR mutation status in matched plasma and tumor tissue of NSCLC patients from a phase I study of rociletinib (CO-1686). Clin Cancer Res. 2016; 22(10):2386-2395.
29. Katakami N, Atagi S, Goto K, et al. LUX-Lung 4: a phase II trial of afatinib in patients with advanced non–small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both. J Clin Oncol. 2013; 31(27):3335-3341.
30. Krug AK, Enderle D, Karlovich C, et al. Improved EGFR mutation detection using combined exosomal RNA and circulating tumor DNA in NSCLC patient plasma. Ann Oncol. 2018; 29(3):700-706.
31. Laurent-Puig P, Cayre A, Manceau G, et al. Analysis of PTEN, BRAF, and EGFR status in determining benefit from cetuximab therapy in wild-type KRAS metastatic colon cancer. J Clin Oncol. 2009; 27(35):5924-5930.
32. Li C, He Q, Liang H et al. Diagnostic accuracy of droplet digital PCR and amplification refractory mutation system PCR for detecting EGFR mutation in cell-free DNA of lung cancer: A meta-analysis. Front Oncol. 2020; 10:290.
33. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med. 2004; 350(21):2129-2139.
34. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non–small-cell lung cancer with mutated EGFR. N Engl J Med. 2010; 362(25):2380-2388.
35. Miller VA, Hirsh V, Cadranel J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol. 2012; 13(5):528-538.
36. Mitsudomi T, Kosaka T, Endoh H, et al. Mutations of the epidermal growth factor receptor gene predict prolonged survival after gefitinib treatment in patients with non-small-cell lung cancer with postoperative recurrence. J Clin Oncol. 2005; 23(11):2513-2520.
37. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol. 2010; 11(2):121–128.
38. Mok TS, Wu Y-L, Ahn M-J, et al.; AURA3 Investigators. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med. 2017; 376(7):629-640.

39. Mok T, Wu YL, Lee JS, et al. Detection and dynamic changes of EGFR mutations from circulating tumor DNA as a predictor of survival outcomes in NSCLC patients treated with first-line intercalated Erlotinib and chemotherapy. Clin Cancer Res. 2015; 21(14):3196-3203.
40. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009; 361(10):947-957.
41. Mok TS, Wu YL, Yu CJ, et al. Randomized, placebo-controlled, phase II study of sequential erlotinib and chemotherapy as first-line treatment for advanced non-small-cell lung cancer. J Clin Oncol. 2009; 27(30):5080-5087.
42. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science. 2004; 304(5676):1497-1500.
43. Papadimitrakopoulou VA, Han JY, Ahn MJ, et al. Epidermal growth factor receptor mutation analysis in tissue and plasma from the AURA3 trial: Osimertinib versus platinum-pemetrexed for T790M mutation-positive advanced non-small cell lung cancer. Cancer. 2020; 126(2):373-380.
44. Park CK, Cho HJ, Choi YD, et al. A Phase II Trial of Osimertinib in the second-line treatment of non-small cell lung cancer with the EGFR T790M mutation, detected from circulating tumor DNA: LiquidLung-O-Cohort 2. Cancer Res Treat. 2019; 51(2):777-787.
45. Parra HS, Cavina R, Latteri F, et al. Analysis of epidermal growth factor receptor expression as a predictive factor for response to gefitinib ('Iressa', ZD1839) in non-small-cell lung cancer. Br J Cancer. 2004; 91(2):208-212.
46. Passiglia F, Rizzo S, Di Maio M et al. The diagnostic accuracy of circulating tumor DNA for the detection of EGFR-T790M mutation in NSCLC: a systematic review and meta-analysis. Sci Rep. 2018; 8(1):13379.
47. Pirker R, Pereira JR, von Pawel J, et al. EGFR expression as a predictor of survival for first-line chemotherapy plus cetuximab in patients with advanced non-small-cell lung cancer: analysis of data from the phase 3 FLEX study. Lancet Oncol. 2012; 13(1):33-42.
48. Ramalingam SS, O'Byrne K, Boyer M, et al. Dacomitinib versus erlotinib in patients with EGFR-mutated advanced nonsmall-cell lung cancer (NSCLC): pooled subset analyses from two randomized trials. Ann Oncol. 2016; 27(3):423-429.
49. Rosell R, Carcereny E, Gervais R, et al.; Spanish Lung Cancer Group in collaboration with Groupe Français de Pneumo-Cancérologie and Associazione Italiana Oncologia Toracica. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012; 13(3):239-246.
50. Rosell R, Moran T, Queralt C, et al.; Spanish Lung Group. Screening for epidermal growth factor receptor mutations in lung cancer. N Engl J Med. 2009a; 361(10):958-967.
51. Rosell R, Perez-Roca L, Sanchez JJ, et al. Customized treatment in non-small-cell lung cancer based on EGFR mutations and BRCA1 mRNA expression. PLoS One. 2009b; 4(5):e5133.
52. Saarilahti K, Bono P, Kajanti M, et al. Phase II prospective trial of gefitinib given concurrently with cisplatin and radiotherapy in patients with locally advanced head and neck cancer. J Otolaryngol Head Neck Surg. 2010; 39(3):269-276.
53. Sequist LV, Joshi VA, Jänne PA, et al. Response to treatment and survival of patients with non-small cell lung cancer undergoing somatic EGFR mutation testing. Oncologist. 2007; 12(1):90-98.
54. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol. 2013; 31(27):3327-3334.
55. Srividya MR, Thota B, Arivazhagan A, et al. Age-dependent prognostic effects of EGFR/p53 alterations in glioblastoma: study on a prospective cohort of 140 uniformly treated adult patients. J Clin Pathol. 2010; 63(8):687-691.

56. Sundaresan TK, Sequist LV, Heymach JV, et al. Detection of T790M, the acquired resistance EGFR mutation, by tumor biopsy versus noninvasive blood-based analyses. Clin Cancer Res. 2016; 22(5):1103-1110.
57. Takano T, Ohe Y, Sakamoto H, et al. Epidermal growth factor receptor gene mutations and increased copy numbers predict gefitinib sensitivity in patients with recurrent non-small-cell lung cancer. J Clin Oncol. 2005; 23(28):6829-6837.
58. Tan EH, Ramlau R, Pluzanska A, et al. A multicentre phase II gene expression profiling study of putative relationships between tumour biomarkers and clinical response with erlotinib in non-small-cell lung cancer. Ann Oncol. 2010; 21(2):217-222.
59. Tanaka T, Matsuoka M, Sutani A, et al. Frequency of and variables associated with the EGFR mutation and its subtypes. Int J Cancer. 2010; 126(3):651-655.
60. Tsao MS, Sakurada A, Cutz JC, et al. Erlotinib in lung cancer - molecular and clinical predictors of outcome. N Engl J Med. 2005; 353(2):133-144.
61. Usui K, Yokoyama T, Naka G, et al. Plasma ctDNA monitoring during epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor treatment in patients with EGFR-mutant non-small cell lung cancer (JP-CLEAR trial). Jpn J Clin Oncol. 2019; 49(6):554-558.
62. Van Damme N, Deron P, Van Roy N, et al. Epidermal growth factor receptor and K-RAS status in two cohorts of squamous cell carcinomas. BMC Cancer. 2010; 10:189.
63. van Zandwijk N, Mathy A, Boerrigter L, et al. EGFR and KRAS mutations as criteria for treatment with tyrosine kinase inhibitors: retro- and prospective observations in non-small-cell lung cancer. Ann Oncol. 2007; 18(1):99-103.
64. Wang Z, Cheng Y, An T, et al. Detection of EGFR mutations in plasma circulating tumour DNA as a selection criterion for first-line gefitinib treatment in patients with advanced lung adenocarcinoma (BENEFIT): a phase 2, single-arm, multicentre clinical trial. Lancet Respir Med. 2018; 6(9):681-690.
65. Weber B, Meldgaard P, Hager H, et al. Detection of EGFR mutations in plasma and biopsies from non-small cell lung cancer patients by allele-specific PCR assays. BMC Cancer. 2014; 14:294.
66. Wu YL, Cheng Y, Zhou X, et al. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. Lancet Oncol. 2017; 18(11):1454-1466.
67. Wu YL, Zhong WZ, Li LY, et al. Epidermal growth factor receptor mutations and their correlation with gefitinib therapy in patients with non-small cell lung cancer: a meta-analysis based on updated individual patient data from six medical centers in mainland China. J Thorac Oncol. 2007; 2(5):430-439.
68. Yang JC, Hirsh V, Schuler M, et al. Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations J Clin Oncol. 2013; 31(27):3342-3350.
69. Yang JC, Sequist LV, Geater SL, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. Lancet Oncol. 2015; 16(7):830-838.
70. Yang JC, Shih JY, Su WC, et al. Afatinib for patients with lung adenocarcinoma and epidermal growth factor receptor mutations (LUX-Lung 2): a phase 2 trial. Lancet Oncol. 2012; 13(5):539-548.
71. Yoshida K, Yatabe Y, Park JY, et al. Prospective validation for prediction of gefitinib sensitivity by epidermal growth factor receptor gene mutation in patients with non-small cell lung cancer. J Thorac Oncol. 2007; 2(1):22-28.
72. Yung WK, Vredenburgh JJ, Cloughesy TF, et al. Safety and efficacy of erlotinib in first-relapse glioblastoma: a phase II open-label study. Neuro Oncol. 2010; 12(10):1061-1070.

73. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2011; 12(8):735-742.
74. Zhu CQ, da Cunha Santos G, Ding K, et al.; National Cancer Institute of Canada Clinical Trials Group Study BR.21. Role of KRAS and EGFR as biomarkers of response to erlotinib in National Cancer Institute of Canada Clinical Trials Group Study BR.21. J Clin Oncol. 2008; 26(26):4268-4275.

PIK3CA Mutation Analysis

1. André F, Ciruelos E, Rubovszky G, et al. Alpelisib for PIK3CA-Mutated, Hormone Receptor-Positive Advanced Breast Cancer. N Engl J Med. 2019; 380(20):1929-1940.
2. Arsenic R, Treue D, Lehmann A, et al. Comparison of targeted next-generation sequencing and Sanger sequencing for the detection of PIK3CA mutations in breast cancer. BMC Clin Pathol. 2015; 15:20.
3. Baselga J, Im SA, Iwata H, et al. Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Oncology. 2017; 18(7):904-916.
4. Cappuzzo F, Varella-Garcia M, Finocchiaro G, et al. Primary resistance to cetuximab therapy in EGFR FISH-positive colorectal cancer patients. Br J Cancer. 2008; 99(1):83-89.
5. Chae YK, Davis AA, Jain S, et al. Concordance of genomic alterations by next-generation sequencing in tumor tissue versus circulating tumor DNA in breast cancer. Molecular cancer therapeutics. 2017; 16(7):1412-1420.
6. Dearden S, Stevens J, Wu YL, Blowers D. Mutation incidence and coincidence in non small-cell lung cancer: meta-analyses by ethnicity and histology (mutMap). Ann Oncol. 2013; 24(9):2371-2376.
7. De Roock W, Claes B, Bernasconi D, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. Lancet Oncol. 2010; 11(8):753-762.
8. De Stefano A, Carlomagno C. Beyond KRAS: Predictive factors of the efficacy of anti-EGFR monoclonal antibodies in the treatment of metastatic colorectal cancer. World J Gastroenterol. 2014; 20(29):9732-9743.
9. Ellis MJ, Lin L, Crowder R, et al. Phosphatidyl-inositol-3-kinase alpha catalytic subunit mutation and response to neoadjuvant endocrine therapy for estrogen receptor positive breast cancer. Breast Cancer Res Treat. 2010; 119(2):379-390.
10. Fiala O, Pesek M, Finek J, et al. Gene mutations in squamous cell NSCLC: insignificance of EGFR, KRAS and PIK3CA mutations in prediction of EGFR-TKI treatment efficacy. Anticancer Res. 2013; 33(4):1705-1711.
11. Hahn AW, Gill DM, Maughan B, et al. Correlation of genomic alterations assessed by next-generation sequencing (NGS) of tumor tissue DNA and circulating tumor DNA (ctDNA) in metastatic renal cell carcinoma (mRCC): potential clinical implications. Oncotarget. 201; 8(20):33614-33620.
12. Henry NL, Schott AF, Hayes DF. Assessment of PIK3CA mutations in human epidermal growth factor receptor 2–positive breast cancer: clinical validity but not utility. J Clin Oncol. 2014; 32(29):3207-3209.
13. Higgins MJ, Jelovac D, Barnathan E, et al. Detection of tumor PIK3CA status in metastatic breast cancer using peripheral blood. Clinical cancer research. 2012; 18(12):3462-3469.
14. Hynes NE, Lane HA. ERBB receptors and cancer: the complexity of targeted inhibitors. Nat Rev Cancer. 2005; 5(5):341-354.
15. Kalinsky K, Jacks LM, Heguy A, et al. PIK3CA mutation associates with improved outcome in breast cancer. Clin Cancer Res. 2009; 15(16):5049-5059.
16. Karapetis CS, et al. PIK3CA, BRAF, and PTEN status and benefit from cetuximab in the treatment of advanced colorectal cancer- results from NCIC CTG/AGITG CO. 17. Clin Cancer Res. 2014; 20(3):744-53.

17. Kawano O, Sasaki H, Endo K, et al. PIK3CA mutation status in Japanese lung cancer patients. Lung Cancer. 2006; 54(2):209-215.
18. Kidess E., Heirich K., Wiggin M., et al. Mutation profiling of tumor DNA from plasma and tumor tissue of colorectal cancer patients with a novel, high-sensitivity multiplexed mutation detection platform. Oncotarget, 6(4), p.2549-2561.
19. Kodahl AR, Ehmsen S, Pallisgaard N, et al. Correlation between circulating cell-free PIK 3 CA tumor DNA levels and treatment response in patients with PIK 3 CA-mutated metastatic breast cancer. Molecular oncology. 2018; 12(6):925-935.
20. Krasinskas AM. EGFR Signaling in Colorectal Carcinoma. Patholog Res Int. Pathology Research International, vol. 2011, Article ID 932932, 6 pages, 2011.
21. Lin JS, Webber EM, Senger CA, et al. Systematic review of pharmacogenetic testing for predicting clinical benefit to anti-EGFR therapy in metastatic colorectal cancer. Am J Cancer Res. 2011; 1(5):650-662.
22. Loi S, Michiels S, Lambrechts D, et al. Somatic mutation profiling and associations with prognosis and trastuzumab benefit in early breast cancer. J Natl Cancer Inst. 2013, 105(13):960-967.
23. Mao C, Yang ZY, Hu XF, et al. PIK3CA exon 20 mutations as a potential biomarker for resistance to anti-EGFR monoclonal antibodies in KRAS wild-type metastatic colorectal cancer: a systematic review and meta-analysis. Ann Oncol. 2012; 23(6):1518-1525.
24. Normanno N, Rachiglio AM, Lambiase M, ET AL. Heterogeneity of KRAS, NRAS, BRAF and PIK3CA mutations in metastatic colorectal cancer and potential effects on therapy in the CAPRI GOIM trial. Ann Oncol. 2015; 26(8):1710-1714.
25. Ogino S, Liao X, Imamura Y, et al. Predictive and prognostic analysis of PIK3CA mutation in stage III colon cancer intergroup trial. J Natl Cancer Inst. 2013; 105(23):1789-1798.
26. Ogino S, Nosho K, Kirkner GJ, et al. PIK3CA mutation is associated with poor prognosis among patients with curatively resected colon cancer. J Clin Oncol. 2009; 27(9):1477-1484.
27. Papaxoinis G, Kotoula V, Alexopoulou Z, ET AL. Significance of PIK3CA Mutations in Patients with Early Breast Cancer Treated with Adjuvant Chemotherapy: A Hellenic Cooperative Oncology Group (HeCOG) Study. PLoS One. 2015; 10(10):e0140293.
28. Prenen H, De Schutter J, Jacobs B, et al. PIK3CA mutations are not a major determinant of resistance to the epidermal growth factor receptor inhibitor cetuximab in metastatic colorectal cancer. Clin Cancer Res. 2009; 15(9):3184-3188.
29. Razis E, Bobos M, Kotoula V, et al. Evaluation of the association of PIK3CA mutations and PTEN loss with efficacy of trastuzumab therapy in metastatic breast cancer. Breast Cancer Res Treat. 2011, 128(2):447-456.
30. Rothe F, Laes JF, Lambrechts D, et al. Plasma circulating tumor DNA as an alternative to metastatic biopsies for mutational analysis in breast cancer. Ann Oncol. 2014; 25(10):1959-1965.
31. Sartore-Bianchi A, Martini M, Molinari F, et al. PIK3CA mutations in colorectal cancer are associated with clinical resistance to EGFR-targeted monoclonal antibodies. Cancer Res. 2009; 69(5):1851-1857.
32. Tol J, Dijkstra JR, Klomp M, et al. Markers for EGFR pathway activation as predictor of outcome in metastatic colorectal cancer patients treated with or without cetuximab. Eur J Cancer. 2010; 46(11):1997-2009.

RAS Mutation Analysis

1. Al-Jehani RM, Jeyarajah AR, Hagen B, et al. Model for the molecular genetic diagnosis of endometrial cancer using K-ras mutation analysis. J Natl Cancer Inst. 1998; 90(7):540-542.
2. Amado RG, Wolf M, Peeters M et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008; 26(10):1626-1634.

3. Bokemeyer C, Bondarenko I, Hartmann JT, et al. KRAS status and efficacy of first-line treatment of patients with metastatic colorectal cancer (mCRC) with FOLFOX with or without cetuximab: The OPUS experience. J Clin Oncol 26: 2008 (May 20 suppl; abstr 4000).
4. Bokemeyer C, Cutsem EV, Rougier P, et al. Addition of cetuximab to chemotherapy as first-line treatment for KRAS wild-type metastatic colorectal cancer: pooled analysis of the CRYSTAL and OPUS randomised clinical trials. Eur J Cancer 2012; 48(10):1466-1475.
5. Caduff RF, Johnston CM, Frank TS. Mutations of the Ki-ras oncogene in carcinoma of the endometrium. Am J Pathol 1995; 146(1):182-188.
6. Cervantes A, Macarulla T, Martinelli E, et al. Correlation of KRAS status (wild type [wt] vs. mutant [mt]) with efficacy to first-line cetuximab in a study of cetuximab single agent followed by cetuximab + FOLFIRI in patients (pts) with metastatic colorectal cancer (mCRC). J Clin Oncol 26: 2008 (May 20 suppl; abstr 4129).
7. Cuatrecasas M, Villanueva A, Matias-Guiu X, Prat J. K-ras mutations in mucinous ovarian tumors: a clinicopathologic and molecular study of 95 cases. Cancer. 1997; 79(8):1581-1586.
8. De Roock W, Piessevaux H, De Schutter J, et al. KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab. Ann Oncol. 2008; 19(3):508-515.
9. Douillard JY, Shepherd FA, Hirsh V, et al. Molecular predictors of outcome with gefitinib and docetaxel in previously treated non-small-cell lung cancer: data from the randomized phase III INTEREST trial. J Clin Oncol. 2010; 28(5):744-752.
10. Duggan BD, Felix JC, Muderspach LI, et al. Early mutational activation of the c-Ki-ras oncogene in endometrial carcinoma. Cancer Res. 1994; 54(6):1604-1607.
11. Eberhard DA, Johnson BE, Amler LC et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. J Clin Oncol 2005; 23(25):5900-5909.
12. Esteller M, García A, Martínez-Palones JM, et al. The clinicopathological significance of K-RAS point mutation and gene amplification in endometrial cancer. Eur J Cancer. 1997; 33(10):1572-1577.
13. Fujimoto I, Shimizu Y, Hirai Y, et al. Studies on ras oncogene activation in endometrial carcinoma. Gynecol Oncol. 1993; 48(2):196-202.
14. Hogdall EV, Hogdall CK, Blaakaer J, et al. K-ras alterations in Danish ovarian tumour patients. From the Danish "Malova" Ovarian Cancer study. Gynecol Oncol. 2003; 89(1):31-36.
15. Hunt JD, Mera R, Strimas A, et al. KRAS mutations are not predictive for progression of preneoplastic gastric lesions. Cancer Epidemiol Biomarkers Prev. 2001; 10(1):79-80.
16. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med. 2008; 359(17):1757-1765.
17. Khalid A, McGrath KM, Zahid M, et al. The role of pancreatic cyst fluid molecular analysis in predicting cyst pathology. Clin Gastroenterol Hepatol. 2005; 3(10):967-973.
18. Khalid A, Zahid M, Finkelstein SD et al. Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PANDA study. Gastrointest Endosc. 2009; 69(6):1095-1102.
19. Khambata-Ford S, Harbison CT, Hart LL, et al. Analysis of potential predictive markers of cetuximab benefit in BMS099, a phase III study of cetuximab and first-line taxane/carboplatin in advanced non-small-cell lung cancer. J Clin Oncol. 2010; 28(6):918-927.
20. Mao C, Qiu LX, Liao RY, et al. KRAS mutations and resistance to EGFR-TKIs treatment in patients with non-small cell lung cancer: a meta-analysis of 22 studies. Lung Cancer 2010; 69(3):272-278.
21. Messersmith WA, Ahnen DJ. Targeting EGFR in colorectal cancer. N Engl J Med. 2008; 359(17):1834-1836.

22. Olsen C, Schefter T, Chen, et al. Results of a phase I trial of 12 patients with locally advanced pancreatic carcinoma combining gefitinib, paclitaxel, and 3-dimensional conformal radiation: report of toxicity and evaluation of circulating K-ras as a potential biomarker of response to therapy. Am J Clin Oncol. 2009; 32(2):115-121.
23. Peeters M, Douillard JY, Van Cutsem E, et al. Mutant KRAS codon 12 and 13 alleles in patients with metastatic colorectal cancer: assessment as prognostic and predictive biomarkers of response to panitumumab. J Clin Oncol. 2013; 31(6):759-765.
24. Rockacy MJ, Zahid M, McGrath KM, et al. Association between KRAS mutation, detected in pancreatic cyst fluid, and long-term outcomes of patients. Clin Gastroenterol Hepatol. 2013; 11(4):425-429.
25. Schneider CP, Heigener D, Schott-von-Romer K et al. Epidermal growth factor receptor-related tumor markers and clinical outcomes with erlotinib in non-small cell lung cancer. J Thorac Oncol. 2008; 3(12):1446-1453.
26. Semczuk A, Postawski K, Przadka D et al. K-ras gene point mutations and p21ras immunostaining in human ovarian tumors. Eur J Gynaecol Oncol. 2004; 25(4):484-488.
27. Sorich MJ, Wiese MD, Rowland A, et al. Extended RAS mutations and anti-EGFR monoclonal antibody survival benefit in metastatic colorectal cancer: a meta-analysis of randomized, controlled trials. Ann Oncol. 2015; 26(1):13-21.
28. Van Cutsem E, Lang I, D'haens G, et al. KRAS status and efficacy in the first-line treatment of patients with metastatic colorectal cancer (mCRC) treated with FOLFIRI with or without cetuximab: The CRYSTAL experience. Clin Oncol 26: 2008 (May 20 suppl; abstr 2).
29. Varras MN, Sourvinos G, Diakomanolis E, et al. Detection and clinical correlations of ras gene mutations in human ovarian tumors. Oncology. 1999; 56(2):89-96.

Government Agency, Medical Society, and Other Authoritative Publications:

1. American Board of Genetic Counselors. Genetic Counselors' Scope of Practice. Available at: https://www.nsgc.org/p/cm/ld/fid=18#scope. Accessed on February 2, 2021.
2. American Society of Clinical Oncology. American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. J Clin Oncol. 2003; 21(12):2397-2406.
3. Canadian Retinoblastoma Society. National Retinoblastoma Strategy Canadian Guidelines for Care. Can J Ophthalmol. 2009; 44 Suppl 2: S1-88. Available at: https://www.canadianjournalofophthalmology.ca/article/S0008-4182(09)80179-8/pdf. Accessed on February 2, 2021.
4. Casali PG, Abecassis N, Bauer S, et al. Gastrointestinal stromal tumours: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2018; 29 Suppl 4: iv68-iv78.
5. Decker J, Neuhaus C, Macdonald F, et al. Clinical utility gene card for: von Hippel-Lindau (VHL). Eur J Hum Genet. 2014; 22(4).
6. Else T, Greenberg S, Fishbein L. Hereditary Paraganglioma-Pheochromocytoma Syndromes. 2008 May 21 [Updated 2018 Oct 4]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020.
7. Green RC, Berg JS, Grody WW, et al. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. Genet Med. 2013; 15(7):565-574.
8. Hampel H, Bennett RL, Buchanan A, et al. A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. Genet Med. 2015; 17(1):70-87.

9. Kalia SS, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2017; 19(2):249-255.
10. Lohmann DR, Gallie BL. Retinoblastoma. 2000 Jul 18 [Updated 2018 Nov 21]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1452/. Accessed on February 2, 2021.
11. NCCN Clinical Practice Guidelines in Oncology®. © 2021 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: visit the NCCN website: http://www.nccn.org/index.asp. Accessed on December 22, 2020.
    - Non-Small Cell Lung Cancer (V2.2021) Revised December 15, 2020
    - Soft Tissue Sarcoma V6. V1.2021. Updated October 30, 2020.
12. Nielsen SM, Rhodes L, Blanco I, et al. von Hippel-Lindau Disease: genetics and role of genetic counseling in a multiple neoplasia syndrome. J Clin Oncol. 2016; (34)18: 2172-2181.
13. No authors listed. CORRIGENDUM: Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2017; 19(4):484.
14. Raman G, Avendano EE, Chen M. Update on Emerging Genetic Tests Currently Available for Clinical Use in Common Cancers. Evidence Report/Technology Assessment. No. (Prepared by the Tufts Evidence-based Practice Center under Contract No. 290-2007-10055-I.). Rockville, MD: Agency for Healthcare Research and Quality (AHRQ). July 2013. Available at: https://www.ncbi.nlm.nih.gov/books/NBK285327/ . Accessed on February 2, 2021.
15. Smith RA, Cokkinides V, Brawley OW. Cancer screening in the United States, 2009: a review of current American Cancer Society guidelines and issues in cancer screening. CA Cancer J Clin. 2009; 59(1):27-41.
16. Sun F, Bruening W, Erinoff E, Schoelles KM. Addressing Challenges in Genetic Test Evaluation: Evaluation Frameworks and Assessment of Analytic Validity [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011 Report No.: 11-EHC048-EF. AHRQ Methods for Effective Health Care. Available at: https://www.ncbi.nlm.nih.gov/books/NBK56750/. Accessed on February 2, 2021.
17. U.S. Food and Drug Administration (FDA).
    - FDA-Approved Drugs: Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&varApplNo=210861. Accessed on February 2, 2021.
    - In Vitro Companion Diagnostic Devices - Guidance for Industry and Food and Drug Administration Staff. August 6, 2014. Available at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf . Accessed on February 2, 2021.
    - Laboratory Developed Tests. Rockville, MD: FDA. September 27, 2018. Available at: https://www.fda.gov/medical-devices/vitro-diagnostics/laboratory-developed-tests. Accessed on February 2, 2021.
    - List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). Content current as of November 16, 2020. Available at: https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools. Accessed on February 2, 2021.
18. van Leeuwaarde RS, Ahmad S, Links TP, et al. Von Hippel-Lindau Syndrome. 2000 May 17 [Updated 2018 Sep 6]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020.

BRAF Mutation Analysis

1. Bonis PA, Trikalinos TA, Chung M, et al. Hereditary Nonpolyposis Colorectal Cancer: Diagnostic Strategies and Their Implications. Evidence Report/Technology Assessment No. 150 (Prepared by Tufts-New England Medical Center Evidence-based Practice Center under Contract No. 290-02-0022). AHRQ Publication No. 07-E008. Rockville, MD: Agency for Healthcare Research and Quality. May 2007.
2. Diamond EL, Subbiah V, Lockhart AC, et al. FDA approval summary: Vemurafenib for the treatment of patients with Erdheim-Chester Disease with the BRAFV600 mutation. Oncologist. 2018; 23(12):1520-1524.
3. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: can testing of tumor tissue for mutations in EGFR pathway downstream effector genes in patients with metastatic colorectal cancer improve health outcomes by guiding decisions regarding anti-EGFR therapy? Genet Med. 2013; 15(7):517-527.
4. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. Genet Med. 2009; 11(1):35-41.
5. Garbe C, Peris K, Hauschild A, et al. Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline--Update 2012. Eur J Cancer. 2012; 48(15):2375-2390.
6. Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the U.S. Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2014; 80(2):197-220.
7. Hedge M, Ferber M, Mao R, et al. ACMG technical standards and guidelines for genetic testing for inherited colorectal cancer (Lynch syndrome, familial adenomatous polyposis, and MYH-associated polyposis). Genet Med. 2014; 16(1):101-116.
8. National Comprehensive Cancer Network®. NCCN Drugs & Biologics Compendium™ (electronic version). For additional information, visit the NCCN website: http://wwe.nccn.org. Accessed on July 17, 2020.
9. NCCN Clinical Practice Guidelines in Oncology™. © 2021 National Comprehensive Cancer Network, Inc. For additional information visit NCCN website: http://www.nccn.org/index.asp. Accessed on December 16, 2020.
    - Colon Cancer (V4.2020). Revised June 15, 2020.
    - Central Nervous System Cancers (V3.2020). Revised September 11, 2020.
    - Cutaneous Melanoma (V1.2021). Revised November 25, 2020.
    - Genetic/Familial High-Risk: Colorectal (V1.2020). Revised July 21, 2020.
    - Hairy Cell Leukemia (V1.2021). Revised September 28, 2020.
    - Non-Small Cell Lung Cancer (V1.2021). Revised November 25, 2020.
    - Ovarian Cancer, Including Fallopian Tube Cancer and Primary Peritoneal Cancer (V1.2020). Revised March 11, 2020.
    - Rectal Cancer (V6.2020). Revised June 25, 2020.
    - Soft Tissue Sarcoma (V1.2021). Revised October 30, 2020.
    - Thyroid Carcinoma (V2.2020). Revised July 15, 2020.
10. Odogwu L, Mathieu L, Blumenthal G, et al. FDA approval Summary: Dabrafenib and Trametinib for the treatment of metastatic non-small cell lung cancers harboring BRAF V600E mutations. Oncologist. 2018; 23(6):740-745.
11. Palomaki GE, McClain MR, Melillo S, et al. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. Genet Med. 2009; 11(1):42-65.

12. Planchard D, Mazieres J, Riely GJ, et al. Interim results of phase II study BRF113928 of dabrafenib in BRAF V600E mutation–positive non-small cell lung cancer (NSCLC) patients. J Clin Oncol 31, 2013 (suppl; abstr 8009).
13. U.S. Food and Drug Administration. Label and approval information: Mekinist (trametinib). Updated June 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/204114s016lbl.pdf. Accessed on February 3, 2021.
14. U.S. Food and Drug Administration. Label and approval information: Tafinlar (dabrafenib). Updated April 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202806s015lbl.pdf. Accessed on February 3, 2021.
15. U.S. Food and Drug Administration. Label and approval information: Zelboraf (vemurafenib) Tablet, 240mg. Updated May 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202429s019lbl.pdf. Accessed on February 3, 2021.
16. U.S. Food and Drug Administration. List of cleared or approved companion diagnostic devices (in vitro and imaging tools). Updated 11/16/2020. Available at: https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm. Accessed on February 3, 2021.
17. United States Food and Drug Administration (FDA). Premarket Approval Letter (PMA). cobas® 4800 BRAF V600 Mutation Test, PMA # P110020. Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf11/P110020a.pdf. Accessed on February 3, 2021.
18. U.S. Food and Drug Administration. Premarket Notification Database. THxID™ BRAF Kit for use on the ABI 7500 Fast Dx Real-Time PCR Instrument Summary of Safety and Effectiveness. Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf12/P120014b.pdf. Accessed on February 3, 2021.
19. U.S. Food and Drug Administration. Summary of Safety and Effectiveness Data (SEED). THxID™ BRAF Kit for use on the ABI 7500 Fast Dx Real-Time PCR Instrument. Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf12/P120014b.pdf. Accessed on February 3, 2021.

Circulating Tumor DNA

1. Merker JD, Oxnard GR, Compton C, et al. Circulating tumor DNA analysis in patients with cancer: American Society of Clinical Oncology and College of American Pathologists joint review. J Clin Oncol. 2018; 36(16):1631-1641. Accessed on January 4, 2021.
2. National Cancer Institute. Definition of liquid biopsy - NCI Dictionary of Cancer Terms. National Cancer Institute. Available at: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/liquid-biopsy. Accessed on February 2, 2021.

EGFR Mutation Analysis

1. Hanna N, Johnson D, Temin S, Masters G. Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology Clinical Practice Guideline update summary. J Oncol Pract. 2017; 13(12):832-837.
2. Keedy VL, Temin S, Somerfield MR, et al. American Society of Clinical Oncology provisional clinical opinion: epidermal growth factor receptor (EGFR) mutation testing for patients with advanced non-small-cell lung cancer considering first-line EGFR tyrosine kinase inhibitor therapy. J Clin Oncol. 2011; 29(15):2121-2127.
3. Lindeman NI, Cagle PT, Aisner DL, et al. Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors: guideline from the College of American

Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. J Mol Diagn. 2018; 20(2):129-159.
4. Masters GA, Temin S, Azzoli CG, et al.; American Society of Clinical Oncology Clinical Practice. Systemic therapy or stage IV non-small-cell lung Cancer: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2015; 33(30):3488-515.
5. Merker JD, Oxnard GR, Compton C, et al. Circulating tumor DNA analysis in patients with cancer: American Society of Clinical Oncology and College of American Pathologists joint review. J Clin Oncol. 2018; 36(16):1631-1641.
6. National Comprehensive Cancer Network (NCCN). © 2021 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website at: http://www.nccn.org/index.asp.
   - Non-Small Cell Lung Cancer (V6.2020). Revised June 15, 2020.
7. Travis WD, Brambilla E, Nicholson AG, et al. On behalf of the WHO Panel. The 2015 World Health Organization classification of lung tumors. Impact of genetic, clinical, and radiologic advances since the 2004 classification. J Thorac Oncol. 2015; 10(9):1243-1260.
8. U.S. Food and Drug Administration (FDA). Vizimpro package insert. FDA 2018(a). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211288s000lbl.pdf. Accessed on February 2, 2021.
9. U.S. Food and Drug Administration (FDA). Gilotrif package insert. FDA 2018(b) Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/201292s014lbl.pdf. Accessed on February 2, 2021.
10. U.S. Food and Drug Administration (FDA). Iressa package insert. FDA 2018(c). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206995s003lbl.pdf. Accessed on February 2, 2021.
11. U.S. Food and Drug Administration (FDA). Tagrisso package insert. FDA 2018(d). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208065s008lbl.pdf. Accessed on February 2, 2021.
12. U.S. Food and Drug Administration (FDA). Tarceva package insert. (FDA, 2016(a). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021743s025lbl.pdf. Accessed on February 2, 2021.
13. U.S. Food and Drug Administration Premarket Approval Database. Cobas EGFR Mutation Test V2 Summary of Safety and Effectiveness. P150047. Rockville, MD: FDA 2016(b). June 1, 2016. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf15/P150047B.pdf. Accessed on February 2, 2021.
14. U.S. Food and Drug Administration Premarket Approval Database. Cobas EGFR Mutation Test V2 Summary of Safety and Effectiveness. P150044. Rockville, MD: FDA (2016c). February 2, 2021. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf15/p150044b.pdf. Accessed on February 2, 2021.

PIK3CA Mutation Analysis

1. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: can testing of tumor tissue for mutations in EGFR pathway downstream effector genes in patients with metastatic colorectal cancer improve health outcomes by guiding decisions regarding anti-EGFR therapy? Genet Med. 2013; 15(7):517-527.
2. National Center for Biotechnology Information (NCBI). GTR: Genetic Testing Registry. PIK3CA Mutation by Sequencing. Last updated September 13, 2017. Available at: http://www.ncbi.nlm.nih.gov/gtr/tests/514565/performance-characteristics/. Accessed on February 2, 2021.
3. National Comprehensive Cancer Network (NCCN).© 2021 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website at: http://www.nccn.org/index.asp. Accessed on December 16, 2020.
   - Breast Cancer (V6.2020). Revised September 8, 2020.

4. U.S. Food and Drug Administration Premarket Approval Database. Therascreen PIK3CA RGQ PCR Kit. Summary of Safety and Effectiveness. P190001. Rockville, MD: FDA. 2019(a). Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf19/P190001B.pdf. Accessed February 2, 2021.
5. U.S. Food and Drug Administration Premarket Approval Database. Therascreen PIK3CA RGQ PCR Kit. Summary of Safety and Effectiveness. P19004B. Rockville, MD: FDA. 2019(b). Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf19/P190004B.pdf. Accessed February 2, 2021.

RAS Mutation Analysis

1. Allegra CJ, Rumble RB, Hamilton SR, et al. Extended RAS gene mutation testing in metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update 2015. J Clin Oncol. 2016; 34(2):179-185.
2. Cetuximab (systemic). In: DrugPoints® System (electronic version). Truven Health Analytics, Greenwood Village, CO. Updated December 6, 2019. Available at: http://www.micromedexsolutions.com. Accessed on April 13, 2020.
3. Elta GH, Enestvedt BK, Sauer BG, Lennon AM. ACG Clinical Guideline: Diagnosis and Management of Pancreatic Cysts. Am J Gastroenterol. 2018; 113(4):464-479.
4. Erbitux (cetuximab) [Product Information]. Branchburg, NJ. ImClone Systems Incorporated. Revised June 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125084s269lbl.pdf. Accessed on April 13, 2020.
5. Kalemkerian GP, Narula N, Kennedy EB, et al. Molecular testing guideline for the selection of patients with lung cancer for treatment with targeted tyrosine kinase inhibitors: American Society of Clinical Oncology Endorsement of The College of American Pathologists/International Association for the Study of Lung Cancer/Association for Molecular Pathology Clinical Practice Guideline Update. J Clin Oncol. 2018; 36(9):911-919.
6. Khalid, A, Brugge, W. ACG practice guidelines for the diagnosis and management of neoplastic pancreatic cysts. Am J Gastroenterol. 2007; 102(10):2339-2349.
7. Lindeman NI, Cagle PT, Aisner DL, et al. Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors: Guideline from the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. Arch Pathol Lab Med. 2018; 142(3):321-346.
8. Lorenzen S, Langer R, Rothling N, et al. Absence of mutations of the K-ras gene in squamous cell carcinoma of the esophagus: Analysis from the randomized oesotux phase II study (cetuximab and cisplatin/5-FU versus cisplatin/5-FU alone). ASCO. 2009; Suppl Abstract No.38
9. NCCN Clinical Practice Guidelines in Oncology™. © 2020 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed April 13, 2020.
   - Anal Carcinoma (V1.2020). Revised November 19, 2019.
   - Colon Cancer (V2.2020). Revised March 3, 2020.
   - Non-Small Cell Lung Cancer (V3.2020). Revised February 11, 2020.
   - Pancreatic Adenocarcinoma (V1.2020). Revised July 2, 2019.
   - Rectal Cancer (V2.2020). Revised March 3, 2020.
10. Panitumumab (systemic). In: DrugPoints® System (electronic version). Truven Health Analytics, Greenwood Village, CO. Updated December 6, 2019. Available at: http://www.micromedexsolutions.com. Accessed on April 13, 2020.

11. Sepulveda AR, Hamilton SR, Allegra CJ. Et al. Molecular biomarkers for the evaluation of colorectal cancer: Guideline from the American Society for Clinical Pathology, College of American Pathologists, Association for Molecular Pathology, and the American Society of Clinical Oncology. J Clin Oncol. 2017; 35(13):1453-1486.
12. Tanaka M, Chari S, Adsay V, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology. 2006; 6(1-2):17-32.
13. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016; 27(8):1386-422.
14. Van Cutsem E, Cervantes A, Nordlinger B, et al. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014; 25 Suppl 3:iii1-9.
15. Vectibix (Panitumumab) [Product Information], Thousand Oaks, CA. Amgen. Revised June 2017. Available at: https://pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/vectibix/vectibix_pi.pdf. Accessed on February 2, 2021.

Websites for Additional Information

1. American Cancer Society. What Is Targeted Cancer Therapy? Last revised January 29, 2021. Available at: https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/targeted-therapy/what-is.html. Accessed on February 2, 2021.
2. National Library of Medicine (NLM). Genetics Home Reference. Published August 31, 2020. Available at: http://ghr.nlm.nih.gov/. Accessed on February 2, 2021.
3. National Society of Genetic Counselors' Definition Task Force, Resta R, Biesecker BB, et al. A new definition of Genetic Counseling: National Society of Genetic Counselors' Task Force report. J Genet Couns. 2006; 5(2):77-83.
4. Robson ME, Storm CD, Weitzel J, et al. American Society of Clinical Oncology policy statement update: genetic and genomic testing for cancer susceptibility. J Clin Oncol. 2010; 28(5):893-901.

BRAF Mutation Analysis

1. Genetics Home Reference:
   - BRAF. Reviewed August 1, 2018. Available at: http://ghr.nlm.nih.gov/gene/BRAF. Accessed on February 2, 2021.
   - Erdheim-Chester Disease. Reviewed April 1, 2017. Available at: https://ghr.nlm.nih.gov/condition/erdheim-chester-disease. Accessed on February 2, 2021.
2. National Institutes of Health. Genetic and Rare Diseases Information Center. Langerhans cell histiocytosis. Available at: https://rarediseases.info.nih.gov/diseases/6858/langerhans-cell-histiocytosis. Accessed on February 2, 2021.

Circulating Tumor DNA

1. American Cancer Society. Liquid Biopsies: Past, Present, and Future. February 12, 2018. Available at: https://www.cancer.org/latest-news/liquid-biopsies-past-present-future.html. Accessed on September 30, 2020.
2. National Cancer Institute. Liquid biopsy: using DNA in blood to detect, track, and treat cancer. November 8, 2017. Available at: https://www.cancer.gov/news-events/cancer-currents-blog/2017/liquid-biopsy-detects-treats-cancer. Accessed on September 30, 2020

3. National Cancer Institute. What is circulating tumor DNA and how is it used to diagnose and manage cancer?. Published September 21, 2020. Available at: https://ghr.nlm.nih.gov/primer/testing/circulatingtumordna . Accessed on February 2, 2021.

Epidermal Growth Factor Receptor (EGFR) Mutation Analysis

1. American Cancer Association. Lung Cancer - Non-Small Cell. Available at: http://www.cancer.org/Cancer/LungCancer-Non-SmallCell/DetailedGuide/index. Accessed on February 2, 2021.
2. National Cancer Institute. Non-Small Cell Cancer Treatment (PDQ®). Available at: http://www.cancer.gov/cancertopics/pdq/treatment/non-small-cell-lung/HealthProfessional/page2. Accessed on February 2, 2021.
3. National Library of Medicine. Medical Encyclopedia: Non-Small Cell Lung Cancer. Available at: http://www.nlm.nih.gov/medlineplus/ency/article/007194.htm. Accessed on February 2, 2021.

PIK3CA Mutation Analysis

1. National Center for Biotechnology Information (NCBI). Genetic Testing Registry (GTR). Genetic tests for PIK3CA. Available at: https://www.ncbi.nlm.nih.gov/gtr/tests/514565.1/. Last updated: May 26, 2015. Accessed on February 2, 2021.

RAS Mutation Analysis

1. National Library of Medicine. Genetics Home Reference. HRAS. Last updated: August 18, 2020. Available at: https://ghr.nlm.nih.gov/gene/HRAS. Accessed on February 2, 2021.
2. National Library of Medicine. Genetics Home Reference. KRAS. Last updated August 18, 2020. Available at: http://ghr.nlm.nih.gov/gene/KRAS. Accessed on February 2, 2021.
3. National Library of Medicine. Genetics Home Reference. NRAS. Last updated: August 18, 2020. Available at: https://ghr.nlm.nih.gov/gene/NRAS. Accessed on February 2, 2021.

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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
	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.