SENTARA HEALTH PLANS, INC.
CLINICAL CARE SERVICES

Medical Policy: **Medical 34 A**

Subject: **Genetic Testing-Cancer Prevention, Diagnosis and Treatment**

Also see other Genetic Testing Policies:

See Genetic Testing 34 B	Pre-Treatment or Post Intervention
See Genetic Testing 34 C	Cardioneurovascular and Developmental Diagnosis
See Genetic Testing 34 D	Preconceptional /Prenatal /Preimplantation Genetic Testing for Preconceptional /Prenatal /Preimplantation
See Genetic Testing 34 E	Pharmacogenetic Testing
See Genetic Testing 34 F	Medicare Coverage

Effective Date: February 2009

Review Date: November 2010; 2/14; 2/15, 2/16, 10/19, 4/21

Revised Date: April 2009; 6/09; 7/10; 12/10; 3/11; 4/11; 6/11; 7/11; 9/11; 10/11; 12/11; 2/12; 3/12; 6/12; 7/12; 9/12; 10/12; 11/12; 2/13; 4/13; 6/13; 7/13; 8/13; 10/13; 1/14; 3/14; 4/14; 5/14; 6/14; 7/14; 8/14; 9/14; 10/14; 11/14; 12/14; 2/15; 4/15; 5/15; 6/15; 7/15; 8/15; 10/15; 11/15; 12/15; 1/16; 2/16; 3/16; 4/16; 5/16, 6/16, 7/16, 7/19, 8/19, 2/20, 10/20, 2/21, 4/21, 5/21, 6/21, 7/21, 10/21, 11/21, 1/22, 2/22, 3/22, 6/22, 7/22, 8/22, 9/22, 10/22, 11/22, 12/22, 1/23, 2/23

Notes: **Effective 2/28/2023, genetic panels of not more than 75 genes are approved for cancer management and treatment. Please disregard any exceptions below that contradict this.**

Covered: **See appropriate benefit document for specific coverage determination.**

Exceptions: **Based on current scientific evidence, the requested test is considered not medically necessary because the result of**

genetic testing has not been shown to direct clinical management that results in an improvement of clinical outcomes:

- 4K score (0010M)
- Ambry's PCDNext panel ARMC4, CCDC39, CCDC40, CCDC103, CCDC114, CFTR, DNAAF1, DNAAF2, DNAAF3, DNAAF5, DNAH5, DNAH11, DNAI1, DNAI2, LRRC6, OFD1, RPGR, RSPH4A, RSPH9, SPAG1, NME8 (TXNDC3)-81222, 81223, 81479
- Amsterdam,
- Archer DX FusionPlex Kits for blood cancer assays, oncology Research Panel, Thyroid Panel, Solid Tumor Panel, ALK, RET, ROS1 Panel, Sarcoma Panel, NTRK Panel, FGFR Panel, and My Fusion Plex kit
- ATK1
- AXIN2
- BAG1
- BARD1,
- bioTheranostics Cancer Type ID (81540)
- BIRC4 test is testing for X-linked lymphoproliferative syndrome (XLP), caused by alterations, also known as "mutations," at a specific area within an individual's genetic information.
- BluePrint,
- BluePrint™ (also referred to as "80-gene profile")
- Bone Marrow Failure Syndrome
- Breast Cancer Gene Expression Ratio (Theros H/I
- BreastNext panel,
- BreastOncPX™
- BreastPRS
- Brevagen
- BRIP1
- CA 15-3 is considered experimental/investigational. CA 15-
- 3 is not sensitive or specific enough to be considered useful as a tool for cancer screening. Its main use is as a tumor marker to monitor a patient's response to breast cancer treatment and to watch for breast cancer recurrence,
- CancerNext Genetic Testing,
- Carcino Embryonic Antigen Cell Adhesion Molecule 6 (CEACAM6),
- Caris Life Sciences panels
- CDC6
- CDK2AP1
- CDK4

- CDKN2A
- Chemo FX Assay test- Precision Therapeutics, a tool to help direct primary therapy for many types of cancer (81535, 81536).
- Chromosome 3 Gene Test for myeloid disorders
- C-KIT D816V,
- Colonext
- ColonSentry
- ColoSeq and ColoSeq Tumor Panels
- ConfirmMDx (Methylation of GSTP1, APC and RASSF1) for Prostate cancer,
- Cowden Syndrome- there is insufficient evidence in the
- CSF1R
- CTNNA1
- CTNNB1
- CxBladder
- DDR2
- DecisionDx: all Decision DX tests (except DecisionDX Uveal Melanoma for Optima Medicare only) including Cutaneous Melanoma, Esophageal Cancer, Mesothelioma, and Glioblastoma Multiforme
- DetermaRX
- Digene HPV test is not medically necessary
- Duke University Colon Hotspot NGS panel: Genes ABL1 EGFR GNAS KRAS PTPN11 AKT1 ERBB2 GNAQ MET RB1 ALK ERBB4 HNF1A MLH1 RET APC EZH2 HRAS MPL SMAD4 ATM FBXW7 IDH1 NOTCH1 SMARCB1 BRAF FGFR1 JAK2 NPM1 SMO CDH1 FGFR2 JAK3 NRAS SRC CDKN2A FGFR3 IDH2 PDGFRA STK11 CSF1R FLT3 KDR PIK3CA TP53 CNNTB1 GNA11 KIT PTEN and VHL (81445, 88381)
- ELANE(ELA2 test),
- ERBB2
- ERBB3
- ERBB4
- ESD
- Exome Sequence Analysis (81415, 81416, 81417)
- FBXW7
- Fecal DNA for Colorectal Cancer Screening (**81528**),
- FGFR1
- FGFR2
- FGFR3
- FH (fumarate hydratase) gene
- Foundation One® Heme lab test
- FoundationOne Liquid CDx Testing

- FUT3
- GALNT12
- GeneDX OncoGene Dx panel
- Genome Sequence Analysis (81425, 81426, 81427)
- Genomic grade index,
- GNAQ
- GNAS
- GREM1
- Home genetic testing
- HRAS
- IDH1/2 Gene
- IGK (Immunoglobulin Kappa Light Chain Locus)-**81264**
- IL11
- Immunoscore Colon test
- Insight® DX Breast Cancer Profile
- Insight® DX Breast Cancer Profile,
- $JAK2^{V617F}$ testing for any other indication that is not addressed by the criteria below including, but not limited to, unexplained thrombosis (see coverage below in clinical indications)
    - Janus Kinase 2 (JAK2; $JAK2^{V617F}$) gene mutation for: Diagnostic assessment of myeloproliferative disorders (MPD)/myeloproliferative neoplasms (MPN) in children; or
- KDR
- KIR TYPING (killer immunoglobulin like receptor)
- Know error system (Forensic testing)
- KRAS testing for any other indication not listed below
- LCK
  literature to include fibrocystic disease of the breast, fibromas and uterine fibroids as diagnostic criteria (NCCN)
- LungLB®
- MammaTyper®
- Mammostrat
- Mammostrat
- MAP2K1
- Melaris test, p16 mutations are the most common cause of inherited cancer risk in families with melanoma and pancreatic cancer.
- MET amplifications (e.g., cMET)
- Microculture Kinetic (MiCK) Apoptosis Assays (e.g., Correct Chemo assay)
- MITF (microphthalmia-associated transcription factor) gene
- MRE11
- MRE11A

- MYCN gene for Neuroblastoma,
- MyPRS test for Multiple Myeloma,
- myRisk
- NBN,
- NexCourse® Breast IHC4
- NOTCH1
- NPI+ and Randox Breast Cancer Array,
- NRAS testing related to melanoma or any other indication not listed in criteria below
- Nuclear Matrix Protein 22 (NMP-22) for screening of bladder cancer, evaluation of hematuria, and all other indications, (Also see clinical indications below),
- NuvoSelect™ eRx 200-Gene Assay
- Oncomap™ ExTra
- Oncotype DX Breast Cancer Assay with DCIS recurrence score (covered for Medicare only-see criteria below)
- Oncotype DX for Colon Cancer (81525)
- Oncotype DX for lobular carcinoma in situ (LCIS)
- Oncovue,
- OnDose is a test that measures the 5-FU concentration in a patient's plasma and calculates an individualized area under the curve (AUC) for use in adjusting 5-FU dose (**84999**).
- OvaNext Next Generation Sequencing Panel (Check individual gene to see if covered or not)
- PAM50
- PancraGen panel or Pancreatic cyst/tumor testing for mutations in: VHL, OGG1, PTEN, MX11, TP53, SMAD4, DCC, CDKN2A, RNF43, NME1, PSEN2, TFF1, CMM1, LMYC, MCC, APC, NF2, KRAS, or GNAS
- Paraganglioma-Pheochromocytoma (Hereditary) Gene Panels (see approved clinical indications below) (81437 and 81438)
- Pathwork Tissue of Origin test or the Pathwork Tissue of Origin test kit-FFPE
- PDGFR
- Pervenio Lung RS panel (BAG1, BRCA1, CDC6, CDK2AP1, ERBB3, FUT3, IL11, LCK, RND3, SH3BGR, WNT3A, ESD, TBP, and YAP)
- PIK3CA
- POLD1
- POLE
- PreOvar test
- PRKAR1A) and other mutations associated with Carney Syndrome Complex
- Prosigna Breast Panel,

- Prostate Cancer Gene or PCA3 Gene or DD3 or UpM3,
- PTCH1
- Quantitative assessment of JAK2V617F allele burden subsequent to qualitative detection of JAK2V617F
- RAD50
- RAD51C
- RAD51D
- Repeat/Duplicative genetic testing
- RND3
- ROS1 gene mutations
- Rotterdam
- RPS20
- SelectMDx
- SEPT9 (Septin 9 Gene Test For Colon Cancer)
- SH3BGR
- Somatic mutation testing for the detection of Lynch syndrome (ColoSeq single gene testing or panel testing)
- SYMPHONY™ Genomic Breast Cancer Profile
- Target Now testing is an immunohistochemistry (IHC) analysis
- Targetprint
- TargetPrint®
- TCD (T cell antigen receptor, delta) gene test for leukemia and lymphoma
- Telomerase reverse transcriptase (TERT)
- The 41-gene signature assay
- The 41-gene signature assay.
- The 76-gene "Rotterdam signature" assay
- The 76-gene “Rotterdam signature” assay
- TheraGuide 5-FU for patients' risk for an adverse reaction to 5-FU-related chemotherapy.
- TheraPrint ™
- THEROS Breast Cancer Index
- TPB
- TRB@/TRG@ (T Cell Antigen Receptor Beta and Gamma)- **81340, 81341, 81342**
- VeriStrat testing for all indications including non-small cell lung cancer (81538),
- VistaSeq panel
- Whole Exome Sequencing (WES);
- Whole Genome Sequencing
- WNT3A
- XRCC2
- YAP

Authorization: Pre-certification by the Plan is required.

Procedure:
Hereditary cancer is a cancer that has developed as a result of a gene mutation passed down from a parent to a child. Inheriting a gene mutation does not necessarily mean that person will develop cancer, but increases their risk.
Research and studies have found that certain gene mutations increase the chances of a person to develop certain kinds of cancers, depending on family history, or to respond to certain therapies for cancer, based on the genetic components of the tumor.
Autosomal recessive: A genetic condition that appears only in individuals who have received two copies of an autosomal gene, one copy from each parent. The gene is on an autosome, a nonsex chromosome. The parents are carriers who have only one copy of the gene and do not exhibit the trait because the gene is recessive to its normal counterpart gene.
X-linked recessive inheritance - hereditary pattern in which a recessive gene on the X chromosome results in the manifestation of characteristics in male offspring and a carrier state in female offspring.

Genetic Testing is considered medically necessary for the prevention, diagnosis and treatment of cancer of patients who meet the following:

1. There is an approved mutation specific treatment available;

OR

2. There is sufficient Published Scientific Evidence or 3rd party Consensus in the Medical Community that the results of the specific genetic Testing directs clinical management and improves clinical outcomes;

AND

3. After completion of a thorough history, physical examination, pedigree analysis, genetic counseling, relevant diagnostic and biochemical tests (if any), the patient meets criteria for any of the following approved tests: (**criteria are listed individually for each test below**)

    a. **BRCA1 and BRCA2 and BRCA Analysis Rearrangement Testing and Clinical Indications for Testing of Additional Genes Associated with Breast Cancer ATM, CDH1, CHEK2, PALB2, PTEN, STK11, and/or TP53**
    b. **Familial Adenomatous Polyposis (FAP): APC and MUTYH genes (e.g., Colaris AP)**
    c. **HNPCC/Colaris/ COLARIS*AP* and PMS2/EPCAM**
    d. **KRAS and NRAS Testing**
    e. **Multiple endocrine neoplasia type 1(MEN1)**
    f. **Multiple endocrine neoplasia type 2 (MEN2)**
    g. **Thyroid Cancer Mutation Panel**
    h. **Afirma Gene Test for Thyroid Cancer**

ThyroSeq Panel

i. **Oncotype DX for breast cancer**
j. **TP 53 gene**
k. **PTEN gene**
l **MYH-associated Polyposis (MAP).**
m. **BCR-ABL mutation analysis**
n **Pathfinder TG**
o. **Genetic Testing for Other potential malignant diseases**
p. **Von Hippel-Lindau syndrome (VHL)**
q**. Acute myeloid leukemia (CBFB/MHY 11)**
r. **KIT Test (9C Kit/V Kit Hardy Zuckerman Oncogene)**
s. **BRAF**
t. **FLT3 (fms-related tyrosine kinase 3)/CEBPA/ NPM1** (nucleophosmin, nucleolar phosphoprotein B23, Numatrin)
u. **STK11**
v. **CDH1**
w. **Janus Kinase 2 (JAK2, MPL and CALR)**
x. **Immuno Globulin Heavy Chain (IGH)**
y. **PML/RAR Alpha (Promyelocytic Leukemia)**
z. **Retinoblastoma (RB1)**
aa. **Calreticulin Exon 9 (CALR)**
bb. **EGFR for patients with non-small cell lung cancer**
cc. **ALK Gene**
dd. **SMAD4 and BMPR1A**
ee. **Bladder Tumor Marker Testing**
ff. **MYD88 Gene Testing**
gg. **Hereditary Paraganglioma-Pheochromocytoma (PGL/PCC) Syndrome**
hh. **EndoPredict Panel Testing**
ii. **Percepta Bronchial Genomic Classifier**
jj. FoundationOne CDx
kk. **Bone Marrow Targeted Genomic Sequencing by Trusight for Acute Myeloid Leukemia**
ll. **Mammaprint**
mm. **Oncotype DX Breast Cancer Assay with DCIS recurrence score**
nn. **Decipher®**
oo. **Oncotype DX® for Prostate**
pp. **Prolaris®**
qq. **ProMark®**
rr. **ExoDX Prostate (EPI, ExosomeDx Prostate, IntelliScore)**
ss **DecisionDx – Uveal Melanoma**
tt. **Signatera**
uu. **CSF3R gene**
vv. **DermTech Pigmented Lesion Assay (PLA)**

ww. **ClonoSEQ**
xx. **Breast Cancer Index (BCI)**
yy. **PGDx, Genomics solid tumor gene panel**
zz. **BDX-XL2**

First, Second and Third Degree Relative Definition

- A **first-degree** relative is defined as a relative which includes the individual's parents, full siblings, or children
- A **second-degree** relative is defined as a blood relative which includes the individual's grandparents, grandchildren, aunts, uncles, nephews, nieces or half-siblings
- A **third-degree** relative is defined as a blood relative which includes the individual's first-cousins, great-grandparents or great grandchildren

A. **BRCA1 and BRCA 2 and BRCA Analysis Rearrangement Testing (BART)**

Procedure:
Breast/Ovarian Cancer-Tests to detect mutations in BRCA1 and BRCA2, the two genes associated with most cases of familial breast cancer, are performed to determine whether an individual has inherited a mutated version of the gene. Inheriting a mutation places a woman at very high risk of developing breast cancer and, for BRCA1, ovarian cancer. A man who inherits one of these mutations has an elevated risk of breast cancer, prostate cancer and other non-ovarian cancers. **BRCA Analysis Rearrangement Testing** assesses a woman's risk of developing breast or ovarian cancer based on detection of mutations in the BRCA1 and BRCA2 genes. Individuals with a BRCA1 *or* BRCA2 mutation have a 50% (or 1 in 2) chance of passing that mutation on to each of their offspring.

Clinical Indications-BRCA: Covered without Preauthorization

Clinical Indications-BRCA Analysis Rearrangement Testing (BART): Covered without preauthorization.

Clinical Indications for Testing of Additional Genes ATM, CDH1, CHEK2, PALB2, PTEN, STK11, and/or TP53 Associated with Hereditary Cancers: Epithelial Ovarian, Fallopian Tube, Prostate Cancer, or Primary Peritoneal Cancer. Genes ATM, CDH1, CHEK2, PALB2, PTEN, STK11, and/or TP53:

Breast/Ovarian Cancer- Per NCCN Guidelines for genetic/familial breast and ovarian cancer the genes ATM, CDH1, CHEK2, PALB2, PTEN, STK11, and/or TP53 may be tested for individuals over the age of 18 who meet the following clinical indications when test results are used to make clinical management decisions in conjunction with genetic counseling.

1. Biologically-related individual from a family with a known BRCA1, BRCA2, ATM, CDH1, CHEK2, PALB2, PTEN, STK11, and/or TP53 mutation;

OR

2. Personal history of breast cancer and **ANY** of the following:

   a. Diagnosed at age 45 or younger;

   OR

   b. Diagnosed at age 50 or younger with:

      (1) An additional breast cancer primary,
      (2) At least one close blood relative with breast cancer at any age
      (3) At least one close blood relative with epithelial ovarian, fallopian tube, or primary peritoneal cancer
      (4) At least one close blood relative with pancreatic cancer
      (5) At least one close blood relative with prostate cancer (Gleason score greater than or equal to 7)
      (6) An unknown or limited family history (e.g. fewer than two first- or second-degree female relatives or female relatives surviving beyond 45 years in the relevant maternal and/or paternal lineage);

   OR

   c. Diagnosed at age 60 or younger with a triple negative breast cancer (ER, PR and HER);

   OR

   d. Diagnosed at any age with:
      (1) At least one close blood relative with breast cancer diagnosed at age 50 or younger
      (2) At least two close blood relatives with breast cancer at any age
      (3) At least one close blood relative with epithelial ovarian, fallopian tube, or primary peritoneal cancer
      (4) At least two close blood relatives with pancreatic cancer and/or prostate cancer (Gleason score greater than or equal to 7) at any age
      (5) At least one close male blood relative with breast cancer
      (6) Individual of Ashkenazi Jewish descent, no additional family history required

OR

3. Personal history of epithelial ovarian, fallopian tube, or primary peritoneal cancer at any age

OR

4. Personal history of male breast cancer at any age

OR

5. Women or men with a personal history of pancreatic cancer at any age who have at least one close blood relative on the same side of the family with;

(1) Breast cancer at age 50 or younger
(2) Ovarian cancer at any age
(3) Pancreatic cancer at any age

OR

6. Individual of Ashkenazi Jewish descent, no additional family history required;

OR

7. Personal history of prostate cancer (Gleason score greater than or equal to 7) at any age with at least one close blood relative with:
   a. Breast cancer at age 50 or younger
   b. Ovarian cancer at any age
   c. Pancreatic cancer at any age
   d. Prostate cancer (Gleason score greater than or equal to 7) at any age

OR

8. No personal history of breast or ovarian cancer and a family history of first- or second-degree blood relative meeting any of the above criteria;

OR

9. No personal history of breast or ovarian cancer and a family history of a third-degree blood relative with breast and/or epithelial ovarian/fallopian tube/primary peritoneal cancer with two or more close blood relatives with breast and/or ovarian cancer (with at least one close blood relative with breast cancer prior to age 50);

OR

10. Individuals with a combination of breast cancer with **one** of the following:

    a. Thyroid cancer;

    OR

    b. Sarcoma;

    OR

    c. Adrenocortical cancer;

    OR

    d. Endometrial cancer;

    OR

    e. Pancreatic cancer;

    OR

    f. Brain tumors;

    OR

    g. Gastric cancer;

    OR

    h. Leukemia;

    OR

    i. Lymphoma.

B. **Familial Adenomatous Polyposis (FAP): APC and MUTYH genes (e.g., Colaris AP)**

Procedure:

Genetic testing for mutations in the **Familial Adenomatous** Polyposis (**FAP),** an inherited colorectal cancer syndrome clinically characterized by onset at an early age, hundreds to thousands of colorectal adenomas with increased risk of cancer, allowing at risk individuals to make informed decisions regarding surveillance, management, and prevention strategies.
Colaris AP is a predictive medicine product for risk of hereditary colorectal polyps and cancer. Colaris AP® detects mutations in the APC and MYH genes, which cause adenomatous polyposis syndromes, including familial adenomatous polyposis (FAP), tenuated FAP (AFAP), and MYH -associated polyposis (MAP).

Clinical Indications for Familial Adenomatous Polyposis (FAP) or attenuated familial adenomatous polyposis (AFAP):

There is sufficient evidence to support the use of genetic testing for FAP/ AFAP with any **ONE** of these indications:

1. To confirm the diagnosis of FAP in an affected patient;

OR

2. To provide presymptomatic testing for at -risk relatives (first- or second- or third degree relative) of an affected patient;

OR

3. To confirm the diagnosis of FAP in those with 10 or more adenomas;

OR

4. To provide presymptomatic testing for at -risk relatives (first- or second- or third degree relative) of an affected patient

C. **Hereditary Nonpolyposis colorectal cancer (HNPCC)/Colaris Testing for Lynch Syndrome:**

Procedure:
In families with suspected or clinically diagnosed hereditary nonpolyposis colorectal cancer **(HNPCC) or Lynch syndrome** genetic testing for mutations on one of several mismatch repair(MMR) genes is used to determine whether an individual has an increased risk for colorectal cancer or other HNPCC-associated cancers(endometrial), improving cancer risk assessment in these individuals and families. Testing may also include microsatellite instability (MSI) analysis and/or

immunohistochemical staining of the tumor tissue of an affected family member as an initial screen(s) before germline mutation testing is performed.
COLARIS® testing assesses a person's risk of developing hereditary colorectal cancer and a woman's risk of developing hereditary uterine cancer.
COLARIS^{PLUS} detects disease-causing mutations in the MLH1, MSH2, MSH6, PMS*2*, EPCAM, and MYH genes which are responsible for the majority of Lynch syndrome and MYH-associated polyposis (MAP) cases.
COLARISAP® testing assesses a person's risk of developing hereditary colorectal polyps and cancer. COLARISAP^{PLUS} detects mutations in the APC and MYH genes, which cause adenomatous polyposis colon cancer syndromes, including familial adenomatous polyposis (FAP), attenuated FAP (AFAP), and MYH -associated polyposis (MAP).
PMS2 is associated with cases of the dominantly inherited disorder hereditary nonpolyposis colon cancer (HNPCC) but more clearly associated with a variation of HNPCC known as Turcot syndrome.

Clinical Indications: Must meet ANY of the following 3 criteria for Colaris COLARIS AP and/or MUTYH, APC, MLH1, MSH2, MSH6, PMS2, EPCAM, MYH gene testing (1, 2 or 3):

1. Member should meet **ALL** of the following criteria based on Amsterdam criteria combined I and II (based on **family history**) (NCCN, 2014 for Clinical Definition of Lynch Syndrome (LS):

    a. At least three relatives with CRC or with an HNPCC-associated cancer (colorectal cancer, endometrial cancer, ovarian cancer, cancer of the stomach, small bowel, pancreas, ureter or renal pelvis, biliary tract, brain/CNS, sebaceous gland adenomas or keratocanthomas as seen in Muir-Torre syndrome);

    AND

    b. One member should be a first degree relative of the other two;

    AND

    c. At least two successive generations should be affected;

    AND

    d. At least one member should be diagnosed with Colorectal Cancer or a cancer associated with Lynch syndrome (colorectal cancer, endometrial cancer, ovarian cancer, cancer of the stomach, small bowel, pancreas, ureter or renal pelvis, biliary tract, brain/CNS, sebaceous gland adenomas or keratocanthomas as seen in Muir-Torre syndrome); before age 50;

    OR

2. Member should meet **ANY** of the following criteria based on revised **Bethesda guidelines** (based on **personal history)** (NCCN, 2014) 2014for Clinical Definition of Lynch Syndrome (LS):

   a. Colorectal cancer diagnosed in an individual younger than 50 years;

   OR

   b. Presence of synchronous or metachronous, colorectal or other Lynch-Syndrome related tumor (colorectal cancer, endometrial cancer, ovarian cancer, cancer of the stomach, small bowel, pancreas, ureter or renal pelvis, biliary tract, brain/CNS, sebaceous gland adenomas or keratocanthomas as seen in Muir-Torre syndrome); regardless of age;

   OR

   c. Colorectal cancer with MSI-high (MSI-H) pathologic –associated features diagnosed in an individual younger than 60 years (i.e, presence of tumor infiltrating lymphocytes, Crohn's like lymphocytic reaction, mucinous/signet -ring differentiation, or medullary growth pattern);

   OR

   d. Colorectal cancer or Lynch syndrome-associated tumor (colorectal cancer, endometrial cancer, ovarian cancer, cancer of the stomach, small bowel, pancreas, ureter or renal pelvis, biliary tract, brain/CNS, sebaceous gland adenomas or keratocanthomas as seen in Muir-Torre syndrome); diagnosed in a member AND in at least one first degree relative younger than 50 years;

   OR

   e. Colorectal cancer or Lynch syndrome-associated tumor (colorectal cancer, endometrial cancer, ovarian cancer, cancer of the stomach, small bowel, pancreas, ureter or renal pelvis, biliary tract, brain/CNS, sebaceous gland adenomas or keratocanthomas as seen in Muir-Torre syndrome); diagnosed in a member AND in at least two first or second degree relatives at any age.

   OR

   f. For a member from a family with known high risk syndrome associated with colorectal cancer, with or without known mutation,

   OR

   g. Member with a desmoid tumor

   OR

3. Lynch syndrome testing in patients with at least a 5% risk to carry a mutation using ANY of the following 3 Lynch Syndrome Risk Assessment

models:

a. PREMM 1,2,6: http://premm.dfci.harvard.edu/
b. MMR Predict: http://hnpccpredict.hgu.mrc.ac.uk/
c. MMRPro: https://www4.utsouthwestern.edu/breasthealth/cagene/

D. **KRAS and NRAS Testing**

Procedure:
Recent research has shown that people with a certain change or mutation in the KRAS gene in their tumor **do not benefit from either Erbitux or Vectibix**. Since efficacy of these drugs is confined to patients with Wild Type (WT) KRAS tumors. KRAS status should be considered in selecting patients as candidates for these interventions. This is true whether these medicines are used alone *(*monotherapy*)* or added to chemotherapy.

Clinical Indications. Must meet **ONE** of the following criteria**:**

1. If currently being considered for treatment with Erbitux® (cetuximab) or Vectibix™ (panitumumab) for colorectal cancer;

OR

2. Before beginning Erbitux or Vectibix treatment, either as single medicines or in combination with chemotherapy;

OR

3. When first diagnosed with advanced colon or rectal cancer and are planning a treatment strategy.

OR

1. KRAS and NRAS—All patients with metastaic colorectal Cancer (CRC) should have tumor tissue genotyping for RAS mutations both KRAS and NRAS.

E. **Multiple Endocrine Neoplasia Type 1(MEN1):**

Procedure:
Multiple endocrine neoplasia type 1 (**MEN** 1) is a relatively uncommon inherited disease. Individuals who inherit the gene for MEN 1 have an increased chance of developing overactivity and enlargement of certain endocrine glands. The endocrine glands most commonly affected by MEN 1 are the parathyroid, pancreas, and pituitary glands.

Clinical Indications:

MEN1 or RET gene testing may be indicated when the following are present:

1. Clinical suspicion or family history of multiple endocrine neoplasia syndrome, as indicated by **1 or more** of the following:

    a. Patient with 2 or more endocrine tumors;

    OR

    b. Patient with family history of 2 or more endocrine tumors;

    OR

    c. Patient with "red flag" tumor, as indicated by **1 or more** of the following:

        (1) Medullary carcinoma of thyroid;

        OR

        (2) Pheochromocytoma;

        OR

        (3) Parathyroid carcinoma;

        OR

        (4) Paraganglioma;

    OR

    d. MEN1 testing in patient with **1 or more** of the following:

        (1) Appropriate primary hyperparathyroidism feature, as indicated by **1 or more** of the following:

            (a) Multiglandular hyperparathyroidism;

            OR

            (b) Onset of primary hyperparathyroidism at age 30 years or younger;

            OR

            (c) Relative with primary hyperparathyroidism;

        OR

        (2) Gastrinoma;

        OR

        (3) Multifocal pancreatic endocrine tumors;

        OR

        (4) Relative of patient with known MEN1 mutation

F. **Medullary Thyroid Cancer and Multiple Endocrine Neoplasia Type 2 (MEN2), RET testing:**

Procedure:
Genetic testing for the RET proto-oncogene point mutations for the purposes of assessing multiple endocrine neoplasia type 2 (MEN2) or medullary thyroid cancer risk.

Clinical Indications:
Covered in members who meet **ANY ONE** of the following criteria:

1. Among members of families with defined RET gene mutations;

OR

2. Among members of families known to be affected by inherited medullary thyroid cancer but not previously evaluated for RET mutations;

OR

3. In members with sporadic medullary thyroid cancer.

G. **Molecular and/or gene expression classifiers for molecular markers for the evaluation of thyroid nodules (See clinical indications below for the Thyroid Cancer Mutation Panel, the Afirma Gene Test for Thyroid Cancer, or ThyroSeq)**

1. Thyroid Cancer Mutation Panel (BRAF, RAS, RET/PTC, PAX8/PPAR)

Clinical Indications for molecular diagnostic testing to detect individual mutations or pattern recognition approaches using molecular classifiers:

a. The result of fine needle aspiration sampling of the thyroid nodule is indeterminate.

H. **2**. **Afirma Gene Test for Thyroid Cancer**

Afirma: This test represents a novel Gene Expression Classifier (GEC) that measures the gene expression of 142 genes and applies a multi-dimensional algorithm to classify whether a thyroid nodule with indeterminate or suspicious cytopathology is benign or suspicious. If the test is negative, then the nodule is considered benign and no open biopsy is recommended.

Clinical Indications:
The Afirma test is considered medically necessary unless there is evidence of the lesion being clearly benign or malignant

3. ThyroSeq Panel

Clinical Indications:

a. This test is considered medically necessary when there is a follicular or Hürthle cell neoplasm

OR

b. Atypia of undetermined significance or follicular lesion of undetermined significance

I. **Oncotype DX Genetic Assay:**

Procedure for Oncotype DX for Breast Cancer (81519):
Oncotype DX is a clinically validated, multi-gene assay that provides a quantitative assessment of the likelihood of distant breast cancer recurrence and also assesses the benefit from chemotherapy.

Clinical Indications for Oncotype DX for Breast Cancer:
Reverse transcriptase polymerase chain reaction assay for breast cancer gene expression (Oncotype DX) is indicated when **ALL** of the following are present:

1. Axillary node biopsy is negative for tumor or Tumor is pN0 (node negative) or pN1mi with axillary lymph node micrometastasis less than or equal to 2mm; or with 1-3 positive Axillary Lymph Nodes (ALN) (e.g., Oncotype DX for ductal carcinoma in situ without DCIS recurrence score);

OR

2. Newly diagnosed invasive ductal or invasive lobular carcinoma of breast, stage I or II;

AND

3. The outcome of testing will guide decision making regarding adjuvant chemotherapy;

AND

4. Patient is female;

AND

5. Primary tumor is estrogen receptor-positive.

AND

6. Primary tumor is HER-2 receptor-negative.

J. **TP53 Gene**

Procedure:
Used for BRCA Indications as well as Li-Fraumeni.
Li-Fraumeni syndrome (LGS) is a rare autosomal dominant condition that is characterized by the development of multiple tumors including soft tissue

sarcomas, osteosarcomas, leukemias, brain tumors, adrenocortical malignancies, and early onset breast cancer; 50 percent of carriers develop some form of cancer by age 30; 90 percent do so by age 70. Inherited mutations of P53 in families with Li-Fraumeni syndrome are rare, but when they occur are associated with a high risk of early onset breast cancer.

Clinical Indications:

1.

TP53 gene testing for members with a suspected or known clinical diagnosis of **Li-Fraumeni** syndrome (LFS) or Li-Fraumeni-Like syndrome, or a known family history of a P53 mutation may be indicated.

Testing in members whose medical and/or family history is consistent with **ANY ONE** of these:

a. A relative with a known deleterious TP53 gene mutation;

OR

b. A diagnosis of classic Li-Fraumeni syndrome, defined by **ALL** of the following:

(1) Diagnosis of sarcoma before the age of 45 years;

AND

(2) A parent, child, or full sibling diagnosed with cancer before the age of 45 years;

AND

(3) An additional first- or second-degree relative in the same lineage with cancer diagnosed before age 45 years, or a sarcoma at any age;

OR

c. A diagnosis of Li-Fraumeni-Like syndrome defined by all of the following:

(1) Diagnosis of a childhood tumor or sarcoma, brain tumor, or adrenocortical carcinoma diagnosed before age 45 years;

AND

(2) A first- or second-degree relative with typical Li-Fraumeni syndrome tumor* at any age;

AND

(3) Another first- or second-degree relative with cancer diagnosed before age 60 years;

OR

d. A diagnosis of breast cancer before age 35 years with a negative BRCA1/2 test especially if there is a family history of sarcoma, brain tumor or adrenocortical carcinoma.

OR

2. For member with multiple primary tumors, 2 of which are sarcoma, brain or breast cancer and/or adrenocortical cancer before age 36;

OR

3. Individual with adrenocortical cancer and choroid plexus ca at any age.

Note: Tumors no longer considered to be associated with LFS include gastrointestinal stromal tumors, desmoid tumor, and angiosarcoma (in addition to Ewing's sarcoma).

K. **PTEN Gene**

Procedure:

The PTEN gene belongs to a family of genes called **PTP** (protein tyrosine phosphatases). Changes in the PTEN gene increase the risk of developing breast cancer as part of a rare inherited cancer syndrome called Cowden syndrome. These inherited mutations are thought to account for only a small fraction of all breast and other cancer cases.

Other names for the PTEN gene or gene products include:

- BZS
- MHAM
- MMAC1
- Mutated in multiple advanced cancers 1
- Phosphatase and tensin homolog
- Protein-tyrosine phosphatase PTEN
- PTEN1
- PTEN_HUMAN
- PTEN-MMAC1 protein
- TEP1
- TEP1 phosphatase

Clinical Indications for PTEN: Should meet criteria for either Operational Diagnosis in member (1) or Operational diagnosis for family where one member is diagnostic for Cowden Syndrome (2). Definitions listed below for **Pathognomic, Major** and **Minor. (check exceptions)**

1. **Operational Diagnosis in a Member:** Should meet **ONE** of the following:

   a. Mucocutaneous lesions alone with **ONE** of the following:

      (1) There are 6 or more facial papules, of which 3 or more must be trichilemmoma;

      OR

      (2) Cutaneous facial papules and oral mucosal papillomatosis;

      OR

      (3) Oral mucosal papillomatosis and acral keratoses;

      OR

      (4) Palmoplantar keratoses, 6 or more;

      OR

   b. Two or more major criteria but one must include macrocephaly or Lhermitte-Duclos disease (LDD);

      OR

   C 1 major and 3 minor criteria;

      OR

   d. 4 minor criteria.

      OR

2. **Operational diagnosis in a family where one person is diagnostic for Cowden syndrome:** Should meet **ONE** of the following:

   a. Any pathognomonic criterion;

      OR

   b. Any one major criterion with or without minor criteria;

      OR

   c. Two minor criteria;

      OR

   d. History of Bannayan-Riley-Ruvalcaba syndrome.

Pathognomic Criteria, Major Criteria and **Minor Criteria** definitions are listed below:

1. **Pathognomonic criteria:**

a. Mucocutaneous lesions:

(1) Trichilemmomas, facial
(2) Acral keratoses
(3) Papillomatous lesions
(4) Mucosal lesions

b. Adult Lhermitte-Duclos disease (LDD)(cerebellar tumors)

2. **Major criteria:**

a. Breast carcinoma
b. Follicular thyroid cancer
c. Macrocephaly (eg, ⩾97th percentile) (megalocephaly)
d. Endometrial cancer

3. **Minor criteria:**

a. Other thyroid lesions (eg, goiter, adenomas)
b. Mental retardation (ie, IQ ⩽75)
c. GI hamartomas
d. Fibrocystic disease of the breast
e. Lipomas
f. Fibromas
g. GU tumors (especially renal cell carcinoma), GU structural manifestations
h. Uterine fibroids or malformation
i. Colon cancer,
j. Esophageal glycogenic acanthosis,
k. Papillary or follicular variant of papillary thyroid cancer,
l. Testicular lipomatosis,
m. Vascular anomalies (including multiple intracranial developmental venous anomalies*).*

L. **MYH-associated Polyposis (MAP)**

Procedure:
MYH-associated polyposis (MAP) is a hereditary condition. People with MAP tend to develop multiple adenomatous colon polyps during their lifetime and will have an increased risk of colorectal cancer.

Clinical Indications for MYH-associated Polyposis (MAP):

Genetic testing for MYH-associated polyposis (MAP) is appropriate when #1 OR #2 of the following criteria is met:

1. Members with greater than 10 adenomatous colonic polyps; or greater than 15 cumulative adenomas in 10 years and have either:

    a. Who have a recessive inheritance (family history positive only for siblings);

    OR

    b. Who have undergone testing for adenomatous polyposis coli (APC) with negative results;

    OR

2. The asymptomatic siblings of individuals with known MYH-associated polyposis (MAP) and/or Colon Cancer.

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M. **BCR-ABL mutation analysis**

Procedure:

BCR-ABL mutation analysis has been proposed as diagnostic test to detect secondary mutations in the ABL portion of the BCR-ABL oncogene that causes chronic myelogenous leukemia (CML). Standard treatment of newly diagnosed Philadelphia chromosome positive (Ph+) CML is typically an agent from the class of drugs called protein tyrosine kinase inhibitors. This assay will detect the BCR-ABL and T315I mutation

Clinical Indications for BCR-ABL mutation analysis:

BCR-ABL and T315-I mutation analysis is covered for the diagnosis and management of members with Philadelphia chromosome positive (Ph+) Chronic Myelogenous Leukemia (CML), or acute lymphoblastic leukemia (ALL),

OR

As part of the workup for myelodysplastic syndrome (MDS) myeloproliferative neoplasm (MPN) that includes persistent leukocytosis, thrombocytosis, or cytopenias

OR

BCR-ABL mutation other than T315-I for patients considered for treatment with dasatinib (Sprycel®) or nilotinib (Tasigna)

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N. **Pathfinder TG**

Procedure:

The patented PathFinderTG® test is a molecular test to be used adjunctively in cases in which a definitive pathologic diagnosis cannot be rendered on a tissue or cytology specimen, either due to inadequate specimen or equivocal histologic or cytologic findings.

Clinical Indications for Pathfinder TG:

To be used adjunctively in cases in which a definitive pathologic diagnosis cannot be rendered on a tissue or cytology specimen, either due to inadequate specimen or equivocal histologic or cytologic findings.

O. **Genetic testing for susceptibility to malignant diseases not listed above** is covered when **ALL** of the following criteria are met:

1. The genetic disorder is associated with a potentially significant cancer or has a lethal natural history;

AND

2. The risk of the type of cancer from the genetic disorder cannot be identified through biochemical or other testing;

AND

3. Specific mutation(s) have been established in the scientific literature to be reliably associated with the disease;

AND

4. The results of the genetic test may impact the medical management of the individual;

AND

5. The use of the genetic test in managing therapy decisions will likely result in an improvement in health outcomes;

AND

6. Testing is accompanied by genetic counseling.

P. **Von Hippel-Lindau syndrome (VHL)**

Clinical Indications when **ALL** of the following are met:

1. The member displays clinical features, or is at direct risk of inheriting the mutation in question (pre-symptomatic);

AND

2. The result of the test will directly impact the treatment being delivered to the member;

AND

3. After history, physical examination, pedigree analysis, genetic counseling, and completion of conventional diagnostic studies, a definitive diagnosis remains uncertain.

Q. **CBFB/MHY 11(acute myeloid leukemia)**
To diagnose acute myelomonocytic leukemia (AML) with abnormal eosinophils.

Clinical Indications for acute myeloid leukemia (CBFB/MHY 11)
Covered without criteria.

R. **KIT Test (9C Kit/V Kit Hardy Zuckerman Oncogene), (81272, 81273)**
Gastrointestinal Stromal Tumor (GIST) is a mesenchymal neoplasm that arises primarily in the gut wall and is typically characterized by the expression of the receptor tyrosine kinase KIT (CD117).

Clinical Indications: covered without criteria.

S. **BRAF**
More than 30 mutations of the BRAF gene associated with human cancers have been identified.

Clinical Indications: covered without criteria.

T. **FLT3 (fms-related tyrosine kinase 3)/ CEBPA/ NPM1**
(This test may also be ordered as a soft FLDV)

The **FLT3** gene is one of the most frequently mutated genes in acute myeloid leukemia.
It has been shown that mutation of **CEBPA** has been linked to good outcome in both adult and pediatric acute myeloid leukemia patients.
Mutations in nucleophosmin **NPM1** are the most frequent acquired molecular abnormalities in acute myeloid leukemia (AML).

Clinical Indications:

Any member that is diagnosed with acute myeloid leukemia.

U. **STK11** Germline mutations in the STK11 gene are associated with Peutz-Jeghers syndrome (PJS), an autosomal dominant disorder in which affected individuals develop hamartomatous polyps of the gastrointestinal tract, pigmented macules on the lips and buccal mucosa, and a variety of gastrointestinal malignancies.

Clinical Indications:

For any member with harmatomatous polyps AND breast cancer with hyperpigmented macules of the lip and oral mucosa.

V. **CDH1-** There is an association between mutations in the cadherin (CDH1) gene and invasive lobular breast cancers. Lobular breast cancers have been observed to occur in 20 to 54 percent of women from families with hereditary diffuse gastric cancer who carry germline mutations in the CDH1 gene.

Clinical Indications for CDH1 Testing:
For individuals with **ANY** of the following (1-4):

1. ≥2 cases of diffuse gastric cancer in first degree relatives, with at least one diagnosed at <50 years,

OR

2. ≥3 cases of documented diffuse cancer in first or second degree relatives independent of age of onset;

OR

3. Personal history of diffuse gastric cancer diagnosed at <40 years regardless of family history;

OR

4. A personal or family history of diffuse gastric cancer **AND** lobular breast cancer with one diagnosed at <50 years

W. **JAK2 (including exons 12 and 13 or JAK2^{V617F}), Myeloproliferative Leukemia gene (MPL), and Calrecticulin Mutation Analysis (CALR)**

Clinical Indications:

1. JAK2^{V617F}, MPL, and/or CALR for initial testing of clinical and laboratory features suggestive of polycythemia vera;

OR

2. Clinical, laboratory, and/or bone marrow features suggestive of essential thrombocytosis;

OR

3. Clinical, laboratory, and/or bone marrow features suggestive of primary myelofibrosis (chronic leukemia) or leukocytosis.

OR

4. JAK2 tyrosine kinase mutation (e.g., in exon 12) testing when JAK2^{V617F} testing is negative

X. **Immuno Globulin Heavy Chain (IGH)**

The **immunoglobulin heavy chain** (IgH) is the large polypeptide subunit of an antibody (immunoglobulin).

Clinical Indications:

For the diagnosis and management of patients with any one below:

2. Multiple Myeloma,

OR

2. Status post Bone Marrow /Stem Cell Transplantation,

OR

3. Acute myeloid leukemia (AML), also known as acute myelogenous leukemia or acute nonlymphocytic leukemia (AML .or ANLL)

Y. **PML/RAR Alpha (Promyelocytic Leukemia--81315, 81316)**
Acute promyelocytic leukemia is a subtype of acute myelogenous leukemia (AML), a cancer of the blood and bone marrow. In APL, there is an abnormal accumulation of immature granulocytes called promyelocytes. The disease is characterized by a chromosomal translocation involving the retinoic acid receptor alpha (*RARα* or *RARA*) gene and is unique from other forms of AML in its responsiveness to all trans retinoic acid (ATRA) therapy.

Clinical Indications:
For Relapse monitoring: Check PML-RAR alpha PCR cytogenetics, at the end of consolidation treatment, and monitor PML-RAR alpha PCR every 3months for 2years; the assay can be performed every 3-6mo for the next 3 years; if a positive test result is obtained, repeat testing from bone marrow in 2-4wks, or for high risk members >60y/o or who had interruptions during consolidation or not able to tolerate maintenance.

Z. **Retinoblastoma (RB1)** Retinoblastoma is the most common intraocular cancer in children. It is a malignant tumor of the retina that occurs in young children, usually before the age of 5 years. Approximately 40% to 50% of retinoblastomas are classified as hereditary and are caused by mutations in the RB1 tumor suppressor gene, that's inherited in an autosomal dominant manner. Hereditary retinoblastoma is the result of a germline mutation followed by a somatic mutation in the RB1 gene. Sporadic (nonhereditary) retinoblastoma results from somatic mutations in both alleles of the RB1 gene.

Clinical Indications for RB1 Testing:

Diagnosis or screening for hereditary retinoblastoma, as indicated by **1 or more** of the following:

1. First-degree relative of patient with known RB1 mutation
2. Patient with retinoblastoma, with or without family history of retinoblastoma

AA. **Calreticulin Exon 9 (CALR, (81219))**

Clinical Indications: covered without criteria or Preauthorization.

BB. **EGFR for patients with non-small cell lung cancer**

Clinical Indications:

Analysis of mutations of epidermal growth factor receptor (EGFR) [for example, Therascreen] is considered medically necessary as a technique to predict treatment response for individuals with non-small cell, non-squamous cell lung cancer undergoing treatment with EGFR tyrosine kinase inhibitor therapy (for example, erlotinib [Tarceva], gefitinib [Iressa], or afatinib [Gilotrif]).

CC. **ALK gene**

Clinical Indications:
ALK gene is approved for members with lung cancer or for consideration of treatment of any drug which requires ALK gene testing as part of FDA indication.

DD. **Juvenile polyposis syndrome (JPS SMAD4 and BMPR1A)**

Clinical Indications for Juvenile polyposis syndrome
Individuals with five or more juvenile polyps in the colorectum or any juvenile polyps in other parts of the GI tract should undergo genetic evaluation for possible JPS which includes testing for SMAD4 and BMPR1A mutations.

EE. **Bladder Tumor Marker Testing**
Bladder Tumor Marker Testing (e.g. UroVysion, bladder tumor antigen test, nuclear matrix protein 22 testing (NMP-22), or fibrin/fibrinogen degradation products test)

Clinical Indications:
Considered medically necessary for any of the following conditions:

1. Follow-up of treatment for bladder cancer;

OR

2. Monitoring for eradication of bladder cancer;

OR

3. Recurrences after eradication.

FF. **MYD88 Gene**

Clinical Indications:
Bone marrow testing for MYD88 gene mutation is covered for members being evaluated for Waldenström Macroglobulinemia or Lymphoplasmacytic Lymphoma.

GG. **Hereditary Paraganglioma-Pheochromocytoma (PGL/PCC) Syndrome**

Clinical Indications:

1. The member has a first-degree relative with a known SDHB, SDHC, SDHD, or TMEM127 mutation

FOR

2. A member with paraganglioma or pheochromocytoma characterized by **1 or more** of the following:
   a. Malignant tumor
   b. Previous head and neck paraganglioma (e.g., carotid body tumor)
   c. Recurrent tumor
   d. Tumor diagnosed before age 45 years
   e. Two or more metachronus (diagnosed at different times) tumors
   f. Two or more synchronous (simultaneous) tumors

OR

3. A member with pheochromocytoma without clinical findings suggestive of neurofibromatosis type 1, von Hippel-Lindau syndrome, or multiple endocrine neoplasia type 2.

HH. **Endopredict Panel Testing**

Clinical Indications:F

1. Individual has already had the oncotype Dx and is considering additional chemo and/or hormonal therapy where the results would help informed treatment

II. **Percepta Bronchial Genomic Classifier** for Optima Medicare only and **ALL** of the following conditions are met:

1. Individual is a current or former smokers

2. Individual is age 21 or greater

3. Individual has a physician-assessed low or intermediate pretest risk of malignancy based upon 1 of the following:

a) Individual is low risk (<10%): Nodules <10mm with <10 pack/year smoking history

b) Individual is intermediate risk (10-60%): Nodules 10-30mm with 10 to 60 pack/year smoking history

4. Individual has had a bronchoscopy that is non-diagnostic (actionable benign or malignant diagnosis cannot be reached)

5. The results from the Percepta Bronchial Genomic Classifier test will be utilized to determine whether computerized tomography (CT) surveillance is appropriate in lieu of further invasive biopsies or surgical procedures as outlined below:

Pre-Test Risk:	Post-Test Risk:	Post-Test Diagnostic Strategy:
Intermediate	Intermediate	Proceed to further work up
Intermediate	Low Risk	CT surveillance
Low Risk	Low Risk	CT surveillance
Low Risk	Very Low Risk	CT surveillance

6. The test is ordered by physician certified in Percepta Certification and Training Registry (CTR)
7. The individual is monitored for malignancy (suggested monitoring includes serial computerized tomography (CT) scans at 3 to 6, 9 to 12, and 18 to 24 months, using thin sections and non-contrast, low-dose techniques)
8. The physician will report outcomes in all risk groups including those monitored initially and those who undergo immediate intervention
9. Clinical management is consistent with the post-test diagnostic strategy described above in ≥80% of tested individuals
10. The physician intends to act upon the test result

JJ. FoundationOne CDx for Optima Medicare only and ALL of the following conditions are met:

1. Next Generation Sequencing (NGS) for Patients with Somatic (Acquired) and Germline (Inherited) Cancer may be covered for **1 or more** of the following:
    a. Diagnostic testing of somatic (acquired) cancer when **ALL** of the following criteria are met
        i. Patient is appropriate for testing as indicated by **ALL** of the following:

1. Patient has recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer

AND

2. Patient has not been previously tested with same test using next generation sequencing (NGS) for same cancer genetic content

AND

3. Patient has decided to seek further cancer treatment (eg, therapeutic chemotherapy)

OR

b. Diagnostic testing of germline (inherited) cancer when **ALL** of the following criteria are met:
    i. Patient is appropriate for testing as indicated by **ALL** of the following:
        1. Patient has ovarian or breast cancer.

        AND

        2. Patient has clinical indication for germline (inherited) testing for hereditary breast or ovarian cancer.

        AND

        3. Patient has risk factor for germline (inherited) breast or ovarian cancer.

        AND

        4. Patient has not been previously tested with same germline test using next generation sequencing (NGS) for same germline genetic content.

KK. Bone Marrow Targeted Genomic Sequencing by Trusight for Acute Myeloid Leukemia for Optima Medicare only and **ALL** of the following conditions are met:

1. MolDX: Next-Generation Sequencing Lab-Developed Tests for Myeloid Malignancies and Suspected Myeloid Malignancies may be covered for ALL of the following:
    a. Test specifically indicated for patient known to have myeloid malignancy at time of testing

    AND

    b. Patient with appropriate condition, as indicated by 1 or more of the following:
        i. Acute myeloid leukemia

        OR

        ii. Myelodysplastic syndrome

OR

iii. Myeloproliferative neoplasms

OR

iv. Suspected, but not confirmed, diagnosis of myeloid malignancy and ALL of the following:

1. Undefined cytopenia for greater than 4 months

AND

2. Other possible causes have been reasonably excluded.

c. Assay performed includes at least minimum genes and positions indicated for its intended use:

d. Testing performed on **1 or more** of the following:

i. Bone marrow biopsy

AND/OR

ii. Bone marrow aspirate

AND/OR

iii. Bone marrow clot

AND/OR

iv. Peripheral blood sample

AND/OR

v. Extramedullary site suspected of harboring myeloid malignancy

LL. Mammaprint is covered for Optima Medicare upon request. Mammaprint for Optima Commercial or Optima Virginia Medicaid Plans for individuals with **all of the following**:

1. Breast tumor is anatomic stage 1 or stage 2
2. Histologic type is ductal, lobular, mixed (ductal/lobular), or metaplastic
3. Node negative OR 1-3 positive node breast cancer
4. Breast tumor is estrogen receptor positive and/or progesterone receptor positive
5. Breast tumor is HER2-negative
6. Patient is a candidate for chemotherapy (i.e., chemotherapy not precluded due to other factors)
7. Adjuvant chemotherapy is being considered and this testing is being ordered to assess recurrence risk to guide decision making as to whether or not adjuvant chemotherapy will be utilized.

MM. Oncotype DX Breast Cancer Assay with DCIS recurrence score is covered only when **all of the following** clinical conditions are met:

1. Individual has Optima Medicare Plan

2. Pathology (excisional or core biopsy) reveals ductal carcinoma in situ of the breast (no pathological evidence of invasive disease)
3. FFPE specimen with at least 0.5 mm of DCIS length
4. Individual is a candidate for and is considering breast conserving surgery alone as well as breast conserving surgery combined with adjuvant radiation therapy
5. Test result will be used to determine treatment choice between surgery alone vs. surgery with radiation therapy
6. Individual has not received and is not planning on receiving a mastectomy

NN. Decipher® may be covered for **one or more of the** following:

1. Individual has Optima Medicare Plan with **ALL of the** following:
    a. Individual has localized or biochemically recurrent adenocarcinoma of prostate (ie, no clinical evidence of metastasis).
    b. Individual has estimated life expectancy of greater than or equal to 10 years.
    c. Individual is candidate for and considering (or being considered for) **1 or more** of the following:
        I. Conservative management, yet would be eligible for definitive therapy (radical prostatectomy, radiation, or brachytherapy)
        II. Radiation therapy, yet would be eligible for addition of brachytherapy boost
        III. Radiation therapy, yet would be eligible for addition of short-term androgen deprivation therapy (ADT)
        IV. Radiation therapy with short-term ADT, yet would be eligible for use of long-term ADT
        V. Radiation with standard ADT, yet would be eligible for systemic therapy intensification using next-generation androgen signaling inhibitors or chemotherapy
        VI. Observation post-prostatectomy, yet would be eligible for addition of post-operative adjuvant radiotherapy
        VII. Salvage radiotherapy post-prostatectomy, yet would be eligible for addition of ADT
    d. Assay performed on formalin-fixed paraffin embedded (FFPE) prostate biopsy tissue with at least 0.5 mm of linear tumor diameter or FFPE tissue from prostate resection specimen.
    e. Result will be used to determine treatment according to established practice guidelines.
    f. Individual has not received pelvic radiation or ADT prior to biopsy or prostate resection specimen.
    g. Individual will be monitored for disease progression according to established standards of care.

2. Individual has Optima Commercial or Optima Virginia Medicaid Plan with **ALL of the** following criteria:
    a. Individual has not had previous tumor-based assay (Prolaris®, Oncotype DX®, Promark®, OR Decipher®) to guide management of prostate cancer in individual's lifetime
    b. Individual is a candidate for definitive therapy or active surveillance
    c. life expectancy greater than 10 years
    d. PSA persistence after radical prostatectomy
    e. PSA recurrence after radical prostatectomy
    f. Individual must fall into **one of the** following stages:
        I. Low Risk
        II. Favorable Intermediate Risk
        III. Unfavorable intermediate
        IV. High-risk

OO. Oncotype DX® for Prostate may be covered for **one or more of the** following:
1. Individual has Optima Medicare Plan with **ALL of the** following:
    a. Individual has localized or biochemically recurrent adenocarcinoma of prostate (ie, no clinical evidence of metastasis).
    b. Individual has estimated life expectancy of greater than or equal to 10 years.
    c. Individual is candidate for and considering (or being considered for) **1 or more** of the following:
        I. Conservative management, yet would be eligible for definitive therapy (radical prostatectomy, radiation, or brachytherapy)
        II. Radiation therapy, yet would be eligible for addition of brachytherapy boost
        III. Radiation therapy, yet would be eligible for addition of short-term androgen deprivation therapy (ADT)
        IV. Radiation therapy with short-term ADT, yet would be eligible for use of long-term ADT
        V. Radiation with standard ADT, yet would be eligible for systemic therapy intensification using next-generation androgen signaling inhibitors or chemotherapy
        VI. Observation post-prostatectomy, yet would be eligible for addition of post-operative adjuvant radiotherapy
        VII. Salvage radiotherapy post-prostatectomy, yet would be eligible for addition of ADT

d. Assay performed on formalin-fixed paraffin embedded (FFPE) prostate biopsy tissue with at least 0.5 mm of linear tumor diameter or FFPE tissue from prostate resection specimen.
e. Result will be used to determine treatment according to established practice guidelines.
f. Individual has not received pelvic radiation or ADT prior to biopsy or prostate resection specimen.
g. Individual will be monitored for disease progression according to established standards of care.

2. Individual has Optima Commercial or Optima Virginia Medicaid Plan with **ALL of the** following criteria:
    a. Individual has not had previous tumor-based assay (Prolaris®, Oncotype DX®, Promark®, OR Decipher®) to guide management of prostate cancer in individual's lifetime
    b. Individual is a candidate for definitive therapy or active surveillance
    c. life expectancy of greater than 10 years
    d. Individual must fall into one of the following stages:
        I. Very Low Risk
        II. Low Risk
        III. Favorable Intermediate Risk

PP. Prolaris® may be covered for **one or more of the** following:

1. Individual has Optima Medicare Plan with **ALL of the** following:
    a. Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement)
    b. Formalin fixed paraffin-embedded (FFPE) prostate biopsy specimen with at least 0.5 mm of cancer length
    c. Individual stage as indicated by **1 or more** of the following:
        I. Very Low-Risk Disease as indicated by **ALL of the** following:
            a. T1c ≤ 6
            b. Gleason Score ≤ 6
            c. PSA ≤ 10 ng/mL
            d. Less than 3 prostate cores with tumor
            e. Less than or equal to 50% tumor in any core
            f. PSA density of < 0.15 ng/mL/g)
            g. Test is ordered by physician certified in Myriad Prolaris™ Certification and Training Registry (CTR)
        II. Low-Risk Disease with **ALL of the** following:
            a. T1-T2a ≤ 6
            b. Gleason Score ≤ 6
            c. PSA ≤ 10 ng/mL
            d. Test is ordered by physician certified in Myriad Prolaris™ Certification and Training Registry (CTR)
        III. Favorable Intermediate Risk Disease indicated by **ALL of the** following:

a. Predominant Gleason grade 3 (ie, Gleason score 3+4 = 7)
b. Percentage of positive cores < 50%
c. No more than 1 NCCN intermediate-risk factor (NCCN intermediate-risk factors include T2b to T2c, Gleason score 7, and PSA 10 to 20 ng/mL)

d. Individual has estimated life expectancy of greater than or equal to 10 years.
e. Individual is candidate for and is considering conservative therapy and yet would be eligible for definitive therapy (radical prostatectomy, radiation therapy, or brachytherapy).
f. Result will be used to determine treatment between definitive therapy and conservative management.
g. Individual has not received pelvic radiation or androgen deprivation therapy prior to biopsy.
h. Individual is monitored for disease progression according to established standard of care.

2. Individual has Optima Commercial or Optima Virginia Medicaid Plan with **ALL of the** following criteria:
    a. Individual has not had previous tumor-based assay (Prolaris®, Oncotype DX®, Promark®, OR Decipher®) to guide management of prostate cancer in individual's lifetime
    b. Individual is a candidate for definitive therapy or active surveillance
    c. life expectancy of greater than 10 years
    d. Individual must fall into one of the following stages:
        I. Low Risk
        II. Favorable Intermediate Risk
        III. Unfavorable intermediate
        IV. High-risk

QQ. ProMark® Risk Score may be covered for **one or more of the** following:

1. Optima Medicare Plan with ALL of the following:
    a. Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement)
    b. Individual stage as indicated by 1 or more of the following:
        I. Very Low-Risk Disease as indicated by ALL of the following:
            a. T1c ≤ 6
            b. Gleason Score ≤ 6
            c. PSA ≤ 10 ng/mL
            d. Less than 3 prostate cores with tumor
            e. Less than or equal to 50% cancer in any core
            f. PSA density of < 0.15 ng/mL/g)
        II. Low-Risk Disease with ALL of the following:

a. T1-T2a ≤ 6
b. Gleason Score ≤ 6
c. PSA ≤ 10 ng/mL

c. Individual has estimated life expectancy of greater than or equal to 10 years.
d. Individual is candidate for and is considering conservative therapy and yet would be eligible for definitive therapy (radical prostatectomy, radiation therapy, or brachytherapy).
e. Individual has not received pelvic radiation or androgen deprivation therapy prior to biopsy.
f. Test is ordered by physician certified in Metamark Genetics Certification and Training Registry (CTR).
g. Individual is monitored for disease progression according to established standard of care.

2. Individual has Optima Commercial or Optima Virginia Medicaid Plan with **ALL of the** following criteria:
    a. Individual has not had previous tumor-based assay (Prolaris®, Oncotype DX®, Promark®, OR Decipher®) to guide management of prostate cancer in individual's lifetime
    b. Individual is a candidate for definitive therapy or active surveillance
    c. life expectancy of greater than 10 years
    d. Individual must fall into one of the following stages:
        IV. Low Risk
        V. Favorable Intermediate Risk

RR. ExoDX Prostate (EPI, ExosomeDx Prostate, IntelliScore) is considered medically necessary once in an individual's lifetime with **1 or more of the** following criteria:
1. Individual with PSA >3.0 ng/mL with or without previous benign prostate biopsy
2. Individual with Digital rectal exam suspicious for cancer

SS. DecisionDx- Uveal Melanoma (UM) is covered for individual with all of the following:
1. Individual has Optima Medicare plan
2. Individual has confirmed diagnosis of uveal melanoma
3. Individual has no evidence of metastatic disease

TT. Signatera (liquid biopsy minimal residual disease) testing is considered medically necessary for all of the following:
1. Individual previously diagnosed with Colorectal cancer

UU. CSF3R gene is covered for individual with all of the following:

1. Individual has Optima Medicare Plan:

   The following must be present for coverage eligibility:

   a. For tests indicated in patients whom are known to have a MYELOID malignancy at the time of testing, NCD 90.2 applies.
   b. The patient has a diagnosis of AML, MDS, or MPN unless classified as refractory and/or metastatic cancers and fulfil the NCD 90.2 criteria.
   c. The test has satisfactorily completed a TA by MolDX® for the stated indications of the test.
   d. The assay performed includes at least the minimum genes and positions indicated for its intended use, as described in an associated coverage Article or found in the TA forms.
   e. For patients that do not have a diagnosis of a MYELOID malignancy, where one is suspected, the patient must have an undefined cytopenia for greater than 4 months, when other possible causes have been reasonably excluded.
   f. Testing may be performed on bone marrow biopsies, bone marrow aspirates, bone marrow clots, peripheral blood samples, or extramedullary sites suspected of harboring a MYELOID malignancy.

   The test in question will be non-covered if:

   a. Another NGS test was performed on the same surgical specimen/ blood draw (specimen obtained on the same date of service).
   b. Testing falls within scope of NCD 90.2 and has been tested with the same test for the same genetic content.

2. Individual has Optima Commercial or Optima Virginia Medicaid Plan:

   The following must be present for coverage eligibility:

   a. The following must be present for coverage eligibility:
   b. For tests that are specifically indicated in patients who are known to have a MYELOID malignancy at the time of testing, NCD 90.2 applies.
   c. The patient has a diagnosis of AML, MDS, or MPN. AML, MDS, and MPN are herein classified as refractory and/or metastatic cancers and fulfil the NCD 90.2 criteria.
   d. The test has satisfactorily completed a TA by MolDX® for the stated indications of the test.
   e. The assay performed includes at least the minimum genes and positions indicated for its intended use, as described in an associated coverage Article or found in the TA forms.
   f. For patients that do not have a diagnosis of a MYELOID malignancy, where one is suspected, the patient must have an undefined cytopenia for greater than 4 months; other possible causes have been reasonably excluded.

g. Testing is performed on bone marrow biopsies, bone marrow aspirates, bone marrow clots, peripheral blood samples, or extramedullary sites suspected of harboring a MYELOID malignancy.

The test in question will be non-covered if:

a. A TA has not been satisfactorily completed by MolDX®. For tests that are currently covered but a TA submission has not been made, providers must submit completed TA materials by February 10th, 2020 or coverage will be denied.
b. Another NGS test was performed on the same surgical specimen/ blood draw (specimen obtained on the same date of service).
c. Testing falls within scope of NCD 90.2 and has been tested with the same test for the same genetic content.

VV. DermTech Pigmented Lesion Assay (PLA) meets criteria for all of the following:

- Individual has Optima Medicare
- Diagnosis of melanoma is being considered for pigmented skin lesion.
- The pigmented lesion must meet **all of the** following characteristics:
  - The lesion must meet **1 or more** of the following ABCDE criteria:
    - Asymmetry
    - Border
    - Color
    - Diameter
    - Evolving
  - Primary melanocytic skin lesions between 5mm and 19mm
  - Lesions where the skin is intact (i.e., non-ulcerated or non-bleeding lesions)
  - Lesions that do not contain a scar or were previously biopsied
  - Lesions not located in areas of psoriasis, eczema or similar skin conditions
  - Lesions not already clinically diagnosed as melanoma, or for which the clinical suspicion is sufficiently high that the treating clinician believes melanoma is a more likely diagnosis than not
  - Lesions in areas other than palms of hands, soles of feet, nails, mucous membranes and hair covered areas that cannot be trimmed
- The ordering clinician must also have a plan at the time of ordering the test to continue to monitor the skin lesion for changes if the test is negative.
- The record must also contain a photograph of the lesion at the time that the PLA is ordered to allow for appropriate evaluation in subsequent follow-up.
- The ordering physician must clearly document the lesion site on the patient's body.
- The test may not be ordered for the same lesion a second time.

WW. **ClonoSEQ** testing is considered medically necessary for individuals with 1 or more of the following:

- acute lymphocytic leukemia (ALL)
- multiple myeloma (MM)
- chronic lymphoblastic leukemia (CLL)

XX. Breast Cancer Index (BCI) testing is considered medically necessary to assess the risk for recurrence in an individual when all of the following criteria are met:

- Individual has undergone surgery and/or full pathological staging prior to testing
- There is no evidence of distant metastatic breast cancer
- Breast cancer is nonmetastatic (node negative) or with 1-3 involved ipsilateral axillary lymph nodes
- Breast tumor is estrogen receptor and/or progesterone receptor positive
- Breast tumor is HER2 receptor negative
- Postmenopausal or 50 years of age
- Patient is a candidate for chemotherapy or endocrine therapy
- Adjuvant chemotherapy is being considered and this testing is being ordered to assess recurrence risk to guide decision making as to whether or not adjuvant chemotherapy will be utilized
- No more than one predictive Gene Expression Test for the same breast tumor has been performed

YY. PGDx, Genomics solid tumor gene panel is considered medically necessary for **ALL** of the following:
- Individual has Optima Medicare Plan
- Testing meets National Coverage Determination 90.2, as indicated by **ALL** of the following:
    - Individual diagnosed with **1 or more** of the following:
        - Recurrent cancer
        - Relapsed cancer
        - Refractory cancer
        - Metastatic cancer
        - Advanced cancer (stage III or IV)
    - Individual not previously tested by same test for same genetic content
    - Individual seeking further treatment
- Test has satisfactorily completed technical assessment by MolDX® for stated indications of test
- Assay performed includes **ALL** of the following:
    - At least minimum genes and genomic positions required for identification of clinically relevant FDA-approved therapies
    - Companion diagnostic biomarker as well as other biomarkers known to be necessary for clinical decision making for its intended use that can be reasonably detected by test

ZZ. BDX-XL2 may be covered if ALL of the following are met:
- Individual has Optima Medicare
- Individual is at least 40 years of age

- Individual has lung nodule of diameter 8 to 30 mm
- Pre-test risk of cancer, as determined by Mayo risk prediction algorithm, is 50% or less

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CPT/HCPCS:

0005U	Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score
0080U	Oncology (lung), mass spectrometric analysis of galectin-3-binding protein and scavenger receptor cysteine-rich type 1 protein M130, with five clinical risk factors (age, smoking status, nodule diameter, nodule-spiculation status and nodule location), utilizing plasma, algorithm reported as a categorical probability of malignancy
0288U	Oncology (lung), mRNA, quantitative PCR analysis of 11 genes (BAG1, BRCA1, CDC6, CDK2AP1, ERBB3, FUT3, IL11, LCK, RND3, SH3BGR, WNT3A) and 3 reference genes (ESD, TBP, YAP1), formalin-fixed paraffin-embedded (FFPE) tumor tissue, algorithmic interpretation reported as a recurrence risk score
0037U	Targeted genomic sequence analysis, solid organ neoplasm, DNA analysis of 324 genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
0045U	Oncology (breast ductal carcinoma in situ), mrna, gene expression profiling by real-time rt-pcr of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score
0047U	Oncology (prostate), mRNA, gene expression profiling by real-time RT-PCR of 17 genes (12 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a risk score
0048U	Oncology (solid organ neoplasia), DNA, targeted sequencing of protein-coding exons of 468 cancer-associated genes, including interrogation for somatic mutations and microsatellite instability, matched with normal specimens, utilizing formalin-fixed paraffin-embedded tumor tissue, report of clinically significant mutation(s)
0050U	Targeted genomic sequence analysis panel, acute myelogenous leukemia, DNA analysis, 194 genes, interrogation for sequence variants, copy number variants or rearrangements

0089U	Oncology (melanoma), gene expression profiling by RTqPCR, PRAME and LINC00518, superficial collection using adhesive patch(es)
0171U	Targeted genomic sequence analysis panel, acute myeloid leukemia, myelodysplastic syndrome, and myeloproliferative neoplasms, DNA analysis, 23 genes, interrogation for sequence variants, rearrangements and minimal residual disease, reported as presence/absence
0211U	Oncology (pan-tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded tissue, interpretative report for single nucleotide variants, copy number alterations, tumor mutational burden, and microsatellite instability, with therapy association
0239U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free DNA, analysis of 311 or more genes, interrogation for sequence variants, including substitutions, insertions, deletions, select rearrangements, and copy number
0242U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 55-74 genes, interrogation for sequence variants, gene copy number amplifications, and gene rearrangements
0244U	Oncology (solid organ), DNA, comprehensive genomic profiling, 257 genes, interrogation for single-nucleotide variants, insertions/deletions, copy number alterations, gene rearrangements, tumor-mutational burden and microsatellite instability, utilizing formalin-fixed paraffin-embedded tumor tissue
0250U	Oncology (solid organ neoplasm), targeted genomic sequence DNA analysis of 505 genes, interrogation for somatic alterations (SNVs [single nucleotide variant], small insertions and deletions, one amplification, and four translocations), microsatellite instability and tumor-mutation burden
0261U	Oncology (colorectal cancer), image analysis with artificial intelligence assessment of 4 histologic and immunohistochemical features (CD3 and CD8 within tumor-stroma border and tumor core), tissue, reported as immune response and recurrence-risk
0317U	Oncology (lung cancer), four-probe FISH (3q29, 3p22.1, 10q22.3, 10cen) assay, whole blood, predictive algorithm generated evaluation reported as decreased or increased risk for lung cancer
0326U	Targeted genomic sequence analysis panel, solid organ neoplasm, cell-free circulating DNA analysis of 83 or more genes, interrogation for sequence variants, gene

	copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden
0329U	Oncology (neoplasia), exome and transcriptome sequence analysis for sequence variants, gene copy number amplifications and deletions, gene rearrangements, microsatellite instability and tumor mutational burden utilizing DNA and RNA from tumor with DNA from normal blood or saliva for subtraction, report of clinically significant mutation(s) with therapy associations
S3840	DNA analysis for germline mutations of the RET proto-oncogene for susceptibility to multiple endocrine neoplasia type 2
S3841	Genetic testing for retinoblastoma
S3854	Gene expression profiling panel for use in the management of breast cancer treatment
81170	ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (e.g., acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain
81201	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
81202	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
81203	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
81206	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
81207	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative
81208	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative
81218	CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (e.g., acute myeloid leukemia), gene analysis, full gene sequence
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)
81245	FLT3 (fms-related tyrosine kinase 3)
81246	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; tyrosine kinase

domain (TKD) variants (eg, D835, I836)

81261 IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); amplified methodology (eg, polymerase chain reaction)

81262 IGH@ (Immunoglobulin heavy chain locus) (eg, leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); direct probe methodology (eg, Southern blot)

81263 IGH@ (Immunoglobulin heavy chain locus) (eg, leukemia and lymphoma, B-cell), variable region somatic mutation analysis

81270 JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant

81275 KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (e.g., carcinoma) gene analysis, variants in codons 12 and 13

81276 KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; additional variant(s) (e.g., codon 61, codon 146)

81292 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

81294 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

81295 MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

81297 MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

81298 MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

81300 MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants

81301 Microsatellite instability analysis (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (eg, BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed

81311	NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (e.g., colorectal carcinoma), gene analysis, variants in exon 2 (e.g., codons 12 and 13) and exon 3 (e.g., codon 61)
81314	PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) (e.g., gastrointestinal stromal tumor [GIST]), gene analysis, targeted sequence analysis (e.g., exons 12, 18)
81315	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; common breakpoints (eg, intron 3 and intron 6), qualitative or quantitative
81316	PML/RARalpha, (t(15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (eg, promyelocytic leukemia) translocation analysis; single breakpoint (eg, intron 3, intron 6 or exon 6), qualitative or quantitative
81317	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81318	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
81319	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
81322	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
81323	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant
81345	TERT (telomerase reverse transcriptase) (eg, thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (eg, promoter region
81403	MOLECULAR PATHOLOGY PROCEDURE LEVEL 4 (Killer cell immunoglobulin-like receptor (KIR) gene family (eg, hematopoietic stem cell transplantation), genotyping of KIR family genes)
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)
81432	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 14 genes, including ATM, BRCA1, BRCA2, BRIP1, CDH1, MLH1, MSH2, MSH6, NBN, PALB2, PTEN, RAD51C, STK11, and TP53
81433	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11
81435	Hereditary colon cancer disorders (eg, Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11
81436	Hereditary colon cancer syndromes (eg, Lynch syndrome, familial adenomatosis polyposis); duplication/deletion gene analysis panel, must include analysis of at least 8 genes, including APC, MLH1, MSH2, MSH6, PMS2, EPCAM, CHEK2, and MUTYH
81445	Targeted genomic sequence analysis panel, solid organ neoplasm, DNA analysis, 5-50 genes (eg, ALK, BRAF, CDKN2A, EGFR, ERBB2, KIT, KRAS, NRAS, MET, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
81455	Targeted genomic sequence analysis panel, solid organ or hematolymphoid neoplasm, DNA analysis, and RNA analysis when performed, 51 or greater genes (eg, ALK, BRAF, CDKN2A, CEBPA, DNMT3A, EGFR, ERBB2, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MLL, NPM1, NRAS, MET, NOTCH1, PDGFRA, PDGFRB, PGR, PIK3CA, PTEN, RET), interrogation for sequence variants and copy number variants or rearrangements, if performed
81479	Unlisted molecular pathology procedure
81541	Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a disease-specific mortality risk score
81542	Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed

	paraffin-embedded tissue, algorithm reported as metastasis risk score
81518	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 11 genes (7 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithms reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy
81519	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score
81521	Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis
81522	Oncology (breast), mRNA, gene expression profiling by RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk score
81552	Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis
81599	Unlisted multianalyte assay with algorithmic analysis
86386	Nuclear Matrix Protein 22 (NMP22), qualitative

See Specific Test for coverage before using the following codes:

81401	Molecular pathology procedure, Level 2
81402	Molecular pathology procedure, Level 3, gene rearrangement analysis, evaluation to detect abnormal clonal population
81403	Molecular pathology procedure, Level 4, targeted sequence analysis
81404	Molecular pathology procedure, Level 5, targeted sequence analysis

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_X_	Government Regulations	_X_	Literature Review
_X_	NCD/LCD		
_X_	Specialty Advisors OnDose 03/09 Kras 04/09	_X_	Milliman
_X_	Winifred S. Hayes, Inc.	_X_	UpToDate
_X_	Relevant Other Payer Approaches		

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