

## OHCA Guideline

<b>Medical Procedure Class:</b>	<b>Genetic and Molecular Pathology</b>	
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* This document is not a contract, and these guidelines do not reflect or represent every conceivable situation. Although all items contained in these guidelines may be met, this does not reflect, or imply any responsibility of this agency or department to change the plan provision to include the stated service as an eligible benefit.		
<input type="checkbox"/> New Criteria <span style="float: right;"><input checked="" type="checkbox"/> Revision of Existing Criteria</span>		
<b>Summary</b>		
<b>Purpose:</b>	To provide additional information and clarification on whether and under what circumstances specific genetic tests and technologies may meet the definition of medical necessity as outlined in OHCA's Genetic Testing Policy.	
<b>Definitions</b>		
<p><b>Common Variants</b>—Type of gene analysis that identifies deletions (missing segments of DNA) or duplications (extra copies of DNA segments) not readily detectable by sequence analysis.</p> <p><b>Constitutional</b>—synonymous with germline, often used in reference to the genetic code that is present at birth.</p> <p><b>Genetic Variants / Mutations / Polymorphisms</b>—Differences in genetic material that may vary between individuals may be referred to as genetic variants, mutations, or polymorphisms. Types of variation include single nucleotide polymorphism (SNP)—differences in a single nucleotide between individuals—as well as copy-number variation such as deletions (missing segments of DNA) and duplications (extra copies of DNA segments).</p> <p><b>Full Deletion / Duplication Analysis</b>—Type of gene analysis that identifies deletions (missing segments of DNA) or duplications (extra copies of DNA segments) not readily detectable by sequence analysis.</p> <p><b>Full Gene Sequence</b>—Type of gene analysis where the nucleotide sequence is determined for a segment of DNA.</p> <p><b>Known Familial Variant</b>—Type of gene analysis where an at-risk family member is tested only for the pathogenic variant already identified in a proband.</p> <p><b>Proband</b>—The affected individual first identified/diagnosed in a family with a genetic disorder. The proband may or may not be the individual presenting for genetic counseling or evaluation. Once a molecular diagnosis has been made in the proband, at-risk family members may be tested for the identified familial variant.</p> <p><b>Relative</b>—Member of someone's family. Further defined as:</p>		

**First-degree relatives**—Parents, siblings, and children

**Second-degree relatives**—Grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings

**Third-degree relatives**—Great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins

**Close blood relatives**—Includes first-, second-, and third-degree relatives on the same side of the family

**Somatic**—synonymous with acquired, referring to genetic code alterations that develop after birth (e.g., occurring in neoplastic cells).

### Description

Genetic and Molecular pathology procedures are medical laboratory procedures involving the analyses of nucleic acid (i.e., DNA, RNA) to detect variants in genes. Gene variants may be indicative of germline (constitutional disorders) or somatic (e.g., neoplasia) conditions. Testing is also done to test for histocompatibility antigens (HLA).

### CPT Codes Covered Requiring Prior Authorization (PA)

**Molecular Pathology (CPT 81105 – 81479)**

**Multianalyte Assays with Algorithmic Analyses (MAAA) (CPT 81490 – 81599)**

**Proprietary Laboratory Analyses (0001U – 0284U)**

Note: Genetic testing and molecular pathology services may not be limited to the codes listed above. Therefore, all codes/tests must meet medical necessity requirements per OHCA policy, or as determined by OHCA physician review.

\*\*Please see CPT manual for complete description of codes.

### Approval Criteria

#### I. GENERAL

- A. Genetic testing and other molecular pathology services are covered when medically necessary as per Oklahoma Administrative Code (OAC) 317:30-5-2(a)(1) (FF). Genetic testing may be considered medically necessary when the following conditions are met:
1. The member displays clinical features of a suspected genetic condition, is at direct risk of inheriting the genetic condition in question (e.g., a causative familial variant has been identified) or has been diagnosed with a condition where identification of specific genetic changes will impact treatment or management; and
  2. Clinical studies published in peer-reviewed literature have established strong evidence that the result of the test will positively impact the clinical decision-making or clinical outcome for the member; and
  3. The testing method is proven to be scientifically valid for the identification of a specific genetically linked inheritable disease or clinically important molecular marker; and
  4. A medical geneticist, physician, or licensed genetic counselor provides documentation that supports the recommendation for testing based on a review of risk factors, clinical scenario, and family history.
- B. OHCA considers a molecular pathology test that examines multiple genes or incorporates multiple types of analysis (e.g., full sequencing, common variants, plication/deletion/variants, etc.) in a single run or report to be a single test. As such, a single CPT code is appropriate for billing such tests. If an appropriate single CPT code does not exist to describe a laboratory's molecular pathology test, then one unit of 81479 should be billed.

- C. It would be expected that a member would not routinely need more than one (1) distinct laboratory genetic testing procedural service on a single date of service.
- D. Genetic testing is expected to influence treatment of the condition toward which the testing is directed and will be used in the management of the SoonerCare member's specific medical problem. Therefore, it is expected documentation provided with prior authorization will indicate how testing will influence treatment.
- E. It is expected the ordering/referring provider have an established provider-patient relationship as evidenced by ALL of the following:
  - At least two E/M visits provided by the ordering/referring practitioner over the previous six months; or at least 1 E/M from the ordering practitioner and 2 from the referring practitioner over the previous six months AND
  - Evidence that the test results will be utilized by the ordering/referring practitioner in the management of the patient's specific medical problem; AND
  - The referring/ordering practitioner has expertise in ordering and interpreting the results of all requested molecular pathology tests.
- F. Documentation should be included indicating the medical necessity of the molecular pathology tests being ordered for the member as evidenced by ALL of the following:
  - Patient's specific medical problem; AND
  - Specific molecular pathology tests ordered; AND
  - Documentation in the medical record including, but not limited to, history and physical or exam findings that support the decision making, problems/diagnoses, relevant data (e.g., lab testing, imaging results)

## II. INDICATIONS

The following section will outline the services of molecular pathology testing available, and in some instances may further define requirements or restrictions for certain tests if applicable. The following icons are used to highlight any documentation requirements and/or restrictions that may in be place for each CPT code.

- ▲ Service is currently covered without documentation requirements.
- Prior Authorization required. Supporting documentation must be submitted with PA request.
- ⌘ Service is manually priced. Supporting documentation must be submitted.
- ⊘ Service is not considered medically necessary at this time.

### A. Hereditary Cancer Testing

#### *Hereditary Breast and Ovarian Cancer*

- 81162--*BRCA1, BRCA2* (e.g., hereditary breast and ovarian cancer) gene analysis; **full sequence analysis and full duplication/deletion analysis**
- 81163--*BRCA1, BRCA2* (e.g., hereditary breast and ovarian cancer) gene analysis; **full sequence analysis**
- 81164--*BRCA1, BRCA2* (e.g., hereditary breast and ovarian cancer) gene analysis; **full duplication/deletion analysis**
- ▲ 81212--*BRCA1, BRCA2* (breast cancer 1 and 2) (e.g., hereditary breast and ovarian cancer) gene analysis; **185delAG, 5385insC, 6174delT variants**

- 81165--*BRCA1* (e.g., hereditary breast and ovarian cancer) gene analysis; **full sequence analysis**
- 81166--*BRCA1* (e.g., hereditary breast and ovarian cancer) gene analysis; **full duplication/deletion analysis**
- ▲ 81215--*BRCA1* (breast cancer 1) (e.g., hereditary breast and ovarian cancer) gene analysis; **known familial variant**
- 81216--*BRCA2* (breast cancer 2) (e.g., hereditary breast and ovarian cancer) gene analysis; **full sequence analysis**
- 81167--*BRCA2* (e.g., hereditary breast and ovarian cancer) gene analysis; **full duplication/deletion analysis**
- ▲ 81217--*BRCA2* (breast cancer 2) (e.g., hereditary breast and ovarian cancer) gene analysis; **known familial variant**

Comprehensive *BRCA1* and *BRCA2* full sequencing analysis and deletion/duplication analysis may be considered necessary for members meeting at least one of the following NCCN criteria:

- ◇ Personal history of breast cancer and one or more of the following:
  - Diagnosed at age  $\leq 45$
  - Diagnosed at  $\leq 50$  with at least one of the following:
    - An additional breast cancer primary
    - $\geq 1$  close blood relative with breast cancer at any age
    - $\geq 1$  close blood relative with prostate cancer (Gleason score  $\geq 7$ )
    - An unknown or limited family history
  - Diagnosed at age  $\leq 60$  with a triple negative breast cancer
  - Diagnosed at any age with at least one of the following:
    - $\geq 1$  close blood relative with breast cancer diagnosed  $\leq 50$
    - $\geq 1$  close blood relative with ovarian carcinoma
    - $\geq 1$  close male blood relative with breast cancer
    - $\geq 1$  close blood relative with metastatic prostate cancer or pancreatic cancer
    - $\geq 2$  additional diagnoses of breast cancer at any age in patient and/or in close blood relatives
  - Ashkenazi Jewish ethnicity with a negative test for common variants (CPT 81212)
- ◇ Personal history of ovarian carcinoma
- ◇ Personal history of male breast cancer
- ◇ Personal history of metastatic prostate cancer
- ◇ Personal history of high-grade prostate cancer (Gleason score  $\geq 7$ ) at any age with at least one of the following:
  - $\geq 1$  close blood relative with ovarian carcinoma, pancreatic cancer, or metastatic prostate cancer
  - $\geq 1$  close blood relative with breast cancer  $\leq 50$
  - Two or more relatives with breast or prostate cancer (any grade)
  - Ashkenazi Jewish ancestry
- ◇ Coverage for testing of unaffected family members is limited to testing for the identified familial variant (CPT 81215 or 81217) unless no affected family member is available for testing and one of the following applies:
  - The member has a first- or second-degree relative that meets any of the above criteria

Note: "Close blood relatives" includes first-, second-, and third-degree relatives on the same side of the family.

**When more than one gene is analyzed, coverage is limited to the single, most appropriate panel testing CPT code. See the separate criteria in this section for multi-gene hereditary cancer testing panels.**

When a familial variant has already been identified, coverage for unaffected family members is limited to testing for the identified familial variant.

- 81307--*PALB2* (*partner and localizer of BRCA2*) (e.g., breast and pancreatic cancer gene analysis; **full gene sequence**)

*PALB2* may be considered medically necessary for members that meet criteria for comprehensive BRCA1/2 testing but have previously tested negative for BRCA1/2 pathogenic mutations.

- ▲ 81308--*PALB2* (*partner and localizer of BRCA2*) (e.g., breast and pancreatic cancer) gene analysis; **known familial variant**

#### *Familial Adenomatosis Polyposis*

- 81201--*APC* (*adenomatous polyposis coli*) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; **full gene sequence**
- ▲ 81202--*APC* (*adenomatous polyposis coli*) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; **known familial variants**
- 81203--*APC* (*adenomatous polyposis coli*) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; **deletion/duplication variants**

*APC* full sequencing analysis and deletion/duplication analysis may be considered necessary for members with a personal history of at least 20 colonic polyps.

Coverage for testing of unaffected family members is limited to testing for the identified familial variant (CPT 81202).

#### *Lynch Syndrome*

- 81292--*MLH1* (*mutL homolog 1, colon cancer, nonpolyposis type 2*) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; **full sequence analysis**
- ▲ 81293--*MLH1* (*mutL homolog 1, colon cancer, nonpolyposis type 2*) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; **known familial variants**
- 81294--*MLH1* (*mutL homolog 1, colon cancer, nonpolyposis type 2*) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; **duplication/deletion variants**
- 81295--*MSH2* (*mutS homolog 2, colon cancer, nonpolyposis type 1*) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; **full sequence analysis**
- ▲ 81296--*MSH2* (*mutS homolog 2, colon cancer, nonpolyposis type 1*) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; **known familial variants**
- 81297--*MSH2* (*mutS homolog 2, colon cancer, nonpolyposis type 1*) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; **duplication/deletion variants**

- 81298--*MSH6* (mutS homolog 6 [*E. coli*]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; **full sequence analysis**
- ▲ 81299--*MSH6* (mutS homolog 6 [*E. coli*]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; **known familial variants**
- 81300--*MSH6* (mutS homolog 6 [*E. coli*]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; **duplication/deletion variants**
- ▲ 81301--Microsatellite instability analysis (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) of markers for mismatch repair deficiency (e.g., BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
- 81317--*PMS2* (postmeiotic segregation increased 2 [*S. cerevisiae*]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; **full sequence analysis**
- ▲ 81318--*PMS2* (postmeiotic segregation increased 2 [*S. cerevisiae*]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; **known familial variants**
- 81319--*PMS2* (postmeiotic segregation increased 2 [*S. cerevisiae*]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; **duplication/deletion variants**
- 81435--Hereditary colon cancer disorders; **genomic sequence analysis panel**, must include analysis of at least 7 genes, including APC, CHEK2, MLH1, MSH2, MSH6, MUTYH, and PMS2
- 81436--Hereditary colon cancer disorders; duplication/deletion analysis panel, must include analysis of at least 8 genes, including APC, MLH1, MSH2, MSH6, MUTYH, and PMS2

Comprehensive Lynch Syndrome testing, including full sequencing analysis and deletion/duplication analysis of *MLH1*, *MSH2*, *MSH6*, and *PMS2*, may be considered necessary for members meeting at least one of the following NCCN criteria:

- ◇ An individual with colorectal or endometrial cancer at any age with tumor showing evidence of mismatch repair (MMR) deficiency, either by microsatellite instability (MSI) or loss of MMR protein expression
- ◇ An individual with colorectal or endometrial cancer and any of the following:
  - Diagnosed less than 50 years of age
  - Another synchronous or metachronous Lynch Syndrome (LS)-related cancer (e.g., colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain, small intestinal cancers, sebaceous gland adenomas, and keratoacanthomas)
  - At least one first-degree or second-degree relative with LS-related cancer diagnosed less than 50 years of age
  - At least two first-degree or second-degree relatives with LS-related cancers regardless of age
- ◇ An individual with a colorectal tumor with MSI-high histology
- ◇ Family history of any of the following:
  - At least one first-degree relative with colorectal or endometrial cancer diagnosed less than 50 years of age
  - At least one first-degree relative with colorectal or endometrial cancer and another synchronous or metachronous LS-related cancer
  - At least two first-degree or second-degree relatives with LS-related cancer, including at least one diagnosed less than 50 years of age
  - At least three first-degree or second-degree relatives with LS-related cancers, regardless of age
- ◇ An individual with at least a 5% risk of having an MMR gene pathogenic variant based on predictive models (i.e., PREMM5, MMRpro, or MMRpredict)

**If more than one Lynch Syndrome gene is being analyzed, the single, most appropriate panel testing CPT code must be used (e.g., 81432--81436, 81479).** See the separate criteria in this section for multi-gene panel testing for other hereditary cancer syndromes.

When a familial variant has already been identified, coverage for unaffected family members is limited to testing for the identified familial variant.

Testing of individual Lynch Syndrome genes may be considered medically necessary in the following cases:

- ◇ MLH1 gene analysis when one of the following criteria is met:
  - Tumor testing show MSI-High result
  - IHC tumor testing indicates an absence of MLH1 protein
  - IHC tumor testing indicates an absence of PMS2 protein AND the member is negative for PMS2 mutations
- ◇ MSH2 gene analysis when one of the following criteria is met:
  - Tumor testing shows MSI-High result
  - IHC tumor testing indicates an absence of MSH2 protein
  - IHC tumor testing indicates an absence of MSH6 protein AND member is negative for MSH6 mutations
- ◇ MSH6 gene analysis when one of the following criteria is met:
  - IHC tumor testing indicates an absence of MSH6 protein
  - All of the following:
    - Tumor vesting shows MSI-High result
    - Negative for mutations MLH1
    - Negative for mutations in MLH2
- ◇ PMS2 gene analysis when one of the following criteria is met:
  - IHC tumor testing indicates an absence of PMS2 protein product and the presence of MLH1 protein product
  - IHC tumor testing indicates an absence of MLH1, MSH2, MSH6, and PMS2 protein products
  - All of the following:
    - MSI-High result
    - Negative for mutations in MLH1
    - Negative for mutations in MSH2
    - Negative for mutations in MSH6

#### *Cowden Syndrome / PTEN Hamartoma Tumor Syndrome*

- 81321--*PTEN* (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; **full sequence analysis**
- ▲ 81322--*PTEN* (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; **known familial variant**
- 81323--*PTEN* (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; **duplication/deletion variant**

*PTEN* gene analysis for Cowden Syndrome may be considered medically necessary for members meeting at least one of the following NCCN criteria:

- ◇ Individual meeting clinical diagnostic criteria for Cowden Syndrome/PHTS by having one of the following:

- Three or more major criteria, with one of those criteria being macrocephaly, Lhermitte-Duclos disease, or GI hamartomas
- Two major and three minor criteria
- ◇ Individual with a personal history of:
  - Bannayan-Riley Ruvalcaba syndrome (BRRS) OR
  - Adult Lhermitte-Duclos disease (cerebellar tumors) OR
  - Autism spectrum disorder and macrocephaly OR
  - Two or more biopsy-proven trichilemmomas OR
  - Two or more major criteria (one must be macrocephaly) OR
  - Three major criteria, without macrocephaly OR
  - One major and at least three minor criteria OR
  - At least four minor criteria
- ◇ At-risk individual with a relative with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed
  - The at-risk individual must have any one major criterion OR two minor criteria

Major Criteria:

- ◇ Breast Cancer
- ◇ Endometrial cancer
- ◇ Follicular thyroid cancer
- ◇ Multiple GI hamartomas or ganglioneuromas
- ◇ Macrocephaly (megalcephaly) (i.e., 97%, 58cm in adult women, 60cm in adult men)
- ◇ Macular pigmentation of glans penis
- ◇ Mucocutaneous lesions:
  - One biopsy-proven trichilemmoma
  - Multiple palmoplantar keratosis
  - Multifocal or extensive oral mucosal papillomatosis
  - Multiple cutaneous facial papules (often verrucous)

Minor Criteria:

- ◇ Autism spectrum disorder
- ◇ Colon cancer
- ◇ At least three esophageal glycogenic acanthoses
- ◇ Lipomas
- ◇ Intellectual disability (i.e., IQ less than 76)
- ◇ Papillary or follicular variant of papillary thyroid cancer
- ◇ Thyroid structural lesions (e.g., adenoma, nodules(s), goiter)
- ◇ Renal cell carcinoma
- ◇ Single GI hamartoma or ganglioneuroma
- ◇ Testicular lipomatosis
- ◇ Vascular anomalies (including multiple intracranial developmental venous anomalies)

When a familial variant has already been identified, coverage for unaffected family member is limited to testing for the identified familial variant.

*Hereditary Cancer Testing Panels*

- 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
- 81435-- Hereditary colon cancer disorders; **genomic sequence analysis panel**, must include analysis of at least 7 genes, including APC, CHEK2, MLH1, MSH2, MSH6, MUTYH, and PMS2
- 81436-- Hereditary colon cancer disorders; **duplication/deletion analysis panel**, must include analysis of at least 8 genes, including APC, MLH1, MSH2, MSH6, MUTYH, and PMS2
- 81437—Hereditary neuroendocrine tumor disorders (e.g., medullary thyroid carcinoma, malignant pheochromocytoma or paraganglioma; **genomic sequence analysis panel**, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TMEM127, and VHL)
- 81438-- Hereditary neuroendocrine tumor disorders (e.g., medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma; **duplication/deletion analysis panel**, must include analyses for SDHB, SDHC, SDHD, and VHL)

Multi-gene panel testing for hereditary cancer syndromes may be considered medically necessary for:

- Members meeting Lynch Syndrome testing criteria as described earlier in the [Lynch Syndrome](#) section of this document.
- Members meeting Hereditary Breast and Ovarian Cancer Syndrome testing criteria as described earlier in the [Hereditary Breast and Ovarian Cancer Syndrome](#) section of this document.

## B. Pharmacogenetic Testing

### Single-Gene Testing

- ⊘ 81225--*CYP2C19* (cytochrome P450, family 2, subfamily C, polypeptide 19) (e.g., drug metabolism), gene analysis, **common variants** (e.g., \*2, \*3, \*4, \*8, \*17)
- 81226--*CYP2D6* (Cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis; **common variants**

*CYP2D6* testing is not covered as part of a pharmacogenetic testing panel for any indication, including psychotropic or pain medication prescribing

*CYP2D6* testing may be considered medically necessary for members meeting at least one of the following criteria:

- ◇ Members receiving doses (or considering receiving doses) of Pimozide of more than 4mg/day in adults or 0.05mg/kg/day for children
  - ◇ Members receiving doses (or considering receiving doses) of tetrabenazine (Xenazine) of more than 50mg/day
  - ◇ Members with Gaucher disease type I who are considering treatment with eliglustat (Cerdelga)
- ⊘ 81227--*CYP2C9* (cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g., drug metabolism), gene analysis, **common variants** (e.g., \*2, \*3, \*5, \*6)
  - ⊘ 81230--*CYP3A4* (cytochrome P450 family 3 subfamily A member 4) (e.g., drug metabolism), gene analysis, **common variant(s)** (e.g., \*2, \*22)

- ∅ 81231--*CYP3A5* (cytochrome P450 family 3 subfamily A member 5) (e.g., drug metabolism), gene analysis, **common variants** (e.g., \*2, \*3, \*4, \*5, \*6, \*7)
- ∅ 81232--*DPYD* (dihydropyrimidine dehydrogenase) (e.g., 5-fluorouracil/5-FU and capecitabine drug metabolism), gene analysis, **common variant(s)** (e.g., \*2A, \*4, \*5, \*6)
- ∅ 81283--*IFNL3* (interferon, lambda 3) (e.g., drug response), gene analysis, **rs12979860 variant**
- 81306-- *NUDT15* (nudix hydrolase 15) (e.g., drug metabolism) gene analysis; **common variants**

*NUDT15* testing may be considered medically necessary for members prior to beginning thiopurine therapy

- ∅ 81328--*SLCO1B1* (solute carrier organic anion transporter family, member 1B1) (e.g., adverse drug reaction), gene analysis, **common variant(s)** (e.g., \*5)
- 81335--*TPMT* (thiopurine S-methyltransferase) (e.g., drug metabolism), gene analysis, common variants (e.g., \*2, \*3)
- ∅ 81346--*TYMS* (thymidylate synthetase) (e.g., 5-FU drug metabolism), gene analysis, **common variant(s)** (e.g., tandem repeat variant)
- ∅ 81350--*UGT1A1* (UDP glucuronosyltransferase 1 family, polypeptide A1) (e.g., irinotecan metabolism), gene analysis, **common variants** (e.g., \*28, \*36, \*37)
- ∅ 81355--*VKORC1* (vitamin K epoxide reductase complex, subunit 1) (e.g., warfarin metabolism), gene analysis, **common variants** (e.g., -1639/3673)

### Pharmacogenetic Testing Panels

Multi-gene pharmacogenetic testing panels are not considered medically necessary. Examples of non-covered tests include but are not limited to the following:

- ◇ Genecept™ Assay
- ◇ Genesight® Analgesic
- ◇ GeneSight® Psychotropic
- ◇ Pain Medication DNA Insight®
- ◇ Millennium PGT
- ◇ AmpliChip® CYP450 Test
- ◇ SureGene Test for Antipsychotic and Antidepressant Response (STA2R)
- ◇ Proove panels such as Proove Drug Metabolism, Proove Opioid Risk, Proove Pain Perception, Proove Opioid Response, Proove Non-Opioid Response, Proove NSAID Risk, Proove Medically Assisted Treatment, and Proove Epidural with Fentanyl
- ◇ YouScript Polypharmacy

### C. Single-Gene Diagnostic Testing

#### Known Familial Variant(s)

- ▲ 81174--*AR* (androgen receptor) (e.g., spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; **known familial variant**
- ▲ 81186--*CACNA1A* (calcium voltage-gated channel subunit alpha1 A) (e.g., spinocerebellar ataxia) gene analysis; **known familial variant**
- ▲ 81190--*CSTB* (cystatin B) (e.g., Unverricht-Lundborg disease) gene analysis; **known familial variant**

- ▲ 81221--*CFTR* (cystic fibrosis transmembrane conductance regulator) (e.g., cystic fibrosis) gene analysis; **known familial variants**
- ▲ 81248--*G6PD* (glucose-6-phosphate dehydrogenase) (e.g., hemolytic anemia, jaundice), gene analysis; **known familial variant**
- ▲ 81253--*GJB2* (gap junction protein, beta 2, 26kDa; connexin 26) (e.g., nonsyndromic hearing loss) gene analysis; **known familial variants**
- ▲ 81258--*HBA1/HBA2* (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, **known familial variant**
- ▲ 81281--Long QT Syndrome gene analysis; known familial sequence variant
- ▲ 81289--*FXN* (frataxin) (e.g., Friedreich ataxia), **known familial variant(s)**
- ▲ 81303--*MECP2* (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; **known familial variant**
- ▲ 81326--*PMP22* (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; **known familial variant**
- ▲ 81337--*SMN1* (survival of motor neuron 1, telomeric) (e.g., spinal muscular atrophy), **known familial sequence variant(s)**
- ▲ 81362--*HBB* (hemoglobin, subunit beta) (e.g., sickle cell anemia, beta thalassemia, hemoglobinopathy); **known familial variant(s)**

Testing of at-risk relatives **for the familial variant only** may be considered medically necessary when a pathogenic familial variant has already been identified.

#### *Confirming/Establishing a Diagnosis in a Proband*

Single-gene testing may be appropriate for members with clinical features highly suggestive of a specific condition that can be confirmed or ruled out with a single-gene test. For members with clinical features that may be compatible with a number of genetic conditions and/or a genetic condition that may be caused by a number of genes, panel testing may be a more appropriate option. **Multiple single-gene test codes will not be approved for panel tests.** If an appropriate single CPT code does not exist to describe a panel test, then one unit of 81479 should be requested.

- 81161-- *DMD* (dystrophin) (e.g., Duchenne/Becker muscular dystrophy) **deletion analysis, and duplication analysis, if performed**

*DMD* testing may be considered medically necessary for confirmatory diagnostic testing in members with clinical features strongly suggestive of Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD). Carrier testing may also be allowed for testing in females at risk for inheriting a *DMD* mutation based on family history if an affected family member is not available for testing.

- 81171-- *AFF2* (AF4/FMR2 family, member 2[FMR2]) (e.g., fragile X mental retardation2 [FRAXE]) gene analysis; **evaluation to detect abnormal (e.g., expanded) alleles**
- 81172-- *AFF2* (AF4/FMR2 family, member 2[FMR2]) (e.g., fragile X mental retardation2 [FRAXE]) gene analysis; **characterization of alleles (e.g., expanded size and methylation status)**

*AFF2* testing may be considered medically necessary in members with a family history of expanded CCG repeats in *AFF2*. *AFF2* single-gene testing is not considered medically necessary for members with clinical features of Fragile XE syndrome, such as mild intellectual disability.

- 81204--*AR* (androgen receptor) (e.g., spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; **characterization of alleles (e.g., expanded size and methylation status)**
- 81173--*AR* (androgen receptor) (e.g., spinal and bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) gene analysis; **full gene sequence**

*AR* testing may be considered medically necessary in members with clinical features strongly suggestive of spinal and bulbar muscular atrophy.

- 81177--*ATN1* (atrophin 1) (e.g., dentatorubral-pallidoluysian atrophy) gene analysis; **evaluation to detect abnormal (e.g., expanded) alleles**
- 81178--*ATXN1* (ataxin 1) (e.g., spinocerebellar ataxia) gene analysis; **evaluation to detect abnormal (e.g., expanded) alleles**
- 81179--*ATXN2* (ataxin 2) (e.g., spinocerebellar ataxia) gene analysis; **evaluation to detect abnormal (e.g., expanded) alleles**
- 81180--*ATXN3* (ataxin 3) (e.g., spinocerebellar ataxia, Machado-Joseph disease) gene analysis; **evaluation to detect abnormal (e.g., expanded) alleles**
- 81181--*ATXN7* (ataxin 7) (e.g., spinocerebellar ataxia) gene analysis; **evaluation to detect abnormal (e.g., expanded) alleles**
- 81182--*ATXN8OS* (ataxin 8 opposite strand [non-protein coding]) (e.g., spinocerebellar ataxia) gene analysis; **evaluation to detect abnormal (e.g., expanded) alleles**
- 81183--*ATXN10* (ataxin 10) (e.g., spinocerebellar ataxia) gene analysis; **evaluation to detect abnormal (e.g., expanded) alleles**
- 81184--*CACNA1A* (calcium voltage-gated channel subunit alpha1 A) (e.g., spinocerebellar ataxia) gene analysis; **evaluation to detect abnormal (e.g., expanded) alleles**
- 81185--*CACNA1A* (calcium voltage-gated channel subunit alpha1 A) (e.g., spinocerebellar ataxia) gene analysis; **full gene sequence**
- 81187--*CNBP* (CCHC-type zinc finger nucleic acid binding protein) (e.g., myotonic dystrophy type 2) gene analysis; **evaluation to detect abnormal (e.g., expanded) alleles**
- 81188--*CSTB* (cystatin B) (e.g., Unverricht-Lundborg disease) gene analysis; **evaluation to detect abnormal (e.g., expanded) alleles**
- 81189--*CSTB* (cystatin B) (e.g., Unverricht-Lundborg disease) gene analysis; **full gene sequence**
- 81220--*CFTR* (Cystic Fibrosis Transmembrane Conductance Regulator) (e.g., cystic fibrosis) gene analysis; **common variants**
- 81222--*CFTR* (Cystic Fibrosis Transmembrane Conductance Regulator) (e.g., Cystic Fibrosis) gene analysis; **duplication/deletion variants**
- 81223--*CFTR* (Cystic Fibrosis Transmembrane Conductance Regulator) (e.g., Cystic Fibrosis) gene analysis; **full gene sequence**

*CFTR* common variant testing is covered as a first-line diagnostic test in infants with an elevated immunoreactive trypsinogen (IRT) value on newborn screening.

*CFTR* full gene sequencing and/or duplication/deletion testing may be considered medically necessary for confirmatory diagnostic testing in members meeting at least one of the following criteria:

- ◇ Infants with suspected Cystic Fibrosis (CF) based on elevated IRT value on newborn screening when the *CFTR* common mutation test identified less than two pathogenic *CFTR* mutations
- ◇ Members with clinical signs and symptoms suggestive of CF when the *CFTR* common mutation test identified less than two pathogenic *CFTR* mutations

Testing of at-risk relatives for the familial variant only may be considered medically necessary when a pathogenic familial variant has already been identified.

- 81234--*DMPK* (DM1 protein kinase) (e.g., myotonic dystrophy type 1), **evaluation to detect abnormal (expanded) alleles**
- 81239--*DMPK* (DM1 protein kinase) (e.g., myotonic dystrophy type 1), **characterization of alleles (e.g., expanded size)**
- 81238--*F9* (coagulation factor IX) (e.g., hemophilia B), **full gene sequence**
- 81361--*HBB* (hemoglobin, subunit beta) (e.g., sickle cell anemia, beta thalassemia, hemoglobinopathy); **common variant(s)** (e.g., HbS, HbC, HbE)
- 81363--*HBB* (hemoglobin, subunit beta) (e.g., sickle cell anemia, beta thalassemia, hemoglobinopathy); **duplication/deletion variant(s)**
- 81364--*HBB* (hemoglobin, subunit beta) (e.g., sickle cell anemia, beta thalassemia, hemoglobinopathy); **full gene sequence**
- 81271--*HTT* (huntingtin) (e.g., Huntington disease), **evaluation to detect abnormal (expanded) alleles**
- 81274--*HTT* (huntingtin) (e.g., Huntington disease), **characterization of alleles (e.g., expanded size)**
- 81284--*FXN* (frataxin) (e.g., Friedreich ataxia), **evaluation to detect abnormal (expanded) alleles**
- 81285--*FXN* (frataxin) (e.g., Friedreich ataxia), **characterization of alleles (e.g., expanded size)**
- 81286--*FXN* (frataxin) (e.g., Friedreich ataxia), **full gene sequence**
- 81312--*PABPN1* (poly[A] binding protein nuclear 1) (e.g., oculopharyngeal muscular dystrophy), **evaluation to detect abnormal (expanded) alleles**
- 81333--*TGFB1* (transforming growth factor beta-induced) (e.g., corneal dystrophy), **common variants**
- 81336--*SMN1* (survival of motor neuron 1, telomeric) (e.g., spinal muscular atrophy), **full sequence analysis**
- 81343--*PPP2R2B* (protein phosphatase 2 regulatory subunit Bbeta) (e.g., spinocerebellar ataxia), **evaluation to detect abnormal (expanded) alleles**
- 81344--*TBP* (TATA box binding protein) (e.g., spinocerebellar ataxia), **evaluation to detect abnormal (expanded) alleles**
- 81240--*F2* (Prothrombin, Coagulation Factor II) (e.g., hereditary hypercoagulability) gene analysis, **20210G>A variant**
- 81241--*F5* (Coagulation Factor V) (e.g., hereditary hypercoagulability) gene analysis, **Leiden variant**

Hereditary hypercoagulability testing for the F2 20210G>A variant and/or the F5 Leiden variant may be considered medically necessary for members meeting at least one of the following criteria:

- ◇ Adolescents with spontaneous thrombosis
- ◇ Neonates / children with non-catheter-related venous thrombosis or stroke
- ◇ Members with recurrent VTE

Testing is not considered medically necessary in other cases, including but not limited to:

- ◇ Routine screening in pregnant women
- ◇ Miscarriage
- ◇ Adults with idiopathic venous thromboembolism (VTE)
- ◇ Asymptomatic adult family members of individuals with identified mutations

- 81243--*FMR1* (Fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; **evaluation to detect abnormal (e.g., expanded) alleles**

- ▲ 81244--*FMR1* (Fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; **characterization of alleles** (e.g., expanded size and methylation status)

Fragile X diagnostic testing may be considered medically necessary for individuals with unexplained intellectual disability, developmental delay, or autism.

Fragile X premutation carrier testing may be considered medically necessary for members with at least one of the following:

- ◇ Family history of Fragile X-related disorders
- ◇ Family history of undiagnosed intellectual disability
- ◇ Premature ovarian insufficiency

Fragile X carrier testing is not considered medically necessary for general population screening in the absence of any of the criteria listed above.

- 81247-- *G6PD* (glucose-6-phosphate dehydrogenase) (e.g., hemolytic anemia, jaundice), gene analysis; **common variant(s)** (e.g., A, A-)
- 81249--*G6PD* (glucose-6-phosphate dehydrogenase) (e.g., hemolytic anemia, jaundice), gene analysis; **full gene sequence**
- ▲ 81252--*GJB2* (gap junction protein, beta 2, 26kDa; connexin 26) (e.g., nonsyndromic hearing loss) gene analysis; **full gene sequence**
- ▲ 81254--*GJB6* (gap junction protein, beta 6, 30kDa, connexin 30) (e.g., nonsyndromic hearing loss) gene analysis, **common variants** (e.g., 309kb [del (GJB6-D13S1830)] and 232kb [del (GJB6-D13S1854)])

*GJB2* and *GJB6* gene analysis may be considered medically necessary for members with nonsyndromic hearing loss that is suspected to be hereditary

Testing of at-risk relatives **for the familial variant only** may be considered medically necessary when a pathogenic familial variant has already been identified.

- ▲ 81256 – *HFE* (hemochromatosis) (e.g., hereditary hemochromatosis) gene analysis, **common variants** (e.g., C282Y, H63D)

*HFE* gene analysis of common variants may be considered medically necessary for members with abnormal iron studies and/or evidence of liver disease

- 81257-- *HBA1/HBA2* (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, for **common deletions or variant** (e.g., Southeast Asian, Thai, Filipino, Mediterranean, alpha3.7, alpha4.2, alpha20.5, and Constant Spring)

*HBA1 / HBA2* gene analysis of common variants may be considered medically necessary for confirmatory diagnostic testing in members with suspected alpha thalassemia

- 81259-- *HBA1/HBA2* (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, **full gene sequence**
- 81269--*HBA1/HBA2* (alpha globin 1 and alpha globin 2) (e.g., alpha thalassemia, Hb Bart hydrops fetalis syndrome, HbH disease), gene analysis, **duplication / deletion variants**
- 81291--*MTHFR* (5,10-methylenetetrahydrofolate reductase) (e.g., hereditary hypercoagulability) gene analysis, **common variants** (e.g., 677T, 1298C)

- ▲ 81302--*MECP2* (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; **full sequence analysis**

- ▲ 81304--*MECP2* (methyl CpG binding protein 2) (e.g., Rett syndrome) gene analysis; **duplication/deletion variants**

*MECP2* gene analysis may be considered medically necessary for confirmatory diagnostic testing in members with suspected Rett Syndrome

- ▲ 81324--*PMP22* (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; **duplication/deletion analysis**
- ▲ 81325--*PMP22* (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; **full sequence analysis**

*PMP22* gene analysis may be considered medically necessary for confirmatory diagnostic testing in members with suspected Charcot-Marie-Tooth neuropathy type 1 (CMT1) or Hereditary Neuropathy with liability to Pressure Palsies (HNPP).

- ▲ 81331--*SNRPN/UBE3A* (small nuclear ribonucleoprotein polypeptide N and ubiquitin protein ligase E3A) (e.g., Prader-Willi syndrome and/or Angelman syndrome), **methylation analysis**

*SNRPN/UBE3A* methylation analysis may be considered medically necessary for confirmatory diagnostic testing in members with suspected Prader-Willi or Angelman syndrome.

- ▲ 81332--*SERPINA1* (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (e.g., alpha-1-antitrypsin deficiency), gene analysis, **common variants** (e.g., \*S and \*Z)

*SERPINA1* gene analysis of common variants may be considered medically necessary for confirmatory diagnostic testing in members with suspected alpha-1 antitrypsin deficiency.

#### D. Microarray Testing

- 81228-- Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number variants (e.g., Bacterial Artificial Chromosome [BAC] or oligo-based comparative genomic hybridization [CGH] microarray analysis)
- 81229 – Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities
- 81349 – Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and loss-of-heterozygosity variants for chromosomal abnormalities

Microarray testing may be considered medically necessary as a first-line test for the following indications:

- ◇ At least one major congenital anomaly or multiple congenital anomalies, other than those associated with an obvious, specific, and well-defined genetic syndrome
- ◇ Developmental delay (DD) or Intellectual Disability (ID) when all of the following are met:
  - There is no known etiology for the DD/ID (e.g., trauma or infection)

- The DD/ID is not suspected to be related to an obvious, specific, and well-defined genetic syndrome
- ◇ Autism spectrum disorders

- 81277-- Cytogenomic neoplasia (genome-wide) microarray analysis, interrogation of genomic regions for copy number and loss-of-heterozygosity variants for chromosomal abnormalities

Microarray testing for cancer indications may be considered medically necessary when recommended by the NCCN guidelines for molecular profiling of specific tumor types.

#### E. Non-Invasive Pre-natal Testing

- 81420--Fetal chromosomal aneuploidy genomic sequence analysis panel, circulating cell-free fetal DNA in maternal blood, must include analysis of chromosomes 13, 18, and 21
- 81422--Fetal chromosomal microdeletion(s) genomic sequence analysis (e.g., DiGeorge syndrome, Cri-du-chat syndrome), circulating cell-free fetal DNA in maternal blood
- 81507--Fetal aneuploidy (trisomy 21, 18, and 13) DNA sequence analysis of selected regions using maternal plasma, algorithm reported as a risk score for each trisomy

Non-invasive prenatal testing for trisomy 21, 18, and 13 may be considered medically necessary for pregnant women at high risk of aneuploidy as defined by one or more of the following criteria:

- ◇ Maternal age 35 years or older at delivery
- ◇ Fetal ultrasound finding indicating an increased risk of aneuploidy, specifically for trisomies 13, 18, or 21
- ◇ History of prior pregnancy with a trisomy detectable by cfDNA screening (trisomies 13, 18, or 21)
- ◇ Positive screening results for aneuploidy including a first trimester, sequential, integrated, or quadruple screen
- ◇ Parental balanced Robertsonian translocation with increased risk of fetal trisomy 13 or 21

Non-invasive prenatal testing for any indication beside trisomy 21, 18, and 13 is not considered medically necessary.

#### F. Carrier Screening

Carrier screening is not considered medically necessary for routine screening of pregnant women or general population screening.

##### Single-Gene Testing

- 81200-- *ASPA* (e.g., Canavan disease) gene analysis, **common variants**
- 81205--*BCKDHB* (e.g., Maple syrup urine disease) gene analysis, **common variant**
- 81209--*BLM* (e.g., Bloom syndrome) gene analysis, **2281del6ins7 variant**
- 81220--*CFTR* (Cystic Fibrosis Transmembrane Conductance Regulator) (e.g., cystic fibrosis) gene analysis; **common variants**
- 81242--*FANCC* (e.g., Fanconi anemia, type C) gene analysis, **common variant**
- 81243--*FMR1* (Fragile X mental retardation 1) (e.g., fragile X mental retardation) gene analysis; **evaluation to detect abnormal (e.g., expanded) alleles**
- 81250--*G6PC* (e.g., Glycogen storage disease, Type 1a) gene analysis, **common variants**

- 81251--*GBA* (e.g., Gaucher disease) gene analysis, **common variants**
- 81255--*HEXA* (e.g., Tay-Sachs disease) gene analysis, **common variants**
- 81260--*IKBKAP* (e.g., familial dysautonomia) gene analysis, **common variants**
- 81290--*MCOLN1* (e.g., Mucopolidosis, type IV) gene analysis, **common variants**
- 81329--*SMN1* (survival of motor neuron 1, telomeric) (e.g., spinal muscular atrophy), **dosage/deletion analysis (e.g., carrier testing), includes SMN2 analysis, if performed**
- 81330--*SMPD1* (e.g., Niemann-Pick disease, Type A) gene analysis, **common variants**

A single-gene test for common variants in one of these genes may be considered medically necessary for:

- ◇ Members with a family history that places them at high risk of being a carrier for one of these conditions OR
- ◇ Confirmatory diagnostic testing in members with clinical features suggestive of one of these conditions

### *Multi-Gene High-Risk Screening*

- 81412-- Ashkenazi Jewish associated disorders (e.g., Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), **genomic sequence analysis panel**, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1)

Expanded carrier screening for Ashkenazi Jewish associated disorders using a genomic sequence analysis panel may be considered medically necessary for members of Ashkenazi Jewish ancestry.

## G. **Somatic (Tumor) Gene Testing**

Testing for specific somatic/tumor-related variants may be considered medically necessary when testing is recommended to aid in diagnosis or treatment decision-making by the National Comprehensive Cancer Network (NCCN). **Multiple single-gene test codes will not be approved for panel tests.** See the section on [Genomic Sequencing and Multi-Gene Panels](#) for examples of panel codes that may be requested. If an appropriate single CPT code does not exist to describe a panel test, then one unit of 81479 should be requested.

- ▲ 81120--*IDH1* (isocitrate dehydrogenase 1 [NADP+], soluble) (e.g., glioma), **common variants** (e.g., R132H, R132C)
- ▲ 81121--*IDH2* (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (e.g., glioma), **common variants** (e.g., R140W, R172M)
- ▲ 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**
- ▲ 81175--*ASXL1* (additional sex combs like 1, transcriptional regulator) (e.g., myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; **full gene sequence**
- ▲ 81176--*ASXL1* (additional sex combs like 1, transcriptional regulator) (e.g., myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; **targeted sequence analysis** (e.g., exon 12)
- ▲ 81206--*BCR/ABL1* (t (9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; **major breakpoint, qualitative or quantitative**
- ▲ 81207--*BCR/ABL1* (t (9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; **minor breakpoint, qualitative or quantitative**

- ▲ 81208--*BCR/ABL1* (t (9;22)) (e.g., chronic myelogenous leukemia) translocation analysis; **other breakpoint, qualitative or quantitative**
- ▲ 1210--*BRAF* (v-raf murine sarcoma viral oncogene homolog B1) (e.g., colon cancer), gene analysis, **V600E variant**
- ▲ 81218--*CEBPA* (CCAAT/enhancer binding protein [C/EBP], alpha) (e.g., acute myeloid leukemia), gene analysis, **full gene sequence**
- ▲ 81219--*CALR* (calreticulin) (e.g., myeloproliferative disorders), gene analysis, **common variants in exon 9**
- 81168--*CCND1/IGH* (t [11;14]) (e.g., mantle cell lymphoma) translocation analysis, **major breakpoint, qualitative and quantitative**, if performed
- 1233--*BTK* (Bruton's tyrosine kinase) (e.g., chronic lymphocytic leukemia), **common variants** (e.g., C481S, C481R, C481F)
- 81236--*EZH2* (enhancer of zeste 2 polycomb repressive complex 2 subunit) (e.g., diffuse large B-cell lymphoma), **full gene sequence**
- 81237--*EZH2* (enhancer of zeste 2 polycomb repressive complex 2 subunit) (e.g., diffuse large B-cell lymphoma), **common variant(s)** (e.g., codon 646)
- ▲ 81235--*EGFR* (epidermal growth factor receptor) (e.g., non-small cell lung cancer) gene analysis, **common variants** (e.g., exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
- ▲ 81245--*FLT3* (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis, **internal tandem duplication (ITD) variants** (i.e., exons 14, 15)
- ▲ 81246--*FLT3* (fms-related tyrosine kinase 3) (e.g., acute myeloid leukemia), gene analysis, **tyrosine kinase domain (TKD) variants** (e.g., D835, I836)
- ▲ 81261--*IGH@* (Immunoglobulin heavy chain locus) (e.g., leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); **amplified methodology** (e.g., polymerase chain reaction)
- ▲ 81262--*IGH@* (Immunoglobulin heavy chain locus) (e.g., leukemias and lymphomas, B-cell), gene rearrangement analysis to detect abnormal clonal population(s); direct **probe methodology** (e.g., Southern blot)
- ⊗ 81263--*IGH@* (Immunoglobulin heavy chain locus) (e.g., leukemia and lymphoma, B-cell), **variable region somatic mutation analysis**
- 81278--*IGH@/BCL2* (t [14;18]) (e.g., follicular lymphoma) translocation analysis, **major breakpoint region (MBR) and minor cluster region (mcr) breakpoints, qualitative or quantitative**
- ▲ 81264--*IGK@* (Immunoglobulin kappa light chain locus) (e.g., leukemia and lymphoma, B-cell), gene rearrangement analysis, **evaluation to detect abnormal clonal population(s)**
- ▲ 81270--*JAK2* (Janus kinase 2) (e.g., myeloproliferative disorder) gene analysis, **p. Val617Phe (V617F) variant**
- 81279--*JAK2* (*Janus kinase 2*) (e.g., myeloproliferative disorder) **targeted sequence analysis** (e.g., exons 12 and 13)
- ▲ 81272--*KIT* (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (e.g., gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, **targeted sequence analysis** (e.g., exons 8, 11, 13, 17, 18))
- ▲ 81273--*KIT* (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (e.g., mastocytosis), gene analysis, **D816 variant(s)**
- ▲ 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))
- ▲ 81287--*MGMT* (O-6-methylguanine-DNA methyltransferase) (e.g., glioblastoma multiforme), **methylation analysis**
- ▲ 81288--*MLH1* **promoter methylation analysis**

- ▲ 81301--Microsatellite instability analysis (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) of **markers for mismatch repair deficiency** (e.g., BAT25, BAT26), includes comparison of neoplastic and normal tissue, if performed
- 81338--*MPL* (*MPL* proto-oncogene, thrombopoietin receptor) (e.g., myeloproliferative disorder) gene analysis; **common variants** (e.g., W515A, W51K, W515L, W515R)
- 81339-- *MPL* (*MPL* proto-oncogene, thrombopoietin receptor) (e.g., myeloproliferative disorder) gene analysis; **sequence analysis**, exon 10
- 81305--*MYD88* (myeloid differentiation primary response 88) (e.g., Waldenstrom's macroglobulinemia, lymphoplasmacytic leukemia), **p. Leu265Pro (L265P) variant**
- 81191--*NTRK1* (*neurotrophic receptor tyrosine kinase 1*) (e.g., solid tumors) translocation analysis
- 81192--*NTRK2* (*neurotrophic receptor tyrosine kinase 2*) (e.g., solid tumors) translocation analysis
- 81193--*NTRK3* (*neurotrophic receptor tyrosine kinase 3*) (e.g., solid tumors) translocation analysis
- 81194--*NTRK* (*neurotrophic-tropomyosin receptor tyrosine kinase 1, 2, and 3*) (e.g., solid tumors) translocation analysis
- 81309--*PIK3CA* (e.g., colorectal and breast cancer), **common variants**
- ▲ 81310--*NPM1* (nucleophosmin) (e.g., acute myeloid leukemia) gene analysis, **exon 12 variants**
- ▲ 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/RAR*alpha, (t (15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (e.g., promyelocytic leukemia) translocation analysis; **common breakpoints** (e.g., intron 3 and intron 6), qualitative or quantitative
- ▲ 81316--*PML/RAR*alpha, (t (15;17)), (promyelocytic leukemia/retinoic acid receptor alpha) (e.g., promyelocytic leukemia) translocation analysis; **single breakpoint** (e.g., intron 3, intron 6 or exon 6), qualitative or quantitative
- 81320--*PLCG2* (phospholipase C gamma 2) (e.g., chronic lymphocytic leukemia), **common variant(s)**
- 81334--*RUNX1* (runt related transcription factor 1) (e.g., acute myeloid leukemia, familial platelet disorder with associated myeloid malignancy), gene analysis, **targeted sequence analysis (e.g., exons 3-8)**
- 81347--*SF3B1*(*splicing factor [3b] subunit B1*) (e.g., myelodysplastic syndrome/acute myeloid leukemia) gen analysis, **common variants** (e.g., A672T, E622D, L833F, R625C, R625L)
- 81348--*SRSF2* (*serine and arginine-rich splicing factor 2*) (e.g., myelodysplastic syndrome, acute myeloid leukemia) gene analysis, **common variants** (e.g., P95H, P95L)
- 81351--*TP53* (*tumor protein 53*) (e.g., Li-Fraumeni syndrome) gene analysis; full gene sequence
- 81352--*TP53* (*tumor protein 53*) (e.g., Li-Fraumeni syndrome) gene analysis; **targeted sequence analysis** (e.g., 4 oncology)
- ▲ 81340--*TRB@* (T cell antigen receptor, beta) (e.g., leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s), **using amplification methodology** (e.g., polymerase chain reaction)
- ▲ 81341--*TRB@* (T cell antigen receptor, beta) (e.g., leukemia and lymphoma), gene rearrangement analysis to detect abnormal clonal population(s), **using direct probe methodology** (e.g., Southern blot)

- 81345--*TERT* (telomerase reverse transcriptase) (e.g., thyroid carcinoma, glioblastoma multiforme), **targeted sequence analysis (e.g., promoter region)**
- 81357--*U2AF1* (*U2 small nuclear RNA auxiliary factor 1*) (e.g., myelodysplastic syndrome, acute myeloid leukemia) gene analysis, **common variants** (e.g., S34F, S34Y, Q157R, Q157P)
- 81360--*ZRSR2* (*zinc finger CCCH-type RNA binding motif and serine/arginine-rich 2*) (e.g., myelodysplastic syndrome, acute myeloid leukemia) gene analysis, **common variant(s)** (e.g., E65fs, E122fs, R448fs)

#### H. HLA Testing

- 81370--HLA Class I and II typing, low resolution (e.g., antigen equivalents); HLA-A, -B, -C, -DRB1/3/4/5, and -DQB1
- 81371 – HLA-A, -B, and -DRB1/3/4/5 (e.g., verification typing)
- 81372--HLA Class I typing, low resolution (e.g., antigen equivalents); **complete** (HLA-A, -B, and -C)
- 81373--HLA Class I typing, low resolution (e.g., antigen equivalents); **one locus** (e.g., HLA-A, -B, or -C), each
- 81374--HLA Class I typing, low resolution (e.g., antigen equivalents); **one antigen equivalent** (e.g., B\*27), each
- 81375--HLA Class II typing, low resolution (e.g., antigen equivalents); HLA-DRB1/3/4/5 and -DQB1
- 81376--HLA Class II typing, low resolution (e.g., antigen equivalents); **one locus** (e.g., HLA-DRB1/3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each
- 81377--HLA Class II typing, low resolution (e.g., antigen equivalents); **one antigen equivalent**, each
- 81378--HLA Class I and II typing, high resolution (i.e., alleles or allele groups), HLA-A, -B, -C, and -DRB1
- 81379--HLA Class I typing, high resolution (i.e., alleles or allele groups); **complete** (HLA-A, -B, and -C)
- 81380--HLA Class I typing, high resolution (i.e., alleles or allele groups); **one locus** (e.g., HLA-A, -B, or -C), each
- 81381--HLA Class I typing, high resolution (i.e., alleles or allele groups); **one allele or allele group** (e.g., B\*57:01P), each
- 81382--HLA Class II typing, high resolution (i.e., alleles or allele groups); **one locus** (e.g., HLA-DRB1, -DRB3, -DRB4, -DRB5, -DQB1, -DQA1, -DPB1, or -DPA1), each
- 81383--HLA Class II typing, high resolution (i.e., alleles or allele groups); **one allele or allele group** (e.g., HLA-DQB1\*06:02P), each

HLA testing may be considered medically necessary for HLA matching of donor or recipient for solid organ transplant or hematopoietic stem cell/bone marrow transplant.

In addition, HLA testing may be considered medically necessary in the following circumstances:

- ◇ Low resolution HLA Class I typing of one antigen equivalent (i.e., 81374) may be considered medically necessary for diagnostic testing in members with suspected ankylosing spondylitis
- ◇ Low- or high-resolution HLA Class II typing of one locus, allele, or antigen equivalent (i.e., 81376, 81377, 81382, 81383) may be considered medically necessary for diagnostic testing in members with an unclear diagnosis of celiac disease

- ◇ High resolution HLA Class I typing of one allele or allele group (i.e., 81381) may be considered medically necessary for members beginning treatment with abacavir or carbamazepine

## I. Genomic Sequencing and Multi-Gene Panels

- ∅ Pharmacogenetic multi-gene testing panels are not considered medically necessary and are not covered services at this time
- ∅ Intellectual disability/autism multi-gene sequencing panels are not considered medically necessary and are not covered services at this time when intellectual disability/autism is not accompanied by other congenital anomalies
- 81410--Aortic dysfunction or dilation (e.g., Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome) **genomic sequence analysis panel**, must include sequencing of at least 9 genes, including FBN1, TGFBR1, TGFBR2, COL3A1, MYH11, ACTA2, SLC2A10, SMAD3, and MYLK
- 81411--Aortic dysfunction or dilation (e.g., Marfan syndrome, Loeys Dietz syndrome, Ehler Danlos syndrome type IV, arterial tortuosity syndrome) **duplication/deletion analysis panel**, must include analyses for TGFBR1, TGFBR2, MYH11, and COL3A1

Panel testing may be considered medically necessary for members with clinical features of Marfan syndrome, Loeys Dietz syndrome, or Ehler Danlos syndrome type IV when a diagnosis cannot be established based on clinical criteria alone.

- 81412--Ashkenazi Jewish associated disorders (e.g., Bloom syndrome, Canavan disease, cystic fibrosis, familial dysautonomia, Fanconi anemia group C, Gaucher disease, Tay-Sachs disease), **genomic sequence analysis panel**, must include sequencing of at least 9 genes, including ASPA, BLM, CFTR, FANCC, GBA, HEXA, IKBKAP, MCOLN1, and SMPD1)

Expanded carrier screening for Ashkenazi Jewish associated disorders using a genomic sequence analysis panel may be considered medically necessary for members of Ashkenazi Jewish ancestry.

Expanded carrier screening is not considered medically necessary at this time for routine screening of pregnant women.

- 81413--Cardiac ion channelopathies (e.g., Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia), **genomic sequence analysis panel**, must include sequencing of at least 10 genes, including ANK2, CASQ2, CAV3, KCNE1, KCNE2, KCNH2, KCNJ2, KCNQ1, RYR2, and SCN5A
- 81414--Cardiac ion channelopathies (e.g., Brugada syndrome, long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia), **duplication/deletion gene analysis panel**, must include analysis of at least 2 genes, including KCNH2 and KCNQ1

Multi-gene testing for Long QT Syndrome using the CPT codes described above may be medically necessary for members meeting one of the following:

- ◇ Strong clinical index of suspicion for LQTS based on examination of the patient's clinical history, family history, and expressed electrocardiographic (resting 12-lead ECGs and/or provocative stress testing with exercise or catecholamine infusion) phenotype

- ◇ symptomatic patient with QT prolongation in the absence of other clinical conditions that might prolong the QT interval (such as electrolyte abnormalities, hypertrophy, bundle branch block, etc., i.e., otherwise idiopathic) on serial 12-lead ECGs defined as QTc  $\geq$  480 ms (prepuberty) or  $\geq$  500 ms (adults)

If a familial variant has already been identified, coverage is limited to CPT 81281.

- 81415--Exome (e.g., unexplained constitutional or heritable disorder or syndrome) **sequence analysis**

Whole exome sequencing (WES) may be considered medically necessary for members with complex clinical features when all of the following criteria have been met:

- ◇ exome sequencing results will have a direct outcome on treatment and/or management for the member
- ◇ The clinical features of the member strongly implicate a genetic etiology, as evidenced by at least one of the following:
  - Multiple abnormalities affecting unrelated organ systems
  - At least two of the following:
    - Abnormality affecting a single organ system
    - Significant intellectual disability, symptoms of a complex neurodevelopmental disorder, or a severe neuropsychiatric condition
    - Period of unexplained developmental regression (unrelated to autism or epilepsy)
  - No other circumstances, such as environmental exposures, injury, or infection, can explain the clinical features
  - Clinical features do not fit a well-described syndrome for which single-gene testing is available
  - The member's clinical features would qualify him/her for multiple single-gene tests, and WES results may eliminate the need for multiple and/or invasive procedures, follow-up, or screening that would be recommended in the absence of testing

Exome testing is not considered medically necessary for any of the following indications:

- ◇ Prenatal testing
- ◇ testing for intellectual disability, autism, obesity, or seizure/epilepsy in the absence of other congenital anomalies

- 81417--Exome (e.g., unexplained constitutional or heritable disorder or syndrome); re-evaluation of previously obtained exome sequence.

Reanalysis of previously obtained uninformative WES is considered medically necessary when at least 18 months has passed since last analysis and any of the following criteria is met:

- ◇ There has been onset of additional symptoms that broadens the phenotype assessed during the original exome evaluation.
- ◇ There has been a birth or diagnosis of a similarly affected first-degree relative that has expanded the clinical picture.
- ◇ New Scientific knowledge suggests a previously unknown link between the patient's findings and specific genes/pathogenic or likely pathogenic variants.

- 81416 – Exome (e.g., unexplained constitutional or heritable disorder or syndrome) sequence analysis, each comparator genome (e.g., parents, siblings)

OHCA cannot cover services for family members, even if the result may impact the treatment/diagnosis of a member. Therefore, comparator testing is not a covered service.

- ∅ 81425--Genome (e.g., unexplained constitutional or heritable disorder or syndrome) sequence analysis
- ∅ 81426--Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, each comparator exome (e.g., parents, siblings)
- ∅ 81427--Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis, re-evaluation of previously obtained genome sequence (e.g., updated knowledge or unrelated condition/syndrome)

Whole genome sequencing is not considered medically necessary at this time.

- 81430--Hearing loss **genomic sequence analysis panel** (e.g., nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); must include sequencing of at least 60 genes, including CDH23, CLRN1, GJB2, GPR98, MTRNR1, MYO7A, MYO15A, PCDH15, OTOF, SLC26A4, TMC1, TMPRSS3, USH1C, USH1G, USH2A, and WFS1
- 81431--Hearing loss **deletion/duplication analysis panel**; must include copy number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes

Targeted panel testing may be considered medically necessary for members with non-syndromic hearing loss.

- 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
- 81434--Hereditary retinal disorders (e.g., retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy) **genomic sequence analysis panel**, must include sequencing of at least 15 genes, including ABCA4, CNGA1, CRB1, EYS, PDE6A, PRPF31, PRPH2, RDH12, RHO, RP1, RP2, RPE65, RPGR, and USH2A
- 81435--Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatous 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 disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatous polyposis); **duplication/deletion analysis panel**, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11

See the section on [Hereditary Cancer Testing](#) for criteria for hereditary breast cancer and/or hereditary colon cancer disorders.

- 81437--Hereditary neuroendocrine tumor disorders (e.g., medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); **genomic sequence analysis panel**, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TMEM127, and VHL)

- 81438--Hereditary neuroendocrine tumor disorders (e.g., medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma; **duplication/deletion analysis panel**, must include analyses for SDHB, SDHC, SDHD, and VHL)

[Endocrine Society](#) recommends a clinical feature driven algorithm for performing genetic testing in patients with pheochromocytoma and paraganglioma (PPGL).

Panel testing may be considered medically necessary with a PPGL diagnosis with non-syndromic presentation per the Endocrine Society guidelines.

- 81439--Inherited cardiomyopathy (e.g., hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy) **genomic sequence analysis panel**, must include sequencing of at least 5 genes, including DSG2, MYBPC3, MYH7, PKP2, and TTN
- 81440--Nuclear encoded mitochondrial genes (e.g., neurologic or myopathic phenotypes), **genomic sequence panel**, must include analysis of at least 100 genes, including BCS1L, C10orf2, COQ2, COX10, DGUOK, MPV17, OPA1, PDSS2, POLG, POLG2, RRM2B, SCO1, SCO2, SLC25A4, SUCLA2, SUCLG1, TAX, TK2, and TYMP

Targeted panel testing for nuclear encoded mitochondrial genes is not considered medically necessary at this time.

- 81442--Noonan spectrum disorders (e.g., Noonan syndrome, cardio-facio-cutaneous syndrome, Costello syndrome, LEOPARD syndrome, Noonan-like syndrome), **genomic sequence analysis panel**, must include sequencing of at least 12 genes, including BRAF, CBL, HRAS, KRAS, MAP2K1, MAP2K2, NRAS, PTPN11, RAF1, RIT1, SHOC2, and SOS1)

Targeted panel testing may be considered medically necessary for confirmatory diagnostic testing in members with clinical features suggestive of Noonan spectrum disorder(s).

- 81443--Genetic testing for severe inherited conditions (e.g., cystic fibrosis, Ashkenazi Jewish-associated disorders, beta hemoglobinopathies, phenylketonuria, galactosemia), genomic sequence analysis panel, must include sequencing of at least 15 genes
- ▲ 81445--Targeted genomic sequence analysis panel, **solid organ neoplasm**, DNA analysis, **5-50 genes**, interrogation for sequence variants and copy number variants or rearrangements, if performed
- 81448--Hereditary peripheral neuropathies (e.g., Charcot-Marie-Tooth, spastic paraplegia), **genomic sequence analysis panel**, must include sequencing of at least 5 peripheral neuropathy related genes
- ▲ 81450--Targeted genomic sequence analysis panel, **hematolymphoid neoplasm or disorder**, DNA and RNA analysis when performed, **5-50 genes**, interrogation for sequence variants and copy number variants or rearrangements or isoform expression or mRNA expression levels, if performed
- 81455--Targeted genomic sequence analysis panel, **solid organ or hematolymphoid neoplasm**, DNA and RNA analysis when performed, **51 or greater genes**

Targeted tumor sequencing panels including 5-50 genes may be considered medically necessary for members with solid organ or hematolymphoid neoplasms when NCCN guidelines recommend testing for variants in at least 5 genes. Testing panels including more than 50 genes are not considered medically necessary at this time.

- ∅ 81460--Whole mitochondrial genome (e.g., Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes [MELAS], myoclonic epilepsy with ragged-red fibers [MERFF], neuropathy, ataxia, and retinitis pigmentosa [NARP], Leber hereditary optic neuropathy [LHON], genomic sequence, **must include sequence analysis of entire mitochondrial genome** with heteroplasma detection

- ∅ 81465--Whole mitochondrial genome **large deletion analysis panel**

Whole mitochondrial genome testing is not considered medically necessary at this time

- ∅ 81470--X-linked intellectual disability (XLID) **genomic sequence analysis panel**, must include sequencing of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2

- ∅ 81471--X-linked intellectual disability (XLID) **duplication/deletion gene analysis**, must include analysis of at least 60 genes, including ARX, ATRX, CDKL5, FGD1, FMR1, HUWE1, IL1RAPL, KDM5C, L1CAM, MECP2, MED12, MID1, OCRL, RPS6KA3, and SLC16A2

Panel testing for intellectual disability is not considered medically necessary at this time.

#### J. **Multianalyte Assays with Algorithmic Analyses (MAAA)**

- ∅ 81490--Vectra® DA, Crescendo Bioscience, Inc.; test for detecting genes associated with rheumatoid arthritis using immunoassay technique

Vectra DA is not considered medically necessary at this time

- ▲ 81493 – Corus® CAD, CardioDx, Inc.; test for detecting genes associated with heart vessels diseases

Corus CAD may be considered medically necessary for the evaluation of nondiabetic adults with chest pain or angina equivalent symptoms who have no history of obstructive coronary artery disease.

- 81518--Oncology (breast) mRNA gene expression profiling by real-time RT-PCR of 11 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score
- 81519--Oncology (breast) mRNA gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy

Oncotype DX Breast may be considered necessary for members meeting the following criteria:

- ◇ Breast cancer stage I or II tumor
- ◇ Breast tumor size greater than 0.5cm
- ◇ Sentinel/axillary node negative, micromets less than 2mm, or 1-3 involved ipsilateral axillary lymph nodes
- ◇ Breast tumor is Estrogen Receptor (ER) positive OR Progesterone Receptor (PR) positive
- ◇ HER2 negative breast tumor
- ◇ Result of the test will be used to determine the appropriateness of adjuvant therapy
- ◇ Member has not already been approved for another gene expression profile test

(i.e., 81519 **OR** 81520 **OR** 81521 **OR** 81522)

- 81520--Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score

ProSigna Breast Cancer Prognostic Gene Signature Assay may be considered necessary for members meeting the criteria outlined for code 81519.

- 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

MammaPrint may be considered necessary for members meeting the criteria outlined for code 81519.

- 81522--Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk score

EndoPredict may be considered necessary for members meeting the criteria outlined for code 81519.

- 81523—Oncology (breast), mRNA, next-generation sequencing of breast cancer profiling 70 content genes and 31 housekeeping genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk to distant metastasis

- ∅ 81525--Oncotype DX® Colon Cancer Assay, Genomic Health; Oncology (colon), 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 a recurrence score

Oncotype DX Colon is not considered medically necessary at this time.

- ▲ 81528--Cologuard®, Exact Sciences, Inc.; Oncology (colorectal) screening, quantitative real-time target and signal amplification of 10 DNA markers (KRAS mutations, promoter methylation of NDRG4 and BMP3) and fecal hemoglobin, utilizing stool, algorithm reported as a positive or negative result

Cologuard® may be considered medically necessary as an option for colorectal cancer screening for members aged 50-85.

- 81529--Oncology (cutaneous melanoma), mRNA, gene expression profiling by real-time RT-PCR of 31 genes (28 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk, including likelihood of sentinel lymph node metastasis

- ∅ 81535--ChemoFX®, Helomics, Corp. Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score; first single drug or drug combination

- ◊ 81536--ChemoFX®, Helomics, Corp. Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score; each additional single drug or drug combination

ChemoFX assays for predicting drug response are not considered medically necessary at this time

- ▲ 81538--VeriStrat, Biodesix, Inc.; Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival

VeriStrat may be considered medically necessary for members with advanced non-small cell lung cancer (NSCLC) if the following criteria are met:

- ◇ Member has failed first-line chemotherapy
- ◇ Member's tumor lacks EGFR mutation(s)
- ◇ Test results will aid in deciding whether an EGFR-targeted agent such as erlotinib or efitinib may be an appropriate treatment

- ▲ 81539 – Oncology (high-grade prostate cancer), biochemical assay of four proteins (Total PSA, Free PSA, Intact PSA, and human kallikrein-2 [hK2]), utilizing plasma or serum, prognostic algorithm reported as a probability score

4KScore may be considered medically necessary for members 45 and older with intermediate PSA levels.

- ◊ 81540 – CancerTYPE ID, bioTheranostics, Inc.; Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a probability of a predicted main cancer type and subtype

Molecular pathology assays to determine tissue of origin, such as CancerTYPE ID, are not considered medically necessary at this time.

- 81541--Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a disease-specific mortality risk score

May be considered medically necessary for members meeting all of the following criteria:

- ◇ Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement), and
- ◇ Patient stage as defined by the one of the following:
  - Very Low Risk Disease (T1c AND Gleason Score = 6 AND PSA = 10 ng/mL)
  - Low Risk Disease (T1-T2a AND Gleason Score = 6 AND PSA = 10 ng/mL)
- ◇ Patient has a life expectancy of ≥ 10 years
- ◇ Patient is a candidate for and is considering conservative therapy and yet and would be eligible for definitive therapy (radical prostatectomy, radiation therapy or brachytherapy), and
- ◇ Patient has not received pelvic radiation or androgen deprivation therapy prior to the biopsy, and
- ◇ Test is ordered by a physician certified in the Myriad Prolaris™ Certification and Training Registry (CTR)

- 81542-- Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score

May be considered medically necessary for low risk and very low risk prostate cancer when all of the following conditions are met:

- ◇ Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement)
  - ◇ Low risk or very low risk as defined by the NCCN as follows:
    - Low Risk
      - Stage T1 or T2a
      - PSA less than 10ng/ml
      - Gleason score 6 or less (Grade Group 1)
    - Very low risk
      - Stage T1c
      - PSA less than 10ng/ml
      - Gleason score 6 or less (Grade Group 1)
      - Not more than 2 cores with cancer
      - Less than or equal to 50% of core involved with cancer
      - PSA density less than 0.15
    - Patient has an estimated life expectancy of at least 10 years
    - Patient is a candidate for as is considering conservative therapy yet would be eligible for definitive therapy (radical prostatectomy, radiation, or brachytherapy)
    - Result will be used to determine treatment
    - Patient has not received pelvic radiation or androgen deprivation therapy prior to the biopsy
- 81546—Oncology (thyroid), mRNA, gene expression analysis of 10,196 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (e.g. benign or suspicious)

Afirma Gene Expression Classifier may be considered medically necessary as an option for evaluating thyroid nodules of undetermined significance.

- 81551--Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a likelihood of prostate cancer detection on repeat biopsy
- 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 recurrence

May be considered medically necessary for members with primary, localized uveal melanoma with no evidence of metastatic disease.

- ▲ 81595--AlloMap®, CareDx, Inc.; Cardiology (heart transplant), mRNA, gene expression profiling by real-time quantitative PCR of 20 genes (11 content and 9 housekeeping), utilizing subfraction of peripheral blood, algorithm reported as a rejection risk score

AlloMap may be considered medically necessary to aid in management of heart transplant recipients.

- 81596--Infectious disease, chronic hepatitis virus (HCV) infection, six biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, and haptoglobin) utilizing serum, prognostic algorithm reported as scores for fibrosis and necroinflammatory activity in liver

#### K. Other Specific Molecular Pathology Testing

- ∅ 81105--Human Platelet Antigen 1 genotyping (HPA-1), (e.g., neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-1a/b (L33P)
- ∅ 81106--Human Platelet Antigen 2 genotyping (HPA-2), (e.g., neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-2a/b (T145M)
- ∅ 81107--Human Platelet Antigen 3 genotyping (HPA-3), (e.g., neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-3a/b (I843S)
- ∅ 81108--Human Platelet Antigen 4 genotyping (HPA-4), (e.g., neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-4a/b (R143Q)
- ∅ 81109--Human Platelet Antigen 5 genotyping (HPA-5), (e.g., neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-5a/b (K505E)
- ∅ 81110--Human Platelet Antigen 6 genotyping (HPA-6w), (e.g., neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-6a/b (R489Q)
- ∅ 81111--Human Platelet Antigen 9 genotyping (HPA-9w), (e.g., neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-9a/b (V837M)
- ∅ 81112--Human Platelet Antigen 15 genotyping (HPA-15), (e.g., neonatal alloimmune thrombocytopenia [NAIT], post-transfusion purpura), gene analysis, common variant, HPA-15a/b (S682Y)
- ▲ 81265--Comparative analysis using Short Tandem Repeat (STR) markers; **patient and comparative specimen** (e.g., pre-transplant recipient and donor germline testing, post-transplant non-hematopoietic recipient germline [e.g., buccal swab or other germline tissue sample] and donor testing, twin zygosity testing, or maternal cell contamination of fetal cells)
- ▲ 81266--Comparative analysis using Short Tandem Repeat (STR) markers; **each additional specimen** (e.g., additional cord blood donor, additional fetal samples from different cultures, or additional zygosity in multiple birth pregnancies) (List separately in addition to code for primary procedure)

Comparative analysis using STR markers may be considered medically necessary for pre-transplant analysis when allogenic stem cell transplant is considered medically necessary.

- ▲ 81267--Chimerism (engraftment) analysis, post transplantation specimen (e.g., hematopoietic stem cell), includes comparison to previously performed baseline analyses; **without cell selection**
- ▲ 81268--Chimerism (engraftment) analysis, post transplantation specimen (e.g., hematopoietic stem cell), includes comparison to previously performed baseline analyses; **with cell selection** (e.g., CD3, CD33), each cell type

Chimerism analysis may be considered medically necessary post-transplant to detect the presence of donor leukocytes in the host's peripheral blood or bone marrow.

∅ 81313--PCA/KLK3 ratio (e.g., prostate cancer)

Analysis of the PCA/KLK3 ratio for screening, diagnosis, or management of prostate cancer is not considered medically necessary at this time.

∅ 81327--SEPT9 (Septin9) (e.g., colorectal cancer) methylation analysis

Analysis of SEPT9 methylation for screening of colorectal cancer is not considered medically necessary at this time.

#### L. Nonspecific Molecular Pathology Codes

- 81400--Molecular pathology procedure, Level 1 (e.g., identification of single germline variant [e.g., SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
- 81401--Molecular pathology procedure, Level 2 (e.g., 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)
- 81402--Molecular pathology procedure, Level 3 (e.g., >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants 1 exon)
- 81403--Molecular pathology procedure, Level 4 (e.g., 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)
- 81404--Molecular pathology procedure, Level 5 (e.g., 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)
- 81405--Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons)
- 81406--Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)
- 81407--Molecular pathology procedure, Level 8 (e.g., analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
- 81408--Molecular pathology procedure, Level 9 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis)
- \$81479--Unlisted molecular pathology procedure
- \$81599--Unlisted multianalyte assay with algorithmic analysis

Nonspecific molecular pathology codes may be considered medically necessary if OHCA's genetic testing policy criteria are met and claims for these codes are considered on a case-by-case basis. In general, types of tests that may be considered medically necessary include:

- ◇ Testing at-risk family members for already-identified familial variants
- ◇ Single-gene diagnostic testing for members with clinical features that are highly suggestive of a particular genetic condition for which a single-gene test is appropriate
- ◇ Multi-gene panel testing for members with clinical features that are highly suggestive of a particular genetic condition or group on conditions that is/are genetically

heterogeneous. **For panels that do not have a single CPT code that fully describes the test being performed, OHCA does not consider billing multiple codes to be appropriate. Instead, billing one unit of 81479 is appropriate.**

Examples of tests that may be considered medically necessary when billed using nonspecific codes may include:

- 81599--EndoPredict may be considered necessary for members meeting the criteria outlined for cod 81519

#### M. **Proprietary Laboratory Analyses**

**Proprietary Laboratory Analyses are not covered services except as described below:**

- 0001U--Red blood cell antigen typing, DNA, human erythrocyte antigen gene analysis of 35 antigens from 11 blood groups, utilizing whole blood, common RBC alleles reported
- 0016U--Oncology (hematolymphoid neoplasia), RNA, BCR/ABL1 major and minor breakpoint fusion transcripts; quantitative PCR amplification, blood or bone marrow, report of fusion not detected or detected with quantitation
- 0017U--Oncology (hematolymphoid neoplasia), JAK2 mutation, DNA, PCR amplification of exons 12-14 and sequence analysis, blood or bone marrow, report of JAK2 mutation not detected or detected
- 0018U--Oncology (thyroid), microRNA profiling by rt-pcr of 10 microRNA sequences, utilizing fine needle aspirate, algorithm reported as a positive or negative result for moderate to high risk of malignancy
- 0022U--Targeted genomic sequence analysis panel, non-small cell lung neoplasia, DNA and RNA analysis, 23 genes, interrogation for sequence variants and rearrangements, reported as presence/absence of variants and associated therapy(ies) to consider
- 0023U--Oncology (acute myelogenous leukemia), DNA, genotyping of internal tandem duplication, p.d835, p.i836, using mononuclear cells, reported as detection or non-detection of FLT3 mutation and indication for or against the use of midostaurin
- 0026U--Oncology (thyroid), DNA and mRNA of 112 genes, NGS, algorithmic analysis reported as a categorical result
- ▲ 0027U--JAK2 gene analysis, targeted sequence analysis exons 12-15
- 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

FoundationOne CDx may be considered medically necessary for members with advanced cancer (i.e., recurrent, metastatic, relapsed, refractory, or stages III-IV cancer) to identify patients with certain genetic mutations that may benefit from FDA-approved treatments.

- 0047U--Oncology (prostate), mRNA, gene expression profiling by real-time PCR of 17 genes, algorithm reported as a risk score

May be considered medically necessary for members meeting all of the following criteria:

- ◇ Needle biopsy with localized adenocarcinoma of prostate (no clinical evidence of metastasis or lymph node involvement), and
- ◇ Patient stage as defined by one of the following:
  - Very Low Risk Disease (T1c AND Gleason Score = 6 AND PSA = 10 ng/mL)
  - Low Risk Disease (T1-T2a AND Gleason Score = 6 AND PSA = 10 ng/mL)
- ◇ Patient has a life expectancy of  $\geq 10$  years

- ◇ Patient is a candidate for and is considering conservative therapy and yet and would be eligible for definitive therapy (radical prostatectomy, radiation therapy or brachytherapy), and
- ◇ Patient has not received pelvic radiation or androgen deprivation therapy prior to the biopsy, and
- ◇ Test is ordered by a physician certified in the Genomic Health™ Oncotype DX® Prostate Cancer Assay Certification and Training Registry (CTR)

- 0111U--Praxis Extended RAS Panel, Oncology (color cancer), targeted KRAS and NRAS gene analysis

May be considered medically necessary for members with colon cancer considering treatment with anti-EGFR therapies.

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