

CAUTION: Read the [ICD-9 Policy Holding Library](#) page about policy in this document.

Pathology: Molecular Pathology

This section contains information to help providers bill for clinical laboratory tests or examinations related to molecular pathology and diagnostic services.

Molecular Pathology Code Chart

The chart included later in this section correlates molecular pathology CPT-4 and HCPCS Level II codes with the following:

- *Treatment Authorization Request* (TAR) and claim documentation requirements
- Allowable diagnosis (ICD-9-CM) codes
- Once-in-a-lifetime and other frequency limitations for reimbursement
- Select modifier and split-billing information

Note: Policy for most molecular pathology codes fits within the chart; however, some policy was too lengthy or complex for the chart and is covered outside of the chart.

Modifiers

For a description of the modifiers billed with certain codes, refer to the *Modifiers: Approved List* section in this manual.

Tier 1 Code Correlation Chart Providers should refer to the CPT-4 or HCPCS Level II code book, as appropriate, for full descriptions of the following codes.

CPT-4 Code Description	TAR Required	TAR and/or Billing Requirements	Frequency
81201 APC gene analysis; full gene sequence	No	One of the following ICD-9-CM codes is required on the claim: 153.0 – 153.9, 211.3, V12.72	Once-in-a-lifetime
81202 APC gene analysis; known familial variants	Yes	Requires documentation on the TAR of a family history of familial adenomatous polyposis that includes a relative with a known deleterious APC mutation	Once-in-a-lifetime
81203 APC gene analysis; duplication/deletion variants	No	One of the following ICD-9-CM codes is required on the claim: 153.0 – 153.9, 211.3, V12.72	Once-in-a-lifetime
81206 BCR/ABL1 translocation analysis; major breakpoint	No	One of the following ICD-9-CM codes is required on the claim: 204.00 – 204.02 or 205.10 – 205.12	1 per month
81207 BCR/ABL1 translocation analysis; minor breakpoint	No	One of the following ICD-9-CM codes is required on the claim: 204.00 – 204.02 or 205.10 – 205.12	1 per month
81208 BCR/ABL1 translocation analysis; other breakpoint	No	One of the following ICD-9-CM codes is required on the claim: 204.00 – 204.02 or 205.10 – 205.12	1 per month
81210 BRAF (v-raf murine sarcoma viral oncogene homolog B1) gene analysis, V600E variant	No	One of the following ICD-9-CM codes is required on the claim: 153.0 – 153.9, 172.0 – 172.9 or 198.2	Once-in-a-lifetime

CPT-4 Code Description	TAR Required	TAR and/or Billing Requirements	Frequency
81211 BRCA1, BRCA2 gene analysis; full sequence analysis	Yes	<p>A TAR for code 81211 requires documentation of <u>one or more</u> of the following numbered criteria:</p> <p>1. For women without diagnosis of breast or ovarian cancer:</p> <ul style="list-style-type: none"> • Two first-degree relatives with breast cancer, one of whom was diagnosed at <u>age ≤ 50</u>; OR • A combination of three or more first- or second-degree relatives with breast cancer regardless of age at diagnosis; OR • A combination of both breast and ovarian cancer among first- and second-degree relatives; OR • A first-degree relative with bilateral breast cancer; OR • A combination of two or more first- or second-degree relatives with ovarian cancer, regardless of age at diagnosis; OR • A first- or second-degree relative with both breast and ovarian cancer at any age; OR • History of breast cancer in a male relative; OR • For women of Ashkenazi Jewish descent, any first-degree relative (or two second-degree relatives on the same side of the family) with breast or ovarian cancer; <u>OR</u> <p>2. A family history of breast or ovarian cancer that includes a relative with a known deleterious BRCA mutation; <u>OR</u></p> <p style="text-align: right;"><i><u>continued on next page</u></i></p>	Once-in-a-lifetime

CPT-4 Code Description	TAR Required	TAR and/or Billing Requirements	Frequency
81211 BRCA1, BRCA2 gene analysis (<i>cont'd.</i>)	Yes	<p>3. Personal history of breast cancer plus one or more of the following:</p> <ul style="list-style-type: none"> • Diagnosed at <u>age ≤ 45; OR</u> • Diagnosed at <u>age ≤ 50</u> with <u>≥ 1</u> close blood relatives with breast cancer diagnosed at <u>age ≤ 50</u> and/or <u>≥ 1</u> close blood relatives with <u>epithelial ovarian cancer at any age; OR</u> • Two breast primaries when first breast cancer diagnosis occurred <u>at age ≤ 50; OR</u> • <u>Diagnosed at age ≤ 60 with a triple negative breast cancer; OR</u> • <u>Diagnosed at age ≤ 50 with a limited family history; OR</u> • Diagnosed at any age, with <u>≥ 2</u> close blood relatives with breast and/or epithelial ovarian/fallopian tube/primary peritoneal cancer at any age; <u>OR</u> • <u>Diagnosed at any age with ≥ 2 close blood relatives with pancreatic cancer at any age; OR</u> • Close male blood relative with breast cancer; <u>OR</u> • For an individual of ethnicity associated with higher mutation frequency (for example, founder populations of Ashkenazi Jewish, Icelandic, Swedish, Hungarian or other) no additional family history may be required; <u>OR</u> <p>4. Personal history of epithelial ovarian cancer/fallopian tube/primary peritoneal cancer; <u>OR</u></p> <p>5. Personal history of male breast cancer; <u>OR</u></p> <p>6. <u>Personal history of pancreatic cancer at any age with ≥ 2 close blood relatives with breast and/or ovarian and/or pancreatic cancer at any age.</u></p>	Once-in-a-lifetime
81211 (Reflex BRCA1, BRCA2 gene analysis billed with modifier QP)	Yes	<p>A TAR for code 81211 billed with modifier QP requires documentation of the following:</p> <ul style="list-style-type: none"> • A negative result in the single mutation (codes 81215 or 81217) or three-mutation (code 81212) analysis, and • One or more criteria listed under code 81211 	Once-in-a-lifetime

CPT-4 Code Description	TAR Required	TAR and/or Billing Requirements	Frequency
81212 BRCA1, BRCA2 gene analysis; variants	Yes	Requires documentation on the TAR of the following: <ul style="list-style-type: none"> An individual is of an ethnicity associated with the Ashkenazi Jewish population No additional family history may be required 	Once-in-a-lifetime
81213 BRCA1, BRCA2 gene analysis; uncommon duplication/deletion variants	Yes	Requires documentation on the TAR of the following: <ul style="list-style-type: none"> A negative result in the full sequence analysis and common duplication/ deletion variants in BRCA (CPT-4 code 81211), and One or more criteria listed under CPT-4 code 81211 	Once-in-a-lifetime
81215 BRCA1 (breast cancer 1) gene analysis; known familial variant	Yes	Requires documentation on the TAR of family history of breast or ovarian cancer that includes a relative with a known deleterious BRCA mutation	Once-in-a-lifetime
81217 BRCA2 (breast cancer 2) gene analysis; known familial variant	Yes	Requires documentation on the TAR of family history of breast or ovarian cancer that includes a relative with a known deleterious BRCA mutation	Once-in-a-lifetime
81220 CFTR (cystic fibrosis transmembrane conductance regulator) gene analysis; common variants	No	When used to bill for cystic-fibrosis screening requires ICD-9-CM code V26.31 or V26.34 Not reimbursable with code 81224 for same date of service, recipient and provider May be billed separately with an appropriate National Correct Coding Initiative (NCCI) associated modifier Refer to the <i>Genetic Counseling and Screening</i> section for additional information	Once-in-a-lifetime
81235 EGFR (epidermal growth factor receptor) gene analysis, common variants	No	One of the following ICD-9-CM codes is required on the claim: 162.0 – 162.9	Once-in-a-lifetime
81243 FMR1 (fragile X mental retardation 1) gene analysis; evaluation to detect abnormal alleles	No	One of the following ICD-9-CM codes is required on the claim: 299.00, 299.01, 315.00 – 315.9, 317, 318.0 – 318.2, 319	Once-in-a-lifetime

CPT-4 Code Description	TAR Required	TAR and/or Billing Requirements	Frequency
81244 FMR1 (fragile X mental retardation 1) gene analysis; characterization of alleles	No	One of the following ICD-9-CM codes is required on the claim: 299.00, 299.01, 315.00 – 315.9, 317, 318.0 – 318.2, 319	Once-in-a- lifetime
81250 G6PC (glucose-6- phosphatase, catalytic subunit) gene analysis, common variants	No	Document patient has clinical features suspicious for, or requires the laboratory service as a diagnostic test for glycogen storage disease, type Ia	Once-in-a- lifetime
81256 HFE (hemochromatosis) gene analysis, common variants	No	One of the following ICD-9-CM codes is required on the claim: 275.01, 275.03 or 275.09	Once-in-a- lifetime
81260 IKBKAP (inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase complex- associated protein) gene analysis, common variants	Yes	Requires documentation on the TAR of: <ul style="list-style-type: none"> • Hypotonia in infancy • Decreased or absent deep tendon reflexes • Decreased taste and absence of fungiform papillae of the tongue • Absence of overflow tears with emotional crying (alacrima) • Absence of axon flare response after intradermal histamine injection • Pupillary hypersensitivity to parasympathomimetic agents 	Once-in-a- lifetime

CPT-4 Code Description	TAR Required	TAR and/or Billing Requirements	Frequency
81265 Comparative analysis using Short Tandem Repeat markers	No	One of the following ICD-9-CM codes is required on the claim: 200.00 – 208.92, 996.85 or 996.88	Once-in-a-lifetime
81266 Comparative analysis using Short Tandem Repeat markers; each additional specimen	No	One of the following ICD-9-CM codes is required on the claim: 200.00 – 208.92, 996.85 or 996.88	Once-in-a-lifetime
81267 Chimerism (engraftment) analysis, post transplantation specimen; without cell selection	No	One of the following ICD-9-CM codes is required on the claim: 996.85 or 996.88	1 per month
81268 Chimerism (engraftment) analysis, post transplantation specimen; with cell selection	No	One of the following ICD-9-CM codes is required on the claim: 996.85 or 996.88	1 per month
81270 JAK2 (Janus kinase 2) gene analysis, p. Val617Phe (V617F) variant	No	One of the following ICD-9-CM codes is required on the claim: 238.4, 238.71 or 238.76	Once-in-a-lifetime

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CPT-4 Code Description	TAR Required	TAR and/or Billing Requirements	Frequency
81275 KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) gene analysis, variants in codons 12 and 13	No	One of the following ICD-9-CM codes is required on the claim: 153.0 – 153.4, 153.6 – 154.2, 159.0, 230.4 or 235.2	Once-in-a- lifetime
81280 Long QT syndrome gene analyses; full sequence analysis	Yes	Not split-billable and must not be billed with modifier 26, 99 or TC Document on the TAR a copy of the report of the physician-interpreted 12-lead electrocardiogram (ECG) with pattern consistent with or suspicious for prolonged QT interval, <u>and</u> clinical documentation of one or more of the following: <ul style="list-style-type: none"> • Torsade de pointes in the absence of drugs known to prolong QT interval • T-wave alternans • Notched T-wave in three leads • Syncope • Family members with LQTS • Sudden death in family members less than 30 years of age without defined cause 	Once-in-a- lifetime
81281 Long QT syndrome gene analyses; known familial sequence variant	Yes	Not split-billable and must not be billed with modifier 26, 99 or TC Document on the TAR: <ul style="list-style-type: none"> • The family member being tested is a Medi-Cal recipient, and • There is clinical documentation of at least one first-degree relative (parent, sibling or offspring) with a laboratory-confirmed LQTS genetic mutation 	Once-in-a- lifetime
81287 MGMT (0-6 methylguanin-DNA methyltransferase) methylation analysis	No	Requires documentation of the following: <ul style="list-style-type: none"> • The patient has the diagnosis of glioblastoma multiforme, and • Treatment strategy will be contingent on the test results 	Once-in-a- lifetime, any provider

CPT-4 Code Description	TAR Required	TAR and/or Billing Requirements	Frequency
81292 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) gene analysis; full sequence analysis	No	One of the following ICD-9-CM codes is required on the claim: 153.0 – 153.4 or 153.6 – 153.9	Once-in-a-lifetime
81293 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) gene analysis; known familial variants	Yes	Document on the TAR family history of Lynch Syndrome that includes a relative with a known deleterious MLH1 mutation	Once-in-a-lifetime
81294 MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) gene analysis; duplication/deletion variants	Yes	Document on the TAR patient history of colon cancer and a negative result for MLH1 full sequence analysis	Once-in-a-lifetime
81295 MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) gene analysis; full sequence analysis	No	One of the following ICD-9-CM codes is required on the claim: 153.0 – 153.4 or 153.6 – 153.9	Once-in-a-lifetime
81296 MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) gene analysis; known familial variants	Yes	Document on the TAR family history of Lynch Syndrome that includes a relative with a known deleterious MSH2 mutation	Once-in-a-lifetime

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CPT-4 Code Description	TAR Required	TAR and/or Billing Requirements	Frequency
81297 MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) gene analysis; duplication/deletion variants	Yes	Document on the TAR patient history of colon cancer and a negative result for MSH2 full sequence analysis	Once-in-a- lifetime
81298 MSH6 (mutS homolog 6 [E. coli]) gene analysis; full sequence analysis	No	One of the following ICD-9-CM codes is required on the claim: 153.0 – 153.4 or 153.6 – 153.9	Once-in-a- lifetime
81299 MSH6 (mutS homolog 6 [E. coli]) gene analysis; known familial variants	Yes	Document on the TAR family history of Lynch Syndrome that includes a relative with a known deleterious MSH6 mutation	Once-in-a- lifetime
81300 MSH6 (mutS homolog 6 [E. coli]) gene analysis; duplication/deletion variants	Yes	Document on the TAR patient history of colon cancer and a negative result for MSH6 full sequence analysis	Once-in-a- lifetime

CPT-4 Code Description	TAR Required	TAR and/or Billing Requirements	Frequency
81301 Microsatellite instability analysis of markers for mismatch repair deficiency	No	One of the following ICD-9-CM codes is required on the claim: 153.0 – 153.4 or 153.6 – 153.9	Once-in-a- lifetime
81315 PML/RAR-alpha (promyelocytic leukemia/retinoic acid receptor alpha) translocation analysis; common breakpoints	No	One of the following ICD-9-CM codes is required on the claim: 205.00 – 205.02	1 per month
81316 PML/RAR-alpha (promyelocytic leukemia/retinoic acid receptor alpha) translocation analysis; single breakpoint	No	One of the following ICD-9-CM codes is required on the claim: 205.00 – 205.02	1 per month
81317 PMS2 (postmeiotic segregation increased 2 [<i>S. cerevisiae</i>]) gene analysis; full sequence analysis	No	One of the following ICD-9-CM codes is required on the claim: 153.0 – 153.4 or 153.6 – 153.9	Once-in-a- lifetime
81318 PMS2 (postmeiotic segregation increased 2 [<i>S. cerevisiae</i>]) gene analysis; known familial variants	Yes	Document on the TAR family history of Lynch Syndrome that includes a relative with a known deleterious PMS2 mutation	Once-in-a- lifetime

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CPT-4 Code Description	TAR Required	TAR and/or Billing Requirements	Frequency
81319 PMS2 (postmeiotic segregation increased 2 [<i>S. cerevisiae</i>]) gene analysis; duplication/deletion variants	Yes	Document on the TAR patient history of colon cancer and a negative result for PMS2 full sequence analysis	Once-in-a-lifetime
81321 PTEN (phosphatase and tensin homolog) gene analysis; full sequence analysis	Yes	<p>A TAR for CPT-4 code 81321 requires documentation of one or more of the following numbered criteria:</p> <p>1. Individual with a personal history of:</p> <ul style="list-style-type: none"> • Bannayan-Riley-Ruvalcaba syndrome, or • Adult Lhermitte-Duclos disease, or • Autism spectrum disorder AND macrocephaly, or • Two or more biopsy-proven trichilemmomas, or • Two or more major criteria (one macrocephaly), or • Three major criteria without macrocephaly, or • One major and three or more minor criteria, or • Four or more minor criteria (please see list below) <p>2. At-risk individual: With a relative who has a clinical diagnosis of Cowden syndrome or Bannayan-Riley-Ruvalcaba syndrome for whom testing has not been performed AND who has any one major criterion or two minor criteria</p> <p style="text-align: right;"><i>(continued on next page)</i></p>	Once-in-a-lifetime

CPT-4 Code Description	TAR Required	TAR and/or Billing Requirements	Frequency
81321 <u>PTEN gene analysis; full sequence analysis (continued)</u>	<u>Yes</u>	<p>Major Criteria</p> <ul style="list-style-type: none"> • <u>Breast cancer</u> • <u>Mucocutaneous lesions</u> • <u>One biopsy-proven trichilemmoma</u> • <u>Multiple palmoplantar keratosis</u> • <u>Multifocal or extensive oral mucosal papillomatosis</u> • <u>Multiple cutaneous facial papules (often verrucous)</u> • <u>Macular pigmentation of glans penis</u> • <u>Macrocephaly (megalencephaly, ie, ≥97th percentile)</u> • <u>Endometrial cancer</u> • <u>Non-medullary thyroid cancer</u> • <u>Multiple GI tract hamartomas or ganglioneuromas</u> <p>Minor Criteria</p> <ul style="list-style-type: none"> • <u>Other thyroid lesions (adenoma, nodule, goiter)</u> • <u>Mental retardation (IQ ≤75)</u> • <u>Autism spectrum disorder</u> • <u>Single GI tract hamartoma or ganglioneuroma</u> • <u>Fibrocystic disease of the breast</u> • <u>Lipomas</u> • <u>Fibromas</u> • <u>Renal cell carcinoma</u> • <u>Uterine fibroids</u> 	<u>Once-in-a-lifetime</u>
81322 <u>PTEN gene analysis; known familial variant</u>	<u>Yes</u>	<u>Requires documentation on the TAR that patient is from a family with a known PTEN mutation</u>	<u>Once-in-a-lifetime</u>
81323 <u>PTEN gene analysis; duplication/deletion variant</u>	<u>Yes</u>	<u>Requires documentation on the TAR of a negative result in the full sequence analysis in PTEN (CPT-4 code 81321), and that patient meets one or more criteria listed under code 81321</u>	<u>Once-in-a-lifetime</u>

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CPT-4 Code Description	TAR Required	TAR and/or Billing Requirements	Frequency
81331 SNRPN/UBE3A methylation analysis	Yes	Document the following age-specific criteria on the TAR <ul style="list-style-type: none"> • <u>Birth to 2 years</u>: Hypotonia with poor suck • <u>2 – 6 years</u>: Hypotonia with history of poor suck and global development delay • <u>6 – 13 years</u>: History of hypotonia with poor suck (hypotonia often persists); global development delay; and excessive eating (hyperphagia; obsession with food) with central obesity if uncontrolled • <u>13 years – adult</u>: Cognitive impairment – usually mild mental retardation; excessive eating (hyperphagia; obsession with food) with central obesity if uncontrolled; and hypothalamic hypogonadism and/or typical behavior problems (including temper tantrums and obsessive-compulsive features) 	Once-in-a-lifetime

**Tier 2, Molecular Pathology
Procedure, Level 1**

Coverage for CPT-4 code 81400 (molecular pathology procedure, Level 1) is limited to the listed services. Reimbursement for code 81400 requires an approved *Treatment Authorization Request* (TAR), is limited to once in a lifetime and requires providers to document one of the following on the TAR:

- Human Platelet Antigen genotyping:
 - The patient has clinical features suspicious for, or requires the service as a confirmatory test for neonatal alloimmune thrombocytopenia, or,
 - The patient has clinical features suspicious for, or requires services as a confirmatory test for post transfusion purpura
- CCR5 (chemokine C-C motif receptor 5):
 - Initial test:
 - ❖ The use of a CCR5 inhibitor is being considered, or
 - ❖ The patient exhibits virologic failure on a CCR5 inhibitor
 - Subsequent tests:
 - ❖ A previous Trofile test was performed including the test date and the results showing that the recipient has a CCR5 virus, and,
 - ❖ The recipient's previous Trofile test was not less than 90 days from subsequent request, and,
 - ❖ The recipient has clinical scenario such as, but not limited to the following:
 - The treatment with CCR5 antagonist drug therapy was interrupted and the clinician wishes to reinstitute CCR5 antagonist drug therapy, or,
 - The recipient had a Trofile test performed previously that showed that the recipient had the CCR5 virus, but the CCR5 antagonist drug therapy was never initiated.
- SMN1 (spinal muscular atrophy) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for spinal muscular atrophy
- IL28B
 - The patient has genotype 1 hepatitis C virus infection, and,
 - Treatment will be contingent on the test results.

Claims without documentation showing the preceding criteria have been met will be denied.

**Tier 2, Molecular Pathology
Procedure, Level 2**

Coverage for CPT-4 code 81401 (molecular pathology procedure, Level 2) is limited to the listed services. Reimbursement for code 81401 requires an approved TAR and requires providers to document one of the following on the TAR:

- ABCC8 (familial hyperinsulinism):
 - The patient has persistent hyperinsulinemic hypoglycemia of infancy (PHHI), failed medical therapy, and
 - The patient is under evaluation for surgical intervention
- ABL (c-abl oncogene 1, receptor tyrosine kinase) – The patient has chronic myeloid leukemia (CML) and failed tyrosine kinase inhibitor (TKI) therapy
- AR (spinal & bulbar muscular atrophy, Kennedy disease, X chromosome inactivation) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for spinal and bulbar muscular atrophy or Kennedy disease
- ATN1 (dentatorubral-pallidoluysian atrophy) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for dentatorubral pallidoluysian atrophy
- ATXN1 (spinocerebellar ataxia) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for spinocerebellar ataxia
- ATXN2 (spinocerebellar ataxia) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for spinocerebellar ataxia
- ATXN3 (spinocerebellar ataxia, Machado-Joseph disease) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for spinocerebellar ataxia
- ATXN7 (spinocerebellar ataxia) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for spinocerebellar ataxia
- ATXN10 (spinocerebellar ataxia) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for spinocerebellar ataxia
- ATXN80S (spinocerebellar ataxia) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for spinocerebellar ataxia
- CACNA1A (spinocerebellar ataxia) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for spinocerebellar ataxia
- CNBP (myotonic dystrophy, type 2) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for myotonic dystrophy, type 2

- CSTB (Unverricht-Lundborg disease):
 - The patient has clinical features suspicious for, or requires the service as a confirmatory test for myoclonic epilepsy type 1, and
 - Treatment will be contingent on test results
- DMPK (dystrophia myotonica-protein kinase) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for myotonic dystrophy type 1
- E2A/PBX1 (acute lymphocytic leukemia):
 - The patient has the diagnosis of acute lymphocytic/lymphoblastic leukemia, and
 - Treatment or monitoring strategy will be contingent on the test results
- ETV6/RUNX1 (acute lymphocytic leukemia) – The patient has the diagnosis of acute lymphocytic or lymphoblastic leukemia, and requires the test for assessment of cancer prognosis
- FXN (Friedreich ataxia) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for Friedreich ataxia
- H19 (Beckwith-Wiedemann syndrome) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for Beckwith-Wiedemann syndrome
- KCNQ1OT1 (Beckwith-Wiedemann syndrome) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for Beckwith-Wiedemann syndrome
- MLL/AFF1 (acute lymphoblastic leukemia):
 - The patient has the diagnosis of acute lymphoblastic leukemia, and
 - Treatment or monitoring strategy will be contingent on the test results
- MLL/MLLT3 (acute myeloid leukemia):
 - The patient has the diagnosis of acute myeloid leukemia, and
 - Treatment or monitoring strategy will be contingent on the test results
- MUTYH (MYH-associated polyposis) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for MUTYH-associated polyposis
- MT-ATP6 (neuropathy with ataxia and retinitis pigmentosa [NARP], Leigh syndrome) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for NARP or Leigh syndrome

- PPP2R2B (spinocerebellar ataxia) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for spinocerebellar ataxia
- PRSS1 (hereditary pancreatitis):
 - An unexplained documented episode of acute pancreatitis in childhood, or
 - Recurrent acute attacks of pancreatitis of unknown cause, or
 - Chronic pancreatitis of unknown cause, particularly with onset younger than 25 years of age, or
 - A family history of recurrent acute pancreatitis, chronic pancreatitis of unknown cause, and/or childhood pancreatitis of unknown cause consistent with autosomal dominant inheritance
- PYPGM (glycogen storage disease type V, McArdle disease) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for glycogen storage disease type V (McArdle disease)
- RUNX1/RUNX1T1 (t[8;21]) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for acute myeloid leukemia
- TBP (spinocerebellar ataxia) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for spinocerebellar ataxia

Claims without documentation showing the preceding criteria have been met will be denied.

Tier 2, Molecular Pathology Procedure, Level 3

Coverage for CPT-4 code 81402 (molecular pathology procedure, Level 3) is limited to the listed services. Reimbursement for code 81402 requires an approved TAR and requires providers to document one of the following on the TAR:

- KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) – The patient has clinical features suspicious for, or requires the service as a diagnostic test for mastocytosis
- Chromosome 1p-/19q- (e.g. glial tumors), deletion analysis – The patient has oligodendroglioma tumor

Claims without documentation showing the preceding criteria have been met will be denied.

Tier 2, Molecular Pathology Procedure, Level 4

Coverage for CPT-4 code 81403 (molecular pathology procedure, Level 4) is limited to the listed services. Reimbursement for code 81403 requires an approved TAR and requires providers to document one of the following on the TAR:

- DNMT3A (acute myeloid leukemia):
 - The patient has diagnosis of acute myeloid leukemia, and
 - The treatment strategy will be contingent on test results
- EPCAM (Lynch syndrome) – The patient has colorectal cancer and/or Lynch syndrome
- JAK 2 (Janus kinase 2) – The patient has clinical features suspicious for, or requires the service as a diagnostic test for myeloproliferative disorder
- KCNC3 (spinocerebellar ataxia) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for spinocerebellar ataxia
- KCNJ11 (familial hyperinsulinism):
 - The patient has persistent hyperinsulinemic hypoglycemia of infancy (PHHI) and failed medical therapy, and
 - The patient is under evaluation for surgical intervention
- KIR (killer cell immunoglobulin-like receptor for hematopoietic stem cell transplantation):
 - The patient has diagnosis of acute myeloid leukemia, and
 - The test is used for donor search process for patients considering hematopoietic stem cell transplantation

- KRAS (Carcinoma), exon 3, codon 61:
 - The patient has colorectal cancer, and
 - The intention to treat or not to treat with anti-EGFR antibodies (cetuximab or panitumumab) will be contingent on the test results
- MICA (solid organ transplantation):
 - The patient is undergoing evaluation for kidney transplantation, or
 - The patient is post kidney transplantation
- MPL (myeloproliferative leukemia virus oncogene, thrombopoietin receptor, TPOR) – The patient has clinical features suspicious for, or requires the service as a diagnostic test for myeloproliferative disorder
- NDP (Norrie disease) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for Norrie disease
- SH2D1A (X-linked lymphoproliferative syndrome) – The patient is a male with the diagnosis of:
 - Common variable immune deficiency, or
 - Hypogammaglobulinemia, or
 - Hemophagocytic lymphohistiocytosis, or
 - Severe infectious mononucleosis, or
 - Lymphoma, or
 - Family history of X-linked lymphoproliferative syndrome
- VHL (von Hippel-Lindau tumor suppressor), deletion/duplication analysis – The patient has clinical features suspicious for, or requires the service as a diagnostic test for von Hippel-Lindau syndrome

Claims without documentation showing the preceding criteria have been met will be denied.

**Tier 2, Molecular Pathology
Procedure, Level 5**

Coverage for CPT-4 code 81404 (molecular pathology procedure, Level 5) is limited to the listed services. Reimbursement for code 81404 requires an approved *Treatment Authorization Request* (TAR) and requires providers to document one of the following on the TAR:

- CD40LG (X-linked hyper IgM syndrome) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for hyperimmunoglobulin M syndromes
- CSTB (Unverricht-Lundborg disease) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for Unverricht-Lundborg disease
- DMPK (dystrophia myotonica-protein kinase) – The patient has clinical features suspicious for, or requires the service as a diagnostic test for myotonic dystrophy
- EMD (Emery-Dreifuss muscular dystrophy) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for Emery-Dreifuss muscular dystrophy
- EPM2A (progressive myoclonus epilepsy) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for progressive myoclonus epilepsy
- FHL1 (Emery-Dreifuss muscular dystrophy) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for Emery-Dreifuss muscular dystrophy
- FXN (Friedreich ataxia) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for Friedreich ataxia
- NDP (Norrie disease) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for Norrie disease
- PRNP (genetic prion disease) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for genetic prion disease
- PRSS1 (hereditary pancreatitis):
 - An unexplained documented episode of acute pancreatitis in childhood, or
 - Recurrent acute attacks of pancreatitis of unknown cause, or
 - Chronic pancreatitis of unknown cause, particularly with onset younger than 25 years of age, or
 - A family history of recurrent acute pancreatitis, chronic pancreatitis of unknown cause, and/or childhood pancreatitis of unknown cause consistent with autosomal dominant inheritance

- RET (ret proto-oncogen), common variants
 - The patient has a personal history of primary C cell hyperplasia, Medullary Thyroid Carcinoma (MTC), or Multiple Endocrine Neoplasia (MEN), type 2B, or
 - The patient has a family history consistent with MEN, type 2B or MTC, and at risk for autosomal dominant inheritance of the syndrome
- SH2D1A (X-linked lymphoproliferative syndrome) – The patient is a male with the diagnosis of:
 - Common variable immune deficiency, or
 - Hypogammaglobulinemia, or
 - Hemophagocytic lymphohistiocytosis, or
 - Severe infectious mononucleosis, or
 - Lymphoma, or
 - Family history of X-linked lymphoproliferative syndrome
- SPINK1 (hereditary pancreatitis):
 - An unexplained documented episode of acute pancreatitis in childhood, or
 - Recurrent acute attacks of pancreatitis of unknown cause, or
 - Chronic pancreatitis of unknown cause, particularly with onset younger than 25 years of age, or
 - A family history of recurrent acute pancreatitis, chronic pancreatitis of unknown cause, and/or childhood pancreatitis of unknown cause consistent with autosomal dominant inheritance

Claims without documentation showing the preceding criteria have been met will be denied.

**Tier 2, Molecular Pathology
Procedure, Level 6**

Coverage for CPT-4 code 81405 (molecular pathology procedure, Level 6) is limited to the listed services. Reimbursement for code 81405 requires an approved TAR and requires providers to document one of the following on the TAR:

- ABCD1 (adrenoleukodystrophy):
 - The patient has clinical features suspicious for adrenoleukodystrophy, and
 - Measurement of plasma concentration of very long chain fatty acids (VLCFA) is inconclusive, and
 - The service is required as a confirmatory test for the diagnosis of adrenoleukodystrophy
- EMD (Emery-Dreifuss muscular dystrophy) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for Emery-Dreifuss muscular dystrophy
- LAMP2 (Danon disease) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for glycogen storage disease IIb (Danon disease)
- NF2 (neurofibromatosis, type 2):
 - The patient has clinical features suspicious for, or requires the service as a confirmatory test for type 2 neurofibromatosis, OR
 - The patient is at high risk for neurofibromatosis with one or more of the following:
 - ❖ A first-degree relative with type 2 neurofibromatosis
 - ❖ Multiple spinal tumors (schwannomas, meningiomas)
 - ❖ Cutaneous schwannomas
 - ❖ Sporadic vestibular schwannoma younger than 30 years of age, or spinal tumor or meningioma younger than 20 years of age
- NPHS2 (steroid resistant nephrotic syndrome [SRNS])
 - The patient has clinical diagnosis of SRNS, and
 - Treatment will be contingent on the test results

- OTC (ornithine transcarbamylase deficiency) – The patient has clinical signs and symptoms of urea cycle disorders with positive biochemical laboratory results and requires the service as a confirmatory test for ornithine transcarbamylase deficiency
- RET (multiple endocrine neoplasia [MEN], type 2A and familial medullary thyroid carcinoma [MTC]) – exons 10, 11, 13 – 16:
 - The patient has a personal history of MTC, or MEN, type 2A, or
 - The patient has pheochromocytoma and a family history of MTC or pheochromocytoma, or
 - The patient has sporadic MEN2-related tumors and is younger than 35 years of age, multicentric tumors in one organ, and/or two different organs affected, or
 - The patient has a family history consistent with MEN, type 2A
- RET (ret proto-oncogen), targeted sequence analysis:
 - The patient has a personal history of primary C cell hyperplasia, MTC, or MEN, type 2A, or
 - The patient has a family history consistent with MEN, type 2A or MTC, and at risk for autosomal dominant inheritance of the syndrome
- SLC2A1 (glucose transporter type 1 [GLUT 1] deficiency syndrome) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for GLUT 1 deficiency syndrome
- SMN1 (spinal muscular atrophy) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for spinal muscular atrophy
- SPRED1 (Legius syndrome) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for Legius syndrome
- TCF4 (Pitt-Hopkins syndrome) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for Pitt-Hopkins syndrome

Claims without documentation showing the preceding criteria have been met will be denied

**Tier 2, Molecular Pathology
Procedure, Level 7**

Coverage for CPT-4 code 81406 (molecular pathology procedure, Level 7) is limited to the listed services. Reimbursement for code 81406 requires an approved TAR and requires providers to document one of the following on the TAR:

- ACADVL (very long chain acyl-coenzyme A dehydrogenase deficiency) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for ACADVL
- AFG3L2 (spinocerebellar ataxia) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for spinocerebellar ataxia
- ATP7B (Wilson disease):
 - The patient has clinical features suspicious for Wilson disease, and
 - Diagnosis cannot be made based on the results of biochemical testing and liver biopsy, and
 - The patient requires the service as a confirmatory test for Wilson disease
- BTK (X-linked agammaglobulinemia):
 - The male patient has clinical features suspicious for X-linked agammaglobulinemia, and
 - The male patient has less than two percent CD19+ B cells
- CDH1 (hereditary diffuse gastric cancer):
 - Two gastric cancer cases in family, one confirmed diffuse gastric cancer younger than 50 years of age, or
 - Three confirmed diffuse gastric cancer cases in first or second degree relatives, regardless of age, or
 - Diffuse gastric cancer diagnosed younger than 40 years of age, or
 - Personal or family history of diffuse gastric cancer and lobular breast cancer, one diagnosed younger than 50 years of age
- CNTNAP2 (Pitt-Hopkins-like syndrome) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for Pitt-Hopkins syndrome
- GLUD1 (familial hyperinsulinism):
 - The patient has persistent hyperinsulinemic hypoglycemia of infancy (PHHI) and failed medical therapy, and
 - The patient is under evaluation for surgical intervention

- JAG1 (Alagille syndrome) – duplication/deletion – The patient has clinical features suspicious for, or requires the service as a confirmatory test for Alagille syndrome
- MUTYH (MYH-associated polyposis) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for MUTYH-associated polyposis
- NF2 (neurofibromatosis, type 2):
 - The patient has clinical features suspicious for, or requires the service as a confirmatory test for type 2 neurofibromatosis, or
 - The patient is at high risk for neurofibromatosis with one or more of the following:
 - ❖ A first-degree relative with type 2 neurofibromatosis
 - ❖ Multiple spinal tumors (schwannomas, meningiomas)
 - ❖ Cutaneous schwannomas
 - ❖ Sporadic vestibular schwannoma younger than 30 years of age, or spinal tumor or meningioma younger than 20 years of age
- PRKCG (spinocerebellar ataxia) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for spinocerebellar ataxia
- PYGM (glycogen storage disease type V, McArdle disease) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for glycogen storage disease type V (McArdle disease)
- SCNN1A (pseudohypoaldosteronism) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for pseudohypoaldosteronism
- SCNN1B (Liddle syndrome, pseudohypoaldosteronism) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for Liddle syndrome, pseudohypoaldosteronism
- SCNN1G (Liddle syndrome, pseudohypoaldosteronism) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for Liddle syndrome, pseudohypoaldosteronism
- SLC37A4 (glycogen storage disease, type Ib) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for glycogen storage disease, type Ib
- TCF4 (Pitt-Hopkins syndrome) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for Pitt-Hopkins syndrome

- UMOD (glomerulocystic kidney disease with hyperuricemia and isosthenuria) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for glomerulocystic kidney disease with hyperuricemia and isosthenuria
- WAS (Wiskott-Aldrich syndrome) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for Wiskott-Aldrich syndrome

Claims without documentation showing the preceding criteria have been met will be denied.

Tier 2, Molecular Pathology Procedure, Level 8

Coverage for CPT-4 code 81407 (molecular pathology procedure, Level 8) is limited to the listed services. Reimbursement for code 81407 requires an approved TAR and requires providers to document one of the following on the TAR:

- ABCC8 (familial hyperinsulinism):
 - The patient has persistent hyperinsulinemic hypoglycemia of infancy (PHHI) who failed medical therapy, and
 - The patient is under evaluation for surgical intervention
- AGL (glycogen storage disease type III) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for glycogen storage disease type III
- JAG1 (Alagille syndrome) – full gene sequence – The patient has clinical features suspicious for, or requires the service as a confirmatory test for Alagille syndrome
- NPHS1 (congenital Finnish nephrosis)
 - The patient has clinical diagnosis of steroid-resistant nephritic syndrome (SRNS)/congenital Finnish nephrosis, and
 - Treatment will be contingent on the test results
- SPTBN2 (spinocerebellar ataxia) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for spinocerebellar ataxia

Claims without documentation showing the preceding criteria have been met will be denied.

Tier 2, Molecular Pathology Procedure, Level 9

Coverage for CPT-4 code 81408 (molecular pathology procedure, Level 9) is limited to the listed services. Reimbursement for code 81408 requires an approved *Treatment Authorization Request* (TAR) and requires providers to document one of the following on the TAR:

- ITPR1 (spinocerebellar ataxia) – The patient has clinical features suspicious for, or requires the service as a confirmatory test for spinocerebellar ataxia

Human Leukocyte Antigen Typing

CPT-4 codes 81370 – 81380, 81382 and 81383 (human leukocyte antigen typing) are reimbursable only with an ICD-9-CM diagnosis in the range of V42.0 – V42.9.

CPT-4 code 81381 (HLA Class I typing, high resolution, one allele or allele group) is only reimbursable with an ICD-9-CM diagnosis of 042, 296.00 – 296.06, 296.40 – 296.46, 296.50 – 296.56, 296.60 – 296.90, 345.00 – 345.91, 350.1, 795.71, V08 or V42.0 – V42.9.

Noninvasive Prenatal Testing for Fetal Aneuploidy - Cell Free Fetal DNA Testing

Noninvasive prenatal testing for fetal aneuploidy may be billed with either CPT-4 code 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) or CPT-4 code 81479 (unlisted molecular pathology procedure). A *Treatment Authorization Request* (TAR) is required. A TAR for the test requires documentation of the following criteria:

- Patient with singleton gestation only.
- The patient has an increased risk of aneuploidy due to one or more of the following:
 - Maternal age 35 years or older at delivery
 - Fetal ultrasonographic findings indicating an increased risk of aneuploidy
 - History of a prior pregnancy with a trisomy
 - Positive test result for aneuploidy, including first trimester, sequential, or integrated screen, or a quadruple screen
 - Parental balanced Robertsonian translocation with increased risk of fetal trisomy 13 or trisomy 21

Reference

The American College of Obstetricians and Gynecologists Committee on Genetics and The Society for Maternal-Fetal Medicine Publications Committee. Committee Opinion Number 545, December 2012.

**Multianalyte Assays With
Algorithmic Analyses**

CPT-4 codes 81500, 81503, 81506 – 81512 encompass all analytical services required in addition to the algorithmic analysis itself.

Codes 81500, 81503 and 81507 – 81512 are reimbursable for females only.

Reimbursement for code 81507 is limited to once a year, any provider.

Codes 81500 and 81503 are reimbursable only when billed in conjunction with one of the following ICD-9-CM diagnosis codes:

150.5	163.1	230.3
150.9	163.8 – 163.9	233.0 – 233.39
151.0 – 151.4	174.0 – 174.6	236.0 – 236.3
151.8	174.8 – 174.9	239.3
151.9	175.0	338.3
153.0 – 153.5	175.9	620.0 – 620.2
153.8 – 153.9	179	789.30
154.0 – 154.1	180.0 – 180.1	789.39
156.8 – 156.9	180.8 – 180.9	795.82
157.0 – 157.2	182.0 – 182.1	795.89
157.8 – 157.9	182.8	V10.00
158.0	183.0	V10.05
158.8 – 158.9	183.2 – 183.5	V10.09
159.9	183.8 – 183.9	V10.3
162.2 – 162.3	184.0 – 184.4	V10.40 – V10.44
162.5	184.8 – 184.9	V66.2
162.8 – 162.9	198.6	V67.1
163.0	198.82	V67.2

Codes 81508 – 81512 are reimbursable only when billed in conjunction with one of the following ICD-9-CM diagnosis codes:

158.0	197.6	640.00 – 640.03
158.8	198.6	642.30 – 642.34
164.2	198.82	642.40 – 642.74
164.3	236.1	642.90 – 642.94
164.8	623.8	995.29
164.9	625.9	V10.09
181	630	V10.29
183.0	631.0	V10.43
183.8	631.8	V10.47
186.0	632	V22.0 – V22.1
186.9	633.00 – 633.91	V23.1
194.4	634.00 – 634.92	V28.89
197.1	637.00 – 637.92	