Genetic Testing for Diagnosis of Inherited Conditions

Humana®

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Medical Coverage Policy

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Description

Genetic testing may be performed to analyze an individual's deoxyribonucleic acid (DNA) to detect gene variants to assist in confirming a diagnosis in those who exhibit disease signs and symptoms of inherited conditions and to aid with treatment decisions. Examples of genetic conditions that may be evaluated by genetic testing include, but are not limited to, achondroplasia, amyotrophic lateral sclerosis (ALS), dystrophic epidermolysis bullosa, fragile X syndrome, hereditary angioedema, polycystic kidney disease (PKD) and Rett syndrome.

Multigene (or expanded) panels analyze a broad set of genes simultaneously (as opposed to single gene testing that searches for variants in one specific gene) and have been proposed to evaluate the DNA of an individual with a personal and/or family history of more than one hereditary condition or syndrome. Panels often include medically actionable genes but may also include those with unclear medical management. **Targeted (or focused) multigene panels** analyze a limited number of genes targeted to a specific condition.

Coverage Determination

Any state mandates for genetic testing for diagnosis of inherited conditions take precedence over this medical coverage policy.

Genetic testing may be excluded by certificate. Please consult the member's individual certificate regarding Plan coverage.

Apply General Criteria for Genetic and Pharmacogenomics Tests when disease- or gene-specific criteria are not available on a medical coverage policy. For information regarding **general criteria for genetic tests**, please refer to Genetic Testing Medical Coverage Policy.

Achondroplasia (*FGFR3* Gene)

Humana members may be eligible under the plan for ***FGFR3* gene testing to confirm a diagnosis of achondroplasia** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
- Epiphyses are confirmed open by diagnostic imaging; **AND**
- Testing performed prior to initiation of treatment with vosoritide (Voxzogo)

Alpha-1 Antitrypsin Deficiency (*SERPINA1*)

Humana members may be eligible under the Plan for ***SERPINA1* gene testing (81332) to confirm a diagnosis of alpha-1 antitrypsin deficiency** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
- Individual to be tested diagnosed with any of the following:
  - Chronic obstructive pulmonary disease (COPD); **OR**
  - Granulomatosis with polyangiitis; **OR**
  - Necrotizing panniculitis; **OR**
  - Unexplained bronchiectasis; **OR**
  - Unexplained chronic liver disease

Amyotrophic Lateral Sclerosis (*SOD1*)

Humana members may be eligible under the Plan for ***SOD1* gene testing for amyotrophic lateral sclerosis (ALS)** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
- Individual to be tested has a diagnosis of definite or probable ALS as determined by a health care provider who specializes in the treatment of ALS (eg, neurologist, neuromuscular specialist); **AND**
- Ability to independently perform all or some activities of daily living (ADLs); **AND**
- Absence of tracheostomy or invasive ventilation; **AND**
- Elevated plasma (serum) neurofilament light chain (NfL) at baseline; **AND**
- Testing performed to establish eligibility for treatment with tofersen (Qalsody)

Dystrophic Epidermolysis Bullosa (*COL7A1*)

Humana members may be eligible under the Plan for ***COL7A1* gene testing for dystrophic epidermolysis bullosa (DEB)** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
- Individual to be tested exhibits clinical characteristics of DEB (eg, fragility of the skin, blistering and erosions, dystrophic or absent nails)

Fragile X Syndrome (*FMR1* Gene)

Please refer to **Coverage Limitations section** for *AFF2* gene testing for fragile X syndrome.

Humana members may be eligible under the Plan for ***FMR1* gene testing*** **for fragile X syndrome** (81243, 81244) when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
    - Individual to be tested diagnosed with unexplained primary ovarian insufficiency (POI) (also known as premature ovarian failure), defined as female younger than 40 years of age with irregular menses in association with follicle stimulating hormone (FSH) levels in the postmenopausal range; **OR**
    - Individual to be tested has a first-degree relative with a KFV (test KFV); **OR**
    - Individual to be tested has autism spectrum disorder (ASD), developmental delay (DD) or intellectual disability (ID); **OR**
    - Individual to be tested is 50 years of age or younger with late-onset tremor or cerebellar ataxia of unknown origin

Hearing Loss

Humana members may be eligible under the Plan **for single gene (eg, GJB2 [81252, 81253, S3844], GJB6 [81254]) or multigene panel testing (81430) and deletion/duplication analysis panel (81431) for hearing loss** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
- Individual to be tested has been diagnosed with bilateral sensorineural hearing loss (SNHL); **AND**
- Lacks physical findings suggestive of a known genetic syndrome; **AND**
- Environmental (nongenetic) cause for loss of hearing has been ruled out

Hereditary Angioedema

Humana members may be eligible under the Plan for **single gene testing (eg, *C1INH [SERPING1], ANGPT1, F12, HS3ST6, KNG1, MYOF, PLG*) or multigene panel testing for hereditary angioedema (HAE)** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
- Individual to be tested is 2 years of age or older; **AND**
- Clinical suspicion of HAE (common symptoms include recurrent cutaneous angioedema [in the absence of urticaria], abdominal symptoms from gastrointestinal angioedema and airway symptoms due oropharyngeal/laryngeal swelling); **AND**

- Low C4 level (below lower limit of normal laboratory reference range); **AND**
    - Low C1 inhibitor (C1INH) antigenic level (below lower limit of normal laboratory reference range); **OR**
    - Low C1INH functional level (less than 50% or below lower limit of normal laboratory reference range); **AND**
- Is being treated by a specialist in HAE (allergist and/or immunologist); **AND**
- Testing is performed to establish eligibility for treatment with any of the following:
    - Berotralstat (Orladeyo)
    - C1 esterase inhibitor, human (Berinert, Cinryze, Haegarda, Ruconest)
    - Ecallantide (Kalbitor)
    - Icatibant (Firazyr)
    - Lanadelumab-flyo (Takhzyro)

Hereditary Transthyretin Amyloidosis (*TTR* Gene)
Humana members may be eligible under the Plan for ***TTR* gene testing for hereditary transthyretin amyloidosis** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
- Individual to be tested diagnosed with polyneuropathy and a comprehensive neurologic examination has ruled out other causes of sensorimotor/autonomic neuropathy (eg, chronic inflammatory demyelinating polyneuropathy); **AND**
- No history of liver transplant; **AND**
- Polyneuropathy disability (PND) scoring system indicates stage I, II, IIIa or IIIb; **AND**
- Testing performed prior to initiation of treatment with a hereditary transthyretin amyloidosis agent (eg, vutrisiran [Amvuttra], patisiran [Onpattro] or inotersen [Tegsedi]

Inherited Retinal Disorders
Humana members may be eligible under the Plan for **multigene panel for inherited retinal disorders (81434)** (eg, retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy) when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**

- Individual to be tested diagnosed with an inherited retinal disorder (eg, retinitis pigmentosa, Leber congenital amaurosis, cone-rod dystrophy); **AND**

- Individual to be tested exhibits progressive loss of photoreceptor function accompanied by vision loss

Polycystic Kidney Disease Autosomal Dominant (*PKD1*, *PKD2* Genes)

Please refer to **Coverage Limitations** section for deletion/duplication analysis of *PKHD1* gene and *DNAJB11, GANAB* gene testing for PKD autosomal dominant.

Humana members may be eligible under the Plan for ***PKD1* and *PKD2* simultaneous sequence analysis and deletion/duplication analysis to diagnose autosomal dominant polycystic kidney disease** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
- Individual to be tested has equivocal or uninformative imaging results

Polycystic Kidney Disease Autosomal Recessive (*PKHD1* Gene)

Please refer to **Coverage Limitations section** for deletion/duplication analysis of *PKHD1* gene and *DZIP1L* gene testing for PKD autosomal recessive.

Humana members may be eligible under the **Plan for *PKHD1* gene testing to diagnose autosomal recessive polycystic kidney disease** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
- Individual to be tested has equivocal or uninformative imaging results

Primary Hyperoxaluria Type 1 (*AGXT* Gene)
Humana members may be eligible under the Plan for ***AGXT* genetic testing for primary hyperoxaluria type 1** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
    - Less than 12 months of age with failure to thrive and impaired kidney function; **OR**
    - Less than 18 years of age presenting with first kidney stone; **OR**
    - Nephrocalcinosis; **OR**
    - Oxalate crystals identified in any biologic fluid or tissue; **OR**

- Recurrent nephrolithiasis; **OR**
- Reduced kidney function or end-stage renal disease at any age with a history of renal stones or nephrocalcinosis; **OR**
- Stone composition of pure calcium oxalate monohydrate (whewellite);

  AND any of the following laboratory findings (refer to laboratory reference ranges):

  - Elevated plasma oxalate concentration; **OR**
  - Elevated urinary glycolic acid (glycolate) concentration; **OR**
  - Elevated urinary oxalate excretion persistently greater than 0.7 mmol/1.73 m/day or above the age-related reference range(s); **OR**
  - Plasma oxalate concentrations greater 50 µmol/L; **OR**
  - Substantially elevated values are the rule when GFR less than 30 mL/min/1.73 m

Progressive Familial Intrahepatic Cholestasis (*ABCB4, ABCB11, ATP8B1, TYP2* Genes)
Humana members may be eligible under the Plan for ***ABCB4, ABCB11, ATP8B1* and/or *TYP2* single gene or targeted multigene panel testing for progressive familial intrahepatic cholestasis** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
- Clinically significant cholestasis-associated pruritus; **AND**
- Elevated serum bile acids above the upper limit (refer to laboratory reference range); **AND**
- Individual between 3 months and 17 years of age; **AND**
- Ordering provider is a specialist (eg, gastroenterologist, hepatologist)

***PTEN* Gene Testing for Autism Spectrum Disorder**
Humana members may be eligible under the Plan for ***PTEN* gene testing** (eg, Genomic Unity *PTEN* Analysis [0235U] [81321, 81322, 81323]) when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
- Performed for the evaluation of ASD; **AND**
- Head circumference is greater than 2.5 standard deviations above the mean

Rett Syndrome (*MECP2, CDKL5, FOXG1* Genes)
Humana members may be eligible under the Plan for ***MECP2*** (eg, Genomic Unity *MECP2*) (0234U) (81302, 81304), ***CDKL5, FOXG1*** **single gene or multigene panel testing and deletion/duplication analysis to confirm a diagnosis of Rett syndrome (classic or atypical [variant])** when the following criteria are met:

- Pre- and post-test genetic counseling; **AND**
    - Individual to be tested exhibits 2 or more of the following characteristics suggestive of Rett syndrome:
        - A period of regression followed by recovery or stabilization
        - Gait abnormalities
        - Partial or complete loss of acquired purposeful hand skills
        - Partial or complete loss of acquired spoken language
        - Stereotypic hand movements including clapping/tapping, hand wringing/squeezing, mouthing and washing/rubbing automatisms; **OR**
    - Individual to be tested has postnatal deceleration of head growth; **OR**
    - Individual to be tested is a female presenting with developmental problems of unknown etiology and some features suggestive of Rett syndrome; **OR**
    - Individual to be tested is a male infant with severe encephalopathy

Testing strategy for single gene testing for Rett syndrome begins with full gene sequencing and deletion/duplication analysis of the *MECP2* gene. If negative, proceed to *CDKL5* and *FOXG1* gene analysis.

FMR1 gene testing for fragile X syndrome may be performed adjunctively with CGH/ CMA if criteria for CGH/CMA are also met. For information regarding **CGH/CMA for fragile X syndrome**, please refer to Comparative Genomic Hybridization/Chromosome Microarray Analysis Medical Coverage Policy.

Coverage Limitations

Humana members may **NOT** be eligible under the Plan for **genetic testing for noncancer indications** for the following:

- Deletion/duplication information is obtained as part of the sequencing procedure but submitted as an independent analysis
- Individual to be tested has an affected first-, second- or third-degree relative with a negative genetic testing result for the associated condition

- Individual to be tested is unaffected and an affected first-, second- or third-degree relative is available for genetic testing

- KFV analysis using a multigene panel that includes the KFV

- Sequencing, deletion/duplication analysis and large genomic rearrangement analysis of a single gene, multigene panel or sequentially for the detection of a KFV without the KFV results of a relative

These are considered **not medically necessary** as defined in the member's individual certificate. Please refer to the member's individual certificate for the specific definition.
Humana members may **NOT** be eligible under the Plan for **genetic testing for the diagnosis** of any indications other than those listed above including, but may not be limited to:

- Familial hemiplegic migraine including, but may not be limited, to the following genes:

  - *ATP1A2 (FHM2)*
  - *CACNA1A (FHM1)*
  - *SCN1A* (*FHM3)*

- Fragile X syndrome *AFF2* gene testing (81171, 81172)

- Lactose intolerance (C/T 13910 genotype testing) (eg, LactoTYPE)

- Multigene panels unless **ALL** genes in the panel meet disease- or gene-specific criteria (for single genes included in a panel, apply appropriate criteria) for any of the following:

  - ASD, DD or ID or XLID including, but may not be limited to:

    - Autism/ID Panel
    - Autism/ID Xpanded Panel
    - AutismFirst
    - AutismNext
    - Autism NGS Panel
    - Autism Spectrum Disorders (ASD) Panel Test
    - Intellectual Disability Panel
    - Intellectual Disability NGS Panel
    - Non-Specific Intellectual Disability Panel
    - XLID genomic sequencing panel of 60 or more genes (81470)
    - XLID deletion/duplication gene analysis of 60 or more genes (81471)

- PKD for any of the following:

- *DNAJB11* or *GANAB* gene testing for autosomal dominant PKD
- *DZIP1L* gene testing for autosomal recessive PKD
- *PKHD1* deletion/duplication analysis

- POC test (Fetal aneuploidy short tandem-repeat [STR] comparative analysis of fetal DNA obtained from products of conception [POC]) (0252U)

These are considered experimental/investigational as they are not identified as widely used and generally accepted for the proposed uses as reported in nationally recognized peer-reviewed medical literature published in the English language.

Humana members may **NOT** be eligible under the Plan for **genetic testing for epilepsy** including, but may not be limited to, the following genes/tests:

- *EMP2A*
- *EMP2B*
- *TSC1*
- *TSC2*
- Multigene panels (81419) including, but may not be limited to:

  - Actionable Epilepsy NGS Panel
  - Adolescent/Adult Epilepsy NGS Panel
  - Comprehensive Epilepsy and Seizure Panel Test
  - Childhood Epilepsy NGS Panel
  - Comprehensive Epilepsy NGS Panel
  - Early Infantile Epileptic Encephalopathy NGS Panel
  - Epilepsy Comprehensive NGS Panel
  - Epilepsy Genomic Sequencing Analysis Panel (81419)
  - Epilepsy/Seizure NGS Panel
  - Genomic Unity Epilepsy Analysis
  - Infantile Epilepsy Panel
  - Invitae Epilepsy Panel
  - Neonatal Epilepsy NGS Panel

These are considered not medically necessary as defined in the member's individual certificate. Please refer to the member's individual certificate for the specific definition.

Coding Information

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments
81171	AFF2 (AF4/FMR2 family, member 2 [FMR2]) (eg, fragile X mental retardation 2 [FRAXE]) gene analysis; evaluation to detect abnormal (eg, expanded) alleles	**Not Covered**
81172	AFF2 (AF4/FMR2 family, member 2 [FMR2]) (eg, fragile X mental retardation 2 [FRAXE]) gene analysis; characterization of alleles (eg, expanded size and methylation status)	**Not Covered**
81188	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles	
81189	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; full gene sequence	**Not Covered**
81190	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; known familial variant(s)	
81243	FMR1 (fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; evaluation to detect abnormal (eg, expanded) alleles	
81244	FMR1 (fragile X mental retardation 1) (eg, fragile X mental retardation) gene analysis; characterization of alleles (eg, expanded size and promoter methylation status)	
81252	GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; full gene sequence	
81253	GJB2 (gap junction protein, beta 2, 26kDa, connexin 26) (eg, nonsyndromic hearing loss) gene analysis; known familial variants	
81254	GJB6 (gap junction protein, beta 6, 30kDa, connexin 30) (eg, nonsyndromic hearing loss) gene analysis, common variants (eg, 309kb [del(GJB6-D13S1830)] and 232kb [del(GJB6-D13S1854)])	
81302	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; full sequence analysis	
81304	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome) gene analysis; duplication/deletion variants	
81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis	
81322	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant	
81323	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant	

81332	SERPINA1 (serpin peptidase inhibitor, clade A, alpha-1 antiproteinase, antitrypsin, member 1) (eg, alpha-1-antitrypsin deficiency), gene analysis, common variants (eg, *S and *Z)	
81403	MOLECULAR PATHOLOGY PROCEDURE LEVEL 4	**Not Covered if used to report any test outlined in Coverage Limitations section**
81404	MOLECULAR PATHOLOGY PROCEDURE LEVEL 5	**Not Covered if used to report any test outlined in Coverage Limitations section**
81405	MOLECULAR PATHOLOGY PROCEDURE LEVEL 6	**Not Covered if used to report any test outlined in Coverage Limitations section**
81406	MOLECULAR PATHOLOGY PROCEDURE LEVEL 7	**Not Covered if used to report any test outlined in Coverage Limitations section**
81407	MOLECULAR PATHOLOGY PROCEDURE LEVEL 8	**Not Covered if used to report any test outlined in Coverage Limitations section**
81408	MOLECULAR PATHOLOGY PROCEDURE LEVEL 9	**Not Covered if used to report any test outlined in Coverage Limitations section**
81419	Epilepsy genomic sequence analysis panel, must include analyses for ALDH7A1, CACNA1A, CDKL5, CHD2, GABRG2, GRIN2A, KCNQ2, MECP2, PCDH19, POLG, PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, SLC2A1, SLC9A6, STXBP1, SYNGAP1, TCF4, TPP1, TSC1, TSC2, and ZEB2	**Not Covered**
81430	Hearing loss (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); genomic sequence analysis panel, 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 (eg, nonsyndromic hearing loss, Usher syndrome, Pendred syndrome); duplication/deletion analysis panel, must include copy number analyses for STRC and DFNB1 deletions in GJB2 and GJB6 genes	

81434	Hereditary retinal disorders (eg, 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, PDE6B, PRPF31, PRPH2, RDH12, RHO, RP1, RP2, RPE65, RPGR, and USH2A	
81470	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic 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	**Not Covered**
81471	X-linked intellectual disability (XLID) (eg, syndromic and non-syndromic 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	**Not Covered**
81479	Unlisted molecular pathology procedure	**Not Covered if used to report any test outlined in Coverage Limitations section**
96040	Medical genetics and genetic counseling services, each 30 minutes face-to-face with patient/family	
0232U	CSTB (cystatin B) (eg, progressive myoclonic epilepsy type 1A, Unverricht-Lundborg disease), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, short tandem repeat (STR) expansions, mobile element insertions, and variants in non-uniquely mappable regions	**Not Covered**
0234U	MECP2 (methyl CpG binding protein 2) (eg, Rett syndrome), full gene analysis, including small sequence changes in exonic and intronic regions, deletions, duplications, mobile element insertions, and variants in non-uniquely mappable regions	
0252U	Fetal aneuploidy short tandem-repeat comparative analysis, fetal DNA from products of conception, reported as normal (euploidy), monosomy, trisomy, or partial deletion/duplications, mosaicism, and segmental aneuploidy	**Not Covered**
CPT® Category III Code(s)	**Description**	**Comments**
No code(s) identified		
HCPCS Code(s)	**Description**	**Comments**

S0265	Genetic counseling, under physician supervision, each 15 minutes	
S3800	Genetic testing for amyotrophic lateral sclerosis (ALS)	
S3844	DNA analysis of the connexin 26 gene (GJB2) for susceptibility to congenital, profound deafness	

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Appendix

Appendix A
Pre- and Post-Test Genetic Counseling Criteria

Pre- and post-test genetic counseling performed by any of the following qualified medical professionals

Genetic counselor who is board-certified or board-eligible by the American Board of Medical Genetics and Genomics (ABMGG) or American Board of Genetic Counseling, Inc (ABGC) and is not employed by a commercial genetic testing laboratory; **OR**
Genetic clinical nurse (GCN) or advanced practice nurse in genetics (APNG) who is credentialed by the Genetic Nursing Credentialing Commission (GNCC) or the American of Nurses Credentialing Center (ANCC) and is not employed by a commercial genetic testing laboratory; **OR**
Medical geneticist who is board-certified or board-eligible by ABMGG; **OR**
Treating physician who has evaluated the individual to be tested and has completed a family history of three generations

Appendix B
Family Relationships

Degree of Relationship	Relative of the Individual to be Tested
First-degree	Child, full-sibling, parent
Second-degree	Aunt, uncle, grandchild, grandparent, nephew, niece, half-sibling
Third-degree	First cousin, great aunt, great-uncle, great-grandchild, great-grandparent, half-aunt, half-uncle

Appendix C
Polyneuropathy Disability (PND) Scoring System[58]

Stage	Description
0	No symptoms of neuropathy
I	Sensory disturbance but with preserved walking capacity
II	Unassisted walking but with difficulty
IIIa	One stick or crutch is required for walking
IIIb	Two sticks or crutches are required for walking
IV	Wheelchair-bound or bedridden

Change Summary

- 03/28/2024 Update, Coverage Change.