Blue Cross and Blue Shield of Nebraska (BCBSNE) is proud to work with our provider network to serve your patients, our members. We are updating several medical policies. Please review the changes and effective dates outlined here:

Revised Medical Policies

Medical Policy: V.73 Genetic Testing: Aortopathies and Connective Tissue Disorders
Effective Date: 07/01/2022
Preauthorization Required: Yes
Policy Statement

Marfan Syndrome
FBN1 Sequencing and/or Deletion/Duplication Analysis

B. member has a close relative with a documented clinical diagnosis of Marfan syndrome and symptoms of Marfan syndrome, but the member does not meet clinical criteria for diagnosis of an individual with a family history of Marfan syndrome

1. Clinical diagnostic criteria for an individual with a family history of Marfan syndrome is as follows:
    a. Ectopia Lentis, **OR**
    b. Multiple systemic features (see above), **OR**
    c. A dilated aortic root (if over 20 years, greater than two standard deviations; if younger than 20, greater than three standard deviations)

Medical Policy: V.59 Genetic Testing: Hereditary Cancer Susceptibility Syndromes
Effective Date: 07/01/2022
Preauthorization Required: Yes
Policy Statement

Hereditary Breast Cancer Susceptibility Panels

A hereditary breast cancer susceptibility panel includes genes that are associated with inherited susceptibility to breast cancer.

I. Genetic testing using a hereditary breast cancer susceptibility panel (81162, 81163, 81164, 81165, 81166, 81167, 81216, 81432, 81433, 0102U, 0129U) is considered **medically necessary** when:
    A. The member is 18 years or older, **AND**
    B. The member meets at least one of the following:
        1. The member has a personal history of any of the following:
            a) Male breast cancer
            b) Bilateral breast cancer
            c) Triple-negative breast cancer, **OR**
        2. The member is a female who has a personal history of breast cancer, **AND**
            a) Diagnosed ≤45 years, **OR**
            b) Diagnosed 46-50 with **ANY**
                (1) Unknown or limited family history
                (2) Multiple primary breast cancers (synchronous or metachronous)
                (3) At least 1 close relative with breast, ovarian, pancreatic, or prostate cancer at any age
            c) Diagnosed >50 years, **AND**
                (1) One or more close relatives with
                    (a) Breast cancer <50 years **OR**
                    (b) Male breast cancer at any age, **OR**
                    (c) Ovarian cancer at any age, OR
                    (d) Pancreatic cancer at any age, OR

(e) Metastatic, intraductal/cribriform histology, or high- or very-high risk group prostate cancer at any age, OR

(2) **Three or** or more close relatives with breast cancer including patient at any age, **OR**

(3) Two or more close relatives with either breast or prostate cancer at any age, **OR**

(4) An unknown or limited family history, **OR**

d) Ashkenazi Jewish ancestry, **OR**

3. The member does not meet any of the above criteria, but has one or more first- or second-degree relatives meeting any of the above criteria, **OR**
4. The member is being considered for PARP inhibitor therapy and has a personal history of recurrent or metastatic breast cancer, **OR**
5. The member is being considered for Olaparib therapy, and has a personal history of high-risk, HER-2 negative breast cancer, **AND**
6. The panel includes, at a minimum, sequencing of the following genes: *BRCA1*, *BRCA2*,

Hereditary Prostate Cancer Susceptibility Panels

A hereditary prostate cancer susceptibility panel is one that includes genes that are associated with inherited susceptibility to prostate cancer.

I. Genetic testing using a hereditary prostate cancer susceptibility panel (0133U, 81162, 81163, 81164, 81165, 81166, 81167, 81216, 81292, 81294, 81295, 81297, 81298, 81300, 81317, 81319) is considered **medically necessary** when:
   A. The member is 18 years or older, **AND**
   B. The member meets at least one of the following:
      1. The member has a personal history of metastatic prostate cancer, **OR**
      2. The member's prostate cancer has intraductal, cribriform or ductal histology, **OR**
      3. The member's prostate cancer has a high- or very high-risk classification, OR
      4. The member has family history that includes at least one relative with any the following
         a) Breast cancer at age 50 or younger, **OR**
         b) Ovarian cancer at any age, **OR**
         c) Pancreatic cancer at any age, **OR**
         d) Prostate cancer with metastasis, intraductal/cribriform histology, or a high- or very high-risk classification, **OR**
      5. The member meets criteria for *BRCA1* and *BRCA2* sequencing and/or deletion/duplication gene testing (see *BRCA1* and *BRCA2* sequencing and/or deletion/duplication criteria below), **AND**
      6. The panel includes, at a minimum, sequencing of the following genes: *BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, HOXB13*

Hereditary Neuroendocrine Cancer Susceptibility Panels

A hereditary neuroendocrine cancer susceptibility panel is one that includes genes that are associated with inherited susceptibility to a neuroendocrine cancer.

I. Genetic testing using a hereditary neuroendocrine cancer susceptibility panel (81437, 81438) is considered **medically necessary** when:
   A. The member meets criteria for sequencing and/or deletion/duplication analysis for at least one of the following (see specific coverage criteria sections below):
      1. Von-Hippel Lindau syndrome (VHL), **OR**
      2. Hereditary Paraganglioma-Pheochromocytoma syndrome (PGL/PCC), **OR**
      3. Multiple Endocrine Neoplasia Type 1 (MEN1), **OR**
      4. Multiple Endocrine Neoplasia Type 2 (MEN2), **AND**
   B. The panel includes, at a minimum, sequencing of the following genes: *MAX, SDHB, SDHC, SDHD, TMEM127, SDHAF2, SDHA, VHL*, *MEN1, RET*

II. Genetic testing using a hereditary neuroendocrine cancer susceptibility panel (81437, 81438) is considered **investigational** for all other indications

Medical Policy: V.60 Oncology Molecular Analysis of Solid Tumors and Hematologic Malignancies
Effective Date: 07/01/2022
Preauthorization Required: Yes
Policy Statement

Tumor Agnostic Molecular Profiling Panel Tests with IHC and Cytogenetic Analyses

I. Tumor Agnostic Molecular Profiling Panel Tests with IHC and Cytogenetic Analyses (0211U, 81445, 81455) may be considered **medically necessary** when:
   A. The member has recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer, **AND**
   B. The member is seeking further cancer treatment (e.g., therapeutic chemotherapy), **AND**
   C. One of the following:
      2. The member has not had previous comprehensive tumor molecular profiling or multi-technology molecular profiling for the primary cancer diagnosis, **OR**
      3. The member *HAS* had previous comprehensive tumor molecular profiling or multi-technology molecular profiling and has a **new** primary cancer diagnosis for which this testing is being ordered.

II. Tumor Agnostic Molecular Profiling Panel Tests with IHC and Cytogenetic Analyses (0211U, 81445, 81455) are considered **investigational** for all other indications.

Medical Policy: V.65 Genetic Testing: Epilepsy, Neurodegenerative and Neuromuscular Disorders
Effective Date: 07/01/2022
Preauthorization Required: Yes
Policy Statement

SCN1A Seizure Disorders and Epilepsy Multigene Panel

I. Epilepsy multigene panel (81419) may be considered **medically necessary** when:
   A. does not have any metabolic or brain structural abnormalities that predispose to epilepsy, **AND**
   B. The member has any of the following:
      1. Infantile- or early-childhood-onset epilepsy, **OR**
      2. Precipitation of seizure with fever, warmth, or vaccination, **OR**
      3. Prolonged or hemi convulsive seizures, **OR**
      4. Seizure provocation with overstimulation or flashing/patterned visual stimulus, **OR**
      5. Worsening of seizures with medications that inhibit sodium channel function as the primary mechanism of action (e.g., carbamazepine, oxcarbazepine, phenytoin, lamotrigine).

III. The use of an epilepsy multigene panel (81419) is considered **investigational** for all other indications.

Medical Policy: V.77 Genetic Testing: Dermatological Conditions
Effective Date: 07/01/2022
Preauthorization Required: Yes
Policy Statement

Epidermolysis Bullosa Multigene Panel

I. Multigene panel analysis that includes at least EXPH5, TGM5, KRT5, KRT14, ITGA6, ITGB4, PLEC, to establish or confirm a diagnosis of epidermolysis bullosa (8147981406, 81479, 81525) is considered **medically necessary** when:
   A. The member has fragility of the skin manifested by blistering with little or no trauma, **AND**

B. The member has the presence of blistering that:
    1. May be present in the neonatal period**, OR**
    2. Primarily affects the hands and feet but can affect the whole body, **OR**
    3. Occurs in annular or curvilinear groups or clusters**, OR**
    4. Can lead to progressive brown pigmentation interspersed with hypopigmented spots on the trunk and extremities that frequently disappears in adult life**, OR**
    5. Is associated with palmar and plantar hyperkeratosis that may be severe **AND**
C. The member has one or more of the following:
    1. Nail dystrophy**, OR**
    2. Milia**, OR**
    3. Congenital pyloric atresia**, OR**
    4. Ureteral and renal anomalies, including hydronephrosis, ureterocele, absent bladder, dysplastic kidneys, urinary collecting system/kidney duplication, obstructive uropathy, and glomerulosclerosis.

II. Multigene panel analysis to establish or confirm a diagnosis of epidermolysis bullosa (81406, 81479, 81525) is considered **investigational** for all other indications.

Medical Policy: V.76 Genetic Testing: Skeletal Dysplasia
Effective Date: 07/01/2022
Preauthorization Required: Yes
Policy Statement

Osteogenesis Imperfecta

I. *COL1A1* and *COL1A2* variant analysis (81408, 81479) or multigene panel analysis (81408, 81479) that includes COL1A1 and COL1A2 to establish or confirm a diagnosis of osteogenesis imperfecta (OI) is considered **medically necessary** when:
    A. The member has any of the following:
        1. Fractures with minimal or no trauma in the absence of other factors, such as non-accidental trauma (NAT) or other known disorders of bone, **OR**
        2. Short stature, often with bone deformity, **OR**
        3. Blue/gray scleral hue, **OR**
        4. Dentinogenesis imperfecta (DI), **OR**
        5. Progressive, postpubertal hearing loss, **OR**
        6. Ligamentous laxity or other signs of connective tissue abnormality, **OR**
        7. Family history of OI, typically with autosomal dominant inheritance, **OR**
        8. Fractures of varying ages and stages of healing (often of the long bones), **OR**
        9. “Codfish” vertebrae, **OR**
        10. Wormian bones, **OR**
        11. Protrusio acetabuli, **OR**
        12. Low bone mass or osteoporosis

II. *COL1A1* and *COL1A2* variant analysis (81408, 81479) or multigene panel analysis (81408, 81479) for osteogenesis imperfecta is considered **investigational** for all other indications.

Multigene panel, analysis for skeletal dysplasia or rare disorder

I. Multigene panel analysis (81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408) to confirm or establish a diagnosis of a skeletal dysplasia or a rare bone disorder may be considered **medically necessary** when:
    A. The member displays one or more of the following clinical features of a skeletal dysplasia:
        1. Prenatal ultrasound showing shortening of the bones of the arms and legs >3 standard deviations below the mean, **OR**
        2. Prenatal ultrasound showing head circumference greater than 75th percentile, **OR**
        3. Prenatal ultrasound showing bone irregularities (e.g., bowed, fractured, thickened, thin, undermineralized, etc.), **OR**
        4. Prenatal ultrasound showing abnormal ribs or a small chest circumference, **OR**

5. Postnatal short stature with height or length less than 3rd percentile**, AND**

B. The differential diagnosis includes more than one type of skeletal dysplasia or bone disorder.

II. Multigene panel analysis (81400, 81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408) to confirm or establish a diagnosis of a skeletal dysplasia or a rare bone disorder is considered **investigational** for all other indications.

Medical Policy: V.62 Genetic Testing: Multisystem Inherited Disorders
Effective Date: 07/01/2022
Preauthorization Required: Yes
Policy Statement

***PIK3CA* Sequencing and/or Deletion/Duplication Analysis**

I. *PIK3CA* sequencing and/or deletion/duplication analysis (81479) to establish a diagnosis of PIK3CA-Related Segmental Overgrowth is considered **medically necessary** when:
   A. The member displays two or more of the following clinical features
      1. Sporadic and mosaic overgrowth in adipose, muscle, nerve, or skeletal tissues
      2. Vascular malformations including capillary, venous, arteriovenous malformation, or lymphatic.
      3. Epidermal nevus, **OR**
   B. The member displays one or more of the following clinical features, with a congenital or early childhood onset
      1. Large isolated lymphatic malformation
      2. Isolated macrodactyly OR overgrown splayed feet/ hands, overgrown limbs
      3. Truncal adipose overgrowth
      4. Hemimegaloencephaly (bilateral)/ dysplastic megalocephaly/ focal cortical dysplasia
      5. Epidermal nevus
      6. Seborrheic keratoses
   C. Benign lichenoid keratoses

II. *PIK3CA* sequencing and/or deletion/duplication analysis (81479) to establish a diagnosis of PIK3CA-Related Segmental Overgrowth is considered **investigational** for all other indications.

Note: Because the vast majority of reported *PIK3CA* pathogenic variants are mosaic and acquired, more than one tissue type may need to be tested (e.g., blood, skin, saliva). Failure to detect a PIK3CA pathogenic variant does not exclude a clinical diagnosis of *PIK3CA*-associated segmental overgrowth disorders in individuals with suggestive features, given that low-level mosaicism is observed in many individuals.

Medical Policy: V.61 Oncology: Circulating Tumor DNA and Circulating Tumor Cells
Effective Date: 07/01/2022
Preauthorization Required: Yes
Policy Statement

Colorectal Cancer Focused Panel Tests via Circulating Tumor DNA (ctDNA)

I. Colorectal cancer focused panel tests via circulating tumor DNA (ctDNA) (81210, 81275, 81276, 81311) are considered **medically necessary** when:
   A. Member has metastatic colorectal cancer, **AND**
   B. Panel includes *KRAS, NRAS and BRAF* analysis.

II. Colorectal cancer focused panel tests via circulating tumor DNA (ctDNA) (81210, 81275, 81276, 81311) for all other indications are considered **investigational**.

Medical Policy: V.69 Genetic Testing: Kidney Disorders
Effective Date: 07/01/2022
Preauthorization Required: Yes
Policy Statement

Targeted Variant Analysis

I. *PKD1*, *PKD2*, *GANAB*, *DNAJB11* or *PKHD1* targeted variant analysis (81403) to establish a diagnosis of autosomal dominant polycystic kidney disease is considered **medically necessary** when:
   A. The member has a close relative with a known pathogenic or likely pathogenic variant in *PKD1*, *PKD2*, *GANAB*, *DNAJB11, or PKHD1.*

II. *PKHD1* targeted variant analysis (81403) to establish a diagnosis of autosomal recessive polycystic kidney disease is considered **medically necessary** when:
   A. The member has a sibling with known biallelic pathogenic or likely pathogenic variants in *PKHD1*.

III. *PKD1*, *PKD2*, *GANAB*, *DNAJB11,* or *PKHD1* targeted variant analysis (81403) to establish a diagnosis of autosomal dominant or autosomal recessive polycystic kidney disease is considered **investigational** for all other indications.

Single Gene or Multigene Panel Analysis

I. *PKD1* (81407), *PKD2* (81406), *GANAB* (81479), *DNAJB11* (81479), *PKHD1* (81479) sequencing and/or deletion/duplication analysis or multigene panel analysis (81404, 81405, 81406, 81407, 81408, 81479) to confirm or establish a diagnosis of polycystic kidney disease is considered **medically necessary** when:
   A. The member has any of the following clinical features of polycystic kidney disease:
      1. Multiple bilateral renal cysts
      2. Cysts in other organs (especially the liver, seminal vesicles, pancreas, and arachnoid membrane)
      3. Hypertension in an individual younger than age 35
      4. Intracranial aneurysm
      5. Bilaterally enlarged and diffusely echogenic kidneys
      6. Poor corticomedullary differentiation
      7. Hepatobiliary abnormalities with progressive portal hypertension
      8. Congenital hepatic fibrosis (CHF) with portal hypertension,

II. *PKD1* (81407), *PKD2* (81406), *GANAB* (81479), *DNAJB11* (81479), *PKHD1* (81479) sequencing and/or deletion/duplication analysis or multigene panel analysis (81404, 81405, 81406, 81407, 81408, 81409, 81479) to confirm or establish a diagnosis of polycystic kidney disease is considered **investigational** for all other indications.

Comprehensive Kidney Disease Panels

I. Genetic testing for kidney disease via a comprehensive kidney disease panel (81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479) is considered **medically necessary** when:
   A. The member has chronic kidney disease with an undetermined cause after undergoing standard-of-care workup studies (e.g., history and physical examination, biochemical testing, renal imaging, or renal biopsy), **AND**
   B. The member meets at least one of the following:
      1. Onset of chronic kidney disease under 40 years of age, **OR**
      2. One or more first- or second-degree relatives with chronic kidney disease, **OR**
      3. Consanguineous family history, **AND**
   C. The member is being considered for a kidney transplant.

II. Genetic testing for kidney disease via a comprehensive kidney disease panel (81401, 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479) is considered **investigational** for all other indications.

Other Covered Kidney Disorders

The following is a list of conditions that have a known genetic association. Due to their relative rareness, it may be appropriate to cover these genetic tests to establish or confirm a diagnosis.

I. Genetic testing to establish or confirm one of the following genetic kidney disorders to guide management is considered **medically necessary** when the member demonstrates clinical features* consistent with the disorder (the list is not meant to be comprehensive, see II below):

   A. Alport Syndrome

B. C3 Glomerulopathy
C. Congenital nephrotic syndrome
D. Cystinosis
E. Cystinuria
F. Fabry Disease
G. Genetic (familial) atypical hemolytic-uremic syndrome (aHUS)
H. Primary Hyperoxaluria

II. Genetic testing to establish or confirm the diagnosis of all other kidney disorders not specifically discussed within this or another medical policy will be evaluated by the criteria outlined in *General Approach to Genetic Testing* (see policy for coverage criteria).

*Clinical features for a specific disorder may be outlined in resources such as GeneReviews, OMIM, National Library of Medicine, Genetics Home Reference, or other scholarly source.

Medical Policy: V.35 Genetic Testing: Hereditary Hearing Loss
Effective Date: 07/01/2022
Preauthorization Required: Yes
Policy Statement

Known Familial Variant Analysis

I. Targeted variant analysis for known familial variant(s) to establish a diagnosis of hereditary hearing loss (81253, 81403) is considered **medically necessary** when:
   A. The member has a close relative with pathogenic or likely pathogenic variant(s) in *GJB2*, *GJB6*, or another gene known to cause hereditary hearing loss.

GJB2 and GJB6 Sequencing and/or Deletion Duplication Analysis or Multigene Panel Analysis

I. *GJB2* (81252, S3844) and/or *GJB6* (81254, 81479) sequencing and/or deletion/duplication analysis or multigene panel analysis (81430, 81431) to establish a diagnosis of hereditary hearing loss is considered **medically necessary** when:
   A. The member has hearing loss, **AND**
   B. There is no known acquired cause of the hearing loss (e.g., TORCH, bacterial infection, age-related or noise-related hearing loss).

II. *GJB2* (81252, S3844) and/or *GJB6* (81254, 81479) sequencing and/or deletion/duplication analysis or multigene panel analysis (81430, 81431) to establish a diagnosis of hereditary hearing loss is considered **investigational** for all other indications.

Medical Policy: V.67 Genetic Testing: Gastrointestinal (Non-Cancerous)
Effective Date: 07/01/2022
Preauthorization Required: Yes
Policy Statement

Hereditary Inflammatory Bowel Disease / Crohn's Disease Panel Tests

I. Genetic testing for inflammatory bowel disease (81479), including Crohn's disease via a multigene panel is considered medically necessary to confirm a diagnosis and/or determine appropriate treatment when:
   A. Patient has very early onset of typical IBD symptoms before age 2 years, **OR**
   B. Patient is under the age of 18 with aggressive, refractory, or unusual IBD presentation, **OR**
   C. Patient is under the age of 18 with IBD symptoms, and also has a family history of IBD or immunodeficiency.
   D. The panel includes at a minimum the following genes: IKBKG, TTC7, ADAM17, NCF2, NCF4, SLC37A4, XIAP, LRBA, CD40LG; WAS, IL10R, IL10, FOXP3

Genetic testing for inflammatory bowel disease (81479), including Crohn's disease, via a multigene panel is considered **investigational** for all other indications.