

Clinical Policy: Genetic Testing: Dermatologic Conditions

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Description

Genetic testing for dermatologic conditions and disorders that have many dermatologic findings may be used to confirm a diagnosis in a patient who has signs and/or symptoms of the disease. Confirming the diagnosis may alter some aspects of management and may eliminate the need for further diagnostic workup. This document addresses genetic testing for dermatologic conditions.

Below is a list of higher volume tests and the associated laboratories for each medical necessity criteria section. This list is not all inclusive.

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81479	Capillary Malformation-Arteriovenous Malformation Syndrome (CM-AVM) Panel, Sequencing and Deletion/Duplication (ARUP) CM-AVM_Germline (Fairview Diagnostics)	Capillary Malformation-Arteriovenous Malformation Syndrome (CM-AVM)	Q27.3, Q27.9
81443, 81479	Ichthyosis Panel (Blueprint Genetics) Ichthyosis NGC Panel (Connective Tissue Gene Tests) Invitae Congenital Ichthyosis Panel (Invitae)	Congenital Ichthyosis Multigene Panels	Q80
81443, 81479	Epidermolysis Bullosa Panel (Blueprint Genetics) Epidermolysis Bullosa NGS Panel (Connective Tissue Gene Tests) Invitae Epidermolysis Bullosa and Palmoplantar Keratoderma Panel (Invitae)	Epidermolysis Bullosa Multigene Panels	Q81

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CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81401-81408, 81479	See below	Covered Dermatologic Conditions	Varies

This policy document provides criteria for Genetic Testing for Dermatologic Conditions. Please refer to:

- ***CP.MP.225 Genetic Testing: Hereditary Cancer Susceptibility*** for criteria related to hereditary cancer syndromes that may have or present with dermatologic findings.
- ***CP.MP.230 Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for criteria related to tuberous sclerosis, neurofibromatosis, HHT, incontinentia pigmenti, proteus syndrome, pseudoxanthoma elasticum, and other disorders that affect the skin and other organ systems.
- ***CP.MP.222 Genetic Testing: General Approach to Genetic Testing*** for criteria related to genetic testing for a dermatologic condition that is not specifically discussed in this or another more specific policy.

Policy/Criteria

Known Familial Variant Analysis for Dermatologic Conditions

- I. It is the policy of health plans affiliated with Centene Corporation® that targeted mutation analysis for a known familial variant (81403) may be considered medically necessary when:
 - A. The member/enrollee has a close relative with a known pathogenic or likely pathogenic variant causing the condition.
- II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support targeted mutation analysis for a known familial variant (81403) for all other indications.

Capillary Malformation-Arteriovenous Malformation (CM-AVM) Syndrome

- I. It is the policy of health plans affiliated with Centene Corporation that RASA1 and EPHB4 sequencing and/or deletion/duplication analysis or multi-gene panel analysis (81479) to establish a diagnosis of capillary malformation-arteriovenous malformation (CM-AVM) syndrome is considered medically necessary when the member/enrollee displays one or more of the following:
 - A. Capillary malformations
 - B. Arteriovenous malformations/arteriovenous fistulas
 - C. Parkes Weber syndrome phenotype, a cutaneous capillary malformation associated with underlying multiple micro-AVFs and soft-tissue and skeletal hypertrophy of the affected limb

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- II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support RASA1 and EPHB4 sequencing and/or deletion/duplication analysis or multi-gene panel analysis (81479) to establish a diagnosis of capillary malformation-arteriovenous malformation (CM-AVM) syndrome is considered investigational for all other indications.

Congenital Ichthyosis

Congenital Ichthyosis Multigene Panel

- I. It is the policy of health plans affiliated with Centene Corporation that multigene panel analysis to establish or confirm a diagnosis of congenital ichthyosis (81479) is considered medically necessary when meeting both of the following:
- A. The member/enrollee has scaly skin with or without a history of harlequin ichthyosis, collodion membrane, or thick, hyperkeratotic skin;
 - B. One or more of the following:
 - 1. Ectropion (eversion of eyelids)
 - 2. Eclabium (eversion of lips)
 - 3. Scarring alopecia
 - 4. Palmar and/or plantar hyperkeratosis
 - 5. Erythroderma (red skin).
- II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support multigene panel analysis to establish or confirm a diagnosis of congenital ichthyosis (81479) for all other indications.

Epidermolysis Bullosa

Epidermolysis Bullosa Multigene Panel

- I. It is the policy of health plans affiliated with Centene Corporation that multigene panel analysis to establish or confirm a diagnosis of epidermolysis bullosa (81479) is considered medically necessary when meeting both of the following:
- A. The member/enrollee has fragility of the skin manifested by blistering with little or no trauma;
 - B. One or more of the following:
 - 1. Nail dystrophy
 - 2. Milia
 - 3. Congenital pyloric atresia.
- II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support multigene panel analysis to establish or confirm a diagnosis of epidermolysis bullosa (81479) for all other indications.

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Other Dermatologic Conditions

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

- I. It is the policy of health plans affiliated with Centene Corporation that genetic testing to establish or confirm one of the following dermatologic conditions to guide management is considered medically necessary when the member/enrollee demonstrates clinical features* consistent with the condition (the list is not meant to be comprehensive, see II below):
 - A. Hidrotic Ectodermal Dysplasia 2 (Clouston Syndrome)
 - B. Hypohidrotic Ectodermal Dysplasia
 - C. Ocular albinism, X-linked
 - D. Oculocutaneous albinism

- II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support genetic testing to establish or confirm the diagnosis of all other dermatologic conditions not specifically discussed within this or another medical policy will be evaluated by the criteria outlined in General Approach to Genetic Testing (see policy medical necessity 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.

Notes and Definitions

1. Close relatives include first, second, and third degree blood relatives:
 - a. **First-degree relatives** are parents, siblings, and children
 - b. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings
 - c. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins

Background

American College of Medical Genetics and Genomics

American College of Medical Genetics and Genomics (2012) issued guidelines on the evaluation of adolescents or adults with some features of Marfan syndrome (MFS), which recommendations included the following:

- If there is no family history of MFS, then the subject has the condition under any of the following four situations:
 - A dilated aortic root (defined as greater than or equal to two standard deviations above the mean for age, sex, and body surface area) and ectopia lentis
 - A dilated aortic root and a mutation [pathogenic variant] in FBN1 that is clearly pathologic
 - A dilated aortic root and multiple systemic features or

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- Ectopia lentis and a mutation [pathogenic variant] in FBN1 that has previously been associated with aortic disease.
- If there is a positive family history of MFS (independently ascertained with these criteria), then the subject has the condition under any of the following three situations:
 - Ectopia lentis
 - Multiple systemic features or
 - A dilated aortic root (if over 20 years, greater than two standard deviations; if younger than 20, greater than three standard deviations)

American College of Cardiology Foundation, et. al.

American College of Cardiology Foundation and 9 other medical associations published joint evidence-based guidelines (2010) for the diagnosis and management of thoracic aortic disease, including Marfan syndrome, which included the following guidelines regarding genetic testing:

- If the mutant gene (FBN1, TGFBR1, TGFBR2, COL3A1, ACTA2, MYH11) associated with aortic aneurysm and/or dissection is identified in a patient, first-degree relatives should undergo counseling and testing. Then, only the relatives with the genetic mutation [pathogenic variant] should undergo aortic imaging. [class 1, level of evidence C.]
- The criteria for Marfan syndrome is based primarily on clinical findings in the various organ systems affected in the Marfan syndrome, along with family history and FBN1 mutations [pathogenic variants] status.

2017 International Classification of the Ehlers-Danlos Syndromes

The 2017 International Classification of the Ehlers-Danlos Syndromes included the following clinical features for the associated conditions:

Classical EDS (cEDS):

Major criteria

1. Skin hyperextensibility and atrophic scarring
2. Generalized joint hypermobility (GJH)

Minor criteria

1. Easy bruising
2. Soft, doughy skin
3. Skin fragility (or traumatic splitting)
4. Molluscoid pseudotumors
5. Subcutaneous spheroids
6. Hernia (or history thereof)
7. Epicanthal folds
8. Complications of joint hypermobility (e.g., sprains, luxation/subluxation, pain, flexible flatfoot)
9. Family history of a first degree relative who meets clinical criteria

Minimal Criteria suggestive for cEDS:

- Major criterion (1): skin hyperextensibility and atrophic scarring
- Plus
- Either major criterion (2): GJH
- And/or: at least three minor criteria

Confirmatory molecular testing is obligatory to reach a final diagnosis.

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Vascular EDS (vEDS)

Major criteria

1. Family history of vEDS with documented causative variant in COL3A1
2. Arterial rupture at a young age
3. Spontaneous sigmoid colon perforation in the absence of known diverticular disease or other bowel pathology
4. Uterine rupture during the third trimester in the absence of previous C-section and/or severe peripartum perineum tears
5. Carotid-cavernous sinus fistula (CCSF) Formation in the absence of trauma

Minor criteria

1. Bruising unrelated to identified trauma and/or in unusual sites such as cheeks and back
2. Thin, translucent skin with increased venous visibility
3. Characteristic facial appearance
4. Spontaneous pneumothorax
5. Acrogeria
6. Talipes equinovarus
7. Congenital hip dislocation
8. Hypermobility of small joints
9. Tendon and muscle rupture
10. Keratoconus
11. Gingival recession and gingival fragility
12. Early onset varicose veins (under age 30 and nulliparous if female)

Minimal criteria suggestive for vEDS:

- A family history of the disorder, arterial rupture or dissection in individuals less than 40 years of age, unexplained sigmoid colon rupture, or spontaneous pneumothorax in the presence of other features consistent with vEDS should all lead to diagnostic studies to determine if the individual has vEDS. Testing for vEDS should also be considered in the presence of a combination of the other “minor” clinical features listed above. Even for experienced clinicians the clinical diagnosis of vEDS may be difficult. Because of implications for treatment, natural history, and recurrence risk, the diagnosis of vEDS rests on the identification of a causative variant in one allele of COL3A1.

CSANZ Cardiovascular Genetic Diseases Council

CSANZ Cardiovascular Genetic Diseases Council (2017) published a position statement with updates on the diagnosis and management of inherited aortopathies, including Marfan syndrome, that stated the following key points:

1. A number of inherited conditions can predispose the aorta, and less commonly other blood vessels, to dilatation and/ or rupture.
2. Broadly speaking, these conditions are recognised as syndromic when accompanied by a number of systemic features or non-syndromic when the aortic dilatation appears to exist in isolation.
3. The commonest syndromic aortopathy is Marfan syndrome and the commonest non-syndromic aortopathy is that which accompanies congenital bicuspid aortic valve.
4. Mutations in a number of genes have been identified, particularly in syndromic aortopathy.

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5. Although genotype-phenotype relationships exist, the phenotypes of the syndromic aortopathies may have significant overlap.
6. When a syndromic aortopathy is suspected, review by a clinical geneticist is instrumental in characterising the clinical signs and the family history.
7. Confirmation of a diagnosis (either clinically or by gene testing) allows identification of individuals at increased risk of aortic sequelae who will benefit from active medical management.
8. Medical management is usually undertaken by a cardiologist with referral to other specialists (eg cardiothoracic surgeons) as appropriate.
9. At risk family members should be offered predictive testing if a mutation is identified, and should otherwise be screened in keeping with the presumptive clinical diagnosis and assessment of risk.
10. Pregnancy and the post-partum period confer a higher risk for aortic complications:
 - a. Women with a personal or family history of aortopathy need appropriate pre-conception screening and counselling.
 - b. Intervention may be required pre-conception and they should be managed closely throughout pregnancy, ideally in a high-risk obstetric clinic, with joint management by an obstetrician and a cardiologist.
 - c. Management may include appropriate cessation and commencement/continuation of medication ((ACE inhibitors and ARB are teratogenic and contraindicated in pregnancy, beta blockers can be used in pregnancy) and should include involvement of a cardiologist in the management during pregnancy and decision making for delivery.
11. A clinical diagnosis of an inherited aortopathy can be made in the absence of a positive genetic test if the systemic features are consistent with a specific syndromic aortopathy. A familial history of aortic dissection in the absence of both a positive gene test and systemic examination findings may be more difficult to manage without a working clinical diagnosis. However, an inherited risk of dissection should nonetheless be considered in this setting, particularly if the process has affected young individuals and/or in the absence of traditional risk factors.

Coding Implications

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Reviews, Revisions, and Approvals	Revision Date	Approval Date
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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical

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Note: For Medicaid members/enrollees, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at <http://www.cms.gov> for additional information.

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