

GENETIC TESTING: DERMATOLOGIC CONDITIONS

OVERVIEW

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.

POLICY REFERENCE TABLE

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

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
Known Familial Variant Analysis for Dermatologic Conditions				
Known Familial Variant Analysis for Dermatologic Conditions	Targeted Mutation Analysis for a Known Familial Variant	81403		8
Capillary Malformation-Arteriovenous Malformation Syndrome (CM-AVM)				
Capillary Malformation-Arteriovenous Malformation Syndrome (CM-AVM)	Capillary Malformation-Arteriovenous Malformation Syndrome (CM-AVM) Panel, Sequencing and Deletion/Duplication (ARUP Laboratories)	81479	Q27.3, Q27.9	1
	Vascular Malformation Sequencing Panel (Greenwood Genetic Center)			

	RASA1 Full Gene Sequencing and Deletion/Duplication (Invitae)			
	EPHB4 Full Gene Sequencing and Deletion/Duplication (Invitae)			
<u>Congenital Ichthyosis</u>				
Congenital Ichthyosis Multigene Panels	Ichthyosis Panel (Blueprint Genetics)	81405, 81479, 81252	Q80	2
	Ichthyosis NGS Panel (Connective Tissue Gene Tests)			
	Invitae Congenital Ichthyosis Panel (Invitae)			
<u>Epidermolysis Bullosa</u>				
Epidermolysis Bullosa Multigene Panels	Epidermolysis Bullosa Panel (Blueprint Genetics)	81406, 81479	Q81	3, 4
	Epidermolysis Bullosa NGS Panel (Connective Tissue Gene Tests)			
	Invitae Epidermolysis Bullosa and Palmoplantar Keratoderma Panel (Invitae)			
<u>Covered Dermatologic Conditions</u>				
Covered Dermatologic Conditions	See Below	81401-81408, 81479	Varies	5, 6, 7

OTHER RELATED POLICIES

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

- ***Genetic Testing: Hereditary Cancer Susceptibility*** for coverage criteria related to hereditary cancer syndromes that may have or present with dermatologic findings.
- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for coverage criteria related to tuberous sclerosis,

neurofibromatosis, HHT, incontinentia pigmenti, proteus syndrome, pseudoxanthoma elasticum, and other disorders that affect the skin and other organ systems.

- **Genetic Testing: General Approach to Genetic Testing** for coverage criteria related to genetic testing for a dermatologic condition that is not specifically discussed in this or another more specific policy.

COVERAGE CRITERIA

KNOWN FAMILIAL VARIANT ANALYSIS FOR DERMATOLOGIC CONDITIONS

- I. Targeted mutation analysis for a known familial variant (81403) in a dermatologic condition may be considered **medically necessary** when:
 - A. The member has a [close relative](#) with a known pathogenic or likely pathogenic variant causing the condition.
- II. Targeted mutation analysis for a known familial variant (81403) in a dermatologic condition is considered **investigational** for all other indications.

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CAPILLARY MALFORMATION-ARTERIOVENOUS MALFORMATION (CM-AVM) SYNDROME

***RASA1* and *EPHB4* Sequencing and/or Deletion/Duplication Analysis or Multigene Panel**

- I. *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:
 - A. The member displays one or more of the following:

1. Capillary malformations, **OR**
 2. Arteriovenous malformations/arteriovenous fistulas, **OR**
 3. Parkes Weber syndrome phenotype, a cutaneous capillary malformation associated with underlying multiple micro-AVFs and soft-tissue and skeletal hypertrophy of the affected limb.
- II. *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.

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CONGENITAL ICHTHYOSIS

Congenital Ichthyosis Multigene Panel

- I. Multigene panel analysis to establish or confirm a diagnosis of congenital ichthyosis (81405, 81479, 81252) is considered **medically necessary** when:
 - A. The member has scaly skin with or without a history of harlequin ichthyosis, collodion membrane, or thick, hyperkeratotic skin, **AND**
 - B. One or more of the following:
 1. Ectropion (eversion of eyelids), **OR**
 2. Eclabium (eversion of lips), **OR**
 3. Scarring alopecia, **OR**
 4. Palmar and/or plantar hyperkeratosis, **OR**
 5. Erythroderma (red skin), **AND**
 - C. The panel includes, at a minimum, the following genes: *ABCA12*, *SLC27A4*, and *TGM1*.

- II. Multigene panel analysis to establish or confirm a diagnosis of congenital ichthyosis (81405, 81479, 81252) is considered **investigational** for all other indications.

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EPIDERMOLYSIS BULLOSA

Epidermolysis Bullosa Multigene Panel

- I. Multigene panel analysis to establish or confirm a diagnosis of epidermolysis bullosa (81406, 81479) 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, **AND**
 - D. The panel includes, at a minimum, the following genes: *EXPH5*, *KRT5*, *KRT14*, *PLEC*.
- II. Multigene panel analysis to establish or confirm a diagnosis of epidermolysis bullosa (81406, 81479) is considered **investigational** for all other indications.

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OTHER COVERED 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 cover these genetic tests to establish or confirm a diagnosis.

- I. Genetic testing to establish or confirm one of the following dermatologic conditions to guide management is considered **medically necessary** when the member 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. 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 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.

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

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BACKGROUND AND RATIONALE

Known Familial Variant Analysis for Dermatologic Conditions

Genetic Support Foundation

The Genetic Support Foundation's Genetics 101 information on inheritance patterns says the following about testing for familial pathogenic variants:

Genetic testing for someone who may be at risk for an inherited disease is always easier if we know the specific genetic cause. Oftentimes, the best way to find the genetic cause is to start by testing someone in the family who is known or strongly suspected to have the disease. If their testing is positive, then we can say that we have found the familial pathogenic (harmful) variant. We can use this as a marker to test other members of the family to see who is also at risk.

Capillary Malformation-Arteriovenous Malformation Syndrome (CM-AVM)

GeneReviews: Capillary Malformation-Arteriovenous Malformation Syndrome

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. The recommended diagnostic testing for CM-AVM is as follows:

"CM-AVM syndrome should be suspected in individuals who have any of the following:

- Capillary malformations (CMs), the hallmark of CM-AVM syndrome. CMs are generally:
 - Multifocal, atypical pink-to-reddish brown, multiple, small (1-2 cm in diameter), round-to-oval lesions sometimes with a white halo;
 - Composed of dilated capillaries in the papillary dermis
 - Mostly localized on the face and limbs;
 - Seen in combination with arteriovenous malformations (AVMs) or arteriovenous fistulas (AVF), but may be the only finding.
- AVMs/AVFs in soft tissue, bone, and brain that may be associated with overgrowth
- Parkes Weber syndrome phenotype, a cutaneous capillary malformation associated with underlying multiple micro-AVFs and soft-tissue and skeletal hypertrophy of the affected limb"

"The diagnosis of CM-AVM syndrome is established in a proband with suggestive clinical findings and a heterozygous pathogenic variant in *EPHB4* or *RASA1* identified by molecular genetic testing."

"When the phenotypic and laboratory findings suggest the diagnosis of CM-AVM syndrome, molecular genetic testing approaches can include use of a multigene panel. A multigene panel that includes *EPHB4*, *RASA1*, and other genes of interest is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype."

Congenital Ichthyosis Multigene Panels

GeneReviews: Autosomal Recessive Congenital Ichthyosis

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. The recommended diagnostic testing for nonsyndromic congenital ichthyosis is as follows:

"Autosomal recessive congenital ichthyosis (ARCI) encompasses several forms of nonsyndromic ichthyosis. Although most neonates with ARCI are collodion babies, the clinical presentation and severity of ARCI may vary significantly, ranging from harlequin

ichthyosis, the most severe and often fatal form, to lamellar ichthyosis (LI) and (nonbullous) congenital ichthyosiform erythroderma (CIE). These phenotypes are now recognized to fall on a continuum; however, the phenotypic descriptions are clinically useful for clarification of prognosis and management."

- The diagnosis of ARCI is established in a proband (typically an infant):
 - With scaly skin with or without a history of harlequin ichthyosis, collodion membrane, or thick, hyperkeratotic skin AND the later development of ONE of the following:
 - Classic lamellar ichthyosis (LI). Brown, plate-like scale over the entire body, associated with ectropion (eversion of eyelids), eclabium (eversion of lips), scarring alopecia, and palmar and plantar hyperkeratosis
 - (Nonbullous) congenital ichthyosiform erythroderma (CIE). Erythroderma (red skin) with fine, white scale and often with palmoplantar hyperkeratosis
 - Intermediate forms with some features of both LI and CIE, or nonLI/nonCIE form with mild hyperkeratosis;

AND/OR

- By identification of biallelic pathogenic variants in one of the genes listed below.

"The twelve genes known to be associated with ARCI are *ABCA12*, *ALOX12B*, *ALOXE3*, *CASP14*, *CERS3*, *CYP4F22*, *LIPN*, *NIPAL4*, *PNPLA1*, *SDR9C7*, *SLC27A4*, and *TGM1*. A multigene panel that includes these genes is the diagnostic test of choice. If such testing is not available, single-gene testing can be considered starting with *ABCA12* in individuals with harlequin ichthyosis, *TGM1* in individuals with ARCI without harlequin presentation at birth and *SLC27A4* in those presenting with ichthyosis-prematurity syndrome."

Epidermolysis Bullosa Multigene Panels

GeneReviews: Epidermolysis Bullosa Simplex

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. The recommended diagnostic testing for epidermolysis bullosa simplex and epidermolysis bullosa with pyloric atresia is as follows:

The diagnosis of epidermolysis bullosa simplex (EBS) is best established in a proband by the identification of biallelic pathogenic variants in *EXPH5* or *TGM5* or heterozygous (or rarely biallelic) pathogenic variants in *KRT5* or *KRT14* by molecular genetic testing

"The diagnosis of epidermolysis bullosa simplex (EBS) should be suspected in individuals with the following clinical findings:

- Fragility of the skin manifested by blistering with little or no trauma, which typically heals without scarring
- Blistering that:
 - May be present in the neonatal period
 - Primarily affects the hands and feet but can affect the whole body
 - Occurs in annular or curvilinear groups or clusters
 - Can lead to progressive brown pigmentation interspersed with hypopigmented spots on the trunk and extremities that frequently disappears in adult life
 - Is associated with palmar and plantar hyperkeratosis that may be severe
- Nail dystrophy
- Milia
- Family history that is consistent with either an autosomal recessive or autosomal dominant inheritance pattern

Note: Absence of a known family history of EBS does not preclude the diagnosis."

GeneReviews: Epidermolysis Bullosa - Pyloric Atresia

"The diagnosis of epidermolysis bullosa simplex (EBS) is best established in a proband by the identification of biallelic pathogenic variants in *EXPH5* or *TGM5* or heterozygous (or rarely biallelic) pathogenic variants in *KRT5* or *KRT14* by molecular genetic testing. A multigene panel that includes *EXPH5*, *KRT5*, *KRT14*, *TGM5* and other genes of interest may also be considered."

"Epidermolysis bullosa with pyloric atresia (EB-PA) should be suspected in newborns with the following clinical features:

- Congenital pyloric atresia with vomiting and abdominal distension resulting from complete obstruction of the gastric outlet. Radiographs reveal that the stomach is distended and filled with air
- Fragility of the skin with:

- Blistering with little or no trauma. Blistering may be mild or severe; however, blisters generally heal with no significant scarring
- Significant oral and mucous membrane involvement
- Large areas of absent skin (aplasia cutis congenita), often with a thin membranous covering, affecting the extremities or head
- Ureteral and renal anomalies, including hydronephrosis, ureterocele, absent bladder, dysplastic kidneys, urinary collecting system/kidney duplication, obstructive uropathy, and glomerulosclerosis."

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