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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

The tests and associated laboratories and CPT codes contained within this document serve only as examples to help users navigate claims and corresponding coverage criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage. Please see the Concert Genetics Platform for a comprehensive list of registered tests.

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	Ref
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)			
Congenital Ichthyosis				

Congenital Ichthyosis Multigene Panels	Ichthyosis Panel (Blueprint Genetics)	81405, 81479	Q80	2
	Ichthyosis NGS Panel (Connective Tissue Gene Tests)			
	Invitae Congenital Ichthyosis Panel (Invitae)			
Covered Dermatologic Conditions				
Other Covered Dermatologic Conditions	See Below	81401-81408, 81479	Varies	3, 4, 5

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 and Molecular Testing*** for coverage criteria related to genetic testing for a dermatologic condition that is not specifically discussed in this or another more specific policy.

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COVERAGE CRITERIA

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 Panels

I. Multigene panel analysis to establish or confirm a diagnosis of congenital ichthyosis (81405, 81479) 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)

II. Multigene panel analysis to establish or confirm a diagnosis of congenital ichthyosis (81405, 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 and Molecular 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 sources.

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BACKGROUND AND RATIONALE

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*, *SULT2B1*, 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."

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