

[Revision log](#)

# CONCERT GENETICS GENETIC TESTING: DERMATOLOGIC CONDITIONS

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

## 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

### Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2022, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

. Please see the [Concert Genetics Platform](#) for a comprehensive list of registered tests.

<a href="#">Criteria Sections</a>	Example Tests (Labs)	Common CPT Codes	Common ICD Codes	<a href="#">Ref</a>
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Concert Genetics Genetic Testing: Dermatologic Conditions  
V1.2024  
Date of Last Revision: 10/1/2023  
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<b><u>Known Familial Variant Analysis for Dermatologic Conditions</u></b>				
<a href="#"><u>Known Familial Variant Analysis for Dermatologic Conditions</u></a>	Targeted Mutation Analysis for a Known Familial Variant	81403		8
<b><u>Capillary Malformation-Arteriovenous Malformation Syndrome (CM-AVM)</u></b>				
<a href="#"><u>Capillary Malformation-Arteriovenous Malformation Syndrome (CM-AVM)</u></a>	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)			
<b><u>Congenital Ichthyosis</u></b>				
<a href="#"><u>Congenital Ichthyosis Multigene Panels</u></a>	Ichthyosis Panel (Blueprint Genetics)	81405, 81479	Q80	2
	Ichthyosis NGS Panel (Connective Tissue Gene Tests)			
	Invitae Congenital Ichthyosis Panel (Invitae)			
<b><u>Epidermolysis Bullosa</u></b>				
<a href="#"><u>Epidermolysis Bullosa Multigene Panels</u></a>	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)			
<b><u>Covered Dermatologic Conditions</u></b>				
<a href="#"><u>Other Covered Dermatologic Conditions</u></a>	See Below	81401-81408, 81479	Varies	5, 6, 7

## OTHER RELATED POLICIES

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

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

## CRITERIA

It is the policy of health plans affiliated with Centene Corporation<sup>®</sup> that the specific genetic testing noted below is **medically necessary** when meeting the related 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/enrollee 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**

### ***RASAI* and *EPHB4* Sequencing and/or Deletion/Duplication Analysis or Multigene Panel**

- I. *RASAI* 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/enrollee 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. *RASAI* 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/enrollee 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 *TGMI*.
- 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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## EPIDERMOLYSIS BULLOSA

### Epidermolysis Bullosa Multigene Panels

- I. Multigene panel analysis to establish or confirm a diagnosis of epidermolysis bullosa (81406, 81479) is considered **medically necessary** when:
  - A. The member/enrollee has fragility of the skin manifested by blistering with little or no trauma, **OR**
  - B. The member/enrollee has the presence of blistering that:
    1. Is 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. Leads to progressive brown pigmentation interspersed with hypopigmented spots on the trunk and extremities (frequently disappears in adult life), **OR**
    5. Is associated with palmar and plantar hyperkeratosis that may be severe, **OR**

- C. The member/enrollee has one or more of the following:
1. Nail dystrophy, **OR**
  2. Milia, **OR**
  3. Congenital pyloric atresia, **OR**
  4. Natal teeth, **OR**
  5. 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/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. 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 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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## 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 genetic testing 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 *RASAI* 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*, *RASAI*, 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 *TGMI*. 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, *TGMI* 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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Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed.	03/23	03/23
Semi-annual review. Updated title to reflect V1.2024 version. Overview, coding, reference-table, background and references updated. Throughout policy: replaced "coverage criteria" with "criteria. For Other Related Policies: added "Molecular". For Congenital Ichthyosis Multigene Panels: removed "81252" throughout. For Epidermolysis Bullosa Multigene Panels: in I.A. replaced "AND" with "OR"; in I.B.1 replaced with "May be" with "Is"; in I.B.4. replaced "Can lead" with "Leads"; in I.B.5. replaced "AND" with "OR"; in I.C. added "4. Natal teeth, OR". For Other Covered Dermatologic Conditions: added "and Molecular". For Background and Rationale: replaced "inheritance patterns" with "genetic testing".	10/23	10/23

## REFERENCES

1. Bayrak-Toydemir P, Stevenson DA. Capillary Malformation-Arteriovenous Malformation Syndrome. 2011 Feb 22 [Updated 2019 Sep 12]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK52764/>
2. Richard G. Autosomal Recessive Congenital Ichthyosis. 2001 Jan 10 [Updated 2017 May 18]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1420/>
3. So JY, Teng J. Epidermolysis Bullosa Simplex. 1998 Oct 7 [Updated 2022 Aug 4]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1369/>
4. Pfendner EG, Lucky AW. Epidermolysis Bullosa with Pyloric Atresia. 2008 Feb 22 [Updated 2017 Sep 7]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1157/>

5. Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1116/>
6. Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD). World Wide Web URL: <https://omim.org/>
7. MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US). Available from: <https://medlineplus.gov/genetics/>
8. Genetic Support Foundation. Genetics 101 Genetic Testing: Familial Pathogenic Variant. Accessed 10/4/2022. <https://geneticsupportfoundation.org/genetics-101/#>

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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 information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of member/enrollees. This clinical policy is not intended to recommend treatment for member/enrollees. Member/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

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**Note: For Medicaid member/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 member/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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