"I LIVE WITH BLISTERS AND NAIL PROBLEMS AND HAVE BEEN TOLD DIFFERENT REASONS WHY."

WE LEARNED DYSTROPHIC EB (DEB) HAS SERIOUS RISKS.

WE PUSHED FOR ANSWERS— FOR AN ACCURATE DIAGNOSIS AND ACCURATE CARE.

"I WAS BORN WITH BLISTERS BUT THEY WEREN'T WHAT WE FIRST THOUGHT."

JENNY, LIVING WITH DDEB

ABBY, LIVING WITH RDEB

Learn about DEB

Understand the risks

See why it can be missed

Get diagnosed

Find resources

Manage DEB

DEB, or dystrophic epidermolysis bullosa, is a type of epidermolysis bullosa or EB.

It's a genetic disorder that makes skin fragile. Symptoms can include blisters, wounds, scarring, and nails that can thicken or discolor. It can often be mistaken for other EB types and even other skin conditions, but DEB has serious risks.

You can get proactive care and a clearer view of the future the sooner you learn if your blisters are DEB.

Not all blisters are the same. Could yours be DEB? Ask your doctor about a genetic test for DEB.

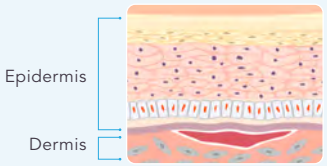
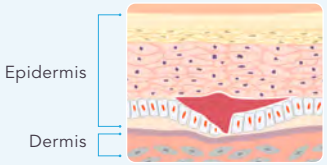
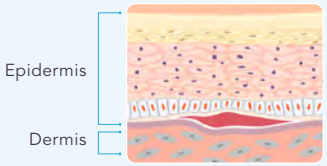
Krystal

What is epidermolysis bullosa (EB)?

EB is not one disorder—it is a group of genetic blistering disorders that share symptoms of fragile skin, which means the skin easily tears and blisters

The 3 major types* of EB are dystrophic epidermolysis bullosa (DEB), epidermolysis bullosa simplex (EBS), and junctional epidermolysis bullosa (JEB). Each type of EB has a unique genetic cause, affecting the body's ability to make different proteins and causing separation in the layers of the skin. The changes in the genes that cause EB are passed down within families. The fragile skin associated with EB can lead to blisters, wounds, skin infections, and scarring. People with EB can also have problems with their fingernails and toenails, including poor growth or thick, yellow nails. EB occurs in every racial and ethnic group and affects both genders equally.

Affected genes, proteins, and skin layers by EB type

	EB Type	Affected Genes	Affected Proteins	Affected Skin Layer
	**Dystrophic epidermolysis bullosa** (DEB)	*COL7A1*	Collagen VII	Dermis
	**Epidermolysis bullosa simplex** (EBS)	*CD151, DST, EXPH5, KLHL24, KRT5, KRT14, PLEC*	BPAG1, Exophilin 5, Kelch-like protein 24, Keratin 5, Keratin 14, Plectin, Tetraspanin 24	Epidermis
	**Junctional epidermolysis bullosa** (JEB)	*COL17A1, ITGA3, ITGA6, ITGB4, LAMA3, LAMB3, LAMC2*	Collagen XVII, Integrin α3 subunit, Integrin α6ß4, Laminin-332	Between dermis and epidermis

*Kindler epidermolysis bullosa (KEB) is a very rare type of EB. It occurs in less than 1% of patients and affects multiple skin layers due to lack of the kindlin-1 protein.
Adapted from De Rosa L, Latella MC, Secone Seconetti A, et al. *Cold Spring Harb Perspect Biol.* 2020.

DEB and EBS are the most common EB types.
About 95% of people with EB in the United States are diagnosed with either DEB or EBS.

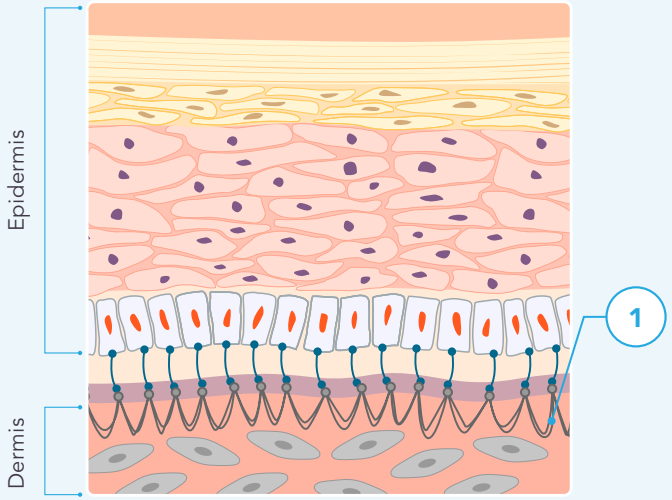
People can have very different experiences with EB.
Even within one EB type, symptoms can vary from mild to severe. But all people with EB have fragile skin.

What is dystrophic epidermolysis bullosa (DEB)?

DEB is caused by mutations in a gene called *COL7A1* that result in a lack of working type VII (type 7) collagen protein

The *COL7A1* gene provides instructions for making type VII collagen protein. Type VII collagen is important because it helps hold together the outer and inner layers of the skin and the lining of some organs. Type VII collagen plays an important role in strengthening and stabilizing the skin. With DEB, this protein is either missing or there is not enough of the working protein.

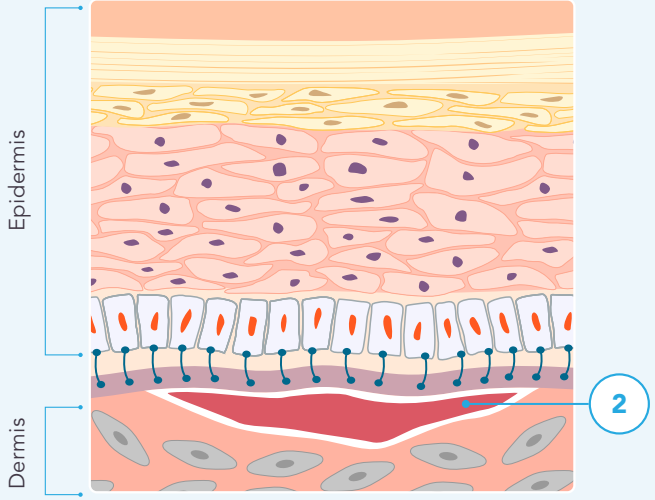
SKIN NOT AFFECTED BY DEB



In skin not affected by DEB, type VII collagen protein helps form anchoring fibrils.

Anchoring fibrils help hold, or anchor, the inner (dermis) and outer (epidermis) skin layers together.

DEB-AFFECTED SKIN



In people with DEB, the mutation in the *COL7A1* gene means the body can't create any type VII collagen protein or enough working type VII collagen protein.

This leads to a lack of or reduced anchoring fibrils. Without anchoring fibrils, the skin layers can easily separate due to friction.

1. Anchoring fibrils (collagen VII) **2.** Blister

Adapted from De Rosa L, Latella MC, Secone Seconetti A, et al. *Cold Spring Harb Perspect Biol*. 2020.

The underlying cause of DEB is mutations in the *COL7A1* gene.

What are the types of DEB?

There are 2 types of DEB

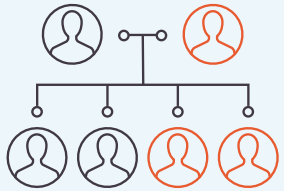
DEB can be inherited in a dominant or recessive pattern

People receive 2 versions of each gene, 1 from each parent. In dominant inheritance, only 1 copy of the gene with a mutation is sufficient to cause a disorder. In recessive inheritance, 2 copies are required.

DDEB

Dominant dystrophic epidermolysis bullosa

DDEB occurs when a child inherits 1 copy of a dominant *COL7A1* gene mutation.



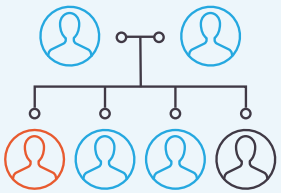
Within each pregnancy:

- There is a **50% chance** that a child of the affected parent will be born with DDEB
- There is a **50% chance** the child will be unaffected

RDEB

Recessive dystrophic epidermolysis bullosa

RDEB occurs when a child inherits 2 copies of a recessive *COL7A1* gene mutation.



Within each pregnancy:

- There is a **25% chance** that a child will inherit gene mutations from both parents and be born with RDEB
- There is a **50% chance** the child will be an unaffected carrier
- There is a **25% chance** the altered gene will not be passed on, and the child will be unaffected

Unaffected | Carrier | Person with DEB

In some cases, a DEB gene mutation can happen for the first time in a family member without inheriting the gene mutation from a parent. This is called a de novo mutation.

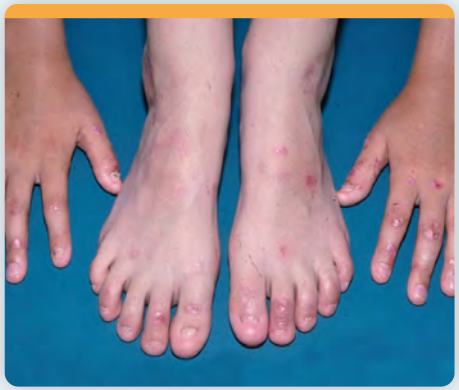
DDEB and RDEB symptoms range in severity, with similar symptoms and risks across both types.

What are the signs and symptoms across DEB?

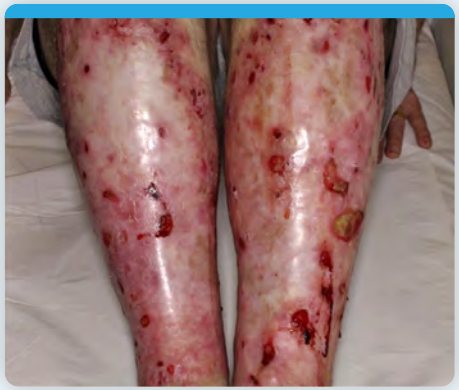
The most common symptom of DEB is fragile skin

This fragile skin can lead to blisters, wounds, skin infections, and scarring. People living with DEB can also have problems with their fingernails and toenails, including poor growth or thick, yellow nails. DEB symptoms are similar to those across other EB types and even other skin conditions. DDEB and RDEB symptoms range in severity, with similar symptoms and risks across both types. Symptoms range in severity from localized to intermediate to severe.

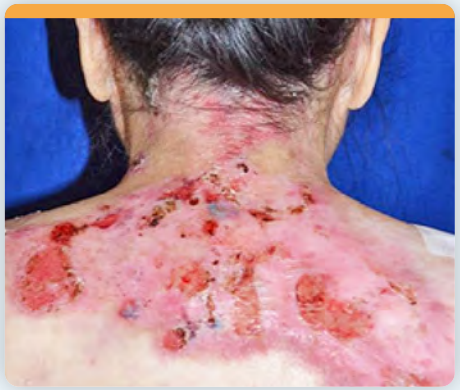
Localized DDEB



Intermediate DDEB



Intermediate RDEB



Severe RDEB

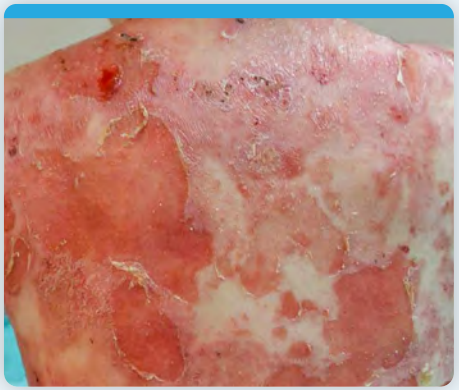


Image sources: (Localized DDEB): Reprinted from *Orphanet Journal of Rare Diseases*, 5, Fine JD. Inherited epidermolysis bullosa. 2010;5(1):12:1-17. Copyright (2010). Licensed under the Creative Commons Attribution 2.0 Generic License. **(Intermediate DDEB):** Reprinted from *JAAD International*, 2, Rogers CL, Gibson M, Kern JS, et al. A comparison study of outcome measures for epidermolysis bullosa: Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) and the Instrument for Scoring Clinical Outcomes of Research for Epidermolysis Bullosa (iscorEB). 2021;2:134-152. Copyright (2021), with permission from Elsevier. **(Intermediate RDEB):** Reprinted from *Journal of Tissue Viability*, 30, Wong T-W, Yang C-C, Hsu C-K, Liu C-H, Yu-Yun Lee J. Transplantation of autologous single hair units heals chronic wounds in autosomal recessive dystrophic epidermolysis bullosa: a proof-of-concept study. 2021;30(1):36-41. Copyright (2021), with permission from Elsevier. **(Severe RDEB):** Reprinted from *Actas Dermo-Sifiliográficas (English Edition)*, 110, Imbernón-Moya A, Maseda-Pedrero R, Feito M, de Lucas R. Dilated cardiomyopathy in a child with recessive dystrophic epidermolysis bullosa. 2019;110(1):81-83. Copyright (2019), with permission from Elsevier.

All DEB wounds should be taken seriously. It's possible for any DEB wound, large or small, to develop complications such as infections or cancer.

What are the signs and symptoms across DEB?

External symptoms can vary from localized to severe

External signs and symptoms across DEB include:

Localized DDEB

Fragile skin on fingers and toes

Nails that thicken, discolor, or fall off

The fingernails and toenails have changes in shape, color, and texture

Shared Intermediate DDEB and RDEB

Blisters

A bubble on the skin filled with liquid caused by friction, burning, or other damage

Nails that thicken, discolor, or fall off

Milk spots (milia)

Small white bumps that appear on the skin

Skin infections

Open skin from wounds can become infected by germs (often bacteria or viruses)

Wounds

Open or broken skin

Scarring

A mark or marks left on the skin where the skin did not completely heal

Unusual skin coloring (pigmentation)

Changes in the coloring of the skin

Squamous cell cancer (SCC)

Severe RDEB

Widespread blistering and wounds

Mitten deformity ("mitten" hands)

Fingers and toes can fuse together due to scarring

Nail and hair loss

Squamous cell cancer (SCC)

DEB has symptoms you may not see.

Beyond symptoms that are visible on the skin, DEB can impact multiple organs and body systems, including the eyes, mouth, gastrointestinal tract, and urinary tract.

What are the serious risks of DEB?

DEB can pose a serious cancer risk

Over time, DEB wounds are potentially at risk for developing an **aggressive** form of squamous cell cancer (SCC).

SCC is more common in people diagnosed with DEB than with other EB types

An SCC can develop in any type of DEB wound, whether RDEB or DDEB. It can happen in wounds that are large or small, those that heal, and those that come back.

What is SCC?

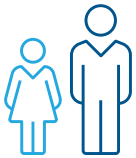
Squamous cell cancer (SCC) is a serious form of skin cancer.

- It is the second most common form of skin cancer and is usually caused by sun damage or exposure to ultraviolet radiation
- SCCs can appear as scaly red patches; open sores; rough, thickened, or wart-like skin; or raised growths with a central depression

SCC in people living with DEB is different than SCC in the general population, which can be caused by sun damage

Higher risk

People diagnosed with DEB are more likely to get SCC than those in the general population



Younger diagnosis

DEB patients are more likely to get SCC at a younger age, and the risk increases as they get older*

Multiple tumors

SCC in people living with DEB can be more aggressive, causing multiple tumors that can more easily spread beyond the skin

While all people with DEB are at risk for SCC, the risk is highest in people with RDEB.

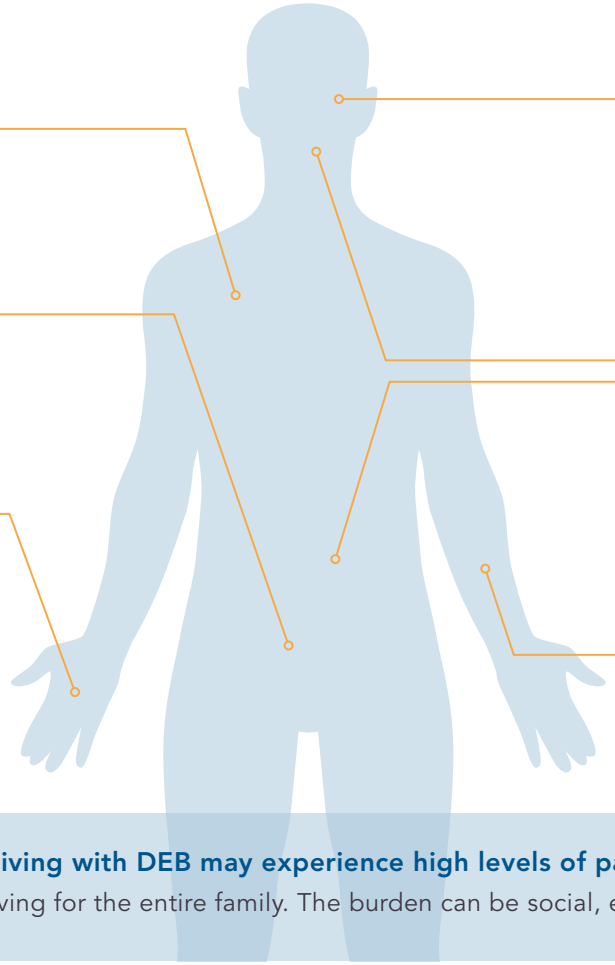
*The median age at SCC diagnosis is 32.5 years in RDEB and 45 years in DDEB.

It's important for people living with DEB to watch for and get screened for SCC early and regularly.

How can DEB impact the rest of the body?

DEB can affect more than the skin

Blistering can affect epithelial tissues or the lining of organs inside the body in places like the mouth, throat, and intestines.



- Infection of open skin wounds
- Problems with urination
- Mitten deformity ("mitten" hands)—fusion of fingers and toes
- Eye problems such as infection and scarring, poor vision, or vision loss
- Wounds in the mouth and digestive tract, which can cause problems with swallowing, digestion, nutrition, and constipation
- Anemia—low numbers of red blood cells due to iron deficiency, chronic disease, and blood loss from open wounds

In addition, some people living with DEB may experience high levels of pain and/or loss of mobility.

DEB can negatively affect daily living for the entire family. The burden can be social, emotional, physical, and financial.

Active care from your healthcare team can help monitor or manage these problems.

DEB can be mistaken for another type of EB

A missed or delayed diagnosis of DEB can happen

For many, the path to an accurate DEB diagnosis can be long and challenging. While DEB is often diagnosed at birth, it can also be missed. Similar symptoms on the skin may cause DEB to be mistaken for another type of EB or a different skin condition.

Some people may not have symptoms until later in life, which can lead to a late diagnosis. Many people experience a delay between seeing symptoms and receiving an accurate diagnosis.

Shared external symptoms across EB types

External Symptoms	DEB	EB Simplex	Junctional EB
Blisters	✓	✓	✓
Wounds	✓	✓	✓
Nails that thicken, discolor, or fall off	✓	✓	✓
Scarring	✓	✓	✓
Milk spots (milia)	✓	✓	✓
Unusual skin coloring (pigmentation)	✓	✓	✓
Skin infections	✓	✓	✓
Blisters of the mouth	✓	✓	✓

If you or a loved one has fragile skin that easily blisters, it's important to accurately know if it's DEB.

DEB can be mistaken for other skin conditions

Similar symptoms on the skin may cause DEB to be mistaken for another form of EB or a different skin condition.

In the most common EB type, EB simplex (EBS), **nearly half or 50% of people were diagnosed by symptoms alone**, without confirmatory testing (biopsy or genetic testing).

Although EB is genetic, **only 56% of people with EB have had genetic testing to confirm which gene is affected**.

DEB has symptoms similar to other skin conditions

External Symptoms	DEB	Other Genetic Blistering Conditions*	Select Autoimmune Disorders†	Select Infectious Diseases‡
Blistering of the skin	✓	✓	✓	✓
Skin ulcer	✓	✓	✓	
Scarring	✓		✓	
Reddening of the skin	✓	✓	✓	✓
Nail issues	✓	✓	✓	
Infections	✓	✓	✓	✓
Inflammation	✓	✓		
Eye and mouth problems	✓		✓	✓
Digestive tract problems	✓		✓	

*Other genetic blistering conditions include epidermolytic ichthyosis and eczema of the hand.
†Select autoimmune blistering conditions include linear IgA bullous dermatosis, bullous pemphigoid, and pemphigus vulgaris.
‡Select infectious diseases include staphylococcal scalded skin syndrome.

What could an accurate DEB diagnosis mean for you?

There's value in knowing if you or a loved one is living with DEB

Knowing if it's DEB can help you or someone you love recognize the risks, get accurate care, and prepare for the future.

Proactive management
Your healthcare team can give more tailored and active care specific to DEB.

A connected community
You can connect with other people and families who are living with DEB to share knowledge, experience, and support.

Comprehensive and proactive risk monitoring
You and your healthcare team can closely watch for risks specific to DEB, including SCC and internal complications.

Family planning
When planning for the future, a genetic counselor can discuss personalized family planning with you.

A clearer future
You can find information and resources specific to DEB.

Not all blisters are the same. Could yours be DEB? Learn more about the importance of genetic testing on pages 12 and 13.

How is DEB diagnosed?

Only genetic testing or skin biopsy can accurately diagnose DEB

It's important for you or a loved one to accurately confirm DEB.

DEB symptoms can appear the same as other EB types and even other skin conditions. This means diagnosis based on symptoms alone can be unreliable.

Skin biopsy

Skin biopsy can help show EB type, but biopsy may not be able to distinguish DDEB from RDEB. Biopsy can sometimes be incomplete or inaccurate.

Genetic testing

Genetic testing can accurately identify DEB. In people living with DEB, a genetic test can determine:

- The specific *COL7A1* gene mutation(s)
- Whether it's DDEB or RDEB

Genetic testing uses a sample of blood or a cheek swab to confirm EB type.

Experts recommend genetic testing to accurately diagnose DEB

Who should get confirmatory testing?

If you or a loved one:

- Has DEB-like blisters, wounds, or symptoms

OR

- Was diagnosed with EB but doesn't know the specific EB type

OR

- Was diagnosed with any type of EB based on symptoms alone

AND/OR

- If a family member has been diagnosed with EB or DEB

EB medical experts recommend genetic testing for the diagnosis of EB type.

Your doctor can provide more information about genetic testing

Talking to your doctor is an important first step to confirming your diagnosis. Prepare for your appointment by gathering family history and writing down any symptoms and questions you may have.

Consider asking questions like:

- How can I get a genetic test?
- Will my insurance cover genetic testing?
- How do I provide a sample for testing?
- How long before my test results are ready?
- What are the next steps after I receive my results?

Genetic testing programs may be available to patients at no cost.

With Krystal Connect™, you are not alone on your DEB journey

Krystal Biotech is committed to providing resources to help you learn more about DEB and talk with your healthcare provider about diagnosis and testing

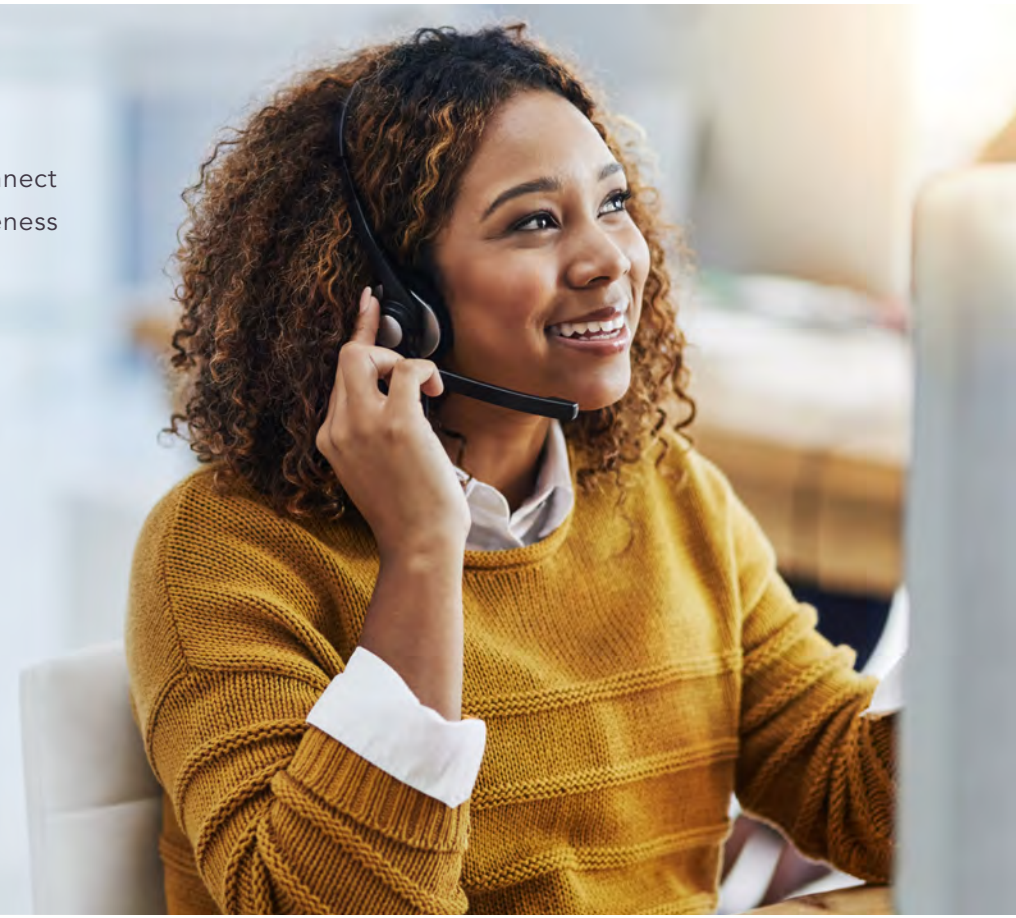
Krystal CONNECT™
Personalized Support Services

Krystal Connect personalized support

Whether you just want to keep in touch or need additional support, Krystal Connect is here to help. Krystal Connect Community Education Liaisons help raise awareness of DEB and can help you and your family learn more about DEB by:

- **Connecting you with helpful tools and resources about DEB**
- **Providing education about family trees, inheritance, and genetic testing for you or family members**
- **Providing educational opportunities via one-on-one, family, or group meetings**

Krystal Community Education Liaisons have nursing or genetic counseling backgrounds.



Contact a Community Education Liaison at 1-844-5-KRYSTAL.

How is DEB managed?

There are currently no treatments available that address the underlying cause of DEB

To manage DEB, healthcare teams focus on guiding supportive care and watching for and treating complications.

Supportive care includes:

Wound management

Bandages, also called dressings, are meant to prevent infection and protect the skin from damage and trauma while it is healing.

Anti-itch treatments may include topical steroids for severe itch.

Bathing and wound cleansing

Antimicrobial, vinegar, or salt soaks are sometimes used in the bath or shower.

Pain control

Pain medication may be recommended for people who need it.

Gene therapies that address the underlying cause of DEB—mutations in the *COL7A1* gene—are in development.

Management of complications includes:

Infection control

Topical or oral antibiotics may be prescribed to prevent or stop a skin infection.

Squamous cell cancer

Surgery, chemotherapy, or radiotherapy may be used for treatment.

Narrowing of the esophagus

A procedure may be used to open up the narrowing of the throat.

Mitten deformity ("mitten" hands)

Surgery may be required to separate fingers or toes.

Anemia

Iron supplements, intravenous iron, or blood transfusions may be used.

Eye care

Care may include preventing dryness, treating inflammation, and avoiding injury.

Lack of proper nutrition/growth delays

A feeding tube may be used to provide needed nutrition.

Knowing if it's DEB could open potential future treatment options for you or your loved one.

WE PUSHED FOR ANSWERS— AND LEARNING IT WAS DEB MADE A DIFFERENCE.

It's important to know if you or a loved one is living with DEB

DEB can have serious risks and complications

An accurate diagnosis can help you get proactive care and prepare for the future

Talk to your doctor about genetic testing

Not all blisters are the same. Could yours be DEB? Ask your doctor about a genetic test for DEB.

For support and resources about DEB and accurate diagnosis, visit DEBFacts.com or contact a Krystal Community Education Liaison at 1-844-5-KRYSTAL.

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