Beyond the Surface:

Specialized Insights into Epidermolysis Bullosa

DISCLAIMER

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Meet The Presenters

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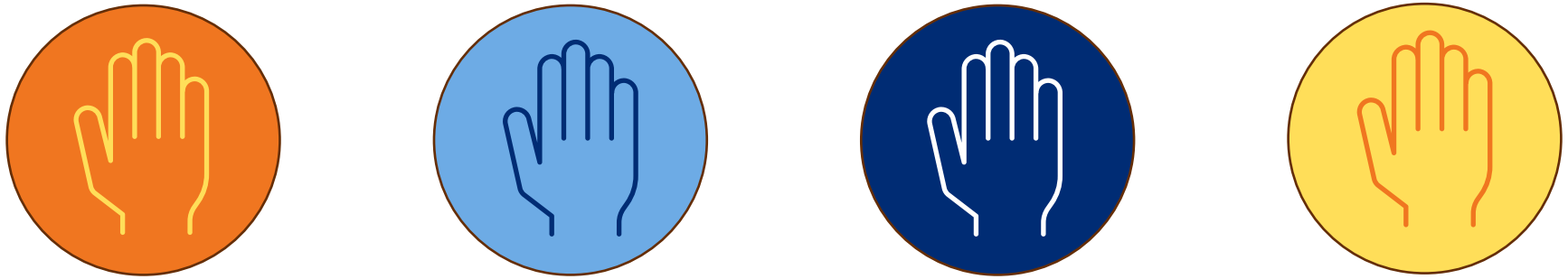
SPEAKER DISCLOSURES

We have no relevant financial conflicts of interest in relation to this activity to disclose.

How many of you have heard of Epidermolysis Bullosa?



Learning Objectives

1. Review Epidermolysis Bullosa (EB) disease characteristics and subtypes

2. Discuss the current and emerging treatment landscape for Epidermolysis Bullosa (EB).

3. Review the role of specialty pharmacy in Epidermolysis Bullosa (EB) patient care.

Patient Journey:
Meet the William's Family

https://www.goodhousekeeping.com/health/a42608/epidermolysis-bullosa-jonah-williams/

https://www.debra.org/personal-stories/williams-familys-story

Jonah's Journey

Birth

- Knew something was wrong from the beginning
- Skin missing from his elbows down and from his knees down
- Purple blisters all over his body

Immediate Challenges

- Transferred to Brenner children's Hospital
- Doctors there 99% sure he had EB
- Spent 32 days in the NICU

Rocky Beginning

- Once home, the care continued
- Dressing changes would take up to three hours
- Malnutrition leading to gastronomy tube at 14 months

Getting Older

- Most mornings, Jonah wakes up with blisters or wounds
- Now at 8 he is able to communicate his "boo boos"
- He is a normal kid in most ways

https://www.goodhousekeeping.com/health/a42608/epidermolysis-bullosa-jonah-williams/
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Integumentary System[1-2]

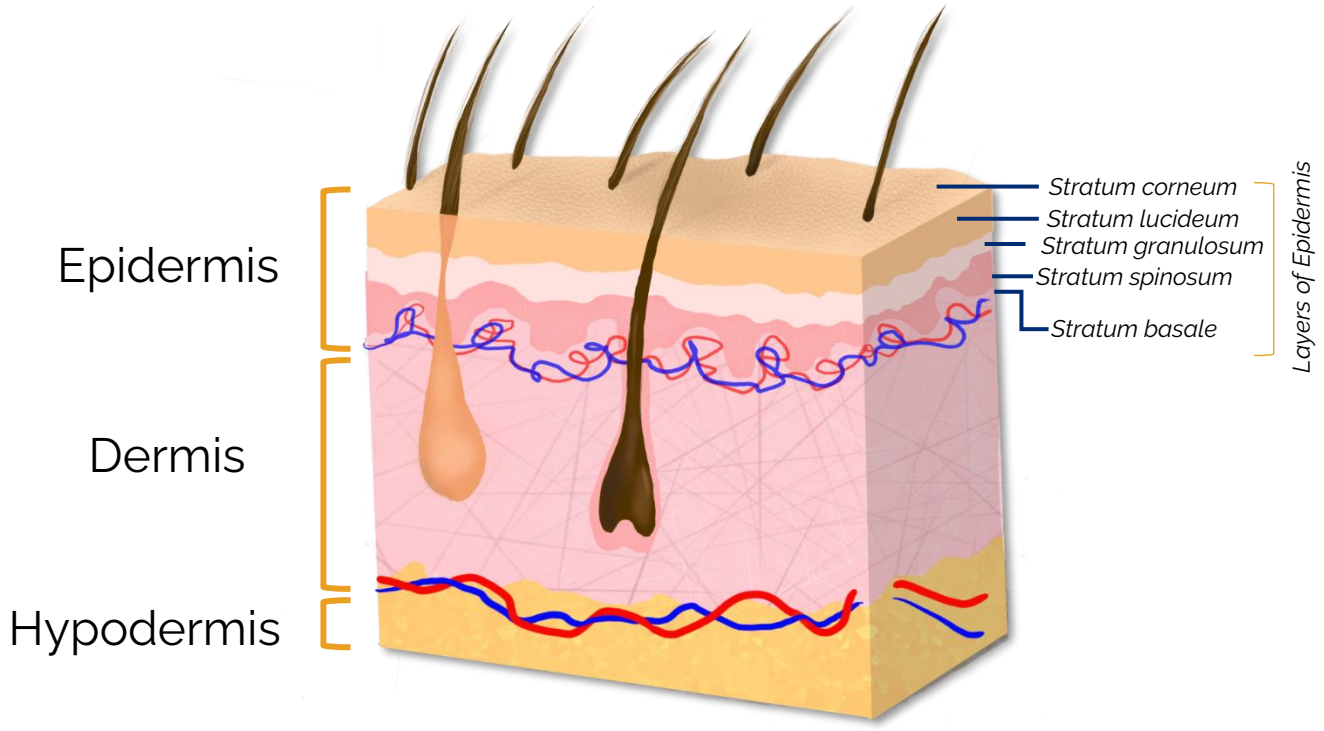
Functions of the skin

- Sensation
- Thermoregulation
- Protection
- Metabolism

Integumentary System[3]

Epidermis	Dermis	Hypodermis
Protective barrier	Contains collagen & elastin	Contains fat that cushions muscles and bones
Makes new skin	Vascular Layer	Stores energy
Contains keratin	Connects to the epidermis through the basement membrane zone (BMZ)	Connects skin to muscle and bones

Layers of the Skin



Integumentary System [1-4]

Keratinocytes

- Skin Cells

Intermediary Filament Network

- Cells cytoskeleton

Integrins

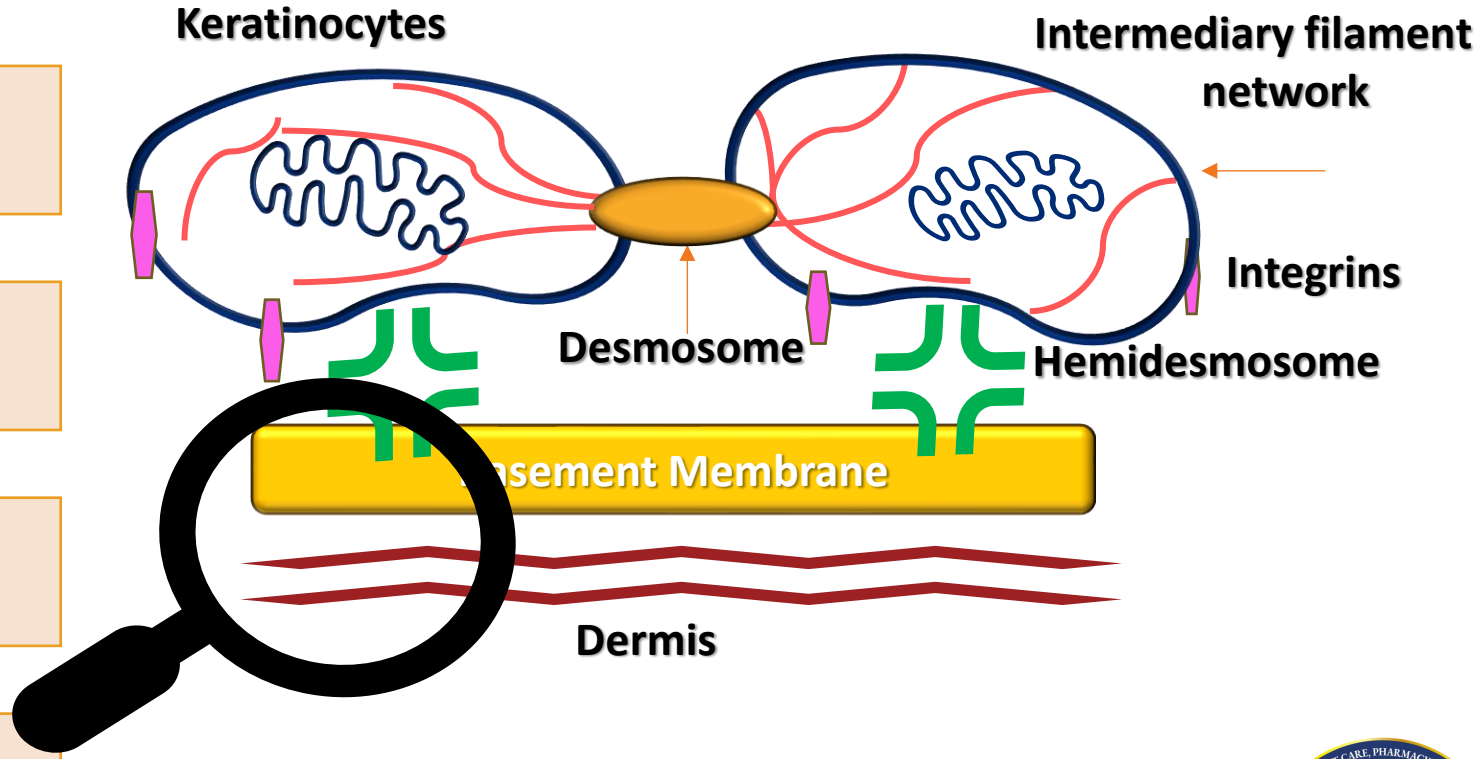
- Transmembrane receptors

Desmosome

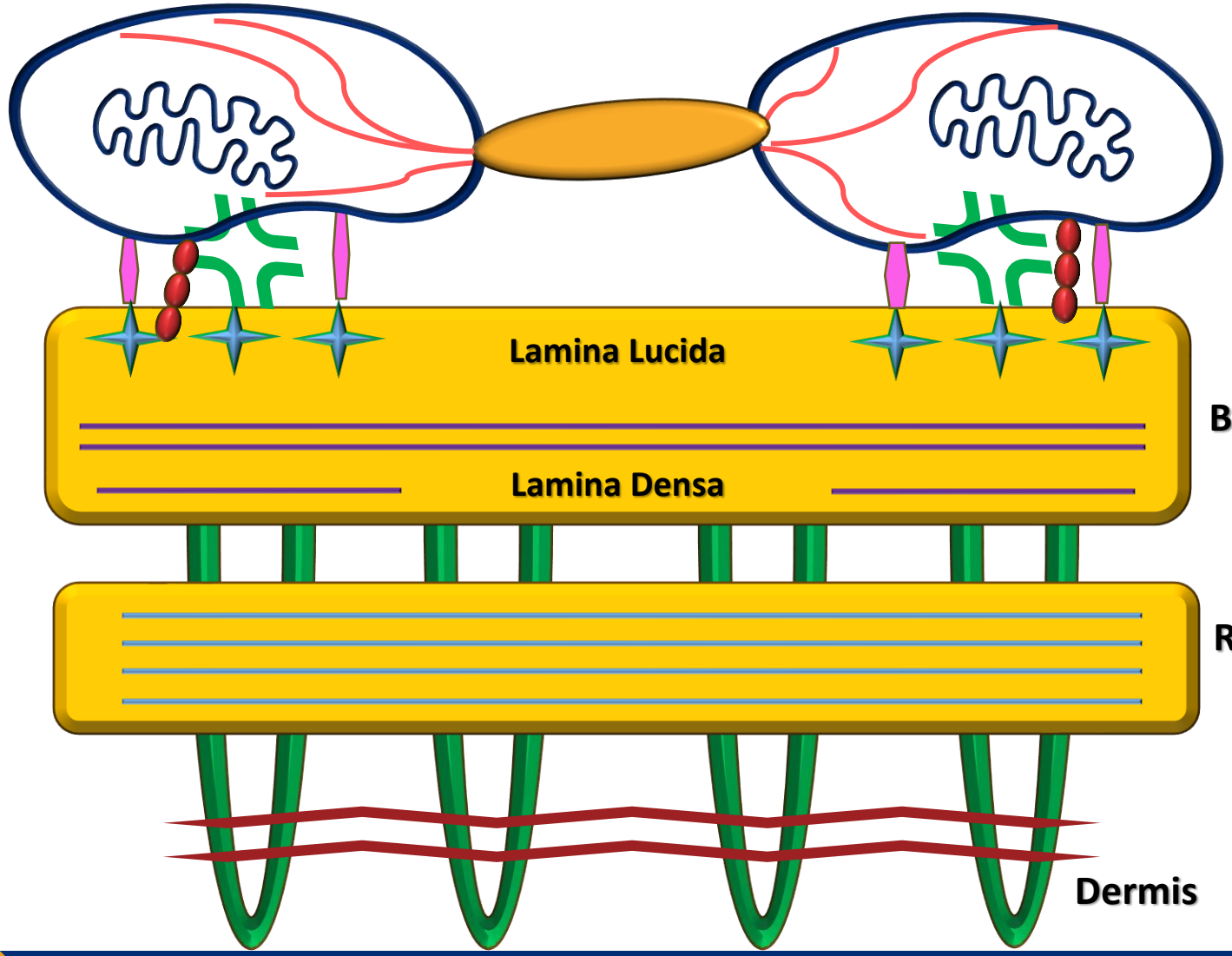
- Connects cells to cells

Hemidesmosome

- Connects cells to extracellular matrix



Integumentary System[3-7]



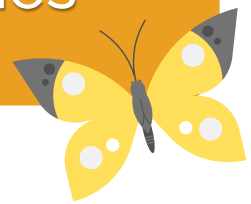
Proteins of the BMZ

- Laminins
- Collagen Type VII
- Collagen Type III
- Collagen Type IV
- Collagen Type XVII
- Integrins

Disease Characteristics & Subtypes

Background[8-10]

EB is a group of **genetic disorders** that are characterized by **skin fragility** leading to **recurrent blistering** of the skin and mucous membranes



Rare Disorder

Incidence

19.57 per 1 million live births

Prevalence

11.07 per 1 million population

No preference for gender or ethnicity

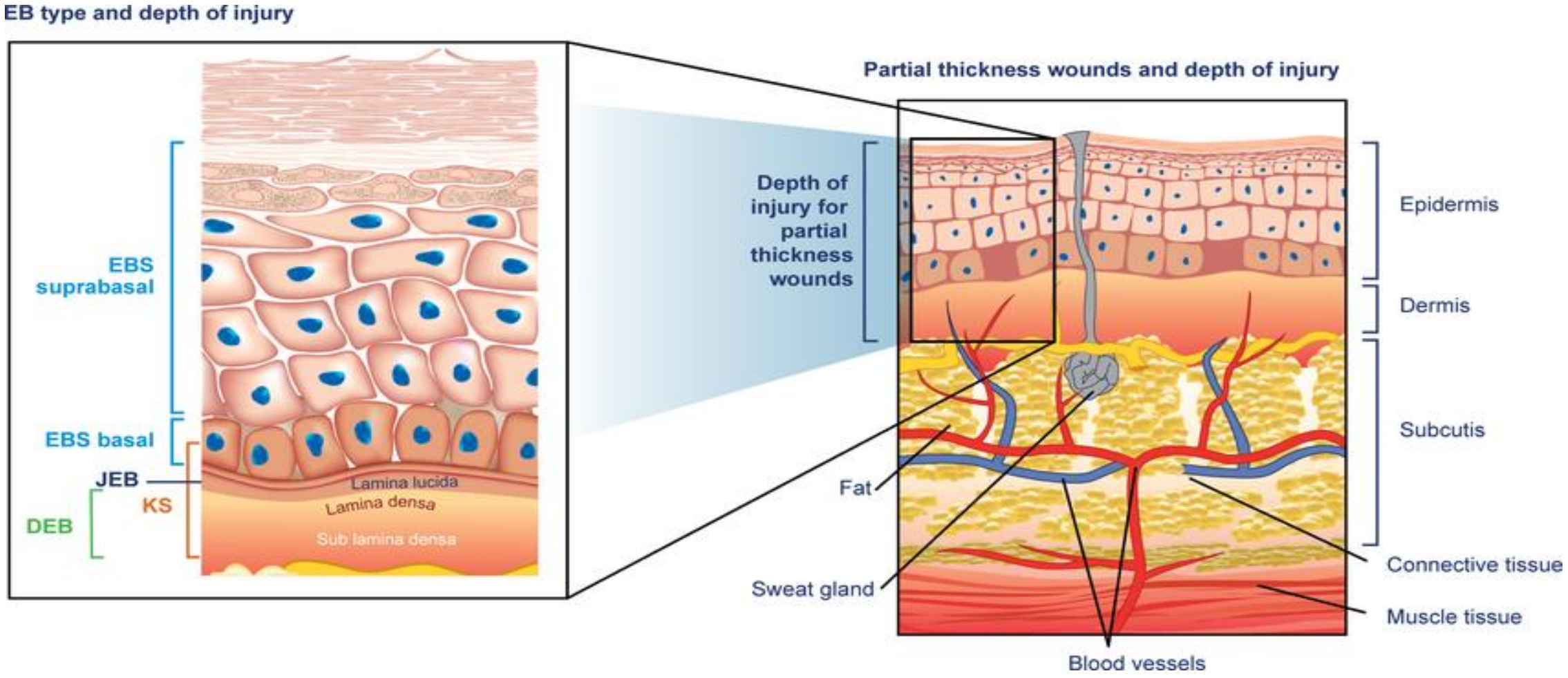
Classification[11,12]

EB is broken into 4 major types based on the skin layer where the blisters/tissue separation are forming

- Epidermolysis bullosa simplex (EBS)
- Junctional epidermolysis bullosa (JEB)
- Dystrophic epidermolysis bullosa (DEB)
- Kindler syndrome (KS)

Clinical manifestations range in severity based on type and subtype

Classification[13]



Schwieger-Briel A, Ott H, Kiritsi D, Laszczyk-Lauer M, Bodemer C. Mechanism of Oleogel-S10: A triterpene preparation for the treatment of epidermolysis bullosa. *Dermatol Ther*. 2019;32(4):e12983. doi:10.1111/dth.12983

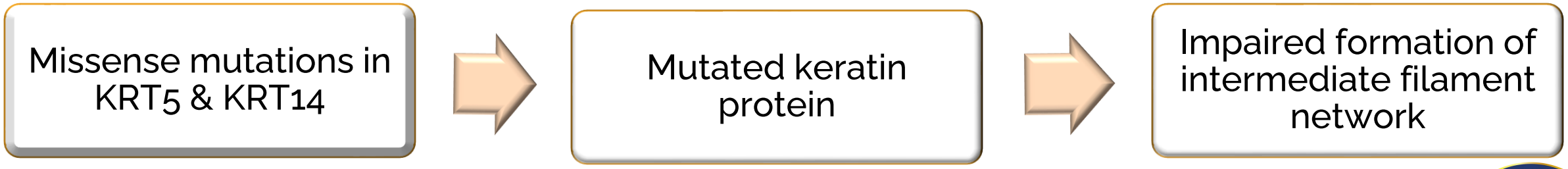
Pathophysiology[8]

Genetically Heterogeneous
Mutations in the anchoring proteins throughout the skin

- Keratinocyte organization
- Keratin filament network
- Laminin
- Collagen
- Hemidesmosomes
- Integrins

Epidermolysis Bullosa Simplex[6,8,14]

- Autosomal dominant or autosomal recessive inheritance pattern
- Blisters occur within the epidermis
- 14 subtypes associated with 7 different genes
  - Localized, intermediate, severe subtypes caused by mutations in KRT5 & KRT14 gene
  - Proteins affected provide structural support to keratinocytes



Epidermolysis Bullosa Simplex[6,8,14]

Clinical Manifestations of Subtypes

Localized

- Blisters are limited to areas of high friction such as hands and feet
- Worsen in warm weather
- Appear during early childhood when the child starts to crawl and walk

Intermediate

- Blisters visible at birth
- Widespread distribution of blisters but mostly found on hands and feet

Severe

- Large generalized blisters prone to hemorrhage
- Blisters form on hands, feet, mouth, trunk, and neck

Junctional Epidermolysis Bullosa[6,8,14]

- Autosomal recessive inheritance
- Blisters occur in the lamina lucida of BMZ
- 9 subtypes associated with 7 different genes
  - Common genes affected encode for laminin 332 & COL17A1
  - Results in complete absence or decreased formation of laminin and collagen XVII

Junctional Epidermolysis Bullosa[6,8,14]

Clinical Manifestations of Subtypes

Localized	Intermediate	Severe
• Blisters limited to limbs • Dystrophy or absence of nails, • Hypoplasia of tooth enamel/cavity formation	• Generalized distribution of blisters • Patients may have alopecia, enamel defects, absence of nails	• Extensive skin and mucus membrane fragility • Death common within the first year of life due to infection

Dystrophic Epidermolysis Bullosa[6,8,14]

- Autosomal dominant or autosomal recessive pattern of inheritance
- Blisters occur in the lamina densa of BMZ
- Subtypes are associated with a mutation in the **COL7A1** gene
  - Encodes for type VII collagen anchoring fibrils
    - Collagen VII is reduced or absent
    - Creates separation of the BMZ and dermis

Dystrophic Epidermolysis Bullosa[6,8,14]

Clinical Manifestations of Subtypes

Severe Recessive

- Blisters forming through the body resulting in mutilating scars
- Involvement in the oral mucosa, corneal, and gastrointestinal epithelium
- Risk of squamous cell carcinoma

Pruriginosa

- Generalized blister formation
- Patients suffer from severe pruritus

Self-Improving

- Less severe form that improves as the child approaches the second year of life

Kindler Syndrome[6,8,14]

- Autosomal recessive pattern of inheritance
- Blisters occur in multiple layers
  - Intraepidermal
  - Lamina lucida
  - Sublamina densa
- Subtypes are associated with a mutation in the **FERMT1 gene**
  - Encodes kindlin-1 protein
  - Affects integrins and focal adhesion formation
  - Disorganized keratinocytes

Kindler Syndrome[6,8,14]

Clinical Manifestations

- Extensive blistering with skin atrophy
- Extracutaneous findings
  - Gum erosions
  - Ocular, esophageal, gastrointestinal, genitourinary involvement

Unique Clinical Manifestations

Hypo or hyper-pigmentation (poikiloderma)	Clusters of blood vessels	Photosensitivity

Diagnosis[8,15,16]

Family History & Clinical Manifestations

- Clinical manifestations may overlap

Immunofluorescence Mapping

- Determine main type by identifying where skin cleavage is occurring

Transmission Electron Microscopy

- Determines subtype by detection of protein structures present

Genetic Testing

- Definitive diagnosis of the subtype and associated inheritance pattern

Which statement best describes Epidermolysis Bullosa?

A. Multiple benign tumor-like growths with increased risk for breast, thyroid, and uterine cancers
B. Periodic reduction in blood flow to fingers, toes, or other body parts causing numbness and color changes
C. Dry itchy skin that leads to swelling, cracking, or scaliness
D. Skin fragility leading to recurrent blistering of the skin and/or mucus membranes

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EB Skin and Wound Care International Consensus 2017[17-20]

Management of EB is supportive and not curative

Ability to Heal

EB type

Age

Nutrition

Anemia

Patient Concerns

Pain

Itching

Mobility

Adherence

Wound Care

Location/ characteristics

Cleanse

Debride

Assess infection, inflammation and cancer

Aftercare

Wound dressings

Healing status or reopening

Stalled wounds

Wound prevention

Support

Wound care plan

Multidisciplinary team

Patient and Caregiver Resources

- Home nursing
- Physical/ Occupational therapy
- Dietician
- Financial assistance

Treatment Landscape[21-23]

FDA approved agents

Gene Therapies

- Gene replacement
- Exon skipping
- Gene Editing
- PTC Readthrough

Cell Therapies

- Skin grafts
- Intradermal/subcutaneous injection
- IV Injection
- Topical sprays

Symptom Relief Therapies

- Topical and systemic anti-inflammatory agents
- Topical and systemic anti-fibrotics

beremagene geperpavec- svdt[24]

- Approved May 2023 and manufactured by Krystal Biotech, Inc
- Treatment of wounds in adults and pediatric patients ≥6 months with dystrophic epidermolysis bullosa (DEB) with mutation(s) in COL7A1 gene
- HSV-1 vector-based gene therapy delivering COL7A1 gene directly into skin cells in DEB wounds to promote healing
- Dose is based on age and applied to wounds once a week
- Only treatment that addresses the genetic cause of DEB to help wound healing in a topical formulation

beremagene geperpavec- svdt[24]

- Biological suspension mixed with excipient gel by specialty pharmacy for topical application by healthcare provider
- Apply to wounds until they are closed before selecting new wound(s) to treat
- Prioritize weekly treatment to previously treated wounds if they re-open
- In the case of missed doses, apply as soon as possible and resume weekly dosing
- Store at -13˚F to 5˚F or 35.6° to 46.4°F for up to 1 month

  After mixing, store at 68˚ to 77˚F for up to 8 hours or up to 48 hours in 35.6° to 46.4°F

Gem-3 Trial[24]

Background:

- Randomized, double-blind, intra-subject placebo-controlled trial of subjects ≥ 1 year with DEB with COL7A1 gene
- Two comparable wounds in each subject selected and randomized to receive either topical application of study gel or placebo weekly for 26 weeks

Population (N=31 patients):

- 20 males/11 females
  - 30 autosomal recessive DEB
  - 1 autosomal dominant DEB

Primary Endpoint:

- Wound closure at 24 Weeks confirmed at 2 consecutive study visits 2 weeks apart
- Assessed between 22 and 26 weeks
- Compared study gel treated wounds and placebo treated wounds

Results:

- Efficacy supported by the difference in the proportion of complete wound closure assessed at weeks 8 and 10 or at weeks 10 and 12 between the study group and the placebo treated wounds

Safety:

- The most common side effects (>5%) were itching, chills, redness, rash, cough, and runny nose

birch triterpenes[13,25]

- Approved December 2023 and marketed by Chiesi USA
- Treatment of wounds related to dystrophic and junctional epidermolysis bullosa in adult and pediatric patients >6 months of age
- Mechanism is not fully understood. Triterpenes, the active ingredient, is from birch tree bark and stimulates wound healing through pro and anti-inflammatory effects, increasing keratinocyte migration and differentiation
- Apply 1 mm thick layer of gel to affected wound surface(s) at each dressing change until the wound is healed
- Supplied as single use, sterile tubes for topical use

birch triterpenes[13,25]

- Clean wounds before applying or as instructed by healthcare provider
- Apply to wound(s) or directly to a dressing with a clean/gloved hand
- Do not rub into the wound
- Due to single use tubes, discard any remaining gel and the tube after use
- Store at room temperature 68˚ F to 77˚F

EASE Trial[25,26]

Background:

- Randomized, double-blind, vehicle-controlled, phase III study to determine the efficacy and safety of the topical birch triterpenes gel in EB
- Two phases including a 90-day, double blind phase and a 24-month, open label phase

Population: (N=223 patients):

- 195 dystrophic EB (DEB)
  - 175 recessive DEB (RDEB)
  - 20 dominant DEB (DDEB)
- 26 junctional EB (JEB)
- 2 simplex EB were not included in results

Primary Endpoint:

- Proportion of patients with first complete closure of target wound by 45 of 90-day study

Results:

- Efficacy supported by 41.3% of patients in treatment group experiencing complete wound closure within 45 days compared to 28.9% in the control group

Safety:

- The most common side effect was application site reactions, including pain and itch. 4 subjects developed squamous cell carcinoma (SCC)

EB Pipeline Summary[27-40]

	Investigational drug	Mechanism of Action	Route of Administration	Indication
Phase III	Pz-cel/EB-101 (prademagene zamikeracel)	Gene correcting	Transplanted Epidermal Sheet	RDEB
	Allo-APZ2-OTS	Stem Cell Therapy	IV	RDEB & JEB
	D-Fi/FCX-007 (dabocemagene autoficel)	Autologous cell-based gene therapy	Intradermal Injection	RDEB
	AC-203 (Diacerin 1%)	Anti-fibrotic/anti-inflammatory	Topical	EBS
	Hologene-5	Gene correcting LAMB3	Transplanted Epidermal Sheet	JEB
Phase II	BBP-589/PTR-01	Recombinant Collagen type VII (C7)	IV	RDEB
	beremagene geperpavec-svdt ophthalmic	Gene correcting COL7A1	Ophthalmic	Ocular complications of DEB
	PTW-002	antisense oligonucleotide (ASO) skip both mutant and wild-type exon 73	Topical	DDEB & RDEB
Phase I	ZKN-013	Overcome non-sense mutation	Oral	RDEB & JEB

Which FDA approved Epidermolysis Bullosa treatment requires unique storage and mixing requirements by the specialty pharmacy prior to being administered to wounds by a healthcare provider?

A. beremagene geperpavec- svdt
B. birch triterpenes
C. Both A and B
D. None of the above

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EB Patient and Caregiver Burden[19]

- Cutaneous wounds
- Extracutaneous complications
- High treatment burden
- Unmet needs
- Financial
- Quality of life

- Neonatology/ Pediatrician
- Dermatology
- Pathology
- Genetics

- Ophthalmology
- Endocrinology
- Gastroenterology
- Otolaryngology
- Oncology

- Cardiology
- Nephrology
- Radiology
- Dentistry
- Neurology

Multidisciplinary Approach[20]

Surgery:
- Pediatrics
- Orthopedic
- Plastic
- Anesthesiologist

- Pain Specialist
- Social Services
- Dietician
- Specialized nursing

- Physical Therapy
- Occupational Therapy
- Speech Therapy
- Psychology/ Psychiatry

Financial Impact of EB[19,41]

Caregiver Reported

- **20.4%** "a lot" of financial burden
- **37.6%** "moderate" financial burden
- **96.8%** had health insurance
- Commercial **52.7%**
  Medicaid **41.9%**
- Mean Non-reimbursable expenses **$682.16 per month**

Patient Reported

- **31.7%** "a lot" of financial burden
- **22.2%** "moderate" financial burden
- **95.2%** had health insurance
- Commercial **36.5%**
  Medicare **27.0%**
  Medicaid **23.8%**
- Mean Non-reimbursable expenses **$262.34 per month**

Quality of Life Impact of EB[19,41]

Daily Activities	▪ Mobility at home ▪ Bathing/Shower ▪ Eating ▪ Sleeping ▪ Participating in sports
Pain	▪ 40% patients /48% caregivers - *occasional pain* ▪ 22% patients /15% caregivers - *constant pain* ▪ 16% patients /12% caregivers - *frequent pain*
Emotional burden	▪ Frustration ▪ Embarrassment ▪ Anxiety or worry ▪ Depression
Other	▪ Social ▪ Life decisions ▪ Hope for future treatment

Specialty Pharmacy Solutions[42,43]

Medication Access

- Payor, manufacturer and HUB relationships
- Financial assistance
- Dispensing, storage and delivery coordination

Provider Support

- Education on current and new to market therapies
- Authorization guidance
- Collaborative patient assessment and monitoring

Patient Care

- Expert staff for support during patient journey
- Customized coordination of care
- Adverse event reporting and management
- Adherence, persistence, and patient goals

Patient Outcomes

- Data analysis
- Patient reported outcome and quality of life tools

Additional Support

- Disease and drug education
- Connecting to support services or advocacy programs

EB Patient and Caregiver Support

Debra
debra.org

Debra International
debra-international.org

EB Research Partnership
ebresearch.org

Pediatric Dermatology Research Alliance (PeDRA)
pedraresearch.org

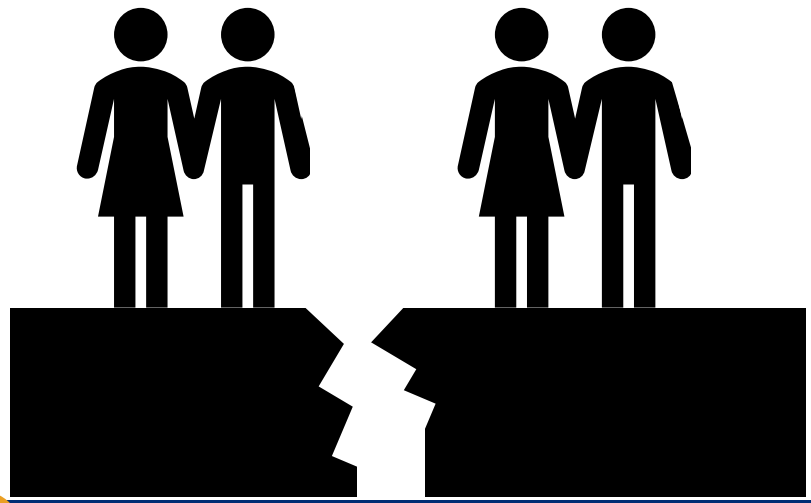
EB Medical Research Foundation
ebmrf.org

The Butterfly Children Fund
butterflychildrenfund.org

National Organization for Rare Disorders (NORD)
rarediseases.org

Specialty Pharmacy and Continuity of Care

Closing the Gaps



It is important to address patient barriers as well as relay updates on a patient's progress to the patient's healthcare team.

- Dressing change frequency
- Appropriate medication quantities
- Wound closure/reopening
- Adherence
- Infection
- Pain/itching
- Mobility
- Drug interactions
- Side effects
- Patient's support changes
- Access to dressings or medical supplies

Which of the following solutions do specialty pharmacies provide for Epidermolysis Bullosa patients, their caregivers, manufacturers and healthcare specialists? (Select all that apply)

A. Financial assistance through manufacturer and/or foundation support, if eligible
B. Collaborative patient assessment and monitoring
C. Dispensing, storage and delivery coordination of specialty medications
D. Adverse event reporting and management strategies
E. Access to patient support services and advocacy programs

Summary

EB is a rare and complex genetic disease associated with skin fragility

EB is categorized into four main types (each with multiple subtypes) with unique clinical manifestations and complications

The therapeutic landscape has been focused on targeting specific gene mutations associated with the different types of EB

EB requires a multidisciplinary approach which includes specialty pharmacy

Supplemental Resources

debra

- www.debra.org

EB Clinical Practice Guidelines

- https://www.eb-clinet.org/clinical-guidelines/completed-eb-guidelines/

Jonah's Journey

- https://www.debra.org/personal-stories/williams-familys-story

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Thank You!

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