JAMA Dermatology | Original Investigation

Assessment of the Timing of Milestone Clinical Events in Patients With Epidermolysis Bullosa From North America

James A. Feinstein, MD, MPH; Purevsuren Jambal, MA, MPH; Kathleen Peoples, BA; Anne W. Lucky, MD; Phuong Khuu, MD; Jean Y. Tang, MD, PhD; Irene Lara-Corrales, MD; Elena Pope, MD, MSc; Karen Wiss, MD; Kristen P. Hook, MD; Laura E. Levin, MD; Kimberly D. Morel, MD; Amy S. Paller, MD; Catherine C. McCuaig, MD; Julie Powell, MD; Lawrence F. Eichenfield, MD; Harper Price, MD; Moise L. Levy, MD; Lawrence A. Schachner, MD; John C. Browning, MD; Susan Bayliss, MD; Marla Jahnke, MD; Tor Shwayder, MD; Sharon A. Glick, MD; Anna L. Bruckner, MD, MSCS

Author Audio Interview

IMPORTANCE Children with epidermolysis bullosa (EB) comprise a rare population with high morbidity and mortality. An improved understanding of the clinical trajectory of patients with EB, including age at time of clinical diagnosis and major clinical events, is needed to refine best practices and improve quality of life and clinical outcomes for patients with EB.

OBJECTIVES To describe demographics, clinical characteristics, milestone diagnostic and clinical events (such as initial esophageal dilation), and outcomes in patients with EB using the Epidermolysis Bullosa Clinical Characterization and Outcomes Database and to determine what characteristics may be associated with overall EB severity and/or disease progression.

DESIGN, SETTING, AND PARTICIPANTS This cohort study included data on patients with EB who were enrolled in the Epidermolysis Bullosa Clinical Characterization and Outcomes Database from January 1, 2011, to June 30, 2017; 17 participating EB centers in the United States and Canada contributed data to this study.

EXPOSURES Type of EB, including recessive dystrophic epidermolysis bullosa (RDEB), junctional epidermolysis bullosa (JEB), dominant dystrophic epidermolysis bullosa (DDEB), and epidermolysis bullosa simplex (EBS).

MAIN OUTCOMES AND MEASURES Demographic information, clinical characteristics (including age at onset of signs of EB and subsequent clinical diagnosis), types of diagnostic testing performed, and milestone clinical events for patients with RDEB.

RESULTS Of 644 enrolled patients from 17 sites included in this study, 323 were male (50.2%), with a mean (SD) age of 14.4 (11.7) years; 283 (43.9%) had RDEB, 194 (30.1%) had EBS, 104 (16.2%) had DDEB, and 63 (9.8%) had JEB. Signs of disease were present at birth in 202 patients with RDEB (71.4%), 39 with JEB (61.9%), 60 with DDEB (57.7%), and 74 with EBS (38.1%). For those with signs of disease at birth, a clinical diagnosis was made at the time of birth in 135 patients with RDEB (67.0%), 31 with DDEB (52.6%), 35 with EBS, (47.3%) and 18 with JEB (46.2%). Patients with JEB had the highest rate of any confirmatory testing (51 of 63 [81.0%]), followed by RDEB (218 of 283 [77.0%]), DDEB (71 of 104 [68.3%]), and EBS (100 of 194 [51.5%]). For all types of EB, both electron microscopy and immunofluorescence microscopy were performed at younger ages than genetic analysis. Among 283 patients with RDEB, 157 (55.5%) had esophageal dilation, 104 (36.7%) had gastrostomy tube placement, 62 (21.9%) had hand surgery, 18 (6.4%) developed squamous cell carcinoma, and 19 (6.7%) died.

CONCLUSIONS AND RELEVANCE The findings suggest that diagnostic testing for EB is more common for patients with severe phenotypes. Earlier diagnostic testing may enable improved characterizations of patients so that appropriate counseling and clinical care may be offered, especially pertaining to milestone events for those with RDEB.

JAMA Dermatol. 2019;155(2):196-203. doi:10.1001/jamadermatol.2018.4673
Published online December 26, 2018.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Anna L. Bruckner, MD, MSCS, Department of Dermatology, University of Colorado School of Medicine, 13123 E 16th Ave, Mailstop B570, Aurora, CO 80045 (anna.bruckner@ucdenver.edu).

© 2018 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 03/04/2022

Epidermolysis bullosa (EB) is a group of rare genetic disorders characterized by fragility of the skin and mucosa. The disease affects approximately 1 of 50 000 births in the United States.[1,2] Clinical disease severity ranges from mild to devastating, and there is no widely available, disease-modifying treatment or cure for any form of EB at this time.[3,4] Although several trials of emerging therapies are under way, the timeline for such treatments is in future years in most cases.[3,5-8] In parallel with such efforts, research that advances our understanding of the clinical trajectory of patients with EB, including their diagnosis, clinical care, and major clinical events and outcomes is needed.[9-11] We have termed these outcomes *milestone events* to connote key events in the clinical course of an individual with EB. Events include when and how the patient's diagnosis was made and was confirmed as well as objective interventions, such as placement of a gastrostomy tube, which may be a marker of disease severity or progression.[1,12-15]

Because of the rarity of EB, creating a generalizable understanding of real-world care and variation in care has been difficult, especially for milestone clinical events in the disease process. Little evidence exists to guide best practices related to these events. For example, objective guidance is lacking for the appropriate time to place a gastrostomy tube when a child shows signs of nutritional failure[13,16] or when to perform hand surgery to repair contractures and pseudosyndactyly.[12,15] By anticipating the timing of such interventions in patients with different types of EB, potentially modifiable targets for intervention can better be anticipated and more reliable information to counsel patients and parents about prognosis can be used.

The Epidermolysis Bullosa Clinical Research Consortium is a collaborative clinical research group that was initially formed in 2010. The consortium now includes 20 sites in the United States and Canada and functions as the EB working group of the Pediatric Dermatology Research Alliance. The principal investigator of each consortium site is a dermatologist (most commonly, a board-certified pediatric dermatologist) who treats patients with EB. The EB care at each site is provided in a general dermatology clinic or a dedicated EB clinic, which often includes multiple specialists with an interdisciplinary approach. Each Epidermolysis Bullosa Clinical Research Consortium site collaborates in the Epidermolysis Bullosa Clinical Characterization and Outcomes Database (EBCCOD) to catalog well-described patient cohorts with EB for future studies and to generate longitudinal data about the course, complications, and treatment of patients with EB.[17]

The primary objective of this study was to describe the patients with EB within the EBCCOD, specifically reporting patient demographic information, clinical characteristics (including patient age at initial signs of EB and at clinical diagnosis), types of diagnostic testing performed, and milestone events for patients with recessive dystrophic EB (RDEB). This study gives the types of patients with EB presenting to pediatric dermatologists and EB centers to highlight gaps in the diagnosis of EB and to provide a summary of major interventions for patients with RDEB and when they occur. In addition, this study sought to build the foundation for subsequent longitudinal analyses of the association of patient characteristics and clinical care with specific milestone events to identify key targets and timing for clinical interventions and evaluation of effectiveness.

Key Points

Question What are the clinical trajectories of patients with epidermolysis bullosa, specifically regarding the timing of diagnosis and subsequent major clinical events?

Findings In this cohort study of 644 patients with epidermolysis bullosa, patients with recessive dystrophic epidermolysis bullosa were the most likely to receive a clinical diagnosis at birth if they had signs of disease at birth, and patients with junctional epidermolysis bullosa had the highest rate of confirmatory testing.

Meaning The findings suggest that diagnostic testing for epidermolysis bullosa is more common for patients with severe phenotypes; understanding the course of major clinical events may enable improved counseling on prognosis and management of epidermolysis bullosa.

Methods

Design and Data Source

The EBCCOD is a Research Electronic Data Capture database that is housed and managed at the University of Colorado, Denver, at the Anschutz Medical Campus in Aurora, Colorado. Each participating site has approval from its local institutional review board for participation in the database, and patients gave written informed consent and enrolled as they presented for care. Data collection is ongoing and typically occurs at major annual or biannual patient clinic visits. Data are collected contemporaneously during clinic visits and through review of medical records and are entered into the database. Clinical assessments include the use of the patient-directed symptom questionnaires and outcome instruments to document clinical signs and patient-reported symptoms and disease severity.[18] For this study, deidentified data were exported from Research Electronic Data Capture and analyzed. This study was approved by the Colorado Multiple Institutional Review Board, Aurora, Colorado.

Study Population

This study included patients enrolled in the EBCCOD with completed demographic and milestone event data. Seventeen participating EB centers in the United States and Canada contribute data to the EBCCOD. All patients who provided consent and enrolled from January 1, 2011, through June 30, 2017, were eligible. Types of EB were categorized as RDEB, junctional EB (JEB), dominant dystrophic EB (DDEB), and EB simplex (EBS). We excluded 41 patients without a reported diagnosis of EB type because major diagnosis type was needed to complete the planned analyses. We also excluded 3 patients with Kindler syndrome because of the rarity of the disorder.

Milestone Clinical Events and Clinical Outcomes

Baseline demographic and clinical characteristics, stratified by EB type, included (1) age, sex, race/ethnicity, and primary site of care; (2) patient age at initial signs of EB (such as blisters, erosions or wounds, and oral mucosal changes); (3) patient age at initial clinical diagnosis; (4) age at which confirmatory testing (electron microscopy [EM], immunofluorescence microscopy [IFM], or genetic analysis) was performed; and (5) proportion of patients

© 2018 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 03/04/2022

Table 1. Patient Demographics in Epidermolysis Bullosa Clinical Characterization and Outcomes Database

Characteristic	Type of Epidermolysis Bullosa, Patients, No. (%)				
	Total (N = 644)	EBS (n = 194)	JEB (n = 63)	DDEB (n = 104)	RDEB (n = 283)
Age as of July 1, 2017, y					
<1	19 (3.0)	6 (3.1)	4 (6.4)	5 (4.8)	4 (1.4)
1-9	263 (40.8)	95 (49.0)	38 (60.3)	40 (38.5)	90 (31.8)
10-19	220 (34.2)	65 (33.5)	14 (22.2)	30 (28.9)	111 (39.2)
20-29	81 (12.6)	12 (6.2)	2 (3.2)	13 (12.5)	54 (19.1)
30-39	30 (4.7)	9 (4.6)	2 (3.2)	6 (5.8)	13 (4.6)
40-49	21 (3.3)	5 (2.6)	1 (1.6)	7 (6.7)	8 (2.8)
≥50	10 (1.6)	2 (1.0)	2 (3.2)	3 (2.9)	3 (1.1)
Sex					
Male	323 (50.2)	102 (52.6)	29 (46.0)	46 (44.2)	146 (51.6)
Female	321 (49.8)	92 (47.4)	34 (54.0)	58 (55.8)	137 (48.4)
Race					
American Indian/Alaska Native	4 (0.6)	0	2 (3.2)	1 (1.0)	1 (0.4)
Asian	35 (5.4)	5 (2.6)	4 (6.3)	5 (4.8)	21 (7.4)
Native Hawaiian/Pacific Island	1 (0.2)	1 (0.5)	0	0	0
Black/African American	38 (5.9)	14 (7.2)	7 (11.1)	11 (10.6)	6 (2.1)
White	430 (66.8)	141 (72.7)	31 (49.2)	67 (64.4)	191 (67.5)
Middle Eastern/North African	55 (8.5)	7 (3.6)	12 (19.1)	6 (5.8)	30 (10.6)
Unknown	81 (12.6)	26 (13.4)	7 (11.1)	14 (13.4)	34 (12.0)
Ethnicity					
Not Hispanic or Latino	456 (70.8)	145 (74.8)	52 (82.5)	74 (71.1)	185 (65.4)
Hispanic or Latino	106 (16.5)	22 (11.3)	4 (6.4)	11 (10.6)	69 (24.4)
Ashkenazi Jewish	4 (0.6)	1 (0.5)	0	1 (1.0)	2 (0.7)
Unknown	78 (12.1)	26 (13.4)	7 (11.1)	18 (17.3)	27 (9.5)
Primary epidermolysis bullosa center					
Cincinnati Children's Hospital	156 (24.2)	42 (21.7)	19 (30.2)	22 (21.2)	73 (25.8)
Children's Hospital Colorado	81 (12.6)	28 (14.4)	3 (4.8)	14 (13.5)	36 (12.7)
Lucile Packard Children's Hospital Stanford	79 (12.4)	20 (10.3)	4 (6.3)	5 (4.8)	50 (18.0)
Hospital for Sick Children	59 (9.2)	22 (11.4)	6 (9.5)	12 (11.5)	19 (6.7)
University of Massachusetts	55 (8.6)	17 (8.8)	6 (9.5)	11 (10.6)	21 (7.4)
University of Minnesota	45 (6.8)	5 (2.6)	10 (15.9)	7 (6.7)	23 (7.8)
Columbia University Medical Center	38 (5.9)	12 (6.2)	1 (1.6)	9 (8.6)	16 (5.7)
Lurie Children's Hospital	36 (5.6)	13 (6.7)	5 (7.9)	7 (6.7)	11 (3.9)
CHU Sainte-Justine	22 (3.4)	13 (6.7)	2 (3.2)	4 (3.8)	3 (1.1)
Rady Children's Hospital	20 (3.1)	5 (2.6)	4 (6.3)	4 (3.8)	7 (2.5)
Phoenix Children's Hospital	9 (1.4)	3 (1.5)	0	2 (1.9)	4 (1.4)
Dell Children's Medical Center	9 (1.4)	3 (1.5)	0	1 (1.0)	5 (1.8)
University of Miami	8 (1.2)	3 (1.5)	1 (1.6)	0	4 (1.4)
Children's Hospital of San Antonio	8 (1.2)	0	1 (1.6)	1 (1.0)	6 (2.1)
Washington University in St Louis	6 (0.9)	4 (2.1)	0	1 (1.0)	1 (0.3)
Henry Ford Hospital	5 (0.8)	3 (1.5)	0	1 (1.0)	1 (0.3)
State University of New York Downstate Medical Center	2 (0.3)	0	1 (1.6)	1 (1.0)	0
Unknown	6 (0.9)	1 (0.5)	0	2 (1.9)	3 (1.1)
Vital status after enrollment					
Living	590 (91.6)	183 (94.3)	50 (79.4)	101 (97.1)	256 (90.5)
Deceased	32 (5.0)	1 (0.5)	12 (19.0)	0	19 (6.7)
Unknown	22 (3.4)	10 (5.2)	1 (1.6)	3 (2.9)	8 (2.8)

Abbreviations: DDEB, dominant dystrophic epidermolysis bullosa; EBS, epidermolysis bullosa simplex; JEB, junctional epidermolysis bullosa; RDEB, recessive dystrophic epidermolysis bullosa.

with confirmatory testing. Because genetic analysis has become more widely available during the past decade, we also analyzed the proportion of patients who underwent genetic analysis and were younger than 10 years during the study period.[19] When possible, actual dates were obtained and ages were calculated. Categorical data were used for age at onset of first clinical signs and initial clinical diagnosis because this often relied on patient and/or parent recall and accurate dates were not always available.

Only the first occurrence of events that may occur more than once during a patient's lifetime was reported. For all patients, we reported whether aplasia cutis (absence of skin) was present at birth and whether an enrolled patient had died during the study

© 2018 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 03/04/2022

Table 2. Clinical Signs and Diagnosis of Epidermolysis Bullosa, by Age

Patient Age	Type of Epidermolysis Bullosa, No. (%)			
	EBS (n = 194)	JEB (n = 63)	DDEB (n = 104)	RDEB (n = 283)
Age at onset of first clinical signs, y				
Prenatal	0	0	1 (1.0)	1 (0.4)
Birth	74 (38.1)	39 (61.9)	59 (56.7)	201 (71.0)
<1 y	58 (29.9)	12 (19.1)	23 (22.1)	18 (6.4)
>1 y	18 (9.3)	1 (1.6)	2 (1.9)	5 (1.8)
Unknown	44 (22.7)	11 (17.4)	19 (18.3)	58 (20.4)
Age at time of clinical diagnosis, y				
Prenatal	0	2 (3.1)	2 (1.9)	3 (1.0)
Birth	35 (18.1)	19 (30.2)	31 (29.8)	136 (48.1)
<1 y	74 (38.1)	26 (41.3)	45 (43.3)	65 (23.0)
>1 y	39 (20.1)	8 (12.7)	8 (7.7)	18 (6.4)
Unknown	46 (23.7)	8 (12.7)	18 (17.3)	61 (21.5)

Abbreviations: DDEB, dominant dystrophic epidermolysis bullosa; EBS, epidermolysis bullosa simplex; JEB, junctional epidermolysis bullosa; RDEB, recessive dystrophic epidermolysis bullosa.

period. Additional events for patients with RDEB were esophageal dilation, gastrostomy tube placement, hand surgery to release contractures and pseudosyndactaly, and diagnosis of squamous cell carcinoma.[1,12-15] We chose to focus on these events in patients with RDEB only because they are uncommon in patients with other forms of EB and may be associated with the course of disease progression in RDEB.

Statistical Analysis

Missing data were counted as unknown or negative responses depending on the variable. To generate descriptive statistics, we calculated percentages, proportions, and means of the outcomes of interest described above. A 2-sided $P = .05$ was set a priori to represent a statistically significant difference. We used *t* tests, tests of proportions, and χ^2 tests to assess for differences in demographic and clinical characteristics by type of EB. All statistical analyses were performed using Stata, version 15.1 (StataCorp).

Results

Within the EBCCOD

Of the 644 enrolled patients from 17 sites included in this study, 323 (50.2%) were male, with a mean (SD) age of 14.4 (11.7) years. The median study time that each patient contributed to the EBCCOD was 3.7 years (interquartile range [IQR], 1.6-5.1 years). Among the enrolled patients, 194 (30.1%) had EBS, 63 (9.8%) had JEB, 104 (16.2%) had DDEB, and 283 (43.9%) had RDEB. Patient demographics varied by the type of EB (**Table 1**). For each type of EB, the EBCCOD contained patients of all ages, although patients older than 10 years consisted of 59 patients with DDEB (56.7%) and 189 patients with RDEB (66.8%). There were no significant differences in sex across types of EB. For all types, enrolled patients were primarily white race (430, [66.8%]) (except patients with JEB) and not of Hispanic or Latino ethnicity. In addition, 316 (49.2%) of all patients received care from 3 referral EB centers. The EBCCOD includes records of 32 patients (5.0%) who died during the study period. Of the 32 decedents, 19 (59.4%) had RDEB with a median age at death of 17.9 years (IQR, 8.2-21.5 years), 12 (37.5%) had JEB with a median age at death of 0.5 years (IQR, 0.3-0.9 years), and 1 (3.1%) had EBS.

Patient Age at Onset of Clinical Symptoms and Subsequent Clinical Diagnosis

Symptoms were present at birth in most patients with RDEB (202 of 283 [71.4%]), JEB (39 of 63 [61.9%]), and DDEB (60 of 104 [57.7%]), but not for EBS (74 of 194 [38.1%]) (**Table 2**). The incidence of aplasia cutis at birth was significantly higher among patients with RDEB (172 [60.6%]) compared with other types of EB (DDEB, 15 of 104 [14.4%]; JEB, 7 of 63 [11.1%]; and EBS, 26 of 194 [13.4%]). By the first year of life, signs were present in most patients with RDEB (220 [77.8%]), JEB (51 [81.0%]), DDEB (83 [79.8%]), and EBS (132 [68.0%]). Some patients with EBS (18 [9.3%]) did not exhibit signs until after 1 year of life. For a proportion of patients with each EB type, the timing of onset of clinical symptoms was unknown. The lag time between the onset of clinical signs and a subsequent clinical diagnosis varied based on the type of EB. For those with signs at birth, a clinical diagnosis of EB was made at the time of birth in patients with RDEB (135 [67.0%]), JEB (18 [46.2%]), DDEB (31 [52.6%]), and EBS (35 [47.3%]). Although the majority of patients received a clinical diagnosis within the first year of life, a smaller number within each category did not receive a diagnosis until they were older than 1 year (RDEB, 18 [6.4%]; DDEB, 8 [7.7%]; JEB, 8 [12.7%]; and EBS, 39 [20.1%]). A diagnosis of EB in a parent was known for 47 patients with DDEB (45.2%) and 85 patients with EBS (43.8%); DDEB and EBS are autosomal dominant disorders, and testing the child is not necessary if the parent has a known diagnosis.

Confirmatory Laboratory Diagnostic Testing and Subtype Classification

The percentage of patients with confirmatory laboratory testing (EM, IFM, or genetic analysis) to characterize EB subtype varied by type of EB (**Table 3**). Patients with JEB had the highest rate of any confirmatory testing (51 of 63 [81.0%]), followed by RDEB (218 of 283 [77.0%]), DDEB (71 of 104 [68.3%]), and EBS (100 of 194 [51.5%]). A subset of children had multiple confirmatory tests performed (JEB, 43 [68.3%]; RDEB, 178 [62.9%]; DDEB, 50 [48.1%]; and EBS, 87 [44.8%]). Regarding specific types of confirmatory tests, genetic analysis was the most common test for all patients (359 of 644 [55.7%] patients), followed by IFM (237, 36.8%) and EM (188, 29.2%). With the

© 2018 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 03/04/2022

Table 3. Types of Confirmatory Laboratory Testing for Epidermolysis Bullosa and Patient Age at Testing[a]

Type of Laboratory Test and Age at the Time of the Test	Type of Epidermolysis Bullosa (N = 644)			
	EBS (n = 194)	JEB (n = 63)	DDEB (n = 104)	RDEB (n = 283)
Any confirmatory tests	100 (51.5)	51 (81.0)	71 (68.3)	218 (77.0)
Multiple confirmatory tests	87 (44.8)	43 (68.3)	50 (48.1)	178 (62.9)
Electron microscopy	40 (20.6)	21 (33.3)	29 (27.9)	98 (34.6)
Age, median (IQR), mo	3.6 (0.2-21.2)	0.4 (0.1-18.3)	3.1 (0.2-145.4)	1.4 (0.2-51.6)
Immunofluorescence microscopy	52 (26.8)	33 (52.4)	36 (34.6)	116 (41.0)
Age, median (IQR), mo	2.8 (0.2-15.8)	0.5 (0.1-4.4)	3.0 (0.6-15.5)	0.6 (0.1-12.1)
Genetic analysis	72 (37.1)	45 (71.4)	57 (54.8)	184 (65.0)
Age, median (IQR), mo	22.3 (5.4-68.9)	12.7 (2.2-38.6)	17.5 (4.6-164.5)	40.4 (4.8-137.2)

Abbreviations: DDEB, dominant dystrophic epidermolysis bullosa; EBS, epidermolysis bullosa simplex; IQR, interquartile range; JEB, junctional epidermolysis bullosa; RDEB, recessive dystrophic epidermolysis bullosa.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

Table 4. Diagnostic Types and Subtypes Represented Within the Epidermolysis Bullosa Clinical Characterization and Outcomes Database

Epidermolysis Bullosa Type and Subtype	Patients, No. (%)
Epidermolysis bullosa simplex (n = 194)	
Generalized severe	51 (26.3)
Generalized intermediate	24 (12.4)
Localized	55 (28.4)
Other	51 (26.2)
Unspecified or unknown	13 (6.7)
Junctional epidermolysis bullosa (n = 63)	
Generalized severe	12 (19.1)
Generalized intermediate	19 (30.2)
Localized	4 (6.4)
Other	9 (14.1)
Unspecified or unknown	19 (30.2)
Dominant dystrophic epidermolysis bullosa (n = 104)	
Generalized	20 (19.2)
Nongeneralized	52 (50.0)
Unspecified or unknown	32 (30.8)
Recessive dystrophic epidermolysis bullosa (n = 283)	
Generalized severe	109 (38.5)
Nonsevere	111 (39.2)
Unspecified or unknown	63 (22.3)

exception of EBS, among patients younger than 10 years, there were significantly higher proportions with genetic analysis compared with those older than 10 years (JEB: 35 [83.3%] vs 10 [47.6%], $P = .003$; DDEB: 32 [71.1%] vs 25 [42.4%], $P = .004$; and RDEB: 70 [74.5%] vs 114 [60.3%], $P < .018$). Both EM and IFM were performed at significantly younger median ages than genetic analysis for all types of EB, even after restricting the comparison to those patients younger than 10 years. **Table 4** contains the final diagnostic types and subtypes of EB represented within this EBCCOD study population.

Milestone Clinical Events Specific to RDEB

Among the 283 patients with RDEB, 157 (55.5%) had an initial esophageal dilation at a median age of 6.6 years (IQR, 3.5-10.7 years) and 104 (36.7%) had gastrostomy tube placement at a median age of 5.5 years (IQR, 2.0-10.3 years) (**Figure**). Patients with RDEB (62 [21.9%]) had an initial hand surgery at a median age of 8.1 years (IQR, 5.5-12.1 years). Patients with RDEB (18, 6.4%) had a history of squamous cell carcinoma, with a median age at initial diagnosis of 22.6 years (IQR, 20.0-27.7 years). Finally, among the 19 (6.7%) of patients with RDEB who died, the most common attributed causes included respiratory failure (3 [15.8%]), cardiac failure (3 [15.8%]), neoplasm (1 [5.3%]), and renal failure (1 [5.3%]).

Discussion

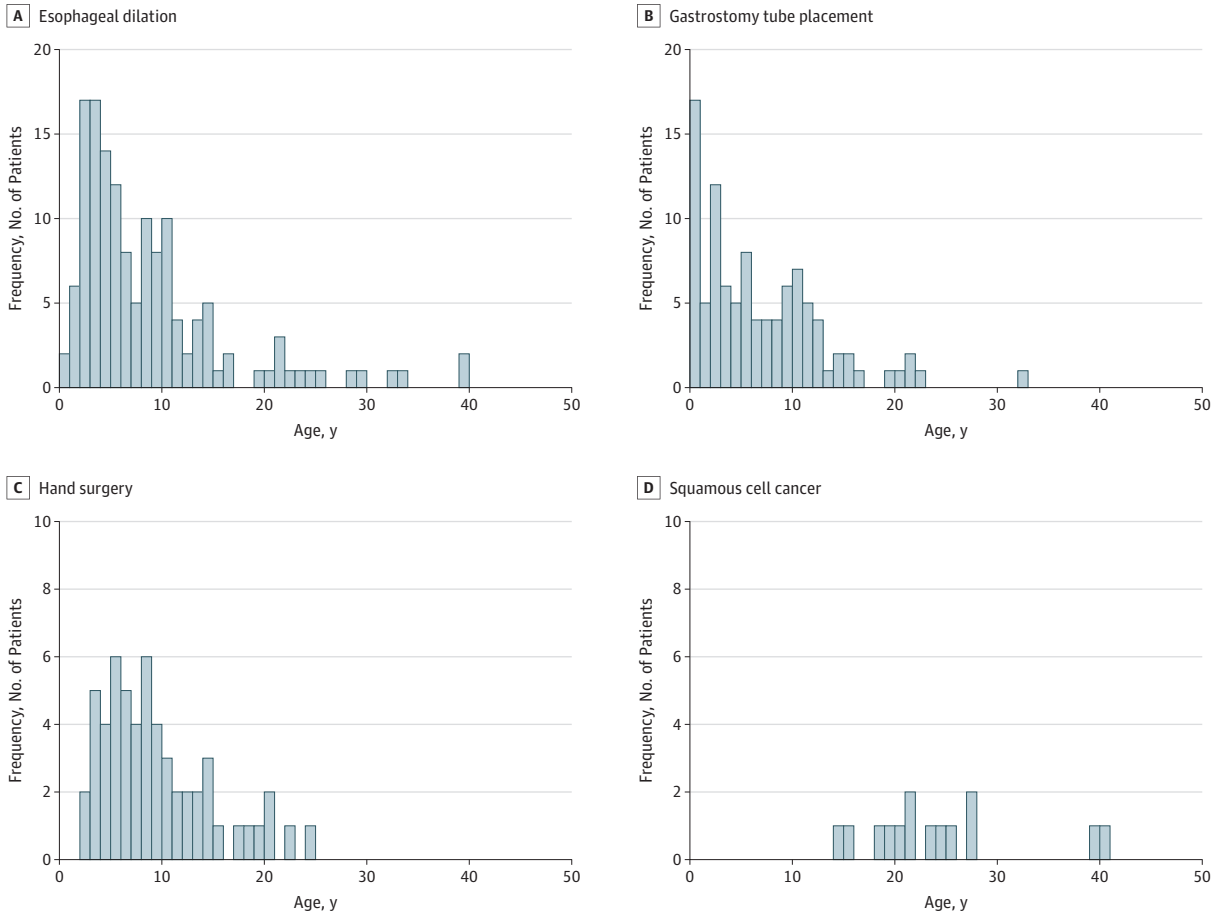
The EBCCOD contains clinical information pertaining to a large population of patients with EB representing all types of EB diagnoses, although most of the enrolled patients had RDEB. For patients within the EBCCOD, signs of EB, such as skin or mucosal erosions or blistering, were present at the time of birth in most of the patients with RDEB, JEB, and DDEB, but less so for patients with EBS. For those with signs at birth, a clinical diagnosis of EB was made at the time of birth in 67.0% of patients with RDEB and 52.6% of those with JEB, 47.3% of those with DDEB, and 46.2% of those with EBS. Patients with JEB had the highest rate of any confirmatory testing, followed by patients with RDEB, DDEB, and EBS. A subset of children had multiple confirmatory tests performed. For all types of EB, both EM and IFM were performed at younger median ages than genetic analysis. Among the patients with RDEB, the most frequent milestone clinical event was esophageal dilation, followed by gastrostomy tube placement, hand surgery, squamous cell carcinoma, and death.

Three findings from our study warrant discussion. First, use of the EBCCOD for all types of EB depends on the availability of clinical and outcomes data for patients with all types of EB. Although EBS is the most prevalent diagnosis in the general population, the EBCCOD is enriched with patients with RDEB likely because of their frequent contact with the medical system, particularly at specialty centers, and significant clinical needs that require ongoing clinical care. The EBCCOD provides rich population-level demographic and clinical data beyond what has previously been available. Although electronic health record data are increasingly available to collect and analyze, clinical registries and databases remain relevant and important to enable the identification of affected patients or children with rarer disease processes.[20,21] Although *International Statistical Classification of Diseases and Related Health Problems, Tenth Edition* includes a code for EB (Q81) and some subtype-specific subcodes, *International Classification of Diseases, Ninth Revision* did not have a specific code for EB,

© 2018 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 03/04/2022

Figure. Age at First Occurrence of Selected Milestone Events in Patients With Recessive Dystrophic Epidermolysis Bullosa



Each panel displays the distribution of ages at which patients with recessive dystrophic epidermolysis bullosa first experienced selected milestone events in 142 of 157 patients with known age of first esophageal dilation (A), 101 of 104 patients with known age of gastrostomy tube placement (B), 56 of 62 patients with known age of first hand surgery (C), and 14 of 18 patients with known age of squamous cell cancer onset (D).

making analysis of large administrative and clinical databases, such as outpatient Medicaid or inpatient Pediatric Hospital Information System databases difficult. To improve our knowledge of longer-term outcomes in patients with all types of EB, enrollment of patients, including those with milder forms of EB, will be critical.[17]

Second, an opportunity exists to improve earlier diagnosis of EB. Our study indicated that there was a lag between the observation of clinical signs and subsequent confirmatory testing, particularly genetic analysis. Our data may reflect the traditional paradigm of using EM and/or IFM to guide genetic analysis of a single candidate gene. However, the recent advent of less costly gene panels that test for all of the known EB genes simultaneously may be changing this practice. Genetic diagnosis is considered to be the criterion standard for the diagnosis of genetic disorders, and there are potential faults with clinical or biopsy-based diagnoses of EB.[10] It is well established that the clinical findings of all forms of EB can be similar in newborns, but the prognosis varies widely based on the ultimate diagnosis of subtype. Clinicians can use genetic analysis to more accurately and definitively counsel families about their child's diagnosis of EB and its expected course. Genetic analysis can also permit accurate counseling about the likelihood of recurrence with future pregnancies and provide opportunity for prenatal or preimplantation genetic diagnosis.[22] In addition, even though a diagnosis may be supported by clinical signs and initial nongenetic diagnostic testing, as new therapies emerge for EB, particularly genetic-based therapy, it will be important to have a specific genetic diagnosis made as early as possible.[7,23] Overall, only 61% of the cohort younger than 10 years and even fewer older than 10 years had genetic analysis done. This study did not examine specific factors contributing to lacking a genetic diagnosis, but we suspect that limited availability at the time of testing, particularly for older patients, and financial factors play key roles.

Third, for patients with RDEB, our population-level description of the prevalence and timing of milestone clinical events may enhance clinical care. These data should allow clinicians, families, and patients to better anticipate and plan for the occurrence of milestone events in RDEB, such as esophageal dilation, gastrostomy tube placement, hand surgery, diagnosis of squamous cell carcinoma, or death. This

© 2018 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 03/04/2022

knowledge also aids clinicians in the initiation of counseling and planning at an optimal time, rather than overwhelming families with too much information at an initial visit. It may also help families accept that certain events, such as placement of a gastrostomy tube, are to be expected in RDEB and are not a failure on their part. These data will also help guide further study of patient-specific and systematic factors that might be associated with variation among milestone events. Identification of variation in management may provide valuable information to Epidermolysis Bullosa Clinical Research Consortium sites to support efforts to standardize management or develop clinical algorithms for common interventions. The Dystrophic Epidermolysis Bullosa Research Association International has commissioned expert panels to generate clinical guidelines for common EB issues; the EBCCOD may yield opportunities to supplement these expert recommendations with current, real-world evidence using a large available sample of patients with EB.

Limitations

Our findings must be interpreted within the context of several predictable limitations. Although the EBCCOD is a large, contemporary clinical database of patients with EB in North America, it only captures patients presenting for medical care at the participating EB centers. The nature of these centers biases the EBCCOD to patients with moderate to severe EB because it is conceivable that those with less severe forms of EB may seek care elsewhere or not at all. For instance, although EBS is the most prevalent diagnosis in the general population, the EBCCOD is enriched with patients with RDEB because of their frequent contact with the medical system and significant clinical needs requiring ongoing clinical care. However, the EBCCOD may not sufficiently capture patients, particularly infants, with lethal forms of EB (namely, JEB generalized severe) because they may die before study enrollment can occur. For instance, 68% of patients with JEB in the EBCCOD were older than 5 years, which likely reflects the survival of more patients with nonlethal forms of JEB based on subtype. Some patients had missing data, which we reported as unknown or a negative result depending on the variable. This decision could have led to bias in our results, such as the presence of a lag between signs for both symptoms and clinical diagnosis in either direction in the case of onset of first clinical symptoms or age at time of clinical diagnosis. The strategy for missing data may also have led to underreporting of some testing results, mainly in EM and IFM testing in older patients for whom reports were not readily available. Also, we attempted to assess for differences in the occurrence and timing of milestone events based on RDEB subtype classifications, but the completeness of the subtype data and the low frequencies of milestone events limited our ability to make meaningful comparisons between the RDEB subtypes. These analyses will be more feasible as the EBCCOD accrues more patients with complete data.

Conclusions

Approximately 33.0% of patients with RDEB and 53.8% of patients with JEB had a delay between the presence of signs at birth and subsequent clinical diagnosis of EB. Earlier diagnostic testing may enable improved characterizations of patients so that appropriate and timely counseling and clinical care may be offered, especially regarding milestone clinical events for patients with RDEB. The EBCCOD contains comprehensive patient data, especially for patients with RDEB, which will enable longitudinal studies of patient characteristics and clinical care and assist in the identification of key targets and timing for clinical interventions and evaluations of effectiveness.

ARTICLE INFORMATION

Accepted for Publication: October 20, 2018.

Published Online: December 26, 2018. doi:10.1001/jamadermatol.2018.4673

Author Affiliations: Department of Pediatrics, University of Colorado School of Medicine, Aurora (Feinstein, Bruckner); Adult and Child Consortium for Health Outcomes Research and Delivery Science, University of Colorado, Aurora (Feinstein); Children's Hospital Colorado, Aurora (Feinstein, Peoples, Bruckner); Department of Dermatology, University of Colorado School of Medicine, Aurora (Jambal, Bruckner); Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio (Lucky); Department of Dermatology, Stanford University School of Medicine, Stanford, California (Khuu, Tang); Section of Dermatology, Division of Paediatric Medicine, Hospital for Sick Children, Toronto, Ontario, Canada (Lara-Corrales, Pope); Division of Dermatology, Department of Medicine, University of Massachusetts Medical School, Worcester (Wiss); Department of Dermatology, University of Minnesota Medical School, Minneapolis (Hook); Department of Dermatology, Columbia Irving Medical Center, New York, New York (Levin, Morel); Department of Pediatrics, Columbia Irving Medical Center, New York, New York (Morel); Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, Illinois (Paller); Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, Illinois (Paller); Department of Dermatology, Ann and Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois (Paller); CHU Sainte-Justine, University of Montreal, Montreal, Quebec, Canada (McCuaig, Powell); Department of Dermatology, University of California San Diego, San Diego (Eichenfield); Department of Pediatrics, University of California San Diego, San Diego (Eichenfield); Department of Pediatric and Adolescent Dermatology, Rady Children's Hospital, San Diego, California (Eichenfield); Department of Dermatology, Phoenix Children's Hospital, Phoenix, Arizona (Price); Departments of Internal Medicine, Dell Medical School, University of Texas, Austin (Levy); Departments of Pediatrics, Dell Medical School, University of Texas, Austin (Levy); Department of Pediatric Dermatology, Dell Children's Medical Center, Austin, Texas (Levy); Department of Dermatology, University of Miami Miller School of Medicine, Miami, Florida (Schachner); Department of Pediatric Dermatology, Children's Hospital San Antonio, San Antonio, Texas (Browning); Division of Dermatology, Department of Medicine, Washington University in St Louis, St Louis, Missouri (Bayliss); Department of Dermatology, Henry Ford Hospital, Detroit, Michigan (Jahnke, Shwayder); Department of Dermatology, State University of New York Downstate Medical Center, Brooklyn (Glick); Associate Editor, *JAMA Dermatology* (Bruckner).

Author Contributions: Drs Bruckner and Feinstein had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Feinstein, Lucky, Paller, Bruckner.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Feinstein, Tang, Bruckner.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Feinstein, Schachner.
Obtained funding: Feinstein, Pope, Eichenfield, Bruckner.
Administrative, technical, or material support: Jambal, Peoples, Khuu, Tang, Pope, Hook,

© 2018 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 03/04/2022

Paller, McCuaig, Eichenfield, Levy, Browning, Glick, Bruckner.
Supervision: Lucky, Tang, Hook, Morel, Paller, Bayliss, Jahnke, Shwayder, Bruckner.

Conflict of Interest Disclosures: Dr Lucky has been a consultant and/or investigator for Abeona Therapeutics, Castle Creek Pharmaceuticals, Fibrocell Science, ProQR, and Scioderm. Dr Tang has been a consultant and/or investigator for Abeona Therapeutics, Amicus/Scioderm, Fibrocell Science, and Phoenix Tissue Repair. Dr Lara-Corrales has been a consultant and/or investigator for Amicus/Scioderm. Dr Hook has been a consultant and/or investigator for Amicus/Scioderm and Castle Creek Pharmaceuticals. Dr Levin reports receiving grants from the Epidermolysis Bullosa Research Partnership outside the submitted work and having a patent to CU16297 issued. Dr Morel has been a consultant and/or investigator for Amicus/Scioderm. Dr Paller has been a consultant and/or investigator for Amicus/Scioderm, Castle Creek Pharmaceuticals, and G-tree Pharmaceuticals. Dr Eichenfield has been a consultant and/or investigator for Amicus/Scioderm. Dr Price has been a consultant and/or investigator for Amicus/Scioderm and Castle Creek Pharmaceuticals. Dr Levy has been a consultant and/or investigator for Amicus/Scioderm and Castle Creek Pharmaceuticals. Dr Schachner has been a consultant and/or investigator for Berg Pharma. Dr Browning has been a consultant and/or investigator for Amryt Pharma, Castle Creek Pharmaceuticals, G-tree Pharmaceuticals/Lenus Therapeutics, and Scioderm. Dr Bayliss has been a consultant and/or investigator for Amicus/Scioderm. Dr Bruckner has been a consultant and/or investigator for Abeona Therapeutics, Amicus/Scioderm, Castle Creek Pharmaceuticals, Fibrocell Science, and ProQR. No other conflicts were reported.

Funding/Support: This study was supported by an investigator-initiated grant from Amicus Therapeutics. Dr Feinstein was supported by grant K23HD091295 from the Eunice Kennedy Shriver National Institute for Child Health and Human Development. The Epidermolysis Bullosa Clinical Characterization and Outcomes Database is funded jointly by Epidermolysis Bullosa Research Partnership and Epidermolysis Bullosa Medical Research Foundation. Research Electronic Data Capture is supported by Colorado Clinical Translational Science Award grant UL1 TR002535 from the National Institutes of Health/National Center for Advancing Translational Sciences.

Role of the Funder/Sponsor: The funding organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: Dr Bruckner is Associate Editor of *JAMA Dermatology*, but she was not involved in any of the decisions regarding review of the manuscript or its acceptance.

Additional Contributions: We thank the patients who participated in this study. The following individuals provided research support for this study: Bret Augsburger (Cincinnati Children's Hospital); Melissa Barriga (Lucile Packard Children's Hospital Stanford); Hanna Fadzeyeva (Hospital for Sick Children); Kristen Corey, MD, and Julia Siegel, MD (University of Massachusetts); Solveig Hagen, MD, Brooke Hanson, MD, and Melissa Dodds, MD (University of Minnesota); Hannah Singer, MD and Eloise Galligan, BA (Columbia University Vagelos College of Physicians and Surgeons); Thy Huynh, MD and Rema Zebda, DO (Northwestern University); Philippe Sylvestre, MD (CHU Sainte-Justine, University of Montreal); Jenna Borok, MD and Allison Han, BA (University of California San Diego); Kellie Badger, RN (Phoenix Children's Hospital); Sarah H. Schwartz (Dell Children's Medical Center); Taylor L. Braunberger, MD (Henry Ford Hospital); and Gregory Phillips (State University of New York Downstate Medical Center). Many of these individuals are paid research coordinators whose job description includes supporting the Epidermolysis Bullosa Clinical Characterization and Outcomes Database. The others are students or trainees functioning as research coordinators.

REFERENCES

1. Fine JD, Eady RA, Bauer EA, et al. The classification of inherited epidermolysis bullosa (EB): report of the Third International Consensus Meeting on Diagnosis and Classification of EB. *J Am Acad Dermatol*. 2008;58(6):931-950. doi:10.1016/j.jaad.2008.02.004

2. Fine JD. Epidemiology of inherited epidermolysis bullosa based on incidence and prevalence estimates from the National Epidermolysis Bullosa Registry. *JAMA Dermatol*. 2016;152(11):1231-1238. doi:10.1001/jamadermatol.2016.2473

3. Uitto J, Bruckner-Tuderman L, Christiano AM, et al. Progress toward treatment and cure of epidermolysis bullosa: summary of the DEBRA International Research Symposium EB2015. *J Invest Dermatol*. 2016;136(2):352-358. doi:10.1016/j.jid.2015.10.050

4. Uitto J. Epidermolysis bullosa: prospects for cell-based therapies. *J Invest Dermatol*. 2008;128(9):2140-2142. doi:10.1038/jid.2008.216

5. Sebastiano V, Zhen HH, Haddad B, et al. Human COL7A1-corrected induced pluripotent stem cells for the treatment of recessive dystrophic epidermolysis bullosa. *Sci Transl Med*. 2014;6(264):264ra163. doi:10.1126/scitranslmed.3009540

6. Gorell ES, Leung TH, Khuu P, Lane AT. Purified type I collagen wound matrix improves chronic wound healing in patients with recessive dystrophic epidermolysis bullosa. *Pediatr Dermatol*. 2015;32(2):220-225. doi:10.1111/pde.12492

7. Siprashvili Z, Nguyen NT, Gorell ES, et al. Safety and wound outcomes following genetically corrected autologous epidermal grafts in patients With recessive dystrophic epidermolysis bullosa. *JAMA*. 2016;316(17):1808-1817. doi:10.1001/jama.2016.15588

8. Wally V, Hovnanian A, Ly J, et al. Diacerein orphan drug development for epidermolysis bullosa simplex: A phase 2/3 randomized, placebo-controlled, double-blind clinical trial. *J Am Acad Dermatol*. 2018;78(5):892-901.e7. doi:10.1016/j.jaad.2018.01.019

9. Schwieger-Briel A, Chakkittakandiyil A, Lara-Corrales I, et al. Instrument for scoring clinical outcome of research for epidermolysis bullosa: a consensus-generated clinical research tool. *Pediatr Dermatol*. 2015;32(1):41-52. doi:10.1111/pde.12317

10. Fine JD, Bruckner-Tuderman L, Eady RA, et al. Inherited epidermolysis bullosa: updated recommendations on diagnosis and classification. *J Am Acad Dermatol*. 2014;70(6):1103-1126. doi:10.1016/j.jaad.2014.01.903

11. Morel T, Cano SJ. Measuring what matters to rare disease patients–reflections on the work by the IRDiRC taskforce on patient-centered outcome measures. *Orphanet J Rare Dis*. 2017;12(1):171. doi:10.1186/s13023-017-0718-x

12. Luria S, Radwan S, Zinger G, Eylon S. Hand surgery for dystrophic epidermolysis bullosa. *J Pediatr Orthop*. 2014;34(7):710-714. doi:10.1097/BPO.0000000000000152

13. Haynes L, Mellerio JE, Martinez AE. Gastrostomy tube feeding in children with epidermolysis bullosa: consideration of key issues. *Pediatr Dermatol*. 2012;29(3):277-284. doi:10.1111/j.1525-1470.2011.01612.x

14. Kim M, Murrell DF. Update on the pathogenesis of squamous cell carcinoma development in recessive dystrophic epidermolysis bullosa. *Eur J Dermatol*. 2015;25(suppl 1):30-32.

15. Bernardis C, Box R. Surgery of the hand in recessive dystrophic epidermolysis bullosa. *Dermatol Clin*. 2010;28(2):335-341, xi. doi:10.1016/j.det.2010.01.013

16. Sousa MC, Paula CD, Tauil PL, Costa IM. Correlation between nutritional, hematological and infectious characteristics and classification of the type of epidermolysis bullosa of patients assisted at the Dermatology Clinic of the Hospital Universitário de Brasília. *An Bras Dermatol*. 2015;90(6):922-924. doi:10.1590/abd1806-4841.20154575

17. Kodra Y, Posada de la Paz M, Coi A, et al. Data quality in rare diseases registries. *Adv Exp Med Biol*. 2017;1031:149-164. doi:10.1007/978-3-319-67144-4_8

18. Bruckner AL, Fairclough DL, Feinstein JA, et al. Reliability and validity of the instrument for scoring clinical outcomes of research for epidermolysis bullosa (iscorEB). *Br J Dermatol*. 2018;178(5):1128-1134. doi:10.1111/bjd.16350

19. Uitto J, McGrath JA, Rodeck U, Bruckner-Tuderman L, Robinson EC. Progress in epidermolysis bullosa research: toward treatment and cure. *J Invest Dermatol*. 2010;130(7):1778-1784. doi:10.1038/jid.2010.90

20. Brigo F, Leo A, Russo E, Striano P, Belcastro V. Intravenous carbamazepine for the treatment of epilepsy. *Expert Opin Pharmacother*. 2018;19(7):743-747. doi:10.1080/14656566.2018.1462338

21. Lacaze P, Millis N, Fookes M, et al. Rare disease registries: a call to action. *Intern Med J*. 2017;47(9):1075-1079. doi:10.1111/imj.13528

22. Yan EG, Paris JJ, Ahluwalia J, Lane AT, Bruckner AL. Treatment decision-making for patients with the Herlitz subtype of junctional epidermolysis bullosa. *J Perinatol*. 2007;27(5):307-311. doi:10.1038/sj.jp.7211694

23. Has C, Kiritsi D. Molecular therapies for epidermolysis bullosa. *G Ital Dermatol Venereol*. 2013;148(1):65-72.

© 2018 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ on 03/04/2022