

Epidermolysis Bullosa Clinical Diagnostic Matrix

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Development of a clinical diagnostic matrix for characterizing inherited epidermolysis bullosa*

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Linked Comment: McGrath. *Br J Dermatol* 2017; 176:1442–1443



[Yenamandra VK, et al. Br J Dermatol. 2017 Jun;176\(6\):1624-1632](#)



Epidermolysis Bullosa (EB)

- Diverse group of genodermatoses, characterized by fragile skin in response to mechanical trauma



Mild Sub-type:
EB Simplex- Localised
(Weber Cockayne)



Severe Sub-type:
Generalised Severe Recessive
Dystrophic EB (Hallopeau-Siemens)

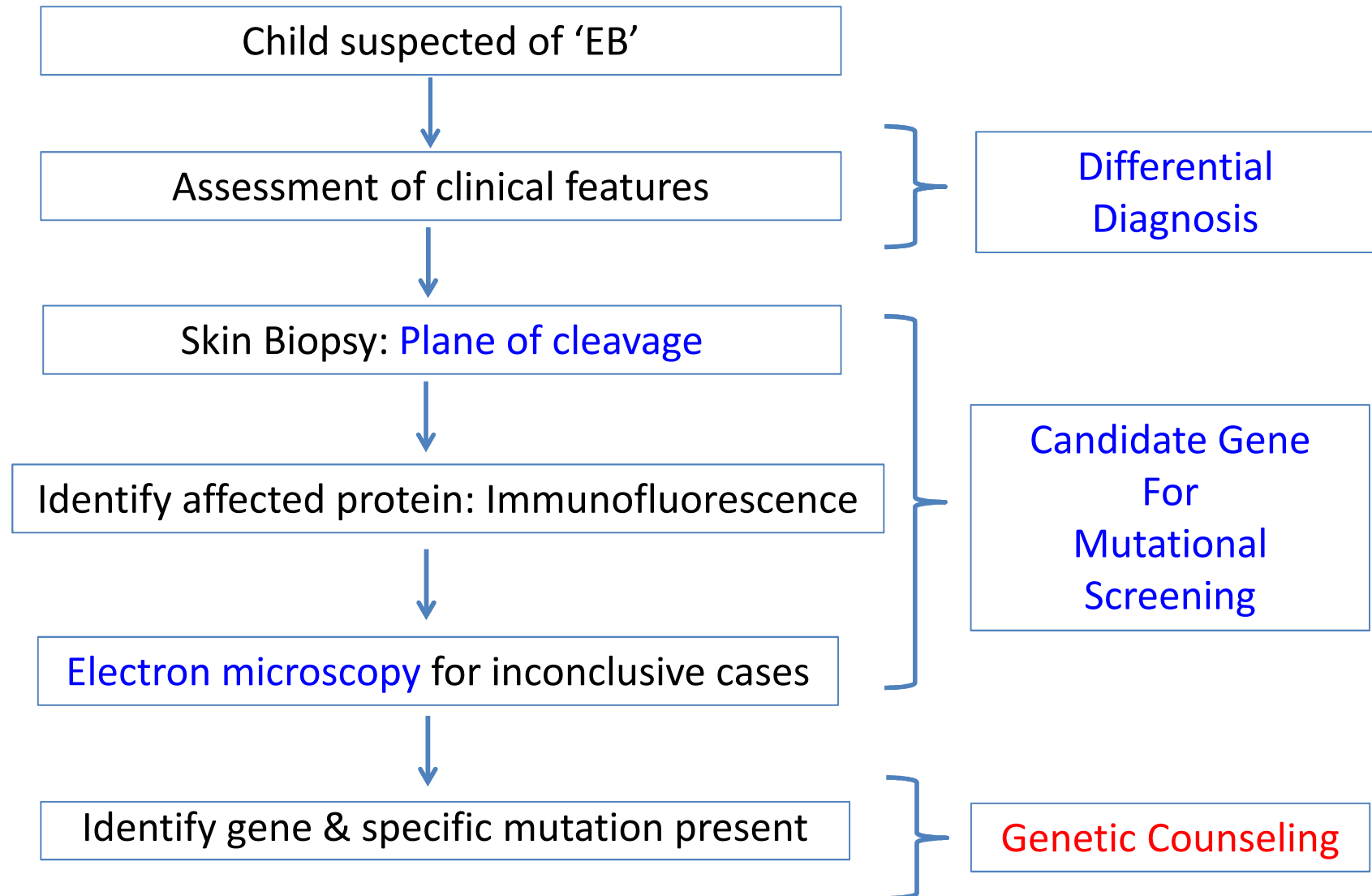
Classification of Epidermolysis Bullosa (EB)

- Great phenotypic variability exists between the different types
- Accurate diagnosis is critical for management and genetic counseling
- International Consensus Recommendation: “Onion Skin” Classification



*Fine et al. J Am Acad Dermatol 2014; 70(6):1103-26.

Diagnosis based on “Onion Skin” Approach



EB in Resource Limited Settings

- Diagnostic techniques are limited: Financial & Infrastructure



- Practical clinical diagnostic tool for subtyping EB (>6 months)

Clinical Diagnostic Matrix (AIIMS-BCH Collaboration)

[illegible]

Consensus Scoring Scheme

Clinical Feature	EBS-L	EBS-GI	EBS-GS	JEB-GS	JEB-GI	DDEB	RDEB-GS	RDEB-GI	KS
Distribution of skin lesions			Generalised/ Herpetiform						
Excess Granulation tissue									
Scarring									
Milia									
Nail Dystrophy									
Nail loss									
Mucosal erosions									
Eye involvement									
Hoarseness									
Microstomi/Ankyloglossia									
Poor Dental Enamel									
Keratoderma									
Chronic Wounds									
Syndactyly									
Alopecia									
Poikiloderma									
Relative Growth Failure									
Survival after 2 yrs									
Parents affected									
Total number of boxes ticked									



Consensus Scoring Scheme

Clinical Feature	EBS-L	EBS-GI	EBS-GS	JEB-GS	JEB-GI	DDEB	RDEB-GS	RDEB-GI	KS
Distribution of skin lesions									
Excess Granulation tissue				+					
Scarring									
Milia									
Nail Dystrophy									
Nail loss									
Mucosal erosions									
Eye involvement									
Hoarseness									
Microstomia/Ankyloglossia									
Poor Dental Enamel									
Keratoderma									
Chronic Wounds									
Syndactyly									
Alopecia									
Poikiloderma									
Relative Growth Failure									
Survival after 2 yrs									
Parents affected									
Total number of boxes ticked									



Consensus Scoring Scheme

Clinical Feature	EBS-L	EBS-GI	EBS-GS	JEB-GS	JEB-GI	DDEB	RDEB-GS	RDEB-GI	KS
Distribution of skin lesions									
Excess Granulation tissue									
Scarring									
Milia									
Nail Dystrophy									
Nail loss									
Mucosal erosions									
Eye involvement									
Hoarseness									
Microstomia/ Ankyloglossia									
Poor Dental Enamel									
Keratoderma									
Chronic Wounds									
Syndactyly									
Alopecia									
Poikiloderma									
Relative Growth Failure									
Survival after 2 yrs									
Parents affected									
Total number of boxes ticked									



+ or ++

Consensus Scoring Scheme

Clinical Feature	EBS-L	EBS-GI	EBS-GS	JEB-GS	JEB-GI	DDEB	RDEB-GS	RDEB-GI	KS
Distribution of skin lesions									
Excess Granulation tissue									
Scarring									
Milia									
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Nail loss									
Mucosal erosions									
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Poor Dental Enamel									
Keratoderma									
Chronic Wounds									
Syndactyly									
Alopecia									
Poikiloderma									
Relative Growth Failure									
Survival after 2 yrs									
Parents affected									
Total number of boxes ticked									

+

Consensus Scoring Scheme

[illegible]

Consensus Scoring Scheme

[illegible]

Consensus Scoring Scheme

[illegible]

Clinical Diagnostic Matrix

[illegible]

Scoring with the Diagnostic Matrix

- Score every cell 1 or 0

Observed in Patient	Content of Cell	Score
Yes	Yes	1
No	No	1
Yes	No	0
No	Yes	0

- Add up columns
- Column with highest score = diagnosis
- If ≥ 2 scored equally = Inconclusive (look for with more specific features)

Example 1

[illegible]

Example 1

[illegible]

Example 1

Clinical Feature	EBS-L	EBS-GI	EBS-GS	JEB-GS	JEB-GI	DDEB	RDEB-GS	RDEB-GI	KS
Distribution of skin lesions	0	0	1	0	0	0	0	0	0
Excess Granulation tissue	1	1	1	0	1	1	1	1	1
Scarring	1	1	1	1	1	0	0	0	1
Milia	1	1	1	1	1	0	0	0	1
Nail Dystrophy	0	0	1	1	1	1	1	1	1
Nail loss	1	1	1	0	1	1	0	1	1
Mucosal erosions	0	0	1	1	1	1	1	1	1
Eye involvement	1	1	1	1	1	1	1	1	1
Hoarseness	1	1	1	0	1	1	1	1	1
Microstomia/ Ankyloglossia	1	1	1	1	1	1	1	1	1
Poor Dental Enamel	1	1	1	0	0	1	1	1	1
Keratoderma	1	1	1	0	0	0	0	0	1
Chronic Wounds	1	1	1	1	1	1	1	1	1
Syndactyly	1	1	1	1	1	1	0	1	1
Alopecia	1	1	1	1	0	1	1	1	1
Poikiloderma	1	1	1	1	1	1	1	1	0
Relative Growth Failure	1	1	1	0	1	1	0	1	1
Survival after 2 yrs	1	1	1	0	1	1	1	1	1
Parents affected	0	0	1	1	1	0	1	1	1
Total number of boxes ticked	15	15	19	11	15	14	12	15	17

Example 1

Clinical Feature	EBS-L	EBS-GI	EBS-GS	JEB-GS	JEB-GI	DDEB	RDEB-GS	RDEB-GI	KS
Distribution of skin lesions	0	0	1	0	0	0	0	0	0
Excess Granulation tissue	1	1	1	0	1	1	1	1	1
Scarring	1	1	1	1	1	0	0	0	1
Milia	1	1	1	1	1	0	0	0	1
Nail Dystrophy	0	0	1	1	1	1	1	1	1
Nail loss	1	1	1	0	1	1	0	1	1
Mucosal erosions	0	0	1	1	1	1	1	1	1
Eye involvement	1	1	1	1	1	1	1	1	1
Hoarseness	1	1	1	0	1	1	1	1	1
Microstomia/Ankyloglossia	1	1	1	1	1	1	1	1	1
Poor Dental Enamel	1	1	1	0	0	1	1	1	1
Keratoderma	1	1	1	0	0	0	0	0	1
Chronic Wounds	1	1	1	1	1	1	1	1	1
Syndactyly	1	1	1	1	1	1	0	1	1
Alopecia	1	1	1	1	0	1	1	1	1
Poikiloderma	1	1	1	1	1	1	1	1	0
Relative Growth Failure	1	1	1	0	1	1	0	1	1
Survival after 2 yrs	1	1	1	0	1	1	1	1	1
Parents affected	0	0	1	1	1	0	1	1	1
Total number of boxes ticked	15	15	19	11	15	14	12	15	17

Example 2

[illegible]

Example 2

[illegible]

Example 2

Clinical Feature	EBS-L	EBS-GI	EBS-GS	JEB-GS	JEB-GI	DDEB	RDEB-GS	RDEB-GI	KS
Distribution of skin lesions		1	1	1	1	1	1	1	1
Excess Granulation tissue	0	0	0	1	1	0	0	0	0
Scarring	1	1	1	1	1	0	0	0	1
Milia	1	1	1	1	1	0	0	0	1
Nail Dystrophy	0	0	1	1	1	1	1	1	1
Nail loss	1	1	1	0	1	1	0	1	1
Mucosal erosions	0	0	1	1	1	1	1	1	1
Eye involvement	0	0	0	1	1	0	1	1	0
Hoarseness	1	1	1	0	1	1	1	1	1
Microstomia/Ankyloglossia	1	1	1	1	1	1	1	1	1
Poor Dental Enamel	0	0	0	1	1	0	0	0	0
Keratoderma	1	1	1	1	1	1	1	1	1
Chronic Wounds	1	1	1	1	1	1	1	1	1
Syndactyly	1	1	1	1	1	1	0	1	1
Alopecia	0	0	0	0	1	0	1	1	0
Poikiloderma	1	1	1	1	1	1	1	1	0
Relative Growth Failure	0	0	0	1	0	0	1	0	0
Survival after 2 yrs	1	1	1	0	1	1	1	1	1
Parents affected	0	0	1	1	1	0	1	1	1
Total number of boxes ticked	10	11	14	15	18	11	13	14	13

Example 2

Clinical Feature	EBS-L	EBS-GI	EBS-GS	JEB-GS	JEB-GI	DDEB	RDEB-GS	RDEB-GI	KS
Distribution of skin lesions		1	1	1	1	1	1	1	1
Excess Granulation tissue	0	0	0	1	1	0	0	0	0
Scarring	1	1	1	1	1	0	0	0	1
Milia	1	1	1	1	1	0	0	0	1
Nail Dystrophy	0	0	1	1	1	1	1	1	1
Nail loss	1	1	1	0	1	1	0	1	1
Mucosal erosions	0	0	1	1	1	1	1	1	1
Eye involvement	0	0	0	1	1	0	1	1	0
Hoarseness	1	1	1	0	1	1	1	1	1
Microstomia/Ankyloglossia	1	1	1	1	1	1	1	1	1
Poor Dental Enamel	0	0	0	1	1	0	0	0	0
Keratoderma	1	1	1	1	1	1	1	1	1
Chronic Wounds	1	1	1	1	1	1	1	1	1
Syndactyly	1	1	1	1	1	1	0	1	1
Alopecia	0	0	0	0	1	0	1	1	0
Poikiloderma	1	1	1	1	1	1	1	1	0
Relative Growth Failure	0	0	0	1	0	0	1	0	0
Survival after 2 yrs	1	1	1	0	1	1	1	1	1
Parents affected	0	0	1	1	1	0	1	1	1
Total number of boxes ticked	10	11	14	15	18	11	13	14	13

Example 3

[illegible]

Example 3

[illegible]

Example 3

Clinical Feature	EBS-L	EBS-GI	EBS-GS	JEB-GS	JEB-GI	DDEB	RDEB-GS	RDEB-GI	KS
Distribution of skin lesions	0	1	1	1	1	1	1	1	1
Excess Granulation tissue	1	1	1	0	1	1	1	1	1
Scarring	0	0	0	0	0	1	1	1	0
Milia	0	0	1	0	0	1	1	1	0
Nail Dystrophy	1	1	1	0	1	1	1	1	1
Nail loss	0	0	0	1	1	0	1	1	0
Mucosal erosions	0	0	0	1	0	0	1	0	0
Eye involvement	0	0	0	1	1	0	1	1	0
Hoarseness	1	1	1	0	1	1	1	1	1
Microstomia/Ankyloglossia	0	0	0	0	0	0	1	1	0
Poor Dental Enamel	0	0	0	1	1	0	0	0	0
Keratoderma	1	1	1	1	1	1	1	1	1
Chronic Wounds	0	0	0	1	1	1	1	1	1
Syndactyly	0	0	0	0	0	0	1	0	0
Alopecia	1	1	1	1	0	1	1	1	1
Poikiloderma	1	1	1	1	1	1	1	1	0
Relative Growth Failure	0	0	0	1	1	0	1	1	1
Survival after 2 yrs	1	1	1	0	1	1	1	1	1
Parents affected	0	0	1	1	1	0	1	1	1
Total number of boxes ticked	7	8	10	11	13	11	18	16	10

Example 3

Clinical Feature	EBS-L	EBS-GI	EBS-GS	JEB-GS	JEB-GI	DDEB	RDEB-GS	RDEB-GI	KS
Distribution of skin lesions	0	1	1	1	1	1	1	1	1
Excess Granulation tissue	1	1	1	0	1	1	1	1	1
Scarring	0	0	0	0	0	1	1	1	0
Milia	0	0	1	0	0	1	1	1	0
Nail Dystrophy	1	1	1	0	1	1	1	1	1
Nail loss	0	0	0	1	1	0	1	1	0
Mucosal erosions	0	0	0	1	0	0	1	0	0
Eye involvement	0	0	0	1	1	0	1	1	0
Hoarseness	1	1	1	0	1	1	1	1	1
Microstomia/Ankyloglossia	0	0	0	0	0	0	1	1	0
Poor Dental Enamel	0	0	0	1	1	0	0	0	0
Keratoderma	1	1	1	1	1	1	1	1	1
Chronic Wounds	0	0	0	1	1	1	1	1	1
Syndactyly	0	0	0	0	0	0	1	0	0
Alopecia	1	1	1	1	0	1	1	1	1
Poikiloderma	1	1	1	1	1	1	1	1	0
Relative Growth Failure	0	0	0	1	1	0	1	1	1
Survival after 2 yrs	1	1	1	0	1	1	1	1	1
Parents affected	0	0	1	1	1	0	1	1	1
Total number of boxes ticked	7	8	10	11	13	11	18	16	10

Testing the Matrix

- 74 genetically characterized patients aged 7 months to 24 years.
 - Phase 1 (Retrospective): 50 patients from Birmingham Children Hospital, UK
 - Phase 2 (Prospective): 24 patients from AIIMS, New Delhi, India
- 2-7 cases of each diagnosis
- Using the matrix, each case was classified by an investigator blinded to molecular diagnosis
- Finally, matrix diagnoses were compared with genetic diagnoses for concordance

Comparison of Genetic vs Matrix Diagnosis

Matrix Diagnosis

Genetic Diagnosis									
DIAG	EBS-L	EBS-GI	EBS-GS	JEB-GS	JEB-GI	DDEB	RDEB-GS	RDEB-GI	KS
EBS-L	4	0	0	0	0	0	0	0	0
EBS-GI	0	4	0	0	0	0	0	0	0
EBS-GS	0	0	10	0	3	0	0	0	0
JEB-GS	0	0	0	2	0	0	0	0	0
JEB-GI	0	0	0	2	9	0	0	0	0
DDEB	0	0	0	0	0	7	0	0	0
RDEB-GS	0	0	0	0	0	0	9	1	0
RDEB-GI	0	0	0	0	0	1	0	7	0
KS	0	0	0	0	0	0	0	0	4
Inconclusive	1	0	1	0	0	4	1	4	0
Total(n=74)	5	4	11	4	12	12	10	12	4

Concordance between Matrix vs Genetic Diagnosis

- Concordance for all sub-types:
 - Correctly identified sub type in 56 of 74 cases
 - 75.7% [Kappa co-efficient: 0.73 (95% C.I: 0.69±0.77; p < 0.001)]
- Concordance for all major types:
 - Correctly identified major type in 68 of 74 cases
 - 91.9% [Kappa co-efficient: 0.88 (95% C.I: 0.81±0.95; p < 0.001)]

Conclusion

- On preliminary testing, the matrix appears acceptably accurate in classifying the type and subtype of EB.
- An electronic application was developed to simplify usage.
- Necessitates full documentation of clinical features:
Facilitates Phenotype genotype correlations.
- Less accurate in infants and children < 6months.
- Further, prospective testing in different international clinical settings is planned.

Electronic Version

The app interface consists of three main screens:

- Home Screen:** Displays the iscorEB logo and the text "Instrument for scoring clinical outcomes of research for Epidermolysis Bullosa".
- Skin Section:** A list of symptoms with checkboxes: Blisters, Erosions (checked), Crusting, Wounds, and Infections. Below the list, two human figures show the percentage of affected area: 49% on the left and 0% on the right.
- Pain Section:** Two rating questions: "1. Rate OVERALL PAIN:" and "2. Rate SKIN PAIN:". Each has a dropdown menu with a smiley face icon. Below these is a slider for "Please rate how much SKIN PAIN you (your child) typically experienced in the last 4 weeks:" with a scale from None to Worst.

Epidermolysis Bullosa Clinical Diagnostic Matrix

All India Institute of Medical Sciences

Birmingham Children's Hospital

NHS Foundation Trust



START

[Click here to email for support or comments](#)

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Dental Enamel

Keratoderma

Chronic Wounds

Syndactyly

Alopecia

Poikiloderma

Growth Failure

Survival

Parents affected

Institution and patient data

Name of scorer	
Name of patient	
Hospital registration ID	
Date of birth	(Enter as dd/mm/yyyy)
Date of scoring	☐ Τίχκ φορ τοδαση
Age	
Sex	☐ Μαλε ☐ Φεμαλε

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Generalised



Limited



Hands and feet



Herpetiform

- ☒ Γενεραλισειδ
- ☐ Λιμνιδ
- ☐ Χανδα & φειτ
- ☐ Ηερπετιφορμ

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Nail loss

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Examples of loss of nails

- ☐ No λασσ οφ ναιλα
- ☐ Λασσ οφ φειερ την 10 ναιλα +
- ☐ Λασσ οφ 10 ορ μορε ναιλα ++

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Syndactyly

Alopecia

Poikiloderma

Growth Failure

Survival

Parents affected

		EB simplex			Junctional EB		Dystrophic EB			KS
		EBS-L	EBS-GI	EBS-GS	JEB-GS	JEB-GI	DDEB	RDEB-GS	RDEB-GI	
1	Distribution of skin lesions	0	1	1	1	1	1	1	1	1
2	Excess Granulation tissue	1	1	1	0	1	1	1	1	1
3	Scarring	1	1	1	1	1	0	0	0	1
4	Milia	1	1	1	1	1	0	0	0	1
5	Nail Dystrophy	0	0	1	1	1	1	1	1	1
6	Nail loss	1	1	1	0	1	1	0	1	1
7	Mucosal erosions	0	0	1	1	1	1	1	1	1
8	Eye involvement	1	1	1	1	1	1	1	1	1
9	Hoarseness	1	1	1	0	1	1	1	1	1
10	Microstomia/Ankyloglossia	1	1	1	1	1	1	1	1	1
11	Poor Dental Enamel	1	1	1	0	0	1	1	1	1
12	Keratoderma	1	1	1	0	0	0	0	0	1
13	Chronic Wounds	1	1	1	1	1	1	1	1	1
14	Syndactyly	1	1	1	1	1	1	0	1	1
15	Alopecia	1	1	1	1	0	1	1	1	1
16	Poikiloderma	1	1	1	1	1	1	1	1	0
17	Relative Growth Failure	1	1	1	0	1	1	0	1	1
18	Survival after 2 yrs	1	1	1	0	1	1	1	1	1
19	Parents affected	0	0	1	1	1	0	1	1	1
Total Score		15	16	19	12	16	15	13	16	18
		EBS-L	EBS-GI	EBS-GS	JEB-GS	JEB-GI	DDEB	RDEB-GS	RDEB-GI	KS

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View/Print/Save
Report

Reset scores and go to
Start

The most probable diagnosis is beneath the number highlighted in green. If multiple diagnoses share the highest score please click the button below for an algorithm that may help to ascertain the most likely diagnosis

Algorithm

Epidermolysis bullosa diagnostic matrix tool report

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Scorer Vamsi Yenamandra

Patient EB_CLINET 2017

Male

Date 27/09/17

Score

EB simplex			Junctional EB		Dystrophic EB			KS
EBS-L	EBS-GI	EBS-GS	JEB-GS	JEB-GI	DDEB	RDEB-GS	RDEB-GI	
15	16	19	12	16	15	13	16	18

Print report

Save report

Development of a clinical diagnostic matrix for characterizing inherited epidermolysis bullosa*

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⁴Sadd Maareb Medical Centre, Abu Dhabi, U.A.E.

⁵CSIR-Institute of Genomics and Integrative Biology, New Delhi, India

Linked Comment: McGrath. *Br J Dermatol* 2017; 176:1442–1443

Supporting Information

Filename

Description

[bjd15221-sup-0001-TableS1.docx](#)
Word document, 17K

Table S1. Sensitivity and specificity of the clinical diagnostic matrix in the diagnosis of (a) major types and (b) subtypes of epidermolysis bullosa.

[bjd15221-sup-0002-TableS2.docx](#)
Word document, 27K

Table S2. Details of diagnostic matrix findings by age (in years) in (a) a U.K. series and (b) an Indian series.

[bjd15221-sup-0003-supinfo.xlsm](#)
application/vnd.ms-excel.sheet.macroenabled.12,
11424K

Table S3. Electronic diagnostic matrix.

[bjd15221-sup-0004-VideoS1.m4v](#)
video/x-m4v, 63360K

Video S1. Author video.



Aims of the Initiative

Work Streams

Status

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EB Literature

EB Clinical Diagnostic Matrix ▶

Contact

Epidermolysis Bullosa Clinical Diagnostic Matrix



[Download the Tool \(Excel File containing Makros, 11,4MB\)](#)

To improve clinical diagnostic accuracy, particularly in resource-poor settings, a novel EB diagnostic system has been developed.

This simple electronic version automatically computes the most likely diagnosis. It incorporates illustrations to help practitioners recognise relevant clinical features.

An accurate diagnosis is essential for managing and counselling patients with EB. The latest EB classification lists more than 30 subtypes and high levels of clinical and laboratory expertise are required to differentiate them. Unfortunately such facilities are inaccessible to many.

To improve clinical diagnostic accuracy, particularly in resource-poor settings, EB experts in India, Abu Dhabi and the UK have developed a novel EB diagnostic system, recently accepted for publication by the British Journal of Dermatology (see <http://onlinelibrary.wiley.com/doi/10.1111/bjd.15221/abstract>).

Professor Celia Moss, one of the co-authors, says "We know this tool is not perfect, but we hope it will be a useful guide for non-expert dermatologists. We will be pleased for others to use it, translate it and adapt it to their needs. An email link on the title screen invites comments and feedback."

Acknowledgements

- Prof. G. Sethuraman, Prof. Celia Moss, Prof. V. Sreenivas, and Dr. Sridhar Sivasubbu
- Dr. Murtaza Khan
- Prof. John McGrath, St John's Institute of Dermatology, London
- Dr. Fiona Browne, OLCHE, Dublin, Ireland
- Prof. Jemima Mellerio, Guy's & St Thomas' Hospital, London
- Dr. Anna Martinez, GOSH, London
- Dr. Malobi Ogboli, BCH, Birmingham
- Dr. Rahul Mahajan, AIIMS, New Delhi
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