LABORATORY DIAGNOSIS

Information for people living with epidermolysis bullosa (EB), their families, and caregivers

This is how life feels to people with EB.

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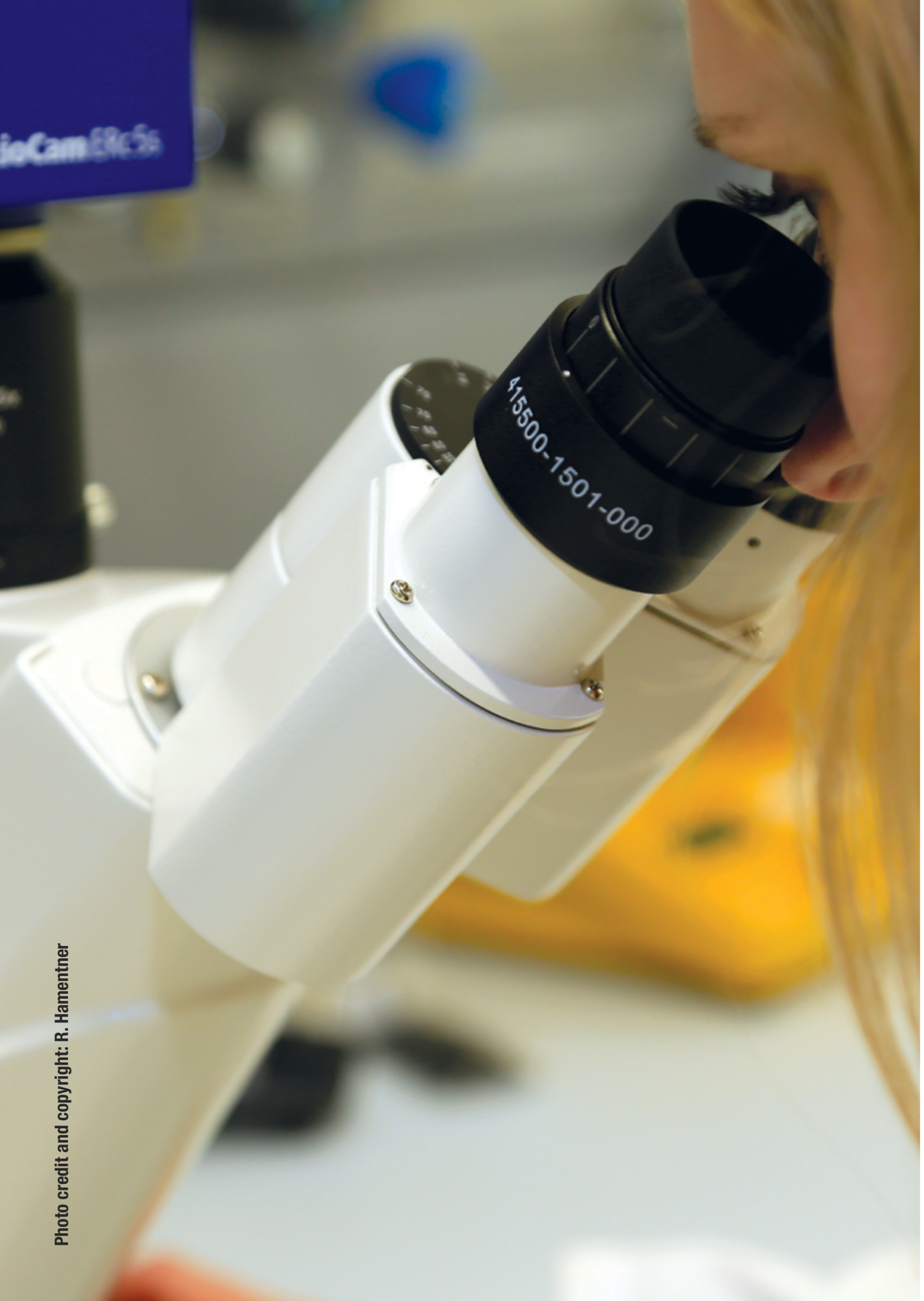
WHAT IS EPIDERMOLYSIS BULLOSA?

EB is a group of rare genetic disorders characterised by fragility of the skin and mucous membranes and mechanically induced blistering. EB comprises four main types - EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler EB (KEB), with more than 30 subtypes. EB is clinically heterogeneous including a broad spectrum of severity.

COVER PHOTO: Janaína Rodrigues Pereira, living with recessive dystrophic EB, aged 40, Brazil (photo credit: Suelen Szymanski)



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Miguel Kingerski da Silva Calgaro, living with recessive dystrophic EB, aged 6, Brazil (photo credit: Suelen Szymanski)

Who is this booklet for?

This booklet is for people living with EB, their families, and caregivers. It will be informative if:

- you, your child, or a family member is clinically suspected of having EB
- you would like to understand the process of EB laboratory diagnosis
- you would like to know about the consequences and considerations of living with EB
- you would like to know your options for future family planning

What is this booklet about?

This booklet provides information on laboratory diagnosis in EB.

Topics covered in this booklet include:

- what EB is
- the importance of getting an accurate diagnosis when someone is suspected of having EB
- the steps in making an accurate EB diagnosis
- the latest EB laboratory diagnosis methods and considerations
- the connection between analysis results and decision-making for EB patient care management
- inheritance patterns and genetic counselling possibilities for patients and their families
- how EB laboratory diagnosis works in practice
- who should perform EB laboratory diagnoses and where

Where does the information in this booklet come from?

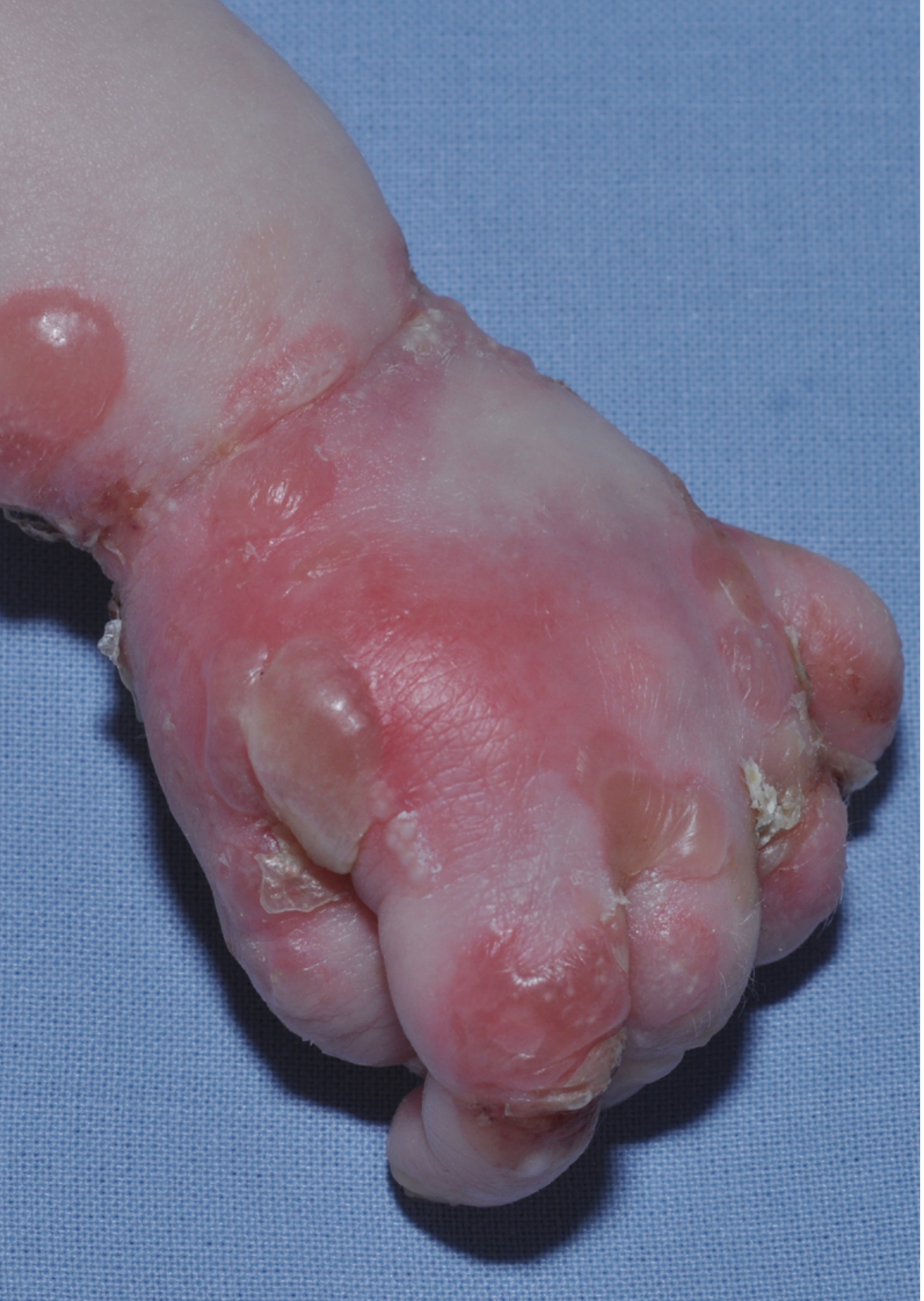
The information and recommendations in this booklet are derived directly from the “Clinical practical guidelines for laboratory diagnosis of epidermolysis bullosa”. The guidelines were written in 2019 by a group of EB healthcare professionals, individuals living with EB, and family members. The information and recommendations in the guidelines come from a variety of sources including clinical research and expert opinion.

There are three different types of recommendation in this booklet:

STRONG RECOMMENDATION
based on good-quality research evidence

RECOMMENDATION
based on research evidence

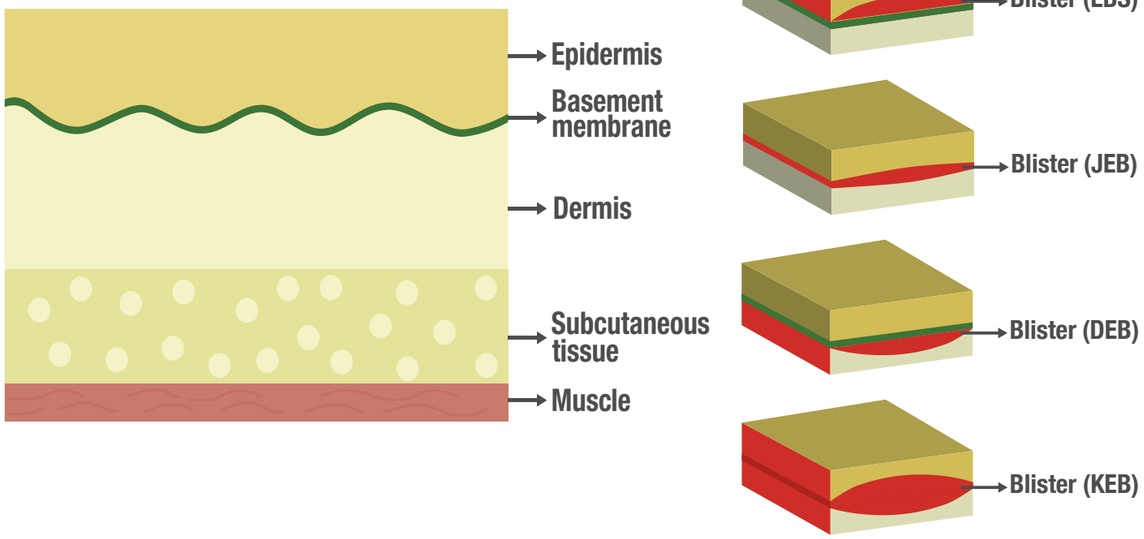
RECOMMENDATION
based on clinical experience



EB is a group of rare genetic disorders characterised by fragility of the skin and mucous membranes, and mechanically induced blistering. EB comprises four main types - EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler EB (KEB); with more than 30 subtypes. EB is clinically heterogeneous including a broad spectrum of severity. In newborns and in people with mild symptoms, determining their EB (sub)type relies on laboratory diagnosis. The inheritance pattern (a parent passing a gene on to their child) cannot be determined without genetic testing in families with a first case of EB.

Classification of EB into four main types is based on where splitting occurs in the different layers of skin. In EBS, splitting occurs within the upper layer of the skin, the epidermis (intraepidermal); in JEB, splitting occurs within the structure that keeps the epidermis and the underlying dermis together, the basement membrane (junctional); in DEB, splitting occurs below the basement membrane within the superficial dermis (dermal); and in KEB, blistering can occur at multiple and different levels within the skin.

Disease-causing (pathogenic) variants in more than 20 genes are associated with EB. These genes contain the information that is translated into proteins such as collagens, laminins, and integrins, which are present in the skin and assure its integrity and resistance.



The image above and to the left shows the structure of the skin with the upper layer being the epidermis, and then progressively lower, the basement membrane, the dermis, and the subcutaneous tissue (fat), which is on top of the muscles. The image on the right shows the main levels of where splitting occurs in EB skin: intra-epidermal, junctional, and dermal.

> When a diagnosis is based on just visual evidence or clinical opinions, it can cause a person to live for years with possibly more pain, more health problems than if they got proper laboratory diagnosis. They could have targeted or custom treatment and know how to look after themselves more effectively. It's easier to prepare for the future when you know for certain what type of EB or health issue you have, in turn making living with EB more manageable.

Lisa Brains, living with recessive dystrophic EB aged 47, Australia

WHY IS EB LAB DIAGNOSIS IMPORTANT?

Laboratory diagnosis is essential to determine the (sub)type of EB and the precise cause at the genetic (DNA) and protein levels.

This is important for someone with EB and their immediate family for:

- accurate genetic counselling
- prediction of disease severity
- informed decision-making
- appropriate global patient care
- prenatal diagnosis
- benefit of specialised medical care and wound dressings
- personalised medicine
- participation in clinical trials
- ongoing treatment

> As a clinician working in EB, sometimes I feel as if I am looking after children with different conditions as each type can vary so much in their presentation and other conditions. Obtaining an accurate diagnosis from birth enables the EB multidisciplinary team to work with families to plan for the future and make relevant decisions about their care package. Some types of EB have a poor prognosis, despite presenting clinically stable at birth, therefore diagnosis is crucial to ensure appropriate management and support. Determining the inheritance of the condition is also paramount for these families who are planning future pregnancies, so that we can support them with prenatal testing processes.

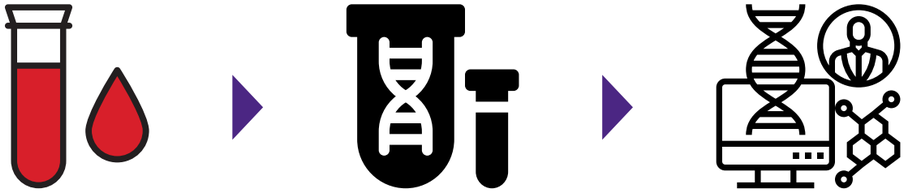
Katie Plevey, Senior EB Clinical Nurse Specialist in association with DEBRA UK, Great Ormond Street Hospital, United Kingdom

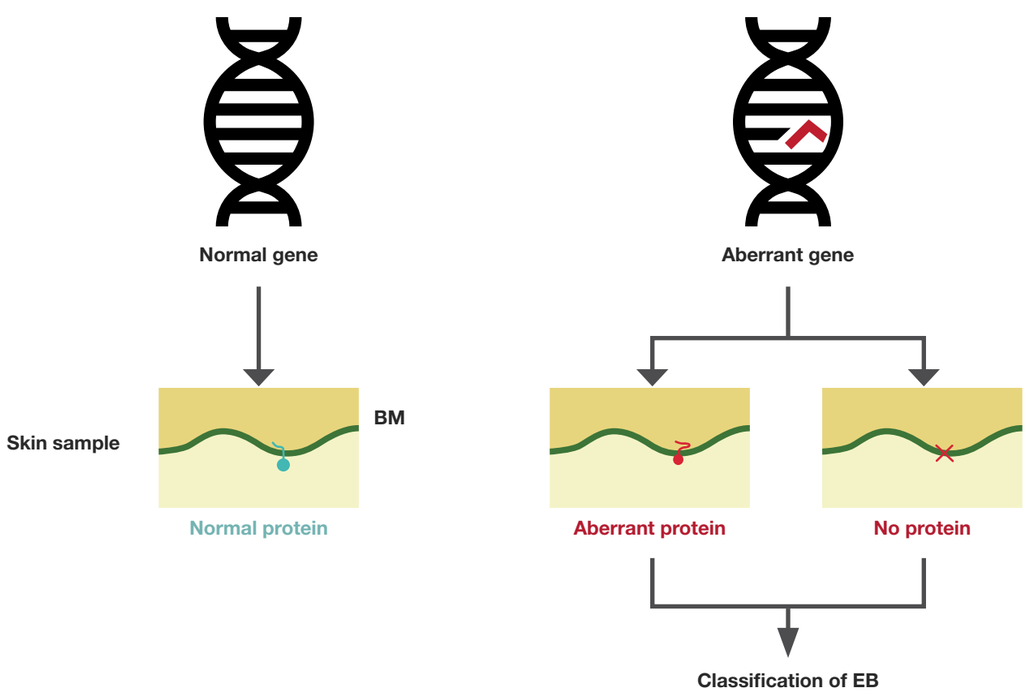
There are two main methods used in EB laboratory diagnosis:

Genetic testing is aimed at identifying the specific disease-causing sequence variant(s) on DNA obtained from a blood sample.

Skin sample analysis using techniques that work on the protein level looks at changes in protein expression, localisation and ultrastructural modifications (changes in skin components that can only be seen by electron microscopy).

Methods for EB laboratory diagnosis





WHAT ARE THE STEPS?

Strong recommendations

- If clinical features are observed and family history are suggestive of EB, laboratory diagnosis is always recommended after informed consent is given by the patient, parents, or legal guardians.
- As a first step, a standard routine evaluation is necessary to rule out other inherited or acquired skin disorders.
- Ideally, both genetic testing on a blood sample and analysis of a skin sample should be performed to allow complete characterisation of EB both at the genetic and protein levels. These methods provide complementary information that enables prediction of the course of the disease.
- When EB laboratory diagnosis is planned, the benefit to people with EB and their families, the availability of different methods, national regulations, and economic factors must be considered. The prioritisation of strategies can shorten the time to diagnose and save resources but requires expertise of the clinicians and of the diagnostic scientists. The following main prioritisation strategies of EB laboratory diagnosis can be considered:

  - In newborns, analysis of a skin sample should be the first diagnostic step because it delivers rapid results. At the same time, genetic testing should always be performed.
  - In cases with typical clinical features, genetic testing by different techniques, in particular Sanger sequencing (SS) or next generation sequencing (NGS), can deliver a final diagnosis.
  - In EB (sub)types with an expected complex genetic background, or in cases with uncharacteristic clinical features, or an unclear cause, genetic testing by NGS is recommended.

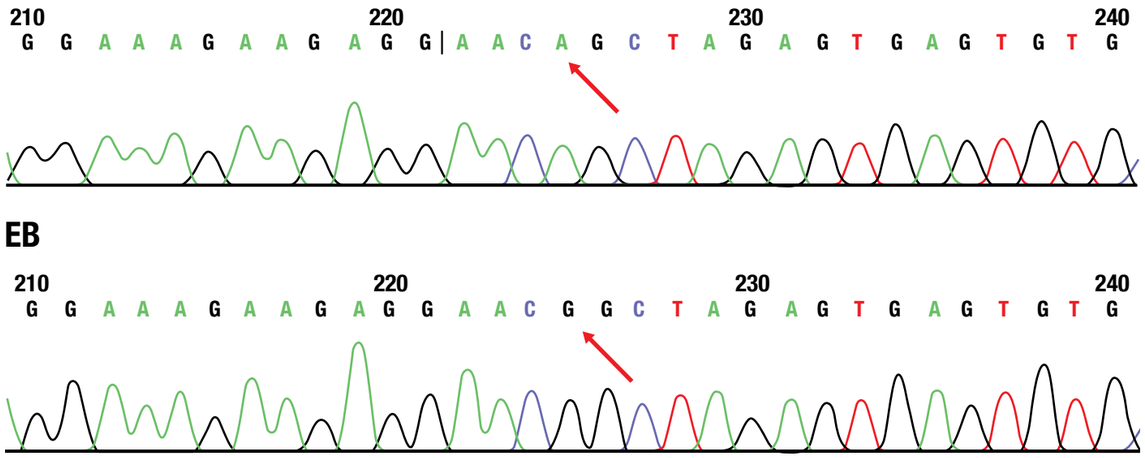
- If a disease-causing variant (or variants) is detected by genetic testing in a person with EB, their parents should be tested to determine the pattern of inheritance. Other family members can be tested to allow genetic counselling.
- If no disease-causing variant (or variants) is detected in a person with EB, the diagnostic steps must be re-evaluated.

Genetic testing

To perform genetic testing, blood samples are taken from the person with EB and their parents. The samples are used for the extraction of genomic DNA.

Genomic DNA contains all the information about our individual genetic make-up. It consists of about 24,000 genes each of which carries a unique sequence code that has a specific function as a protein. The sequence code of each gene is composed of four different molecules called deoxyribonucleic acids (DNA), which are strung in a precise sequence of “letters” A, T, G, and C.

A disease-causing variant (or variants) in EB-associated genes can be detected by Sanger sequencing (SS) of a specific gene or by next generation sequencing (NGS), which can analyse ALL the EB genes at once.



An example of the data generated by SS. The upper panel is the normal DNA sequence and the lower panel is the DNA sequence from a person with EB. The red arrows indicate the normal “A”, and the aberrant “G”, which is the disease-causing variant causing EB in this person.

Recommendation

Genetic testing is always recommended for the diagnosis of EB.

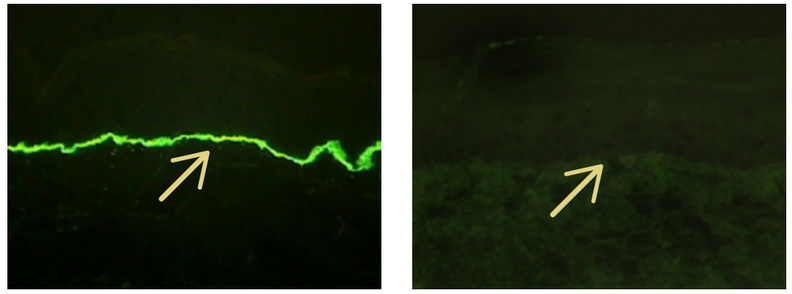
Skin sample analysis

Recommendation

Skin analysis can be done by immunofluorescence mapping (IFM) and/or transmission electron microscopy (TEM).

Immunofluorescence Mapping (IFM)

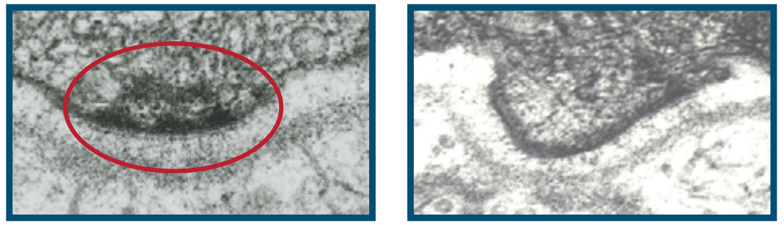
IFM examines the proteins in the skin. EB-associated proteins can be recognised by specific (antibodies) reagents. When compared to a normal skin sample, this technique can show an absent or reduced protein amount.



The picture on the left shows a normal skin sample stained with an antibody that recognises type VII collagen (green line). The picture on the right shows the complete absence of type VII collagen in the skin sample of a person with DEB.

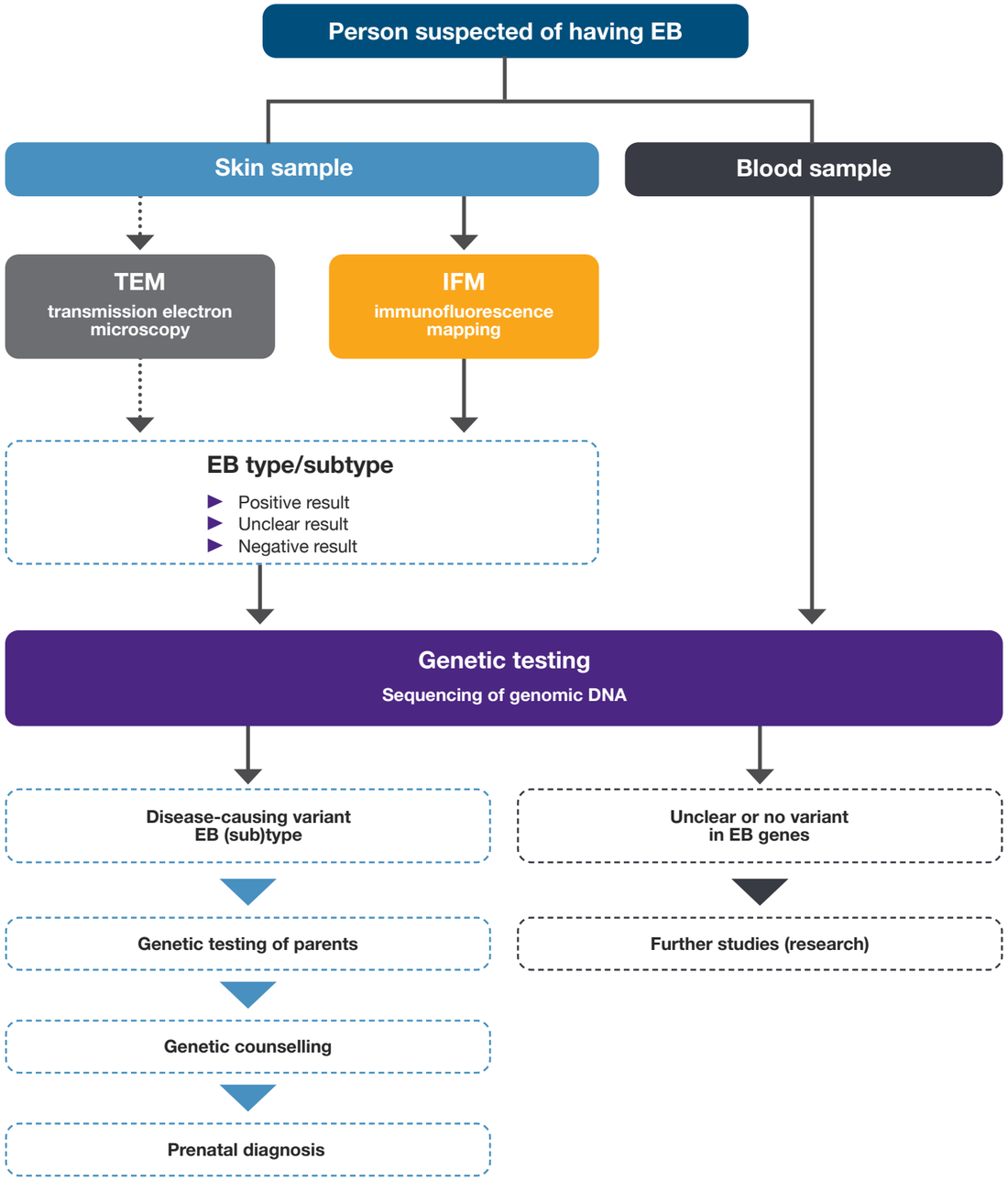
Transmission Electron Microscopy (TEM)

TEM is a technique used to directly examine the skin, the structural components of the skin, which cannot be seen with a conventional microscope (ultrastructure). TEM allows samples to be magnified by as much as 10 million times. It is rarely used in standard EB diagnosis but it can be useful in solving difficult cases.



The picture on the left is from a normal skin sample and the picture on the right is from a person with JEB. The dark structure in the red circle is missing in the patient’s sample.

EB laboratory diagnosis steps



Abbreviations: TEM, transmission electron microscopy; IFM, immunofluorescence mapping

What information should I receive after the EB laboratory diagnosis has been performed?

After each laboratory test is completed, a report will be issued to summarise the results. Whenever and wherever possible, these results will be linked with a patient's clinical features. The laboratory will not usually deliver the diagnostic report directly to the person with EB or to the family. This is to avoid misinterpretation as the report is presented in scientific terms. In accordance with local regulations, the results will be given to the patient and/or their family by genetic counsellors or other specialised personnel. Nevertheless, if a report is directly delivered to a patient or a family member, consultation with a genetic counsellor is always recommended.

There are three scenarios regarding the result from a genetic test:

- **a positive result** means that a disease-causing variant (or variants) has been identified and explains the cause of EB.
- **an unclear result** means that a "new" (previously unknown) variant (or variants) has been identified, and the consequence of this variant is unknown.
- **a negative result** means that no disease-causing variant (or variants) has been identified in EB-associated genes.

Similarly, there are three scenarios regarding the result of IFM of a skin sample:

- **a positive result** means that an EB-associated protein is aberrant or absent when compared to normal skin and that the level of skin separation could be defined, therefore an EB (sub)type has been identified.
- **an unclear result** means that it does not clearly fit to any EB (sub)type.
- **a negative result** means that there is no significant difference between normal and EB skin samples. However, a mild EB (sub)type cannot be excluded.

Recommendation

Results of the EB laboratory diagnosis should be communicated to the patient and family, preferably by geneticists and dermatologists with experience in the field.

Miguel Kingerski da Silva Calgaro, living with recessive dystrophic EB, aged 6, Brazil (photo credit: Suelen Szymanski

Once the disease-causing variant (or variants) has been identified, a person with EB and their family should seek counselling with a genetic counsellor or another specialist. The genetic counsellor should explain to the family:

- what EB is
- the inheritance pattern
- the specific results of laboratory tests
- the prediction of disease severity
- the options for family planning
- the option to perform prenatal diagnosis.

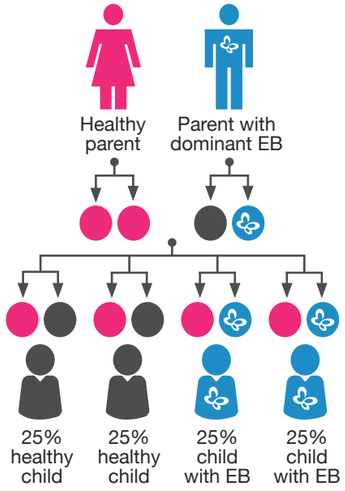
EB can be inherited in three different ways:

- autosomal dominant inheritance
- autosomal recessive inheritance
- *de novo* - in some cases, a disease-causing variant (or variants) causing EB happens spontaneously for the first time in a person. This means that the disease-causing variant (or variants) is not present in their parents' blood.

WHAT IS GENETIC COUNSELLING?

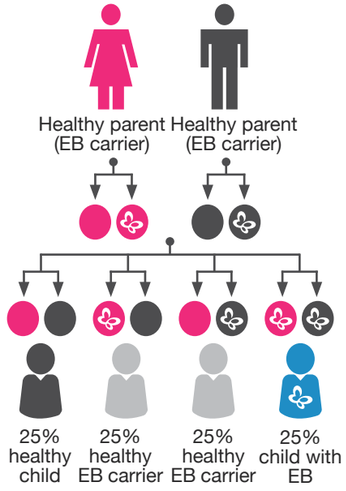
Inheritance patterns in EB

AUTOSOMAL DOMINANT INHERITANCE



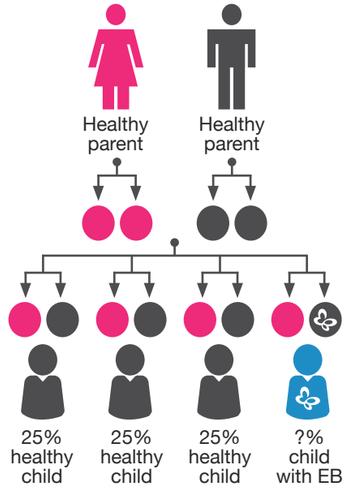
One parent is affected and passes the altered gene on to their child. There is a 50% chance that any child of theirs would be born with EB.

AUTOSOMAL RECESSIVE INHERITANCE



Both parents are unaffected but are carriers of the disease. For any child of theirs to be born with EB, the child would have to inherit the disease-causing variant from both parents. There is a 25% chance of this occurring.

DE NOVO INHERITANCE

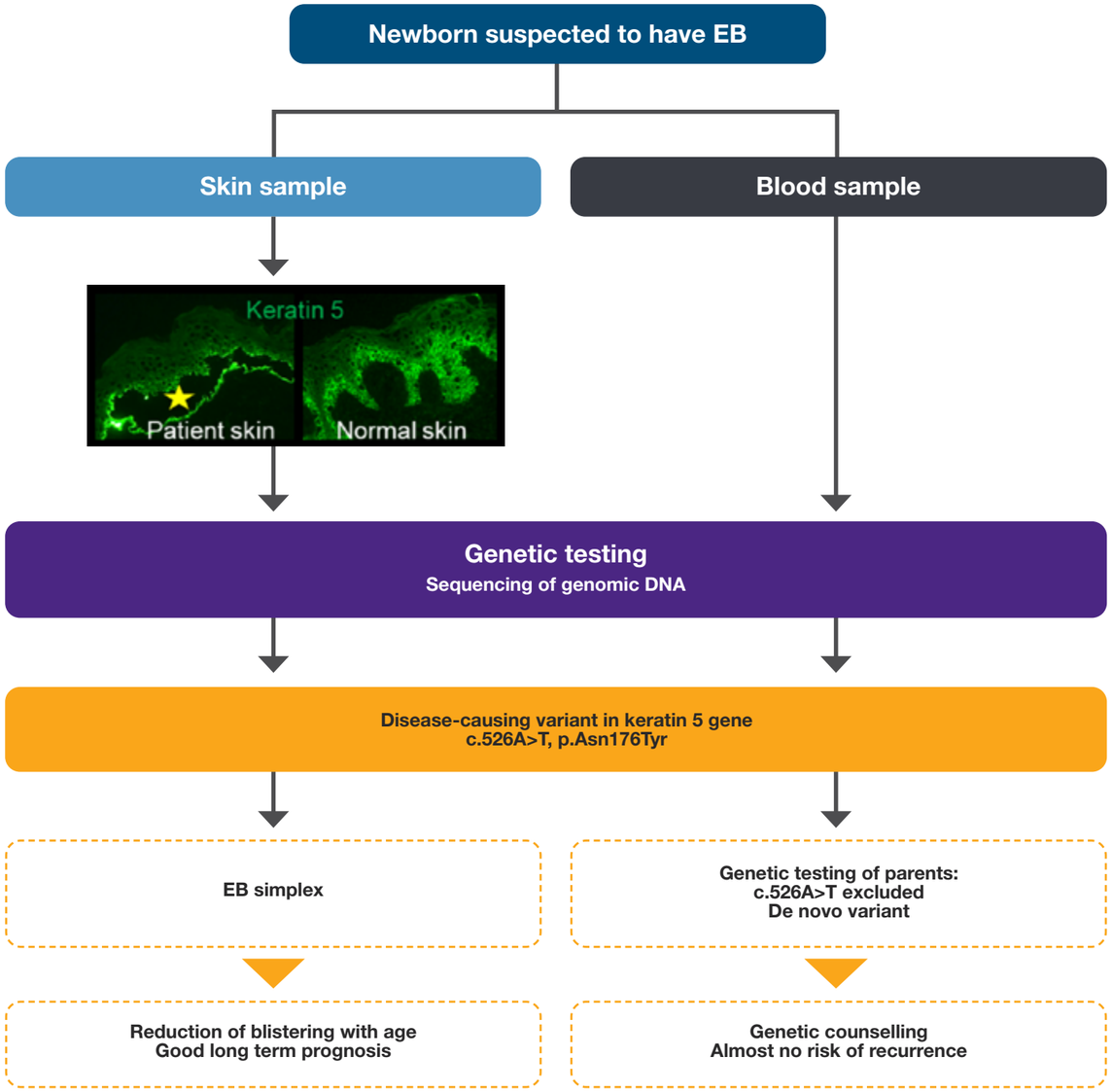


In this situation, having a second child or more with EB from the same parents is very rare. On the other hand, the person carrying a de novo variant has a 50% chance of passing it (and EB) on to their children.

"From a neonatal perspective an early reliable genetic diagnosis can make the world of difference to a family. A confirmed diagnosis can provide information for the family to understand the realistic impact on their life and care requirements looking into the future. It can guide health professionals to appropriate treatment, pain management and wound care. In severe cases it can also help to ensure the family make the most of their time with their newborn with appropriate psychological support. Genetic counselling for families and access to genetic testing is essential in the first few weeks of life with a suspected case of EB."

Rebecca Saad, Clinical Nurse Consultant Epidermolysis Bullosa & Dermatology, SCHN, Sydney, Australia

Steps in EB laboratory diagnosis in a newborn with skin blistering



A newborn baby showing localised absence of skin, blistering, or skin fragility should be referred to an EB diagnostic centre for diagnosis as soon as possible. In addition to a blood sample for the extraction of genomic DNA, a skin sample should also be taken. IFM can provide the diagnosis within hours thus ensuring appropriate newborn care management. Genetic testing is done at the same time. In this baby, EBS was diagnosed allowing a good prognosis. The disease-causing variant was not identified in the healthy parents suggesting its occurrence is *de novo*. Therefore, there is a very low risk of future children of this couple being born with EB.

HOW DOES IT WORK IN PRACTICE?

The following are examples for results presented in a genetic report:

- **Positive result:** “p.Gly2043Arg in *COL7A1* gene is the most common recurrent variant underlying cases of dominant DEB and thus its presence as a heterozygous finding in this patient provides molecular support for this diagnosis.” **CLEAR DOMINANT DEB DIAGNOSIS**
- **Unclear result:** “p.Val848Phe appears to be a new variant; the disease-causing relevance of this change is therefore uncertain. Screening of other family members is likely to be helpful in validating this atypical finding in *COL7A1* as causing disease.” **DEB POSSIBLE**
- **Negative result:** “No evidence of any *COL7A1* disease-causing variant indicative of a diagnosis of DEB.” **DEB IMPROBABLE OR EXCLUDED**

The following are examples for reports of IFM analyses of skin samples:

- **Positive result:** “The absence of laminin 332 in the skin sample of the patient supports the diagnosis of JEB generalized severe.” **CLEAR SEVERE JEB DIAGNOSIS**
- **Unclear result:** “These IFM findings show atypical differences of several EB- associated proteins. These changes are not specifically indicative of any particular EB (sub)type. Thus, no clear cause for the skin blistering can be established. TEM and NGS would be useful to search for diagnostic clues.” **EB POSSIBLE**
- **Negative result:** “There is no clear indication to suggest a diagnosis of epidermolysis bullosa in this sample.” **EB IMPROBABLE**

“I married my Mars bar giving, swarthy Maltese boy who is now a deeply caring and compassionate man. We started to talk about having a family. I spoke with Dr Eisenberg and underwent extensive genetic counselling. He told me that there was a 50% chance I would pass the condition on to my child. I was torn. I DESPERATELY wanted to be a mum. I gambled with the future of my family and decided with Jeff to try anyway.

On 24 March 2005, although there was a substantial risk, I gave birth to a boy. …. our paediatrician checked him over, announced he was EB free and handed our little miracle bundle to me.

That afternoon I called Dr Eisenberg to tell him we’d delivered a healthy baby boy. “What’s his name?” he asked.”

Nina Azzopardi, living with EB simplex, aged 48, Australia

WHO SHOULD PERFORM THE DIAGNOSIS?

Strong recommendation

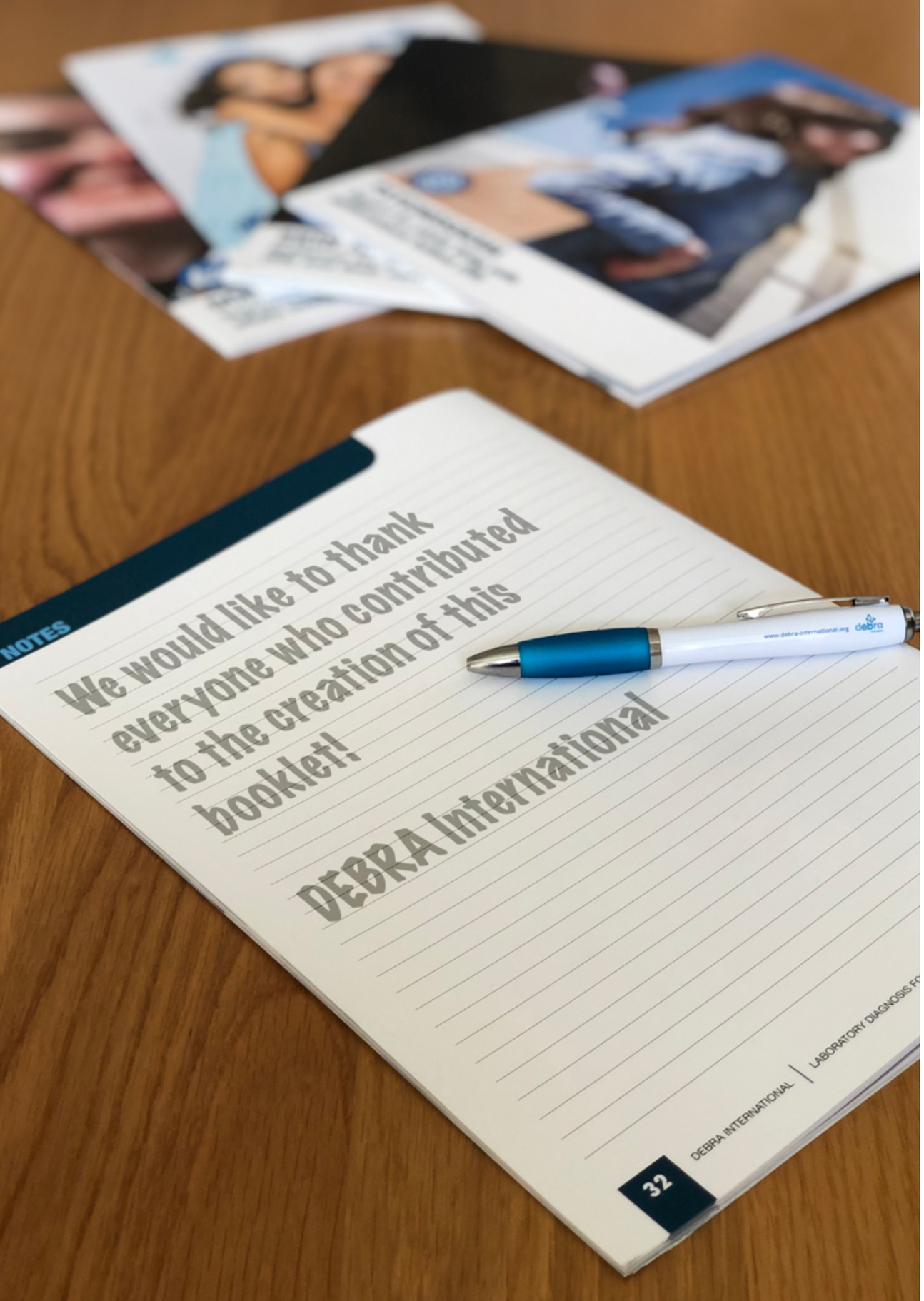
It is strongly recommended that EB laboratory diagnosis be performed in a laboratory with documented specific expertise and experience in the field, and which is accredited.

Any laboratory that undertakes EB diagnosis is therefore recommended to consider the testing criteria formulated and agreed by the “Clinical practical guidelines for laboratory diagnosis of epidermolysis bullosa” (Br J Dermatol. 2019 May 15. doi: 10.1111/bjd.18128.)

However, there are vast variations and differences among EB clinical and diagnostic centres around the world with respect to the diagnostic equipment and methods available, and also between the national health system regulations governing rare disease care and genetic testing, and reimbursement for these services. Therefore, it may be difficult that all the criteria set out in the publication above are met. Such situations may require EB clinicians and diagnostic scientists to make a reasonable adjustment, provided that such adjustment does not deviate significantly from the guideline.

Photo credit and copyright: R. Hamentner

Acquired skin disorders	Not inherited, or present at birth (congenital), but developing after birth due to a gene mutation affecting the skin structure.
Antibodies	A blood protein produced in response to and counteracting a specific antigen. Antibodies combine chemically with substances which the body recognises as alien, such as bacteria, viruses, and foreign substances in the blood.
Clinical features	These are sign of a health problem that can be observed by someone else. A symptom is an effect noticed and experienced only by the person who has the condition. The key difference between features (signs) and symptoms is who observes the effect.
Clinically heterogeneous	Defined as differences in participant, treatment, or outcome characteristics or research setting
Electron microscopy	A microscope with high magnification and resolution, employing electron beams in place of light and using electron lenses
Mechanically induced blistering	A group of inherited disorders characterised by mechanically induced blistering occurring within the epidermis itself as a result of lysis of basal keratinocytes
Mucous membranes	Mucosa is a membrane that lines various cavities in the body and covers the surface of internal organs. It consists of one or more layers of epithelial cells overlying a layer of loose connective tissue.



Tell us what you think

Have your say in the future patient versions of clinical practice guidelines (CPGs) for epidermolysis bullosa (EB)

The purposes of this survey are to:

- assess the quality of the information, presentation, and delivery of the patient versions
- help us to develop a standard for all patient versions now and in the future.

The data collected will help us to improve the information provided and experience of the user in all future CPG patient versions. The data may be used to report the development steps taken to improve their quality; this may be done through conference presentations, posters, abstracts, or studies.

We want to make sure that all patient information provided meets the needs of everyone living with EB.

Help us create new CPGs and patient versions

All responses to the above survey are confidential unless you decide to join the DEBRA International CPG network. Please consider joining the network if you are interested in becoming involved in the development of CPGs and patient versions in the future. To join the network, please complete question 1 on page 7. If you do not complete this question, we will not receive any of your personal details and you will remain anonymous. Joining the CPG network is entirely voluntary and you may choose to opt out at any time by contacting DEBRA International.

If you have any questions when completing this survey or about joining the CPG network, please contact the DEBRA International CPG Coordinator, Kattya Mayre-Chilton by email at: kattya.mayre-chilton@debra-international.org

TELL US WHAT YOU THINK!

Answer the survey to help us improve the patient versions of the CPGs:
www.surveyhero.com/c/PatientVersionsSurvey

Luan Almeida Rocha, living with dominant dystrophic EB, aged 19, Brazil (photo credit: Douglas Rocha de Almeida)

Disclaimer

The information contained in this booklet does not indicate an exclusive course of action or serve as a standard of medical care. Variations, taking individual circumstances into account, may be appropriate. The authors of this booklet have made considerable effort to ensure that the information contained within accurately reflects the content of the guidelines on which it is based. The authors, DEBRA Austria, and DEBRA International accept no responsibility for any inaccuracies, information perceived as misleading, or the success of any recommendations, advice, or suggestions detailed in this booklet. The information provided on the following pages is subject to change without notice. For the most up-to-date information on available clinical practice guidelines, booklets, and contact information, please visit: www.debra-international.org

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Development source

Clinical Practice Guidelines for Epidermolysis Bullosa Laboratory Diagnosis.

This CPG was approved by DEBRA International and funded by DEBRA Austria.

To access the following CPGs and patient version booklets, please visit: www.debra-international.org

Other CPG topics

- Foot care in Epidermolysis bullosa: Evidence-based Guideline
- International Consensus Best Practice Guidelines for Skin and Wound Care in Epidermolysis Bullosa
- Management of Cutaneous Squamous Cell Carcinoma in Patients with Epidermolysis Bullosa: Best Clinical Practice Guidelines
- Occupational therapy for epidermolysis bullosa: clinical practice guidelines
- Oral Health Care for Patients with Epidermolysis Bullosa - Best Clinical Practice Guidelines
- Pain care for patients with epidermolysis bullosa: Best care practice guidelines
- Psychosocial recommendations for the care of children and adults with epidermolysis bullosa and their family: evidence based guidelines

Other languages

We are happy to consider requests for this booklet to be provided in other languages. Please send all enquiries to: office@debra-international.org

How was the Laboratory diagnosis guideline produced?

- The CPG development group consisted of EB experts: dermatologists, paediatric dermatologists, geneticists, biologists, a nurse, and patient representatives.
- All panel members completed written conflict of interest and code of conduct declarations.
- During guideline development, the group met twice in face-to-face meetings to discuss the clinical questions and methodology; to review the evidence (publications in the field of on EB diagnosis research); formulate recommendations; and agree on the guideline's structure and wording.
- CPGs are based on a critical, extensive, and exhaustive review of the most relevant publications in the field of EB laboratory diagnosis together with the personal experiences of the panel members.
- To identify publications, a search of NCBI "All Databases" and PubMed was performed using the terms "Inherited EB and laboratory diagnosis", "EB and mutation", and "EB and prenatal diagnosis" with the search period ending December 2018. In addition, "Epidermolysis bullosa" was used to search articles in GeneReviews.
- A total of 1,485 articles were identified. Finally, 64 papers were appraised, each by two panel members, according to the Critical Appraisal Skills Programme (CASP) and Scottish Intercollegiate Guidelines Network (SIGN) quality rating.

Panel group

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CONTACT INFORMATION

DEBRA International

DEBRA International is the umbrella organisation for a worldwide network of national groups that work on behalf of those affected by the rare genetic skin blistering condition, epidermolysis bullosa (EB). The first DEBRA was created over 40 years ago and is present in over 50 countries around the world.

www.debra-international.org
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EB Without Borders

EB Without Borders is a key initiative of DEBRA International. Its mission is to help patients, families, and doctors in countries where there is no DEBRA structure to support them, and to assist new groups to form and develop.

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EB-CLINET

EB-CLINET is the global clinical network of EB centres and experts.

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