Epidermolysis Bullosa Early Phase Research and Innovation Report

Authors: **Rhiannon Potter, Katie Twentyman, Fiona Pearson, Sonia Garcia Gonzalez-Moral, Adetutu Sadiq, Alex Inskip, Hannah O'Keefe, Chizoba Oprah, Nick Meader, Gill Norman, and Fiona Beyer**

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Professor Dawn Craig
Director

T: +44(0) 191 208 2259
E: info@io.nihr.ac.uk
www.io.nihr.ac.uk

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Mapping the Landscape of Epidermolysis Bullosa Research

Preclinical landscape

- Gene editing therapies
- Gene expression regulation
- Strategies to downregulate inflammation

Future innovations are thought to involve protein replacement and combination therapies

Trial Data

50% of trials focus on symptom management

44% of trials evaluate dressings

- Most trials enrol both children and adults
- 2 clinical trials involve gene therapies
- 5 clinical trials are cell based therapies

Funding

£3.2M in funding from the NIHR across 4 projects

34 funding grants identified in the UK

Debra funded 22/34 projects found

26% Of funded projects were investigating gene therapies

Interventions found

8 would require a clinical setting

7 could be delivered in a home setting

Phase I → Phase II → Phase III → FDA Licencing

- Despite attempts, only few technologies progress past phase II testing
- Only one technology has received FDA licencing

Background

What is Epidermolysis bullosa and how common is it within the UK?

Epidermolysis bullosa (EB) is a rare genetic disorder of the skin whereby blisters and wounds occur from minor friction and trauma. There are four main types of EB and they vary in symptom severity: milder cases involve blistering on the hands and feet alone, whereas in severe cases the blistering is widespread and can affect the internal organs.[1] The UK prevalence of all EB types has been estimated to be 34.8 per million with an incidence of approximately 67.8 cases of any type per million live births.[2a]

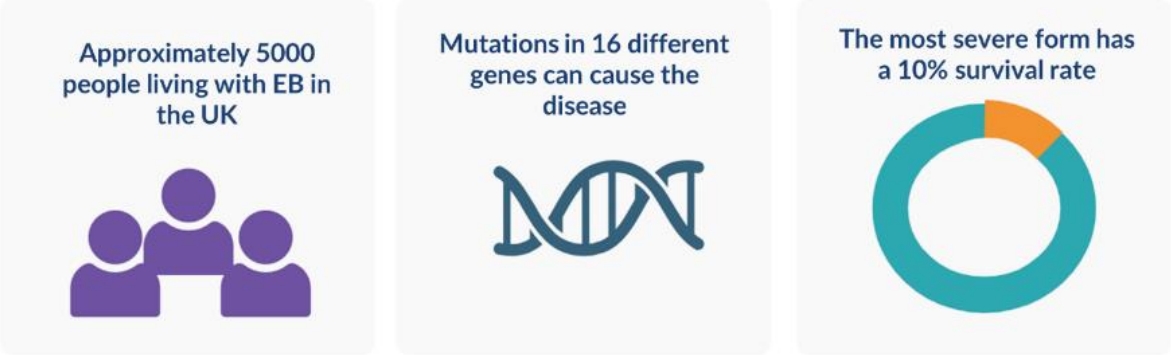

Figure 1: Key facts about EB

Current treatment

There is no cure for EB and current treatments are restricted to symptom alleviation.[2] The aim of treatments is to help avoid skin damage, improve quality of life and reduce the risk of developing complications such as infection and malnutrition. Wound care and pain relief are the most common treatment types, often using interventions such as birch bark extract to speed healing of partial thickness wounds (ones that that affect only the top 1-2 layers of skin e.g. blisters or abrasions[3]). Other interventions include providing advice on behaviour changes that can help to avoid skin trauma, such as wearing loose clothing made from breathable fabrics, and only walking short distances to avoid blisters forming on the soles of the feet.[4]

Unmet needs

Patients with EB report profound effects on their quality of life due to chronic symptoms, incurred treatment costs, reduced work/school productivity and low-mood states, amongst an array of factors. Complications, such as aberrant wound healing, scarring and infection, as well as the psychosocial impact, mean that this disease is clinically challenging and requires expert multidisciplinary management. The prominent unmet need in EB is the lack of a cure or treatments that target the disease itself rather than symptoms, therefore not reducing the burden of the disease.[5]

Methods

Search strategy

Results from the literature, trial, and funding searches all represented technologies or research that has the potential to gain UK Market Access e.g. carried out by a UK company/researcher, UK trial locations, or UK data presented.

Preclinical landscape

A simple targeted search of PubMed for articles published in 2010 or later describing *in vivo* research on EB (("Epidermolysis Bullosa"[Title]) OR (Epidermolysis Bullosa[MeSH Terms])) AND ("in vivo"[Title/Abstract]) was performed to map networks of keywords.

Reviews

A simple targeted search of Embase (Ovid) for review articles published in 2014 or later assessing therapeutic interventions for EB (exp *epidermolysis bullosa/dt,th) was run, with a sensitive UK filter applied.

Trials

Trial registries (Clinicaltrials.gov, the EU Clinical Trials Register, EU Clinical Trials Information System), and registry data platforms (ScanMedicine and ISRCTN) were searched for trials involving EB (plus a limited number of relevant synonyms) with UK relevant trial sites and no date restriction. The trial identifiers and acronyms of identified trials were searched on Embase (Ovid) to identify published trial results. Trial data were then standardised.

Screening and data extraction

Single reviewers screened identified records to ensure they were for health technologies aimed at improving health and care outcomes for those with EB. Single reviewers then extracted data from trial and funding registries for each record to ensure capture of the minimum set of required data items. These were pre-agreed by the research team.

Methodological limitations of approach

This work was undertaken using an ultra-rapid approach. Although undertaken using a systematic approach, processes within the cycle of conducting a horizon scan have all been abbreviated, limiting our certainty about the evidence presented. There has been no formal quality assessment of the information included within this innovation briefing and no quality assurance processes have been undertaken as part of the methodological approach. As a result of this approach, results should be interpreted with caution.

Results

Preclinical landscape

Evolving understanding of the complexity of EB disease mechanisms is important for the development of innovative treatments. We visually mapped the co-occurrence networks of keywords from all identified records of *in vivo* research on EB (figure 2). The most common term clusters were relevant to gene editing therapies, gene expression regulation and inflammation. Other clusters identified include terms related to skin cancer, and to the population of patients with age and gender frequently mentioned.

Clinical research and innovation landscape

Trials

We identified 18 clinical trials that evaluated 13 unique technologies.[6-23] Nine trials were funded by industry and nine were funded by other sources including government or academic institutions. We identified three phase I trials, four phase I/II, three phase II, three phase III, one phase IV, and four trials with an unknown phase. Two technologies that are currently being tested in clinical trials have EMA orphan designations for EB.[24,25]

Trial populations

Nine trials recruited people with recessive dystrophic EB, two EB simplex, one junctional EB and six trials recruited people with EB across sub-types. Twelve trials included paediatric and adult populations, three recruited only children and the remaining three recruited only adults.

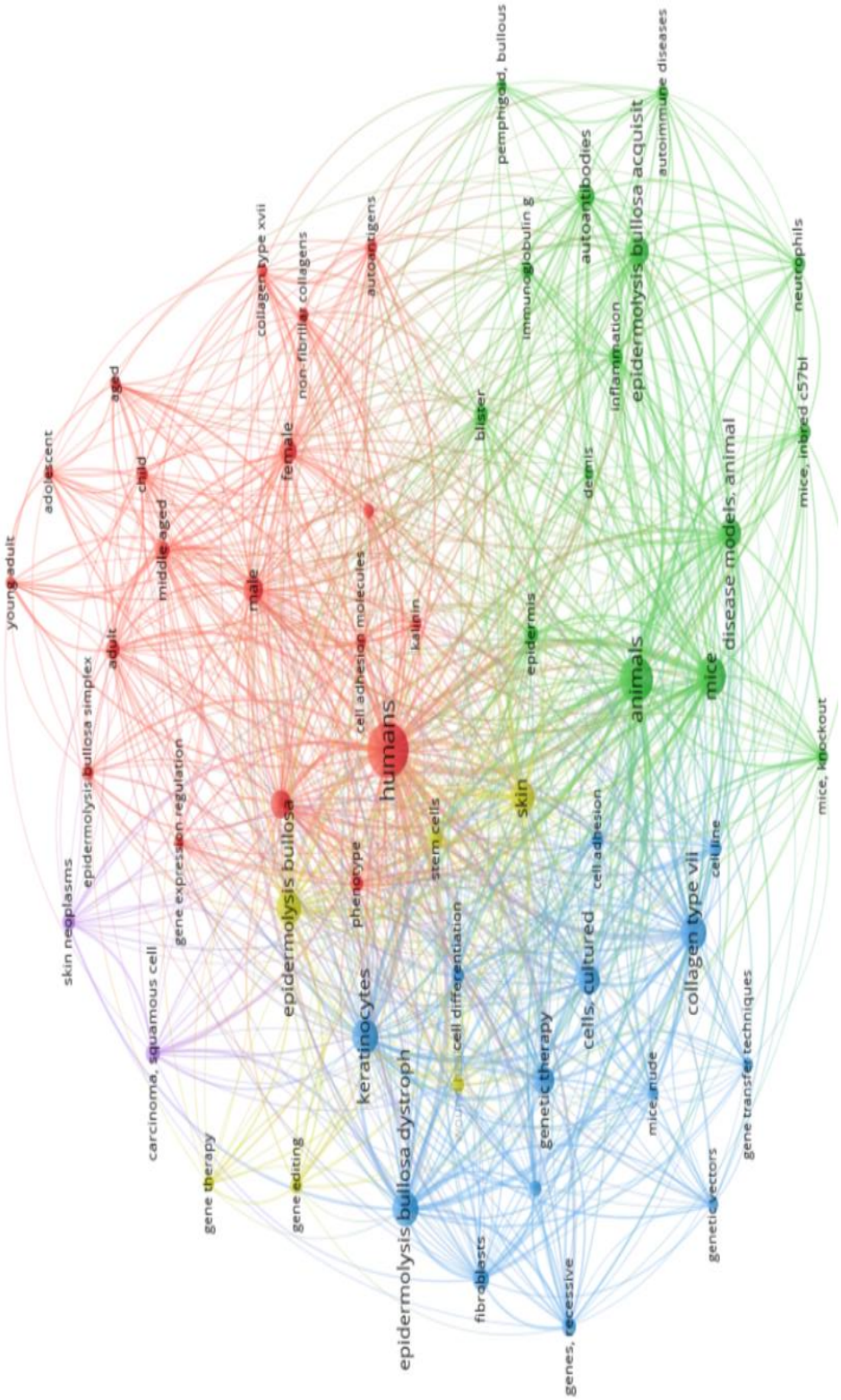

Figure 2: Visualisation of key word use within in-vivo EB research. Cluster size is determined by the frequency each term was identified and colour use denotes groupings

Types of interventions

Eight trials evaluated dressings with or without active treatment, including topical treatments. Amongst these eight trials, zorblisa cream and diacerein 1% ointment are being evaluated in two and three trials respectively. A single trial evaluated oral Amitriptyline for analgesia.

Seven trials evaluated stem cell transplants (n=5) or gene therapies (n=2) to treat underlying mechanisms of EB disease. They use approaches such as increasing production of collagen VII to increase skin strength, hence increasing the time between blistering and reducing disease severity. Two trials are for phenotyping (categorising the presentation) for disease severity and to identify the prognosis of intervention immune tolerance (calculating dosages of interventions before side effects occur).

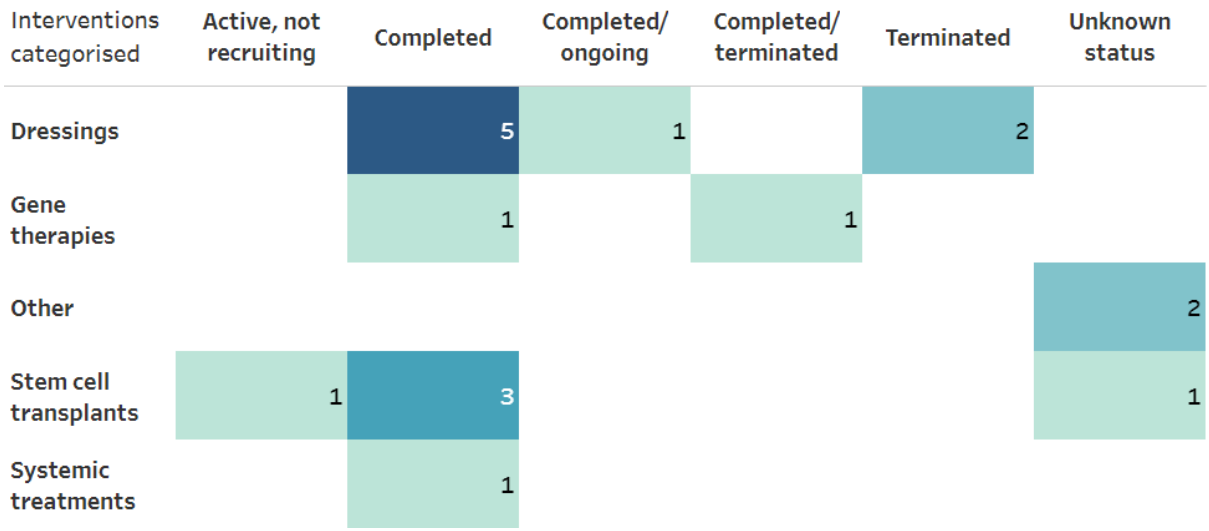

Figure 3: Visualisation of intervention type by trial status

Mode of intervention delivery and position in care pathway

Nine interventions were topically administered (applied to skin), four via intravenous infusion (into the vein), two via intradermal injection (injected into the skin), and one via oral administration.

We mapped each intervention to the EB care pathway.[26] Eight interventions need to be carried out by clinicians in a clinical setting, whereas seven could be carried out by the patient or carer at home, and three interventions were not clear about administrators or delivery setting.

Target outcomes for interventions

Outcomes across the trials varied across and within groups of interventions. Eleven trials focused on interventions to improve EB symptom management, such as skin wounds and blistering, improve the strength of fragile skin, reduce pain, itching and inflammation and improve quality of life. Two trials focused on collagen production/expression within the skin and how that changes with the treatment. Two looked at both symptom management and collagen. Two trials studied pharmacokinetics of the therapies delivered. One trial collected data pertaining to genotypes and phenotypes of patients.

Funding landscape

We identified funding records for 34 active or completed projects on EB. The biggest proportion of total funding spend on EB research in the UK is from the National Institute for Health and Care Research (NIHR). NIHR have funded four projects for a total of £3,240,328, one of which is on-going.[27-30] DEBRA UK, the world's first patient support group for people living with EB, has a total current research

investment portfolio of £2,483,814.[b] This funds 22 projects that are ongoing or due to start soon. Eight of those projects are sponsored by international organisations and the rest by UK research institutes within universities.[31-52] CureEB, a UK charity organisation dedicated to ending painful skin, has funded four active projects for a total of £1,109,042.[53-55] Other funding for EB research has been awarded by the EB Medical Research Foundation (a US charity) the Wellcome Trust (£226,841),[56] and the Medical Research Council (£304,154).[57] Much of the money has been awarded to research based at King's College London.

Where the funding centre was specified and identifiable, nine were hospital-based specialist dermatology services, four were diagnostic genetic services, two hospital ophthalmology services. The remaining ones did not fall into any specific category.

Types of intervention

Gene therapies comprised the largest proportion (26%) of all funded interventions. These included therapies for gene transfer, replacement, and editing for genes coding for skin and connective tissue proteins. Therapies are delivered topically, by injection or other means to improve skin symptoms, wounds, blisters, and skin strength.

Seven funding calls concerned systemic treatments such as steroids, biologics, other standard or experimental treatment, and five concerned stem cell therapies. Two calls covered interventions in each of the following areas: dressings and topical treatment (with or without active treatment), MedTech (medical devices) and supportive interventions such as psychological support for patients and carers.

Seven funding calls did not fit into an intervention category, as the related projects described exploratory objectives for further understanding the disease area, to potentially develop an unspecified intervention in the future.

No funding record was found for skin grafts, for either artificial or cultured skin products.

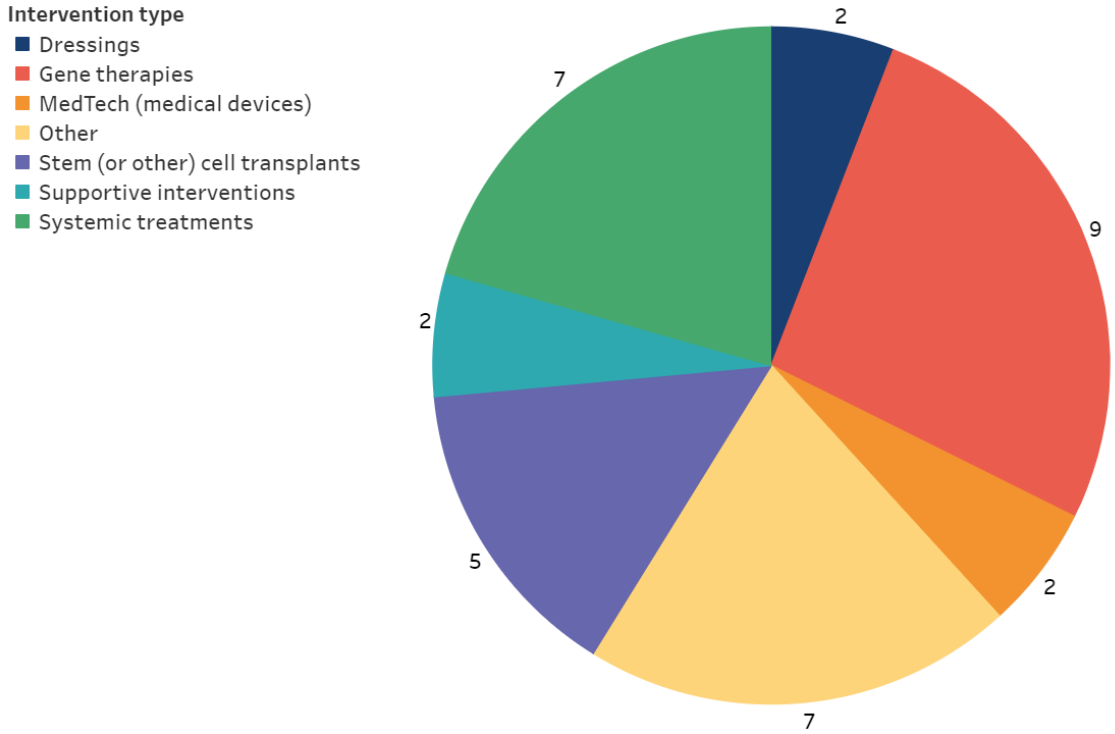

Figure 4: Number of grants awarded by intervention type

[b] Some grants were awarded in Euros. Currency conversion was carried out September 11th 2024 with a rate of £1=€1.19

Target outcomes for innovation

Many interventions found via the funding searches aimed to relieve symptoms such as skin wounds and blistering, improve the strength of fragile skin, and reduce pain and itching. The innovations identified in the trials registry focus on symptom management including pain (including at dressing change), wound healing and itching.[58]

Position of interventions in care pathway

We mapped each intervention to the EB care pathway[26] and found that, where stated, the majority of services were delivered in hospital-based specialist care departments: especially dermatology, genetics and ophthalmology specialist services.

Clinical guidance published in the last 10 years

Four clinical guidelines were identified, intended for use by surgeons, occupational therapists, physiotherapists, hand therapists and doctors working in hospital settings and in the community.[59-62] They aim to aid healthcare provision at every stage of EB disease from mild disease through to severe disease and palliative care. Many of the guidelines highlight the importance of using a multidisciplinary approach when treating EB to maximise quality of life for those living with the disease.

The National Institute of Health and Care Excellence (NICE) issued a highly specialised technologies guidance in 2023 on birch bark extract for the treatment of EB.[63] This recommended use as an option for treatment of partial-thickness wounds associated with dystrophic and junctional EB in adults and children aged over 6 months.

Summary of narrative reviews

Forty-two results were returned from this search.

Eight narrative reviews were identified which mainly discussed gene and cell therapy as key promising interventions. They also identified factors hindering translation of innovative technologies into clinical practice such as the cost of personalised medicine and safety risks that can occur with gene therapy. [64-71]

Continued advancement in gene therapy approaches were seen to hold promise for curing EB. This is reflected in the trial and funding landscape. Cell therapy (such as stem cell, allogenic fibroblasts, skin/keratinocytes, mesenchymal stromal, induced pluripotent stem cells (iPSCs) and bone marrow-derived mesenchymal stromal cell-based cell therapy), was described as offering regenerative potential for damaged skin.[64] This was reflected to some extent in identified UK funding calls. RNA-based therapy was described as mostly at preclinical stages of development.[66] Protein replacement therapy symptom relief was also described, and aims to restore deficient or dysfunctional proteins in EB patients to improve skin integrity and function.[64-66]

Reviews stated that gene, cell and protein therapy need to optimise methods for efficient, specific, and sustained delivery. This needed to be developed alongside improved modes of delivery and strategies to better modulate immune tolerance mechanisms to minimise adverse reactions. Despite advancements in gene editing and other technologies, there are still limitations in scalability (infrastructure and cost), efficiency, and safety that need to be addressed before therapies can be widely implemented in clinical practice.[65,67,69]

Reviews also covered therapies targeting secondary inflammatory pathways or fibrosis e.g., laser therapy or medications such as losortan which could help alleviate symptoms and improve wound healing in EB patients. Inflammation, fibrosis, pain and itch could be improved by repurposing medicines or developing drugs *de novo* for EB. Calcipotiol, JaK inhibitors, cannabinoids, biologics, methotrexate, small molecules, and biologics were all specifically mentioned for EB management. Infection control, surgery for

contracture and treatment for squamous cell cancer, which has very high incidence in EB, also all featured.[65,66,68,70]

Ahead of a curative approach, optimal treatment for EB is likely to involve combinations of different therapeutic modalities, including gene, cell, protein, and drug-based approaches. Reviews recommended tailoring treatment regimens to individual patients based on their specific genetic subtype, clinical phenotype, and disease severity. They acknowledged the need for a deeper understanding of molecular mechanisms (a need for more basic research) to develop curative or more effective treatments. As EB is a rare disease, there are challenges posed in conducting clinical trials due to the small patient population: specifically recruiting enough participants to meet sample size requirements and costly prolonged trial duration. It was, however, recognised that demonstrating the long-term efficacy and safety of EB treatments is crucial for their adoption in clinical practice.[71]

Discussion

The landscape of research and clinical trials for EB in the UK reveals both significant progress and persistent challenges. As highlighted, there is a profound unmet need for treatments that address the underlying causes of EB rather than merely alleviating symptoms. Current treatments, while essential for improving quality of life and managing complications, do not provide a cure or halt disease progression, leaving patients with a lifelong burden of care.

The preclinical and clinical research landscapes demonstrate a promising shift towards innovative therapies, particularly in gene and cell therapy, which hold the potential for more targeted and curative approaches. The dominance of gene therapy in both preclinical research and funding initiatives indicates a strong focus on addressing the genetic basis of EB, reflecting the evolving understanding of the disease's complexity. This matches discussion within narrative reviews which summarise treatments in preclinical and early phase clinical development and feature these technology types prominently.[64-71] The narrative reviews also identified protein therapy and combination therapies as well as further technologies for symptom relief and treatment of complications. A small number of technologies have received designations from regulatory bodies (e.g., orphan drug status) but most are in early (at phase I/II stage) development or are represented by small numbers of case studies; many more are represented by rodent models only. These therapies are also well represented in the UK funding landscape.

In conclusion, while the research landscape for EB is advancing, particularly in the areas of gene and cell therapy, there are still significant challenges and research to be done before these could have the most benefit to patients: many research projects have not yet even begun. This report offers a snapshot of the current research and funding landscape for EB, highlighting both the progress made and the change in focus from symptom-based to potentially curative treatments.

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