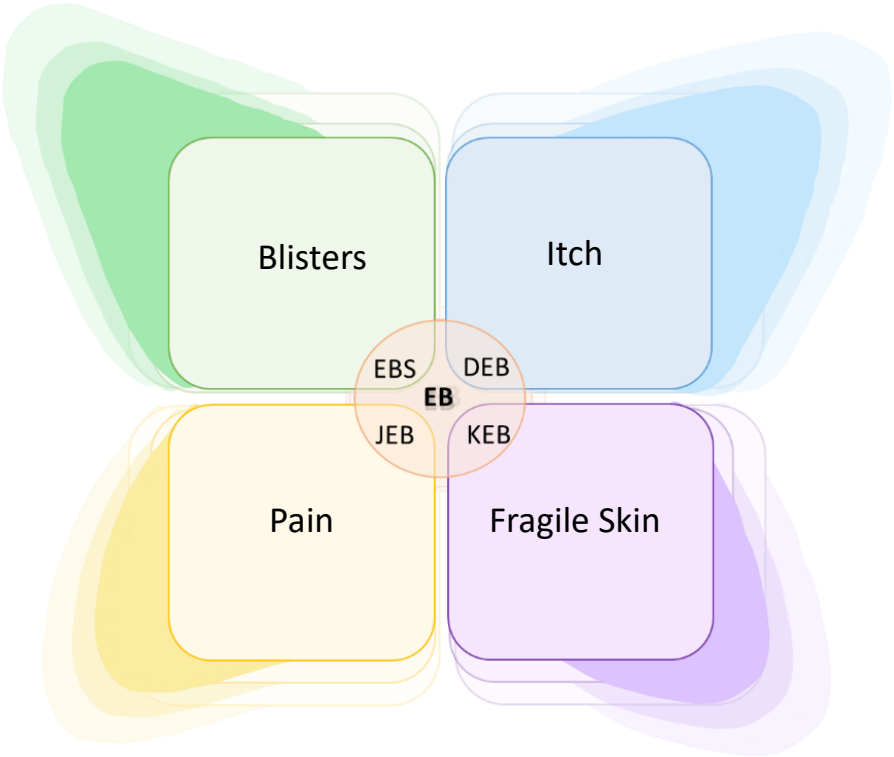
The patient's perspective: a review on epidermolysis bullosa patients' needs as input towards harmonization of outcomes



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Abstract

Epidermolysis Bullosa (EB) comprises a heterogenous group of rare genetic skin disorders, characterized by blistering. EB is classified in four major types: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler EB (KEB), originating from various pathogenic variants and resulting in phenotypic diversity. Despite recent advancements in EB research and therapy, no cure exists, and treatments primarily focus on symptomatic relief. However, the variability in symptoms across EB types poses challenges for consistent assessment of therapeutic targets for clinical trials. A semi-systematic literature search was conducted, encompassing PubMed (MEDLINE), the Orphanet Journal of Rare Diseases, and EB patient organization websites. Studies reporting patient perspectives, including symptoms, impaired abilities, and daily life functions, as well as emotional and social impacts, were included. Pain and itch emerged as the most prevalent and impactful symptoms across major EB types, with itch particularly pronounced in recessive DEB. In EBS patients, pain, and blisters under the soles of the feet led to impaired mobility and reduced quality of life. KEB patients experienced the burden of blisters and fragile skin. DEB and JEB patients experienced wound burdens characterized by size, pain, and slow healing. Impaired sleep and reduced mobility were identified as the most impactful factors reducing quality of life across EB types. However, current outcome domains in EB clinical trials inadequately represent patient-reported outcomes, notably itch, pain, mobility impairments, and sleep difficulties. Specific symptoms, such as neuropathic pain in EBS, scalp blistering, hair loss in JEB, swallowing difficulties, and skin cancer in DEB, are underrepresented in measured outcomes. Our findings offer an overview of needs and disease burden experienced by EB patients of the major types and may serve as a basis for defining core outcome sets in future COSEB meetings. Ultimately, we aim to contribute to the harmonization of outcome domains in EB to enhance the comparability and efficiency of future research and clinical trial design.

Plain language summary

Epidermolysis bullosa (EB), also known as butterfly skin disease, is a rare genetic condition that makes the skin fragile and prone to blister formation. The fragility of the skin is comparable to the delicate wing of a butterfly, where minor friction and force applied to it cause ruptures. EB is caused by faulty genes that affect the production of important proteins responsible for holding the skin layers together, leading to the easy tearing of those layers and blister formation. Different missing or faulty proteins in various skin layers lead to the classification of EB into four types. Symptoms vary among EB subtypes, ranging from localized blistering on hands or feet to widespread blistering and affecting internal organs.

Currently, there is no cure for EB, and treatment focuses on symptom relief for patients. Before new treatments or medicines can be available to the public, doctors and researchers conduct clinical trials to test their safety and effectiveness. To compare treatments across clinical trials it is important to measure in a consistent way how the treatment affects the patient's health and improves their symptoms. However, comparing treatments across clinical trials for EB is challenging due to variations in symptoms among EB patients. Therefore, it is not surprising that there is currently an inconsistency in what is measured in EB clinical trials. This inconsistency makes it difficult to compare and evaluate different treatments for EB. To address this challenge, a collaborative effort aims to define consistent measures in EB clinical trials. Patient perspectives are crucial in this process for understanding how the disease impacts their lives.

To understand the corresponding needs and perspectives of EB patients, we performed a literature search across a scientific database, patient organization websites, and a specific journal for rare diseases. We selected articles describing the results of patients' surveys or interviews to understand their needs and perspectives regarding the most impactful aspects of their disease. We found that pain and itch were the most common and impactful symptoms experienced by EB patients, often related to skin conditions such as wounds or blisters. Blisters under the soles of the feet were particularly impactful for one of the milder EB types (EBS), leading to reduced mobility and reduced quality of life. Whereas patients with other EB types (DEB, JEB) experienced pain related to different wound characteristics, such as the size and slow healing of wounds. Despite variations in symptoms between EB types, all patients experienced difficulties in sleeping and mobility. When comparing patient-reported needs to what was measured in past clinical trials, we found that skin-related symptoms like wounds and blisters were well-covered, while pain and itch, along with EB-type-specific symptoms, were not well represented. Therefore, we compiled a summary of the most common and important symptoms experienced by patients with different types of EB. Our goal is that this overview representing the patient-reported needs contributes to the definition of what should be consistently measured in future clinical trials. Additionally, we suggest conducting further literature research, focus groups, or interviews to better understand and represent specific needs, such as sleep and mental health of EB patients.

Introduction

Epidermolysis bullosa (EB) is composed of a heterogeneous group of genetic skin disorders accompanied by blistering even after minimal mechanical trauma (Has et al., 2020). Multiple pathogenic variants cause EB by affecting different skin layers and proteins which are responsible for skin integrity. EB compromises four major types: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler EB (KEB) (Has et al., 2020). This classification in four major EB types is based on the skin layers in which skin cleavage and blister formation occur (Fine et al., 2014). In EBS the cleavage occurs in the basal layer of keratinocytes, in JEB it occurs within the lamina lucida, and in DEB below the lamina densa of the basement membrane zone (Figure 1) (Bardhan et al., 2020). Whereas in the fourth type, in KEB the cleavage can occur in various levels of the dermal-epidermal junction (Rognoni et al., 2016; Siegel et al., 2003). Next to the differences in affected skin layers and genes, there are differences in inheritance patterns, which influence clinical phenotypes (Has et al., 2020). Namely, differences in the phenotypes of autosomal dominant and recessive forms of DEB are observed, where the dominant form is associated with milder phenotypes (Has et al., 2020). Hence inheritance patterns and molecular features affecting different skin layers contribute to the heterogeneity of the disease.

Despite recent developments in EB research and therapeutical approaches, there are currently only limited treatment options for EB (Filsuvez approved by the EMA in 2022 and FDA in 2023 (Mellerio, 2023), Vyjuvek approved by FDA in 2023 (Khan et al., 2023)), and treatment focuses on symptom relief. However, the symptoms and specific treatment needs vary between patients of different EB types (Bruckner et al., 2020; Schräder et al., 2021), which makes assessment of the effectiveness of therapeutic targets challenging. To achieve good comparison and evaluation between clinical trials for EB treatments, it is essential to define consensus-based outcome domains. A recent scoping review on EB clinical trials demonstrated that in the past 30 years even within studies of similar EB-type intervention and clinical trial phases a considerable heterogeneity in outcome domains and measurement instruments was found (Korte et al. 2023b).

To ensure that the most important outcome domains will be consistently measured and reported in future clinical trials, it is aspired to define a core outcome set (COS) for each EB type (COSEB kick-off meeting (Korte et al., 2024)). Particularly for clinical trials for rare diseases a uniform assessment of outcomes is important to improve comparability and efficiency of future research, since the total number of suitable patient participants is limited (Mellerio and Uitto 2020). This applies to EB, which is considered a rare disease, with a prevalence of 1-25 per million population and an incidence of 2-54 per million live births (Baardman et al., 2021; Fine, 2016; Has et al., 2023; Korte et al., 2023). The COSEB initiative aims to address the issue of missing comparability of outcome domains in EB clinical trials and highlighted the need to involve multiple stakeholders in the decision-making process, one of them being patients and their perspectives (Korte et al., 2024). To match the patient's needs for the treatments and drugs in development in clinical trials, it is critical to identify the patient's perspective on the most important outcome domains and measurement instruments.

Thus, here we aim to summarize EB type-specific patients' needs and perspectives on the most important treatment options or outcome domains as presented in recent literature. We hope that including the patient's perspective of existing literature can feed into the COSEB initiative and contribute to the harmonization of outcome domains in clinical trials and the defining of COSs for each EB subtype. Furthermore, we aspire to reveal, which additional measures have to be taken, e.g. in the form of questionnaires, interviews, or focus groups, to achieve a good representation of the patient's perspective for each EB type.

Objective: Identifying patient's needs and perspectives on important outcome domains for five EB subtypes: EBS, JEB, RDEB, DDEB, and KEB. Involving the patient's perspective in defining important outcome domains aspires to direct the consensus-based definition of COS to improve comparability and efficiency of future research and clinical trial design.

Research question(s): What are patients' reported needs and perspectives on outcome domains for EBS, JEB, RDEB, DDEB, and KEB?

Do patients' needs and perspectives on outcome domains match previously reported outcome domains for clinical trials?

How can the patient-reported needs and perspectives contribute to defining the core outcome sets for EB subtypes?

Understanding the Complexity of EB: exploring the diverse pathomechanisms across the four major EB types

Motivated by our aim to identify patients' needs and perspectives on outcome domains across different EB types, our initial step is to provide an overview of the underlying pathomechanisms driving the diverse phenotypes and heterogeneity of EB. Hence, first, we present a concise summary of the primary pathomechanisms behind the four major EB types.

EB simplex

EBS is the most common EB type, accounting for 45.7% of all EB cases in the Netherlands (Baardman et al., 2021). It arises from pathogenic variants affecting the keratin network, causing cleavage within the basal layer of keratinocytes, leading to skin fragility and blistering (Bardhan et al., 2020). EBS is predominantly inherited in an autosomal dominant manner but can also manifest through a recessive pattern or be caused by *de novo* variants (Has et al., 2020; Supplementary Material). The pathogenic variants in genes such *as KRT5, KRT14, KLHL24, PLEC, DST, EXPH5, CD151,* and *TUFT1* (Jackson et al., 2023)disrupt the structural support in the epidermis (Figure 1)(Bardhan et al., 2020).

Particularly, the most common pathogenic variants in EBS patients: *KRT5 and KRT14*, affect crucial components of the basal keratinocyte cytoskeleton and hence impair the organization of the keratin network (Bardhan et al., 2020; Fine, 2010). These variants, especially those occurring within conserved regions of the helix initiation or termination motifs of *KRT5* and *KRT14*, result in disruption of keratin heterodimerization and thereby determine the severity of the phenotype of EBS. The disruption of keratin heterodimerization leads to severe manifestations, as in the subtype of severe EBS, while variants in other regions may result in milder phenotypes, such as localized EBS (Coulombe & Lee, 2012; Has et al., 2020). Localized EBS is a subtype of EBS and is characterized by localized blister formation primarily on the palms of the hands and soles of the feet (Has et al., 2020). The subtype severe EBS manifests in generalized blister formation, which particularly is prominent at birth and is accompanied by extracutaneous manifestations, such as Gastro-oesophageal reflux, potentially leading to lethal outcomes within the first year of their lives (Has et al., 2020; Supplementary Material).

Moreover, pathogenic variants in genes *PLEC, DST,* and *EXPH5*, encoding dystonin, plectin, and exophilin5, impair the keratin network (Figure 1), potentially leading to keratin cytoskeleton reorganization and collapse (Bardhan et al., 2020; Wiche & Winter, 2011). Certain *KRT5* variants have also been linked to reduced keratin solubility and thermolability, decreasing cytoskeleton stability, and increasing blister formation, particularly in warm environments (Morley et al., 1995).

These diverse variations primarily affecting the keratin network manifest in various clinical presentations, including skin fragility, inflammation, blisters on hands and feet, plantar keratoderma, and dystrophic nails (Has et al., 2020; Supplementary Material).

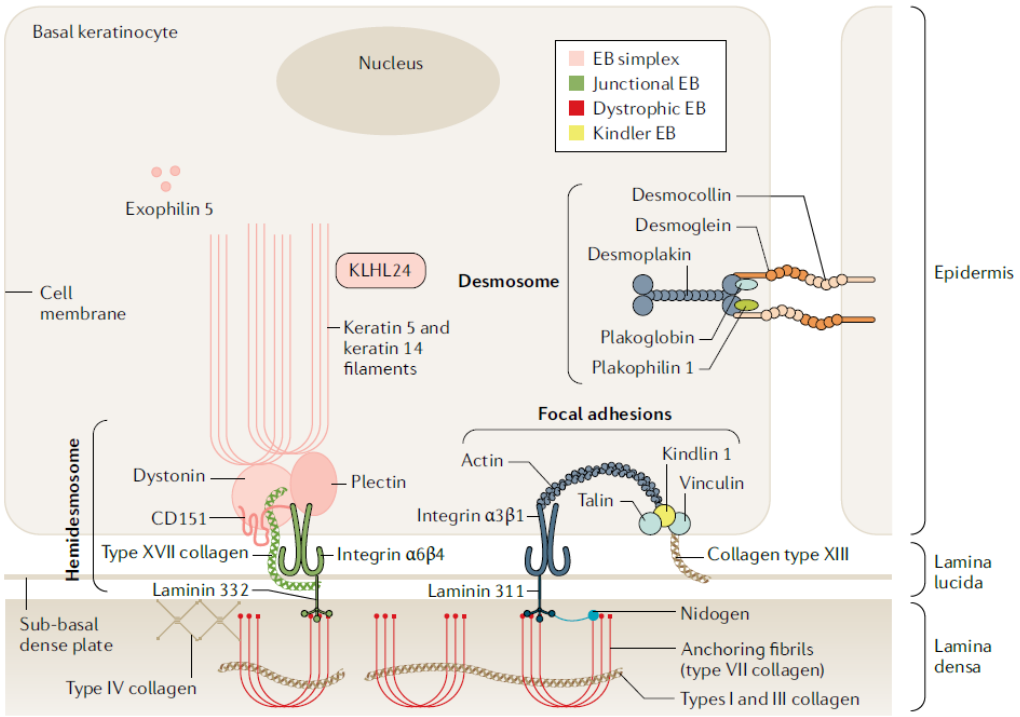

Figure 1: Extracellular matrix proteins and macromolecules that are involved in the pathomechanisms of the four major EB types in the cutaneous dermal-epidermal junction. Schematic of the cutaneous dermal-epidermal junction from (Bardhan et al., 2020)*: Epidermolysis bullosa.* Nature reviews Disease primers, *6(1), 78.*

Junctional EB

In all subtypes of JEB, skin cleavage, and blister formation occur within the lamina lucida of the basement membrane zone, situated at the dermis-epidermis junction (Figure 1) (Bardhan et al., 2020). Junctional EB is mainly inherited in an autosomal recessive manner and results from pathogenic variants affecting various structural proteins responsible for anchoring basal keratinocytes to the basement membrane zone (Figure 1). Genes encoding these structural proteins include *COL17A1* (for type XVII collagen), *LAMA3, LAMB3, LAMC2* (for laminin 332), *ITGA3* (for integrin α3 subunit), as well as *ITGA6* and *ITGB4* (for integrin α6β4).

The *COL17A1* gene encodes for the homotrimer type XVII collagen, which serves as a crucial transmembrane component of hemidesmosomes (Figure 1). Hemidesmosomes have both adhesive and signaling functions within the skin tissue (Bardhan et al., 2020; Franzke et al., 2003). Reduced or abnormal expression of type XVII collagen in JEB patients manifests clinically in blister formation beginning at birth, ruptured blisters leaving erosions, nail deformations, and later also hair loss, depigmentation, carcinogenesis, and skin atrophy (Bardhan et al., 2020; Has et al., 2020).

LAMA3, LAMB3, and LAMC2 encode for laminins, which are glycoproteins consisting of three subunits; α, β, γ, which assemble into a coiled-coiled heterotrimer. Laminin 332 serves an important function as an extracellular ligand for other matrix proteins (e.g. type VII collagen, nidogen1) and for other cellular receptors (e.g. integrin α6β4, type XVII collagen) (Figure 1). Thereby, Laminin 322 influences the migration behavior of basal keratinocytes (Bardhan et al., 2020; Has & Nyström, 2015).

JEB patients deficient in laminin-332 exhibit severe mucocutaneous adhesion defects, such as corneal and laryngeal blistering, due to laminin-332's presence in the epithelial basement membranes of organs like the cornea and gastrointestinal tract (Condrat et al., 2019; Has et al., 2020). Complete loss of laminin-332 leads to severe JEB, characterized by severe blistering, over granulation of tissue, and can cause life-threatening airway obstruction (Fine et al., 2007). Patients with severe JEB have a limited life span, often not becoming older than 2.5 years of age (Hammersen et al., 2016).

Lastly, the genes *ITGA6 and ITAGB4* encode for integrinα6β4, which serves an important function as cell-matrix adhesion receptor in the skin, kidney collecting system, and gastrointestinal mucosa. Specifically, integrinα6β4 acts as an essential linker involved in the formation of hemidesmosomes. Furthermore, it contributes to the migration of keratinocytes during wound healing (Has & Nyström, 2015). Hence, pathogenic variants in ITGA6 and ITAGB4 genes, leading to structural defects in the alpha and beta subunit of the integrinα6β4, results in severe mucocutaneous skin fragility, granulation tissue, and nail dystrophy in JEB (Bardhan et al., 2020; Has et al., 2020; Supplementary Material).

Dystrophic EB

Dystrophic Epidermolysis Bullosa (DEB) is characterized by pathogenic variants in the *COL7A1* gene, leading to subtype-specific clinical manifestations. These pathogenic variants only affect type VII collagen resulting in skin blistering and fragility below the lamina densa of the basement membrane zone (Figure 1)(Bardhan et al., 2020). DEB's skin fragility manifesting deep in the skin tissue, results in fibrosis, milia formation, and mucocutaneous scarring (Bardhan et al., 2020; Has et al., 2020). DEB exhibits autosomal recessive and dominant inheritance patterns, with the dominant subtype generally associated with milder phenotypes (Has et al., 2020).

In recessive DEB (RDEB), pathogenic variants in the *COL7A1* gene often lead to premature termination codons, resulting in reduced or absent type VII collagen in skin or mucosa tissue (Christiano et al., 1994). In severe RDEB, patients experience a greatly increased incidence of aggressive skin and mucosal squamous cell carcinoma (SCC) (Fine et al., 2009). Whereas, dominant DEB (DDEB) is typically caused by pathogenic variants that interfere with the supramolecular assembly of type VII collagen, without causing a complete lack of function, which partly explains the milder phenotypes observed (Has et al., 2018). More precisely, the DEB pathogenic variants result in the absence, reduction in levels or abnormality of type VII collagen, impairing the formation of anchoring fibrils essential for dermal-epidermal cohesion and leading to cleavage in the upper dermis (Bardhan et al., 2020). The triple-helical structure of type VII collagen is important for the correct assembly of anchoring fibrils, and various variants, such as missense variants for example glycine substitutions within the *COL7A1* gene, can disrupt this structure (Christiano et al., 1996; Has et al., 2018; Woodley et al., 2008). The importance of type VII collagen anchoring fibrils is highlighted by their role in connecting laminin332 in the lamina lucida with fibrillar matrix proteins like type I and III collagen in the superficial papillary dermis (Figure 1) (Bardhan et al., 2020).

Kindler EB

Kindler EB (KEB) is the rarest of the four major EB types, accounting only for 0.9% of all EB cases in the Netherlands (Baardman et al., 2021). KEB can be autosomal recessively inherited and caused by pathogenic variants in the *FERMT1* gene encoding for kindlin1. Kindlin-1 belongs to the kindlin family proteins, which function as integrin activators and facilitate focal adhesion (Jobard et al., 2003). Pathogenic variants in the *FERMT1* gene disrupt the keratinocyte cytoskeleton network, cause abnormal integrin activation, and result in subsequent loss of keratinocyte adhesion, affecting the underlying basement membrane zone.

This results in ultrastructural splits within the cutaneous basement membrane zone, giving rise to blister formation at various levels of the dermal-epidermal junction (Rognoni et al., 2016; Siegel et al., 2003). The majority of *FERMT1* variants induce premature termination codons, triggering nonsense-mediated mRNA decay and resulting in the absence of kindlin-1 in epithelial cells (Has et al., 2011). Given that kindlin-1 expression extends beyond skin epithelial cells to tissues and cells of the oral mucosa and the gastrointestinal tract, KEB can manifest in gingivitis with tooth loss and esophageal strictures (Bardhan et al., 2020; Has et al., 2020). Clinically, KEB manifests with acral blistering, photosensitivity, cutaneous atrophy, progressive poikiloderma, and the potential development of SCCs on extremities or mucosal sites in adulthood (Bardhan et al., 2020; Has et al., 2020).

Materials and Methods

Definitions

To enhance clarity and coherence in definitions, we adhere to the terminology established in the scoping review by Korte et al. (2023). In their study, 'outcome' was defined as ‘what’ was measured in clinical trials, while 'outcome domains' served to categorize similar outcomes, and 'outcome areas' grouped these domains (Korte et al., 2023). To compare patient-reported needs with outcome domains assessed in clinical trials, we define outcome domains as the specific patient-reported symptoms and needs that should be measured from the patient's perspective. The patient-reported needs encompass patient statements regarding treatment options, disease impact, burden, and Quality of Life (QoL).

Search Strategy

To ensure a comprehensive understanding of patient needs and perspectives, a semi-systematic search was performed using different sources and search techniques (Table 1). Initially, a MEDLINE search in PubMed was conducted, guided by predefined keywords extracted from relevant studies, particularly from the reference list provided in the Korte et al. (2023) scoping review. Keywords such as "patient," "epidermolysis bullosa," "need(s)," "survey," "quality of life," "burden," and "outcome" were employed in search terms (see Supplementary Material) to retrieve literature reporting about the patients’ perspectives. Subsequently, websites of patient representative organizations including DEBRA International, DEBRA UK, DEBRA Austria, and EB Clinet were searched for reports of surveys, and questionnaires elucidating patient needs and treatment perspectives, which potentially were not published in scientific journals (Table 1).

Table 1: Summary of conducted search steps during literature search for patients' reported needs and perspectives on outcome domains for EB. Search steps are listed in chronological order, characterized by the databank or source that was searched, the search type, and the parameters utilized for the search. More detailed search parameters and results of the searches are elaborated on in the Supplementary Material.

Search	Step1	Step2	Step3	Step4	Step5
Information source	MEDLINE PubMed	Websites of DEBRA International - DEBRA UK - DEBRA Austria - EB Clinet -	MEDLINE PubMed	Orphanet Journal of Rare Diseases	Reference list of previously found literature
Search type	Keyword search	Search for literature on EB patients’ perspectives	MeSH terms and keyword search	Search tool using search string (below)	Scanning reference lists

Search parameters	epidermolysis bullosa, patient, survey, needs, quality of life**,** burden	Search for surveys and questionnaires about patients' needs and perspectives on treatment options.	Search String (Supplementary Material Search Strategy) Time filter: 2020-2024	(1) 'patient needs in epidermolysis bullosa.' (2) ' epidermolysis bullosa patient burden '	Literature reference not already picked up by the previous search

To refine the first search conducted with PubMed and increase the chances of retrieving relevant literature that potentially was not picked up in the previous search, MeSH terms were derived from the previously retrieved literature and the references cited in relevant studies. Subsequently, an additional second MEDLINE search was conducted on PubMed, covering the period from 2020 to 2024. This timeframe was chosen to establish a cutoff for managing the number of publications identified, ensuring feasibility for screening and eligibility assessment within the review's time constraints of 5 weeks full-time. This MEDLINE search employed a predefined search string (see Supplementary Material) comprising the previously defined MeSH terms and specific keywords. Noticing that much of the previously retrieved literature was published in the Orphanet Journal of Rare Diseases, we conducted an additional search in the journal's archives using two search terms composed of keywords (Table 1). This supplementary search aimed to retrieve literature that may have been missed in earlier searches due to limitations in keywords or the time constraints for the published literature. To further enhance the completeness of relevant literature, the reference lists of the previously identified papers were screened. This supplementary search aimed to uncover older publications predating the defined timeframe (pre-2020) that potentially contributed to the review's scope and objectives.

By systematically integrating these search steps, a comprehensive body of literature was identified (Figure 2). To determine the eligibility of the identified literature, titles, and abstracts were initially screened, followed by a thorough examination of full texts against predefined inclusion and exclusion criteria (Table 2). Studies meeting the inclusion criteria and that analyzed the patient's reported needs were then summarized. Relevant data such as the first author, year of publication, publication type, and presented EB patients perspectives per subtype were extracted into a table (Table 3). The extracted data on the publication years, number of publications per EB type, and surveyed patients are graphically represented descriptively (Figures 3 and 4).

Table 2: Eligibility criteria for assessing the relevance of identified literature on inherited EB patients' needs. Included articles must present the needs and perspectives on outcome domains from EB patients' perspectives. This includes direct involvement of EB patients through questionnaires, surveys, interviews, or indirect reporting of patients' needs and perspectives by their caregivers.

	Inclusion	**Exclusion**
Participants	Persons with inherited epidermolysis bullosa (EB) including all four major EB subtypes and DEB divided into RDEB and DDEB, different ages, severity sex, and ethnicity	Persons with other rare diseases, skin diseases, or skin fragility disorders such as EB acquisita. Studies with mixed cohorts of skin disorders
Concept	Reported needs or perspectives on outcomes directly or indirectly presenting the patients' perspectives, including: - somatic symptoms - function/ abilities - emotional and social aspects Definition and validation of EB-specific disease scores or quality of life evaluation	Studies evaluating medical interventions (e.g. treatment options/materials or drugs) or the molecular mechanism of disease. Studies or Information about the healthcare system or burden of healthcare workers, financial burden/cost of disease, epidemiology

Source types	Interviews, Surveys, Questionnaires, Review articles	Guidelines for treatment and healthcare
Context	Studies published in English from different countries and different study designs.	Studies published in different languages than English. In Search Step 3: Studies published before 2020

Summary of study selection and characteristics

In total 241 studies were identified of which 227 studies titles and abstracts were screened, 47 were assessed for eligibility and lastly 22 were included in this review (Figure 2).

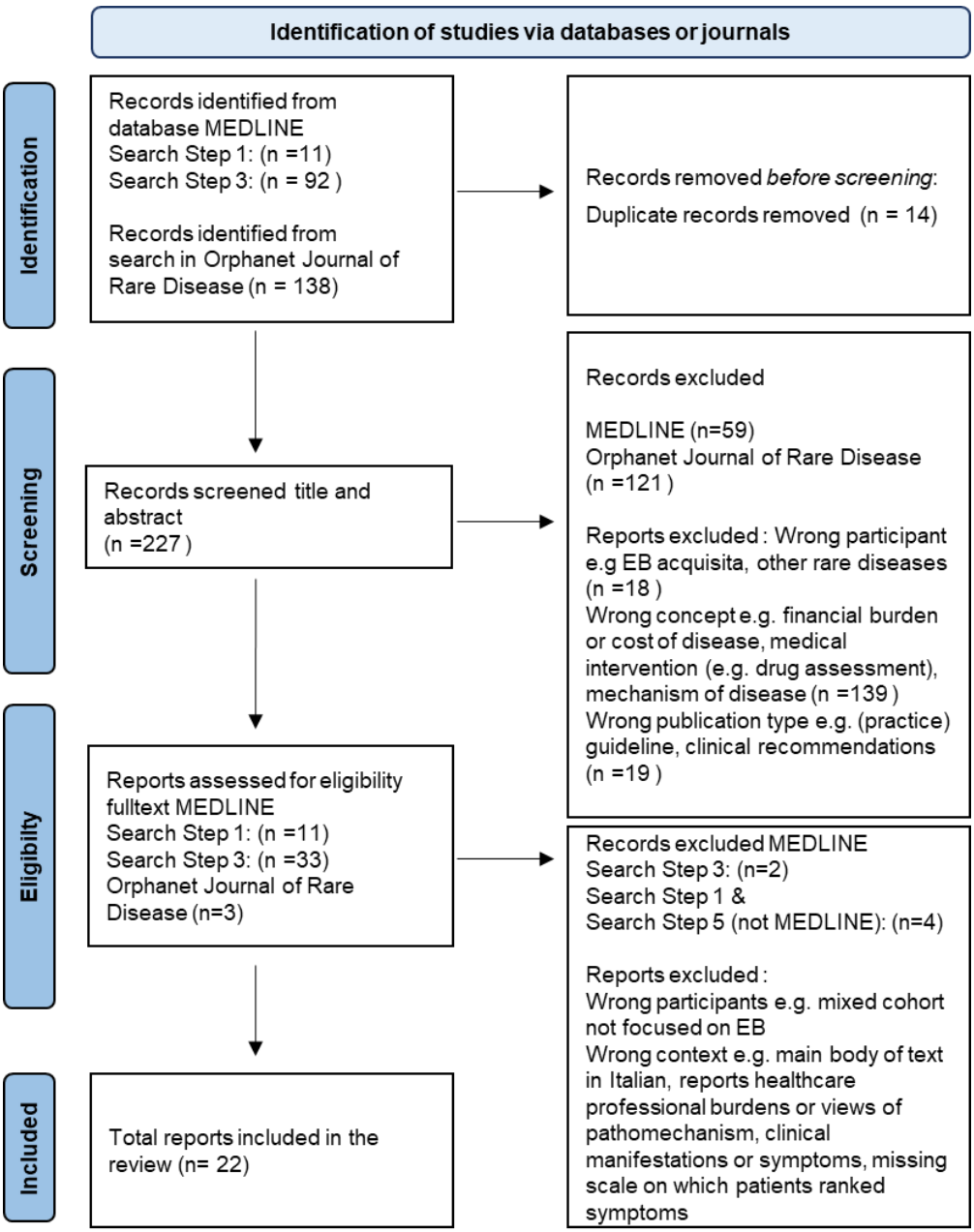

Figure 2: Study identification and selection flowchart adapted from PRISMA (Preferred reporting items for systematic reviews and meta-analyses) guidelines. Our searches identified 241 studies from the MEDLINE database and Orphanet Journal of rare disease, fourteen studies were removed as duplicates, 227 titles, and abstracts were screened for eligibility based on predetermined inclusion and exclusion criteria, 47 full texts were assessed for eligibility and lastly, 22 studies meeting the inclusion criteria were included in this review.

The majority of included studies (72%) that reported patients' needs and perspectives were published in the last four years (Figure 3), which might be an artifact of the time filter (2020-2024) applied in the second PubMed search (Table 1, Step 3). However, considering that the other four search steps had no time constraints on the publication year, this distribution might also indicate an increased awareness and efforts to capture the perspectives of patients in clinical and scientific research in recent years.

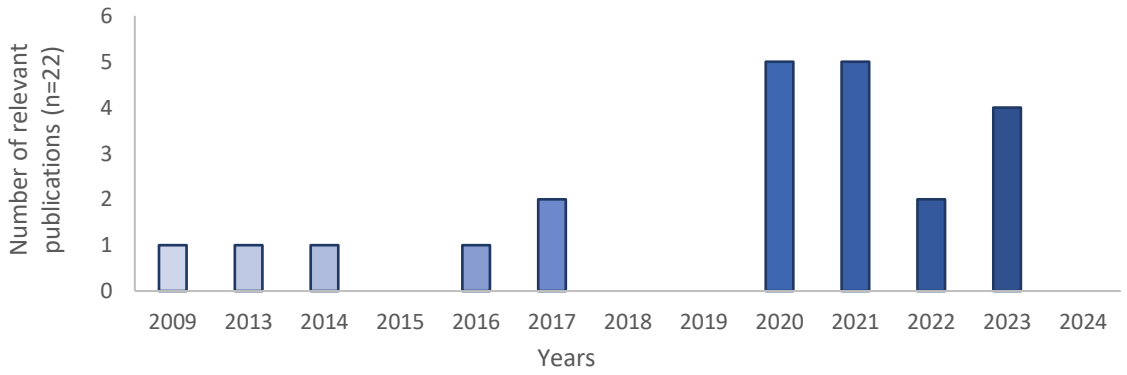

Figure 3: Included studies reporting patients' needs and perspectives grouped based on year of publication (2009-2024)

In the majority of studies (16 out of 22) the EB type was specified when reporting the patient's needs. Among these studies, most focused on reporting the needs of RDEB patients with being most frequently surveyed (10 out of 22 publications), followed closely by EBS patients (9 out of 22) and DDEB patients (7 out of 22) (Figure 4). While 9 out of 22 studies concentrated on a single EB subtype, only seven studies examined multiple EB types for comparison. Among the 22 included studies, six primarily or partly addressed the patients' perspectives on treatment options without specifying the EB type (Bruckner et al., 2020a; Mellerio & Uitto, 2020; Prodinger et al., 2020; Sangha et al., 2021; Tabolli et al., 2009; Uitto et al., 2016). Nonetheless, these studies presented a direct assessment of patients' needs regarding clinical research and treatment options. Hence, these studies were further analyzed despite the lack of specificity of EB type. In the 22 studies, in total 922 patients with EB were surveyed, among which EBS patients (350), followed by RDEB patients (284), and DDEB patients (178) were best represented in the included studies (Figure 4). In contrast, patients with JEB (43 patients) and particularly with KEB (4 patients) were among the least represented subtypes (Figure 4). It is noteworthy that the DEBRA UK 2023 patient insight study was the only report found that included KEB patients. Therefore, the small number of patients representing the needs of KEB should be considered when interpreting the presented needs, symptoms, and disease burden of this group.

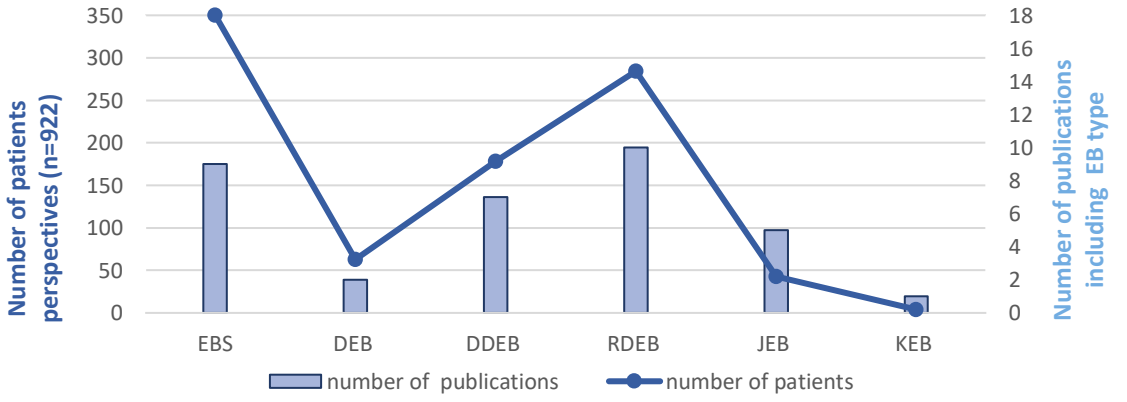

Figure 4: Cohort characteristics of surveyed EB patients, showing the representation of each EB type and their representation in the number of publications in which each EB type was included; DEB: no specification between RDEB and DDEB patients was made.

Table 3: Overview of included studies and extracted data from each study. Including the first author, year of publication, type of publication, the patients' perspectives which were presented in the study with specified EB subtype (EBS, DDEB, RDEB, JEB, and KEB), and whether other perspectives from for example caregivers were represented in the corresponding study; NA: not applicable, meaning studies did not report the EB subtypes, DEB: no specification between RDEB and DDEB patients was made.

	Author	**Year**	**Source type**	**Topic**	**Patient's perspective**	**EBS**	**DDEB**	**RDEB**	**JEB**	**KEB**	**DEB (not specified)**	**EB Sub-types**	**Another perspective e.g. carer**
1	Bruckner et al.	2020	survey	Burden of disease information for EB patients	Yes	21	14	19	8	0	NA	4	Yes
2	Brun et al.	2017	questionnaire	EBS pain and quality of life	Yes	57	0	0	0	0	NA	1	No
3	Choi et al.	2017	abstract from a study of the QoL (QOLEB) questionnaire	Quality of life in recessive dystrophic epidermolysis bullosa: The Alta Voice patient registry, 2012-2015	Yes	0	0	32	0	0	NA	1	No
4	Davila-Seijo et al.	2013	questionnaire and task force selection	Prioritization of therapy uncertainties DEB treatment answers needed	Yes	0	NA	NA	0	0	58	0	Yes
5	Davila-Seijo et al.	2014	letter to the editor	Current dystrophic EB research does not match research needs perceived by patients and clinicians	Yes	NA	NA	NA	NA	NA	NA	0	Yes
6	DEBRA UK	2023	online survey	EB 2023 insight study	Yes	131	27	34	9	4	NA	5	Yes
7	Eng et al.	2021	survey	RDEB Patient-reported outcomes and quality of life	Yes	0	0	85	0	0	NA	1	No
8	Fulchand et al.	2021	survey	DDEB Patient-reported outcomes and quality of life	Yes	0	42	0	0	0	NA	1	No
9	Graham et al.	2020	Interviews and focus groups	Participatory co-design of patient-reported outcome indicators and … evaluation of dressing glove	Yes	0	0	6	0	0	NA	1	Yes
10	Hunjan et al.	2023	QoL questionnaire	Burden of disease EBS	Yes	21	0	0	0	0	NA	1	No
11	Korte et al.	2023	literature review	Heterogeneity of reported outcome in EB in clinical research	No	NA	NA	NA	NA	NA	NA	0	No
12	Mellerio et al.	2023	long time score	Itch in recessive dystrophic EB: findings of PEBLES	Yes	0	0	55	0	0	NA	1	No

			assessment and survey										
13	Mellerio and Uitto	2020	meeting report	Towards Treatment and Cure	Yes	NA	NA	NA	NA	NA	NA	0	Yes
14	Paller et al.	2022	questionnaires and clinical assessment wounds	A prospective short-term study to evaluate methodologies for the assessment of disease DEB	Yes	0	1	29	0	0	NA	2	Yes
15	Prodinger et al.	2020	questionnaire	Patient attitude to improve clinical research	Yes	NA	NA	NA	NA	NA	NA	0	No
16	Sangha et al.	2021	interview psychosocial impact	Psychosocial impact of epidermolysis bullosa on patients: A qualitative study	Yes	2	1	5	0	0	NA	3	No
17	Schräder et al.	2021	questionnaire	EB patient's needs and perceived treatment benefits	Yes	29	23	6	10	0	NA	4	No
18	So et al.	2022	survey	EBS outcome, disease burden, and QoL	Yes	70	0	0	0	0	NA	1	No
19	Tabolli et al.	2009	survey	QoL in patients with EB and to determine disease burden.	Yes	18	70	13	15	0	NA	4	Yes
20	Tang et al.	2021	literature review	Economic, clinical, or humanistic burden of RDEB	No	NA	NA	NA	NA	NA	NA	0	Yes
21	Uitto et al.	2016	meeting report	Progress toward Treatment and Cure of EB	Yes	NA	NA	NA	NA	NA	NA	0	Yes
22	Wu et al.	2020	interviews	Family caregivers' lived experiences of caring for epidermolysis bullosa patients: A phenomenological study	No	1	NA	NA	1	0	5	3	Yes

Understanding the Burden of Epidermolysis Bullosa: Quality of Life, Disease Impact, and Treatment Perspectives

Recent insights from studies and surveys highlight the considerable impact of EB on mental health, self-confidence, and social interactions (DEBRA Patient Insight Study, 2023; Sangha et al., 2021). Young EB patients (< 20 years) highlighted the challenges posed by lengthy dressing changes, hindering their participation in social activities (Sangha et al., 2021). Additionally, parents or caregivers of infants with EB experienced wound care and dressing changes to be lengthy and painful for their babies, leading them to feel overburdened and overwhelmed with the wound care (Wu et al., 2020). Moreover, young EB patients experience teasing and social avoidance at school, along with feelings of guilt for the impact their condition has on their family members (Sangha et al., 2021), adding to the psychosocial burden they experience. In addition, a questionnaire about EB patients' (n=36) attitude toward improving clinical research found, that the main arguments for their participation in a clinical trial were "the hope for better treatments for other EB patients" (87.5%) and "Alleviation of own symptoms" (77.4%) (Prodinger et al., 2020). Given the experienced psychosocial burden, it is not surprising that EB patients express a desire for improved treatments not only for themselves but also for others, emphasizing the need for effective interventions to alleviate symptoms.

Quality of Life (QoL) surveys, such as the Quality of Life in Epidermolysis Bullosa (QOLEB) questionnaire, have been commonly used in studies to assess the impact of EB on patients' lives (Frew et al., 2009; Frew & Murrell, 2010). For example, a 2009 study on QoL in patients with EB, which utilized various questionnaires, revealed challenges in executing work and hobbies, tiredness due to the skin condition, and interference with sexual life (Tabolli et al., 2009). Interestingly, sleep and sex were initially considered as abilities in the generation of the QOLEB questionnaire. However, in the last step, they were excluded due to their complexity and because they did not clearly reflect either the factor functioning or emotion for the QoL scoring (Frew et al., 2009). Nonetheless, the current QOLEB questionnaire focuses on daily activities and emotional impacts, aiming to capture EB's diverse manifestations and their effects on patients' quality of life (Frew et al., 2009).

While reducing pain (73%) emerged as a priority for future treatment options among EB patients (EBS:21, JEB:8, DDEB: 14, RDDEB: 19), along with reducing the risk of skin cancer (77.8%), reducing the number and severity of wounds (73%), and accelerating wound healing and closure (71.4%), other factors like reducing itch (57.4%) and decreasing the time for dressing changes (41.3%) were rated less important (Bruckner et al., 2020). Nonetheless, a 2020 questionnaire found that EB patients (n=36) would consider a clinical study successful if they experienced relief of 36.4% pruritus, 27.3% blistering, or 27.3% pain (Prodinger et al., 2020)presenting itch as an important factor for assessing clinical trials. Additionally, young EB patients (<20 years) expressed that long wound care prevents them from participating in activities and socializing with friends (Sangha et al., 2021), contradicting the perceived relatively low importance of decreasing dressing change time in the previous study of Bruckner et al. Lastly, in meeting reports from EB conferences, it was highlighted that pain as well as itch were categorized as treatment priorities by patients and their families (Uitto et al., 2016) and should be addressed to improve EB patients' quality of life (Mellerio & Uitto, 2020).

Overall, the diverse findings underscore the multifaceted nature of EB and the importance of considering patient perspectives in shaping future treatment approaches. To account for the heterogeneity of EB and its diverse symptoms, especially those that vary among the four major EB types, we conducted separate analyses of patient-reported needs. This approach ensures that differences between EB types, which may arise from variations in clinical manifestations and symptoms, are not overlooked.

EBS

Itch and Pain

A study using the patient benefit index to assess EB patients' needs and their importance found that EBS patients (n=29) rated “to be free of pain” (69%), “to get better skin quickly” (58.6%), and “to be free of itching” (48.3%) as their three most important needs associated with symptoms (Schräder et al., 2021). However, a recent US survey about the disease and wound burden of EB patients revealed that EBS patients reported lower levels of acute pain (4.3), chronic pain (3.2), and itch (4.4) on a scale of 1-10, compared to other EB subtypes (RDEB, DDEB, JEB) (Bruckner et al. 2020). Nonetheless, 214 EBS patients reported pain (73.8%) and itch (55.1%) among their most common symptoms and clinical manifestations, alongside blisters (93%), difficulty walking (43.9%) in 2022 survey analyzing clinical and wound manifestations (So et al., 2022). Furthermore, the study of Brun et al. highlighted the high prevalence of neuropathic pain (75%) in localized EBS patients (n=57) characterized by burning (88%) and itching (86%) sensations (Brun et al., 2017).

Prevalent extracutaneous manifestations reported by EBS patients

Common extracutaneous complications experienced by EBS patients (n=21) were ‘Nail abnormalities’ (71.4%), ‘Hand/foot contractures, webbing, severe scarring’ (52.4%), ‘Eye problems’ (38.1%), ‘Dental problems’ and ‘Oral cavity problems’ (33.3%) (Bruckner et al., 2020). Notably, the term 'hand/foot contractures, webbing, severe scarring' likely refers to patients reporting scarring as a prevalent complication, when comparing those complications to clinical manifestations of EBS (Has et al., 2020). In a separate Debra Insight Study (n=193), fewer EBS patients reported eye problems (23%), while mouth/dental problems (40%) and gastrointestinal (GI) issues (47%) were more commonly reported extracutaneous manifestations (DEBRA Patient Insight Study, 2023). Furthermore, reported EBS patients (n=214) constipation (42.5%), and nail problems (39.3%) among their most common clinical manifestations in a 2022 survey about their disease burden and QoL (So et al., 2022). Highly impactful common extracutaneous manifestations among EBS patients included blisters inside the mouth and throat (28%), painful passing stools (43%), and constipation (26%) (DEBRA Patient Insight Study, 2023).

Wound burden

The US survey study by Bruckner et al. (2020) examined wound impact in 21 EBS patients, with the majority reporting less than 10% body coverage of wounds and spending less than 2 hours per day on wound care. Notably, EBS patients experienced lower wound burden compared to RDEB and DDEB patients, assessed based on the higher body coverage of wounds and longer wound care times (RDEB: > 4h 36.8%) reported by RDEB and DDEB patients (Bruckner et al. 2020). Furthermore, the 2022 survey by So et al. showed that the majority of chronic wounds (54.2%) and recurrent wounds (85.5%) were located at the lower extremities for EBS patients (n=214). These reported wounds were predominantly small (<2.5 cm) (77.1%). Large wounds were presented in only 29% of the EBS patients (n=214) (So et al., 2022). Thus, the wound burden appears to mainly manifest in the lower extremities through recurrent wounds. The clinical manifestations known from literature for localized EBS (Has et al., 2020) match with wounds or blisters manifesting to the lower extremities. Similarly to So et al., EBS patients (n=193) reported predominantly blisters on extremities such as the palms of the hands (70%) and blisters on the soles of the feet (96%) (DEBRA Patient Insight Study, 2023). Additionally, EBS patients (n=57) reported that pain in the feet (100%) and hands (39%) was commonly linked to blister formation during flares and dressing changes (Brun et al., 2017). The DEBRA Insight Study 2023 highlights the impact of ‘blisters on the soles of the feet’ on the disease burden experienced by EBS patients, rating them as high-impact cutaneous manifestations, alongside fragile skin (47%) and pain (51%).

Furthermore, EBS patients (n=180) identified blisters on the soles of their feet (44%) and bladder issues (23%) as the most impactful symptoms on their mental health (DEBRA Patient Insight Study, 2023). Additionally, EBS patients at their worst health reported severe impairments in their mobility (DEBRA Patient Insight Study, 2023). Together these findings demonstrate the major role that blisters on the hands and feet play for EBS patients and how the associated pain can lead to EBS patients reporting difficulties walking and severe impairment of their mobility at their worst health.

Existing EB severity scores like BEBS and EBDASI, which consider factors such as affected body surface area, nail involvement, and SCCs, do not correlate with the measured impact on quality of life for localized EBS patients (n=21) (Hunjan et al., 2023). Therefore, Hunjan et al. suggested alternatively to consider blisters on the feet and hands and keratoderma to evaluate EBS severity (Hunjan et al., 2023).

Physical and social abilities affecting the quality of life in EBS patients

In a questionnaire EBS patients (n=29) reported the highest importance related to their physical and social abilities for "the ability to lead a normal everyday life" (48.2%) and "the ability to engage in normal leisure activities" (48.3%) (Schräder et al., 2021). Similar results were presented in a US-survey study, in which EBS patients (n=21) rated the impact of their disease on their abilities in their daily life (Bruckner et al., 2020). The three most impacted abilities for EBS patients were: the ability to sleep (62%), the ability to move around the home (66.7%), and the ability to write (46%) (Bruckner et al., 2020). Comparable to the US survey study by Bruckner et al., the results of a 2022 survey show that the majority of EBS patients (n=70) experience impairment in their ability to move around the home (70%), while fewer patients report impairment in their ability to write (28.6%) (So et al., 2022). The same 2022 survey found that the EBS patients were moderately impacted in their Quality of Life (mean QOLEB score +/- SD: 14.7 +/- 7.5) and were most impacted by the physical abilities of reduced involvement in sports (68.8%) and the ability to move around outside of the house (72.5%), by occasional to frequent pain (52.9%, 35.7%) as well as by the feelings of frustrations (a little: 48.6%, a lot: 44.3%) (So et al., 2022). Whereas the results from the 2017 QOLEB survey reported (n=30) only a mild impact (mean QOLEB score +/- SD: 6.6 +/-4.9) on the quality of life for localized EBS patients (Brun et al., 2017). However, EBS patients in the 2017 study reported similar impacted abilities, including feeling frustrated (87%), being impacted in their ability to participate in sports (87%), and being affected by their ability to move outside the house (60%) (Brun et al., 2017). These studies highlight that the most impacted abilities reducing the quality of life for EBS patients are physical abilities associated with mobility, while the emotional component most impactful on their QoL was the feeling of frustration.

DEB

The classification of inherited EB combines recessive and dominant dystrophic EB into one type, DEB, motivated by considerable phenotypic overlap (Fine et al., 2014; Has et al., 2020). However, secondary extracutaneous complications are more common in RDEB, such as microstomia, esophageal strictures, and dental caries, leading to nutritional impairment and anemia (Forlino et al., 2021; Has et al., 2020) potentially impacting RDEB patients' perceived disease impact. Thus, we decided to compare patients' reported needs between RDEB and DDEB to investigate in which needs those subtypes are similar and in which they differ.

Research needs

A survey based on previously submitted treatment uncertainties of DEB patients and subsequent assessment by a representative group, consisting of patients, carers, healthcare professionals, and representatives of DEBRA Spain, identified key research needs for DEB patients.

These needs were ranked as follows in decreasing importance: wound care, itch reduction, pain treatment (e.g., during baths and cures), earlier detection of neoplasms and treatment of SSCs, prevention, delay, and correction of syndactyly, and development of new therapies or genetic engineering strategies to alleviate DEB symptoms (Davila-Seijo et al., 2013). These align with the top five future treatment options named by a mixed group of EB patients, primarily consisting of RDEB and DDEB patients (53%), including reducing the risk of skin cancer, reducing the number and severity of wounds, and reducing pain (Bruckner et al., 2020).

Itch and Pain

The majority of DEB (n=97) patients reported fragile (88%), itchy (90%), and painful (79%) skin as prevalent symptoms, according to the DEBRA Patient Insight Study in 2023. Furthermore, Schräder et al. (2021) revealed that painful and itchy skin were also rated among important needs for DEB patients. Moreover, this study found that both RDEB (n=6) and DDEB (n=23) patients prioritized similar aspects such as "To be healed of all skin alterations" (DDEB: 73.9%; RDEB: 100%), "To be free of itching" (DDEB: 69.6%; RDEB: 100%), and "To get better skin quickly" (DDEB: 60.9%; RDEB: 83.3%) (Schräder et al., 2021). Notably, RDEB patients consistently showed higher agreement for these statements. Additionally, the 2020 study from Bruckner et al. (2020) found that RDEB patients reported the highest levels of itch (6.7) and acute pain (5.6) among EB types. DDEB patients reported 12% lower levels of pain and itch compared to RDEB patients (Bruckner et al., 2020). Furthermore, DDEB patients reported a considerably lower prevalence of itch (47.6%) compared to RDEB patients (85-90%) (Table 5) (Fulchand et al., 2021; Eng et al., 2021). These differences in itch and pain align with the findings of a systematic review on RDEB's disease burden, which highlighted high levels of pruritus and pain in RDEB compared to DDEB and EBS patients (Tang et al., 2021). Interestingly, when pain in RDEB and DDEB patients was assessed as ‘worst pain in past 12 months’, they showed similar levels of pain among both subtypes from mild to severe forms (Table 5).

Wound burden

A recent study assessing wound evolution and disease impact on DEB patients found that DEB patients (1 DDEB and 29 RDEB) chose targeted wounds for monitoring based on which had the greatest impact on their QoL. The highest impacts on their QoL were named: pain (44.4%), interference with daily activities (38.9%), chronicity (33.3%), and pruritus (33.3%) (Paller et al., 2022). Another study comparing the wound burden between different EB types (EBS, JEB, and DEB) found that RDEB patients (n=19) had the highest burden with 57.9% reporting to have above 30% of their body covered with wounds and 36.8% requiring more than 4 hours for wound care (Bruckner et al., 2020). In contrast, DDEB patients reported a lower wound burden measured on the same wound characteristics, with 78.6% of DDEB patients reporting to need less than 2 hours for wound care and 35.7% reporting less than 30% body coverage of wounds (Bruckner et al., 2020). This aligns with Fulchand et al.'s findings, indicating that disease severity in DDEB is more impacted by pain and internal clinical manifestations rather than wound size (Fulchand et al., 2021). On the other hand, Eng et al. found that, for RDEB patients, larger wound size correlated with worsening disease severity and reduced quality of life, as assessed by the QOLEB questionnaire (Eng et al., 2021). A systematic literature review of RDEB's disease burden came to a similar conclusion, stating that large wounds next to pain, and itch significantly contributed to RDEB’s disease burden (Tang et al., 2021). Interestingly, wound characteristics reported by RDEB and DDEB patients, such as wound location, size, and number of dressing changes per week, were similar (Table 4 (Eng et al., 2021; Fulchand et al., 2021)). Moreover, wound infections showed similarities between RDEB and DDEB patients with self-reported mild to moderate disease severity, while severe RDEB patients reported a 20-40% higher incidence of infections than the others (Table 4).

In summary, RDEB patients, as compared to DDEB patients, are more affected by their wounds by experiencing greater impact from large wounds and need to invest more time in care.

Table 4: Comparison of patient-reported wound characteristics and QOLEB scores in DDEB and RDEB patients, including wound location, size of wounds, and number of dressing changes per week reported by RDEB patients in the study of Eng et al. (2020) and by DDEB patients in the study of Fulchand et al. (2021); Colours indicating similarity between RDEB and DDEB answers, green: similar answers, orange: different answers

	DDEB (n=42) patients Fulchand et al. (2021)		**RDEB (n=85) patients** Eng et al. (2020)	
Wound characteristics	Mild (n=23)	Moderate or severe (n=16)	Mild (n=22)	Moderate and severe (n= 61)
Recurrent wounds most frequent location Number of patients (N) %	Lower extremities (n=21) 91.3%	Lower extremities (n=16) 81.3%	Lower extremities (n=85) 86% (73/85) (Wounds/ patients (n/N))	
Size of wounds most frequent size Small (<2.5cm) Medium (2.5-7.5 cm)	Small: 65.2% Medium: 43.5%	Small: 43.8% Medium: 56.3%	Small: 47.2% Medium: 37.4%	
Number of dressing changes per week Mean (+/-) SD	6.3(+/-)3.1	4.5(+/-)3.1	5.5 (+/-) 3.2	Moderate: 5.6(+/-)3.5 Severe: 5.1(+/-) 3.5
Infections (Wounds)	30.4%	56.3%	36%	73% and 76%
QOLEB, score mean (+/-) SD	8.3(+/-) 6.3 (n=8)	19.7(+/-)12.7(n=6)	19(+/-)9	Moderate: 20(+/-)7 Severe: 24(+/-)6

Prevalent extracutaneous manifestations

For extracutaneous manifestations, RDEB and DDEB patients show similar prevalences of their most reported complications, including nail abnormalities, oral cavity problems, and hand/foot contractures, webbing, and severe scarring (Bruckner et al., 2020). For RDEB patients correlated their disease severity with anemia and mitten deformity (Eng et al., 2021), which is consistent with findings from a systematic review stating that RDEB's disease burden was associated with anemia, contractures, and difficulty walking (Tang et al., 2021). In comparison to DDEB patients (Fulchand et al., 2021), RDEB patients reported also a 4 to 6 times higher prevalence of mitten deformity of feet (Table 5) (Eng et al., 2021). Esophageal strictures were found to be a prevalent extracutaneous complication in mild to severe RDEB patients (59-71%) (Eng et al., 2021), while only DDEB patients with moderate or severe disease (62.5%) experienced esophageal strictures and swallowing difficulties (Fulchand et al., 2021) (Table 5). DDEB patients (n=39) experienced among other extracutaneous manifestations, constipation (mild to moderate/severe: 39.1 to 68.8%), dental caries (26.1% to 43.8%), and eye problems (26.1 to 31.3%) (Fulchand et al., 2021). The latter manifestation, eye problems (45 to 71%) was similarly prevalent in mild and moderate RDEB patients (n=83) (Table 5) (Eng et al., 2021). The extracutaneous manifestations of 'permanent partial sight or blindness' (5%) and skin cancer (16%) that were reported by a minority of DEB patients (n=97), were found to be the most impactful on their mental health (DEBRA Patient Insight Study, 2023).

Psychological effects

The Bruckner et al study comparing the disease burden between different EB types showed that in DDEB patients (n= 14) "depression requiring treatment" (64.3%) (vs. RDEB (n=19): 31.6%) was more prevalent than in other EB subtypes (Bruckner et al., 2020).

Conversely, Schräder et al. revealed that RDEB patients rated the statement "To feel less depressed" (83.3%) among their most important needs, and showed that this statement was significantly more important for RDEB than for DDEB patients (Schräder et al., 2021). Considerable impairments of RDEB patients' mental health are supported by a QOLEB questionnaire study, in which RDEB patients (n=31) reported a high or severe level of psychological and social impact on depression (31.2%), anxiety (40.6%), and embarrassment (15.6%) (Choi et al., 2017). Lastly, the 2023 Debra insight study showed that DEB, presumably both RDEB and DDEB, patients (n=97) mental health (63%) is comparably more impacted by their disease than for other EB types (DEBRA Patient Insight Study, 2023).

Table 5: Comparison of patient-reported prevalent clinical manifestations in DDEB and RDEB patients, as reported by RDEB patients in the study of Eng et al. (2020) and by DDEB patients in the study of Fulchand et al. (2021); Colours indicating similarity between RDEB and DDEB answers, green: similar answers, orange: different answers

	DDEB (n=42) patients Fulchand et al. (2021)		**RDEB (n=85) patients** Eng et al. (2020)	
Clinical manifestations	Mild (n=23)	Moderate or severe (n=16)	Mild (n=22)	Moderate **and** severe (n= 61)
Worst pain in past 12 months, mean (+/-) SD	3.4(+/-) 3.0	6.8(+/-) 2.5	6.3 (+/-) 3.4	8.0 (+/-) 2.0 and 8.1 (+/-) 2.5
Itch	47.6%	47.6%	86%	85% and 90%
Esophageal strictures (Difficulty swallowing)	21.7%	62.5%	59%	68% and 71%
Complete or partial mitten deformity of foot (/hand)	0 complete 4.3% partial	12.5% complete 6.3% partial	45% foot 5% hand	48% and 80% foot 13% and 24% hand
Eye problems	26.1%	31.3%	45%	45% and 71%

Physical and social abilities affecting the quality of life

A recent study assessing disease impact on DEB patients utilized the QOLEB questionnaire, which revealed that QoL was most impacted by reduced involvement in sports, financial impacts on the family, reduced abilities to bath or shower as well as the ability to eat, and physical pain (Paller et al., 2022). This agrees with Bruckner et al, who showed that for RDEB patients the “ability to eat” next to the “ability to sleep”, “the ability to write” and “the ability to move around the house” were the most impacted activities of their daily life(Bruckner et al., 2020). This is supported by results from a QOLEB questionnaire, which showed that eating (62.5%) next to bathing (53.1%), moving outside the home (37.5%) and writing (28.1%) were most impacted function for RDEB patients (Choi et al., 2017). Bruckner et al. revealed a substantial variation in the ability to write among RDEB patients (n=19). While 57.9% (n=11) reported no impairment in their ability to write, other RDEB patients (n=2) were the only ones among all surveyed EB patients (n=62) to experience complete disability to write (10.5%) (Bruckner et al., 2020). The severity of the impact on writing ability was evident with 10.5% reporting being unable to write and 21.1% finding typing easier (Bruckner et al., 2020), representing a strong impairment compared to other EB types (EBS, JEB, and DDEB). RDEB patients participating in the codesign of a dressing glove indicated when interviewed about their hand mobility that they experienced the loss of the ability to pick up things, of thumb function, and the ability to squeeze (Graham et al., 2020), which indicates a strong impairment for activities involving their hands. Tang et al.’s review stated that RDEB patients experience severe impacts on their daily life, and were found to experience worsened QoL, reduced functioning, and participation in social activities compared to other EB subtypes (Tang et al., 2021).

The QoL for DDEB patients was found to be most impacted by similar abilities as for RDEB, whereas the most impacted ability was the “ability to move around the home” (Bruckner et al., 2020). In other studies, DDEB patients experienced significant impacts on disease perception, notably in terms of pain, the presence of chronic open wounds, difficulty swallowing, difficulty walking, and anal strictures (Fulchand et al., 2021). While one study found that the Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) score failed to reflect disease severity and QoL impact in localized EBS patients (Hunjan et al., 2023), another study by Paller et al. demonstrated that the EDABSI score effectively monitored disease severity in DDEB patients (Paller et al., 2022). In conclusion, both RDEB and DDEB patients commonly experience limitations in mobility, pain, chronic wounds, and reduced ability to perform daily activities. Additionally, RDEB patients may face unique challenges through severe impairment in writing and hand function.

JEB

Itch and Pain

The vast majority of JEB patients experience fragile (92%), itchy (77%), and painful skin (85%) and rate these symptoms among the most impactful (DEBRA Patient Insight Study, 2023). Furthermore, JEB patients experience similarly high levels of chronic pain and itch compared to RDEB patients (Bruckner et al., 2020). An overall high prevalence of pain (92%) and consistently high values in the Skinindex-29, which assesses the health-related QoL in dermatological patients (Ehren et al., 2001; Tabolli et al., 2009), suggest that the skin condition has a high impact on JEB patients. This aligns with the three highest-rated needs by JEB patients (n=10): “To get better skin quickly” (80%), “To be free of pain” (70%) and “To be healed of all skin alterations “(70%) (Schräder et al., 2021).

Prevalent and impactful clinical manifestations

The most prevalent extracutaneous complications experienced by JEB patients were nail abnormalities, dental problems, oral cavity problems, hand/foot contractures, webbing, severe scarring, and problems with the scalp or with hair loss (Bruckner et al., 2020). All except for the last-named complication ‘problems with the scalp or with hair loss’ were also commonly reported among the other EB types surveyed in this study (Bruckner et al., 2020). The Debra insight study identified ‘blisters on the soles of the feet’, ‘Skin cancer’, and ‘Nails that are thick and unformed’ as impactful symptoms in affected JEB patients. Whereas deformations of the nails (89%) next to blisters on the soles of the feet (46%) were noticeably more prevalent than skin cancer (15%) among the surveyed patients (DEBRA Patient Insight Study, 2023). The most impactful symptoms on the mental health for JEB (n=9) were reported as problems with passing urine (25%), scalp blistering and hair loss (25%), and temporary partial sight or blindness (25%) (DEBRA Patient Insight Study, 2023). Scalp blistering and hair loss were the most prevalent symptoms reported by over half (62%) of the surveyed JEB patients (n=13), while 'temporary partial sight or blindness' and 'problems with bladder and passing urine' were only present in approximately one-third (31%) of participants (Debra insight study 2023).

Wound burden

JEB patients (n=13) experience poor wound healing (92%), with a similar prevalence (90%) as reported by DEB patients (n=97) (DEBRA Patient Insight Study, 2023). Additionally, in the DEBRA insight study, wounds that heal slowly (78%) were rated among the five most impactful symptoms by JEB patients (DEBRA Patient Insight Study, 2023). Another study by Bruckner et al. (2020) found that the average percentage of the body covered in wounds for JEB patients falls between the reported values of RDEB and DDEB, with approximately half of the patients (n=8) reporting 10-30% of their body being covered with wounds (Bruckner et al., 2020).

The wound care time of below two hours (75%) is comparable to DDEB patients surveyed in the Bruckner et al. (2020) study but is drastically less when compared to RDEB. The majority of JEB patients (n=8) in the Bruckner et al. study reported their disease severity as moderate to severe (75%). Milder subtypes such as localized JEB experience milder cutaneous manifestation with blisters localized to peripheral parts of the body (Has et al., 2020; Supplementary Material). Hence, the wound burden reported by the JEB patients in the Bruckner et al. study primarily represents moderate to severe subtypes and might not be representative of milder subtypes and for the phenotypical heterogeneity of JEB patients.

Physical and social abilities affecting the quality of life

JEB patients (n=8) rated the three most impacted abilities of their daily life: the ability to write, the ability to sleep, and the ability to move around the home. Whereas an equal percentage of JEB patients reported to be either 'not' (37.5%) or 'a lot' (37.5%) affected by the ability to eat (Bruckner et al., 2020). Similar to these findings, were the ability to exercise, sleep, and engage in everyday mobility highly impacted (DEBRA Patient Insight Study, 2023). Furthermore, stated JEB patients that: 'To be more capable in daily life' and 'to be able to lead a normal everyday life' had high importance for them (Schräder et al., 2021).

KEB

Kindler EB, with only 250 reported cases to date, is the rarest of the four major EB types (Has et al., 2020). Nevertheless, our search yielded a single study addressing the needs and disease burden of KEB patients (Fig. 1). The one identified study, conducted by DEBRA UK, surveyed the needs of KEB patients and their disease burden. It presented responses from up to 5 KEB patients, with the exact number depending on the responses to different questionnaire topics (DEBRA Patient Insight Study, 2023). This study found that the most prevalent skin and blistering-associated symptoms among KEB participants (n=5) were: Fragile (100%), itchy (100%), painful (80%), and thin-looking skin (100%) as well as 'Nail that are thick and unformed' (100%). Whereas the most prevalent non-cutaneous symptoms experienced among all surveyed KEB patients (n=5) were blisters inside the mouth and throat (100%), dental problems (100%), sensitivity to the sun (100%) and GI symptoms (100%), in particular reflux. Despite the high prevalence of the symptoms mentioned previously, they were not rated among the most impactful symptoms, as only 40-60% of affected patients considered them to have a 'High Impact'. In contrast, the most impactful symptoms on KEB patients were reported to be blisters on the soles of the feet (100%), temporary partial sight or blindness (100%), fatigue (100%), and problems with the bladder and passing urine (100%) among affected KEB patients (DEBRA Patient Insight Study, 2023).

Physical and social abilities affecting the quality of life

One of the most affected functions for KEB patients in their daily lives is their ability to take care of themselves, which includes tasks like personal hygiene, eating, and drinking. Regarding mental health impacts, blisters inside the mouth and throat (60%) and thick, unformed nails (20%) were reported as the most impactful symptoms by KEB patients (n=5). Notably, these symptoms were among the most prevalent, experienced by 100% of surveyed KEB patients respectively (DEBRA Patient Insight Study, 2023). Tasks related to self-care are particularly affected, underscoring the profound impact of KEB on daily life functioning.

Table 6: Outcome areas and domains comprising patient-reported needs (Patient-reported outcomes) that were prevalently reported among EB patients or rated as important and impactful needs (Important), are indicated by crosses (x, xx), showing which outcomes were reported by which EB type; 'x' indicates outcomes reported in one study, and 'xx' indicates outcomes reported in two or more studies. Prevalent and important outcome domains per EB type are highlighted in darker tones. The left column corresponds to outcome areas and domains reported in EB clinical trials (Korte et al., 2023). The table extends onto the next page.

Clinical trial reported outcomes (Korte et al., 2023)	**Patient reported outcomes**	**EBS** n(patients)= 350 n(studies)=9		**JEB** n(patients)=43 n(studies)=5		**DDEB** n(patients)=178 n(studies)=7		**RDEB** n(patients)=284 n(studies)=10		**DEB** n(patients)=63 n(studies)=2		**KEB** n(patients)=4 n(studies)=1	
Area Domains	**Area Domains**	**Prevalent**	**Important**	**Prevalent**	**Important**	**Prevalent**	**Important**	**Prevalent**	**Important**	**Prevalent**	**Important**	**Prevalent**	**Important**
Cutaneous manifestations	**Skin and Wound burden**												
Lesion characteristics and appearance	**Thin looking skin**											x	
Total skin involvement	**Average percentage of body covered by wounds**			x				x	x				
Skin resistance	**Fragile skin**		x	x	x	x		x		x	x	x	x
Wound formation	**Reduce number of severity and wounds**								x		x		
	Chronic wounds					x	x		x				
	Recurrent wounds	x				x		x					
	Small or medium wounds	x				x		x					
Blister formation	**Blisters**	xx				x			x		x		
	Blisters inside the mouth and throat		x									x	x
	Blisters on the palms of the hands	xx	xx										
	Blisters on the soles of the feet	xx	x	x	x							x	x
Plantar characteristics	**Manifestation at lower extremities**	x	x			x		x					
Wound healing	**Slow wound healing**			x		xx						x	
Lesion healing	**To be healed of all skin alterations**				x		x		x				
	To get better skin quickly		x		x		x		x				
Cancer formation	**Reduced risk of skin cancer**												
	SCCs and/or Neoplasms				x		x		x		x		
Infection	**Reduce risk of infection**					x		x			x		
Scarring	**Hand/foot contractures, webbing, severe scarring**	x		x		x		xx	x				
	Prevention, delay, correction syndactyly										x		
Resource use													
Duration of wound care	**Longest time on wound care**							x	x		x		
	Long time for dressing change					x		x	x				
	To have to spend less time with daily care						x		x				
Symptoms	**Symptoms**												
Pain associated with EB	**Painful skin (To be free of pain)**	xx	xx	xx	xx	x	xx	x	xx	x	xx	x	
	Acute Pain		x				x		xx				
	Chronic Pain				x		x		xx				
	Neuropathic Pain	x											
Pruritus	**Itch (To be free of itching)**	x	xx	x	x	x	x	x	xx	x	x	x	x
Extracutaneous manifestations													
Oral and dental health	**Oral cavity problems**	x		x		x		x					
	Dental problems	x		x		x		x				x	
	Difficulty swallowing						x	x	x			x	x
	Difficulty walking	x					x		x				

Clinical trial reported outcomes (Korte et al., 2023)		Patient reported outcomes		EBS n(patients)= 350 n(studies)=9		JEB n(patients)=43 n(studies)=5		DDEB n(patients)=178 n(studies)=7		RDEB n(patients)=284 n(studies)=10		DEB n(patients)=63 n(studies)=2		KEB n(patients)=4 n(studies)=1	
Area	Domains	**Area**	**Domains**	**Prevalent**	**Important**	**Prevalent**	**Important**	**Prevalent**	**Important**	**Prevalent**	**Important**	**Prevalent**	**Important**	**Prevalent**	**Important**
Oesophageal strictures		**Esophageal strictures**						x		x				x	
Corneal symptoms		**Eye problems**		x				x		x				x	
		Anemia								x	x				
		Problems with scalp or hair loss				x	x								
		Nail abnormalities		x		x	x	x		x				x	x
		Problems with blader or passing urine			x		x								x
		Temporary partial sight or blindness					x						x		x
Symptoms		**Symptoms**													
Digestion and defaecation		**Gastrointestinal tract symptoms**			xx				x					x	
		Sensitivity to the sun												x	
		Mitten deformation								x	x				
Physical functioning		**QoL**													
Ability to chew and swallow		**Ability to eat and swallow**					x	x	x	xx	xx		x	x	x
Daily functionality and disability		**To be able to lead a normal everyday life**			x		x								
		To be more capable in daily life					x							x	x
		To be able to have a normal working life									x				
		Ability to bath or shower								x	xx		xx		
Ability to move		**Ability to move around the home**			xx	x	x	x	xx	x	xx				
		To be able to engage in normal leisure activities			x										
		Ability to walk		x				x	x	x	x				
		Involvement in sports			xx		x				x		x		
Hand functioning		**Ability to write**			xx		x		x		xx				
Quality of Life															
Contractures		**Hand/foot contractures, webbing, severe scarring**		x		x		x		xx	x				
EB-specific quality of life		**QOLEB**		x				x		x					
General quality of life		**To be able to lead a normal everyday life**			x		x		x						
Psychosocial functioning															
Dermatological quality of life		**QoL assessed in Tabolli et al. (2009)**					x		x		x				
Mental health		**Depression requiring treatment**						x							
		To feel less depressed									x				
Sleep		**Ability to sleep (To be able to sleep better)**		x	x		xx	x	x	x	xx			x	
Family life		**Family carers impacted (Wu et al., 2020)**			x		x						x		
Psychological impact		**To have no fear that the disease will progress**													
		Feeling frustrated		x	x										
Well being		**Fatigue**													x
Social functioning		**To be less of a burden to relatives and friends**									x				

Patient-reported needs are underrepresented in outcomes measured in EB clinical trials

To assess whether patients' needs and perspectives for important outcome domains match measured outcome domains in EB clinical trials, we created an overview of patient-reported needs for EBS, JEB, DEB, and KEB representing prevalently or as impactful and important rated needs (Table 6). For a better overview, we summarized the most prevalent and impactful needs reported per EB type (Figure 5), which were categorized and represented in three distinct outcome areas: Quality of Life (QoL), Symptoms, and Skin and Wound Burden (Figure 5 and Table 6).

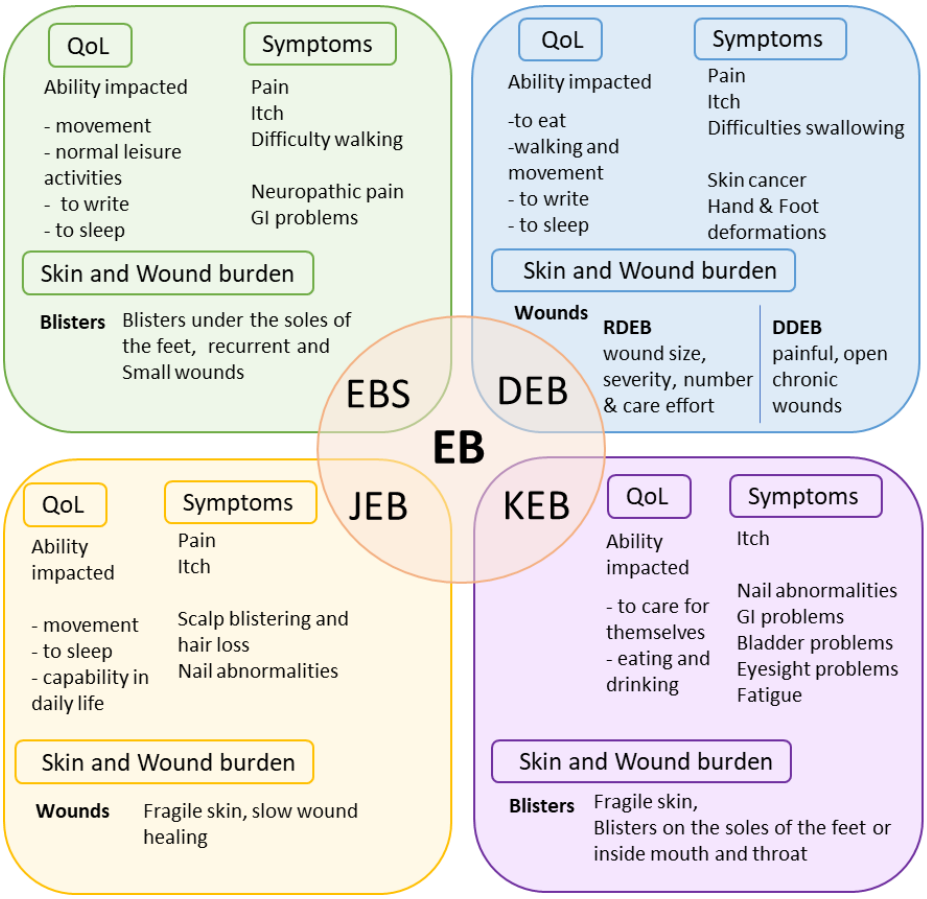

Figure 5: Important outcomes domains and areas for patients of the four major EB types. Outcome domains describe the prevalent and important patient-reported needs (see Table 6) and were divided into three outcome areas compromising the Quality of Life (QoL), Symptoms including clinical manifestations, and Skin and Wound burden. GI: Gastrointestinal tract related symptoms

The outcome area of Skin and Wound burden describes the most impactful and prevalent symptoms experienced for each EB type by their skin conditions. The comparison between the impact and prevalence of cutaneous manifestations and wound characteristics (Table 6, Skin and Wound burden), revealed that the wound burden experienced by EB patients differs between all four types (Figure 5). In EBS patients their skin fragility mainly manifested in blisters under the soles of their feet, which result in small and recurrent wounds and difficulties walking. In RDEB patients wound burden is characterized by size, number, and severity of wounds, resulting in lengthy wound care times. In contrast, the wound burden in DDEB is not characterized by the wound size but by painful, open, and chronic wounds (Table 6). Lastly, JEB patients' wound burden is characterized by fragile skin and slow-healing wounds, while KEB patients' wound burden is defined by fragile skin leading to blisters under the soles of the feet or inside the mouth and throat (Figure 5).

A recent scoping review identified and summarized outcome domains measured in EB clinical trials and found that outcome domains covering cutaneous manifestations were most frequently reported across the assessed studies (Korte et al., 2023). Moreover, the most frequently measured outcome domains identified in that review such as ‘Blister formation’ for EBS and ‘Wound healing ‘for JEB, DEB, and RDEB (Korte et al., 2023, Supplementary Material S4) reflected the characteristics of the here described wound burden and phenotypic appearances (Table 6). However, it became apparent that for RDEB patients’ certain wound characteristics such as wound size and number considerably contributed to the experienced wound burden. However, those outcomes were not separately represented among frequently measured outcome domains for RDEB clinical trials in this recent scoping review (Korte et al., 2023, Supplementary Material S4).

The most prevalent and impactful patient-reported outcome domains among all four major EB types under the outcome area Symptoms were pain and itch (Table 6). These symptoms align with existing outcome domains, 'Pain associated with EB’ and 'Pruritus’ (Table 6) measured in previous clinical trials (Korte et al., 2023). Despite the high prevalence and importance of pain and itch among JEB patients, only 16.7% of studies measuring outcomes for JEB included these symptoms within their corresponding outcome domains(Korte et al., 2023, Supplementary Material S4). Conversely, the outcome domain 'pain associated with EB' was measured in 46.9% of studies for DEB patients and 23.6% for RDEB patients, thus better-represented pain in DEB patients (Korte et al., 2023, Supplementary Material S4). Despite itch being reported as prevalent and impactful among all four EB types (Table 6), pruritus was assessed in only about one-fifth of all past EB clinical trials (Korte et al., 2023), indicating its underrepresentation. Consequently, the infrequent measurement of pain and pruritus as outcome domains in past clinical trials does not capture their prevalence and importance among EB patients.

Despite similarities in pain and itch among EB patients, the phenotypic heterogeneity between EB types is better captured in patient-reported needs related to mucosal membranes, nails, hair, and extracutaneous manifestations, which are also represented in the outcome area Symptoms (Table 6 and Figure 5). These manifestations contribute to the perceived disease burden, particularly evident in their impact on patients' QoL. For instance, KEB patients often experience blisters inside the throat and mouth, which matches their reported difficulty in eating and drinking, highlighted as impactful ability on their QoL (Table 6 and Figure 5). Similarly, DEB patients face challenges swallowing and impairment in their ability to eat (Figure 5) potentially due to oral cavity problems, esophageal strictures, and dental issues reported among their most prevalent symptoms (Table 6). EBS and DEB patients commonly experience impairments in walking and daily movement activities (Table 6). For EBS patients, this can be attributed to characteristic blisters on the soles of the feet. Similarly, DEB patients' impairment aligns with clinical manifestations such as mitten deformities, contractures, webbing, and severe scarring, which cause pain associated with movement. These manifestations but localized on the hands might explain the impacted ability to write for patients with the severe form of DEB (Figure 5). Interestingly, EBS patients also rated difficulties with writing among the most impactful abilities (Table 6) potentially due to the prevalent blisters on the palms of their hands causing pain. Despite variations in severity and manifestation across EB types, patients with EBS, JEB, and DEB consistently report a high impact on their abilities to sleep and move (Figure 5).

In clinical trials, the impaired ability to write for RDEB and DEB patients is frequently measured under 'Hand functioning' (12.5%) and 'Contractures' (11.2%) within physical functioning outcome domains (Korte et al., 2023, Supplementary Material S4). However, the highly impacted ability to eat among DEB patients is noticeably underrepresented, being measured in only 9% of studies, along with the ability to move (3% in DEB) (Korte et al., 2023, Supplementary Material S4), which does not adequately represent the disease impact on the quality of life.

Conversely, the most affected abilities for EBS patients, such as plantar characteristics (14.3%) and the ability to move (9.5%), are more frequently measured within physical functioning outcome domains (Korte et al., 2023, Supplementary Material S4) and better present the experienced impact on their QoL. Despite this, 'Sleep' as an outcome domain is only assessed in mixed EB-type studies, representing 5% of clinical trials (Korte et al., 2023, Supplementary Material S4), which does not align with the reported impact of sleep on EBS, JEB, and DEB patients (Table 6).

Discussion

This review synthesizes data from 22 studies involving 922 EB patients, focusing on their reported symptoms and needs. The majority of relevant literature (72%) was published between 2020-2024, making it representative of current patient needs. To our knowledge, this is the first review to compare EB patients' needs across five subtypes and compare them with outcome domains in EB clinical trials. Considerable heterogeneity exists in important needs across EB types, especially concerning extracutaneous manifestations. Notably, pain and itch emerged as the most impactful symptoms across all EB types. However, these symptoms, along with others like sleep difficulties and mobility impairments, have been underrepresented in past clinical trials.

The current treatment options for EB patients focus on symptom relief, which highlights the need for outcome domains to accurately reflect patients' needs in clinical trials. Our overview of patient-reported needs per EB type can potentially aid in selecting representative outcome domains for future clinical trials, enhancing the representation of those needs. Cutaneous manifestation outcome domains, such as 'Wound healing' and 'Blister formation,' have been frequently used in past EB clinical trials (Korte et al., 2023), indicating their relevance in evaluating new interventions. Our review presents a detailed characterization of the skin and wound burden experienced by patients with different EB types, providing more specific descriptions, like wound size (RDEB), open and chronic wounds (DDEB), blisters under the soles of the feet (EBS), of important outcomes domains for assessing cutaneous manifestations. This overview can help to more accurately define outcome domains that describe the wound burden for each specific EB type.

This illustrates how patient-focused outcomes can inform future clinical trial design. Moreover, it can serve as a template for the COSEB initiative to define COSs per EB type, ensuring a more precise representation of the experienced disease burden by EB patients.

Limitations in the existing literature

The majority of studies used questionnaires and surveys to extract the patient's perspective, symptoms, and needs. However, question-wording can introduce bias or be overly broad, potentially limiting the informative value of the answers. For example, Eng et al. (2021) noted challenges in assessing differences in pain in mild to severe RDEB patients using a question on 'Worst pain in the past 12 months,' suggesting more specific assessment methods like a 24-hour timeframe or situational assessments. Conversely, pain in EBS patients, influenced by blister formation, varies over longer timescales and is affected by seasonal changes and flare-ups. Consequently, surveying EBS patients for median pain within 24 hours may inadequately represent pain prevalence and intensity. Moreover, pain experienced by EBS patients shows different characteristics with neuropathic pain being prevalent, which should be considered when assessing patient-reported pain in the future.

Similarly, sleep difficulties were often overlooked due to the bias in the commonly used QOLEB questionnaire not including sleep, despite its prevalence and impact. Further investigation into the impact of sleep difficulties on different EB types and its potential inclusion as an outcome domain should be discussed in focus groups with representative patients to assess its impact on quality of life.

Strengths and weaknesses of this review

This literature review is limited in its completeness by focusing parts of the search on the past four years for feasibility reasons. Despite the additional search steps conducted this might have resulted in missing relevant literature and patient-reported needs from the years before 2020. While our overview of patient-reported needs can be considered representative of current EB patients, discussing it in subgroup meetings of the COSEB initiative is advisable to ensure essential needs are not overlooked.

Additionally, our search terms did not include keywords for mental health or psychosocial symptoms, limiting information on the psychosocial impact of EB. However, included studies highlighted common feelings of frustration, guilt, social isolation, and depression among EB patients, emphasizing the disease's mental health burden. Given that DEB patients seem more affected than other EB types, discussions in focus groups involving DEB patients, caregivers, and healthcare professionals could explore mental health issues in more detail.

The limited number of included studies and analyses of KEB patients' burden and needs likely stems from the rarity of this EB type rather than shortcomings in the search strategy. Nonetheless, future analyses should expand searches beyond recent years and explore unpublished literature on patients' representative websites for completeness. Contacting patient representative organizations for interviews of KEB patients may provide additional information on their needs and experienced disease burden.

Demographic characteristics like age and severity levels of EB patients weren't analyzed in our review due to time constraints. However, these factors considerably influence symptoms experienced by EB patients. For example, EBS manifestations tend to get milder with age, while JEB and DEB may worsen, with additional manifestations like SCCs occurring in adulthood. Thus, our overview may potentially over or underrepresent certain symptoms. Analyzing available demographic and subtype data from surveyed patients can help better estimate representation and identify any discrepancies. To address limitations in outcome domains and representation of needs and symptoms for EB types, setting up focus groups or sending the overview of important outcome domains to representatives of patients and caregivers could be beneficial. Their feedback can help evaluate domain representativeness and identify any relevant areas or domains missed in the review.

Future prospects and conclusion

This review highlights both similarities and differences in symptoms and needs across the five subtypes of EB. Using these patient-reported needs, we offer a comprehensive overview and template of important outcome domains representative of the disease burden in EBS, JEB, RDEB, and DDEB patients. This overview can serve as a baseline for defining the consensus COS sets within the COSEB initiative. Furthermore, we aim for this template to aid in refining outcome domains to better reflect the disease burden experienced by EB patients and address their treatment priorities in future clinical trials.

References

Baardman, R., Yenamandra, V. K., Duipmans, J. C., Pasmooij, A. M. G., Jonkman, M. F., van den Akker, P. C., & Bolling, M. C. (2021). Novel insights into the epidemiology of epidermolysis bullosa (EB) from the Dutch EB Registry: EB more common than previously assumed? *Journal of the European Academy of Dermatology and Venereology*, *35*(4), 995–1006. https://doi.org/10.1111/JDV.17012

Bardhan, A., Bruckner-Tuderman, L., Chapple, I. L. C., Fine, J.-D., Harper, N., Has, C., Magin, T. M., Marinkovich, M. P., Marshall, J. F., McGrath, J. A., Mellerio, J. E., Polson, R., & Heagerty, A. H. (2020). Epidermolysis bullosa. *Nature Reviews Disease Primers*, *6*(1), 78. https://doi.org/10.1038/s41572-020-0210-0

Bruckner, A. L., Losow, M., Wisk, J., Patel, N., Reha, A., Lagast, H., Gault, J., Gershkowitz, J., Kopelan, B., Hund, M., & Murrell, D. F. (2020b). The challenges of living with and managing epidermolysis bullosa: insights from patients and caregivers. *Orphanet Journal of Rare Diseases*, *15*(1), 1. https://doi.org/10.1186/s13023-019-1279-y

Brun, J., Chiaverini, C., Devos, C., Leclerc-Mercier, S., Mazereeuw, J., Bourrat, E., Maruani, A., Mallet, S., Abasq, C., Phan, A., Vabres, P., Martin, L., Bodemer, C., Lagrange, S., & Lacour, J.-P. (2017). Pain and quality of life evaluation in patients with localized epidermolysis bullosa simplex. *Orphanet Journal of Rare Diseases*, *12*(1), 119. https://doi.org/10.1186/s13023-017-0666-5

Choi, S., Solis, D., Nazaroff, J., Bailey-Healy, I., Barriga, M., Dutt-Singkh, Y., Li, S., Marinkovich, M., Rangel-Miller, V., & Tang, J. Y. (2017). 224 Quality of life in recessive dystrophic epidermolysis bullosa: The AltaVoice patient registry, 2012-2015. *Journal of Investigative Dermatology*, *137*(5), S38. https://doi.org/10.1016/J.JID.2017.02.239

Christiano, A. M., Anhalt, G., Gibbons, S., Bauer, E. A., & Uitto, J. (1994). Premature Termination Codons in the Type VII Collagen Gene (COL7A1) Underlie Severe, Mutilating Recessive Dystrophic Epidermolysis Bullosa. *Genomics*, *21*(1), 160–168. https://doi.org/10.1006/GENO.1994.1238

Christiano, A. M., McGrath, J. A., Tan, K. C., & Uitto, J. (1996). Glycine substitutions in the triple-helical region of type VII collagen result in a spectrum of dystrophic epidermolysis bullosa phenotypes and patterns of inheritance. *American Journal of Human Genetics*, *58*(4), 671. /PMC/articles/PMC1914674/?report=abstract

Condrat, I., He, Y., Cosgarea, R., & Has, C. (2019). Junctional epidermolysis bullosa: Allelic heterogeneity and mutation stratification for precision medicine. *Frontiers in Medicine*, *6*(JAN), 415287. https://doi.org/10.3389/FMED.2018.00363/BIBTEX

Coulombe, P. A., & Lee, C. H. (2012). Defining Keratin Protein Function in Skin Epithelia: Epidermolysis Bullosa Simplex and Its Aftermath. *Journal of Investigative Dermatology*, *132*(3), 763–775. https://doi.org/10.1038/JID.2011.450

Davila-Seijo, P., Hernández-Martín, A., Morcillo-Makow, E., de Lucas, R., Domínguez, E., Romero, N., Monrós, E., Feito, M., Carretero, L., Aranegui, B., & García-Doval, I. (2013). Prioritization of therapy uncertainties in Dystrophic Epidermolysis Bullosa: where should research direct to? an example of priority setting partnership in very rare disorders. *Orphanet Journal of Rare Diseases*, *8*, 61. https://doi.org/10.1186/1750-1172-8-61

DEBRA UK and Synergy Healthcare Research (2023, June). Epidermolysis Bullosa Patient Insights. https://www.debra.org.uk/pages/category/eb-insights-study

Ehren, M.-M., Lasek, R. J., Sahay, A. P., & Sands, L. P. (2001). *Measurement Properties of Skindex-16: A Brief Quality-of-Life Measure for Patients with Skin Diseases*. https://doi.org/10.1007/s102270000010

Eng, V. A., Solis, D. C., Gorell, E. S., Choi, S., Nazaroff, J., Li, S., de Souza, M. P., Murrell, D. F., Marinkovich, M. P., & Tang, J. Y. (2021). Patient-reported outcomes and quality of life in recessive dystrophic epidermolysis bullosa: A global cross-sectional survey. *Journal of the American Academy of Dermatology*, *85*(5), 1161–1167. https://doi.org/10.1016/j.jaad.2020.03.028

Fine, J. D. (2016). Epidemiology of Inherited Epidermolysis Bullosa Based on Incidence and Prevalence Estimates From the National Epidermolysis Bullosa Registry. *JAMA Dermatology*, *152*(11), 1231–1238. https://doi.org/10.1001/JAMADERMATOL.2016.2473

Fine, J. D., Bruckner-Tuderman, L., Eady, R. A. J., Bauer, E. A., Bauer, J. W., Has, C., Heagerty, A., Hintner, H., Hovnanian, A., Jonkman, M. F., Leigh, I., Marinkovich, M. P., Martinez, A. E., McGrath, J. A., Mellerio, J. E., Moss, C., Murrell, D. F., Shimizu, H., Uitto, J., … Zambruno, G. (2014). Inherited epidermolysis bullosa: Updated recommendations on diagnosis and classification. *Journal of the American Academy of Dermatology*, *70*(6), 1103–1126. https://doi.org/10.1016/J.JAAD.2014.01.903

Fine, J. D., Johnson, L. B., Weiner, M., Li, K. P., & Suchindran, C. (2009). Epidermolysis bullosa and the risk of life-threatening cancers: the National EB Registry experience, 1986-2006. *Journal of the American Academy of Dermatology*, *60*(2), 203–211. https://doi.org/10.1016/J.JAAD.2008.09.035

Fine, J. D., Johnson, L. B., Weiner, M., & Suchindran, C. (2007). Tracheolaryngeal Complications of Inherited Epidermolysis Bullosa: Cumulative Experience of the National Epidermolysis Bullosa Registry. *The Laryngoscope*, *117*(9), 1652–1660. https://doi.org/10.1097/MLG.0B013E318093ED8E

Forlino, A., Lasko, P., Nyström, A., Nystroem@uniklinik-, A., Bruckner-Tuderman, L., & Kiritsi, D. (2021). Dystrophic Epidermolysis Bullosa: Secondary Disease Mechanisms and Disease Modifiers. *Frontiers in Genetics | www.Frontiersin.Org*, *1*. https://doi.org/10.3389/fgene.2021.737272

Franzke, C.-W., Tasanen, K., Schumann, H., & Bruckner-Tuderman, L. (2003). Collagenous transmembrane proteins: collagen XVII as a prototype. *Matrix Biology*, *22*, 299–309. https://doi.org/10.1016/S0945-053XŽ03.00051-9

Frew, J. W., Martin, L. K., Nijsten, T., & Murrell, D. F. (2009). Quality of life evaluation in epidermolysis bullosa (EB) through the development of the QOLEB questionnaire: an EB-specific quality of life instrument. *The British Journal of Dermatology*, *161*(6), 1323–1330. https://doi.org/10.1111/j.1365-2133.2009.09347.x

Frew, J. W., & Murrell, D. F. (2010). Quality of life measurements in epidermolysis bullosa: tools for clinical research and patient care. *Dermatologic Clinics*, *28*(1), 185–190. https://doi.org/10.1016/j.det.2009.10.019

Fulchand, S., Harris, N., Li, S., Barriga, M., Gorell, E., de Souza, M., Murrell, D., Marinkovich, M. P., Krishna Yenamandra, V., & Tang, J. Y. (2021). Patient-reported outcomes and quality of life in dominant dystrophic epidermolysis bullosa: A global cross-sectional survey. *Pediatric Dermatology*, *38*(5), 1198–1201. https://doi.org/10.1111/pde.14802

Graham, T., Sooriah, S., Box, R., Gage, H., Williams, P., Clemett, V., & Grocott, P. (2020). Participatory co-design of patient-reported outcome indicators and N-of-1 evaluation of a dressing glove for Epidermolysis bullosa. *Journal of Wound Care*, *29*(12), 751–762. https://doi.org/10.12968/jowc.2020.29.12.751

Hammersen, J., Has, C., Naumann-Bartsch, N., Stachel, D., Kiritsi, D., Söder, S., Tardieu, M., Metzler, M., Bruckner-Tuderman, L., & Schneider, H. (2016). Genotype, Clinical Course, and Therapeutic Decision Making in 76 Infants with Severe Generalized Junctional Epidermolysis Bullosa. *Journal of Investigative Dermatology*, *136*(11), 2150–2157. https://doi.org/10.1016/J.JID.2016.06.609

Has, C., Bauer, J. W., Bodemer, C., Bolling, M. C., Bruckner-Tuderman, L., Diem, A., Fine, J.-D., Heagerty, A., Hovnanian, A., Marinkovich, M. P., Martinez, A. E., McGrath, J. A., Moss, C., Murrell, D. F., Palisson, F., Schwieger-Briel, A., Sprecher, E., Tamai, K., Uitto, J., … Mellerio, J. E. (2020). Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility. *The British Journal of Dermatology*, *183*(4), 614–627. https://doi.org/10.1111/bjd.18921

Has, C., Castiglia, D., del Rio, M., Garcia Diez, M., Piccinni, E., Kiritsi, D., Kohlhase, J., Itin, P., Martin, L., Fischer, J., Zambruno, G., & Bruckner-Tuderman, L. (2011). Kindler syndrome: Extension of FERMT1 mutational spectrum and natural history. *Human Mutation*, *32*(11), 1204–1212. https://doi.org/10.1002/HUMU.21576

Has, C., Hess, M., Anemüller, W., Blume-Peytavi, U., Emmert, S., Fölster-Holst, R., Frank, J., Giehl, K., Günther, C., Hammersen, J., Hillmann, K., Höflein, B., Hoeger, P. H., Hotz, A., Mai, T. A., Oji, V., Schneider, H., Süßmuth, K., Tantcheva-Póor, I., … Reimer-Taschenbrecker, A. (2023). Epidemiology of inherited epidermolysis bullosa in Germany. *Journal of the European Academy of Dermatology and Venereology*, *37*(2), 402–410. https://doi.org/10.1111/JDV.18637

Has, C., & Nyström, A. (2015). Epidermal Basement Membrane in Health and Disease. *Current Topics in Membranes*, *76*, 117–170. https://doi.org/10.1016/BS.CTM.2015.05.003

Has, C., Nyström, A., Saeidian, A. H., Bruckner-Tuderman, L., & Uitto, J. (2018). Epidermolysis bullosa: Molecular pathology of connective tissue components in the cutaneous basement membrane zone. *Matrix Biology*, *71–72*, 313–329. https://doi.org/10.1016/J.MATBIO.2018.04.001

Hunjan, M. K., Bardhan, A., Zuzarte, L., Balacco, D. L., Harper, N., & Heagerty, A. (2023). Are existing validated severity scores for epidermolysis bullosa reflective of the burden of disease in patients with epidermolysis bullosa simplex? *Clinical and Experimental Dermatology*, *48*(6), 706–707. https://doi.org/10.1093/ced/llad069

Jackson, A., Moss, C., Chandler, K. E., Balboa, P. L., Bageta, M. L., Petrof, G., Martinez, A. E., Liu, L., Guy, A., Mellerio, J. E., Lee, J. Y. W., Ogboli, M., Ryan, G., McGrath, J. A., & Banka, S. (2023). Biallelic TUFT1 variants cause woolly hair, superficial skin fragility, and desmosomal defects. *British Journal of Dermatology*, *188*(1), 75–83. https://doi.org/10.1093/BJD/LJAC026

Jobard, F., Bouadjar, B., Caux, F., Hadj-Rabia, S., Has, C., Matsuda, F., Weissenbach, J., Lathrop, M., Prud'homme, J. F., & Fischer, J. (2003). Identification of mutations in a new gene encoding a

FERM family protein with a pleckstrin homology domain in Kindler syndrome. *Human Molecular Genetics*, *12*(8), 925–935. https://doi.org/10.1093/HMG/DDG097

Khan, A., Riaz, R., Ashraf, S., & Akilimali, A. (2023). Revolutionary breakthrough: FDA approves Vyjuvek, the first topical gene therapy for dystrophic epidermolysis bullosa. *Annals of Medicine & Surgery*, *85*(12), 6298–6301. https://doi.org/10.1097/MS9.0000000000001422

Korte, E. W. H., Spuls, P. I., van den Akker, P. C., Kiritsi, D., Laimer, M., Pasmooij, A. M. G., Riedl, R., Vroom, E., Wally, V., Welponer, T., & Bolling, M. C. (2024). Harmonization of outcomes in epidermolysis bullosa: report of the Core Outcome Sets for Epidermolysis Bullosa (COSEB) kick-off meeting. *The British Journal of Dermatology*, *190*(2), 268–270. https://doi.org/10.1093/bjd/ljad361

Korte, E. W. H., Welponer, T., Kottner, J., van der Werf, S., van den Akker, P. C., Horváth, B., Kiritsi, D., Laimer, M., Pasmooij, A. M. G., Wally, V., & Bolling, M. C. (2023). Heterogeneity of reported outcomes in epidermolysis bullosa clinical research: a scoping review as a first step towards outcome harmonization. *The British Journal of Dermatology*, *189*(1), 80–90. https://doi.org/10.1093/bjd/ljad077

Mellerio, J. E. (2023). EASE-y does it: Oleogel-S10 for epidermolysis bullosa wounds. *British Journal of Dermatology*, *188*(1), 10–11. https://doi.org/10.1093/BJD/LJAC034

Mellerio, J. E., & Uitto, J. (2020). Meeting Report: The First Global Congress on Epidermolysis Bullosa, EB2020 London: Toward Treatment and Cure. *Journal of Investigative Dermatology*, *140*(9), 1681–1687. https://doi.org/10.1016/j.jid.2020.05.078

Morley, S. M., Dundas, S. R., James, J. L., Gupta, T., Brown, R. A., Sexton, C. J., Navsaria, H. A., Leigh, I. M., & Lane, E. B. (1995). Temperature sensitivity of the keratin cytoskeleton and delayed spreading of keratinocyte lines derived from EBS patients. *Journal of Cell Science*, *108*(11), 3463–3471. https://doi.org/10.1242/JCS.108.11.3463

OpenAI. (2024). ChatGPT-3.5 (March 2nd version) [Large language model]. https://chat.openai.com/chat; applied for proofreading purposes and feedback function for improving conciseness and cohesiveness of the written text

Paller, A. S., Pope, E., Rudin, D., Malyala, A., Ramsdell, D., Johnson, R., Landy, H., & Murrell, D. F. (2022). A prospective short-term study to evaluate methodologies for the assessment of disease extent, impact, and wound evolution in patients with dystrophic epidermolysis bullosa. *Orphanet Journal of Rare Diseases*, *17*(1), 314. https://doi.org/10.1186/s13023-022-02461-z

Prodinger, C., Diem, A., Ude-Schoder, K., Piñón-Hofbauer, J., Kitzmueller, S., Bauer, J. W., & Laimer, M. (2020). Profiling trial burden and patients' attitudes to improve clinical research in epidermolysis bullosa. *Orphanet Journal of Rare Diseases*, *15*(1), 182. https://doi.org/10.1186/s13023-020-01443-3

Rognoni, E., Ruppert, R., & Fässler, R. (2016). The kindlin family: functions, signaling properties and implications for human disease. *Journal of Cell Science*, *129*(1), 17–27. https://doi.org/10.1242/JCS.161190

Sangha, N., MacLellan, A. N., & Pope, E. (2021). Psychosocial impact of epidermolysis bullosa on patients: A qualitative study. *Pediatric Dermatology*, *38*(4), 819–824. https://doi.org/10.1111/pde.14656

Schräder, N. H. B., Korte, E. W. H., Duipmans, J. C., Stewart, R. E., Bolling, M. C., & Wolff, A. P. (2021). Identifying Epidermolysis Bullosa Patient Needs and Perceived Treatment Benefits: An Explorative Study Using the Patient Benefit Index. *Journal of Clinical Medicine*, *10*(24). https://doi.org/10.3390/jcm10245836

Siegel, D. H., Ashton, G. H. S., Penagos, H. G., Lee, J. V., Feiler, H. S., Wilhelmsen, K. C., South, A. P., Smith, F. J. D., Prescott, A. R., Wessagowit, V., Oyama, N., Akiyama, M., Al Aboud, D., Al Aboud, K., Al Githami, A., Al Hawsawi, K., Al Ismaily, A., Al-Suwaid, R., Atherton, D. J., … Epstein, E. H. (2003). Loss of kindlin-1, a human homolog of the Caenorhabditis elegans actin-extracellular-matrix linker protein UNC-112, causes Kindler syndrome. *American Journal of Human Genetics*, *73*(1), 174–187. https://doi.org/10.1086/376609

So, J. Y., Fulchand, S., Wong, C. Y., Li, S., Nazaroff, J., Gorell, E. S., de Souza, M. P., Murrell, D. F., Teng, J. M., Chiou, A. S., & Tang, J. Y. (2022). A global, cross-sectional survey of patient-reported outcomes, disease burden, and quality of life in epidermolysis bullosa simplex. *Orphanet Journal of Rare Diseases*, *17*(1), 270. https://doi.org/10.1186/s13023-022-02433-3

Tabolli, S., Sampogna, F., Di Pietro, C., Paradisi, A., Uras, C., Zotti, P., Castiglia, D., Zambruno, G., & Abeni, D. (2009). Quality of life in patients with epidermolysis bullosa. *The British Journal of Dermatology*, *161*(4), 869–877. https://doi.org/10.1111/j.1365-2133.2009.09306.x

Tang, J. Y., Marinkovich, M. P., Lucas, E., Gorell, E., Chiou, A., Lu, Y., Gillon, J., Patel, D., & Rudin, D. (2021). A systematic literature review of the disease burden in patients with recessive dystrophic epidermolysis bullosa. *Orphanet Journal of Rare Diseases*, *16*(1), 175. https://doi.org/10.1186/s13023-021-01811-7

Uitto, J., Bruckner-Tuderman, L., Christiano, A. M., McGrath, J. A., Has, C., South, A. P., Kopelan, B., & Robinson, E. C. (2016). Progress toward Treatment and Cure of Epidermolysis Bullosa: Summary of the DEBRA International Research Symposium EB2015. *Journal of Investigative Dermatology*, *136*(2), 352–358. https://doi.org/10.1016/j.jid.2015.10.050

Wiche, G., & Winter, L. (2011). Plectin isoforms as organizers of intermediate filament cytoarchitecture. *BioArchitecture*, *1*(1), 14–20. https://doi.org/10.4161/BIOA.1.1.14630

Woodley, D. T., Hou, Y., Martin, S., Li, W., & Chen, M. (2008). Characterization of Molecular Mechanisms Underlying Mutations in Dystrophic Epidermolysis Bullosa Using Site-directed Mutagenesis *. *THE JOURNAL OF BIOLOGICAL CHEMISTRY*, *283*(26), 17838–17845. https://doi.org/10.1074/jbc.M709452200

Wu, Y.-H. R., Manager, C., Sun, F.-K. R., Lee, P.-Y. R., Professor, A., & Pei-Yu Lee, C. (2020). Family caregivers' lived experiences of caring for epidermolysis bullosa patients: A phenomenological study. *Journal of Clinical Nursing*, *29*(9–10), 1552–1560. https://doi.org/10.1111/JOCN.15209