Global Innovator's Briefing: Rare Diseases

Pemphigus Vulgaris & Foliaceus

How normal genes interacting with a changed environment can induce rare diseases

Pemphigus

- An autoimmune disease of the skin that exists in four main formats: Vulgaris, Foliaceus, erythematosus and paraneoplastic
- A severe and potentially fatal skin disease
- Epidemiologically heterogeneous
- Without treatment, mortality can reach up to 90%, that can be reduced to 5–10% with immunosuppressants
- 5–10% mortality occur because of secondary effects of immunosuppressants, instead of disease and direct comorbidities
- Poses unique healthcare provisions issues due to rural/urban sporadic epidemiology
- Significant need for multistakeholder interfacing and education

Table of contents **Page**

Points in this briefing that may be of interest for the innovator

- *The need for low-tech and/or disposable point of care diagnostics*
- *Integrating normally differentiated healthcare professions*
- *Understanding innovation for rare diseases in rural–urban settings*
- *Could bioengineers provide additional impacts*

Disclaimer: About Echino Innovator Briefings- Rare Diseases,

These briefings are designed as introductions for **early-stage innovators, covering a range of diverse rare diseases**. They are based upon freely available peer reviewed and referenced or professional information, that have been designed as a 'cog' between the two worlds of healthcare need and innovation implementation. Four are planned: some core sections will be identical throughout.

To stimulate or aid the innovator in any global geography, these introduce the state-of-the-art. the stakeholders and their interactions to anyone or any entity that is interested in innovating a solution (interventional, diagnostic, med tech, med device, digital health, healthcare process, occupational and physical therapy, patient support globalisation) for a Rare Disease, whether its social entrepreneurship, charitable or for-profit.

Why Innovator focused specific communication:
There is a knowledge gap with specific relevance to Rare Diseases between innovators and the stakeholder communities that play a pivotal and critical role in making sure innovations deliver real benefit, that has greater pertinence than more frequent diseases due to patient numbers and product development costs. It can be baffling to know where to start.

I have participated in sufficient investment committee review meetings with presentations focusing on rare diseases, often with a feeling of that only one or two stakeholders or issues have been truly considered: this makes the transition of the idea to a beneficial product or solution much more difficult.

Inversely, for an innovator to identify and understand the spectrum of knowledge needed is daunting: a significant amount of the information is very technical in content, with a broad spread across many sources and often focused on the authors immediate communities.

I have not tried to simplify the knowledge (except when it is very clinical terminology, specifically on symptoms), and always provided references. References are provided according to the schedule of people who work in innovation, where possible next to the pertinent information being discussed. For purposes of brevity, I have only indicated the first author et al, in most cases with the link (mainly to PubMed). I know this not the normal standard, but this is tailored for the audience.

References are not designed to favour any given stakeholder or KOL, nor are they are substitutes for digging much deeper if the innovator is serious. If, any KOL has felt they have been left out, this was not the intention (apologies): many more publications were read than referenced (the ones indicated with hyperlinks are *suggested introductory starting points and are technical/specialised in most cases*).

The briefings were started over summer 2022, with the aim to be globally focused and comprehensive… and like all knowledge exploration exercises, the more you discover the more you realise you don't know... so they are not necessarily brief.

They do not include any specific references to standards or regulations applied in the different geographies for product development, manufacture and validation... for the innovator, this information is widely available and for you to find. They also do not include market valuations: there is sufficient information present in these briefs including the supplementary material of the references, plus easily available online price catalogues for you to do the calculation yourself. They are not competitive intelligence reports: company organisations, clinical trial databases and stock exchange company listings are good starting points to identify other commercial endeavours.

Sometimes only specific stakeholders and single geographies are prioritised with a focus on bottom-line returns, this is somewhat understandable but as a general principle Rare Disease focused work is a long-haul and avoiding care disparity is a major goal. This may require a global approach to innovation in solution pricing, and reflection on strategies related to the orphan drug legislation and designation, to make sure investment is not diluted too much on competing too-similar initiatives. A forward movement without balance between all stakeholders is a movement backwards.

Many patients with all types of rare diseases, and their caregivers have stepped up and got involved, knowing full well that their involvement will likely not generate a benefit for them in their lifetime or for the ones they care for, but may help the next generation. I don't think very many of them made that decision with another entities financial ROI as their main objective.

What these are not:
They are unfortunately not multilingual: I only had the time to write them in English. If anyone is interested in generating multilingual/multicultural sensitive versions, please reach out and I am happy to provide the original word doc. for translation.

These are **not adverts**: i.e., after reading, if stimulated, following further detailed reading that is needed first: the innovators next point of contact should be a KOL: Patient Association or a Medical Professional/Researcher.

Declaration:
I have no conflict of interest with any entity (public or private), I represent no faith or faith associated body, I represent no political view or political body, I represent nor am paid by any entity: non-profit, pharmaceutical or biotech, for these briefings.

And I am enormously grateful to the vast array of open-source publications, and authors, databases, charities, associations and NGOs that are making the knowledge and information for these long briefings freely available.

Jonathan Dando PhD

cite: Dando JS. Pemphigus Vulgaris & Foliaceus: Rare Disease Innovators Briefing: Last updated Nov 2022. Accessed from: www.echino.eu/knowledge

Preface:

Your Normal Genetics as a risk-factor for rare disease

The innovator may often come across genetics being presented as a risk factor for a rare (or frequent disease).

It is important to understand the relevance and differences of genetic impacts in rare diseases: that occur either because of the presence of ***an inherited gene that does not function as it should and creates a pathology,*** or because a person has inherited what is considered ***a normal gene, but it can create a risk for pathology development if altered by the environment***. The latter is the focus of this preface.

The presence of this 'risk-factor' gene, plus additional factors that can be additional genes AND what are very frequently external presented stimuli creates a 'misalignment' of the immune system and induces it to attack the body: **autoimmunity**.

There are numerous examples of 'risk-factor' gene mediated autoimmunity, that the innovator would have heard of, based upon a specific patient population having an immunotype.

Immunotypes form the basis of determining whether organs can be donated from one person to another. If the immunotypes do not match, the body (the host) rejects the donated organ.

In many cases identical twins have the same immunotype. It is also the rationale why we bank umbilical cord blood stem cells: if at a later date a person is ill and needs healthy blood cells, the ones that came from them at birth represent an automatic immunotype match.

Some known examples of auto immunities in which the patients immunotype has been identified as a genetic risk factor, that in combination with external factors plays a role in inducing disease pathogenesis:

- Type 1 Diabetes
- Rheumatoid Arthritis
- Coeliac disease
- Multiple Sclerosis
- Systemic Lupus Erythematosus
- Neuromyelitis Optica
- Idiosyncratic Drug Induced Liver Injury

Introducing HLA and why there are so many of them

Immunotypes are defined by a molecular called the major-histocompatibility complex, that are coded with a prefix '**HLA**' standing for **Human Leukocyte Antigen**. Whereas for most other tissues and organs in your body the specific gene for it is fairly similar across all humans, for your immune system, this is not the case.

This has represented a critical component of our evolution, that each of us have our own 'immune lock and key': anything foreign to us, our body will mount a maelstrom of immunity to get rid of it, kill it, shut it down. And to be able to do this for your whole life. This uniqueness is created by the HLA, of which there are hundreds of thousands of types, because of recombination of the genes of which it is formed e.g. if a molecule is composed from 3 different genes, and there are 11 types of gene A, 20 of gene B and 16 of gene C, the number of possible combinations is >3500 outputs. In immunology the number of outputs are significantly greater.

The diversity enables you to be exposed to almost any foreign environment, and in most cases survive. This means they have to be plastic and adaptable.

It also means, exposure to a foreign substance has the potential to corrupt them, and in combination with other factors induce disease, some of them auto immunities.

Dendrou, C., Petersen, J., Rossjohn, J. *et al.* HLA variation and disease. Nat Rev Immunol**18**, 325–339 (2018). Link: https://www.nature.com/articles/nri.2017.143

Choo SY. The HLA system: genetics, immunology, clinical testing, and clinical implications. Yonsei Med J. 2007 Feb 28;48(1):11-23. Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2628004/

Uetrecht J. Mechanistic Studies of Idiosyncratic DILI: Clinical Implications. Front Pharmacol. 2019 Jul 26;10:837. Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6676790/

Blanter M, et al. Genetic and Environmental Interaction in Type 1 Diabetes: a Relationship Between Genetic Risk Alleles and Molecular Traits of Enterovirus Infection? Curr Diab Rep. 2019;19(9):82. Link: https://pubmed.ncbi.nlm.nih.gov/31401790/

Quinn LM, et al. Environmental Determinants of Type 1 Diabetes: From Association to Proving Causality. Front Immunol. 2021;12:737964. Link: https://pubmed.ncbi.nlm.nih.gov/34659229/

Shahi SK, et al. HLA Class II Polymorphisms Modulate Gut Microbiota and Experimental Autoimmune Encephalomyelitis Phenotype. Immunohorizons. 2021;5(8):627-646. Link: https://pubmed.ncbi.nlm.nih.gov/34380664/

Liu B, et al. Current research status of HLA in immune-related diseases. Immun Inflamm Dis. 2021;9(2):340-350. Link: https://pubmed.ncbi.nlm.nih.gov/33657268/

Bodis G, et al. Role of Human Leukocyte Antigens (HLA) in Autoimmune Diseases. Rheumatol Ther. 2018;5(1):5-20.Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5935613/

Raj P, et al. Regulatory polymorphisms modulate the expression of HLA class II molecules and promote autoimmunity. Elife. 2016;5:e12089. Link: https://pubmed.ncbi.nlm.nih.gov/26880555/

Muñiz-Castrillo S, et al. Associations between HLA and autoimmune neurological diseases with autoantibodies. Auto Immun Highlights. 2020;11(1):2.Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7065322/

Part 1

The Patient

1.1 Pemphigus Vulgaris (PV) and Foliaceus (PF), including the endemic form, fogo selvagem

Identified originally by increased prevalence in ethnic or geographic groups (the disease being associated with an ethnic group, or a population inhabiting a certain location), modern day genetic technology has identified that the disease risk factor is linked to HLA type, that can have higher prevalence's in certain populations, but is globally pertinent. There have been three main HLA alleles (=gene types) associated with all types of Pemphigus: HLA-DRB1*04, HLA-DRB1*14, and DQB1*05 that crosses all geographic and ethnic boundaries.

Vodo D, et al. The Genetics of Pemphigus Vulgaris. Front Med (Lausanne). 2018;5:226. **Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6102399/

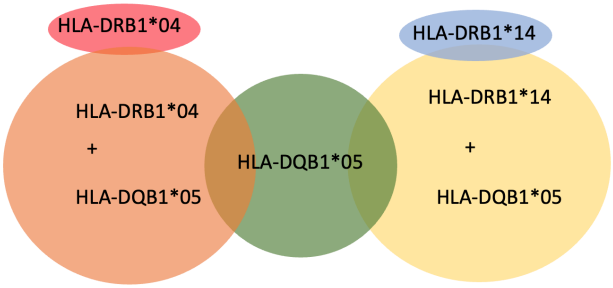
Yan L, et al. Association between HLA-DRB1 polymorphisms and pemphigus vulgaris: a meta-analysis. Br J Dermatol. 2012;167(4):768-77.**Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3485671/

Table 1: Estimate of the at-risk populations by geographic region can be identified: Using the Allele Frequency Net Database (see: http://www.allelefrequencies.net)

	Africa	Asia	Europe	N. America	Oceania	S. America
Number	670,000	3,724,700	476,380	267,300	46,300	372,400

Calculation performed by identifying median allele or haplotype frequency within the specific region's population as presented in the Allele Frequency Net Database, and then this figure applied to the latest population figures available from: https://www.livepopulation.com/

Venn Diagramme and estimation of overall HLA populations that can be considered at risk for Pemphigus



This illustrative calculation is a significant oversimplification:

- Haplotype frequencies (data sets for combinations of HLA genes are lower in number)
- For different geographies, the different forms of pemphigus and ethnic groups, these alleles co-map with additional specific HLA types (see Vodo D et al above)
- Within each country of each continental region, selected areas with their populations will have higher or lower frequencies of the genetic risk factors. This higher-level granularity can be found at the Allele Frequency Net Database.

For the innovator, in the strategic design phase, focusing implementation and validation in very precise locations with known higher risk maybe more beneficial than a broader higher risk approach. Considering that many locations are rural, with constrained healthcare resources and infrastructures, this could be pivotal in defining its benefit.

These HLA-types plus external risk factors can stimulate the occurrence of rare autoimmune disease of the skin; The following 'environmental' risk factors (also known as social determinants of health-SDOH) are linked to Pemphigus:

- Exposure to pesticides (directly or through agricultural water run-off into common water sources)
- Low quality housing
- Poor hygiene practice
- Pollutants containing Sulphur
- Vapors from heavy duty metal work
- Nutritional deficit
- Medicines with a thiol component
- Exposure to ionizing radiation
- Excessive UV light
- Traditional cosmetics
- Insect bite, specifically the black fly and Sand fly (Endemic Pemphigus Foliaceus - fogo selvagem)

Bastuji-Garin S, et al. Possible relation of Tunisian pemphigus with traditional cosmetics: a multicenter case-control study. Am J Epidemiol. 2002;155(3):249-56. **Link:** https://pubmed.ncbi.nlm.nih.gov/11821250/

Celere BS, et al. Spatial Distribution of Pemphigus Occurrence over Five Decades in Southeastern Brazil. Am J Trop Med Hyg. 2017;97(6):1737-1745. **Link:** https://pubmed.ncbi.nlm.nih.gov/29016334/

Kridin K, Schmidt E. Epidemiology of Pemphigus. JID Innov. 2021;1(1):100004. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8659392/

Lim YL, et al: Latest Advances and Emerging Therapies. Front Mol Biosci. 2022;8:808536.Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8855930/

Hans-Filho G, et al. Fogo selvagem: endemic pemphigus foliaceus. An Bras Dermatol. 2018;93(5):638-650. Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6106655/

1.2 Incidence, prevalence and pathogenesis

Table 2: Estimated prevalence of Pemphigus by continental region

	Africa	Asia	Europe	N. America	Oceania	S. America
Number	69,685	239,118	38,465	19,305	2,190	22,782

The combination of genetic risk with a spectrum of potential environmental agents that precipitates a rare autoimmunity means that obtaining clear epidemiological data is challenging: overall, incidence ranges are reported to be from 0.8–7 per million overall inhabitants per year, but in known high-risk groups incidence can reach up to 34 per million inhabitants, while overall prevalence is estimated to be 5.2 cases per 100,000 people. (using the'*live population*' website **Link**: https://www.livepopulation.com we can calculate the above prevalence estimates)

Kridin K, Schmidt E. Epidemiology of Pemphigus. JID Innov. 2021;1(1):100004. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8659392/

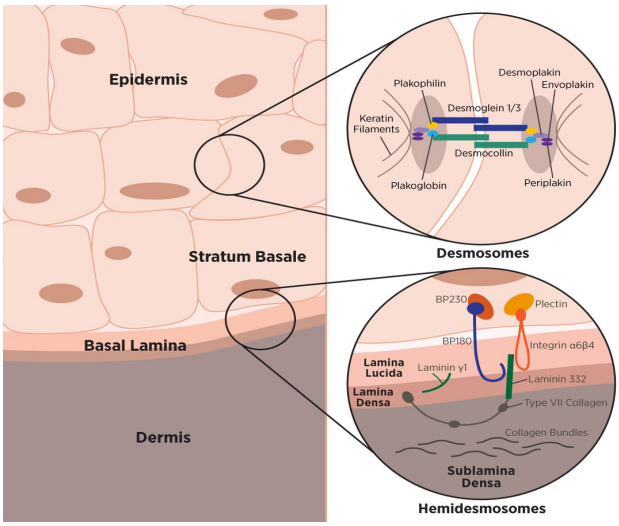
Fernández-Avila D, et al. Prevalence of pemphigus in Colombia from 2013 to 2017 according to data from the National Health Registry. An Bras Dermatol. 2022;97(4):523-526. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9263673/

Wertenteil S, et al A. Prevalence estimates for pemphigoid in the United States: A sex-adjusted and age-adjusted population analysis. J Am Acad Dermatol. 2019;80(3):655-659. **Link**: https://pubmed.ncbi.nlm.nih.gov/30165164/

- Pemphigus Vulgaris typically occurs in around 70–90 % of cases
- Pemphigus Foliaceus typically occurs in 15– 25% of cases (outside of endemic regions, in which the majority of Pemphigus cases are PF)
- The remaining cases corresponds to even rarer forms of the disease, such as paraneoplastic pemphigus

The mean age of onset is 40–50 years. However, the standard deviation indicates that cases can occur at any time point from 22 years to 87 years and there are regional differences (the innovator is strongly encouraged to read all the additional references that best illustrates this e.g. in Germany cases have been reported in age groups as young as 0–9 upwards).

Pathophysiology



Graphical representation of human skin. Figure adapted from Heckler I, et al. Serological Biomarkers and Their Detection in Autoimmune Bullous Skin Diseases. Dermatol. Pract. Concept. 2022; 12(2): e2022116. Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9116534 following the creative commons license http://creativecommons.org/licenses/by/4.0/.

Your skin and mucosal membranes (inside of the mouth, nose, vagina), are composed of different layers of cells. At the deepest level, the dermis, then a basal layer and then the epidermis, that represents the outer most layer.

The epidermis is composed of 4 layers of epidermal cells, that are tightly bound together. The complex that binds the cells together is called the *desmosome*.

Within this are the proteins responsible for the tight binding that are called *Desmogleins*.

There are three types, Desmoglein (Dsg), 1, 2 and 3.

The development of pemphigus, because of HLA types, external factors and additional as yet unknown components, means that **Dsg 1 and 3 are now being considered 'foreign' to the body**.

The response, is the body generating antibodies against Dsg 1 and 3, destroying the tight junctions between the cells, creating ulcers, blisters, abscesses, skin erosion causing pain and extreme morbidity: this also permits further opportunistic diseases such as infections.

The two types of Pemphigus, *Vulgaris* and *Foliaceus* are differentiated by the antibodies that are generated.

Pemphigus Vulgaris:
Antibodies against
Dsg-3 resulting in only mucosal membrane damage, *or*
Dsg-1 and Dsg-3 resulting in skin and mucosal membrane damage

Pemphigus Foliaceus:
Antibodies against

Dsg-1 only resulting in skin damage

The innovator is encouraged to read clinical reports of Pemphigus Vulgaris or Foliaceus, to fully grasp the level of severity that can be manifested in this indication.

Egami S, et al. Autoimmune bullous skin diseases, pemphigus and pemphigoid. J Allergy Clin Immunol. 2020;145(4):1031-1047. **Link:** https://pubmed.ncbi.nlm.nih.gov/32272980/

Malik AM, et al. An Updated Review of Pemphigus Diseases. Medicina (Kaunas). 2021;57(10):1080. **Link:** https://pubmed.ncbi.nlm.nih.gov/34684117/

Sinha AA and Sajda T (2018) The Evolving Story of Autoantibodies in Pemphigus Vulgaris: Development of the "Super Compensation Hypothesis". Front. Med. 5:218. ***Link****: https://www.frontiersin.org/articles/10.3389/fmed.2018.00218/full*

Ahmed AR et al. Monopathogenic vs multipathogenic explanations of pemphigus pathophysiology. Exp Dermatol. 2016;25(11):839-846. Link: https://pubmed.ncbi.nlm.nih.gov/27305362/

1.3 The symptoms of Pemphigus (Vulgaris and Foliaceus) and their heterogeneity

Table 3: Non-exhaustive list of the symptoms experienced by patients diagnosed with Pemphigus types.

Frequency (%)	Pemphigus Vulgaris: Symptom Description	Pemphigus Foliaceus: Symptom Description
80–99	Autoimmunity Weight loss Recurrent infections Atypical skin scarring Urticaria Abnormal oral cavity morphology Abnormal skin blistering Recurrent cutaneous abscess formation Loss of intracellular connections between epidermal cells (Acantholysis) Feeding difficulties in infancy	Autoimmunity Loss of intracellular connections between epidermal cells (Acantholysis)
30–79	-	Pruritus (itching) Abnormality of the scalp Crusting erythematous dermatitis Abnormal blistering of the skin Erythema (rash) Erythematous plaque (skin lesions) Scaling skin Skin erosion
5–29	-	Abnormal oral cavity morphology Skin vesicle Erythroderma (body wide skin inflammation) Oral ulcer
1–<4	-	Psoriasiform dermatitis Hematological neoplasm Neoplasm of the skin Annular cutaneous lesion Pustule

Source of data for table: *Data obtained from Orphanet 'rare diseases: clinical signs and symptoms. For purpose of brevity, symptoms summarised and indicated by organ. The complete list can be found at the original source https://www.orpha.net/consor/cgi-bin/Disease_HPOTerms.php?lng=EN with a detailed explanation of the data.*

The presence of comorbidities in patients with Pemphigus poses logistical treatment considerations: the standard of care is an immunosuppressive regimen (corticosteroid or biologic based).

It is unclear if the comorbidities occur as a result of the autoimmunity itself, or because of the environmental risk factors that can stimulate additional diseases to occur, or in some cases are exacerbated because of treatments.

Known comorbidities of patients diagnosed with Pemphigus

- Hypertension
- Thyroid Disease
- Rheumatoid Arthritis
- Type 2 Diabetes
- Type 1 Diabetes
- Psoriasis
- Fungal infections causing pneumonia (leading cause of mortality)
- Viral infections

Ren Z, et al. Association of serious infections with pemphigus and pemphigoid: analysis of the Nationwide Inpatient Sample. J Eur Acad Dermatol Venereol. 2018;32(10):1768-1776. **Link**: https://pubmed.ncbi.nlm.nih.gov/29575160/

Heelan K, et al. Pemphigus and associated comorbidities: a cross-sectional study. Clin Exp Dermatol. 2015;40(6):593-9.**Link**: https://pubmed.ncbi.nlm.nih.gov/25786337/

Quintarelli L et al. Clinical Patterns, Survival, Comorbidities, and Treatment Regimens in 149 Patients With Pemphigus in Tuscany (Italy): A 12-Year Hospital-Based Study. Front Immunol. 2022;13:895490.**Link:** https://pubmed.ncbi.nlm.nih.gov/35880183/

Nasimi M, et al. Socioeconomic status of patients with pemphigus vulgaris. JBE. 2017;3(1):1-6.**Link:** https://jbe.tums.ac.ir/index.php/jbe/article/view/133

Alcaide-Martín AJ, et al. Epidemiologic study of 20 cases of pemphigus at Hospital Clínico Universitario Virgen de la Victoria de Málaga, Spain. Actas Dermosifiliogr. 2010;101(6):524-33. **Link**: https://pubmed.ncbi.nlm.nih.gov/20738971/

Siddig O, et al (2021) The epidemiology of autoimmune bullous diseases in Sudan between 2000 and 2016. PLoS ONE 16(7): e0254634. **Link**: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0254634

Sánchez-García V, et al. Comorbidities in Patients with Autoimmune Bullous Disorders: Hospital-Based Registry Study. Life (Basel). 2022 ;12(4):595. **Link**: https://pubmed.ncbi.nlm.nih.gov/35455086/

Shah AA, et al. Development of a disease registry for autoimmune bullous diseases: initial analysis of the pemphigus vulgaris subset. Acta Derm Venereol. 2015;95(1):86-90**. Link**: https://pubmed.ncbi.nlm.nih.gov/24691863/

Additional references (observations by continent)

Africa

Aboobaker J, et al. Pemphigus in South Africa. Int J Dermatol. 2001;40(2):115-9. **Link:** https://pubmed.ncbi.nlm.nih.gov/11328392/

Siddig O, et al (2021) The epidemiology of autoimmune bullous diseases in Sudan between 2000 and 2016. PLoS ONE 16(7): e0254634. **Link**: https://pubmed.ncbi.nlm.nih.gov/34255799/

El Hadadi, F et al. Epidemiology of Pemphigus: A Single Center Experience in Morocco. International Journal of Dermatology and Venereology: 2022; 5(1) 20-26. **Link:** https://journals.lww.com/ijdv/Fulltext/2022/03000/Epidemiology_of_Pemphigus__A_Single_Center.4.aspx

Hicham T, et al. Pemphigus Vulgaris: A Clinical Study of 31 Cases (2004-2014) in Morocco. Dermatol Res Pract. 2020 ;2020:8535109**. Link**: https://pubmed.ncbi.nlm.nih.gov/32963520/

Asia

Cai SC, et al. Epidemiology and Factors Associated with Remission of Pemphigus Vulgaris and Foliaceus in Singapore. Ann Acad Med Singap. 2020 ;49(6):367-376**. Link**: https://pubmed.ncbi.nlm.nih.gov/32712634/

Wardhana M et al, Prevalence and quality of life of pemphigus patients at Sanglah General Hospital Bali-Indonesia. Bali Medical Journal. 2013 **Link**: https://ojs.unud.ac.id/index.php/bmj/article/view/5585

Joo JS, et al. Incidence of Bullous Pemphigoid and Pemphigus in Korea. Ann Dermatol. 2021;33(2):193-195.**Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8081997/

Parmar D et al. Prevalence of pemphigus incidence in the Bhuj, Kutch, Gujarat: a cross-sectional study Int J Res Dermatol. 2017;3(4):478-480 **Link**: https://www.ijord.com/index.php/ijord/article/view/237

Vinay KN et al Prevalence of oral lesions in pemphigus vulgaris: a retrospective study Int J Res Dermatol. 2019; 5(3):528-531 **Link**: https://www.ijord.com/index.php/ijord/article/view/673/381

Altun E, et al. Clinical and Demographic Characteristics of Pemphigus Vulgaris Patients. Acta Dermatovenerol Croat. 2018;26(2):119-125. **Link:** https://pubmed.ncbi.nlm.nih.gov/29989867/

Europe

Hübner F, et al. Prevalence and Age Distribution of Pemphigus and Pemphigoid Diseases in Germany. J Invest Dermatol. 2016;136(12):2495-2498. **Link**: https://pubmed.ncbi.nlm.nih.gov/27456755/

Langan S M, et al. Bullous pemphigoid and pemphigus vulgaris—incidence and mortality in the UK: population based cohort study BMJ 2008; 337 **Link**: https://www.bmj.com/content/337/bmj.a180

van Beek N, et al. Incidence of pemphigoid diseases in Northern Germany in 2016 - first data from the Schleswig-Holstein Registry of Autoimmune Bullous Diseases. J Eur Acad Dermatol Venereol. 2021 ;35(5):1197-1202. **Link:** https://pubmed.ncbi.nlm.nih.gov/33428263/

Hübner F, et al. Prevalence and age distribution of pemphigus and pemphigoid diseases among paediatric patients in Germany. J Eur Acad Dermatol Venereol. 2020;34(11):2600-2605. **Link:** https://pubmed.ncbi.nlm.nih.gov/32289873/

Kridin K, et al. Pemphigus Vulgaris and Pemphigus Foliaceus: Differences in Epidemiology and Mortality. Acta Derm Venereol. 2017;97(9):1095-1099. **Link:** https://pubmed.ncbi.nlm.nih.gov/28536732/

North America

Wertenteil S, et al A. Prevalence estimates for pemphigoid in the United States: A sex-adjusted and age-adjusted population analysis. J Am Acad Dermatol. 2019;80(3):655-659. **Link**: https://pubmed.ncbi.nlm.nih.gov/30165164/

Lee J, et al (2019) A Retrospective Study of Patient-Reported Data of Bullous Pemphigoid and Mucous Membrane Pemphigoid From a US-Based Registry. Front. Immunol. 10:2219. **Link***:* https://www.frontiersin.org/articles/10.3389/fimmu.2019.02219/full

South America

Fernández-Avila D, et al. Prevalence of pemphigus in Colombia from 2013 to 2017 according to data from the National Health Registry. An Bras Dermatol. 2022;97(4):523-526. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9263673/

Rocha-Alvarez R, et al; Cooperative Group on Fogo Selvagem Research. Endemic pemphigus vulgaris. Arch Dermatol. 2007 Jul;143(7):895-9. Link: https://pubmed.ncbi.nlm.nih.gov/17638734/

Hans-Filho G, et al. Fogo selvagem: endemic pemphigus foliaceus. An Bras Dermatol. 2018;93(5):638-650**. Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6106655/

Lins GT, et al. Childhood pemphigus vulgaris is a challenging diagnosis. Autops Case Rep. 2021 Apr 30;11:e2021267. Link: https://pubmed.ncbi.nlm.nih.gov/34307224/

Celere BS, et al. Spatial Distribution of Pemphigus Occurrence over Five Decades in Southeastern Brazil. Am J Trop Med Hyg. 2017;97(6):1737-1745. **Link:** https://pubmed.ncbi.nlm.nih.gov/29016334/

Part 2

The Journey

2.1 Care recommendations and guidelines

International

Guidelines for the Diagnosis and Management of Pemphigus have been developed and published in March 2020: leveraging globally based national focuses on standardising processes these guidelines represent the first attempt to generate a global standard.

> Murrell DF, et al. Diagnosis and management of pemphigus: Recommendations of an international panel of experts. J Am Acad Dermatol. 2020 Mar;82(3):575-585.e1. Link: https://pubmed.ncbi.nlm.nih.gov/29438767/

The panel leveraged the European Academy of Dermatology and Venereology/European Dermatology Forum guidelines that have been developed over the past decade.

> Hertl M, et al. Pemphigus. S2 Guideline for diagnosis and treatment--guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV). J Eur Acad Dermatol Venereol. 2015 Mar;29(3):405-14. Link: https://pubmed.ncbi.nlm.nih.gov/25338479/

> Joly P, et al. Updated S2K guidelines on the management of pemphigus vulgaris and foliaceus initiated by the european academy of dermatology and venereology (EADV). J Eur Acad Dermatol Venereol. 2020 Sep;34(9):1900-1913.**Link:** https://pubmed.ncbi.nlm.nih.gov/32830877/

National

It is important that the innovator understands that *de facto*, the international guidelines are applied at the national level, or if national guidelines actually exist. It can take some time and the substantial evidence requirements before national authorities can feel comfortable making adaptations.

Guidelines also have to be adapted to the existing infrastructures and legislations in each country, for example:

Italian guidelines 2018*: 'This guideline for the diagnosis and treatment of pemphigus has been developed by an Italian group of experts taking in account the Italian legislation and local pharmacological governance.'*

> From: Feliciani C, et al. Italian Guidelines in Pemphigus - adapted from the European Dermatology Forum (EDF) and European Academy of Dermatology and Venerology (EADV). G Ital Dermatol Venereol. 2018 Oct;153(5):599-608. **Link**: https://pubmed.ncbi.nlm.nih.gov/29860771/

German Guidelines 2019: '*The methodology of this update of the most recent version of these S2k guidelines (2015) follows the specifications issued by the Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft Wissenschaftlicher Medizinischer Fachgesellschaften, AWMF)'*

> From: Schmidt E, et al. S2k guidelines for the treatment of pemphigus vulgaris/foliaceus and bullous pemphigoid: 2019 update. J Dtsch Dermatol Ges. 2020 May;18(5):516-526. Link: https://pubmed.ncbi.nlm.nih.gov/32413212/

Brazilian Society of Dermatology guidelines 2019:

> Porro AM, et al. Consensus on the treatment of autoimmune bullous dermatoses: pemphigus vulgaris and pemphigus foliaceus - Brazilian Society of Dermatology. An Bras Dermatol. 2019 Apr;94(2 Suppl 1):20-32.Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6544031/

All stakeholders

Pemphigus very frequently manifests first in the mouth, several months before skin manifestation, implying that dentists are often the first specialist that may see an indication: this means that dentists have also generated additional guidelines: The innovator therefore also needs to make sure that all the stakeholders have been included: for example,

> Firkova E. Dental Perspective of Pemphigus Vulgaris – A clinical case with Diagnostic and Treatment Guidelines. *J of IMAB.* 2019 Apr-Jun;25(2):2516-2520. Link: https://www.journal-imab-bg.org/issues-2019/issue2/JofIMAB-2019-25-2p2516-2520.pdf

> Al-Harbawee A, et al. Oral pemphigus vulgaris: dentists take-home message. Clin Case Rep. 2021 Jul 9;9(7):e04494. Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8271215/

In the case of rare diseases with a predominant rural or lower income demographic, this can also mean that access to generalised healthcare can be challenging: in the context of tissue specific specialty such as Dentists, Dermatology or rare dermatological diseases it can become more than a challenge. This impacts innovation uptake.

Finally, reviewing the dates of the publications above, there is no set pattern of adaptation or update, and changes occur outside of the standard times of development for most innovations in healthcare: therefore the innovator needs to stay current with these changes, aligning their solution with them, and the capacity to implement the innovation at the location for which it is designed.

2.2 Diagnostic and Treatment

'The prompt diagnosis of pemphigus is of utmost importance to disrupt disease progression and improve prognosis, but unfortunately, many patients experience long delays to diagnosis. This frustrating undiagnosed period is often due to a lack of health care providers' knowledge of pemphigus manifestations, long waits for a dermatologist visit, and repeated inconclusive diagnostic tools. This ineffective passage of time makes patients feel they have no control over their bodies and escalates their concerns. Consequently, some of them may decide to change their doctors, which means starting this inconvenient process all over again.'

> Kianfar, Nika et al. Burden of pemphigus vulgaris with a particular focus on women: A review. International Journal of Women's Dermatology: 2022; 8(3)p e056. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9529034/

The Clinical journey of the patient can be extracted from the international guidelines and has also been summarised for treatment considerations for refractory pemphigus vulgaris (Both provide significant detail of the care pathway and descriptions of the main medicines used).

> Murrell DF, et al. Diagnosis and management of pemphigus: Recommendations of an international panel of experts. J Am Acad Dermatol. 2020 Mar;82(3):575-585.e1. Link: https://pubmed.ncbi.nlm.nih.gov/29438767/
>
> Gangan R. Refractory pemphigus vulgaris: Treatment options. J Skin Sex Transm Dis 2019;1(2):61-5. : Link: https://jsstd.org/refractory-pemphigus-vulgaris-treatment-options/

An overview:

The Clinical team

The clinical care process should be coordinated by a dermatologist specialised in bullous diseases, working together with:

- Family doctor
- Referring dermatologist
- Specialists in any comorbidities co-presenting with pemphigus
- Nursing staff

Diagnosis is performed by histopathology, direct immunofluorescence, indirect immunofluorescence +/- ELISA assays for Dsg-1 and/or -3 antibodies.

- Medical History is reviewed along with a physical examination
- Clinical assessment is performed using two clinical scores indicated in the HRQoL section: Pemphigus Disease Area Index (PDAI) Score & Autoimmune Bullous Skin Disorder Intensity Score (ABSIS)

↓

Diagnosis is confirmed

↓

Treatment starts: This is considered the baseline by the medical HCP

First line therapies are corticosteroids and anti-CD20 monoclonal antibodies for moderate-to-severe pemphigus (see 'clinically tested solutions' below).

Additional treatments can include

- corticosteroid sparing agents,
- supportive treatments
- prophylaxis against corticosteroid side effects.
- Live vaccines are not recommended

Close monitoring during treatment is recommended due to its immunosuppressive nature

The whole treatment phase is considered the consolidation phase, and takes between 1–3 months.

If approximately 80% of lesions have healed and no new lesions have formed for 2 weeks, then the consolidation phase is considered ended, and the medical HCP can start to reduce ('taper') corticosteroids.

↓

If no new lesions are formed for 2 months while the patient is on 'minimum therapy' (2 months of minimal corticosteroids = 10mg/day), the patient is considered to have achieved complete remission 'on therapy', at which point use of steroids can be reduced down to zero.

↓

If no new lesions are formed for 2 months while the patient is off 'minimum therapy', the patient is considered to have achieved complete remission 'off therapy'

↓

If 3 or more new lesions occur/month that do not heal within 1 week, or established lesions continue, the patient can be considered to have relapsed/had a flare If this occurs, treatment doses should be taken back 2 steps before the relapse occurred and started again: if no disease control is achieved it is recommended to return to the starting dose and repeat the process.

2.3 Early oral manifestations of Pemphigus Vulgaris

'The current wall between doctors and dentists needs to come down. Blending the two disciplines has the potential to promote the early identification and treatment of diseases and conditions, leading to disease prevention, better patient outcomes, more effective management of chronic diseases and reduced costs for health-care systems…. The archaic division between dentistry and medicine is detrimental to overall health and needs to end.'

Molayem S. Dentists and Doctors need to play on the same team. Nature Outlook. Last updated 27 October 2021. Accessed November 2022. https://www.nature.com/articles/d41586-021-02919-3

For Pemphigus Vulgaris, experiences from oral and dental specialists, suggest that earlier steps could potentially enhance the patient journey: for which innovation will be needed.

Recap: In Pemphigus, Vulgaris accounts for up to 90% of cases, Foliaceus up to 25% of cases (unless it is endemic) and paraneoplastic pemphigus up to 5% of cases: Vulgaris, can be mucosal and/or mucocutaneous (oral and/or oral and skin): Foliaceus is exclusively cutaneous (no oral lesions, only skin): Paraneoplastic pemphigus does manifest as oral lesions

- **Oral mucosal lesions can be the first presentation in up to 90% of Pemphigus Vulgaris cases** (potentially >80% of Vulgaris cases) and the following has been reported:

  Malik AM, et al. An Updated Review of Pemphigus Diseases. Medicina (Kaunas). 2021;57(10):1080. **Link:** https://pubmed.ncbi.nlm.nih.gov/34684117/

- '**Diagnostic delays of greater than 6 months** are common in patients with oral pemphigus vulgaris. **The oral cavity may be the only site of involvement for a year or so**.'

  Arpita R, et al. Oral Pemphigus Vulgaris: Case Report. Ethiop J Health Sci. 2015;25(4):367-72. Link: https://pubmed.ncbi.nlm.nih.gov/26949302/

- 'Pemphigus Vulgaris is the main variant and the one that most affects the mouth. **Oral lesions are the first manifestation of the disease in 50-90% of cases. They can be the only clinical symptom for a period of 2-6 months until the appearance of skin lesions, which means that recognizing oral manifestations should be extremely important for both dentists and dermatologists.**

  Clinically, the oral blisters have a very thin wall and rapidly rupture due to oral traumas, resulting in painful and hemorrhagic erosions. The ulcers and erosions bleed easily, do not heal for a long period of time which leads to worse life quality. The patients complain from constant pain, burning sensations and general discomfort.'

  Firkova E. Dental Perspective of Pemphigus Vulgaris – A clinical case with Diagnostic and Treatment Guidelines. *J of IMAB.* 2019;25(2):2516-2520. Link: https://www.journal-imab-bg.org/issues-2019/issue2/vol25issue2p2516-2520.html

- '**Pemphigus Vulgaris: The evolution of PV typically begins with painful mucosal ulceration, especially in the mouth. These ulcers are persistent; individual ulcers may come and go but new lesions continue to appear**. Many patients will develop skin lesions over the following weeks or months and, unlike bullous pemphigoid, these tend not to be itchy. The age at presentation is wide, with peak incidence over the third to the sixth decade of life, hence age is not considered a diagnostic clue.'

  Melchionda V, Harman KE. Pemphigus vulgaris and pemphigus foliaceus: an overview of the clinical presentation, investigations and management. Clin Exp Dermatol. 2019;44(7):740-746. Link: https://pubmed.ncbi.nlm.nih.gov/31378971/

- '**Given the long list of differentials, patients with oral pemphigus could be misdiagnosed and incorrectly treated by dental professionals**. The most frequent differential diagnosis includes recurrent aphthous ulceration, Behçet disease, erosive lichen planus, oral candidiasis, and erythema multiforme.These conditions could be distinguished with careful history and clinical examination; for example, erythema multiforme is characterized by target-shaped skin lesions and involvement of the lips. In youngsters, oral pemphigus should be differentiated from acute herpetic gingivostomatitis, impetigo, linear IgA disease, and epidermolysis bullosa.'

  Al-Harbawee A, et al. Oral pemphigus vulgaris: dentists take-home message. Clin Case Rep. 2021;9(7):e04494.Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8271215/

- **Oral mucosal disease is typically divided into 10 different classifications**, while in a middle-aged population cohort from Northern Finland (born in 1966), 45 different types of oral mucosal lesions were reported: Pemphigus was not one of them.

  See table 1 of: Lin D, et al. Crosstalk between the oral microbiota, mucosal immunity, and the epithelial barrier regulates oral mucosal disease pathogenesis. Mucosal Immunol. 2021;14(6):1247-1258. Link: https://pubmed.ncbi.nlm.nih.gov/34040155/

  See table 4 of: Oivio, UM., et al. Prevalence of oral mucosal normal variations and lesions in a middle-aged population: a Northern Finland Birth Cohort 1966 study. BMC Oral Health 20, 357 (2020). Link: https://bmcoralhealth.biomedcentral.com/articles/10.1186/s12903-020-01351-9

The following is highly recommended reading for the innovator, regarding the need to find a solution at the oral symptom manifestation phase: it is the experience of a registered nurse, a healthcare professional, with oral manifestations of Pemphigus Vulgaris.

https://www.rdhmag.com/career-profession/students/article/16405391/oral-pemphigus-and-pemphigoid-why-are-these-conditions-so-hard-to-diagnose

2.4 The quality of life of patients with pemphigus

The Voice of the Patient:
Key resources are recommended for the innovator to understand what it means to live with Pemphigus

1. Quarterly: Journal of the International Pemphigus & Pemphigoid Foundation (IPPF). Winter 2019 issue no.95: https://www.pemphigus.org/wp-content/uploads/ippf-quarterly-95-web-1.pdf
2. Patient Voices: Pemphigus Vulgaris: available from the 'Dialogues in Dermatology' section of the American Academy of Dermatology Association: https://www.aad.org/member/education/professional-education/dialogues
3. A US FDA Listening Session, held in February 2021, coordinated by the IPPF: https://www.pemphigus.org/wp-content/uploads/IPPF-FDA-Listening-Session.pdf
4. Pemfriends: a UK patient and caregiver support group that publish the newsletter 'Pem Lives': https://www.pemfriendsuk.co.uk/pem-lives-magazine
5. Lowe S. Pemphigus vulgaris. BMJ. 2007 Dec 1;335(7630):1152-4.Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2099509/

Health-related impacts

- Burning and itching sensations caused by skin lesions
- Painful oral lesions, that also interfere with food intake resulting in nutritional deficit
- Skin infections
- Recurrent lesions occur over large parts of body
- Significant pain from erosive blisters
- Mental health comorbidity

Treatment related impacts

- Long-term use of corticosteroids, can cause: immunosuppression, infection, weakness, fatigue, decreased bone density, hypertension, and diabetes.
- Noncorticosteroid drugs, can cause: Gastrointestinal symptoms, hepatotoxicity, bone marrow suppression, and immunosuppression, headache, lethargy, fever, myalgia.

Daily life impacts

- Reduction in social activities and social isolation
- Reduction in productivity due to lost days of work or disability related unemployment
- Self-esteem reduction due to physical disfigurement (large scale cutaneous blisters), that further reduces social engagement, exacerbating mental health related impacts
- Financial burden of recurrent manifestations, increasing anxiety
- Recently reported greater multi-factorial impact on women

Kianfar, Nika et al. Burden of pemphigus vulgaris with a particular focus on women: A review. International Journal of Women's Dermatology: 2022; 8(3)p e056. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9529034/

Narain U, et al. Incidence of infections in patients with pemphigus vulgaris. Int J Adv Med 2022;9:666-9. Link: https://www.ijmedicine.com/index.php/ijam/article/view/1337

Azfar N.A. et al Quality-of-life index evaluation in pemphigus vulgaris patients of Pakistan. Journal of Pakistan Association of Dermatologists. 2021;31(1):3-7. **Link:** https://www.jpad.com.pk/index.php/jpad/article/view/1574

Sajedianfard S, et al. Family dermatology life quality index in patients with pemphigus vulgaris: A cross-sectional study. Indian J Dermatol Venereol Leprol 2021;87:375-8.**Link:** https://ijdvl.com/family-dermatology-life-quality-index-in-patients-with-pemphigus-vulgaris-a-cross-sectional-study/

Segal O, et al. Illness Perception, Perceived Social Support and Quality of Life in Patients with Pemphigus Vulgaris: What Should Dermatologists Know? Acta Derm Venereol. 2021;101(4):adv00441. **Link**: https://pubmed.ncbi.nlm.nih.gov/33723618/

Behkar A, et al. Assessing quality of life in patients with autoimmune bullous diseases using the Persian version of Treatment of Autoimmune Bullous Disease Quality of Life questionnaire finds similar effects in women as men. Int J Womens Dermatol. 2022;8(1):e004. **Link**: https://pubmed.ncbi.nlm.nih.gov/35620025/

Sung JY, et al. Quality of Life Assessment in Korean Patients with Pemphigus. Ann Dermatol. 2015;27(5):492-8. **Link**: https://pubmed.ncbi.nlm.nih.gov/26512162/

Morsya Hanan, et al. Quality-of-life assessment in pemphigus vulgaris in Upper Egypt using the Dermatology Life Quality Index and SF-36 questionnaires. The Egyptian Journal of Dermatology and Venereology. 2016;36(1): 1-3.**Link:** http://www.ejdv.eg.net/text.asp?2016/36/1/1/194152

Nascimento M. A et al. Multi-professional care for the patient affected by pemphigus vulgaris. Research, Society and Development. 2020; 9 (8) p. e778986596 **Link:** https://rsdjournal.org/index.php/rsd/article/view/6596.

Sebaratnam DF, et al. Quality of life in patients with bullous dermatoses. Clin Dermatol. 2012;30(1):103-7. **Link**: https://pubmed.ncbi.nlm.nih.gov/22137233/

Mitev A, et al. Subjective well-being in patients with pemphigus: a path analysis. Eur J Health Econ. 2019;20(Suppl 1):101-107. **Link:** https://pubmed.ncbi.nlm.nih.gov/31098885/

- Connecting a change in a specific clinical outcome to a change in QoL adds definition to the benefit of the solution, with respect to every possible solution.
- QoL changes applies to the **patient and the caregiver**: Using **the Family Dermatology Life Quality Index Questionnaire (FDLQI) that is used to assess the QoL of the caregiver**, impacts across all domains were reported; burden of care (increased hospitalisations a major issue), emotional needs, physical well-being, social life, leisure activities and other people's reactions.

Ghodsi SZ, et al. Family impact of pemphigus disease in an Iranian population using the Family Dermatology Life Quality Index. Int J Womens Dermatol. 2020;6(5):409-413. **Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8060665/

Sajedianfard Set al. Family dermatology life quality index in patients with pemphigus vulgaris: A cross-sectional study. Indian J Dermatol Venereol Leprol. 2021;87(3):375-378. **Link**: https://pubmed.ncbi.nlm.nih.gov/31464197/

International Pemphigus and Pemphigoid Foundation: Coaches corner. **Link**: https://www.pemphigus.org/coaches-corner-caregiver-support/

- Depending on the clinical symptom being targeted and its severity, QoL changes may occur in the short term or over a longer period; or clinical symptom alleviation may not result in an identifiable change in QoL.
- Patient Reported Outcome Measures (PROMs) are designed to measure these. Their complexity can vary between use as *patient monitoring tools* such as in daily patient care, to larger scale multi-dimensional tools used in complex case management and clinical trials.

Introduction to PROMs:

Patient-reported outcome measures (PROMs) as proof of treatment efficacy

Kluzek S, et al. BMJ Evid Based Med. 2022 Jun;27(3):153-155.

Link: https://pubmed.ncbi.nlm.nih.gov/34088713/

When validating the innovation, careful selection needs to be made of the PROMs: the innovator should be aware that PROMs used in clinical studies are typically secondary outcome measures (primary outcomes being clinical measurements).

Patient reported outcome measures used in Patient monitoring or Clinical trials (as secondary outcomes):

Clinical:

- Pemphigus Disease Area Index (PDAI) Score
- Glucocorticoid toxicity index
- Autoimmune Bullous Skin Disorder Intensity Score (ABSIS)
- Oral Disease Severity Score (ODSS)

QoL:

- Autoimmune Bullous Disease Quality of Life (ABQOL)
- EQ-5D/EQ-5D-5L questionnaire
- Dermatology Life Quality Index (DLQI)

Patient reported outcome measures used for patient monitoring and management

- Family Dermatology Life Quality Index
- Dermatology Life Quality Index (DLQI)
- World Health Organisation Quality of Life (WHOQOL)
- Autoimmune Bullous Disease Quality of Life (ABQOL)/Treatment of Autoimmune Bullous Disease Quality of Life (TABQOL)
- Satisfaction with Life Scale (SWLS)
- Skindex-29
- SF-36/EQ-5D
- Visual Analogue Scale

As mental health issues, anxiety and depression have been reproducibly reported in Pemphigus, it is therefore also worthwhile to consider clinically validated PROMs for these indications as well.

Padniewski JJ, et al. Patient Quality of Life Improvement in Bullous Disease: A Review of Primary Literature and Considerations for the Clinician. Clin Cosmet Investig Dermatol. 2022;15:27-42. **Link**: https://pubmed.ncbi.nlm.nih.gov/35046687/

Pattinson RL, et al. Patient-Reported Outcome Measures in Dermatology: A Systematic Review. Acta Derm Venereol. 2021;101(9):adv00559. **Link:** https://pubmed.ncbi.nlm.nih.gov/34263330/

Ní Ríordáin R, et al. World Workshop on Oral Medicine VI: Patient-reported outcome measures and oral mucosal disease: current status and future direction. Oral Surg Oral Med Oral Pathol Oral Radiol. 2015;120(2):152-60.e11. **Link**: https://pubmed.ncbi.nlm.nih.gov/25934415/

Ní Ríordáin R, Wiriyakijja P. Patient reported outcome and experience measures of oral disease in oral medicine. Br Dent J. 2017 c;223(9):713.**Link:** https://pubmed.ncbi.nlm.nih.gov/29097793/

Kendrick T, et al. Patient-reported outcome measures for monitoring primary care patients with depression (PROMDEP): study protocol for a randomised controlled trial. Trials. 2020;21(1):441. **Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7257549/

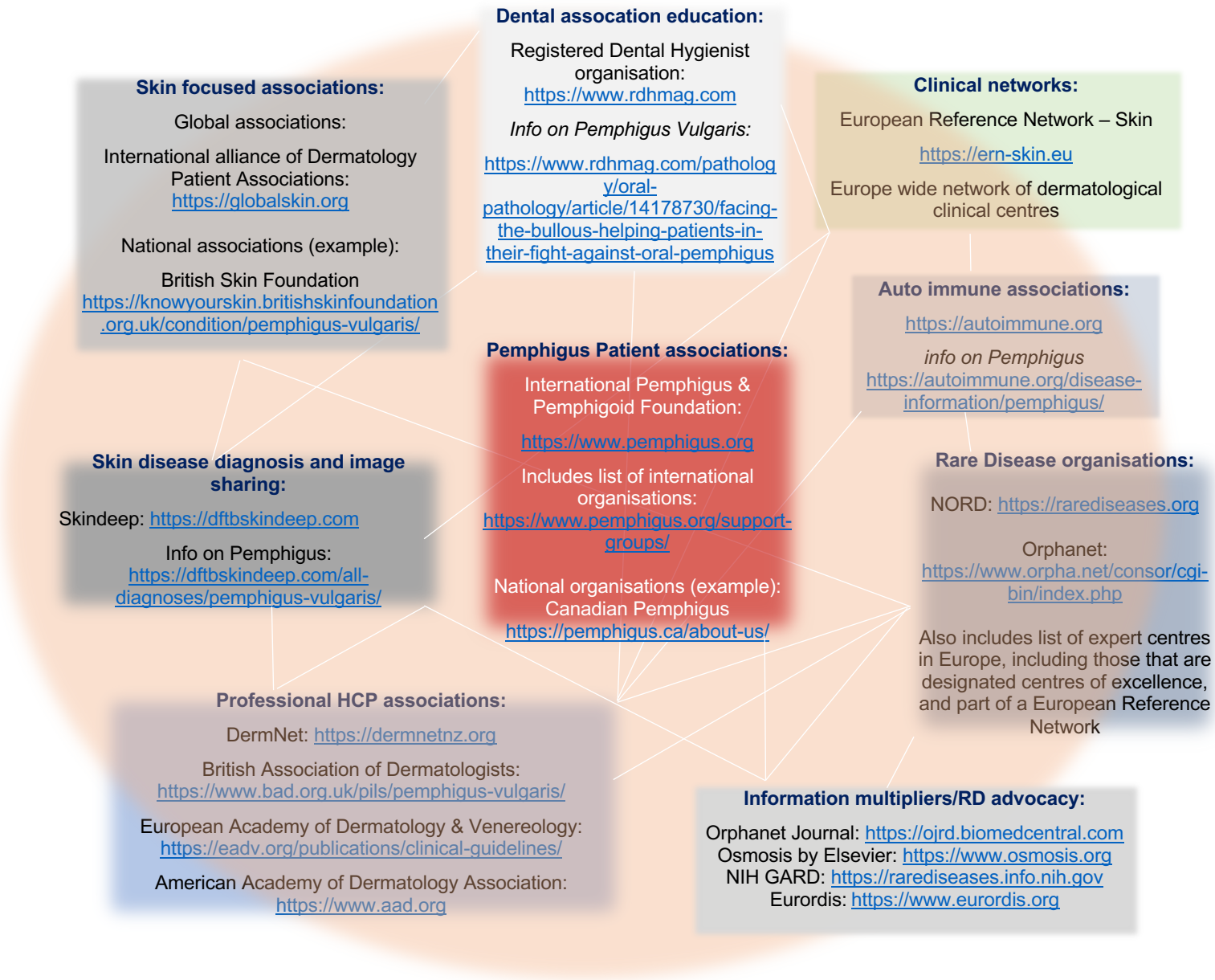
2.6 Patient support: Pemphigus, autoimmune and dermatological diseases

When epidemiology is geographically sporadic and heterogeneous, this poses challenges for providing support throughout the whole stakeholder ecosystem.

Several characteristics such as global maps of clinical reference centres, multilingual and multicultural communication and education resources focused on patients, caregivers and HCPs (across all levels of care) will facilitate innovation.

Many forms of patient associations, information multipliers, overarching organisations and networks exist. These types of organisations are the central cog in rare diseases and move mountains.

The following schematic presents the different entities related to Pemphigus: for an innovator focused on operations, there is space to add incremental add-ons, that could logarithmically increase impact.



Some observations for the innovator:

- Could the ERN-Skin network be globalised?... there are no such networks in rural areas where it is endemic, or in LMIC locations where resources are constrained?
- The prevalence in patient populations speaking Hebrew, Farsi, Brazilian Portuguese or Arabic as a first language does not align to information or tool availability for patients or HCPs. Importance related to time availability of primary care HCPs, their native language and those of their patients: discussed below in unmet needs.

2.7 Healthcare infrastructure and provision in rural settings

Recognizing and understanding the differences and associated factors for an expanded scope of practice is necessary to determine the skills and resources required for practice in rural and urban areas, collaborating in proposals of strategies to improve quality and access of health care services.

> Stralen ACV, et al. The scope of practice of primary health care physicians in rural and urban areas in Brazil. Cad Saude Publica. 2021;37(9):e00211520. Link: https://pubmed.ncbi.nlm.nih.gov/34586168/

The patients' diagnostic and treatment journey have to be placed in the context of the geographic location where the disease initially manifests and available healthcare infrastructure.

A large number of the environmental factors linked to inducing pathogenesis of both Pemphigus Vulgaris and Foliaceus are typically associated with rural, agricultural or peripheral urban areas (located near industrial zones, or areas of low-quality housing with lower ratios of healthcare infrastructure availability).

> Celere BS, et al. Spatial Distribution of Pemphigus Occurrence over Five Decades in Southeastern Brazil. Am J Trop Med Hyg. 2017;97(6):1737-1745. **Link:** https://pubmed.ncbi.nlm.nih.gov/29016334/

Several actions have already been taken to address the problem of caring for rural populations: below are four examples of approaches taken: integrating new solutions with existing or ongoing approaches

Overall strategies

> Strategies for Rural Health Leaders' Success in a post COVID-19 world. American Hospital Association.Last updated May 2022. Accessed November 2022. https://www.aha.org/system/files/media/file/2022/05/playbook-strategies-for-rural-health-leaders-success-in-a-post-covid-19-world.pdf

> Dipeolu, I. O. (2022). New Approaches for Improved Service Delivery in Rural Settings. In (Ed.), Rural Health. IntechOpen. https://doi.org/10.5772/intechopen.101705

Reaching distant populations: mobile clinics and fluvial mobile units for riverside-based populations

> Morris-Paxton AA, et al. Primary healthcare services in the rural Eastern Cape, South Africa: Evaluating a service-support project. Afr J Prim Health Care Fam Med. 2020;12(1):e1-e7.link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7203186/

> Garnelo L, et al. Barriers to access and organization of primary health care services for rural riverside populations in the Amazon. Int J Equity Health. 2020;19(1):54. https://pubmed.ncbi.nlm.nih.gov/32731874/

Addressing insufficient energy availability

Running healthcare facilities and leveraging digital health requires electricity: for rural areas this can pose a problem. It has been reported that over 50% of people in the least developed countries have basic access to electricity, while specifically in sub-Saharan Africa, 1 in 4 healthcare facilities lacks access to electricity, while 3 in 4 lack reliable power: at a higher granularity, rural areas are more adversely affected than urban areas.

The publication of Mechtenberg et al details the healthcare costs of this, while that of Moner-Girona et al presents solutions to try to resolve the problem.

> Mechtenberg A, et al. Health care during electricity failure: The hidden costs. PLoS One. 2020;15(11):e0235760. Link: https://pubmed.ncbi.nlm.nih.gov/33147212/

> Moner-Girona G, et al. Achieving universal electrification of rural healthcare facilities in sub-Saharan Africa with decentralized renewable energy technologies. 2021. Joule; 5(10). 2687-2714. Link: https://www.sciencedirect.com/science/article/pii/S2542435121004384

> Over half of the people in least developed countries lack access to electricity. United Nations Conference on Trade and Development. UNCTAD calculations based on data from the International Energy Agency and UNCTADstat.Last updated July 2021. Accessed November 2022. https://unctad.org/topic/least-developed-countries/chart-july-2021

Digital: covered in more detail in digital health section…but needs broadband (that needs energy)

Strategies for rural health have of course erred towards digital for several decades, but even in developed countries, access to suitable internet connection in rural areas is still problematic. Fibre optic and mobile based connectivity availability, as well as digital health solutions are presented in detail in part 3.

> Rural Health care delivery: connecting communities through technology. California Healthcare Foundation. Last updated: December 2002. Accessed November 2022. https://www.chcf.org/wp-content/uploads/2017/12/PDF-RuralHealthCareDelivery.pdf

> Improving Rural Health and Access to Care with Digital Health Tools. Health Catalyst. Last updated October 4 2022. Accessed November 2022. https://www.healthcatalyst.com/insights/improve-rural-health-with-digital-tools

Table 4: Estimated Dental/Medical HCP personnel per 10,000 population*

Region	Dentists	Family doctors (GPs)	Nurses	Community Health Workers	Pharmacists*
Africa	0.75	2.19	11.29	3.66	1.10
Asia	2.67	3.26	26.24	6.05	5.06
Europe	8.04	9.10	90.83	Not available	7.75
Latin America	1.98	9.87	60.20	6.91	4.85
North America	6.37	7.86	149.44	Not available	9.62
Western Pacific	1.39	7.95	89.63	Not available	12.63

(for western pacific, analysis of Australia and New Zealand apart indicate numbers similar to North America)

*data obtained from: https://www.who.int/data/gho/data/themes/topics/health-workforce

A significant emphasis for innovation therefore needs to focus on the Dental–Primary care HCP interaction, or Primary care HCP alone, if the healthcare infrastructure environment indicates, that no dentists are available, and the work is performed by family doctors, nurses or community health workers.

The availability of tertiary care Hospital facilities are presented in the appendices, that are evidently overstretched.

If the location of pemphigus incidence is not in the immediate vicinity of specialised healthcare systems, the innovator also has the consider rural health or health provision in lower economic settings which is not exclusively delineated by a location being considered developed vs developing, and also involves expert availability: see table 4 above.

During the design phase, it is worthwhile for the innovator to read the following publications to fully grasp the problem: the more the initial solution can create patient benefit without too much capital investment being required either by the innovator or policy maker, the greater the impact it will have.

US National Rural Health Association: About Rural Healthcare. 2022 NFRA website. Accessed November 2022: https://www.ruralhealth.us/about-nrha/about-rural-health-care

Hossain MM, et al. Revitalising general practice in Bangladesh: complementing 'the Bangladesh Paradox'. Br J Gen Pract. 2018;68(675):482. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6145986/

Stralen ACV, et al. The scope of practice of primary health care physicians in rural and urban areas in Brazil. Cad Saude Publica. 2021;37(9):e00211520. Link: https://pubmed.ncbi.nlm.nih.gov/34586168/

Gumede, D.M., et al. Engaging future healthcare professionals for rural health services in South Africa: students, graduates and managers perceptions.BMC Health Serv Res 21, 220 (2021).link: https://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-021-06178-w

Luchuo Engelbert Bain et al. There is an urgent need for a global rural health research agenda. Pan African Medical Journal. 2022;43:147.Link: https://www.panafrican-med-journal.com/content/article/43/147/full/

Falchetta G, et al. Planning universal accessibility to public health care in sub-Saharan Africa. Proceedings of the National Academy of Sciences of the United States of America. 2020;117(50):31760-31769.Link: https://www.pnas.org/doi/10.1073/pnas.2009172117

2.8 Clinically tested solutions for Pemphigus

The innovator needs to be aware of the specific characteristics of treating autoimmune diseases. Immunosuppressants have been a mainstay for many immune based disorders, with corticosteroids being the main types used.

Corticosteroids

This also applies to Pemphigus: corticosteroids are easy to administer and exist in generic formats, making application and reimbursement in low-income settings feasible: but there are drawbacks. See table 1 of the following publication, with up to 100 genes in cells directly regulated by corticosteroids.

> Kridin K. Emerging treatment options for the management of pemphigus vulgaris. Ther Clin Risk Manag. 2018;14:757-778. **Link:** https://pubmed.ncbi.nlm.nih.gov/29740210/

Efforts to reduce toxicity by using in combination with other chemical entity immunosuppressants have also demonstrated little added benefit

> Jain K, et al. A randomised clinical trial to assess the adjuvant potential of methotrexate to corticosteroids in mucosal or limited mucocutaneous pemphigus vulgaris. Sci Rep. 2022;12(1):7525. **Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9085868/

Immunotherapies and personalised therapies

The repositioning of Rituximab, an immunotherapy (anti-CD20 antibody) that targets and depletes certain immune cells (B-cells) has enabled decreases in the use of corticosteroids while enabling disease control, but as for all immunosuppressants also comes with its own potential impacts on the immune system.

> Werth VP, et al. Rituximab versus Mycophenolate Mofetil in Pemphigus Vulgaris. Reply. N Engl J Med. 2021;385(11):1056. **Link:** https://pubmed.ncbi.nlm.nih.gov/34496188/
>
> Varley CD, Winthrop KL. Long-Term Safety of Rituximab (Risks of Viral and Opportunistic Infections). Curr Rheumatol Rep. 2021;23(9):74. **Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8284038/
>
> Khalid SN, et al. A blistering new era for bullous pemphigoid: A scoping review of current therapies, ongoing clinical trials, and future directions. Ann Med Surg (Lond). 2021;70:102799. Link: https://pubmed.ncbi.nlm.nih.gov/34540212/

The personalised approach of immunotherapies has stimulated significant development of additional targeted or personalised approaches: Antibodies and antibody fragments, CAR-T cells, T-reg cells, Tyrosine kinase inhibitors, FC receptor antagonists, reviewed in the following publications:

> Didona D, et al. Pemphigus: Current and Future Therapeutic Strategies. Front Immunol. 2019;10:1418. **Link**: https://pubmed.ncbi.nlm.nih.gov/31293582/
>
> Bieber K, et al. Milestones in Personalized Medicine in Pemphigus and Pemphigoid. Front Immunol. 2021;11:591971.**Link**: https://pubmed.ncbi.nlm.nih.gov/33505392/
>
> Bishnoi A, et al. Biologics in autoimmune bullous diseases: Current scenario. Indian J Dermatol Venereol Leprol. 2021;87(5):611-620. **Link:** https://pubmed.ncbi.nlm.nih.gov/34245525/
>
> Lim YL, et al. Autoimmune Pemphigus: Latest Advances and Emerging Therapies. Front Mol Biosci. 2022;8:808536.**Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8855930/

Important points to consider, that have added weight for rare diseases:

- Routes of administration: if it requires an injection, it requires someone authorized to inject it, plus a healthcare location
- Frequency of administration: combined with the above, how often does it need to be applied
- Impact of treatment: does it need to be used constantly, or in response to flare-ups
- Response to treatment: if the patient relapses, what happens next
- Stage of disease: does the solution have better impact, or selected impact at certain stages or phases of the disease
- Affordability: can the people that need it the most afford it

What has been performed clinically, including staying current: using Clinicaltrials.gov

The NIH and the U.S. National Library of Medicine organise and maintain 'ClinicalTrials.gov' that is '*A database of privately and publicly funded clinical studies conducted around the world… Explore 432,129 research studies from 221 countries.*' This is an excellent source for innovators, and an extremely valuable source of information. Appendix 3 has suggested tips for searching this database.

'Basket trials'

For some dermatological clinical trials, why are there multiple neurological indications listed for the study?

This is a concept termed 'basket trials' and represents a methodology to optimise innovation: as indicated above, regulators understand that diagnosis is difficult, but need is great. It has been widely used for oncological diseases, is being applied in neurology and has been used in other forms of Dermatological disease (see clinicaltrials.gov).

> Park, J.J.H., et al. Systematic review of basket trials, umbrella trials, and platform trials: a landscape analysis of master protocols.Trials 20, 572 (2019). Link https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-3664-1

What is presently being clinically tested:

Search location: clinicaltrials.gov **Condition or disease**: Pemphigus

Filters:

- **Recruiting** (not yet recruiting, recruiting, enrolling by invitation, active not recruiting, completed, terminated)
- **Age and sex**: all
- **Study type**: all
- **Study phases**: early phase 1, phase 1, phase 2, phase 3, phase 4

NCT number	Phase/focus	Status	Indication	Intervention (phase), or Action	Enrollment (number of patients)
NCT05338112	Observational	Active, not recruiting	Pemphigus Vulgaris	Diagnostic Test: Tzanck smear	50
NCT03239470	Phase 1	Active, not recruiting	Pemphigus Foliaceus|Pemphigus Vulgaris	Biological: Cohort 1: 1.0 x 10^8 PolyTregs|Biological: Cohort 2: 2.5x10^8 PolyTregs	5
NCT04117529	Observational	Recruiting	Pemphigus Vulgaris|Pemphigus Foliaceus	Other: Blood sample	40
NCT04096222	Observational	Recruiting	Pemphigus Vulgaris|Bullous Dermatoses|Autoimmune Diseases		42
NCT05284929	Observational	Recruiting	Pemphigus|Bullous Pemphigoid|Stevens-Johnson Syndrome|Toxic Epidermal Necrolyses	Genetic: A single blood sample for HLA typing	120
NCT02753777	Observational	Recruiting	Pemphigus Vulgaris|Pemphigus Foliaceus|Bullous Pemphigoid	Other: Questionnaires	150
NCT04422912	Phase 1	Recruiting	Mucosal -Dominant Pemphigus Vulgaris	Biological: DSG3-CAART	39
NCT04023149	Phase 2	Recruiting	Pemphigus Vulgaris	Drug: recombinant human interleukin-2 (rhIL-2)|Drug: placebo	180
NCT04540133	Phase 2	Recruiting	Oral Lichen Planus|Mucous Membrane Pemphigoid|Pemphigus Vulgaris|Chronic Graft-versus-host-disease	Drug: dexamethasone 0.5mg/5ml solution|Drug: dexamethasone 0.5mg/5ml solution in Mucolox™	30
NCT05000216	Phase 2	Recruiting	Rheumatoid Arthritis|Systemic Lupus Erythematosus (SLE)|Pemphigus Vulgaris|Multiple Sclerosis|Systemic Sclerosis (SSc)|Pediatric SLE|Juvenile Idiopathic Arthritis|Juvenile Dermatomyositis|Pediatric-Onset Multiple Sclerosis (POMS)	Biological: Moderna mRNA-1273|Biological: BNT162b2|Biological: Ad26.COV2.S|Drug: IS (MMF or MPA)|Drug: IS (MTX)|Biological: IS (B cell depletion therapy)	2340
NCT05594472	Phase 3	Recruiting	Pemphigus Vulgaris|Bullous Pemphigoid	Drug: Ozonated olive oil|Drug: Topical garamycin cream	30
NCT04598451	Phase 3	Recruiting	Pemphigus Vulgaris|Pemphigus Foliaceus	Biological: efgartigimod PH20 SC|Other: Placebo|Drug: prednisone	213

NCT04598477	Phase 3	Recruiting	Pemphigus Vulgaris|Pemphigus Foliaceus	Biological: efgartigimod PH20 SC|Drug: prednisone	213
NCT05303272	Phase 4	Recruiting	Pemphigus Vulgaris	Drug: Abatacept Prefilled Syringe|Drug: Mycophenolate Mofetil 500Mg Tab	60
NCT00063752	Phase 1	Completed	Pemphigus Vulgaris	Drug: PI-0824	15
NCT00626678	Phase 2	Completed	Pemphigus Vulgaris	Drug: Azathioprine|Drug: Prednisone|Drug: Placebo	48
NCT02704429	Phase 2	Completed	Pemphigus Vulgaris	Drug: PRN1008	42
NCT00135720	Phase 2	Completed	Pemphigus Vulgaris	Drug: Enbrel (Etanercept)	12
NCT00606749	Phase 2	Completed	Pemphigus Vulgaris	Drug: KC706	20
NCT00283712	Phase 2	Completed	Pemphigus	Drug: Infliximab|Other: Placebo Comparator	20
NCT03334058	Phase 2	Completed	Pemphigus Vulgaris|Pemphigus Foliaceus	Drug: ARGX-113	34
NCT02383589	Phase 3	Completed	Pemphigus Vulgaris	Drug: Mycophenolate Mofetil Placebo|Drug: Mycophenolate Mofetil|Drug: Rituximab|Drug: Rituximab Placebo	135
NCT02828163	Phase 3	Completed	Oral Pemphigus Vulgaris	Other: Autologous Platelet rich plasma|Drug: Triamcinolone Acetonide	11
NCT00683930	Phase 3	Completed	Pemphigus Vulgaris (PV)	Drug: Mycophenolate Mofetil 2 g/Day|Drug: Mycophenolate Mofetil (MMF) 3 g/Day|Drug: Placebo	96
NCT03075904	Phase 1|Phase 2	Terminated	Pemphigus|Pemphigus Vulgaris|Pemphigus Foliaceus	Drug: ALXN1830	8
NCT01930175	Phase 2	Terminated	Pemphigus Vulgaris	Drug: VAY736|Drug: Placebo	13
NCT00429533	Phase 2	Terminated	Pemphigus Vulgaris	Drug: Dapsone	48
NCT00483119	Phase 2	Terminated	Pemphigus Vulgaris	Drug: intravenous immunoglobulin|Drug: cyclophosphamide	9
NCT01920477	Phase 3	Terminated	Pemphigus Vulgaris	Biological: Ofatumumab|Biological: Placebo	35
NCT02613910	Phase 3	Terminated	Pemphigus	Drug: Ofatumumab|Drug: Acetaminophen/paracetamol|Drug: Antihistamine (cetirizine or equivalent)|Drug: Prednisone/Prednisolone	1
NCT03762265	Phase 3	Terminated	Pemphigus	Drug: Rilzabrutinib|Drug: Placebo	131

Part 3:

Innovating for Pemphigus across rural and urban environments

A. The patient:

> *Most patients with pemphigus are not satisfied with the level of information shared with them. They believe that if they get proper attention and meet their expectations, this long period would be more tolerable. Therefore, in addition to attempts to reduce this lengthy diagnostic period, physicians should better understand patients' conditions.'*

Kianfar, Nika et al. Burden of pemphigus vulgaris with a particular focus on women: A review. International Journal of Women's Dermatology: 2022; 8(3)p e056. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9529034/

Increasing patient awareness and understanding of their symptoms is essential throughout the complete patient journey that can reduce anxiety at initial diagnosis, and lay the foundation for better patient-HCP interaction during chronic disease management:

i. Patient level of understanding of biology

Many of clinical study reports indicate as part of the patient population definition, level of education. This is a critical component to be integrated into innovative solutions for a rare disease where education level and socioeconomic factors are closely linked to prevalent disease epidemiology.

Other rare diseases have oriented their patient survey questionnaires using language levels of children aged 13–14 years of age: this could represent a key component to ensuring the patient is informed, and stays informed. Most humans do not understand the complex biology of disease or ramifications of effective healthcare: this is not surprising; most people stop studying biology in their early teenage.

Bijl RC, et al. Patient journey during and after a pre-eclampsia-complicated pregnancy: a cross-sectional patient registry study. **Link**: https://pubmed.ncbi.nlm.nih.gov/35241475/

Azfar N.A. et al Quality-of-life index evaluation in pemphigus vulgaris patients of Pakistan. Journal of Pakistan Association of Dermatologists. 2021;31(1):3-7. **Link:** https://www.jpad.com.pk/index.php/jpad/article/view/1574

Segal O, et al. Illness Perception, Perceived Social Support and Quality of Life in Patients with Pemphigus Vulgaris: What Should Dermatologists Know? Acta Derm Venereol. 2021;101(4):adv00441. **Link**: https://pubmed.ncbi.nlm.nih.gov/33723618/

ii. Targeted communication for Rural settings

Rural communities tend to have larger populations without higher education, lower incomes and more disparate access to health infrastructures.

In addition to considering health provision of solutions for pemphigus in rural settings (see part 2 of this briefing), the innovator also needs to integrate in tailored and targeting communication strategies.

Internet and telephone-based communication appear to be the more frequently used channels when telecommunication infrastructure permits and when it is made easy to use.

Focusing on communities and group communication as a whole rather than specific sections of the community seem to be an approach that has beneficial impacts across continents.

In lower resource settings, radio and printed material may represent the more cost-effective and higher impact channel.

However, in the context of direct interactions between health providers and communities, the availability to download information and apps onto mobile devices, preferably tablet based due to larger screen size, could enable awareness and strengthening of the community/health provider interaction.

The impact of socioeconomic status on health perception is multifaceted with level of income also playing a role:

> *'The perception of very poor households on health problems as a whole is in the medium category. Aspects related to very poor households perception of health problems include the following:*
>
> - *perception of illness and treatment,*
> - *perception of healthy body information,*
> - *perception of alternative healing,*
> - *perception of physician/doctors' ability*
> - *perceptions of the importance of health problems,*
> - *perceptions of health orientation,*
> - *perceptions of alternative health treatment,*
> - *perceptions of treatment to health centers,*
> - *perceptions of the importance of disease discussion,*
> - *perceptions of health related to the management of life and the environment,*
> - *perception of health information needs*
> - *perception of health information through mass media.'*

From: Suryana A et al, The Health Communication Orientation of Poor Community in Rural Areas on West Bandung District, West Java. Proceedings of the International Conference on Media and Communication Studies (ICOMACS 2018). 79(83):2352–5398. https://www.atlantis-press.com/proceedings/icomacs-18/25900602

A Toolkit for communicating healthcare in rural settings:

For innovators looking for starting conceptual needs before moving into design, the University of North Dakota's 'Dissemination of Rural Health Research: A toolkit', represents a comprehensive guide with indication specific case studies of best practice, that may be adaptable across borders.

Schroeder S et al. Dissemination of Rural Health Research: A toolkit. Last updated August 2019. Accessed November 2022. https://www.ruralhealthresearch.org/dissemination-toolkit

Additional references

Annobil, I., et al "From experts to locals hands" healthcare service planning in sub-Saharan Africa: an insight from the integrated community case management of Ghana. BMC Health Serv Res 21, 403 (2021). Link: https://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-021-06407-2

Dogba MJ, et al. Using information and communication technologies to involve patients and the public in health education in rural and remote areas: a scoping review. BMC Health Serv Res. 2019 Feb 19;19(1):128. Link: https://pubmed.ncbi.nlm.nih.gov/30782147/

Aririguzoh S, et al. (2021) Achieving sustainable e-health with information and communication technologies in Nigerian rural communities, Cogent Social Sciences, 7:1, 1887433. Link: https://www.tandfonline.com/doi/full/10.1080/23311886.2021.1887433

Effective Health Communication Campaigns in Rural Communities: What Works?
Robert Lambert. The University of Tennessee, Knoxville School of Advertising and Public Relations. Last updated 2016. Accessed November 2022
https://healthynewsrevival.files.wordpress.com/2016/05/health-communication-paper_lambert-copy.pdf

Improving Rural Health Through Telehealth-Guided Provider-to- Provider Communication*:* Evidence-based Practice Center Systematic Review Protocol. Agency for Healthcare Research and Quality.Last updated February 2021. Accessed November 2022. https://effectivehealthcare.ahrq.gov/products/rural-telehealth/protocol

Martínez A, et al. Analysis of information and communication needs in rural primary health care in developing countries. IEEE Trans Inf Technol Biomed. 2005;9(1):66-72. Link: https://pubmed.ncbi.nlm.nih.gov/15787009/

Hazra B. Role of Communication for Improving the Health of Rural Women: Analysis and Implementation Strategies Used. International Journal of Engineering and Management Research. 2017. 7(6):232-238.Link: https://www.ijemr.net/DOC/RoleOfCommunicationForImprovingTheHealthOfRuralWomenAnalysisAndImplementationStrategiesUsed.pdf

iii. Preferences for communication

Specific patient preferences for communication from their dental or medical HCPs regarding pemphigus is not available: however, several reports address general patient-doctor communication requirements in dermatology as a whole, and also for specific indications with skin involvement such as skin biopsy report, Psoriatic arthritis, and atopic dermatitis.

de Wijs LEM, et al. Needs and preferences of patients regarding atopic dermatitis care in the era of new therapeutic options: a qualitative study. Arch Dermatol Res. 2022:1–9. Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8809237/

Choudhry A, et al. Patients' preferences for biopsy result notification in an era of electronic messaging methods. JAMA Dermatol. 2015;151(5):513-21.Link: https://pubmed.ncbi.nlm.nih.gov/25831475/

Coates LC, et al. Exploring the Quality of Communication Between Patients with Psoriatic Arthritis and Physicians: Results of a Global Online Survey. Rheumatol Ther. 2021;8(4):1741-1758. Link: https://pubmed.ncbi.nlm.nih.gov/34570345/

Szabó C, et al. Dermatology patients' and their doctors' representations about adherence. Open Med (Wars). 2015;10(1):216-223.Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5152978/

Calderón P, et al. A new era for physician-patient communication in dermatology. Cutis. 2018;101(2):83. Link: https://pubmed.ncbi.nlm.nih.gov/29554161/

Kwissa-Gajewska Z et al. Physician-patient agreement on physicians' communication skills and visit satisfaction in dermatology clinics: a one-with-many design. Health Psychology Report 2022;10(1):68–81. Link: https://hpr.termedia.pl/Physician-patient-agreement-on-physicians-r-ncommunication-skills-and-visit-satisfaction,142351,0,2.html

From other rare diseases characteristics of patient focused education and awareness have indicated the following requirements (see: www.echino.eu/knowledge - rare disease briefings)

- Use of graphics
- Information needs to be patient personalised
- That information leads to a shared decision making
- It is consistent across sources
- It is visible and easy to find
- Use of different channels of communication (this applies across all groups in this section)
- It needs to address cultural or sensory (hearing or vision) related factors?
- Most patients want to hear it initially communicated to them by an HCP

B. Dental and Medical HCP awareness and integration

i. The dentist (in the case of oral lesions):

A significant issue is awareness of rare diseases: the number of potential reasons why a patient is presenting with oral lesions is significant, and awareness of rare diseases amongst dental practitioners is repeatedly described in the references below as inadequate and in need of development. The publication of Mijiritsky E et al, is revealing as it also indicates that dentists consider better understanding of rare diseases crucial, while also informing the innovator on preferred methods of communication and education (see table 7).

Mijiritsky E, et al. Knowledge and Associated Factors about Rare Diseases among Dentists in Israel: A Cross Sectional Survey. Int J Environ Res Public Health. 2021;18(13):6830. Link: https://pubmed.ncbi.nlm.nih.gov/34202149/

Putting an end to the desperation: dentists play a critical role in shortening the diagnosis window for this rare autoimmune disease. Dentistry News: last updated January 29th 2018. Accessed November 2022: https://dentistryinsider.tamhsc.edu/putting-an-end-to-the-desperation/

Benz K, et al. Awareness and Knowledge of Rare Diseases in German Dentists, Dental Specialists and Oral and Maxillofacial Surgeons: A Country-Wide Survey. Medicina (Kaunas). 2022;58(8):1114. Link: https://pubmed.ncbi.nlm.nih.gov/36013581/

Friedlander L, et al. Consideration of oral health in rare disease expertise centres: a retrospective study on 39 rare diseases using text mining extraction method. Orphanet J Rare Dis. 2022;17(1):317.Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9392290/

Kühne A, et al. Study to Investigate the Knowledge of Rare Diseases among Dentists, Orthodontists, Periodontists, Oral Surgeons and Craniomaxillofacial Surgeons. Int J Environ Res Public Health. 2020;18(1):139. Link: https://pubmed.ncbi.nlm.nih.gov/33379144/

Toupenay S, et al. Rare diseases with oral components: care course and quality of life. Community Dent Health. 2013;30(1):10-4. Link: https://pubmed.ncbi.nlm.nih.gov/23550500/

While precise awareness of rare diseases is low, if solutions are generated that enable better awareness, the innovator has the benefit of leveraging the extensive training dental specialists undergo in optimal communication with their patients: that represents a career long continued professional development component of their profession:

Chérrez-Ojeda, I., et al The use of information and communication technologies in Latin American dentists: a cross-sectional study from Ecuador. BMC Oral Health 20, 146 (2020).Link: https://bmcoralhealth.biomedcentral.com/articles/10.1186/s12903-020-01137-z

Larsen M, et al. Challenging encounters in clinical dentistry: a qualitative study investigating online reviews of patient satisfaction with Norwegian dentists. Acta Odontol Scand. 2022;80(5):328-337.Link: https://pubmed.ncbi.nlm.nih.gov/34875189/

Misra S, et al. Dentist-patient communication: what do patients and dentists remember following a consultation? Implications for patient compliance. Patient Prefer Adherence. 2013;7:543-9.Link: https://pubmed.ncbi.nlm.nih.gov/23814463/

Waylen A, et al. Patient-clinician communication in a dental setting: a pilot study. Br Dent J. 2015;218(10):585-8; Link: https://pubmed.ncbi.nlm.nih.gov/25998352/

Patient Communications: A Guide for Dentists. Nova Scotia Dental Association. Accessed from: https://www.cda-adc.ca/_files/practice/practice_management/patient_communications/guides/dentalguide-ns.pdf

British General Dental Council standards: principle two: communicate effectively with patients. Accessed from: https://standards.gdc-uk.org/pages/principle2/principle2.aspx

A dental student's guide to… pemphigus and pemphigoid. Last updated 3rd Feb 2022. Accessed November 2022: https://dentistry.co.uk/2022/02/03/a-dental-students-guide-topemphigus-and-pemphigoid/

There are resources available to provide knowledge to the dental team on causes of oral lesions (see patient journey section above): a dental or oral point of care rapid screening solution could be a significant first domino in the process of initiating a comprehensive care pathway, that integrates dental/oral specialties with medical HCPs.

Reasons for oral mucosal lesions table 4 of:

Oivio, UM., et al. Prevalence of oral mucosal normal variations and lesions in a middle-aged population: a Northern Finland Birth Cohort 1966 study. BMC Oral Health 20, 357 (2020). Link: https://bmcoralhealth.biomedcentral.com/articles/10.1186/s12903-020-01351-9

Classifications of oral mucosal lesions table 1 of:

Lin D, et al. Crosstalk between the oral microbiota, mucosal immunity, and the epithelial barrier regulates oral mucosal disease pathogenesis. Mucosal Immunol. 2021;14(6):1247-1258. Link: https://pubmed.ncbi.nlm.nih.gov/34040155/

ii. Dental to medical HCP interfacing and integration

The separation of dental and medical HCP specialties is a problem and creates delays to accurate diagnosis and optimal care for patients with pemphigus: innovative solutions that bring the patient, dentist and medical HCPs, from family doctors to tertiary care specialists onto the same page

Molayem S. Dentists and Doctors need to play on the same team. Nature Outlook. Last updated 27 October 2021. Accessed November 2022. https://www.nature.com/articles/d41586-021-02919-3

'The prompt diagnosis of pemphigus is of utmost importance to disrupt disease progression and improve prognosis, but unfortunately, many patients experience long delays to diagnosis. This frustrating undiagnosed period is ***often due to a lack of health care providers' knowledge of pemphigus manifestations, long waits for a dermatologist visit, and repeated inconclusive diagnostic tools****.*

Kianfar, Nika et al. Burden of pemphigus vulgaris with a particular focus on women: A review. International Journal of Women's Dermatology: 2022; 8(3)p e056. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9529034/

C. HCP understanding: family doctor to dermatologist/ rural to urban medical specialist

This has two clear components: HCP awareness of pemphigus and its diagnosis and healthcare specialist communication (in addition to potential Dental to Medical HCP interfacing)

The transfer of information and transition of care from a rural setting to an urban setting in the instance of need for acute or intensive care also requires consideration for innovation. Communication approaches that reflects the rural context of healthcare implementation, while potentially integrating in digital solutions may address some issues: Misalignment in clinician-clinician communication can result in unforced errors.

Wilson MM, et al. Rural family physician perspectives on communication with urban specialists: a qualitative study. BMJ Open. 2021;11(5):e043470. Link https://pubmed.ncbi.nlm.nih.gov/33986048/

Henderson C, et al. Analysis of patient preferences on patient-provider interactions through the OpenNotes online portal in dermatology. Int J Womens Dermatol. 2021;7(5Part B):793-798.Link: https://pubmed.ncbi.nlm.nih.gov/35028384/

Communication in Healthcare. Center for Optimizing Rural Health. Last updated 2019. Accessed November 2022 https://optimizingruralhealth.org/communication-in-healthcare/

i. Decisions on patients' health is urgent.

The existing guides as they stand may not lend themselves well to resource availability and disease demographics: a specialist needs the time to read them. They may have this time available; in the context of a primary care consultation, they need something short, an algorithm to hand for whichever innovation or process they are using.

A patient with Pemphigus is not the only patient they will see, so they need to be able to quickly switch from one to another, with no decrease in care quality.

Language: If a mentally exhausted HCP has only 43 seconds, then educational resources need to be in local languages and dialects, while also addressing cultural sensitivities.

Facilitating increased awareness for the HCP, enables them to explain it to the patient, who will almost definitely only speak the national language or local dialect fluently.

Public administration staff are not multilingual, their IT systems unreliable, and the understaffing of healthcare everywhere means 'hoping' one of them has the time to translate the latest guide is a stretch. Solutions exist for translation. *This is the responsibility of the innovator*: When designing your innovation, make multi-lingual/mulit-cultural sensitivity an integral part of it.

ii. Availability

A key issue that innovators in awareness, education and communication solution development will need to integrate into a solution or strategy is time availability: the low number of medical HCPs has a direct impact on time availability for accurate and indicative interactions with their patients:

'One hundred and seventy-nine studies were identified from 111 publications covering 28 570 712 consultations in 67 countries. Average consultation length differed across the world, ranging from ***48 s in Bangladesh to 22.5 min in Sweden****. We found that 18 countries representing about 50% of the global population spend 5 min or less with their primary care physicians.'*

Irving G, et al. International variations in primary care physician consultation time: a systematic review of 67 countries. *BMJ Open* 2017;**7:** e017902. **Link**: https://bmjopen.bmj.com/content/7/10/e017902

Indications that have symptoms that are easily visible orally or cutaneously have the capacity to be revolutionised by digital health: for rare diseases with these symptoms, it represents an opportunity to redesign healthcare process.

This does not detract from the complexity of the indication, and the multi tissue morbidity that occurs during pathogenesis as a result of the disease itself or responses to treatment, impacting internal organs. Nor does it detract from the necessity for biochemical tests or imaging systems that could preclude visits to specialist locations (addressed in the following Point of care section).

For Pemphigus there are a few digital health tailored solutions, that permit patient monitoring, diagnosis and follow-up:

- The IPPF have a dedicated patient's section that permits Peer coaching and identifying global doctors and dentists: https://www.pemphigus.org/patients/
- MSD Manuals has a free professional app that can be downloaded that includes information on diagnosis and care for patients with Pemphigus: https://www.msdmanuals.com/professional/resourcespages/mobileapps
- Almostadoctor, that also has a downloadable app, has a section dedicated to Pemphigus disorders: https://almostadoctor.co.uk/encyclopedia/bullous-pemphigus

For the innovator it is therefore worthwhile taking a sideways step and reviewing digital health in oral care, and digital health in skin related indications to conceptualise potential benefits for patients.

Oral Health Telemedicine:

Almost all articles consider this beneficial:

- The publication of Gonzalez J et al, from their experiences in Chile, clearly indicate significant reductions in patient monitoring and care
- Al Mohaya MA et al highlight the benefit for remote diagnosis, but also highlight training on telemedicine is needed for HCPs
- In the context of managing pain Alsafwani Z et al demonstrate clear benefit, also eliminating the need for many patients to travel long distances
- The 2020 article of Flores et al and Alsafwani Z et al, also indicate it as being useful for screening oral mucosal conditions

Oral Health Mobile Apps:

- The American Dental Association have the Oral Pathologist app, that includes aids for diagnosing oral pathologies.

For feasibility studies, and global experiences, several studies on using digital health solutions for oral cancer may aid the innovator in the design of solutions for autoimmune diseases with oral symptoms.

Gonzalez, J et al. (2021). Evaluation of a telemedicine program in oral pathology and preventive oral examination in Hualqui Municipality, Chile. *International journal of interdisciplinary dentistry*, *14*(3), 226-228. **Link:** https://www.scielo.cl/scielo.php?pid=S2452-55882021000300226&script=sci_abstract

Flores APDC et al. Teledentistry in the diagnosis of oral lesions: A systematic review of the literature. J Am Med Inform Assoc. 2020;27(7):1166-1172.Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7647318/

Al Mohaya MA, et al. Telemedicine Among Oral Medicine Practitioners During COVID-19 Pandemic and Its Future Impact on the Specialty. Risk Manag Healthc Policy. 2021;14:4369-4378. Link: https://pubmed.ncbi.nlm.nih.gov/34707420/

Alsafwani, Z., et al. The role of telemedicine for symptoms management in oral medicine: a retrospective observational study. *BMC Oral Health* **22**, 92 (2022).Link: https://bmcoralhealth.biomedcentral.com/articles/10.1186/s12903-022-02133-1

Uthoff RD, et al. Point-of-care, smartphone-based, dual-modality, dual-view, oral cancer screening device with neural network classification for low-resource communities. PLoS One. 2018;13(12):e0207493. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6281283/

Dailah HG. Mobile Health (mHealth) Technology in Early Detection and Diagnosis of Oral Cancer-A Scoping Review of the Current Scenario and Feasibility. J Healthc Eng. 2022;2022:4383303. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9605853/

Dermatology Telemedicine:

In dermatology, it is worthwhile to start with patients' experiences, so the innovator has an idea for motivations, and what enhancements are needed: benefits reported included

- Convenience,
- Being able to present symptoms when they occur,
- Complete privacy,
- Being involved with experts and being better prepared for the physical appointment.

Chow A, et al Patients' Experiences of Telemedicine for Their Skin Problems: Qualitative Study JMIR Dermatol 2022;5(1):e24956. **Link:** https://derma.jmir.org/2022/1/e24956/

The last point is important when considering clinical reports that patients with pemphigus feel most stress at disease outset because of confusion, but following this, mental health impacts decrease.

All of the following articles are recommended to be read by the innovator in considering design or editing of digital health solutions focusing on dermatology

Trettel A, et al. Telemedicine in dermatology: findings and experiences worldwide - a systematic literature review. J Eur Acad Dermatol Venereol. 2018;32(2):215-224. Link: https://pubmed.ncbi.nlm.nih.gov/28516492/

Xu X, et al. Digital Education for Health Professions in the Field of Dermatology: A Systematic Review by Digital Health Education Collaboration. Acta Derm Venereol. 2019;99(2):133-138. Link: https://pubmed.ncbi.nlm.nih.gov/30320871/

Wongvibulsin S, et al. Embracing machine learning and digital health technology for precision dermatology. J Dermatolog Treat. 2020;31(5):494-495. Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6911024/

Greis C, et al. Unmet digital health service needs in dermatology patients. J Dermatolog Treat. 2018;29(7):643-647. Link: https://pubmed.ncbi.nlm.nih.gov/29455570/

Wongvibulsin S, et al. Expanding Personalized, Data-Driven Dermatology: Leveraging Digital Health Technology and Machine Learning to Improve Patient Outcomes. JID Innov. 2022;2(3):100105. Link: https://pubmed.ncbi.nlm.nih.gov/35462957/

Sud E, Anjankar A (August 07, 2022) Applications of Telemedicine in Dermatology. Cureus 14(8): e27740. Link: https://www.cureus.com/articles/106131-applications-of-telemedicine-in-dermatology

MDPI Special Issue: Prevention and Digital Health in Dermatology 2022. **Link:** https://www.mdpi.com/journal/ijerph/special_issues/prevention_dermatology

In the specific context of Pemphigus, the challenge for the innovator is to design a 'seamless' solution that transverses geographies and cultures, the whole patient journey, from initial symptoms, through diagnoses, follow-ups and treatment regimen changes, that ties into molecular diagnostics, environment and HLA-types, to enable AI and ML to provide full benefit for both the patient and the HCP.

Digital health solutions in all their formats are dependent on two infrastructures: fixed connection or fibre optic, that for example would be used for good quality telemedicine, and mobile internet, potentially used for remote monitoring, self-management applications and potential point-of-care IT integrated solutions. In LMIC, the speed of IT development has meant mobile coverage is being developed faster than fibre optics. For the digitally focused innovator 2 connection availability resources are recommended.

Global mobile internet coverage:

The GSMA mobile connectivity index represents an annual update and map country by country of critical parameters related to connectivity: *Infrastructure, Affordability, Consumer readiness, Content and services*

Link: https://www.mobileconnectivityindex.com/#year=2021

Global internet (fixed and mobile) coverage:

For fixed line and fibre optic availability, the International Telecommunication Union, generates an annual Global Connectivity report, that can be downloaded. It is a thorough and comprehensive assessment in key regions of: *Fixed vs. mobile subscriptions and affordability, Percent of population using the internet, Differences between urban and rural areas, Percent of population within reach of an operational fibre-optic network, by distance*

Link: https://www.itu.int/hub/publication/d-ind-global-01-2022/

Evidence of digital healthcare provision in LMIC and a global guide: what works

Known barriers related cost of the subscription, digital literacy across all users and **cost of the device**. But there is space for social innovation and philanthropic entrepreneurship, if there is a motivation. The possibility to trade-in a device when buying a new one (phone, tablet or computer) could have *an additional option for the customer*: the entity could offer to refurbish, tailor with the needed apps/software and *give it for free to HCPs in LMIC* to distribute to their patients during their diagnosis and treatment period to enable a step towards better care.

The following articles have been selected as they are peer-reviewed and based on evidence obtained through actual usage in LMICs. While focused on low resource settings, these insights have equal pertinence in wealthier countries, where healthcare resources are also strained (albeit at a different level).

Dodoo JE, et al. The development of telemedicine programs in Sub-Saharan Africa: Progress and associated challenges. Health Technol (Berl). 2022;12(1):33-46. **Link**: https://pubmed.ncbi.nlm.nih.gov/34849325/

Acharibasam JW, Wynn R. Telemental Health in Low- and Middle-Income Countries: A Systematic Review. Int J Telemed Appl. 2018;2018:9602821. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6241375/

Labrique, A.B., et al. Best practices in scaling digital health in low and middle income countries. Global Health 14, 103 (2018). **Link:** https://globalizationandhealth.biomedcentral.com/articles/10.1186/s12992-018-0424-z

Telehealth around the world: A global guide, from DLA PIPER, written in 2020. *Visit the link, on the right-hand side is 'download pdf' that then permits downloading the full handbook* **Link:** https://www.dlapiperintelligence.com/telehealth/countries/index.html?t=01-availability-of-telehealth

3.3 Innovating for Point-of-Care: rural–urban necessity

Patients, Clinicians and Researchers defined their unmet needs in addressing Pemphigoid diseases; in the top three were needs for:

Quicker diagnosis, easy lab tests and a better understanding of the trigger mechanism

Lamberts A, et al. Unmet Needs in Pemphigoid Diseases: An International Survey Amongst Patients, Clinicians and Researchers. Acta Derm Venereol. 2019;99(2):224-225. **Link**: https://pubmed.ncbi.nlm.nih.gov/30265372/

As the disease has a distinct rural demographic prevalence, and neither Dentists nor medical HCPs are likely to be able to precisely diagnose the disease, but will need to rapidly identify it, two approaches need to be considered by the innovator.

Generation of accurate point-of-care solutions for rapid screening and accurate diagnosis and next-generation solutions. Eventually, they will merge, however evidence generation requirements would suggest keeping them separate as a first step.

A rapid point of care screening tool, will also enable the dentist to quickly define if the exclusively mucosal manifestation occurring before the cutaneous symptoms is pemphigus, while simultaneously permitting the patient to be interviewed to identify what possible triggers they had been exposed to in recent history.

For the HCPs this will enable identifying which patients should have further detailed diagnostics, the level of severity of the disease and planning of treatment regimens accordingly, before the disease becomes severe.

Point of care:

The existing tests of histopathology, direct immunofluorescence, serological detection of antibodies by immunofluorescent microscopy or ELISA, require high tech set ups typically found in tertiary care centres. They do not lend themselves well to resource constrained settings, or locations where the Dentist/Medical HCPs are sparse or unaware of the disease.

Could COVID's lateral flow test concept enable Pemphigus Vulgaris Point-of-Care?

Approaches to screening: dental locations/community health care centres

The COVID pandemic introduced many of us to the concept of the lateral flow test: a saliva or nasal mucus swab (from near the mucosal membranes) when introduced into a disposable piece of plastic informed us whether we were positive for infection, by antibodies being present in the sample interacting with immobilised viral antigens in the device.

Zhou Y, et al. Point-of-care COVID-19 diagnostics powered by lateral flow assay. Trends Analyt Chem. 2021;145:116452. **Link**: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8487324/

Oral mucosal lesions occur for many possible different reasons, that the Dentist/Medical HCP may or may not be aware of. For reasons that result in specific antibody generation and secretion into the saliva, Herpes Simplex Virus, Candida albicans, Paraneoplastic Pemphigus, Mucous membrane pemphigoid and Pemphigus could be the reason.

Are anti-DsG1 and 3 antibodies found in the saliva of patients? Are different ones found for other diseases?

Hallaji Z, et al. Serum and salivary desmoglein 1 and 3 enzyme-linked immunosorbent assay in pemphigus vulgaris: correlation with phenotype and severity. J Eur Acad Dermatol Venereol. 2010 Mar;24(3):275-80. Link: https://pubmed.ncbi.nlm.nih.gov/19709345/

De D, et al. Correlation between salivary and serum anti-desmoglein 1 and 3 antibody titres using ELISA and between anti-desmoglein levels and disease severity in pemphigus vulgaris. Clin Exp Dermatol. 2017;42(6):648-650. Link: https://pubmed.ncbi.nlm.nih.gov/28543318/

Asokan S, et al. Evaluation of the Role of Oral Mucosal Direct Immunofluorescence and Salivary Desmoglein 1 and 3 Enzyme-Linked Immunosorbent Assay in Patients With Oral Mucosal Pemphigus. Indian Dermatol Online J. 2022 5;13(5):617-619. Link: https://pubmed.ncbi.nlm.nih.gov/36304655/

Ali S, et al. Serum and salivary IgG and IgA antibodies to desmoglein 3 in mucosal pemphigus vulgaris. Br J Dermatol. 2016;175(1):113-21.Link: https://pubmed.ncbi.nlm.nih.gov/26799252/

Ptasiewicz M, et al. Immunoglobulin Disorders and the Oral Cavity: A Narrative Review. J Clin Med. 2022;11(16):4873. Link: https://pubmed.ncbi.nlm.nih.gov/36013115/

Potentially differentiating Pemphigus from paraneoplastic pemphigus and erythema multiforme

Landegren N, et al. A gene-centric approach to biomarker discovery identifies transglutaminase 1 as an epidermal autoantigen. Proc Natl Acad Sci U S A. 2021;118(51):e2100687118. Link: https://pubmed.ncbi.nlm.nih.gov/34911754/

Fukiwake N, et al. Detection of autoantibodies to desmoplakin in a patient with oral erythema multiforme. Eur J Dermatol. 2007;17(3):238-41.Link: https://pubmed.ncbi.nlm.nih.gov/17478387/

Could the Desmoglein proteins or antigens be immobilised within a lateral flow device, and are the Dsg-1 and -3 antibody concentrations high enough in saliva to enable Dentists/rural medical HCPs to perform an initial test and screen through lateral flow?

Point-of-care diagnostics*:* community health care centres/clinics – post initial screen

Technology updates of existing diagnostic approaches for pemphigus are being developed and tested: scaling up for field validation in resource constrained or rural settings is a very different question that requires a different level of understanding (see baseline diagnostic requirements below).

i. Fluorescent point of care*:*

Adsul, Neeraj. Fluorescence detection based point-of-care diagnostics platforms : bridging the gap between laboratory and market. 2014, Doctoral Thesis, University of Basel, Faculty of Science. Link: https://edoc.unibas.ch/34913/

Obahiagbon U, et al. A compact, low-cost, quantitative and multiplexed fluorescence detection platform for point-of-care applications. Biosens Bioelectron. 2018;117:153-160. Link: https://pubmed.ncbi.nlm.nih.gov/29894852/

Rai R, Harikumar MV. Comparison of direct immunofluorescence of plucked hair and skin for evaluation of immunological remission in pemphigus. Indian Dermatol Online J 2017;8:319-22. Link: https://pubmed.ncbi.nlm.nih.gov/28979862/

Mohamed HZ, et al. Direct immunofluorescence of the hair follicle in pemphigus: a less invasive method for diagnosis. Egypt J Dermatol Venerol 2020;40:92-8. Link: http://www.ejdv.eg.net/text.asp?2020/40/2/92/286289

ii. Advances in ELISA and Indirect Immunofluorescence:

Gornowicz-Porowska J, et al. Accuracy of molecular diagnostics in pemphigus and bullous pemphigoid: comparison of commercial and modified mosaic indirect immunofluorescence tests as well as enzyme-linked immunosorbent assays. Postepy Dermatol Alergol. 2017;34(1):21-27. Link: https://pubmed.ncbi.nlm.nih.gov/28261028/

Nili A, et al. Current status and prospects for the diagnosis of pemphigus vulgaris. Expert Rev Clin Immunol. 2021;17(8):819-834. Link: https://pubmed.ncbi.nlm.nih.gov/34162306/

In the context of screening/point-of-care, it is also important to place these concepts in context of digital health and mobile communication and discussion of health data. The anticipated requirements for a **point-of-care ecosystem** are described in:

Nayak S, et al. Point-of-Care Diagnostics: Recent Developments in a Connected Age. Anal Chem. 2017;89(1):102-123. **Link**: https://pubmed.ncbi.nlm.nih.gov/27958710/

Confirmation of diagnosis (if necessary, based upon severity) at tertiary care centre:

Existing solutions (plus newly developed point of care, if accurate enough)

Next-generation:

Next generation approaches hinge much more on highly specific molecular signals of pathogenesis and rapid prediction of clinical relapse following immunotherapy.

The molecularly focused approaches illustrated below, to be converted into clinically relevant diagnostic tools, will need high technology laboratories that typically only exist in tertiary care hospitals or high population density urban settings. But the study of Genovese G et al, also refers to body surface area coverage, which may lend itself to digital monitoring via image exchange.

Genovese G, et al. Clinical and serological predictors of relapse in pemphigus: a study of 143 patients. Clin Exp Dermatol. 2022;47(1):98-106. Link: https://pubmed.ncbi.nlm.nih.gov/34288016/

Albers LN, et al. Developing biomarkers for predicting clinical relapse in pemphigus patients treated with rituximab. J Am Acad Dermatol. 2017;77(6):1074-1082. **Link:** https://pubmed.ncbi.nlm.nih.gov/28927663/

Huang, Zx., et al. Transcriptomic profiling of pemphigus lesion infiltrating mononuclear cells reveals a distinct local immune microenvironment and novel lncRNA regulators. *J Transl Med* **20**, 182 (2022).**Link:** https://pubmed.ncbi.nlm.nih.gov/35449056/

Baseline Diagnostic requirements:

Development of precisely a new diagnostic, especially if it is based on molecular signals for a rare disease needs to be carefully considered. The overriding point is that the final product used to measure the molecular signal must:

- Integrate into the existing care pathway and make diagnosis more accurate
- Be easy to use within the actual infrastructure, with little or no specialisation required
- It must also have sufficient patient specific statistical evidence to prove sensitivity and specificity.

Statistics/Biostatistics measurements:

1) Sensitivity and specificity: you must be able to differentiate patients. This is typically done comparing the existing gold standard with your innovation (high false signals stop development)

	Subjects with the disease	Subjects without the disease
Positive	True positive	False positive
Negative	False negative	True negative

2) Predictive values: measuring probability of having the disease in a defined population.

3) Accuracy measurements: this data is essential and ideally should be stratified for the relevant populations: Likelihood ratio, Receiver Operating Characteristic, Diagnostic odds ratio and Youden's index

3.4 Next-generation treatments: a time for bioengineers?

Reviewing the care pathway, cyclical nature of the disease, demographics of the populations, healthcare infrastructure availability in rural areas, types and affordability of healthcare solutions there is significant space for innovation in drug delivery.

The benefits of immunotherapies vs. corticosteroids are unquestionable, although they also present with added barriers.

- Post-rituximab relapses manifest in >80% of patients over 79 months (more linked to severe forms of the disease)
- 10–20% of patients appear completely refractory to rituximab treatment
- Patients can become highly susceptible to bacterial and fungal infections
- Lower response to vaccines
- Virus infections have also been reported, that maybe because of latent virus present in the patient
- Relapse rates can be reduced by adjusting administration schedules and combining approaches

Lim YL, et al. Autoimmune Pemphigus: Latest Advances and Emerging Therapies. Front Mol Biosci. 2022;8:808536. **Link:**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8855930/

The unpredictability of manifestation, requirement for a needle, and emerging evidence that immunotherapies, if applied earlier in the disease course may confer greater benefit suggest that a better 'point-of-care' administration procedure is needed.

The dermal/oral mucosal nature of the disease combined with potential advances that could be achieved through digital monitoring, greater awareness of the disease and early-stage symptoms, with potential 'point-of-care' diagnostics suggests that topical administration of immunotherapies, placed in the hands of the patient could provide some benefit.

If combined with advances in soft tissue repair utilising 'active' biomaterials, this may facilitate localised disease and tissue damage control. It will likely not eliminate the need for systemic application of immunotherapies at some point, but to get the patient to the appropriate care centre, in a non-severe state should provide health and economic benefit.

Topical application of steroids

Joly P, et al. A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. N Engl J Med. 2002;346(5):321-7. Link: https://pubmed.ncbi.nlm.nih.gov/11821508/

Ingen-Housz-Oro S, et al. First-line treatment of pemphigus vulgaris with a combination of rituximab and high-potency topical corticosteroids. JAMA Dermatol. 2015;151(2):200-3. Link: https://pubmed.ncbi.nlm.nih.gov/25354242/

Joly P, et al. The role of topical corticosteroids in bullous pemphigoid in the elderly. Drugs Aging. 2005;22(7):571-6. Link: https://pubmed.ncbi.nlm.nih.gov/16038572/

Topical administration of antibodies

Pitiot A, et al . Alternative Routes of Administration for Therapeutic Antibodies-State of the Art. Antibodies (Basel). 2022;11(3):56. Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9495858/

Christensen RL, et al. Topical Delivery of Nivolumab, a Therapeutic Antibody, by Fractional Laser and Pneumatic Injection. Lasers Surg Med. 2021;53(1):154-161. Link: https://pubmed.ncbi.nlm.nih.gov/32997833/

Kabashima K, et al. Nemolizumab plus topical agents in patients with atopic dermatitis (AD) and moderate-to-severe pruritus provide improvement in pruritus and signs of AD for up to 68 weeks: results from two phase III, long-term studies. Br J Dermatol. 2022;186(4):642-651. Link: https://pubmed.ncbi.nlm.nih.gov/34726262/

Stevens NE & Cowin AJ. Overcoming the challenges of topical antibody administration for improving healing outcomes. Wound Practice and Research. 2017. 25(4). 188–194. Link: https://journals.cambridgemedia.com.au/wpr/volume-25-number-4/overcoming-challenges-topical-antibody-administration-improving-healing-outcomes-review-recent-laboratory-and-clinical-approache

Advances in soft tissue bioengineering

Bardill JR, et al. Topical gel-based biomaterials for the treatment of diabetic foot ulcers. Acta Biomater. 2022 Jan 15;138:73-91. Link: https://pubmed.ncbi.nlm.nih.gov/34728428/

Murray, R.Z., West, Z.E., Cowin, A.J. *et al.* Development and use of biomaterials as wound healing therapies. *Burn Trauma* 7, 2 (2019).Link: https://burnstrauma.biomedcentral.com/articles/10.1186/s41038-018-0139-7

Tu, Z., Zhong, Y., Hu, H. *et al.* Design of therapeutic biomaterials to control inflammation.*Nat Rev Mater* 7, 557–574 (2022).Link: https://www.nature.com/articles/s41578-022-00426-z

Cai L, et alW. Engineered biomaterials for cancer immunotherapy. MedComm (2020). 2020 May 27;1(1):35-46. Link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8489675/

Mazzoni E, et al. Bioactive Materials for Soft Tissue Repair. Front Bioeng Biotechnol. 2021 Feb 19;9:613787. Link: https://pubmed.ncbi.nlm.nih.gov/33681157/

Ma J et al. Bioactive inorganic particles-based biomaterials for skin tissue engineering. Exploration. 2022. 2, 20210083. Link: https://onlinelibrary.wiley.com/doi/full/10.1002/EXP.20210083

Ijaola AO, **et al**. Polymeric biomaterials for wound healing applications: a comprehensive review. J Biomater Sci Polym Ed. 2022 Oct;33(15):1998-2050. Link: https://pubmed.ncbi.nlm.nih.gov/35695023/

3.5 Economic burden and costs

Economic and cost assessments in Pemphigus patient care and management indicate the following:

i. Healthcare costs increase post diagnosis using existing procedures

In the United States, healthcare costs of patients within the 2009–2016 range, with Pemphigus Vulgaris increased from 16,420 +/- 39781 USD in the year before diagnosis, to 30,742 +/- 69,875 USD in the year after diagnosis.

Year before diagnosis: 16420 +/- 39781 USD

- Pharmacy: 2500 +/- 4993
- Inpatient: 5423 +/- 27618
- Outpatient: 8848 +/- 17121

Year after diagnosis: 30742 +/- 69875 USD

- Pharmacy: 3558 +/- 8858
- Inpatient: 5623 +/- 18108
- Outpatient: 21561 +/- 59785
  - Durable medical equipment: 1107 +/-2319
  - Evaluation and management: 2105 +/-2386
  - Unclassified 8717 +/- 41132
  - Imaging 1454 +/- 3066
  - Other 14207 +/- 48573
  - Procedures 4713 +/- 17383
  - Tests 1590 +/- 2604

Best JH, et al. Burden of Illness of Treating Patients with Pemphigus vulgaris [abstract]. Arthritis Rheumatol. 2018; 70 (suppl 9). https://acrabstracts.org/abstract/burden-of-illness-of-treating-patients-with-pemphigus-vulgaris/ Accessed November 25, 2022.US Marketplace

ii. It is important to correctly diagnose Pemphigus as the primary diagnosis rather than wait for the patient to be admitted with complications and Pemphigus then identified as the secondary diagnosis

In the United States in 2012, there was a nearly 10-fold difference in healthcare costs, between Pemphigus being diagnosed as the Primary reason for hospital admission, compared to Pemphigus being diagnosed as the secondary reason for admission, because the primary reason were severe morbidities related to Pemphigus (see Patient and Hospital Characteristics, Reasons for Secondary Admission and Figure 2 from Hsu. D et al) and that hospitalisation costs account for a significant amount of healthcare costs.

Hsu D, et al. Costs of Care for Hospitalization for Pemphigus in the United States. JAMA Dermatol. 2016 1;152(6):645-54. Link: https://pubmed.ncbi.nlm.nih.gov/26865293/

Ständer S, et al. Assessment of healthcare costs for patients with pemphigus and bullous pemphigoid in an academic centre in Germany. Br J Dermatol. 2020;182(5):1296-1297. Link: https://pubmed.ncbi.nlm.nih.gov/31749141/

Tamasi, B. 2018. Disease burden and its importance in patients with pemphigus (Doctoral dissertation, Semmelweis University, Clinical Medicine Doctoral School, Budapest, Hungary. Link: http://old.semmelweis.hu/wp-content/phd/phd_live/vedes/export/tamasibela.e.pdf

iii. That targeted immunotherapies significantly reduce healthcare costs across geographies

In both India and Canada, using Rituximab vs. corticosteroids reduced healthcare costs by 40%. See table 4 of Kanchan R et al.

Kanchan R, et al. (2017) To Compare the Cost of Rituximab and DCP Therapy in Pemphigus in a Government Tertiary Hospital. J Clin Exp Dermatol Res 8: 387. Link: https://www.longdom.org/open-access/to-compare-the-cost-of-rituximab-and-dcp-therapy-in-pemphigus-in-a-government-tertiary-hospital-15647.html

Heelan K, et al. Cost and Resource Use of Pemphigus and Pemphigoid Disorders Pre- and Post-Rituximab. J Cutan Med Surg. 2015; 19(3):274-82. Link: https://pubmed.ncbi.nlm.nih.gov/25775641/

iv. Indirect costs account for a significant burden in Pemphigus patient care and management

That indirect costs account for between 54–58% of healthcare costs, that in India can be reduced to less than 4% of costs when immunotherapies are used.

Kanchan R, et al. (2017) To Compare the Cost of Rituximab and DCP Therapy in Pemphigus in a Government Tertiary Hospital. J Clin Exp Dermatol Res 8: 387. Link: https://www.longdom.org/open-access/to-compare-the-cost-of-rituximab-and-dcp-therapy-in-pemphigus-in-a-government-tertiary-hospital-15647.html

Tamasi, B. 2018. Disease burden and its importance in patients with pemphigus (Doctoral dissertation, Semmelweis University, Clinical Medicine Doctoral School, Budapest, Hungary. Link: http://old.semmelweis.hu/wp-content/phd/phd_live/vedes/export/tamasibela.e.pdf

v. That using generically priced immunotherapies as first line therapeutics is slightly more expensive that corticosteroids, but this is compensated by the longer-term relapses and flares in patients treated with corticosteroids

Hébert V, et al. Comparison of real costs in the French healthcare system in newly diagnosed patients with pemphigus for first-line treatment with rituximab vs. standard corticosteroid regimen: data from a national multicentre trial. Br J Dermatol. 2020;183(1):121-127. Link. https://pubmed.ncbi.nlm.nih.gov/31657454/

Chen MKY, et al. Cost-Utility Analysis of Rituximab vs Mycophenolate Mofetil for the Treatment of Pemphigus Vulgaris. JAMA Dermatol. 2022;158(9):1013-1021. Link: https://pubmed.ncbi.nlm.nih.gov/35895045/

List of generics/biosimilars: https://gabionline.net/biosimilars/general/Biosimilars-of-rituximab

Some final considerations for the innovator:

Join the dots: before designing, consider the whole ecosystem and the actors in it. Look at solutions that have been designed and rolled out, but maybe not expanded. If innovations are adapted, made multi-lingual combined, and those opportunities definitely exist for Pemphigus based on the work that has been done already by all the stakeholders; don't forget it still needs validation in a clinical setting.

PICO: Patient population, Intervention(product), Comparator, Outcome, should be applied to every type of product. The broader the impact the product, the more data and sensitivity you will need, especially if it's anything non-interventional that potentially results in a medical intervention. Rare disease patient populations are heterogeneous: their low number means precise pathogenesis is often incomplete, and as indicated above pathogenesis greatly impacts the type of innovation and its design.

Factor that in: you may consider your innovation to be applicable to a whole Rare Disease patient population, but often solutions are applicable to specific symptoms, age groups, phases or stages and underlying morbidities, or other SDOH related risks that the patient may be exposed to, some of which may be responsible for an idiopathic occurrence.

There is always a comparator, even in Rare Diseases, where interventions do not currently exist. In addition to direct clinical impacts, is your planned product reducing caregiver related burdens and costs, does it reduce burden on HCPs and/or processes, or will it increase the needs for more specialists and dedicated facilities, is your solution equitable, are you addressing the needs of one stakeholder, many or all of them?

Health Economic and Outcomes Research (HEOR): the aspect a lot of Innovators think about too late, it is not the same as clinical outcome, take a short online course on it or HTA to introduce it to yourself. While review and approval bodies are not always national or centralized, the economic evidence assessments they use tend to be based on the same concepts and then adjusted locally. Note that perspectives and calculations of value differ between locations (QALYs vs DALYs, differing PROMs, accepted outcomes).

The ISPOR US Healthcare System Overview-Decision makers and influencers gives a good illustration of what is needed from the pharmacoeconomic angle: https://www.ispor.org/heor-resources/more-heor-resources/us-healthcare-system-overview

While global country information, where available, can be found at their around the world section https://www.ispor.org/heor-resources/more-heor-resources/pharmacoeconomic-guidelines

Note that most of these only apply to therapeutic application, med tech, diagnostics, healthcare process, and now digital health, have differing requirements and are often not nationally homogenous.

Social determinants of health and wealthy countries vs. LMIC

Many available existing sources of information do not include every stakeholder or perspective, and some innovators may not know where to look, to complete the picture. Especially when evidence is generated in different geographies with different healthcare infrastructures e.g., Universal healthcare vs private or hybrid, timing and location of evidence generation and influence of Social Determinants of Health (SDOH) on the patient, their journey, quality of life, available care or infrastructure and epidemiological data.

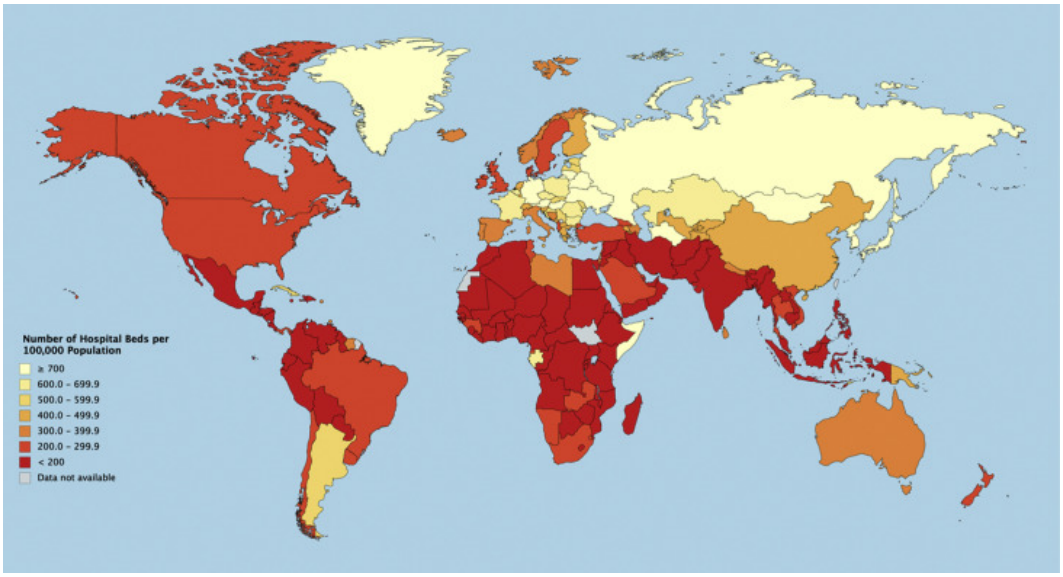
This is relevant for all countries irrespective of overall recognised income status. With this perspective, it may make the identification and development of innovative solutions for Rare Diseases global by design: solutions designed for wealthy countries (even if incidence and prevalence maybe influenced by socioeconomic status, ethnicity and gender within them), where available specialised Rare Disease healthcare is sparse, and SDOH and lifestyle risks can symptoms, may with partnering and redesign be applicable for patients with Rare Diseases in Low- and Middle-Income Countries, where resources are even more stretched, and *vice versa*.

Appendices:

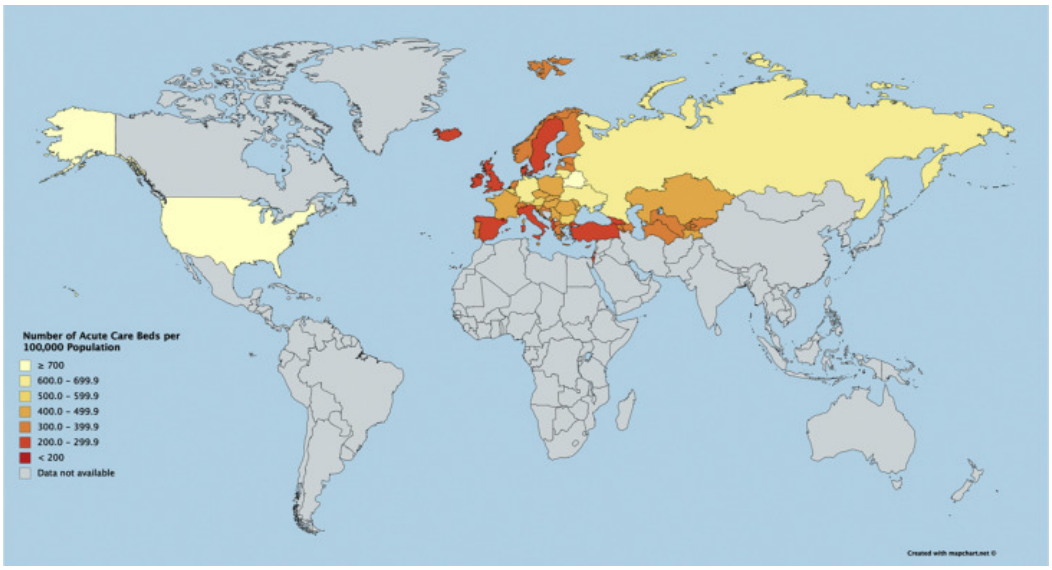
Appendix 1: Healthcare infrastructure as increased hospitalisation

Hospital bed capacity

1) Number of hospital beds per 100,000 population

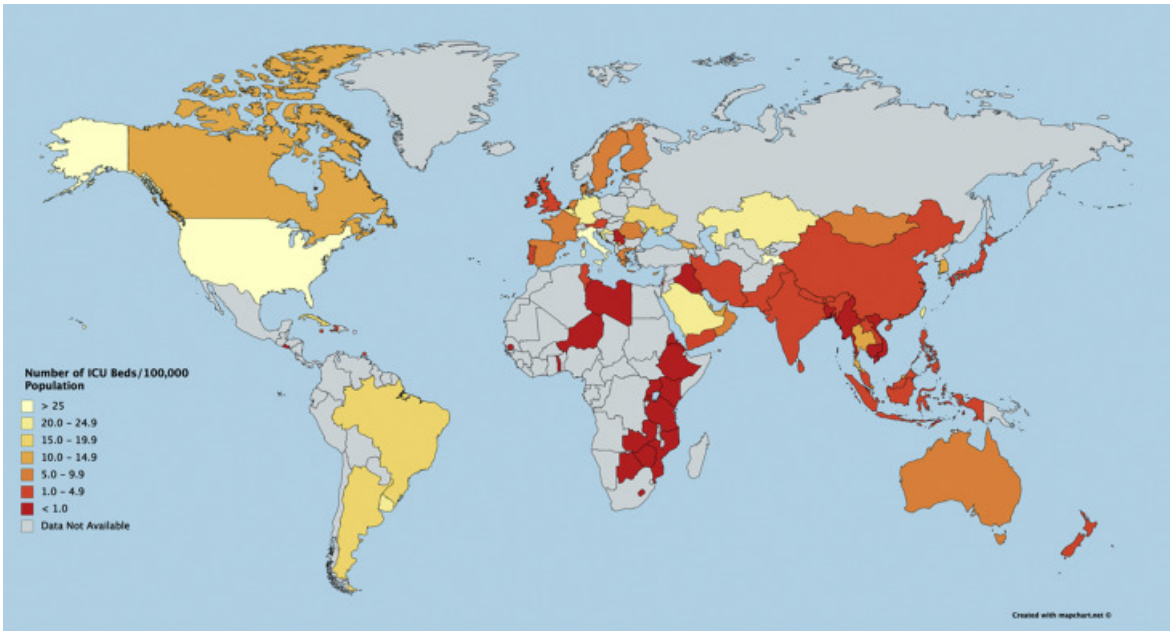


2) Number of acute care beds per 100,000 population



3) Number of ICU beds per 100,000 population

‘



Source of charts: Sen-Crowe B, et al. A Closer Look Into Global Hospital Beds Capacity and Resource Shortages During the COVID-19 Pandemic. J Surg Res. 2021;260:56-63. **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7685049/ (Reproduced following the copyright and license information published on Elsevier connect)

Appendix 2: Innovation development costs (ball park figures: US Marketplace, unknown for LMIC) and pricing considerations for rare diseases

- Rapid POC diagnostic development: 1.4 million USD
- Standard in vitro diagnostic development: 2.5 to 2.8 million USD
- App or Wearable technology development: 425,000 to 500,000 USD
- Electronic Healthcare Record: 150,000 USD
- Health Tracker: 200,000 USD
- Imaging agent: 100 to 150 million USD
- New software solution for imaging platform: 50,000 to 400,000 USD
- Orphan drug (chemical entity/new molecular entity type) 250 million USD (*see Berdud et al, Jayasundara et al refs below*). This changes as a function of whether:
    - the drug is a biologic (antibody, peptide) or an advance therapy medical product (gene therapy, bioengineering)
    - If the rare disease is oncology focused or not (rare oncological diseases have similar patient number requirements as frequent oncological, whereas on average for orphan drugs 2 to 5 fold lower requirement in patient number based on phase of development)

Ball Park figures excludes costs of:

- Multiple clinical trial requirements within and across geographies
- Level of uniqueness of solution (costs can significantly increase to address statistical relevance, long-term impact and evidence requirements if significantly different to existing standard-of-care)
- Post approval studies can cost approximately a further 6 million USD.

Berdud, M., Drummond, M.F., and Towse, A. (2018) Establishing a Reasonable Price for an Orphan Drug. OHE Research Paper**. Available from** https://www.ohe.org/publications/establishing-reasonable-price-orphan-drug#.

Jayasundara K, Hollis A, Krahn M, Mamdani M, Hoch JS, Grootendorst P. Estimating the clinical cost of drug development for orphan versus non-orphan drugs. Orphanet J Rare Dis. 2019 Jan 10;14(1):12. **Link:** https://pubmed.ncbi.nlm.nih.gov/30630499/

Dando, J., Lebmeier, M. A novel valuation model for medical intervention development based on progressive dynamic changes that integrates Health Technology Assessment outcomes with early-stage innovation and indication-specific clinical success rates. J Innov Entrep 9, 1 (2020). **Link:** https://innovation-entrepreneurship.springeropen.com/articles/10.1186/s13731-019-0111-1

Yates, N. and Hinkel, J. (2022), The economics of moonshots: Value in rare disease drug development. Clin Transl Sci, 15: 809-812. **Link:** https://ascpt.onlinelibrary.wiley.com/doi/10.1111/cts.13270

Villa F, Di Filippo A, Pierantozzi A, Genazzani A, Addis A, Trifirò G, Cangini A, Tafuri G, Settesoldi D and Trotta F (2022) Orphan Drug Prices and Epidemiology of Rare Diseases: A Cross-Sectional Study in Italy in the Years 2014–2019. Front. Med. 9:820757. **Link:** https://www.frontiersin.org/articles/10.3389/fmed.2022.820757/full

Pearson C, Schapiro L, Pearson SD. The next generation of rare disease drug policy: ensuring both innovation and affordability. J Comp Eff Res. 2022 Oct;11(14):999-1010. **Link:** https://pubmed.ncbi.nlm.nih.gov/35946484/

Appendix 3: Tips and suggestions for using clinicaltrials.gov

Some tips for searching 'clinicaltrials.gov'

Front page:

Status – select 'All studies'
Insert 'Pemphigus' in 'Condition or disease'

Result page:

Filtering the data: on the left-hand side in the 'List' tab is the option to apply 'Filters'.

Recruitment

- To know what is actually happening select 'not yet recruiting; Recruiting; enrolling by invitation; active – not recruiting'
- To know what happened before select 'completed'
- To know what happened before, but an anticipated negative result happened select 'terminated'

Study type

- Select 'All': this will provide data on therapies, diagnostics, registries, changes in protocols, biomarkers, digital health

Study results: 'All' or 'With results' are both good options

'All' every trial is presented

'With results' when clicking on the actual trial that is displayed after applying the filter, on the three tabs at the top is 'study results'. If you click on this it will take you to the raw data.

This is not the complete Clinical Study Report, but does provide key outcome measurements that have not been charted or plotted. Not all study results are published as articles (where this has happened there are links to the publications at the bottom of the page), so more insight can be obtained here.

When the 'Apply' button is clicked after filter selection, you will be presented with the list of trials:

Each trial can be individually clicked on and information on the study description, study design, interventions, number of patients, dates, sponsors, locations and outcome measures can be viewed.

The show/hide column on the top right, allows you to expand the number of fields you would like to view online.

The 'download' button takes you to a pop-up: In the number of studies you can select all the studies from your search, with further options of the downloaded file show 'all possible columns' or the fields you selected 'displayed'

In the file format: select 'tab-separated values': When downloaded, for most software types, this will display each of the fields in separate columns, allowing you to filter and arrange the data as you see fit.

Note: the downloaded file only contains the information you see on the list of trials: the detail and structure you see online, can only be seen online.

In the context of Basket trials: searching for more broad terms such as Dermatitis will give indications of trial Thinking outside the box, for the innovator, this means other indications can be searched in clinicaltrials.gov to assess if other innovations in clinical development (digital health, diagnostics, and potentially therapeutic) may be repositioned or after modifications edited for use in, enhancing care for Pemphigus.