Review

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Japanese intractable and rare dermatologic diseases: From the official skin-centered nanbyo core to an illustrative mechanism-based framework

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SUMMARY: Japan's designated intractable disease (nanbyo) framework combines a population threshold with unresolved pathogenesis or treatment, long-term care needs, objective diagnostic criteria, and severity-linked assistance with medical expenses. We conducted a targeted narrative review of official Japanese sources and biomedical literature through August 3, 2026. Evidence ranged from regulatory approvals and randomized trials to observational, case-report, and preclinical data, so therapeutic maturity was assessed separately from mechanistic plausibility. We distinguished the 12 official skin/connective-tissue entries from six purposively selected designated entries or disease groups with decisive cutaneous phenotypes or Japan-specific translational value. The resulting 18-entry framework is illustrative, not exhaustive. It highlights Japan-specific biology or evidence regarding xeroderma pigmentosum, acquired idiopathic generalized anhidrosis, DPP-4 inhibitor-related bullous pemphigoid, generalized pustular psoriasis, cold-medicine-related SJS/TEN, anti-MDA5 dermatomyositis, and Nakajo-Nishimura syndrome. Recently approved indications or uses include dupilumab for adult bullous pemphigoid, IL-36 receptor blockade, topical COL7A1 gene delivery, autologous gene-corrected epidermal sheets, MEK inhibition, IL-1 blockade, and topical mTOR inhibition; JAK-interferon strategies remain investigational. We contend that Japan's designation infrastructure could become an interoperable translational platform linking natural-history cohorts, endotype-defined enrollment, mechanism-aligned endpoints, and multinational adaptive trials.

Keywords: autoimmune blistering disease, epidermolysis bullosa, generalized pustular psoriasis, interferonopathy, precision medicine, orphan-disease policy

1. Introduction

Rare dermatologic disorders span immunology, genetics, oncology, toxicology, rheumatology, neurology, and metabolic medicine. This breadth is clinically consequential: the skin may be the dominant organ, an early diagnostic window, or only one organ affected by a lethal multisystem disease. Japan's designated intractable disease system provides an unusually coherent counterweight because it links disease definitions to public policy, longitudinal documentation, and organized research. As of April 2026, 348 diseases are designated under the national framework (*1,2*). The dermatologic value of this system is not limited to the 12 conditions displayed under the official skin and connective-tissue category (*3*); several other designated diseases have highly informative cutaneous phenotypes and are managed jointly by dermatologists and other specialists.

The present review addresses three gaps in the existing literature. First, it explains what is specifically Japanese about nanbyo dermatology and why direct comparison with prevalence-based rare-disease frameworks in the United States and European Union is informative but incomplete. Second, it distinguishes the 12 official skin-centered entries from six selectively expanded designated entries or disease groups in an illustrative mechanism-based framework rather than claiming that they represent an exhaustive spectrum. Third, it links molecular architecture to clinical intractability, biomarker selection, trial endpoints, and recent therapeutic translation. A targeted narrative search strategy and explicit selection criteria are provided to make the scope and evidentiary status transparent. The central question is not whether this framework

constitutes a complete disease catalogue, but whether an official core plus a deliberately illustrative mechanistic layer can more clearly connect policy, disease biology, and trial design.

2. Methods and search strategy

This targeted narrative review searched PubMed, Web of Science, J-STAGE, and Ichushi-Web from database inception through August 3, 2026. Representative queries combined ('nanbyo' OR 'designated intractable disease' OR 'rare dermatology') with the name of, gene for, biomarker of, or therapy for each candidate entry or disease group; syntax was adapted to each database. Official and regulatory sources were searched separately, including the Ministry of Health, Labour and Welfare, the Nanbyo Information Center, the Pharmaceuticals and Medical Devices Agency (PMDA), the Japan Registry of Clinical Trials (jRCT), UMIN-CTR, and ClinicalTrials.gov. English- and Japanese-language sources were included. The final literature search and regulatory-status verification were completed on August 3, 2026.

Acceptable evidence consisted of official diagnostic and policy documents, practice guidelines, randomized trials, prospective or retrospective observational studies, post-marketing surveillance, and selected case reports or preclinical studies when they provided unique mechanistic or emerging therapeutic information. Evidence was classified descriptively as regulatory/approved, randomized clinical, observational or post-marketing, case report/series, or preclinical/mechanistic. When sources conflicted, current regulatory documents and peer-reviewed primary reports were prioritized; registry records were used to ascertain trial status and obtain results not yet available in a full publication. Duplicate reports, non-designated conditions without a decisive cutaneous phenotype or Japan-specific translational rationale, and sources that did not provide material information on the mechanism, diagnosis, treatment, or trial design were excluded. Because this was a targeted narrative review, no quantitative synthesis, PRISMA flow count, or formal risk-of-bias grading was undertaken.

Three units of analysis were distinguished: an official designated entry (an administrative unit), a disease group (clinically or genetically related conditions), and a mechanistic phenotype (a prognostically or therapeutically relevant subset within an entry). The 12 official skin and connective-tissue entries were retained without discretionary selection. The six expanded entries were purposively selected from designated diseases with prominent skin manifestations to illustrate complementary mechanistic and translational models. The three criteria - (i) a decisive cutaneous phenotype, (ii) molecular, epidemiologic, clinical, regulatory, or policy relevance to Japan, and (iii) a mechanism-aligned therapy or trial model with broader translational value - were used to make the selection transparent rather than to generate an exhaustive or uniquely reproducible disease set. The candidate pool also included systemic sclerosis, systemic lupus erythematosus, and vasculitides; these were not selected because their inclusion would duplicate connective-tissue or vascular mechanisms already represented and because their selection would broaden the article beyond a tractable conceptual demonstration. Table 1 indicates the unit of analysis and rationale for each included expansion.

3. Scope and organizing principles

The official core used here contains 12 designated entries or disease groups: neurofibromatosis (NF), pemphigus, inherited epidermolysis bullosa (EB), generalized pustular psoriasis (GPP), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), xeroderma pigmentosum (XP), congenital ichthyosis, Hailey-Hailey disease (HHD), pemphigoid including epidermolysis bullosa acquisita (EBA), acquired idiopathic generalized anhidrosis (AIGA), and pseudoxanthoma elasticum (PXE) (*3*). These entries remain the anchor because their diagnostic criteria and severity classifications are explicitly tied to Japan's designated-disease infrastructure.

The illustrative expanded layer includes Behcet disease, the polymyositis/dermatomyositis (PM/DM) designated entry with a focused discussion of anti-MDA5 dermatomyositis, tuberous sclerosis complex (TSC), cryopyrin-associated periodic syndrome (CAPS), Nakajo-Nishimura syndrome/proteasome-associated autoinflammatory syndrome (NNS/PRAAS), and STING-associated vasculopathy with onset in infancy (SAVI). These are representative choices rather than a complete list of designated diseases with important skin manifestations. Each was purposively selected to illustrate a complementary mechanistic or translational model, as summarized in Table 1. SAVI is especially timely because it was placed on the Japanese designated nanbyo list as disease no. 345 as of April 2025 (*1*). The official 12-entry core and six illustrative expanded entries or disease groups are summarized in Table 2. In this review, PM/DM is treated as an official administrative entry, anti-MDA5 dermatomyositis is treated as a mechanistic phenotype within that entry, CAPS is treated as a disease group, and NNS/PRAAS is treated as a disease spectrum.

4. What is distinctive about the Japanese nanbyo model?

4.1. A clinical-welfare-research framework rather than a prevalence-only label

In the United States, the Orphan Drug Act generally defines a rare disease as one affecting fewer than 200,000 people (*4*). In the European Union, orphan

Table 1. Transparency matrix for the six purposively selected illustrative expanded entries or disease groups

Expanded entry/disease group	Decisive cutaneous phenotype	Japan-specific dimension	Mechanism-aligned therapy or trial model	Illustrative role in framework	Analysis unit
Behcet disease	Oral/genital ulcers, erythema nodosum-like lesions, pathergy	Japanese cohort and prespecified trial-subgroup evidence	Apremilast and anti-TNF strategies	Geographic, neutrophilic, and multisystem inflammatory model	Disease
PM/DM entry (anti-MDA5 DM focus)	Palmar papules, ulcers, livedoid change	Japanese/East Asian cohort and prognostic evidence	Early combination/rescue therapy; JAK approaches investigational	Skin-to-lung prognostic warning model	Official entry plus mechanistic phenotype
Tuberous sclerosis complex	Facial angiofibromas, shagreen patches, periungual fibromas	Japan-specific topical drug development and clinical evaluation	Direct mTORC1 inhibition	Topical pathway-directed therapy model	Disease
CAPS	Urticaria-like neutrophilic eruption	Japanese nationwide cohort and post-marketing evidence	IL-1 blockade	Inflammasome-to-IL-1 treatment and surveillance model	Disease group
NNS/PRAAS	Pernio-like/nodular lesions and lipomuscular atrophy	Japanese founder biology	JAK-interferon targeting remains investigational	Japan-specific founder interferonopathy model	Disease spectrum
SAVI	Acral vasculitis, ulceration, tissue loss	Japan-specific policy and designation context	JAK or IFNAR-directed strategies remain investigational	Newly designated interferon vasculopathy model	Disease

Abbreviations: CAPS, cryopyrin-associated periodic syndrome; DM, dermatomyositis; IFNAR, interferon-α/β receptor; IL-1, interleukin-1; JAK, Janus kinase; MDA5, melanoma differentiation-associated protein 5; mTORC1, mechanistic target of rapamycin complex 1; NNS, Nakajo-Nishimura syndrome; PM, polymyositis; PRAAS, proteasome-associated autoinflammatory syndrome; PSMB8, proteasome subunit β type 8; RELIEF, phase 3 apremilast trial in Behcet syndrome; RP-ILD, rapidly progressive interstitial lung disease; SAVI, STING-associated vasculopathy with onset in infancy; TNF, tumor necrosis factor.

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Table 2. Official 12-entry skin-centered core and six illustrative expanded designated entries or disease groups

Designated entry/ disease group	Scope	Disease-defining mechanism	Japan-specific dimension
Neurofibromatosis entry (NF1/NF2-related schwannomatosis)	Official skin-centered entry	NF1/NF2 tumor suppressor loss, RAS-MAPK or merlin pathway	Japanese clinical evidence: pediatric MEK-inhibitor study; NF2 retained at entry level
Pemphigus	Official skin-centered entry	Anti-Dsg IgG, desmosome disassembly, B/T-cell memory	Japanese prospective clinical evidence: rituximab and BTK-inhibitor studies
Inherited EB	Official skin-centered entry	Structural protein deficiency and chronic wound-fibrosis-cancer axis	Japan regulatory context: Vyjuvek approved following PMDA review
GPP	Official skin-centered entry	IL-36-neutrophil feed-forward inflammation	Japan-specific biology and clinical evidence: recurrent IL36RN variants and spesolimab experience
SJS	Official skin-centered entry	Drug/HLA-specific cytotoxic epithelial injury	Japan-specific pharmacogenetics: cold-medicine ocular phenotype and HLA-A*02:06
TEN	Official skin-centered entry	Extensive granulysin-mediated epidermal necrosis	Population-specific pharmacogenetic context
XP	Official skin-centered entry	Nucleotide excision repair failure and UV mutagenesis	Japan-specific biology and epidemiology: high incidence and XPA founder variant
Congenital ichthyosis	Official skin-centered entry	Lipid, cornification, or protease-regulatory defects	Global mechanism; Japan relevance is designation and genotype/endotype care
Hailey-Hailey disease	Official skin-centered entry	ATP2C1/SPCA1 calcium-manganese homeostasis failure	Global mechanism; no uniquely Japanese biology is claimed
Pemphigoid/EBA	Official skin-centered entry	BMZ autoantibodies, complement/type 2 inflammation, anchoring-fibril injury	Japan-specific prescribing and pharmacogenetic evidence: DPP-4 inhibitor-associated BP
AIGA	Official skin-centered entry	Putative immune- and stress-associated eccrine dysfunction	Japanese criteria, cohorts, and translational evidence
PXE	Official skin-centered entry	ABCC6-dependent ATP/pyrophosphate deficiency	Global systemic mechanism recognized through a skin-centered designated entry
Behcet disease	Illustrative expanded entry	HLA/ERAP1, neutrophils, Th1/Th17, endothelial injury	Japanese cohort and clinical-trial subgroup evidence
PM/DM entry (focus: anti-MDA5 DM)	Illustrative expanded entry	RNA-sensor autoimmunity, type I interferon, macrophage/endothelial injury	Japanese/East Asian cohort evidence for high-risk RP-ILD
Tuberous sclerosis complex	Illustrative expanded entry	TSC1/TSC2 loss and mTORC1 activation	Japan-specific drug development and regulatory context: topical sirolimus
CAPS	Illustrative expanded entry	NLRP3 inflammasome and IL-1β excess	Japanese nationwide cohort and post-marketing evidence

Abbreviations: ABCC6, ATP-binding cassette subfamily C member 6; AIGA, acquired idiopathic generalized anhidrosis; ATP, adenosine triphosphate; ATP2C1, ATPase secretory pathway Ca^{2+} transporting 1; BMZ, basement membrane zone; BP, bullous pemphigoid; BTK, Bruton's tyrosine kinase; CAPS, cryopyrin-associated periodic syndrome; DM, dermatomyositis; DPP-4, dipeptidyl peptidase-4; Dsg, desmoglein; EB, epidermolysis bullosa; EBA, epidermolysis bullosa acquisita; ERAP1, endoplasmic reticulum aminopeptidase 1; GPP, generalized pustular psoriasis; HLA, human leukocyte antigen; IgG, immunoglobulin G; IL, interleukin; IL36RN, interleukin 36 receptor antagonist; MDA5, melanoma differentiation-associated protein 5; MEK, mitogen-activated protein kinase kinase; mTORC1, mechanistic target of rapamycin complex 1; NF1, neurofibromatosis type 1; NF2, neurofibromatosis type 2; NLRP3, NLR family pyrin domain containing 3; NNS, Nakajo-Nishimura syndrome; PM, polymyositis; PMDA, Pharmaceuticals and Medical Devices Agency; PRAAS, proteasome-associated autoinflammatory syndrome; PSMB8, proteasome subunit β type 8; PXE, pseudoxanthoma elasticum; RAS-MAPK, rat sarcoma-mitogen-activated protein kinase; RNA, ribonucleic acid; RP-ILD, rapidly progressive interstitial lung disease; SAVI, STING-associated vasculopathy with onset in infancy; SJS, Stevens-Johnson syndrome; SPCA1, secretory pathway Ca^{2+}/Mn^{2+}-ATPase 1; STING1, stimulator of interferon response cGAMP interactor 1; TEN, toxic epidermal necrolysis; Th1/Th17, T helper 1/T helper 17; TSC1/TSC2, tuberous sclerosis complex 1/2; UV, ultraviolet; XP, xeroderma pigmentosum; XPA, xeroderma pigmentosum group A.

Table 2. Official 12-entry skin-centered core and six illustrative expanded designated entries or disease groups (continued)

Designated entry/ disease group	Scope	Disease-defining mechanism	Japan-specific dimension
NNS/PRAAS	Illustrative expanded entry	PSMB8 immunoproteasome failure, proteotoxic stress, type I interferon	Japan-specific founder biology
SAVI	Illustrative expanded entry	STING1 gain of function and type I interferon vasculopathy	Japan policy and designation context

Abbreviations: ABCC6, ATP-binding cassette subfamily C member 6; AIGA, acquired idiopathic generalized anhidrosis; ATP, adenosine triphosphate; ATP2C1, ATPase secretory pathway Ca^{2+} transporting 1; BMZ, basement membrane zone; BP, bullous pemphigoid; BTK, Bruton's tyrosine kinase; CAPS, cryopyrin-associated periodic syndrome; DM, dermatomyositis; DPP-4, dipeptidyl peptidase-4; Dsg, desmoglein; EB, epidermolysis bullosa; EBA, epidermolysis bullosa acquisita; ERAP1, endoplasmic reticulum aminopeptidase 1; GPP, generalized pustular psoriasis; HLA, human leukocyte antigen; IgG, immunoglobulin G; IL, interleukin; IL36RN, interleukin 36 receptor antagonist; MDA5, melanoma differentiation-associated protein 5; MEK, mitogen-activated protein kinase kinase; mTORC1, mechanistic target of rapamycin complex 1; NF1, neurofibromatosis type 1; NF2, neurofibromatosis type 2; NLRP3, NLR family pyrin domain containing 3; NNS, Nakajo-Nishimura syndrome; PM, polymyositis; PMDA, Pharmaceuticals and Medical Devices Agency; PRAAS, proteasome-associated autoinflammatory syndrome; PSMB8, proteasome subunit β type 8; PXE, pseudoxanthoma elasticum; RAS-MAPK, rat sarcoma-mitogen-activated protein kinase; RNA, ribonucleic acid; RP-ILD, rapidly progressive interstitial lung disease; SAVI, STING-associated vasculopathy with onset in infancy; SJS, Stevens-Johnson syndrome; SPCA1, secretory pathway Ca^{2+}/Mn^{2+}-ATPase 1; STING1, stimulator of interferon response cGAMP interactor 1; TEN, toxic epidermal necrolysis; Th1/Th17, T helper 1/T helper 17; TSC1/TSC2, tuberous sclerosis complex 1/2; UV, ultraviolet; XP, xeroderma pigmentosum; XPA, xeroderma pigmentosum group A.

designation usually requires a life-threatening or chronically debilitating condition affecting no more than 5 in 10,000 people, along with the absence of a satisfactory method or a demonstration of significant benefit (*5*). These definitions are primarily instruments for product development and regulatory incentives. Japan's designated intractable disease framework is not a prevalence-only taxonomy. Its formal conditions combine a patient population generally smaller than approximately 0.1% of the national population with an insufficiently elucidated pathogenesis, lack of an established treatment, a need for long-term care, and objective diagnostic criteria (*1,2,6*). Assistance with medical expenses is not automatic for every diagnosed patient: eligibility is linked to disease-specific severity criteria, with a mild-but-high-cost exception for patients whose repeated expenses exceed the prescribed threshold (*2*). Thus, nanbyo is both an epistemic category and a clinical-welfare-research framework.

This design has two potential benefits. First, the clinical survey form can be used to standardize core variables across institutions and enable disease-specific registries. Second, national policy research groups can iteratively revise diagnostic criteria, severity classifications, and care pathways. These are plausible institutional advantages; this review did not identify direct comparative evidence that designation itself improves trial efficiency or patient outcomes. However, the system also creates an administrative boundary problem because dermatologically important diseases may appear under rheumatologic, neurologic, pediatric, or autoinflammatory categories rather than under the skin category. The two-layer framework used here is an author-defined analytical solution that preserves the official core while recognizing cross-specialty skin biology. Drug-specific post-approval surveillance is implemented through separate PMDA and company pharmacovigilance systems and should not be treated as an automatic consequence of nanbyo designation. The principal structural differences between the Japanese, US, and EU frameworks are summarized in Table 3.

4.2. Japan-specific epidemiology, pharmacogenetics, and disease recognition

Specificity to Japan is assigned here only when supported by one of three dimensions: population biology, Japanese cohort or clinical evidence, or a Japan-specific regulatory and policy context. Japanese clinical guidelines report an XP incidence of approximately 1 in 22,000 (8), which is substantially higher than estimates in many Western populations, while a splice-site founder variant in xeroderma pigmentosum group A (XPA) accounts for a large proportion of Japanese mutant alleles and is carried heterozygously by nearly 1% of the population (7,8). AIGA has been characterized largely through Japanese case series and national research efforts, making Japan a central source of disease definitions and therapeutic experience (*9,10*). Japanese studies also identified a clinically less inflammatory form of dipeptidyl peptidase-4 inhibitor-associated BP and an association with *HLA-DQB1*03:01* (*11-13*). These observations are particularly relevant in an aging population with high exposure to antidiabetic therapy.

Additional examples extend across immunology and pharmacogenetics. Recurrent IL36RN variants helped establish GPP as a distinct autoinflammatory disease in Japanese cohorts (*14,15*). Cold-medicine-related SJS/TEN with severe ocular complications has been found to be associated with HLA, including *HLA-A*02:06*, in contrast to the classic carbamazepine-HLA-B*15:02 signal emphasized in parts of Southeast Asia (*16,17*).

Table 3. Comparison of the Japanese nanbyo framework with US and EU rare-disease/orphan frameworks

Domain	Japan	United States	European Union
Primary concept	Population threshold plus unresolved pathogenesis or treatment, long-term care, objective diagnosis, severity, and public support	Population threshold for a rare disease under the Orphan Drug Act	Prevalence plus seriousness and lack of satisfactory therapy/significant benefit for orphan designation
Current threshold/list	Disease-specific designation; patients generally < approximately 0.1% of the national population	< 200,000 affected persons in the United States	<= 5 per 10,000 in the European Union
Direct patient support	Severity-linked medical-expense subsidy, with a mild-but-high-cost exception	Not intrinsic to rare-disease definition	Not intrinsic to orphan designation
Standardized clinical data	Disease-specific diagnostic criteria, severity classifications, and clinical survey forms	Variable by disease/registry	Variable by disease/registry
Research structure	National policy research groups and disease-linked surveys	NIH/FDA programs and disease registries	European Reference Networks, EMA, and registries
Dermatology-specific limitation	Skin-relevant diseases are distributed across administrative categories	Rare disease and dermatology classifications remain separate	Orphan designation is product-specific, not a clinical disease taxonomy
Post-approval surveillance	Separate PMDA/company pharmacovigilance; not automatic under nanbyo designation	FDA/company pharmacovigilance; separate from rare-disease definition	EMA/company pharmacovigilance; separate from orphan designation

Abbreviations: EMA, European Medicines Agency; EU, European Union; FDA, Food and Drug Administration; NIH, National Institutes of Health; PMDA, Pharmaceuticals and Medical Devices Agency; US, United States.

Anti-MDA5 dermatomyositis is highly relevant in East Asian practice because rapidly progressive interstitial lung disease may overshadow prognosis despite limited muscle disease (*18-20*). NNS is a proteasome disorder initially identified in Japan that connects immunoproteasome failure to type I interferon biology (*21,22*). Together, these examples show that population genetics, prescribing patterns, environmental exposure, and national identification of cases can ascertain disease endotypes that are not fully captured by global averages.

5. Autoimmune blistering diseases

5.1. Pemphigus: Desmosomal autoimmunity, signaling, and immune memory

Mechanism. Pemphigus vulgaris and pemphigus foliaceus are defined by pathogenic IgG against desmoglein (Dsg) 3 and/or Dsg1, but acantholysis is not explained by steric interference alone. Antibody binding promotes the clustering and internalization of desmosomal cadherins, p38 MAPK activation, actin and keratin reorganization, and destabilization of desmosome turnover. The tissue distribution of Dsg1 and Dsg3 helps explain mucosal versus cutaneous phenotypes, whereas epitope spreading and non-Dsg antibodies may modify severity. Disease persistence reflects long-lived plasma cells, autoreactive memory B cells, and T-cell help; therefore, serum antibody decline and clinical remission do not always occur synchronously.

A Japan-specific dimension and treatment evidence. Japan has provided prospective therapeutic evidence rather than relying only on retrospective experience. A multicenter study of 20 Japanese patients substantiated the use of rituximab to treat refractory pemphigus and noted a clinically meaningful reduction in steroids (*23*). A Japanese phase 2 study of the selective Bruton's tyrosine kinase inhibitor tirabrutinib showed that direct suppression of B-cell receptor signaling can induce remission in a subset of refractory patients while reducing corticosteroid exposure (*24*). FcRn blockade remains mechanistically attractive because it accelerates IgG catabolism without eliminating B cells; however, results of clinical development have been heterogeneous, and future studies should integrate pathogenic IgG kinetics, Dsg-specific B-cell assays, and treatment-free remission rather than relying on serum titers alone. The major innovation is a shift from nonspecific immunosuppression to staged control of B-cell activation, plasma-cell output, and IgG persistence.

5.2. Pemphigoid and EBA: Endotype heterogeneity at the dermal-epidermal junction

Mechanism. Bullous pemphigoid (BP) is driven primarily by autoantibodies to BP180/collagen XVII and BP230, whereas EBA targets type VII collagen. Antibody binding activates complement, Fc receptors, eosinophils,

neutrophils, proteases, and type 2 cytokine circuits. The resulting disease is not immunologically uniform. Some patients have complement-rich inflammation and urticarial erythema, some have eosinophil- and IL-4/IL-13-dominant pruritus, and others have relatively non-inflammatory blistering. EBA can be further divided into inflammatory and mechanobullous phenotypes, with trauma, scarring, and milia reflecting the direct compromise of anchoring fibrils.

A Japan-specific dimension, current therapy, and evidence limitations. DPP-4 inhibitor-associated BP often exhibits less erythema, distinct BP180 epitope recognition, and enrichment of *HLA-DQB1*03:01* (*11-13*). National database and registry studies provide evidence of a real drug-associated risk, and especially in susceptible patients soon after exposure. This phenotype indicates the need for medication history, HLA-informed research, and epitope-level serology rather than treating all BP as identical. In LIBERTY-BP ADEPT, sustained remission at week 36 required complete remission with oral corticosteroids discontinued by week 16, no subsequent relapse, and no rescue therapy. The endpoint was achieved in an estimated 18.2% of dupilumab-treated participants and 4.0% of placebo-treated participants (risk difference: 14.2 percentage points; 95% CI: 1.97–27.74; $p = 0.025$) (*25,26*). Dupilumab was subsequently approved for adult BP in the United States in June 2025 and in Japan in March 2026 (*27,28*). At the review cutoff, final numerical results were available from trial registries and regulatory sources rather than a full peer-reviewed efficacy report. FcRn inhibitors, complement inhibitors, and anti-eosinophil strategies remain investigational. Future Japanese trials should pre-specify inflammatory, type 2, drug-associated, and fibrosing/mechanobullous endotypes because a single aggregate endpoint may obscure pathway-specific benefit.

6. DiscusGenetic fragility, cornification, and keratinocyte adhesionsion

6.1. Inherited EB: From supportive care to local gene correction

Mechanism. Inherited EB consists of genetically heterogeneous disorders in which skin cleavage results from defects in keratins, plectin, integrins, laminin-332, collagen XVII, or type VII collagen. Recessive dystrophic EB is the most instructive translational model. COL7A1 deficiency reduces type VII collagen and anchoring fibrils, causing lifelong wounds, inflammation, microbial dysbiosis, progressive fibrosis, mitten deformities, and aggressive cutaneous squamous cell carcinoma. The malignant niche is sustained not only by mutation accumulation but also by chronic tissue damage, TGF-β-driven fibrosis, and an altered extracellular matrix. Effective therapy must therefore address structural correction, wound ecology, fibrosis, pain, nutrition, and cancer surveillance in parallel.

Evidence from approved and investigational treatments. Topical beremagene geperpavec (B-VEC) delivers COL7A1 using a modified herpes simplex virus type 1 vector, and it achieved superior durable wound closure in a phase 3 intrapatient-controlled trial (*29*). Vyjuvek Gel was approved in Japan in July 2025 following PMDA review, giving Japan access to the first locally applied gene therapy for dystrophic EB (*30*). This is a conceptual milestone: treatment can restore a missing structural protein in selected wounds without systemic gene transfer. The limitation is equally important - untreated skin and extracutaneous tissues remain genetically defective, and repeated application is required. *Ex vivo* autologous gene-corrected epidermal sheets, including prademagene zamikeracel, provide a graft-based strategy for chronic RDEB wounds; the product was approved by the US FDA as ZEVASKYN on April 28, 2025 (*31,32*). Unlike repeated topical B-VEC, this autologous cell-sheet approach entails harvesting, *ex vivo* gene modification, and grafting, creating distinct considerations for durability, procedural burden, and treated surface area. Japanese programs involving mesenchymal stromal cells and other regenerative products further reflect the country's distinctive regulatory experience with regenerative medicine. The next generation should combine molecular correction with anti-fibrotic and cancer-prevention strategies and should use digital wound imaging, pain, function, and squamous-cell carcinoma incidence as long-term endpoints.

6.2. Congenital ichthyosis: Genotype-specific barrier failure and immune activation

Mechanism. Congenital ichthyoses arises from defects in epidermal lipid transport, lamellar-body secretion, transglutaminase activity, protease regulation, or keratin/cornified-envelope assembly. The resulting barrier defect increases transepidermal water loss, alters skin surface pH and microbiota, and releases alarmins that activate innate and adaptive inflammation. This explains why erythroderma and pruritus may persist even when scale is partly controlled. The mechanism varies by genotype: TGM1 deficiency disrupts cornified-envelope cross-linking; ABCA12 deficiency impairs lipid transport in harlequin ichthyosis; NIPAL4 and PNPLA1 variants alter lipid processing; and protease imbalance contributes to syndromic forms.

Current management, investigational therapy, and limitations. The 2025 updated international management guidelines emphasize structured neonatal care, temperature and fluid control, ophthalmologic management, infection prevention, keratolysis, and systemic retinoids while acknowledging emerging biologic and small-molecule therapy (*33,34*). Recent cohorts suggest that patients with strong type 2 or IL-

17/IL-23 inflammatory signatures may improve with targeted biologics, although responses are variable and off-label (*35*). Gene replacement, mRNA, enzyme replacement, and lipid-substitution approaches remain experimental. The critical advance is to stop treating congenital ichthyosis as one disease: genotype, inflammatory endotype, and age-specific risk should determine both therapy and trial design.

6.3. HHD: Calcium homeostasis, proteostasis, and environmental amplification

Mechanism. HHD is caused by heterozygous ATP2C1 variants that impair the Golgi secretory-pathway Ca^{2+}/Mn^{2+} ATPase SPCA1. Disturbed calcium and manganese homeostasis consists of desmosomal protein processing, keratinocyte differentiation, mitochondrial function, and oxidative-stress control, producing suprabasal acantholysis. The genetic defect is constitutive, but disease expression is highly environmental: heat, sweat, friction, ultraviolet exposure, infection, and obesity amplify local damage. This genotype-environment interaction explains recurrent flexural erosions and the frequent mismatch between mutation status and clinical severity.

Current management and evidence limitations. Management remains individualized and evidence is predominantly from small series. Antiseptic and anti-inflammatory therapy, topical calcineurin inhibitors, botulinum toxin, low-dose naltrexone, laser or surgical ablation, and systemic agents may be used depending on the trigger pattern and extent (*36*). A 2025 report on topical ruxolitinib added JAK inhibition to the investigational landscape (*37*), but it should not be interpreted as established therapy. Mechanistically informed trials could shed light on inflammatory lesions, measure calcium-dependent adhesion and stress signatures, and separate lesion clearance from relapse prevention.

7. Autoinflammatory and neutrophilic dermatoses

7.1. GPP: The IL-36-neutrophil feed-forward loop

Mechanism and Japan-specific biology. GPP is a systemic autoinflammatory disease and not simply severe plaque psoriasis with pustules. IL-36 cytokines released by keratinocytes activate IL-36 receptor signaling in epithelial and immune cells, inducing release of CXCL chemokines, neutrophil recruitment, and further protease-mediated activation of IL-36. Loss-of-function variants in IL36RN remove a critical brake in this loop; CARD14 and AP1S3 variants can converge on NF-kB and vesicular/autophagic pathways (*38*). Japanese studies identified recurrent IL36RN variants and helped establish the genetic distinction between GPP with and without plaque psoriasis (*14,15*). Infection, pregnancy, drug withdrawal, and systemic stress can then trigger explosive flareups within a genetically or immunologically primed background.

Randomized trial evidence and limitations. Spesolimab, an anti-IL-36 receptor monoclonal antibody, demonstrated rapid pustule clearance in the Effisayil 1 trial and established a direct path from mechanism to acute flareup control (*39*). Effisayil 2 subsequently showed that high-dose subcutaneous spesolimab delayed the first recurrent flareup over 48 weeks compared to a placebo (HR = 0.16, 95% CI 0.05–0.54) (*40*). Asian subgroup analyses and a 2026 Japanese expanded-access report substantiated its relevance and short-term safety in regional practice (*41,42*). Residual molecular inflammation after visible clearance suggests that clinical resolution does not necessarily equal pathway normalization. The remaining questions concern long-term durability, the optimal maintenance dose, cumulative safety, management in pregnancy or infection, and whether genotype or baseline IL-36 signatures predict response. Japan's long-standing recognition of GPP as a separate severe disease places it in a key position to lead longitudinal biomarker and maintenance-treatment studies.

7.2. CAPS: NLRP3 inflammasome disease and somatic mosaicism

Mechanism. CAPS consists of familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease. Gain-of-function NLRP3 variants promote inflammasome assembly, caspase-1 activation, and excessive IL-1β release. The skin phenotype - recurrent urticaria-like neutrophilic eruption - is a visible marker of systemic inflammation that may include fever, arthralgia, sensorineural hearing loss, meningitis, and amyloidosis. Low-level somatic mosaicism is clinically important because conventional sequencing may miss pathogenic variants, and particularly in apparently mutation-negative or late-onset patients.

Evidence from a Japan-specific cohort and approved treatment. A 2024 Japanese nationwide survey refined the national phenotype, genotype spectrum, and treatment experience (*43*). IL-1 blockade with canakinumab can rapidly suppress a rash and systemic inflammation, and 2026 Japanese post-marketing surveillance added real-world safety and effectiveness data (*44*). Persistent hearing or neurologic damage despite inflammatory control underscores the need for early diagnosis. Dermatologists can reduce the diagnostic delay by recognizing that an urticaria-like eruption without typical itching, combined with a fever or cold sensitivity, may represent an inflammasome disease rather than chronic urticaria.

7.3. NNS/PRAAS and SAVI: A disease first found in

Japan and an emerging interferonopathy

Mechanism and a Japan-specific founder biology. NNS is a Japanese form of proteasome-associated autoinflammatory syndrome typically caused by the founder variant PSMB8 p.Gly201Val. Immunoproteasome dysfunction impairs protein degradation, produces proteotoxic and endoplasmic-reticulum stress, and activates type I interferon and JAK-STAT programs. Patients develop pernio-like or nodular skin lesions, recurrent fever, lipomuscular atrophy, and joint contractures (*21,22*). Identification of the disease was pivotal because it linked a protein-quality-control defect to interferon-mediated inflammation. Conventional corticosteroids and immunosuppressants are often incomplete. A Japanese registry indicates that there was a single-arm, open-label study on baricitinib with a target enrollment of five; the registry indicates that the study was suspended/terminated after the study period ended, so it should not be described as actively recruiting (*45*).

Mechanism, Japan regulatory context, and investigational evidence. SAVI results from gain-of-function STING1/TMEM173 variants that constitutively activate TBK1-IRF3 and type I interferon signaling. Acral vasculitic lesions, ulceration, and tissue loss coexist with potentially fatal interstitial lung disease. Its addition to the Japanese designated disease list in 2025 is important because early recognition may prevent irreversible pulmonary damage (*1,46*). JAK inhibitors have resulted in partial responses in interferonopathies, but infection, cytopenia, and incomplete lung control remain concerns (*45,47*). Anifrolumab and hematopoietic stem-cell transplantation are emerging experimental strategies but are not standard care (*48*). NNS and SAVI illustrate a broader innovation: rare skin lesions can act as pathway reporters with which to direct interferon-targeted therapy before multisystem injury becomes evident.

8. Severe cutaneous adverse reactions: SJS and TEN

Mechanism. SJS and TEN are hyperacute immune-mediated diseases in which drug-specific cytotoxic T cells and natural killer cells cause widespread keratinocyte death. HLA-restricted antigen presentation, T-cell receptor specificity, granulysin, perforin/granzyme, Fas-Fas ligand, and inflammatory cytokines interact in a rapidly amplifying network. Granulysin is especially important because blister fluid concentrations correlate with widespread cytotoxic injury (*49*). Once epithelial detachment and mucosal destruction accelerate, treatment is constrained by irreversible damage, infection, fluid loss, and delayed drug withdrawal.

Japan-specific pharmacogenetics and treatment limitations. Japan offers a distinct perspective on prevention and phenotype. Cold-medicine-related SJS/TEN with severe ocular complications has been associated with *HLA-A*02:06* and other population-specific signals (*16*). This differs from the high-value *HLA-B*15:02* screening paradigm for carbamazepine in selected Asian populations, emphasizing that pharmacogenetic prevention is not wholly transferable between ethnic groups or drug classes (*17*). Acute management should integrate immediate culprit withdrawal, severity assessment, critical-care support, and early ophthalmologic intervention. Immunomodulatory evidence for cyclosporine, systemic corticosteroids, intravenous immunoglobulin, and TNF inhibition remains heterogeneous; therefore, future studies should stratify SJS and TEN by causative drug, treatment timing, HLA background, and epithelial injury biomarkers rather than pooling those diseases.

9. DNA repair failure and neurocutaneous tumor syndromes

9.1. XP: A Japan-enriched model of cumulative mutational injury

Mechanism and Japan-specific biology. XP is caused by defects in nucleotide excision repair or translesion synthesis. Failure to remove ultraviolet-induced cyclobutane pyrimidine dimers and 6-4 photoproducts produces extreme photosensitivity, early skin cancer, and, in selected complementation groups, progressive neurodegeneration. Japanese clinical guidelines estimate an incidence of approximately 1 in 22,000 (*8*), whereas the founder splice-site variant in XPA provides the principal population-genetic explanation for the high burden (*7*). This aspect makes XP one of the clearest examples of a genuinely Japan-specific rare dermatologic burden.

Current management and evidence limitations. The therapeutic logic differs from inflammatory disease. Rigorous ultraviolet avoidance, environmental measurement, vitamin D management, frequent skin and ophthalmologic surveillance, and early cancer treatment remain central (*8*). Once mutation burden accumulates, anti-inflammatory therapy cannot reverse it. Recent genotype-phenotype work has improved the understanding of XPA-associated neurodegeneration and it highlights the need for molecular diagnosis before neurologic decline (*50*). Future progress will require systemic approaches capable of protecting neural tissue, while dermatologic care should use digital lesion tracking and lifelong cancer prevention as formal outcomes.

9.2. NF and TSC: Pathway-directed neurocutaneous care

Mechanism, Japan-specific evidence, and treatment. NF1 is caused by loss of neurofibromin, a RAS GTPase-activating protein, leading to persistent RAS-MAPK signaling. Cafe-au-lait macules, axillary freckling, cutaneous neurofibromas, and plexiform neurofibromas provide a dermatologic entry point to a multisystem tumor-predisposition syndrome. MEK inhibition with

selumetinib shrank symptomatic inoperable plexiform neurofibromas; a Japanese pediatric phase 1 study established regional dosing and safety experience (*51*). More recent studies have extended MEK inhibition to cutaneous neurofibromas, using lesion count, volume, and patient-reported visibility or discomfort as endpoints (*52,53*). Because chronic therapy may be required, growth suppression must be balanced against cardiotoxicity, ocular toxicity, skin toxicity, and rebound after discontinuation.

Limitations in scope. The official Japanese NF entry also encompasses NF2-related schwannomatosis. Its predominant morbidity is neurologic and oncologic rather than cutaneous, although cutaneous schwannomas may contribute to recognition. Japan-specific skin-directed therapeutic evidence is substantially stronger for NF1, so the mechanistic and treatment discussion here is NF1-focused; NF2 is retained at the administrative-entry level rather than presented as equivalently covered.

Mechanism, Japan-specific development, and treatment. TSC, added here from outside the skin category, is caused by TSC1 or TSC2 loss and constitutive mTORC1 activation. Facial angiofibromas, shagreen patches, hypomelanotic macules, and periungual fibromas are often diagnostically decisive. Japan has been a leader in topical sirolimus gel, which directly targets mTORC1 in cutaneous lesions and reduces systemic exposure compared to oral therapy. A Japanese 2024 analysis further refined investigator-based scoring for facial angiofibromas (*54*). TSC shows how a visible lesion can serve as both a diagnostic biomarker and a pharmacodynamic readout for a systemic signaling disorder.

10. Sweat-gland dysfunction and ectopic mineralization

10.1. AIGA: A Japan-centered, putative immune- and stress-associated eccrine disorder

Mechanism and Japan-specific evidence. AIGA is characterized by widespread acquired anhidrosis or hypohidrosis without generalized autonomic failure or destructive sweat-gland disease. Many patients experience heat intolerance, cholinergic urticaria-like symptoms, or pain after exertion. Its pathogenesis remains incompletely defined. Proposed mechanisms include impaired acetylcholine signaling through the muscarinic M3 receptor, immune-mediated dysfunction in eccrine glands, reduced receptor expression, T-cell-predominant inflammation, and cellular stress. The clinical literature is disproportionately Japanese, and national criteria have helped distinguish AIGA from neuropathy, endocrinopathy, drug effects, and congenital hypohidrosis (*9*).

Current treatment and investigational biomarkers. Systemic corticosteroid pulse therapy can restore sweating in a subset of patients, and particularly when treatment is early, but relapse and nonresponse are common. A 2026 single-cell and molecular study identified cellular-stress and unfolded-protein-response signatures in affected eccrine units and linked those changes to treatment response (*10*). This finding broadens the disease model beyond simple receptor loss and creates testable biomarkers. Future trials should combine quantitative thermoregulatory sweat testing, regional sweat maps, symptom burden, heat-safety outcomes, and tissue endotypes.

10.2. PXE: The hepatic ATP-pyrophosphate-skin axis

Mechanism. PXE is caused predominantly by biallelic ABCC6 variants. Although the characteristic yellow papules and fragmented calcified elastic fibers are cutaneous, the primary metabolic defect is systemic: hepatic ABCC6-dependent ATP release is reduced, lowering circulating inorganic pyrophosphate, an endogenous inhibitor of mineralization. Progressive calcification affects the skin, Bruch membrane in the retina, and vasculature. This skin-liver-eye-vessel axis explains why dermatologic diagnosis must trigger ophthalmologic and cardiovascular surveillance.

Investigational treatment and evidence limitations. Therapeutic development now targets mineralization rather than skin appearance alone. Etidronate, oral pyrophosphate, magnesium or phosphate-modulating approaches, lansoprazole, and ENPP1-Fc replacement strategies are being clinically investigated (*55-59*). A 2025 preclinical study of liver-directed ABCC6 base editing indicates the possibility of correcting the systemic source defect (*60*). None of these approaches yet constitutes a universal disease-modifying standard. Trials require slow-progression endpoints, quantitative vascular and retinal imaging, and long follow-up, which makes international harmonization particularly important.

11. Systemic designated entries with decisive cutaneous phenotypes

11.1. Behcet disease: Neutrophilic inflammation at a geographic and genetic interface

Mechanism and Japan-specific cohort evidence. Behcet disease is included in the illustrative expanded framework because recurrent oral aphthae, genital ulceration, erythema nodosum-like lesions, acneiform eruptions, and pathergy are central to its recognition. HLA-B*51, ERAP1, innate immune activation, neutrophil hyperreactivity, Th1/Th17 polarization, endothelial injury, and microbiome triggers contribute to pathogenesis. The disease is prevalent along the historical Silk Road, and Japanese cohorts have been essential to phenotype and treatment studies. The key clinical issue is organ stratification: mucocutaneous disease can be disabling, but ocular, neurologic, vascular, or gastrointestinal disease determines irreversible

morbidity.

Current and investigational treatments. Apremilast reduced the oral ulcer burden in the international RELIEF trial, and a prespecified Japanese subgroup analysis of 39 patients confirmed regional efficacy and safety (*61,62*). Anti-TNF therapy remains crucial for severe ocular, vascular, neurologic, or intestinal involvement, while treatments involving the IL-1, IL-17, IL-6, and JAK pathways are under investigation. Cutaneous endpoints should not be isolated from organ activity because the same patient may transition between mucocutaneous and organ-threatening phases.

11.2. Anti-MDA5 dermatomyositis within the PM/DM entry: Skin findings as an early warning for lethal lung disease

Scope, mechanism, and biomarkers. The official PM/DM designated entry is broader than the anti-MDA5 subset. This review focuses on anti-MDA5-positive dermatomyositis because cutaneous signs may precede or outweigh muscle disease and because rapidly progressive interstitial lung disease is particularly important in Japanese and East Asian practice. MDA5 is a cytosolic RNA sensor; autoimmunity is associated with a type I interferon-rich state, macrophage activation, endothelial injury, and severe lung inflammation. Painful palmar papules, ulceration, livedoid changes, alopecia, and oral lesions should raise suspicion. Ferritin, anti-MDA5 titer, KL-6, oxygenation, and radiologic progression can help identify patients at risk of rapidly progressive interstitial lung disease.

Japan-specific cohort evidence, current practice, and limitations. Japanese and East Asian cohorts report a particularly high burden of rapidly progressive lung disease. A 2026 Japanese multicenter study identified anti-MDA5-positive interstitial lung disease without prominent skin or muscle manifestations as a high-risk and potentially overlooked subgroup (*18*). This observation intensifies, rather than weakens, the dermatologic message: characteristic ulcers, palmar papules, or livedoid lesions can be an early warning, but their absence does not rule the disease out. Early combined glucocorticoid, calcineurin inhibitor, and cyclophosphamide therapy has been used in high-risk Japanese patients, while rituximab, plasma exchange, JAK inhibition, and other rescue strategies are substantiated by evolving but nonuniform evidence (*19,20*). The innovation for dermatology is prognostic: when present, specific skin lesions are visible indicators of systemic endothelial and interferon injury that should prompt urgent pulmonary evaluation.

12. Therapeutic translation and trial architecture in Japan

The most persuasive recent programs have a corresponding mechanism and endpoint: B-VEC restores type VII collagen and is evaluated based on wound closure (*29,30*); spesolimab blocks IL-36 receptor signaling and is evaluated based on pustule or flareup control (*39-42*); selumetinib suppresses RAS-MAPK signaling and is evaluated based on tumor volume (*51-53*); canakinumab blocks IL-1β and is evaluated based on inflammatory control (*43,44*); and topical sirolimus inhibits mTORC1 and is evaluated based on facial angiofibroma severity (*54*). Table 4 maps biomarkers, outcomes, and evidence maturity, and Table 5 summarizes recent Japan-relevant therapeutic evidence and jurisdiction-specific status.

Japan's regulatory and research environment consists of distinct but potentially linkable streams: nanbyo diagnostic criteria and clinical survey forms, specialist registries, PMDA review and pharmacovigilance, jRCT and UMIN trial records, and post-marketing surveillance by companies. Post-approval surveillance is not automatically initiated as a result of nanbyo designation. The approval of Vyjuvek Gel in July 2025 and the inclusion of SAVI in the designated list illustrate how regulatory and policy timelines can respond to molecular medicine (*1,30*). Administrative data, specialist registries, genetic laboratories, pathology repositories, and patient-reported outcomes are not always transferable. Rather than describing an existing national standard, we therefore propose a rare dermatologic condition model that maps genotype, autoantibody, endotype, lesion imaging, treatment exposure, and longitudinal function across institutions.

Ultra-small populations also require different statistical logic. Conventional parallel-group trials may be infeasible for NNS, SAVI, AIGA, or EBA. We propose Bayesian borrowing, adaptive randomization, within-patient controls, N-of-1 series, external natural-history controls, and platform protocols to increase information yield, provided that baseline progression and measurement error are well characterized. Japan should combine domestic depth with international scale: national cohorts can define precise phenotypes, while multinational networks provide sufficient sample size for confirmatory inference.

13. Cross-cutting mechanisms and conceptual innovation

Seven partially overlapping mechanistic architectures explain most of the intractability across this illustrative framework. First, constitutive structural or barrier failure produces repeated injury in EB, congenital ichthyosis, and HHD. Second, self-sustaining adaptive autoimmunity produces pathogenic antibody persistence in pemphigus, BP, and EBA. Third, innate immune and neutrophilic feed-forward loops drive GPP, CAPS, and much of Behcet disease. Fourth, cytotoxic or interferon-mediated vascular-epithelial injury creates rapid irreversibility in

Table 4. Mechanism-aligned biomarkers, endpoints, and evidence maturity across the illustrative framework

Entry/disease group	Biomarkers or confirmatory tests	Mechanism-aligned outcomes	Evidence maturity/status
Pemphigus	Anti-Dsg1/3 ELISA, DIF, pathogenic IgG and B-cell assays	PDAI remission, steroid-free remission, pathogenic IgG kinetics	DIF and anti-Dsg ELISA established; pathogenic B-cell assays exploratory
BP	BP180/BP230 serology, DIF, eosinophils, complement, epitope profile	Blister control, pruritus, steroid exposure, sustained remission	DIF/serology established; epitope and type 2 endotyping exploratory
EBA	COL7 serology, DIF/salt-split mapping, scarring phenotype	Blister control, wound healing, scarring, pain and function	Diagnostic mapping established; outcome evidence mainly observational
Inherited EB	Genotype, IF mapping, type VII collagen, digital wound imaging	Durable wound closure, pain/function, cSCC incidence	Genotype/IF mapping established; wound endpoints validated in randomized trials
GPP	IL36RN/CARD14/AP1S3, CRP, IL-36 signature	Pustule clearance, flare duration, flare-free survival	Genetic testing selected; IL-36 signatures exploratory; flare endpoints randomized
SJS/TEN	Drug causality, HLA, granulysin and epithelial-injury markers	Mortality, re-epithelialization, ocular and mucosal sequelae	Clinical causality and mortality endpoints established; biomarkers context-specific
XP	NER genotype/complementation, UV damage, tumor surveillance	New cancers, neurologic progression, adherence to photoprotection	Molecular diagnosis established; long-term outcomes observational
NF1	NF1 genotype, volumetric imaging, RAS-MAPK pathway markers	Plexiform/cutaneous neurofibroma volume, pain, visibility, function	Genotype and volumetric imaging established; cutaneous endpoints emerging
NF2-related schwannomatosis	NF2 testing, MRI tumor burden, audiology	Tumor control, hearing preservation, neurologic function	Genetic testing, MRI, and audiology established
TSC	TSC1/TSC2 genotype, lesion scoring, mTORC1 pathway markers	Facial angiofibroma severity, lesion burden, patient-reported visibility	Genotype and lesion scoring established; topical pathway endpoint randomized
AIGA	Thermoregulatory sweat test, sweat map, eccrine M3 and stress signatures	Recovered sweat area, heat tolerance, symptom burden, relapse	Sweat testing established; tissue stress signatures exploratory
PXE	ABCC6 genotype, plasma pyrophosphate, retinal/vascular imaging	Mineralization progression, visual and vascular events	Genotype/imaging established; pyrophosphate is a research biomarker
CAPS	NLRP3 variant/mosaicism, CRP/SAA, IL-1 activity	Complete inflammatory response, hearing/neurologic preservation	Genotype/CRP/SAA established; mosaicism testing specialized
NNS/PRAAS	PSMB8 genotype, interferon score, inflammatory and functional measures	Skin healing, steroid reduction, fever control, physical function	Genotype established; interferon score and functional endpoints exploratory
SAVI	STING1 genotype, interferon score, HRCT and pulmonary function	Skin healing, ILD stabilization, oxygen requirement, survival	Genotype established; interferon score and lung endpoints early/observational

Abbreviations: ABCC6, ATP-binding cassette subfamily C member 6; AIGA, acquired idiopathic generalized anhidrosis; AP1S3, adaptor related protein complex 1 subunit sigma 3; BP, bullous pemphigoid; BP180, bullous pemphigoid antigen 180; BP230, bullous pemphigoid antigen 230; CAPS, cryopyrin-associated periodic syndrome; CARD14, caspase recruitment domain family member 14; COL7, type VII collagen; CRP, C-reactive protein; cSCC, cutaneous squamous cell carcinoma; DIF, direct immunofluorescence; DM, dermatomyositis; Dsg, desmoglein; EB, epidermolysis bullosa; EBA, epidermolysis bullosa acquisita; ELISA, enzyme-linked immunosorbent assay; GPP, generalized pustular psoriasis; HLA, human leukocyte antigen; HRCT, high-resolution computed tomography; IF, immunofluorescence; IgG, immunoglobulin G; IL, interleukin; ILD, interstitial lung disease; IL36RN, interleukin 36 receptor antagonist; KL-6, Krebs von den Lungen-6; M3, muscarinic acetylcholine receptor M3; MDA5, melanoma differentiation-associated protein 5; MRI, magnetic resonance imaging; mTORC1, mechanistic target of rapamycin complex 1; NER, nucleotide excision repair; NF1, neurofibromatosis type 1; NF2, neurofibromatosis type 2; NLRP3, NLR family pyrin domain containing 3; NNS, Nakajo-Nishimura syndrome; PDAI, Pemphigus Disease Area Index; PRAAS, proteasome-associated autoinflammatory syndrome; PSMB8, proteasome subunit β type 8; PXE, pseudoxanthoma elasticum; RAS-MAPK, rat sarcoma-mitogen-activated protein kinase; RP-ILD, rapidly progressive interstitial lung disease; SAA, serum amyloid A; SAVI, STING-associated vasculopathy with onset in infancy; SJS, Stevens-Johnson syndrome; STING1, stimulator of interferon response cGAMP interactor 1; TEN, toxic epidermal necrolysis; TSC, tuberous sclerosis complex; TSC1/TSC2, tuberous sclerosis complex 1/2; UV, ultraviolet; XP, xeroderma pigmentosum.

Table 4. Mechanism-aligned biomarkers, endpoints, and evidence maturity across the illustrative framework (continued)

Entry/disease group	Biomarkers or confirmatory tests	Mechanism-aligned outcomes	Evidence maturity/status
Behcet disease	Organ-specific activity, CRP, ulcer counts and pain	Oral/genital ulcer control plus ocular, vascular, neurologic and intestinal outcomes	Clinical organ outcomes established; biomarkers nonspecific
Anti-MDA5 DM	Anti-MDA5 titer, ferritin, KL-6, oxygenation, HRCT	RP-ILD survival, oxygen-free survival, lung stabilization, ulcer control	Autoantibody/HRCT established; prognostic thresholds cohort-based

Abbreviations: ABCC6, ATP-binding cassette subfamily C member 6; AIGA, acquired idiopathic generalized anhidrosis; AP1S3, adaptor related protein complex 1 subunit sigma 3; BP, bullous pemphigoid; BP180, bullous pemphigoid antigen 180; BP230, bullous pemphigoid antigen 230; CAPS, cryopyrin-associated periodic syndrome; CARD14, caspase recruitment domain family member 14; COL7, type VII collagen; CRP, C-reactive protein; cSCC, cutaneous squamous cell carcinoma; DIF, direct immunofluorescence; DM, dermatomyositis; Dsg, desmoglein; EB, epidermolysis bullosa; EBA, epidermolysis bullosa acquisita; ELISA, enzyme-linked immunosorbent assay; GPP, generalized pustular psoriasis; HLA, human leukocyte antigen; HRCT, high-resolution computed tomography; IF, immunofluorescence; IgG, immunoglobulin G; IL, interleukin; ILD, interstitial lung disease; IL36RN, interleukin 36 receptor antagonist; KL-6, Krebs von den Lungen-6; M3, muscarinic acetylcholine receptor M3; MDA5, melanoma differentiation-associated protein 5; MRI, magnetic resonance imaging; mTORC1, mechanistic target of rapamycin complex 1; NER, nucleotide excision repair; NF1, neurofibromatosis type 1; NF2, neurofibromatosis type 2; NLRP3, NLR family pyrin domain containing 3; NNS, Nakajo-Nishimura syndrome; PDAI, Pemphigus Disease Area Index; PRAAS, proteasome-associated autoinflammatory syndrome; PSMB8, proteasome subunit β type 8; PXE, pseudoxanthoma elasticum; RAS-MAPK, rat sarcoma-mitogen-activated protein kinase; RP-ILD, rapidly progressive interstitial lung disease; SAA, serum amyloid A; SAVI, STING-associated vasculopathy with onset in infancy; SJS, Stevens-Johnson syndrome; STING1, stimulator of interferon response cGAMP interactor 1; TEN, toxic epidermal necrolysis; TSC, tuberous sclerosis complex; TSC1/TSC2, tuberous sclerosis complex 1/2; UV, ultraviolet; XP, xeroderma pigmentosum.

SJS/TEN, anti-MDA5 dermatomyositis, NNS/PRAAS, and SAVI. Fifth, cumulative or systemic biochemical injury drives XP and PXE. Sixth, tumor-suppressor loss produces pathway-dependent proliferation in NF and TSC. Seventh, organ-specific functional dysregulation and cellular stress provide a working model for AIGA, while acknowledging that its pathogenesis has yet to be completely elucidated.

This classification is clinically useful because it identifies the level of correction a treatment can plausibly achieve. Structural replacement is required for missing proteins such as COL7A1; immune or signaling blockade may control active disease without eliminating immune memory or future triggers; and preventive measures can limit new injury without reversing accumulated mutation or mineralization. Explicitly labeling an intervention as structural, immunologic, signaling, preventive, or symptomatic reduces therapeutic overstatement.

The proposed contribution of a Japanese rare dermatologic condition framework is therefore a linkage model rather than a longer disease list or a claim that designation already improves outcomes. The official 12-entry core can provide policy-defined cohorts, while population-specific biology, Japanese clinical evidence, and mechanism-aligned trials can be linked across administrative boundaries. The six-entry layer is illustrative and neither complete nor unique.

14. Unmet needs and research priorities

The first priority is natural history. AIGA, HHD, NNS, SAVI, EBA, and PXE lack trial-ready progression models. Prospective cohorts should define untreated variability, clinically meaningful change, and irreversible milestones. The second priority is biomarker validation. Candidate markers - Dsg-specific B cells, BP180 epitope profiles, IL-36 signatures, interferon scores, sweat-gland stress states, pyrophosphate levels, and digital wound features - must demonstrate analytical validity and treatment responsiveness before they are used as enrichment or surrogate endpoints.

The third priority is equity and implementation. Genomic testing, advanced biologics, gene therapy, and repeated specialist follow-up may be concentrated at tertiary centers. National designation reduces the financial burden but does not automatically improve geographic access, the transition from pediatric to adult care, or the practical workload of wound care and photoprotection. Patient-reported function, caregiver time, heat safety, vision, pain, itching, stigma, and working should be treated as core outcomes rather than optional supplements.

The fourth priority is durability and late effects. Gene therapy, chronic MEK inhibition, long-term cytokine blockade, and JAK inhibition require surveillance for malignancy, infection, organ toxicity, reproductive effects, and rebound. We recommend prospectively linking the clinical survey infrastructure to treatment exposure and molecular data to support post-marketing science. International data standards are also essential because rare disease populations are not amenable to incompatible definitions, image formats, or outcome measures across countries. These are author-proposed priorities rather than established national standards and are summarized in Table 6.

15. Limitations

Several limitations should temper this work's interpretation. This is a targeted narrative review rather

Table 5. Selected therapeutic advances in Japan: Evidence level and jurisdiction-specific regulatory status

Entry / intervention	Mechanistic target	Evidence level	Status in Japan	Status in US/EU	Status verified as of
Pemphigus / rituximab	CD20-positive B-cell depletion	Prospective Japanese single-arm study plus randomized international evidence	Intravenous rituximab approved for refractory pemphigus vulgaris and foliaceus	US/EU: intravenous rituximab approved for moderate-to-severe pemphigus vulgaris	August 3, 2026
Pemphigus / tirabrutinib	BTK/B-cell receptor signaling	Japanese phase 2 single-arm study	Not approved for pemphigus; investigational oral therapy	US/EU: no pemphigus indication	August 3, 2026
Bullous pemphigoid / dupilumab	IL-4/IL-13 type 2 inflammation	Randomized phase 2/3 registry and regulatory results; final peer-reviewed efficacy report not identified at the cutoff	Subcutaneous dupilumab approved for adult moderate-to-severe BP in March 2026	US: subcutaneous dupilumab approved for adult BP on June 18, 2025; EU: BP is not an approved indication	August 3, 2026
Dystrophic EB / beremagene geperpavec (B-VEC)	Topical COL7A1 gene delivery	Phase 3 randomized intrapatient evidence	Topical gel approved for DEB in July 2025 following PMDA review	US/EU: topical gene therapy approved for DEB wounds	August 3, 2026
Recessive dystrophic EB / prademagene zamikeracel	Autologous gene-corrected epidermal sheets	Phase 3 randomized intrapatient evidence	Not approved	US: approved as ZEVASKYN on April 28, 2025; EU: no marketing authorization identified	August 3, 2026
GPP / spesolimab	IL-36 receptor blockade	Randomized flare-treatment and flare-prevention trials	Intravenous 450-mg formulation approved for treatment of GPP flares; no Japanese subcutaneous flare-prevention indication identified	US/EU: intravenous flare treatment and subcutaneous flare prevention approved; eligible ages and formulations differ	August 3, 2026
NF1 / selumetinib	MEK inhibition	Prospective phase 1/2 and nonrandomized clinical evidence	Oral capsules approved for patients aged 3 years or older with symptomatic, inoperable plexiform neurofibromas	US/EU: oral selumetinib approved for symptomatic, inoperable plexiform neurofibromas in NF1; age/formulation ranges differ	August 3, 2026
TSC / topical sirolimus gel	mTORC1 inhibition	Randomized Japanese trials and observational evidence	Topical sirolimus gel approved for TSC-associated skin lesions	US/EU: no approved topical sirolimus gel for TSC skin lesions identified	August 3, 2026
CAPS / canakinumab	IL-1β neutralization	Clinical-trial, nationwide, and post-marketing evidence	Subcutaneous canakinumab approved for CAPS	US/EU: subcutaneous canakinumab approved for CAPS	August 3, 2026

Abbreviations: BP, bullous pemphigoid; B-VEC, beremagene geperpavec; BTK, Bruton's tyrosine kinase; CAPS, cryopyrin-associated periodic syndrome; CD20, cluster of differentiation 20; COL7A1, collagen type VII alpha 1 chain; DEB, dystrophic epidermolysis bullosa; DM, dermatomyositis; EB, epidermolysis bullosa; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; EU, European Union; GPP, generalized pustular psoriasis; IFNAR, interferon-α/β receptor; IL, interleukin; JAK, Janus kinase; jRCT, Japan Registry of Clinical Trials; MDA5, melanoma differentiation-associated protein 5; MEK, mitogen-activated protein kinase kinase; mTORC1, mechanistic target of rapamycin complex 1; NF1, neurofibromatosis type 1; NNS, Nakajo-Nishimura syndrome; PDE4, phosphodiesterase 4; PMDA, Pharmaceuticals and Medical Devices Agency; PPi, inorganic pyrophosphate; PRAAS, proteasome-associated autoinflammatory syndrome; PXE, pseudoxanthoma elasticum; SAVI, STING-associated vasculopathy with onset in infancy; STAT, signal transducer and activator of transcription; TSC, tuberous sclerosis complex; US, United States.

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Table 5. Selected therapeutic advances in Japan: Evidence level and jurisdiction-specific regulatory status (continued)

Entry / intervention	Mechanistic target	Evidence level	Status in Japan	Status in US/EU	Status verified as of
Behcet disease / apremilast	PDE4-mediated cytokine modulation	Randomized phase 3 evidence and prespecified Japanese subgroup	Oral apremilast approved for Behcet-related oral ulcers inadequately responding to topical therapy	US/EU: oral apremilast approved for adult Behcet-related oral ulcers	August 3, 2026
NNS/PRAAS / baricitinib-JAK inhibition	Type I interferon-JAK-STAT signaling	Small single-arm open-label study	No approved NNS/PRAAS indication; the Japanese jRCT study was suspended/terminated	US/EU: no NNS/PRAAS indication	August 3, 2026
SAVI / JAK- or IFNAR-directed strategies	Type I interferon signaling	Case-series and early clinical evidence	No approved SAVI indication for JAK- or IFNAR-directed therapy	US/EU: no approved SAVI indication	August 3, 2026
PXE / PPi-ENPP1 and mineralization strategies	Restoration of anti-mineralization activity	Randomized/early-phase and preclinical evidence	No approved disease-modifying PPi/ENPP1 therapy	US/EU: no approved disease-modifying PPi/ENPP1 therapy	August 3, 2026
Anti-MDA5 DM / combined and rescue therapy	Interferon, B-cell, T-cell, and macrophage pathways	Observational and case-series evidence	No pathway-specific approved regimen; combination/rescue strategies remain off-label	US/EU: no pathway-specific app roved regimen	August 3, 2026

Abbreviations: BP, bullous pemphigoid; B-VEC, beremagene geperpavec; BTK, Bruton's tyrosine kinase; CAPS, cryopyrin-associated periodic syndrome; CD20, cluster of differentiation 20; COL7A1, collagen type VII alpha 1 chain; DEB, dystrophic epidermolysis bullosa; DM, dermatomyositis; EB, epidermolysis bullosa; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; EU, European Union; GPP, generalized pustular psoriasis; IFNAR, interferon-α/β receptor; IL, interleukin; JAK, Janus kinase; jRCT, Japan Registry of Clinical Trials; MDA5, melanoma differentiation-associated protein 5; MEK, mitogen-activated protein kinase kinase; mTORC1, mechanistic target of rapamycin complex 1; NF1, neurofibromatosis type 1; NNS, Nakajo-Nishimura syndrome; PDE4, phosphodiesterase 4; PMDA, Pharmaceuticals and Medical Devices Agency; PPi, inorganic pyrophosphate; PRAAS, proteasome-associated autoinflammatory syndrome; PXE, pseudoxanthoma elasticum; SAVI, STING-associated vasculopathy with onset in infancy; STAT, signal transducer and activator of transcription; TSC, tuberous sclerosis complex; US, United States.

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Table 6. Priority research agenda, as proposed by the author, for rare Japanese dermatological conditions

Priority	Rationale	Near-term action recommended by the author	High-yield examples
Interoperable natural history	Administrative and specialist data are fragmented	Common data model linking survey forms, genotype, imaging, treatment, and PROs	AIGA, HHD, EBA, PXE, NNS, SAVI
Endotype-defined trials	Rare cohorts cannot absorb biological heterogeneity	Pre-specified antibody, cytokine, interferon, and drug-associated strata	BP, pemphigus, GPP, anti-MDA5 DM
Mechanism-aligned endpoints	Generic skin scores may miss target engagement	Wound closure, flare abortion, tumor volume, sweat recovery, ILD stabilization	EB, GPP, NF1, AIGA, SAVI
Durability and late effects	Advanced therapies may require lifelong exposure or surveillance	Linked post-marketing cohorts and treatment registries	Gene therapy, MEK/mTOR/JAK/IL-1 therapies
Patient-centered implementation	Financial designation does not eliminate access burden	Caregiver time, heat safety, pain, vision, work, transition, regional access	All diseases
International adaptive platforms	Domestic ultra-rare cohorts remain underpowered	Bayesian, platform, within-patient, and external-control designs	NNS, SAVI, EBA, AIGA, CAPS

Abbreviations: AIGA, acquired idiopathic generalized anhidrosis; BP, bullous pemphigoid; CAPS, cryopyrin-associated periodic syndrome; DM, dermatomyositis; EB, epidermolysis bullosa; EBA, epidermolysis bullosa acquisita; GPP, generalized pustular psoriasis; HHD, Hailey-Hailey disease; IL, interleukin; ILD, interstitial lung disease; JAK, Janus kinase; MDA5, melanoma differentiation-associated protein 5; MEK, mitogen-activated protein kinase kinase; mTOR, mechanistic target of rapamycin; NF1, neurofibromatosis type 1; NNS, Nakajo-Nishimura syndrome; PROs, patient-reported outcomes; PXE, pseudoxanthoma elasticum; SAVI, STING-associated vasculopathy with onset in infancy.

than a systematic review; evidence was not quantitatively synthesized or formally risk-of-bias graded. Searches were limited to English and Japanese and to selected biomedical databases, creating language and database-coverage bias. The evidence base spans regulatory documents, randomized trials, observational or post-marketing studies, case reports, and preclinical work, so findings should not be interpreted as a uniform level of therapeutic efficacy.

The six expanded entries are illustrative and purposefully selected, not exhaustive. Other designated diseases with important skin manifestations - including systemic sclerosis, systemic lupus erythematosus, and vasculitides - could satisfy one or more criteria but were not selected because the framework was designed to illustrate complementary mechanisms within a tractable scope; their exclusion does not imply lesser dermatologic importance. The unit of analysis also varies among administrative entries, disease groups, and mechanistic phenotypes. Japanese official classifications and regulatory status are time-sensitive and may change after the August 3, 2026 cutoff. Finally, national data on registry completeness, regional access, and interoperability are limited; proposals for a common data model, adaptive platforms, and linked post-marketing cohorts are author recommendations.

16. Conclusion

Japanese nanbyo dermatology is distinctive because it combines a national care-and-research framework with population-specific disease biology. The 12 entries in the official skin-centered category remain a coherent core, but they do not represent the full dermatologic burden of designated intractable disease. Adding six selectively chosen entries or disease groups - Behcet disease, the PM/DM entry with an anti-MDA5 dermatomyositis focus, TSC, CAPS, NNS/PRAAS, and SAVI - produces an 18-entry illustrative framework that is mechanistically informative but neither exhaustive nor the only defensible expansion.

Recent progress demonstrates the value of precision: anti-IL-36 receptor therapy for GPP, topical COL7A1 gene delivery and autologous gene-corrected epidermal sheets for dystrophic EB, MEK inhibition for NF1, mTOR inhibition for TSC, IL-1 blockade for CAPS, and emerging JAK-interferon approaches for NNS/PRAAS and SAVI. We contend that linking designation data to interoperable natural-history cohorts, endotype-defined enrollment, mechanism-aligned outcomes, and international adaptive trials could help Japan develop its current infrastructure into a more fully translational ecosystem. This is a policy and research recommendation rather than a demonstrated consequence of designation. The central message is that rarity should not be the endpoint of classification; it should be the starting point for biologically specific, patient-centered interventions.

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