

Research Article

# Genodermatoses and Therapeutics on the Horizon: A Review and Table Summary

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## Abstract

Over the last decade with the advent of new genetic technologies such as CRISPR and more recently described, seekRNA, we now have the ability to transfer genetic materials through retroviruses or other tools to directly edit the aberrant genes and repair them. We describe and categorize the genodermatoses in tabular forms devoting each genodermatosis to its own table which describes the clinical characteristics, genetic inheritance pattern, pathophysiology with molecular and genetic pathways, current treatments and future anticipated treatments.

**Keywords:** Genodermatoses; Genetic; Dermatology; Blistering; CRISPR; Basal Cell Carcinoma; Ichthyosis; mTOR; Leiomyoma; Ras; Genetic Engineering; Neurofibroma; Angiofibroma; Polyposis; Connective Tissue; Hedgehog; Leiomyoma

## Introduction

Genodermatoses consist of a broad range of genetic skin disorders that can impact multiple organ systems. The genodermatoses associated with malignant potential are: Basal cell Nevus Syndrome (BCN), also known as Gorlin Syndrome (GS), Gardner Syndrome (GS), Peutz-Jegher Syndrome (PJS), Hereditary Leiomyomatosis and Renal Cell carcinoma (HLRCC), Xeroderma Pigmentosum (XP) and Epidermolysis Bullosa (EB). The genodermatoses associated with disorders of keratinization are: Ichthyoses Vulgaris (IV), Palmoplantar Keratodermas (PK), pachyonychia Congenita (PC), Darier disease (DD) and Hailey-Hailey Disease (HHD). The genodermatoses that are associated with genetic blistering disorders are: Epidermolysis Bullosa (EB) including EB Simplex (EBS), Junctional EB (JEB), Dystrophic EB (DEB) and Kindler EB (KEB). The genodermatoses associated with pigmentation disorders are: Oculocutaneous

Albinism (OA), Piebaldism and Waardenburg Syndrome (WS). The genodermatoses associated with Neuro cutaneous syndromes are: Neurofibromatosis type 1 (NF1), Neurofibromatosis type 2 (NF2), Tuberous Sclerosis Complex (TSC) and Ataxia-Telangiectasia Syndrome (ATS). The genodermatoses associated with vascular disorders are: which also include an overlap with ATS and Hereditary Hemorrhagic Telangiectasia (HHT) -also known as Osler- Weber Rendu syndrome (OWR). The genodermatoses associated with disorders of connective tissue disease are: Ehlers-Danlos Syndrome (EDS), Marfan Syndrome (MS), Osteogenesis Imperfecta (OI), Pseudoxanthoma Elasticum (PXE) and Focal Dermal Hypoplasia (FDH). The genodermatosis associated with X-linked dominant disorders are: Incontinentia Pigmenti (IP), Focal Dermal Hypoplasia-overlapping with disorders of connective tissue (FDH), Congenital hemi dysplasia with Ichthyosiform erythroderma and limb defects or CHILD syndrome and Chondrodysplasia Punctata (CP), also known as Conradi-Hünemann syndrome. The genodermatoses associated with ectodermal dysplasia, including Hypohidrotic Ectodermal Dysplasia (HED), Hypohidrotic Epidermal Dysplasia with immune deficiency (HEDID), Hidrotic Ectodermal Dysplasia2 (HED2) or also called Clouston

Syndrome (CS), Tumor Protein p63-related disorders (TP63) and Focal Dermal Hypoplasia (overlaps with x-linked dominant disorders and ectodermal dysplasias).

Clinicians rarely encounter these conditions; however, clinicians should be aware of their clinical characteristics and treatment options. In the advent of newer technologies and our understanding of the genetic pathways, treatment options are ever expanding. This review of the genodermatoses has been undertaken due to major new discoveries and developments in the molecular and genetic pathways. The goal of this review is to simplify the genodermatoses in an understandable format while discussing future treatment options.

## Material and Methods

A literature review was performed using PubMed. Articles were searched using the respective genodermatosis and the terms therapy, treatment and genetics. The title and abstract of each article were screened for relevance. Selected articles were then reviewed by the individual researcher that chose the article and relevant data was extracted and incorporated into this review. Articles in a language other than English were excluded. Articles that were peer reviewed and had full text access were included. Articles were not excluded due to publication date due to the limited amount of information on these rare conditions.

## Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore, was exempt.

## Results

*Group 1: Malignant Potential (Table 1-5).*

|                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | Basal cell nevus syndrome is characterized clinically by the development of numerous Basal Cell Carcinomas (BCC), palmar pits, jaw cysts and skeletal abnormalities                                                                                                                                                                                                                                                                               |
| <b>Genetic Inheritance Pattern</b>                                        | A rare autosomal dominant genetic condition.<br>The genetic penetrance of PTCH1 mutations appears to be quite high                                                                                                                                                                                                                                                                                                                                |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | Patched-1 is a transmembrane tumor suppressor protein which recognizes the ligand, sonic hedgehog (Shh). In its wild-type and unbound state, patched-1 constitutively inhibits the oncogenic GPCR, smoothened (Smo). Smo inhibition can be suppressed through Shh binding of patched-1.<br>In basal cell nevus syndrome, Smo activation is facilitated via deleterious mutation of PTCH1. Activation of Smo upregulates the Hh signaling pathway. |
| <b>Current Treatments</b>                                                 | -an oral hedgehog inhibitor treatment initiated with oral agents vismodegib 150 mg/d or sonidegib 200 mg/d orally                                                                                                                                                                                                                                                                                                                                 |
| <b>Future Treatments anticipating genetic treatment</b>                   | -using induced pluripotent stem (iPS) cells unique to Gorlin syndrome for the development of modern therapeutics<br>-Transfer of Genetic Materials (GM) by introducing healthy copies of the defective genes through retroviruses or using tools to directly edit the faulty genes & repair them.                                                                                                                                                 |

**Table 1:** Basal cell nevus syndrome (Gorlin Syndrome) [1,2].

|                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Clinical Characteristic<br/>(Cutaneous/Systemic) with brief<br/>definition</b> | Familial Adenomatous Polyposis (FAP) is a genetic intestinal disorder characterized by presence of potentially malignant adenomatous polyps within the intestinal lumen. Gardner Syndrome is a variant of FAP which is further differentiated by presence of extraintestinal manifestations, including desmoid fibromatosis, epidermal inclusion cysts and osteomas.                                                                                                                                                                                                                                                     |
| <b>Genetic Inheritance Pattern</b>                                                | -Mutation of autosomal dominant APC gene (encodes adenomatous polyposis coli)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Pathophysiology of Disease with<br/>molecular and genetic pathways</b>         | <p>-Heterozygous mutation in the adenomatous polyposis coli (APC) ( gene (611731) on chromosome 5q22</p> <p>-Band 5q22.2, on chromosome 5, is linked to the APC gene, a tumor suppressor gene that produces the APC protein, which controls cell growth by timing cell division properly.</p> <p>-Aberration of APC genes leads to uncontrolled cell growth.</p> <p>-Some rare causes include loss of DNA methylation, mutation on the <i>RAS</i> gene on chromosome 12, deletion of the colon cancer gene (<i>DCC</i>) on chromosome 18 or even as well as, a mutation in <i>TP53</i> gene located on chromosome 17</p> |
| <b>Current Treatments</b>                                                         | <p>-No cure present</p> <p>-Radiation is ineffective</p> <p>-Prevention (if aware of the respective familial inheritance or once this is discovered)</p> <p>-healthy diet</p> <p>-NSAIDs such as sulindac</p> <p>-COX2 inhibitor like celecoxib</p> <p>-Surveillance via lower GI endoscopies</p> <p>-If 20 or more polyps are present, colectomy</p> <p>-Precise pathological differentiation for treatment of specific tumors</p>                                                                                                                                                                                      |
| <b>Future Treatments anticipating<br/>genetic treatment</b>                       | <p>-Genetic counseling, cytogenetic testing, microarray testing, comparative bioinformatic techniques</p> <p>-Transfer of GM see Table 1 Future treatments</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

**Table 2:** Gardner syndrome [3-5].

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| <b>Clinical Characteristic<br/>(Cutaneous/Systemic) with brief<br/>definition</b> | <p>Pigmented mucocutaneous macules and gastrointestinal (GI) polyps with a predisposition to colorectal, gastric and pancreatic cancers. Those with PJS also have an increased risk of epithelial malignancies such as of the lung, breast, uterine, cervical, testicles and ovaries.</p> <p>The pigmented mucocutaneous macules ranging in color from between dark blue, brown and black are found in more than 95% of patients with PJS. The lips, perioral regions, buccal mucosa, eyes, nostrils, fingertips, palms, soles and perianal areas are the most often affected locations. Oral pigmentation manifests primarily during the first year of life; macules are rarely present at birth and instead develop during infancy, usually before the age of five. With the exception of those on the buccal mucosa, which persist until adulthood, the macules may disappear between adolescence and adulthood.</p> |
| <b>Genetic Inheritance Pattern</b>                                                | -Autosomal dominant in combination with de novo mutation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Pathophysiology of Disease with<br/>molecular and genetic pathways</b>         | <p>-Dysregulation of <i>STK11/LKB1</i> gene</p> <p>-Mutated portion found on 19p13.3</p> <p>-This gene encodes the tumor suppressor serine/threonine kinase and 50–90% of PJS</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

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|                                                         | cases are due to mutations in this enzyme resulting in the loss of the kinase function. STK11/LKB1 is involved in multiple signaling pathways that control cell-cycle and cell proliferation, including processes such as apoptosis and RAS induced cell transformation.                                                                                                                                                                                                                           |
| <b>Current Treatments</b>                               | <ul style="list-style-type: none"> <li>-Surveillance for malignancies</li> <li>-Genetic Testing</li> <li>-management and surveillance for the presence of symptoms by an interprofessional team consisting of a primary care physician, geneticist, gastroenterologist, general surgeon, dermatologist, urologist and gynecologist, oncology pharmacist.</li> <li>-Upper GI tract, colorectal, pancreatic, breast and testicular examinations as well as genetic testing and counseling</li> </ul> |
| <b>Future Treatments anticipating genetic treatment</b> | Transfer of GM see Table 1 Future treatments                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

**Table 3: Peutz-Jeghers Syndrome (PJS) [6-8].**

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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | <ul style="list-style-type: none"> <li>-development of multiple tumor types including skin leiomyomas, uterine fibroids and HLRCC kidney tumors</li> <li>3-4 clinical features:               <ul style="list-style-type: none"> <li>-renal cancer (RCC) - mean age 41-44 years</li> <li>-cutaneous leiomyomas - mean age 25-45 years</li> <li>-uterine leiomyomas - mean age 30 years</li> <li>-(Rarely) pheochromocytomas and paragangliomas</li> </ul> </li> <li>-Renal lesions are mostly solitary and unilateral, but even small lesions have high potential of metastasis</li> <li>-distant metastasis to mediastinal lymph nodes, bone and liver in almost 50% of the patients in a cohort with median size of tumor as 7.8 cm.</li> <li>-Renal vein and IVC extension are also frequently seen</li> </ul> |
| <b>Genetic Inheritance Pattern</b>                                        | <ul style="list-style-type: none"> <li>-Autosomal dominant with incomplete penetrance</li> <li>-Knudson's two-hit hypothesis of FH allelic inactivation</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | <ul style="list-style-type: none"> <li>-Knudson's two hypotheses must be followed by the pattern of appearance of mutant alleles for HLRCC to exist. An autosomal dominant inheritance pattern is required for the germline mutation that results in the first mutant FH allele. sometimes before the age of 20, but usually later in life, the second FH allele will undergo a mutation. Examining this distinction is crucial because fumarase deficiency, an entirely unique autosomal recessive disorder, results from the bi-allelic inheritance of two defective FH alleles.</li> <li>-FH mutations induce carcinogenesis mainly through the activation of the hypoxia pathway</li> </ul>                                                                                                                   |
| <b>Current Treatments</b>                                                 | <ul style="list-style-type: none"> <li>-Genetic testing</li> <li>-Frequent surveillance starting &lt;20 years of age via dermatologic screening, gynecological screening, MRI, ultrasound</li> <li>-Specialized excision techniques (recommend wide local excision)</li> <li>-hysterectomies</li> <li>-Uterine myomectomies</li> <li>-Treat malignancies as they arise according to standard of care</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                   |

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| <b>Future Treatments anticipating genetic treatment</b> | <ul style="list-style-type: none"> <li>-Genetic testing</li> <li>-Family planning</li> <li>-Transfer of GM see Table 1 Future treatments</li> </ul> |
|---------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|

**Table 4:** Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC) [9-12].

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|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | <p>-Xeroderma pigmentosum is a rare disorder that causes mutations in the Nucleotide Excision Repair (NER) pathway that causes affected people to be unable to fully repair UV radiation damage from the sun. Diagnosis of XP requires clinical assessment that involves recognizing specific symptoms( numerous diagnoses of skin cancers since birth) and/ or genetic testing.</p> <ul style="list-style-type: none"> <li>-Inability to fully repair UV radiation damage from the sun.</li> <li>-Numerous diagnoses of skin cancers since birth including, BCC, SCC, MM, etc..</li> <li>-Numerous pigmented lesions focused on the head and neck area</li> <li>-Decreased elasticity and softness of the dermis and subcutaneous</li> </ul> |
| <b>Genetic Inheritance Pattern</b>                                        | <p>-Inherited disorder(rare autosomal recessive). The 7 complementation groups of XP (XP-A through XP-G) have no significant correlation on whether someone is more susceptible to various cancers or not. XP is more common in countries that have a higher prevalence of incest (Japan, India, Middle East, &amp; Northern Africa).</p>                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | <p>-XP is characterized by several mutations in the NER Pathway, which is responsible for repairing DNA damage that can lead to cancer or other health problems.Due to the mutations in the NER pathway, cells accumulate damage overtime which leads to an increase risk of skin cancers(BCC, SCC, MM, etc.,). XP can also lead to numerous pigmented lesions focused in the head &amp; neck era and decreased elasticity &amp; softness of the dermis and subcutaneous fat layer of the skin.</p>                                                                                                                                                                                                                                           |
| <b>Current Treatments</b>                                                 | <ul style="list-style-type: none"> <li>-Most common treatment is surgery, but this can lead to physical deformities from frequent biopsies and excisions.</li> <li>-Less invasive treatment includes photodynamic therapy (PDT), 5-FU and imiquimod for smaller skin cancers in low-risk locations.</li> <li>-For Melanoma treatment: immunotherapy, immune checkpoint inhibitors (CPI), target therapy, chemotherapy, drugs that block hedgehog signaling and radiotherapy.</li> <li>-Note that all these treatments focus on avoiding recurrence of skin cancers,not offering a complete cure for XP.</li> </ul>                                                                                                                            |
| <b>Future Treatments anticipating genetic treatment</b>                   | Transfer of GM see Table 1 Future treatments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

**Table 5:** Xeroderma pigmentosum [13-15].

Group 2: Disorders of Keratinization (Table 6-13).

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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | Total-body gray scaling (except large flexural surfaces). The ichthyoses are distinguished by orthohyperkeratosis, a characteristic thickening of the stratum corneum. The stratum granulosum is markedly reduced, if not completely absent.                                                                                                                                                                                                                         |
| <b>Genetic Inheritance Pattern</b>                                        | Autosomal semi-dominant FLG gene (encodes filaggrin) mutation                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | The filaggrin gene (FLG) encodes profilaggrin, which subsequently undergoes proteolytic processing by serine proteases in order to yield functional filaggrin. Filaggrin is a structural protein that functions to form a tightly cross-linked matrix of hydrophilic keratin filaments within the stratum corneum. A loss-of-function mutation of FLG impairs filaggrin's ability to compact these keratin filaments, which leads to dehydration of the corneocytes. |
| <b>Current Treatments</b>                                                 | topical use of emollients, keratolytics and retinoids for symptom relief - no curative treatment                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Future Treatments anticipating genetic treatment</b>                   | Transfer of GM see Table 1 Future treatments                                                                                                                                                                                                                                                                                                                                                                                                                         |

**Table 6:** Ichthyosis vulgaris [16-19].

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|---------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | Total-body grey scaling (except large flexural surfaces) that affects almost exclusively all males. There is orthohyperkeratosis, but the stratum granulosum remains normal or is slightly thickened. Also marked by retention hyperkeratosis, which is a deficiency in the degradation of corneodesmosomes.                                                                                                                                                  |
| <b>Genetic Inheritance Pattern</b>                                        | X-linked recessive STS gene (encodes steroid sulfatase) mutation                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | The steroid sulfatase gene (STS) encodes steroid sulfatase, a rough endoplasmic reticulum transmembrane protein that functions to hydrolyze steroid sulfates into hydroxysteroids, which are precursors in sex hormone and cholesterol synthesis. A partial or total deletion of STS gene results in steroid sulfatase deficiency, which results in subsequent accumulation of cholesterol-3-sulfate in the stratum corneum and decreased cholesterol levels. |
| <b>Current Treatments</b>                                                 | Topical use of emollients, keratolytics and retinoids for symptom relief -no curative treatment                                                                                                                                                                                                                                                                                                                                                               |
| <b>Future Treatments anticipating genetic treatment</b>                   | gene therapy: retroviral vector with STS gene (preclinical study from 1997)<br>- Transfer of GM see Table 1 Future treatments                                                                                                                                                                                                                                                                                                                                 |

**Table 7:** X-linked recessive ichthyosis [16-19].

|                                                                           |                                                                                                        |
|---------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | Hyperkeratotic corrugated scaliness with severe blistering often associated with a characteristic odor |
| <b>Genetic Inheritance Pattern</b>                                        | Autosomal dominant                                                                                     |

|                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-----------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Pathophysiology of Disease with molecular and genetic pathways</b> | <p>Molecular Pathophysiology:</p> <p>Tonofilament clumping</p> <p>Suprabasal Cell Cytolysis</p> <p>Increased Basal Cells over joints and flexural sites</p> <p>Xerosis, Erythema, Fissure, Erosions, Anhidrosis, Pruritus and Keratoderma<sup>20</sup></p>                                                                                                                                                                                                                             |
| <b>Current Treatments</b>                                             | <p>Treatment strategies include hydrating creams that contain NaCl, urea, glycerol. Lubricating creams that contain Petrolatum and other Lipids. Keratolytic creams that contain <math>\alpha</math>-Hydroxy acids, urea (&gt;5%), propylene glycol, salicylic acid, N-acetylcysteinamide. Antimicrobial creams that contain Retinoids, calcipotriol. As well as cholesterol-containing creams, Tazarotene, N-acetylcysteine, liarozole and calcipotriol, Isotretinoin (Accutane).</p> |
| <b>Future Treatments anticipating genetic treatment</b>               | Transfer of GM see Table 1 Future treatments                                                                                                                                                                                                                                                                                                                                                                                                                                           |

**Table 8:** Epidermolytic hyperkeratosis [20].

|                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | <p>Diffuse white soft scaliness with erythema that becomes darker and rougher as disease progresses. Associated with palmoplantar hyperkeratosis, nail dystrophy and scarring alopecia</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Genetic Inheritance Pattern</b>                                        | Autosomal recessive                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | <p>Genetic Pathophysiology:</p> <p>Gene mutation in ABCA12, ALOXE3, ALOX12B, CASP14, CERS3, CYP4F22, LIPN, NIPAL4, PNPLA1, SDR9C7, ST14, SUBLT2B1, TGM1, however, more predominantly in ALOXE3 and ALOX12B. These genes are responsible for keratin proteins (mostly 1 and 10)</p> <p>Molecular Pathophysiology:</p> <p>Mutations in transglutaminase-1 (TGM1) gene alters the function of transglutaminase-1 enzyme which creates malformed intercellular lipid layer and disruption of stratum corneum barrier function and can lead to the development of Congenital Ichthyosiform Erythroderma and Lamellar Ichthyosis.</p> <p>Xerosis, Erythema, Fissure, Erosions, Anhidrosis, Pruritus and Keratoderma</p> |
| <b>Current Treatments</b>                                                 | <p>Treatment Strategies:</p> <p>Same treatments as Epidermolytic Hyperkeratosis in addition to:</p> <p>Retinoic Acid Metabolism Blocking Agents (RAMBAs)</p> <p>Acitretin</p> <p>Off label use of Alitretinoin</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Future Treatments anticipating genetic treatment</b>                   | Transfer of GM see Table 1 Future treatments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

**Table 9:** Congenital ichthyosiform erythroderma [20-24].

|                                                                           |                                    |
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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | Diffuse dry, rough skin with scale |
|---------------------------------------------------------------------------|------------------------------------|

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| <b>Genetic Inheritance Pattern</b>                                    | Germline missense mutation in ABCA12 gene or mutation in Transglutaminase-1 (TGM1) gene                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b> | Mutation in TGM1 gene alters the function of transglutaminase-1 enzyme which creates malformed intercellular lipid layer and disruption of stratum corneum barrier function.                                                                                                                                                                                                                                                                                                                    |
| <b>Current Treatments</b>                                             | <p>Symptomatic treatments include topical moisturizing creams that include glycerin, urea and propylene glycol. Likewise, N-acetylcysteine, Acitretin, Retinoids in combination with liarozole (RAMBA), Secukinumab and Imsidolimab (anti-IL-36 receptor monoclonal antibody). Trifarotene has FDA orphan drug status.</p> <p>Enzyme Replacement Treatments include Liposomes with encapsulated recombinant human; TGase-1 (rhTGase-1); and TGase-1-loaded thermoresponsive nanogels (tNGs)</p> |
| <b>Future Treatments anticipating genetic treatment</b>               | <p>Retrovirus encoding the TGM1 gene</p> <p>HSV-1, encoding the TGM1 gene</p> <p>Adenovirus-enhanced transferrin receptor mediated transfection (AVET) system with plasmid DNA encoding the TGM1 gene</p> <p>Adeno-Associated Viruses (AAV) modifications</p>                                                                                                                                                                                                                                   |

**Table 10:** Lamellar ichthyosis [23].

|                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                      |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | Diffuse scaly, rough and red lesions generally on the neck, flexible regions of the epidermis and the lower abdomen. Greatly associated with spastic diplegia and severe learning disabilities. Epileptic seizures occur in about 40% of patients. Some rare characteristics including short stature, kyphoscoliosis, nystagmus and retinal changes, consisting of perivascular pearly white macules |
| <b>Genetic Inheritance Pattern</b>                                        | Autosomal recessive                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | <p>Genetic:<br/>Mutation on gene 17p11.2</p> <p>Molecular:<br/>Deficiency in fatty aldehyde dehydrogenase in fibroblasts can inhibit the oxidation of fatty acid aldehyde chains and subsequently result in the disruption of epidermal moisture barrier</p>                                                                                                                                         |
| <b>Current Treatments</b>                                                 | <p>Reducing intake of fats and supplementing with n-3 and n-6 fatty acids. For severe pruritus, therapeutic trials of Zileuton (5-lipoxygenase inhibitor) appear to help</p> <p>Topical:<br/>moisturizing with emollients and keratolytic agents. As well, topical creams like Calcipotriol and retinoids are useful in treatment.</p>                                                               |
| <b>Future Treatments anticipating genetic treatment</b>                   | <p>Potential for Adeno-associated virus vectors for resolving deficient fatty aldehyde dehydrogenase</p> <p>- Transfer of GM see Table 1 Future treatments</p>                                                                                                                                                                                                                                       |

**Table 11:** Sjogren-larsson syndrome [25].



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|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | Can manifest at birth as generalized erythroderma with scaling and later evolve into keratinization that is typical of ichthyosis vulgaris. Aside from cutaneous symptoms, hair anomalies are also observed, including brittle or stunted growth of the hair of the scalp, eyebrows and eyelashes. Furthermore, bamboo hair (trichorrhexis invaginata) is characteristic of Netherton. Also characterized by thinning of the stratum corneum.                                                                                                                                                                                                                                                                                                             |
| <b>Genetic Inheritance Pattern</b>                                        | Autosomal recessive SPINK5 gene (encodes LEKTI; lympho-epithelial Kazal-type-related inhibitor) mutation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | LEKTI inhibits kallikrein-related peptidases (KLKs), serine proteases which promote corneodesmosome degradation. A LEKTI deficiency (i.e. due to SPINK5 mutation) results in upregulation of KLK activity, which leads to thinning of the stratum corneum.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Current Treatments</b>                                                 | Symptomatic treatments and prevention/treatment of infections                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Future Treatments anticipating genetic treatment</b>                   | <ul style="list-style-type: none"> <li>-small molecule: BPR 277 ointment which completed phase I clinical trial in 2014</li> <li>-gene therapy: skin graft with lentiviral vector with WT SPINK5 which has completed phase I clinical trial in 2018</li> <li>- IL 17A blockers secukinumab , IL 12/23 blockers ustekinumab, IL 4 alpha /IL 13 blocker dupilumab, TNF alpha blocker Infliximab , IL 1beta blocker -anakinra, immunoglobulin replacement therapy IVIG none of these therapies were given in a double blind manner, nor were there large enough numbers to establish efficacy for sure however, the patients treated with these particular agents improved in case reports</li> <li>-Transfer of GM see Table 1 Future treatments</li> </ul> |

**Table 12:** Netherton syndrome [19,26,27].

|                                                                           |                                                                                                                                                                                                                                                                                                         |
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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | Associated with Retinitis Pigmentosa, anosmia, Polyneuropathy (sensory and motor), Sensorineural Hearing Loss, ataxia, ichthyosis, truncated metacarpals and metatarsals present from birth, cardiac arrhythmias and cardiomyopathy symptoms                                                            |
| <b>Genetic Inheritance Pattern</b>                                        | <p>Autosomal dominant</p> <ul style="list-style-type: none"> <li>- 90% pathogenic variants in PHYH</li> <li>- 10% biallelic pathogenic variants in PEX7</li> </ul>                                                                                                                                      |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | <p>Genetic Pathways:</p> <p>Deficiency in PHYH or deficiency of PTS2 receptor encoded by PEX7 disabling PHYH lysis. This causes build up of phytanic acid in tissues.</p>                                                                                                                               |
| <b>Current Treatments</b>                                                 | <p>Plasmapheresis or lipid apheresis, certain dietary restrictions of Phytanic acid with high-calorie diet, IV lipid emulsions (INTRALIPID), low vision aids, ocular surgeries and hydrating creams.</p> <p>Avoid Ibuprofen and Amiodarone</p> <p>Antiarrhythmic &amp; cardiogenic supportive drugs</p> |
| <b>Future Treatments anticipating genetic treatment</b>                   | - Transfer of GM see Table 1 Future treatments                                                                                                                                                                                                                                                          |

**Table 13:** Refsum disease [28].

Group 3: *Palmoplantar Keratoderma* (Table 14-18).

|                                                                                   |                                                                                                                                                   |
|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Clinical Characteristic<br/>(Cutaneous/Systemic) with brief<br/>definition</b> | -focal Palmoplantar Keratoderma (PPK) over areas of pressure and friction<br>-oral leukoplakia<br>-increased risk of developing esophageal cancer |
| <b>Genetic Inheritance Pattern</b>                                                | Autosomal Dominant, mutation in the RHBDF2 gene long arm of chromosome 17<br>(at 17q25).                                                          |
| <b>Pathophysiology of Disease with<br/>molecular and genetic pathways</b>         | RHBDF2 protein is lacking which results in decreased epithelial response to injury<br>in the skin and esophagus                                   |
| <b>Current Treatments</b>                                                         | counseling regarding smoking and alcohol, screening EGDs, retinoids                                                                               |
| <b>Future Treatments anticipating<br/>genetic treatment</b>                       | - Transfer of GM see Table 1 Future treatments                                                                                                    |

**Table 14:** Howel-Evans syndrome [29-31].

|                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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| <b>Clinical Characteristic<br/>(Cutaneous/Systemic) with brief<br/>definition</b> | -sensorineural deafness<br>-diffuse honeycomb keratosis<br>-thickening of the palms and soles of the feet<br>-starfish-like keratotic spot on the dorsal side of the hands and feet<br>-fiber contraction bands in the interphalangeal joints of the hands and feet, which<br>can lead to automatic amputation (ainhum)                                                                                                             |
| <b>Genetic Inheritance Pattern</b>                                                | -Autosomal dominant<br>-Mutations in the LOR and GJB2 genes have been found in VS<br>-GJB2 gene is located on chromosome 13q12<br>-GJB2 mutation is considered to be the classical form of VS<br>-GJB2 encodes connexin 26 (Cx26), which contains transmembrane region (M1-M4),<br>extracellular region (E1, E2), cytoplasmic junction region (CL), cytoplasmic amino<br>terminal (N-terminal) and carboxyl terminal (C-terminal)." |
| <b>Pathophysiology of Disease with<br/>molecular and genetic pathways</b>         | The mutation of the gap junction protein gene expressed in skin will destroy the<br>growth and differentiation of epidermis. The GJB2 mutations that cause classical VS<br>have a common molecular phenotype. Most of them (except p.Gly130Val) aggregate<br>in the E1 domain of Cx26, affecting protein transport and channel permeability.                                                                                        |
| <b>Current Treatments</b>                                                         | Systemic retinoids and vitamin A derivatives. Surgical treatment of ainhum using z-<br>plasty technique. Amputation if necessary                                                                                                                                                                                                                                                                                                    |
| <b>Future Treatments anticipating<br/>genetic treatment</b>                       | Supplement with low doses of TGF- $\beta$ 1 promotes cell proliferation and induces an<br>increase in the frequency of the cell population at G1<br>Low doses of TGF- $\beta$ 1 may improve the abnormal proliferation of VS keratinocytes<br>and up-regulate the expression of Cyclin D1<br>Transfer of GM see Table 1 Future treatments                                                                                           |

**Table 15:** Vohwinkel syndrome [31,32].

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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | <p>-palmoplantar hyperkeratosis, rapid onset of periodontitis and premature shedding of both primary and permanent teeth</p> <p>-diffuse palmoplantar keratoderma (PPK) and frequent pyogenic infections</p> <p>-Palmar-plantar keratosis</p> <p>-severe gingivitis of primary teeth</p> <p>-fast periodontal deterioration</p> <p>-By the age of 16, most permanent teeth may fall out if untreated</p> <p>-impaired neutrophil, lymphocyte or monocyte function</p> <p>-increased vulnerability to bacterial infections</p> <p>-risk of developing recurring pyogenic illnesses including pyoderma, furunculosis, pneumonia and hepatic abscesses</p> |
| <b>Genetic Inheritance Pattern</b>                                        | <p>-autosomal recessive disorder</p> <p>-mutation in the cathepsin C (CTSC) gene</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | Cathepsin C gene mutation results in loss of Cathepsin C enzyme activity. This causes the loss of function of immune defense cells and epithelial tissues, particularly of the gingiva and ventral surface of hands and feet. Clinical signs and symptoms are a result of the free radicals, reactive oxygen species and mitochondrial dysfunction.                                                                                                                                                                                                                                                                                                     |
| <b>Current Treatments</b>                                                 | <p>Early identification</p> <p>Systemic antibiotics are effective in reducing active periodontitis</p> <p>oral prophylactic measures can enhance the quality of life</p> <p>systemic drug therapy of amoxicillin-metronidazole effectively halts the progression of periodontal disease</p> <p>emollients, salicylic acid and urea</p> <p>oral retinoids like acitretin and isotretinoin</p> <p>Genetic counseling should be provided</p>                                                                                                                                                                                                               |
| <b>Future Treatments anticipating genetic treatment</b>                   | <p>Recombinant human CTSC (Cathepsin C) therapy</p> <p>Targeting of mitochondrial dysfunction was treated with topical CoQ10 0.1%</p> <p>Transfer of GM see Table 1 Future treatments</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

**Table 16:** Palpillon-Lefevre syndrome [33,34].

|                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | <p>Pachyonychia congenita (PC), primarily targets epithelial appendages from the ectoderm and typically involves oral leukokeratoses, nail dystrophy and painful palmoplantar keratoderma (PPK). Hypertrophic nail dystrophy, painful palmoplantar keratoderma and blistering, oral leukokeratosis, pilosebaceous cysts (including steatocystoma and vellus hair cysts), palmoplantar hyperhidrosis and follicular keratoses on the trunk and extremities</p> |
| <b>Genetic Inheritance Pattern</b>                                        | <p>A de novo pathogenic variant is believed to be responsible for about 30% of cases. Germline mosaicism has been identified in one instance. The likelihood of contracting the disease is 50% when an affected individual has children.</p>                                                                                                                                                                                                                  |

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| <b>Pathophysiology of Disease with molecular and genetic pathways</b> | Mutations in KRT6A, KRT6B, KRT6C, KRT16 and KRT17, which are typically expressed in skin appendages and produced after injury, are the cause of pachyonychia congenita (PC).                                                                                                                                                                                                                                                                                                       |
| <b>Current Treatments</b>                                             | Emollients, keratolytics, podiatry to manage nails                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Future Treatments anticipating genetic treatment</b>               | Use of Botulinum toxin (BoNT-A) injections showed promising results: it was able to provide pain relief and had antiperspirant effects on the participants. BoNT-A has been shown to inhibit the release of neuropeptides from sensory nerve axons and suppress neurogenic inflammation by targeting nociceptive C fibers in the epidermis.<br>Sirolimus, also called rapamycin, an mTOR (mammalian target of rapamycin) inhibitor<br>Transfer of GM see Table 1 Future treatments |

**Table 17:** Pachyonychia congenita [35-37].

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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | It presents as hyperkeratotic papules on the flexural areas, seborrheic regions, scalp, neck, chest and back<br>Skin: primarily in the seborrheic areas, tiny, highly corneous reddish-brown papules.<br>Nails: V-shaped defects in the free margin, subungual hyperkeratosis and red and white longitudinal bands.<br>Mucosal expression: White, grouped papules with a central depression.<br>Malodor and secondary superinfections. Itching can be present or absent. |
| <b>Genetic Inheritance Pattern</b>                                        | ATP2A2, found on chromosome 12q23-24.1. Autosomal dominant disease. An affected parent has a 50% probability of passing the gene to the offspring. However, everyone who inherits the gene does not express it phenotypically.                                                                                                                                                                                                                                           |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | Studies suggest the abnormal ATP2A2 gene results in deficient SarcoEndoplasmic reticulum calcium ATPase which results in insufficient calcium for the desmosomes to maintain their function                                                                                                                                                                                                                                                                              |
| <b>Current Treatments</b>                                                 | Topical or oral retinoid, emollients, vitamin D analogues, laser treatments, tetracyclines, topical fluorouracil                                                                                                                                                                                                                                                                                                                                                         |
| <b>Future Treatments anticipating genetic treatment</b>                   | Ustekinumab<br>Transfer of GM see Table 1 Future treatments                                                                                                                                                                                                                                                                                                                                                                                                              |

**Table 18:** Darier disease [38-40].

*Group 4: Blistering Disorders (Table 19-23).*

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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | Epidermolysis bullosa simplex (EBS) is a group of hereditary skin diseases characterized by blisters and erosion of the skin due to skin fragility. These blisters occur on the palms, soles, extremities, joints and trunk. They also have defined, irregular borders and are associated with a high risk of developing squamous cell carcinoma |
| <b>Genetic Inheritance Pattern</b>                                        | It is inherited in an autosomal dominant manner, but there is significant genetic                                                                                                                                                                                                                                                                |

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|                                                                       | diversity and some variants can be inherited in a recessive manner.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b> | Mutations in at least 20 different genes can cause EB mutations in the collagen VII gene. Blisters result from a gene mutation that controls the basement membrane which is responsible for maintaining the structure of the basal membrane and keratinocytes. Mutations in these genes that produce keratins, desmosomes, hemidesmosomes or other filaments are responsible for skin cell adhesion. Mutations in either laminin 332 or integrin $\alpha 6\beta 4$ can lead to the disease as well as in the genes KRT5 and KRT14 or LAMA3, LAMB3, LAMC3 and COL7A1                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Current Treatments</b>                                             | There aren't currently any curative treatments. Today, treatment involves precautionary care and effective wound care. The focus is to prevent infection of open blisters and to inhibit new blister growth.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Future Treatments anticipating genetic treatment</b>               | <p>Researchers are currently investigating different types of treatments, such as gene therapies (gene replacement, gene editing, RNA-based therapy and natural gene therapy. Gene replacement and editing involves using a correct copy of the COL7A1 gene packaged into a retrovirus. This virus is used to transfer the gene into the patient's keratinocytes via injection, which are cultured and grown outside the body (<i>ex-vivo</i>). These growing keratinocytes form sheets that can be used as skin grafts, producing the functional type VII collagen protein, which helps prevent blisters OR cell-based therapies (using cells like fibroblasts, bone marrow cells, mesenchymal stromal cells and induced pluripotent stem cells), recombinant protein therapies and Bone marrow transplants.</p> <p>Furthermore Filsuvez (oleogel-S10) is showing promise in patients with JEB and DEB and may be used in EB simplex</p> <p>Transfer of GM see Table 1 Future treatments.</p> |

**Table 19:** EB simplex [41-44].

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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | <p>Junctional epidermolysis bullosa (JEB) is a condition marked by skin and mucous membrane fragility, leading to form blisters with minimal or no injury. These blisters are often accompanied by the formation of granulation tissue around areas like mouth, nose, fingers, toes and internally in and around the upper airway and trachea. Interestingly, these blisters tend to heal without significant scarring.</p> <p>- JEB can be broadly classified into 2 types:</p> <ol style="list-style-type: none"> <li>1) In JEB generalized severe, the blisters are presents at birth or develop shortly after.</li> <li>2) In JEB generalized intermediate, blisters are mostly localized to specific areas such as hands, feet, knees and elbows. Some individuals with this type may not experience blistering beyond the newborn period.</li> </ol> <p>Additionally, JEB shares several features with other form of epidermolysis bullosa, including congenital localized absence of skin (Aplasia cutis congenita), milia, nail problems, sparse hair growth, pseudosyndactyly and other joint contractures.</p> |
| <b>Genetic Inheritance Pattern</b>                                        | Molecular genetic testing identifies JEB is linked to variants in genes which include COL17A1, ITGB4, LAMA3, LAMB3 or LAMC2. JEB is inherited in an autosomal recessive manner. The parents of an affected child are usually obligate heterozygotes (i.e., carriers).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | The most common JEB subtypes are due to pathogenic variants in the LAMA 3, LAMB3 and LAMC2 genes encoding the $\alpha 3$ , $\beta 3$ and $\gamma 2$ chains of laminin-332, as well                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

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|                                                         | <p>as COL17A1 gene, which encodes for type XVII collagen</p> <ul style="list-style-type: none"> <li>- Laminin-332 plays a critical role by linking basal keratinocytes to the basement membrane. At its <math>\alpha</math>-chain C-terminus, it interacts with <math>\alpha 3\beta 1</math> integrins in focal adhesion sites and <math>\alpha 6\beta 4</math> integrins in hemidesmosomes (HD). This connection ensures the structural integrity of the skin. In the dermis, the N-terminus of laminin-332 binds to type VII collagen, establishing direct links between anchor filaments and anchor fibrils. When laminin-332 expression is lost as in generalized severe JEB, the skin becomes extremely fragile and develops excess granulation tissue.</li> <li>- Type XVII collagen is encoded by COL17A1 on chromosome 10q24.3. Mutations in this gene can lead to either complete or partial loss of function of type XVII collagen, resulting in various skin-related conditions such as generalized or localized blistering. About 69% of COL17A1 gene variants are identified as nonsense variants, insertions or deletions, while 19% are missense variants and 12% are splice site variants. In some instances, nonsense mutations can lead to mild manifestations of moderate generalized JEB through alternative splicing mechanisms. While life expectancy is typically not affected, individuals with JEB caused by COL17A1 pathogenic variants often endure extensive blistering from trauma, slow wound healing over time, progressive irreversible hair loss and reduced quality of life.</li> </ul>                                                                                                                                                                                                                                                |
| <b>Current Treatments</b>                               | <p>Despite advancements, effective treatments for EB remain elusive. Management focuses on symptom relief, aiming to prevent flare-ups. The key principles include minimizing blistering, protecting the skin from trauma and preventing complications and infections through meticulous wound care using sterile, non-adhesive bandages.</p> <ul style="list-style-type: none"> <li>- Treatment of granulation tissue can be attempted with high-potency topical steroids, silver nitrate, electrocautery or autologous skin grafts.</li> </ul> <p>Oleogel-S10 (birch triterpenes) has been shown to improve wound healing</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Future Treatments anticipating genetic treatment</b> | <p><i>Ex-vivo</i> gene therapy. This therapy uses viral vectors to replace a missing gene product by isolating patients' cells and inserting a normal gene <i>in-vitro</i> followed by expansion of corrected cells into epidermal sheets and grafting these back onto wounds in patients. This method has been successfully utilized in three patients with junctional EB (JEB) who were carrying mutations in the LAMB3 gene, with a major challenge of identifying the keratinocyte stem cell for the gene therapy. One major hurdle is identifying the specific keratinocyte stem cell needed for the therapy. By targeting the holoclone stem cells, which possess superior self-renewal and proliferation abilities, positive outcomes were achieved without any long-term adverse effects during follow-up. <i>Ex-vivo</i> gene therapy has general drawbacks, such as the need for multiple biopsies to ensure proper stem cell isolation and extensive wound bed preparation through debridement to enhance successful engraftment.</p> <p>Cell-Based Strategy: Revertant Mosaicism (RM) is when a second mutation rescues an inherited mutation, creating a functional protein, acting as a natural gene therapy. This phenomenon is seen in all types of EB, especially intermediate JEB. Mechanisms include back mutations, second-site mutations, gene conversion and DNA repair errors. Detecting RM in the skin is possible through genomic DNA sequence analysis and immunohistochemistry. Exploiting this, healthy skin patches from RM can be expanded <i>in-vitro</i> to aid in healing affected areas.</p> <ul style="list-style-type: none"> <li>- <i>In-vitro</i> studies on protein replacement therapy involving LAMB3 have also shown promising outcomes. However, its effectiveness has not been confirmed in individuals with JEB.</li> </ul> |

- Transfer of GM see Table 1 Future treatments

**Table 20:** Junctional EB [45-47].

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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | <p>Dystrophic epidermolysis bullosa (DEB) is a subset of epidermolysis bullosa characterized by skin blistering. It encompasses several types based on inheritance and severity.</p> <ul style="list-style-type: none"> <li>- Recessive dystrophic epidermolysis bullosa severe generalized (RDEB-sev gen) is the severe, classic form of dystrophic EB, marked by widespread blistering and skin loss at birth, often due to birth trauma. Blisters commonly cover the entire body and mucous membranes.</li> </ul> <p>Additionally, people with RDEB-sev gen have a very high risk of developing a form of skin cancer called squamous cell carcinoma in young adulthood.</p> <ul style="list-style-type: none"> <li>- RDEB-generalized and localized (RDEB-gen and -loc) are less severe, affecting specific body regions like hands, elbows, knee and feet.</li> <li>- Dominant DEB (DDEB) is milder, with blistering primarily on extremities, healing with scarring but less severe than recessive forms. Nail abnormalities are common, potentially leading to nail loss over time.</li> </ul>                                                                                                                  |
| <b>Genetic Inheritance Pattern</b>                                        | <ul style="list-style-type: none"> <li>- Recessive dystrophic epidermolysis bullosa is inherited in an autosomal recessive pattern.</li> <li>- Dominant Dystrophic EB has an autosomal dominant pattern of inheritance.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | <ul style="list-style-type: none"> <li>- Mutations in the COL7A1 gene cause all types of dystrophic epidermolysis bullosa (DEB). This gene instructs the production of type VII collagen, a vital protein for skin strength. Type VII collagen forms anchoring fibrils, linking the epidermis to the dermis. Mutations in COL7A1 alter or disrupt type VII collagen production, leading to various DEB forms. Severe mutations cause RDEB-sev gen, while milder ones result in less severe forms. Abnormal or absent type VII collagen impairs anchoring fibril formation, causing skin layers to separate upon minor trauma, leading to blister formation and scarring during healing.</li> <li>- DEB blister fluids also display heightened levels of IL-8 and matrix metalloproteinase 9 (MMP9), a granular protease present in neutrophils. Moreover, recent findings indicate escalated MMP9 and cathepsin G activity in established and chronic RDEB wounds. These proteases, predominant in neutrophils, are associated with chronic non-healing wounds. Their mechanism involves the degradation of extracellular matrix components, potentially impeding effective wound closure in chronic cases.</li> </ul> |
| <b>Current Treatments</b>                                                 | <p>Most current treatments are supportive and focus on improving wound healing and symptoms.</p> <p>Oleogel-S10 (Betulae cortex), which is composed of 10% birch triterpene extract, has been used in patients to help increase wound healing though inducing keratinocyte migration and regulating inflammation.</p> <p>Vyjuvek (beremagene geperpavec-svdt) is a new medication for DEB that was approved in May, 2023. This novel medication is essentially genetically modified HSV-1 that is applied topically every week to wounds. This medication delivers normal copies of the gene COL7A-1 directly into wounds which is essential in maintaining the integrity of the skin.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

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| <b>Future Treatments anticipating genetic treatment</b> | Future research and treatments are aimed mainly at genetically altering the COL7A1 gene through gene replacement techniques, allele silencing, gene editing or exon skipping. Although there are current promising results in mice, there have not been many trials in humans yet. |
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**Table 21:** Dystrophic EB [48,49].

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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | Kindler Epidermolysis Bullosa (KEB) is the rarest of the 4 major epidermolysis bullosa types as there are only about 400 known cases worldwide. It is characterized by acral blister formation and skin fragility that begins at birth. Blistering can occur in any plane of the dermo-epidermal junction and is seen with various manifestations such as photosensitivity, diffuse cutaneous atrophy, palmoplantar hyperkeratosis, pseudosyndactyly, poikiloderma and mucosal complications. Photosensitivity is seen most prominent in childhood and decreases into adulthood. Common mucosal manifestations seen with KEB include gingivitis, premature tooth loss, periodontal disease, ectropion, phimosis, urethral stenosis and labial leukokeratosis. When KEB is chronic, squamous cell carcinomas can also develop. |
| <b>Genetic Inheritance Pattern</b>                                        | KEB is acquired in an autosomal recessive pattern.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | The FERMT1 gene produces a protein called kindlin-1 which is found in epithelial cells and keratinocytes. In this disease, there is a defect in FERMT1 which results in damaged kindlin-1 proteins. These faulty proteins result in altered cytoskeleton maintenance and integrin activation. In addition, the defective kindlin-1 proteins cause an increase in growth factors and cytokines which results in fibroblasts leading to scarring and fibrosis.                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Current Treatments</b>                                                 | Treatment for this condition involves a multidisciplinary team approach. Current treatments are aimed at symptom control. This includes antibiotics to cover infections, ointments and bandages to cover blisters, avoidance of trauma, moisturizers, sunscreen, artificial tears, regular dental care, esophageal dilation for those with dysphagia, circumcision for those with phimosis and more.                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Future Treatments anticipating genetic treatment</b>                   | As mentioned previously, there are novel treatments and research on epidermolysis bullosa overall and some of the specific types. Due to its rarity, we have not found any specific future treatments on Kindler epidermolysis bullosa but hope that more research comes out soon.<br><br>Transfer of GM see Table 1 Future treatments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

**Table 22:** Kindler EB [50,51].

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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | Hailey-Hailey disease is a rare, autosomal dominant genodermatosis characterized by recurring blistering and erosion of the skin. These blisters occur predominantly in the folds of skin (groin, armpits, breasts, etc). This condition is partnered with thickened dry scales, deterioration/softening/moistening of skin and growth of candida, yellow scale, pruritic/dotted blood vessels and white clouds separated by pink burrows. |
| <b>Genetic Inheritance Pattern</b>                                        | Rare autosomal dominant inherited disorder, occurring in about 1: 50 000 people, regardless of gender. It is inherited from a parent, with an estimated 50% risk of passing it on to any child. The disorder usually presents itself in ages 30 to 40.                                                                                                                                                                                     |



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| <b>Pathophysiology of Disease with molecular and genetic pathways</b> | A mutation in the ATP2C1, which is located on band 3q22.1 gene encoding calcium and manganese pump results in a loss of adhesion between keratinocytes of the epidermis. There are over 200 different mutations in the ATP2C1 gene that can cause HHD. The ATP2C1 gene produces hSPCA1, a protein that aids in the movement of calcium and magnesium within cells. These minerals are stored in the Golgi apparatus. When this protein malfunctions, cells lose their ability to adhere properly, leading to skin damage. Calcium regulates the proliferation of keratinocytes both <i>in-vivo</i> and <i>in-vitro</i> , explaining why ATP2C1 mutations affect the skin.                                                                |
| <b>Current Treatments</b>                                             | Current treatment involve Dermabrasion, Excision, Topical treatments. Systemically, glucocorticosteroids, antibiotics (erythromycin and tetracycline), retinoids and Electron-Beam Radiation Therapy (EBRT), are used to treat aggressive HHD. Avoiding triggers, keeping the affected areas dry, wearing loose-fitting clothing, avoiding sun exposure, applying cool compresses and using topical corticosteroid creams also helps alleviate mild symptoms of HHD.                                                                                                                                                                                                                                                                     |
| <b>Future Treatments anticipating genetic treatment</b>               | Laser (CO2 laser ablation breaks down and regenerates at a subcut. level) and (Fractional CO2 laser release unmutated adjacent cells to surface) is currently being studied with some good results. Counteracting oxidative-stress could be a viable therapeutic approach for HHD. Keratinocytes from HHD lesions exhibit higher oxidative stress lower expression levels of NOTCH1/NRF2. Both NOTCH1 and NRF2 aid in maintaining skin health. NOTCH controls keratinocyte growth and differentiation, while NRF2 directly regulates the transcription of antioxidant genes. Zoryve (roflumilast) 0.3% cream has been shown to be effective in a case report and further research needed<br>Transfer of GM see Table 1 Future treatments |

**Table 23:** Hailey-Hailey disease [52-55].

Group 5: Pigment Disorders (Table 24-26).

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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | reduced pigment of iris, reduced pigment of retina, transiris illumination, fundiscopic examination, foveal hypoplasia with significantly reduced visual acuity                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Genetic Inheritance Pattern</b>                                        | autosomal recessive                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | OCA Type 3: either homozygous nonsense mutation at codon 384 (deletion of 1 base pair) on the TYRP1 gene OR<br>OCA Type 4: biallelic variants (meaning either homozygous or compound heterozygosity); mostly missense mutations, but a small percentage of OCA type 4 cases are due to deletion of one or more bases/change of base on the SLC24A2 gene<br>OCA Type 5: specific genetic mutation has not been identified, but is on chromosome 4q24<br>OCA Type 6: compound heterozygosity for both a nonsense and frameshift mutation on the SLC24A5 gene<br>OCA Type 7: homozygous nonsense mutation on the LRMDA gene<br>OCA Type 8: homozygous missense mutation on the DCT gene |
| <b>Current Treatments</b>                                                 | symptom management (i.e. Correction of refractive errors and use of low vision                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

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|                                                         | aids; preferential seating in school; low-vision consultant as needed; UV-blocking sunglasses)                  |
| <b>Future Treatments anticipating genetic treatment</b> | genetic counseling, oral nitisinone, chemical chaperone therapy<br>Transfer of GM see Table 1 Future treatments |

**Table 24:** Oculocutaneous Albinism (OCA) [56-62].

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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | Localized areas of white depigmented skin (leukoderma) and hair (poliosis) along the ventral midline including the scalp, face, torso and extremities, which is usually present at birth.                                                                                                                                                                                                                                                                                                               |
| <b>Genetic Inheritance Pattern</b>                                        | Autosomal dominant                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | Mutations of the KIT proto-oncogene and SNAI2 gene; within KIT, a mutation on 4q12 will lead to abnormal melanocyte development of the ventral epidermis leading to depigmentation. Similarly, the same has been studied within the 8q11.21 locus with SNAI2.                                                                                                                                                                                                                                           |
| <b>Current Treatments</b>                                                 | - Split skin grafting<br>- Epidermal sheet grafting<br>- Autologous melanocyte transplantation                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Future Treatments anticipating genetic treatment</b>                   | This is a benign condition with treatment targeted at improving cosmetic concerns with make-up, grafting or cell transplantation. However, research has shown that there is correlation between the genetic mutations of the KIT gene with piebaldism and GIST and GIST is very susceptible to tyrosine receptor inhibitors with Imantib. Further research should be conducted to see if these therapies are beneficial to treating piebaldism as well.<br>Transfer of GM see Table 1 Future treatments |

**Table 25:** Piebaldism [63,64].

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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | -Distinctive facial abnormalities<br>-Diminished pigmentation of hair, skin, irises of both eyes<br>-Deafness present at birth                                                                                                                                            |
| <b>Genetic Inheritance Pattern</b>                                        | Typically autosomal dominant<br>However, some cases of Waardenburg Syndrome Type IV have an autosomal recessive pattern                                                                                                                                                   |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | Waardenburg Syndrome types I and III are linked to mutations to the PAX3 gene. Types II are linked to mutations to MITF or SNAI2 gene. The mutation to PAX3 and MITF are responsible for causing deafness. Type IV is linked to mutations in the SOX10, EDN3, EDNRB gene. |
| <b>Current Treatments</b>                                                 | -Genetic counseling<br>-Supportive treatment for hearing impairment with cochlear implants<br>-Sun protection for hypopigmented patches<br>-Surgery in case of association with Hirschsprung Disease                                                                      |
| <b>Future Treatments anticipating genetic treatment</b>                   | Although there aren't any curative treatments for pigment disorders, advancement in technology in tissue-engineered substitutes, genome editing, induced pluripotent stem cells, spheroids and extracellular vesicles shows promise for battling pigment                  |

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|  | disorders.<br>Transfer of GM see Table 1 Future treatments |
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**Table 26:** Waardenburg syndrome [65,66].

Group 6: Neurocutaneous Syndromes (Table 27-31).

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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | <ul style="list-style-type: none"> <li>- Definition: Neurofibromatosis 1 (NF1) is a disorder that impacts several bodily systems, characterized by abundant café au lait spots, freckling in skin creases, multiple neurofibromas on the skin, nerve tissues, including brain, spinal cord and peripheral nerves; and frequently associated with learning disabilities or behavioral issues</li> <li>- Neurofibromatosis 1 accounts for 96% of all cases.</li> <li>- Neurofibromatosis 1 presents with various clinical features affecting the musculoskeletal system such as sphenoid wing dysplasia/hypoplasia, scoliosis, pseudoarthrosis and long bone deformities. Additionally, it can impact the cardiovascular system, leading to conditions like hypertension, renal artery stenosis and pulmonary artery stenosis. Finally, it profoundly affects the central nervous system, elevating the chances of developing macrocephaly, epilepsy, autism, hydrocephalus, aqueductal stenosis and cerebral artery abnormalities</li> </ul>                                                                                                                                                                                                                                                |
| <b>Genetic Inheritance Pattern</b>                                        | <ul style="list-style-type: none"> <li>- Neurofibromatosis 1 (NF1) is an autosomal dominant inherited genetic disorder that is caused by point mutations located in the NF1 gene located on chromosome 17.</li> <li>- The severity of the mutation to the NF1 gene will determine the phenotype of the disorder.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | -When the NF1 gene is mutated, it causes overactivity of Ras (Ras-GTPase-activating protein), which in turn activates the AKT/mTOR and Raf/MEK/ERK pathways. The absence of functional neurofibromin protein, which normally regulates Ras activity negatively, leads to the growth of neurofibromas along the nerves throughout the body.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Current Treatments</b>                                                 | <ul style="list-style-type: none"> <li>-The current treatment approaches for neurofibromatosis type one are surgery to remove neurofibromas in severe cases, anti-ras medications that target downstream components of the Ras signaling pathway, such as MEK 1/2 and PI3K (phosphatidylinositol 3-kinase) pathway to inhibit the growth of neurofibromas</li> <li>-The anti-ras therapies block Ras-GTP (guanosine triphosphate) which is overproduced in neurofibromas Some of these agents are tipifarnib, pirfenidone, sirolimus, pegylated interferon alfa-2b and imatinib.</li> <li>-As well as blocking the downstream mTORC1 pathway which inhibits tumorigenesis using topical sirolimus 0.2-4% gel.</li> <li>-A small trial- pilot study was performed in Osaka, Japan treating cutaneous neurofibromas in neurofibromatosis type one patients using topical 0.2% and 0.4% gel twice a day for 24 weeks. The rationale for the use of this topical agent was to target the mTORC1 pathway and inhibit tumorigenesis.</li> <li>-Mitogen-activated protein kinase (MEK) 1 and 2 protein inhibitor Selumetinib is currently approved in pediatric patients with NF1 with symptomatic inoperable plexiform neurofibromas. MEK1/2 inhibitors block tumor growth. Other MEK</li> </ul> |

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|                                                         | inhibitors such as binimetinib, mirdametinib and trametinib and tyrosine kinase inhibitor cabozantinib are being researched as therapies for plexiform neurofibromatosis type 1. |
| <b>Future Treatments anticipating genetic treatment</b> |                                                                                                                                                                                  |

**Table 27:** Neurofibromatosis Type I [67-72].

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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | <ul style="list-style-type: none"> <li>- Definition: NF2-related schwannomatosis (NF2) is characterized by bilateral vestibular schwannomas and symptoms like tinnitus, hearing loss and balance issues.</li> <li>- In children, clinical findings may include schwannomas along the nervous system, skin plaques, meningiomas, cortical wedge cataracts, retinal hamartomas or mononeuropathy.</li> <li>- In adults, clinical findings might include bilateral or unilateral vestibular schwannoma along with cataract formation.</li> </ul> |
| <b>Genetic Inheritance Pattern</b>                                        | Autosomal dominant, NF2 gene located on chromosome 22                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | Neurofibromatosis Type 2 results from a mutation in the NF2 gene located on chromosome 22. The NF2 gene encodes for an important tumor suppressor gene that inhibits the development of tumors and when this gene is disrupted, there is no regulation resulting in the development of tumors                                                                                                                                                                                                                                                 |
| <b>Current Treatments</b>                                                 | <p>VEGF antibody bevacizumab for rapidly growing vestibular schwannomas; bevacizumab has also shown some clinical benefit in some individuals with ependymoma</p> <p>Treatment of vestibular schwannoma is primarily surgical; stereotactic radiosurgery</p>                                                                                                                                                                                                                                                                                  |
| <b>Future Treatments anticipating genetic treatment</b>                   | <p>1 Tyrosine kinase inhibitor brigatinib</p> <p>Transfer of GM see Table 1 Future treatments</p>                                                                                                                                                                                                                                                                                                                                                                                                                                             |

**Table 28:** Neurofibromatosis type II [73,74].

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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | <ul style="list-style-type: none"> <li>-Tuberous sclerosis complex (TSC) is a neurogenetic disorder that affects multiple organ systems, including the heart, kidneys, eyes, skin and central nervous system. Caused by a defective suppressor of the mTOR system, the TSC1/TSC2 complex</li> <li>-Many patients with TSC present clinically as a newborn or young child with either new-onset seizures or dermatologic manifestations</li> <li>Many children with TSC are afflicted by intractable epilepsy, intellectual disability and/or autism.</li> <li>-Neurologic manifestations - epilepsy, cortical tubers, subependymal nodules and giant cell astrocytomas, intellectual disability, autism spectrum disorder and behavioral problem</li> <li>Renal manifestations - angiomyolipoma, a hamartoma composed of blood vessels, smooth muscle and adipose tissue</li> <li>○ Dermatologic manifestations - hypomelanotic macules or ash-leaf spots, facial angiofibromas or adenoma sebaceum, fibrous plaques in the forehead (20%), shagreen patches in the lumbosacral region (20%) and ungual or gingival</li> </ul> |
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|                                                                       | <p>fibromas (20%)</p> <ul style="list-style-type: none"> <li>○ Cardiac manifestations - Intracardiac rhabdomyomas</li> <li>○ Pulmonary manifestations - LAM, Multifocal micronodular pneumocyte hyperplasia (MMPH)</li> <li>○ Ophthalmic manifestations - Retinal astrocytic hamartomas, retinal achromic patch</li> </ul>                                                                                                                                                                                                                                              |
| <b>Genetic Inheritance Pattern</b>                                    | <ul style="list-style-type: none"> <li>○ Autosomal dominant</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b> | <ul style="list-style-type: none"> <li>○ TSC1 and TSC2 form a complex that regulates the mTOR pathway</li> <li>○ Hyperactivation of mTOR signaling due to an inactivation of one of the <i>TSC</i> genes results in the disinhibition of the mTORC1 complex and leads to increased activation of the 4EBP1 and S6K1/2 downstream pathways, resulting in increased cell growth or and proliferation of benign tumors or hamartomas that can affect multiple organs, including the heart, eyes, kidneys, lungs, skin and brain.</li> </ul>                                |
| <b>Current Treatments</b>                                             | <ul style="list-style-type: none"> <li>○ everolimus, an mtor inhibitor, for treatment of partial seizures. It can also reduce facial angiofibromas, renal angiomyolipomas and Subependymal giant cell astrocytomas</li> <li>○ For infantile spasms-vigabatrin, surgery, ketogenic low glycemic index diet and vagal nerve stimulation.</li> <li>○ Topical tacrolimus with 0.2% sirolimus was shown to be effective in reducing facial angiofibromas in nine patients with tuberous sclerosis complex.</li> </ul>                                                        |
| <b>Future Treatments anticipating genetic treatment</b>               | <ul style="list-style-type: none"> <li>○ One exciting future direction for the treatment of mTORopathies is gene therapy, based on antisense oligonucleotides and clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9-based systems</li> <li>○ Recent data indicate that T cells within LAM nodules and renal angiomyolipomas exhibit features of T-cell exhaustion, with co inhibitory receptor programmed cell death protein 1 (PD-1) expression on tumor-infiltrating T cells</li> <li>○ Transfer of GM see Table 1 Future treatments</li> </ul> |

**Table 29:** Tuberous sclerosis complex [70,75-77].

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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | Ataxia telangiectasia, also known as Louis-Bar syndrome is an autosomal recessive inhibitory mutation on the ATM gene, which is characterized by cutaneous telangiectasias, cerebellar degeneration, immunodeficiency, recurrent sinopulmonary infections, radiation sensitivity and high malignancy.                                                                                                                                                                                                                                                  |
| <b>Genetic Inheritance Pattern</b>                                        | Autosomal recessive, mostly heterozygous nonsense mutations inherited.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | <ul style="list-style-type: none"> <li>- The ATM gene is a phosphatidylinositol 3-kinase which plays many roles in phosphorylating thousands of proteins in response to cell stress, most commonly double strand breaks.</li> <li>- ATM in response to oxidative stress: Increased reactive oxygen species</li> <li>- Normally, ATM is activated and signaled by the MRN protein complex at double strand breaks by a phosphorylation-acetylation cascade to begin a DNA damage response, where ATM phosphorylates the MRN protein complex.</li> </ul> |

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| <b>Current Treatments</b>                               | <ul style="list-style-type: none"> <li>- Immunoglobulin replacement, antioxidants, neuroprotective factors, growth and anti-inflammatory hormones</li> <li>- Antibiotics and anti-inflammatory treatments for sinopulmonary infections               <ul style="list-style-type: none"> <li>- Supplemental gamma globulins - for immunodeficiency</li> <li>- Amantadine, fluoxetine, buspirone to improve ataxia</li> </ul> </li> <li>- Gabapentin, clonazepam, propranolol to improve tremors               <ul style="list-style-type: none"> <li>- Trihexyphenidyl for dystonia</li> </ul> </li> <li>- Vitamin E and alpha-lipoic acid - improve mitochondrial function</li> </ul> |
| <b>Future Treatments anticipating genetic treatment</b> | <ul style="list-style-type: none"> <li>- Current intervention trials: Intra-erythrocyte dexamethasone (glucocorticoids), Nicotinamide riboside, gene therapy, Triheptanoin, N-Acetyl-L-Leucine               <ul style="list-style-type: none"> <li>- Antisense oligonucleotide (ASO) trial</li> </ul> </li> <li>- Bone marrow transplants - implanting functional ATM can increase immune efficiency</li> </ul> <p>Transfer of GM see Table 1 Future treatments</p>                                                                                                                                                                                                                  |

**Table 30:** Ataxia-telangiectasia (Louis-Bar Syndrome) [78-84].

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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | <p>In general, HHT manifests through presence of multiple arteriovenous malformations (AVMs). The most prevalent symptom is spontaneous and repetitive epistaxis which typically onsets on average at age 12 years.</p> <p>Telangiectases are typically present on the lips, tongue, face, fingers, buccal and GI mucosa. Though they can occur in childhood, telangiectases typically manifest later than epistaxis. Large AVMs typically develop in the brain, liver or lungs; bleeding or shunting issues can have an abrupt and fatal effect. Minority of the patients are diagnosed with GI bleeding specifically prior to age 50 years.</p> <p>Diagnosis is obtained through proband with at least three of the listed clinical characteristics: Epistaxis, mucocutaneous telangiectases, visceral AVMs and family history.</p> <p>In cases where clinical symptoms are not conclusive, the diagnosis is established by the identification of a heterozygous pathogenic mutation in ACVRL1, ENG or SMAD4.</p> |
| <b>Genetic Inheritance Pattern</b>                                        | <p>With significant intrafamilial variations, HHT is inherited autosomally dominantly. Most patients have a parent who is impacted. There is a 50% chance that each proband's child and the majority of probands' siblings will inherit the pathogenic mutation.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | <p>Heterozygous mutation of the activin-like receptor kinase 1 (ALK1), commonly referred to as ACVRL1 or the endoglin gene (ENG). Apart from these two genes, a subgroup of patients with HHT and juvenile polyposis (about 2% of cases) have been shown to have SMAD4 alteration. This illness is known as PJ-HHT syndrome and the main clinical symptoms of this disorder are juvenile polyps and anemia. HHT type 1 (HHT1) is caused by disruption of the ENG gene on chromosome 9, while HHT type 2 (HHT2) is caused by mutation of the ACVRL1 gene on chromosome 12. Other less commonly impacted genes are GDF2 and RASA-1. The main pathophysiology is also depicted in the figure in the page below.</p>                                                                                                                                                                                                                                                                                                    |
| <b>Current Treatments</b>                                                 | <p>Current treatments available for the disease are symptom dependent and aid in minimizing the symptoms.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

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|                                                         | <p>Epistaxis is treated using humidification, topical moisturizing therapy, hemostatics, antifibrinolytics, ablation therapy, systemic antiangiogenic drugs, septodermoplasty and nasal closure.</p> <p>Antiangiogenic drugs, iron replacement treatment and blood transfusions, if necessary, are used to treat GI bleeding and anemia.</p> <p>Occlusion is usually necessary for pulmonary AVMs with feeding vessels that are 1-2 mm in diameter or larger in order to prevent strokes.</p> <p>Medical treatment is used to treat symptomatic hepatic AVMs; liver transplantation is advised for patients who do not improve with medication or who experience high-output heart failure. Treatment options for cerebral AVMs include surgery, embolotherapy and/or stereotactic radiosurgery, depending on the size, location and symptoms of the tumor.</p> <p>Treatment recommendations for gastrointestinal polyps are based on those for juvenile polyposis syndrome.</p> |
| <b>Future Treatments anticipating genetic treatment</b> | <p>Drugs that are currently being studied are medications that either restore the disrupted BMP9/10 signaling pathway (Tacrolimus, Sirolimus) or treat the angiogenic abnormalities of HHT patients (Bevacizumab, tyrosine kinase inhibitors, PI3 Kinase inhibitors).</p> <p>Transfer of GM see Table 1 Future treatments</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

**Table 31:** Hereditary Hemorrhagic Telangiectasia (HHT) [85-87].

Group 7: Connective Tissue Disorders (Table 32-35).

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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | <ul style="list-style-type: none"> <li>• soft, velvety, doughy, hyperextensible, fragile skin <ul style="list-style-type: none"> <li>• atrophic and hemosiderotic scarring</li> <li>• generalized joint hypermobility (GJH)</li> </ul> </li> <li>• splitting of the dermis following relatively minor trauma: especially over pressure points (knees, elbows) and areas prone to trauma (shins, forehead, chin) <ul style="list-style-type: none"> <li>• poor wound healing</li> </ul> </li> <li>• mild muscle hypotonia w/ delayed motor development <ul style="list-style-type: none"> <li>• fatigue and muscle cramps</li> </ul> </li> <li>• some skeletal morphologic alterations (scoliosis, pectus deformities, genu valgus, pes planus) <ul style="list-style-type: none"> <li>• Molluscoid pseudotumors</li> <li>• Subcutaneous spheroids</li> <li>• Piezogenic papules</li> </ul> </li> <li>• Elastosis perforans serpiginosa <ul style="list-style-type: none"> <li>• Acrocyanosis</li> <li>• Chilblains</li> </ul> </li> </ul> |
| <b>Genetic Inheritance Pattern</b>                                        | <ul style="list-style-type: none"> <li>• autosomal dominant in subtypes: cEDS(classic), vEDS(vascular), hEDS(hypermobility), aEDS(athrochlasia), pEDS(periodontal) and variable in mEDS (myopathic)</li> <li>• autosomal recessive in subtypes: clEDS(classical-like), cvEDS (cardiac-valvular), dEDS (dermatosparaxis), kEDS(kyphoscoliotic), BCS (brittle cornea syndrome), spEDS (Spondylodysplastic), mcEDS (Musculocontractural) and variable in mEDS</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Pathophysiology of Disease with</b>                                    | <ul style="list-style-type: none"> <li>• Individuals with a molecularly confirmed diagnosis of TNXB-related classical-like</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |

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| <b>molecular and genetic pathways</b>                   | <p>Ehler-Danlos syndrome (eEDS) can have (1) intragenic pathogenic variants, (2) TNXB whole-gene or small deletions or (3) contiguous deletions of TNXB and CYP21A2.</p> <ul style="list-style-type: none"> <li>• vEDS caused by heterozygous pathogenic variant in COL1A1, COL5A1 or COL5A2</li> <li>• mutations in the COL3A1 gene, which encodes the pro-<math>\alpha</math>1 chain of type III procollagen, affecting approximately 1 in 50,000 to 250,000 people.</li> <li>• Genetic mutations that lead to disruption in type III procollagen are responsible for the varying phenotypes             <ul style="list-style-type: none"> <li>• Analysis revealed that ZIP13-KO cells demonstrate an impaired nuclear translocation of the transcription factor SMADs, responding to BMP and TGF-<math>\beta</math>2 necessary for connective tissue development.</li> <li>• An increase in zinc levels in the Golgi apparatus with a decrease in the nucleus was detected in Zip13-KO cells indicating a disruption in intracellular zinc homeostasis.</li> </ul> </li> <li>• aEDS caused by heterozygous mutations resulting in partial or complete loss of exon 6 of the COL1A1 (17q21.33) or COL1A2 (7q21.3) genes causing bilateral congenital hip dislocation, generalized joint hypermobility and hyperextensible and/or fragile skin</li> <li>• Biochemical analysis of lung tissue post-bullectomy in a vEDS patient compared to control lung fibroblasts found lower collagen III levels and less production of type III procollagen relative to type I fibroblasts. These lower levels of type III collagen in the lungs are hypothesized to predispose to increased tissue fragility and risk of pneumothorax</li> <li>• kEDS specific:             <ul style="list-style-type: none"> <li>• Normal collagen biosynthesis and secretion of collagen types I, III and V</li> <li>• Disarray of the main components of the extracellular matrix (collagen type I, III and VI; fibronectin; tenascins; thrombospondin)</li> <li>• Type V collagen is organized in an extracellular network that is similar to control fibroblasts.</li> <li>• Loss of the main receptors of collagens and fibronectin, <math>\alpha</math>2<math>\beta</math>1 and <math>\alpha</math>5<math>\beta</math>1 integrins.</li> </ul> </li> <li>• Marked enlargement of the ER cisterns with accumulation of flocculent material in skin cells of affected individuals by transmission electron microscopy</li> </ul> |
| <b>Current Treatments</b>                               | <ul style="list-style-type: none"> <li>• In an adult male with painful piezogenic (hEDS) x3 injections of a solution of equal parts betamethasone and bupivacaine over the course of 3 months were curative and effects were sustained over a 5-year course.</li> <li>• More recently, painful piezogenic pedal papules have been effectively treated via single injection lipolysis using deoxycholic acid (DCA).             <ul style="list-style-type: none"> <li>• Ascorbic acid has shown to help with wound healing, chronic bruising and hematoma formation in individuals as it is a collagen fibril cross-linking cofactor.</li> <li>• DDAVP may be useful to normalize bleeding time</li> <li>• Prolotherapy to reduce scar formation</li> </ul> </li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Future Treatments anticipating genetic treatment</b> | <ul style="list-style-type: none"> <li>• Therapeutic strategy for SCD-EDS can be achieved through restoring intracellular zinc homeostasis and the removal of mutant ZIP13 protein via the ubiquitin-proteasome pathway. VCP and HSP90 molecules are involved in the unfolding and transport of mutant ZIP13 to the proteasome.</li> <li>• Modification of chaperone inhibitors such as DBeQ and 17AAG to minimize cell toxicity can be an effective therapeutic strategy in the treatment of SCD-EDS</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |



Transfer of GM see Table 1 Future treatments

**Table 32:** Ehlers-Danlos syndrome [88-97].

|                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|---------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | connective tissue disorder, causing instability in support for organ systems mostly affecting skeletal, ocular and cardiovascular systems.<br>Most common symptom is enlargement of the aorta, which can lead to rupture.<br>- Bone overgrowth, craniofacial features, valve and lung abnormalities, muscle and fat hypoplasia                                                                                                                              |
| <b>Genetic Inheritance Pattern</b>                                        | Autosomal dominant                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | <i>FBN1</i> missense variants, insertions and deletions and variants associated with loss of expression from one allele lead to MFS and are demonstrated to result in decreased levels of fibrillin-1 <sup>47</sup> , which is secreted and incorporated into the extracellular matrix. Fibrillin-1 is a major component of extracellular matrix structures called microfibrils, which are found in tissues alone or closely associated with elastin fibers |
| <b>Current Treatments</b>                                                 | beta blockers, angiotensin receptor blockers (as an alternative to beta blockers), aortic treatment                                                                                                                                                                                                                                                                                                                                                         |
| <b>Future Treatments anticipating genetic treatment</b>                   | - Includes experimental treatments done on mice including beta blockers, doxycycline, angiotensin receptor blockers, calcium channel blockers<br>- Mostly includes clinical trials and mouse studies<br>“Currently, the $\beta$ -blocker atenolol is most commonly used to treat pediatric patients with MFS, while atenolol, metoprolol and bisoprolol are used in adult patients.”<br>Transfer of GM see Table 1 Future treatments                        |

**Table 33:** Marfan syndrome [98-100].

|                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | <ul style="list-style-type: none"> <li>• low bone mass</li> <li>• bone fragility causing significant morbidity due to pain             <ul style="list-style-type: none"> <li>• immobility</li> </ul> </li> <li>• skeletal deformities</li> <li>• growth deficiency</li> <li>• Decreased bone strength leads to low-trauma fractures or fractures in atypical locations (such as olecranon and vertebral compression fractures)</li> <li>• Extra-skeletal manifestations may include: dental anomalies, blue-gray sclera, hearing loss, joint hypermobility and more rarely muscle weakness, cardiovascular and pulmonary complications</li> </ul> |
| <b>Genetic Inheritance Pattern</b>                                        | <ul style="list-style-type: none"> <li>• 85–90% of cases associated with dominantly-inherited pathogenic variants in COL1A1 or COL1A2</li> <li>• remaining cases are caused by pathogenic variants in non-collagenous genes, encoding proteins involved in collagen biosynthesis or transcription factors and signaling molecules related to bone cell differentiation and mineralization and are associated with an autosomal recessive (most commonly), dominant or X-linked inheritance</li> </ul>                                                                                                                                              |
| <b>Pathophysiology of Disease with</b>                                    | • severity of COL1A1/COL1A2-related OI is largely dependent on the nature of type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

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| <b>molecular and genetic pathways</b>                   | <p>I collagen mutations.</p> <ul style="list-style-type: none"> <li>• Pathogenic variants that alter the structure of type I collagen are usually associated with a moderate to severe clinical phenotype, with severity generally associated with more carboxyl-terminal glycine substitutions and in glycine substitutions in COL1A1 more than COL1A2.</li> <li>• Pathogenic variants that cause haploinsufficiency result in decreased amount of a structurally normal collagen and typically are associated with milder clinical phenotype.</li> <li>• Pathogenic variants in genes that function in collagen biosynthesis (such as members of the prolyl-3 hydroxylase complex CRTAP, P3H1 and PPIB, the chaperone molecule FKBP10 and others) impact bone strength by disrupting the synthesis, post-translational modifications, intra-cellular trafficking, assembly and cross-linking of the collagen molecule and result in a moderate to severe OI phenotype</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Current Treatments</b>                               | <ul style="list-style-type: none"> <li>• nitrogen-containing bisphosphonates (Pamidronate, Alendronate, Risedronate and Zoledronic acid) are currently the mainstay of pharmacological care in pediatric patients with OI</li> <li>• Osteo-anabolic therapies [Teriparatide: is a parathyroid hormone analogue that was the first anabolic therapy approved for use in osteoporosis]</li> <li>• Anti-TGF<math>\beta</math> antibody: Anti-resorptive and anabolic treatments improve bone mass; however, they do not target the mechanistic basis of type I collagen and matrix abnormality that underlie the bone fragility in OI.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Future Treatments anticipating genetic treatment</b> | <ul style="list-style-type: none"> <li>• Abaloparatide (osteo-anabolic therapy) has demonstrated a potent effect on bone anabolic activity</li> <li>• Stem Cells Transplantation Mesenchymal stem cells (MSCs) are very promising for the treatment of bone diseases because of their ability to differentiate into cells such as osteoblasts, osteocytes and chondrocytes</li> <li>• Genetic Engineering: converting the severe type of OI based on structural defects in col I protein into a less severe quantitative form by silencing or inactivating the mutant gene, leading to allele suppression and haploinsufficiency [use of antisense oligodeoxyribonucleotides (ODNs), short interfering RNA (siRNA) and hammerhead ribozymes</li> <li>• Somatic Cells Reprogramming into iPSCs employing mouse embryonic or adult fibroblasts reprogrammed genetically to a pluripotent state due to transfection with Yamanaka factors, i.e., Oct3/4, Sox2, Klf4 and c-Myc (OSKM) or Thomson factors, i.e., Oct3/4, Sox2, Lin28a and Nanog (OSLN), using Sendai virus; Another way to reprogram somatic cells is the direct introduction of transcriptional factors (Yamanaka or Thomson factors) into cells in the protein form.</li> <li>• <i>In-vivo</i> delivery of Cas9-guide RNA complexes to repair abnormal genes has been successfully developed in murine models of autosomal dominantly inherited diseases <ul style="list-style-type: none"> <li>• Counteraction of ER Stress and UPR: use of the FDA-approved chemical chaperone 4-phenylbutyrate (4-PBA), which additionally exhibits histone deacetylase inhibitor activity, ameliorated cell homeostasis in fibroblasts from dominant and recessive OI patients</li> </ul> </li> </ul> <p>Transfer of GM see Table 1 Future treatments</p> |

**Table 34:** Osteogenesis imperfecta [101].

|                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
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| <b>Clinical Characteristic<br/>(Cutaneous/Systemic) with brief<br/>definition</b> | <ul style="list-style-type: none"> <li>• Skin:           <ul style="list-style-type: none"> <li>- Papules (darker than the skin color), usually seen on the lateral aspect of the neck or the flexural creases, such as the antecubital fossae, axillae, groin or popliteal fossae</li> <li>- Plaques formed by coalescence of papules</li> <li>- Loose, slack or droopy, redundant skin (especially of the neck, axilla and groin) that occurs with time</li> </ul> </li> <li>• Eye:           <ul style="list-style-type: none"> <li>- Peau d'orange generally appearing in the first decade and the late second decade, characterized by diffuse mottling of the fundus</li> <li>- Retinal angioid streaks often appearing in the second decade, consisting of broad grayish to reddish-brown irregular lines caused by breaks in Bruch's membrane* that appear to radiate outward from the optic disk or peripapillary region in a pattern that resembles blood vessels; hence the term "angioid"</li> <li>- Bruch's membrane is the elastin-rich tissue layer of the choroid between the retina and the choriocapillaris.</li> </ul> </li> <li>• Gastrointestinal bleeding, particularly the stomach. The characteristic yellow mucosal lesions of PXE can be seen on gastroscopy.</li> <li>• Vascular. Beginning in the second decade of life, almost all individuals with PXE develop intermittent claudication</li> </ul> |
| <b>Genetic Inheritance Pattern</b>                                                | autosomal recessive disorder with complete penetrance                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <b>Pathophysiology of Disease with<br/>molecular and genetic pathways</b>         | <ul style="list-style-type: none"> <li>• The majority of PXE patients harbor biallelic mutations in the ABCC6 gene, which encodes an efflux transporter protein ABC-binding cassette subfamily C, member 6 (ABCC6), expressed primarily in the liver and to a lesser extent in the proximal tubules in the kidneys [8,9].</li> <li>• ABCC6 is not expressed in tissues demonstrating ectopic mineralization or in the principal cells of such tissues, as for example dermal fibroblasts.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Current Treatments</b>                                                         | <ul style="list-style-type: none"> <li>• Pyrophosphate</li> <li>• Magnesium (limited and conflicting data)</li> <li>• TNAP inhibitor</li> <li>• Phosphate binders/SHPT (limited and conflicting data)</li> <li>• Vitamin K</li> <li>• Bisphosphonates</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Future Treatments anticipating<br/>genetic treatment</b>                       | Preclinical/Clinical trials: <ul style="list-style-type: none"> <li>• Sevelamer hydrochloride               <ul style="list-style-type: none"> <li>• Magnesium</li> <li>• Statins</li> </ul> </li> <li>• chaperone therapy; target/rationale: corrects the trafficking defects of misfolded ABCC6 protein               <ul style="list-style-type: none"> <li>• PTC-read through drug</li> <li>• Bisphosphonates</li> </ul> </li> <li>• PPI administration: Correction of reduced plasma PPI levels in PXE and GACI</li> <li>• ENPP1 protein replacement: ENPP1 is the principal enzyme that generates PPI               <ul style="list-style-type: none"> <li>• TNAP inhibitor: TNAP is the enzyme that breaks down PPI</li> </ul> </li> <li>• Gene therapy: ABCC6 gene therapy to reconstitute hepatic ABCC6               <ul style="list-style-type: none"> <li>• Aluminum hydroxide</li> </ul> </li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

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|  | <ul style="list-style-type: none"> <li>• VEGF antagonists: Bevacizumab and ranibizumab, inhibitors of vascular endothelial growth factor for the treatment of choroidal neovascularization; Aflibercept, an inhibitor of vascular endothelial growth factor for the treatment of choroidal neovascularization</li> <li>• Sevelamer hydrochloride</li> <li>• Sodium thiosulfate</li> </ul> <p>Transfer of GM see Table 1 Future treatments</p> |
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**Table 35:** Pseudoxanthoma elasticum [102-104].

*Group 8. X-Linked Dominant Disorders (Table 36-39).*

|                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | <ul style="list-style-type: none"> <li>• numerous basal cell carcinomas (BCCs)</li> <li>• skeletal, ophthalmic and neurological abnormalities</li> <li>• Congenital patchy skin aplasia. Atrophic and hypoplastic areas of skin that often follow the lines of Blaschko and appear as depressed regions of pink or white color, often with a fibrous texture</li> <li>• Congenital skin hypo- or hyperpigmentation often following a Blaschko linear distribution             <ul style="list-style-type: none"> <li>• Telangiectasias. May be seen on the face, trunk and extremities</li> </ul> </li> <li>• Congenital nodular fat herniation. Soft, yellow-pink nodules on the skin (which represent fat nodules in the dermis) typically seen on the trunk and extremities             <ul style="list-style-type: none"> <li>• Congenital ridged, dysplastic or hypoplastic nails</li> <li>• Syndactyly occurring variably on one or more extremities</li> </ul> </li> <li>• Ectrodactyly. Split-hand/foot malformation that may occur on <math>\geq 1</math> extremity</li> <li>• Oligodactyly. Absent digit(s) may be seen in one or both hands and/or feet. Central digits are more frequently involved.</li> <li>• Long bone reduction defect. Hypoplasia or shortening of the long bones in one or more extremities</li> <li>• Transverse limb defect. Congenital absence of the distal portion of an upper and/or lower limb (e.g., hand, wrist, forearm, elbow) with no distal remaining portions, including acheiria or hemimelia</li> </ul> |
| <b>Genetic Inheritance Pattern</b>                                        | <ul style="list-style-type: none"> <li>• PORCN-related developmental disorders are inherited in an X-linked manner.</li> <li>• Females account for 90% of individuals with PORCN-related developmental disorders; they may have heterozygous or mosaic pathogenic variants in PORCN</li> <li>• Males account for 10% of individuals with PORCN-related developmental disorders</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | <p>caused by mutations in the protein patched homolog 1 (PTCH1) gene that codes for a transmembrane receptor, which recognizes the sonic hedgehog (SHH) signaling protein.</p> <p>Loss of function of PORCN. PORCN encodes protein-serine O-palmitoleoyltransferase porcupine (PORCN), a protein expressed in a wide variety of tissues that palmitoylates various Wnt proteins. Wnt proteins are important secreted morphogens that interact with receptors and coreceptors on target cells. Activation of the Wnt pathway is important for normal development and may be required to activate additional non-canonical Wnt signaling</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Current Treatments</b>                                                 | <ul style="list-style-type: none"> <li>• vismodegib(Erivedge®) has been the first Hh pathway inhibitor approved by FDA</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

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|                                                         | <p>for BCC. Structurally unrelated to cyclopamine, a natural alkaloid steroid and the first molecule known to act as a Hh pathway inhibitor, it binds with high affinity and specificity to SMO, producing a strong inhibitor effect on the Hh pathway.</p> <ul style="list-style-type: none"> <li>• sonidegib (Odomzo®), which interacts with a SMO pocket preventing downstream activation of Hh pathway signaling, so exerting an antagonistic activity</li> <li>• Regarding BCCs, treatment with surgical excision is the gold standard, Mohs micrographic surgery is preferred</li> <li>• Radiotherapy is relatively contraindicated in patients with BCNS, owing to the increased risk of BCCs in the irradiated area</li> <li>• vismodegib and sonidegib, may be indicated in advanced BCC and multiple BCCs</li> <li>• benign abnormalities such as palmoplantar pits, basaloid follicular hamatomas, facial milia and epidermoid cysts do not need treatment</li> </ul> |
| <b>Future Treatments anticipating genetic treatment</b> | - Transfer of GM see Table 1 Future treatments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

**Table 36:** Focal Dermal Hypoplasia (Goltz Syndrome) [105-108].

|                                                                           |                                                                                                                                                                                                                                                               |
|---------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | IP is characterized by lesions in Blaschkoid distribution that range from erythematous, verrucous and hypopigmented to hyperpigmented skin lesions; hair loss, small/missing teeth and abnormalities in fingernails, toenails and eyes                        |
| <b>Genetic Inheritance Pattern</b>                                        | X-linked dominant                                                                                                                                                                                                                                             |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | NF-κB signaling pathway, involving the IKBKG gene encoding NEMO protein                                                                                                                                                                                       |
| <b>Current Treatments</b>                                                 | Skin tx: topical or systemic steroids and/or topical calcineurin inhibitors, retinoids. Dental tx: may involve interim dentures, prosthodontic treatment and orthodontic rehabilitation. Eye tx: may involve argon laser and repeated laser photocoagulations |
| <b>Future Treatments anticipating genetic treatment</b>                   | Clinical treatment involving identifying possible early immunosuppressants to reduce inflammatory markers as a potential treatment strategy to reduce disability leading (ex: retinal and cerebral ischemia)                                                  |

**Table 37:** Incontinentia Pigmenti (IP) [109,110].

|                                                                           |                                                                                                                                                                |
|---------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | CHILD is characterized by unilateral erythematous skin plaque with a midline demarcation from birth; also musculoskeletal problems like hypoplasia to agenesis |
| <b>Genetic Inheritance Pattern</b>                                        | X-linked dominant                                                                                                                                              |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | NSDHL gene encoding the NAD(P)H steroid dehydrogenase-like protein                                                                                             |
| <b>Current Treatments</b>                                                 | systemic retinoids, which can cause dose dependent adverse events                                                                                              |
| <b>Future Treatments anticipating genetic treatment</b>                   | topical isotretinoin ointment formulation to treat congenital ichthyosis (formulation PAT-001 is patented for this use)                                        |

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|  | Transfer of GM see Table 1 Future treatments |
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**Table 38:** CHILD (Congenital Hemidysplasia with Ichthyosiform Erythroderma and limb defects) [109,111].

|                                                                           |                                                                                                                                                                                                                                                                                                                                                                                       |
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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | The Gondradi-Hunermann type (Chondrodysplasia type II) is caused by mutations in the EBP gene. Patients have a short stature, low nasal bridge and skin lesions. The Rhizomelic form (Chondrodysplasia type I) is characterized by short stature, flattened nose, short extremities, cataracts, ichthyosis and nasal hypoplasia.                                                      |
| <b>Genetic Inheritance Pattern</b>                                        | X-linked dominant, X-linked dominant                                                                                                                                                                                                                                                                                                                                                  |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | Gondradi-Hunermann type is caused by mutations in the EBP gene<br>Rhizomelic form is caused by mutations in the PEX7 gene                                                                                                                                                                                                                                                             |
| <b>Current Treatments</b>                                                 | Gondradi-Hunerman- Treatment of respiratory difficulty as per ENT and/or pulmonologist, reconstructive surgery in older individuals with severe maxillary hypoplasia or maxillary retrognathia, cervical collar, spinal fusion and decompression for cervical spine stenosis, hearing aids and pressure equalization tubes,<br>Rhizomelic- Patients will rarely survive past infancy. |
| <b>Future Treatments anticipating genetic treatment</b>                   | -Transfer of genetic materials by introducing healthy copies of the defective genes through retroviruses or using tools to directly edit the faulty genes & repair them.                                                                                                                                                                                                              |

**Table 39:** Chondrodysplasia punctata [112,113].

*Ectodermal Dysplasia* (Table 40-43).

|                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                               |
|---------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | Affects skin, hair, nails, sweat glands and teeth.<br>Hypotrichosis, hypohidrosis (partial or total eccrine sweat gland deficiency), hypopigmented soft skin, sunken cheeks, saddle nose, frontal protrusion, prominent supraorbital crests, periorbital hyperpigmentation, low set ears, dysplastic nails, everted lips, prominent chin, sparse and patchy hair, low facial height with the lower third of the face reduced  |
| <b>Genetic Inheritance Pattern</b>                                        | X-linked HED, Autosomal recessive HED, Autosomal dominant HED                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | EDA/NFKappaB pathway involving genes EDA, EDAR, EDARADD, WNT10A                                                                                                                                                                                                                                                                                                                                                               |
| <b>Current Treatments</b>                                                 | Wigs, skin/hair products for eczema and dry skin, lubricating eye drops. Dental care such as bonding of conical teeth and/or orthodontics/dental implants. Dietary counseling to address chewing or swallowing difficulties, fluoride treatments. Management with PCP, allergist and/or pulmonologist for treatment of recurrent respiratory infections and asthma, Otolaryngologist for nasal secretions. Genetic counseling |
| <b>Future Treatments anticipating genetic treatment</b>                   | Ectodysplasin A (EDA) replacement protein<br>Transfer of GM see Table 1 Future treatments                                                                                                                                                                                                                                                                                                                                     |

**Table 40:** Hypohidrotic ectodermal dysplasia [114-116].

|                                                                           |                                                                                                                                                                                                                                                                                                                              |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | Susceptible to infections such as mycobacteria, pyogenic bacteria and herpesviruses due to the vital role NF- $\kappa$ B signaling plays in both innate and adaptive immunity. Immunologic phenotype varies and is highly mutation dependent. HED-ID often has ectodermal dysplasia, osteoclast abnormalities and lymphedema |
| <b>Genetic Inheritance Pattern</b>                                        | x-linked HED-ID, autosomal HED-ID                                                                                                                                                                                                                                                                                            |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | Hypomorphic mutations of the nuclear factor-kappa beta essential modulator NF- $\kappa$ B essential modulator (NEMO) gene encoded by the X-linked (I $\kappa$ B)-kinase (IKBKG) gene, result in HED with immunodeficiency                                                                                                    |
| <b>Current Treatments</b>                                                 | Intravenous immunoglobulin, prophylactic antibiotics, bone marrow transplantation. Immunologic screening                                                                                                                                                                                                                     |
| <b>Future Treatments anticipating genetic treatment</b>                   | Transfer of GM see Table 1 Future treatments                                                                                                                                                                                                                                                                                 |

**Table 41:** Hypohidrotic Ectodermal Dysplasia with immune deficiency [117,118].

|                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| <b>Clinical Characteristic (Cutaneous/Systemic) with brief definition</b> | (Hypotrichosis) partial-to-complete alopecia, nail dystrophy and palmoplantar hyperkeratosis. Usually no dental anomalies and sweating is preserved. The scalp hair is sparse, pale, fine and brittle or may be completely absent. The eyebrows are sparse or absent. The eyelashes are short and sparse. Axillary and pubic hair is sparse or absent.<br>Palmoplantar keratosis not seen in all people with HED2<br>Clubbing of fingers<br>Hyperpigmentation of skin(especially over joints) |
| <b>Genetic Inheritance Pattern</b>                                        | HED2 is inherited in an autosomal dominant manner. Most individuals with HED2 have an affected parent                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b>     | When Gap junction beta-6 protein , GJB2, is mutated, result in defective trafficking of other gap junction proteins<br>The diagnosis of HED2 is established in a proband with suggestive findings and a heterozygous pathogenic variant in GJB6 identified by molecular genetic testing. Targeted analysis for the four most common GJB6 pathogenic variants detects pathogenic variants in approximately 100% of affected individuals.                                                       |
| <b>Current Treatments</b>                                                 | Dystrophic nails: filling and drilling hyperkeratotic nails, artificial nails<br>Hypotrichosis:conditioning hair care products, wigs/weaves, eyebrow tattoo, artificial hair fibers<br>Palmoplantar hyperkeratosis: skin emollients to soften skin, keratolytic preparations, regular filing and paring of hard skin                                                                                                                                                                          |
| <b>Future Treatments anticipating genetic treatment</b>                   | Transfer of GM see Table 1 Future treatments                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

**Table 42:** Hidrotic ectodermal dysplasia [119].

|                                                                |                                   |
|----------------------------------------------------------------|-----------------------------------|
| <b>Clinical Characteristic (Cutaneous/Systemic) with brief</b> | -ADULT syndrome<br>-EEC3 syndrome |
|----------------------------------------------------------------|-----------------------------------|

|                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>definition</b>                                                     | <p>-AEC (Hay-wells) syndrome<br/>-Limb-mammary syndrome<br/>-orofacial cleft 8</p> <p>Adult Syndrome: chronic tearing, congenital atresia, obstruction of lacrimal ducts, sparse hair on scalp/axilla, onychodysplasia, hypodontia, hypoplastic nipples, breast hypoplasia</p> <p>EEC3 syndrome: ectrodactyly, ectodermal dysplasia, cleft lip/palate</p> <p>AEC (Hay wells) syndrome: alopecia, scalp infections, dystrophic nails, hypodontia, anklyoblepharon, cleft lip/palate</p> <p>Limb mammary syndrome: absence/severe hypoplasia of limbs, polydactyly, syndactyly, symphalangia, breast hypoplasia</p> <p>Orofacial cleft 8 syndrome: unilateral/bilateral cleft lip</p>                                                                                                                                                                                                                                                                                                                   |
| <b>Genetic Inheritance Pattern</b>                                    | Autosomal dominant                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Pathophysiology of Disease with molecular and genetic pathways</b> | <p>ADULT syndrome: pathogenic mutation of TP63 gene which under normal circumstances creates tumor protein 63 which aids in regulating cell proliferation, cell maintenance, cell differentiation, cell adhesion and apoptosis.</p> <p>EEC3 syndrome: pathogenic mutation in the 3q28 chromosome within the TP63 gene which affects the ectodermal and mesodermal tissues to produce a spectrum of phenotypes</p> <p>AEC (hay wells) syndrome: pathogenic mutations in the p63 gene that causes missense mutations that result in amino acid substitutions in the sterile alpha motif (SAM) domains and further impact protein-protein interactions</p> <p>Limb mammary syndrome: Pathogenic mutation of TP63 gene in the 3-cM interval of chromosome 3q27 which results in cleft lip palate and mammary nipple aplasia or hypoplasia</p> <p>Orofacial cleft 8 syndrome: heterozygosity missense mutation for 2-bp duplication in TP63 gene resulting in unilateral or bilateral cleft lip palate</p> |
| <b>Current Treatments</b>                                             | APR246/PRIMA-1 MET: reactivates p53 mutants used in cancer treatment, but due to the high homogeneity of the p53 and p63 genes, it is utilized for p63 mutations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Future Treatments anticipating genetic treatment</b>               | <p>PhiKan083 and CP-31398: other drugs that target cancers due to mutations of p53 gene, but have not been tested for diseases secondary to p63 gene mutations</p> <p>Transfer of GM see Table 1 Future treatments</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

**Table 43:** Tumor protein p63-related disorders [120-124].

## Discussion

The above genodermatoses have multiple newly discovered intricate genetic pathways. There have been significant headways in understanding these pathways and their respective drug development. The inhibition of the mTOR pathway with neurofibromatosis and tuberous sclerosis has been a game changer. The use of topical sirolimus inhibiting the mTOR pathway has demonstrated a non-invasive significant advancement in treatment of these diseases with reduction of the plexiform neurofibromas in neurofibromatosis-1 in a matter of months. Both topical sirolimus and/or combination with tacrolimus appear to reduce the angiofibromas in tuberous sclerosis [78].

With regard to disorders of keratinization, in particular Netherton syndrome, the novel use of biologics particularly IL17A antagonist, secukinumab, IL12/23 antagonist, ustekinumab, IL4/IL13 antagonist dupilumab, TNF alpha inhibitor, infliximab have shown promise in treating this disorder [27]. We anticipate that the proliferation of these biologics will be used for many disorders of keratinization once more specific pathways are discovered.



Among blistering disorders, another significant advancement for dystrophic EB is Vyjuvek (beremagene geperpavec-svdt). This novel medication is a genetically modified HSV-1 that delivers normal copies of the gene COL7A-1 directly into wounds allowing for improved wound healing [49]. Prior to this discovery, other methodologies used to transfer genetic material have been attempted in autosomal recessive congenital ichthyosis. Researchers used the modified HSV-1 carrying wild type gene caring COL7A-1 for RDEB or TGM-1 for autosomal recessive ichthyosis vulgaris. The topical delivery in phase 1 *in-vivo* trials were encouraging, however, the maintenance of the therapeutic genes in the recipient's own cells were short lived due to inadequate integration of the HSV vector. The researchers had to use multiple applications of the HSV vector in the *in-vivo* gene therapy to achieve any clinical results. This mode of topically applied vectors was difficult as the keratinocyte stem cells were found in the lowest level of the epidermis. It appears that other more fastidious viral vectors will need to be developed that can enter the immortal stem cell [125].

CRISPR fractures a target in the DNA and relies on other proteins to insert a newer DNA sequence. This process could lead to more errors. CRISPR technology has been an incredible discovery that has been able to help us in improving genetic sequences in agriculture and particularly help find the cure of sickle cell disease [126,127]. Dr Sandro Ataide at Sydney University was able to develop the SeekRNA technology which delivers a newer pathway for precision gene editing [128]. This technique uses a programmable RNA strand that can pointedly determine where the sites are for inserting preferred genetic sequences. Due to its accuracy it will revolutionize gene editing by simplifying the process and reducing sequencing errors. The SeekRNA came from a family of naturally occurring insertion sequences (IS) IS1111 and IS110 that were found in bacteria and archaea. Multiple researchers have been working on insertion sequence proteins but they did not demonstrate target selectivity. The insertion sequences, IS1111 and IS110, selectively insert genetic sequences with high precision. SeekRNA is a small protein that has 150 amino acids and 75-100 nucleotides. This small size is packed into a biological delivery system using nanoscale vesicles to deliver the preferred genetic package. A very unique feature of SeekRNA is that it has the ability to insert DNA sequences into the target solely by itself without the use of additional proteins. These authors anticipate this technology improving genetic engineering and improving the possibility of curing these conditions with the transfer of genetic material [128].

## Conclusion

It is quite obvious that we are on the cusp of curing the genodermatoses. It will be a matter of research resources committed painstakingly to block or enhance aberrant genetic pathways to alleviate human suffering associated with these genodermatoses. One theme that is threaded throughout the genodermatoses is genetic abnormalities that hinge upon defective suppressor genes. These suppressor genes are not functioning and allow their respective genodermatoses to develop. Unfortunately, current therapies seem to be targeting the end symptoms of the conditions and not the root cause. We have a great understanding of the pathways down to the molecular level. We have the genetic technology to block these pathways and reinforce the faulty suppressor genes via CRISPR-based genome editing and seekRNA. SeekRNA has recently been developed that allows for precise, efficient genetic engineering that decreases the chance of unintended mutations. We look forward to the golden age of medicine where these conditions will be alleviated.

## Conflict of Interests

The authors declare no conflict of interest regarding authorship roles or publication of article.

## Consent

Not applicable because this study is based exclusively on published literature.

## Disclosure

The authors report no conflicts of interest.

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## Authors Contribution

All the authors have equal contribution and all the authors have read and agreed to the published version of the manuscript.

## Data Availability

Not applicable

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