Specific Operationnal Criteria - Ectodermal Dysplasia (ED) including Skin Fragility Disorders & X-linked cutaneous disorders & unclassified disorders

The requested information will be used to define the specific criteria for our project proposal for a European Reference Network (ERN) for Rare and Undiagnosed Skin Disorders. Please note that, each health care provider member of our ERN will have to fulfil these criteria. These criteria have to be realistic/reasonable while ensuring a high level patient management. These criteria have to be based on the evidence and consensus of the scientific, technical and professional community.

NB: A sample of healthcare providers will be selected for on-site audits to validate the information.

Ectodermal Dysplasia (ED) including Skin Fragility Disorders & X-linked cutaneous disorders & unclassified disorders

Rare Diseases(s)	Short description of the rare disease	Code/ ICD/ Orphacode	Epidemiology	Incidence	Prevalence
1.Incontinentia Pigmenti	Genodermatosis affecting neuroecodermal tissue at differnt levels	464	!!00 cases reported in the literature	0,7/100 000	0,7/100 000
Ectodermal dysplasia (ED)	Genodermatosischaracterized by the involvmeent of 2 of the following ectodermal derivates : teeth, nail, sweat glands and hair	79373		1/50 000	1-9/100 000
ED Hypohidrotic/anhidrotic from	Reduction or absence of sweating	248/1810/238468/50944/181			
ED with PPK (Clouston, Papillon-Lefevre, Desmosomal diseases)	Association of ED and palmo-plantar Keratoderma.	189/34217/678			
ED with extracutaneous anomalies (Clefts…, Papillon-Lefevre)	Association of ED and Clefts, genito-urinary malformations….)	320317/1896/3022			

Rare Diseases(s)	Specific challenges associated with the recognition of the condition	Specific challenges associated with the diagnosis	Specific challenges associated with the treatment	Specific challenges associated with care of these patients over their lifespan - Quality of life issues - Gaps accross the care continuum

1.Incontinentia Pigmenti	High frequence of sporadic case (65%), male cases, Highly heterogenous clinical presentation		No specific treatment	Few data on follow up in adult
Ectodermal dysplasia (ED)				Specific adults concerns remain unknown
ED Hypohidrotic/anhidrotic from	Genetic and molecular Heterogeneity. At least 4 involved genes	Detection of the hereozygous carriers and the female cariers (X-linked form)	Hypodontia and Oligodontia needs experts in orodental treatment	Few follow-up at adulthood
ED with PPK (Clouston, Papillon-Lefevre, Desmosomal diseases)	Genetic and molecular challenging diagnosis.	Major cardiac risks for desmosomal diseases (early cardiomyopathy with high risk of sudden death	Pluridisciplianry approach: Dentists, ENT specialists, Cardiologists, Surgeons are mandatory	Few follow-up at adulthood
ED with extracutaneous anomalies (Clefts, ano-genito-urinary anomalies)	Clinical heterogeneity	Possible surgical treatment of extracutaenous mainefestations. High risk of definitive alopecia	Pluridisciplianry approach: Dentists, ENT specialists, Cardiologists, Surgeons are mandatory	Few follow-up at adulthood

Rare Diseases(s)	**Key Diagnostic Tests**	**Key Treatment, Resources or Procedures**
1.Incontinetia Pigmenti	The diagnosis can be performed by a dermatologist based on the presence of cutaneous manifestation. Skin biopsy is highly infomative. The genetic testing can be in convention with other centers; it include Long range PCR, exon sequencing, quantitative PCR. Clinical diagnosis. Connexion with Laboratories of molecular diagnosis are highly suggested	Skin treatment, BBMRI recognized biobank, DATABASE MUTATIONS web site [http://databases.lovd.nl/shared/genes/IKBKG]
Ectodermal dysplasia (ED)		oro-dental management

ED Hypohidrotic/anhidrotic form	NGS sequencing of the four major genes	oro-dental management, dermatological, ENT and ocular care
ED with PPK (Clouston, Papillon-	NGS sequencing (at least 3 major genes for desmosomal diseases), urinary testing (for paillon-Lefevre syndrome)	PPK, dental and dermatological care
ED with extracutaneous anomalies	Gene sequencing	Surgical, dental, dermatological care

Please state the minimum/optimum thresholds that Healthcare Providers within the network will need to meet to maintain competence and expertise. List the measure, threshold, and rationale for this threshold

Rare Diseases(s)	**Minimum Number of patients treated per year at each HCP**			**Minimum Number of new patients diagnosed per year at each HCP**	
	Adults	Paediatric*	Rationale for the threshold	Adults	Paediatric*
1.Incontinentia Pigmenti	3	6	The diagnosis is currently done in infancy	2	3
Ectodermal dysplasia (ED)	6	10	The diagnosis is currently done in infancy	2	5
ED Hypohidrotic/anhidrotic from	5	6	The diagnosis is currently done in infancy		
ED with PPK (Clouston, Papillon-Lefevre, Desmosomal diseases)	1	3	The diagnosis is currently done in infancy		

ED with extracutaneous anomalies (Clefts, Ano-genito-urinary anomalies)	4	1	The diagnosis is currently done in infancy		

Please list the necessary human resources and the profesional qualifications essential to the quality of patient care within the Network's area of expertise.

Rare Diseases(s)	**Health Care Professional (type)**	**Training & Qualifications**	**Minimun of number of procedures per patient per year**	**Rationale**
1.Incontinetia Pigmenti	Dermatologist, Ophtalmologist, Odontologist, Neurologist, Human geneticist	MD, PhD	Five	Multidisciplinary care: clinical analysis of Skin and appendages, teeth, Eye, brain examination. Genetic evaluation of NEMO gene only, analysis trough three sequential steps. Important: 65% cases sporadic
2.Ectodermal dispalsya	Dermatologist, Ophtalmologist, Odontologist, ENT specialist, Neurologist, Human geneticist, Surgeons, Nurses, Physiotherapist,	MD, PhD	4	Multidisciplinary care: clinical analysis of Skin and appendages, teeth, Eye, . Genetic Testing through NGS of the involved genes.

Please list the specialised equipment, infrastructure, and information technology required to support the rare or complex disease(s), condition(s) or highly specialised intervention(s) and describe the importance of each

Rare Diseases(s)	**Specialised equipment, infrastructure, and information technology**	**Threshold**	**Rationale**

1. Incontinentia Pigmenti	Brain examination MRI and MRA, retinal examination. Genetic diagnosis: PCR, Quantitive PCR, next generation sequencing		Clinical analysis of skin and appendages: Skin analysis, presence of four stages, skin biopsy; teeth, Hair presence of atrophíc, scarring baldness, patches of wiry or unruly hair Fingernails presence of ridged or otherwise nisshappen painful subungual tumors; Sweat pores presence of palms and fingers; Nipples presence of more than two nipples Required Eye examination: Strabismus, Cataract , Optic atrophy, Retrolental mass, Mícrophthalmos, Macular/perípheral retínal ischemia, Retinal neovascularizalion, Retinal detachment, Vitreous hernorrhage, Coniunctival pigmentation, Iris pígmentation A baseline MRI and MRA with and without contrast are highly suggested. For infants this is recommended to be completed at age 3-6 months old. Learning Disabilities evaluation at school age or before. A neuro psychological exam to be completed so schools will implement the appropriate assistance for child. Genetic analysis of NEMO/IKBKG:
Ectodermal dysplasia (ED)	Ocular, ENT, dermatologicaland dental examination.. Genetic Testing (Next generation sequencing). Possible of regulation of temperature of outpatient consultation. X-ray dental count.	At least Dental specialist for children	1- Dermatological Examination : nails (number, structure, aspect), hair of the scalp (sparse, absent) and the whole body (eyelids, eyelashes…), sweating (at least quantitative evaluation, intolerance to heat, skin dryness), PPK, nipples anomalies.2- ENT anomalies (nasal dryness, occlusive rhinitis), ocular anomalies (corneal dryness, ulcers, photophobia). Ano-genito-urinary anomalies. Morphological anomalies are conduct according the clinical findings.

Please provide a summary explaining the approach or plans your group will undertake to produce good practice guidelines and implement outcome measure and quality controls
Incontinentia pigmenti (IP; OMIM#308300) is a rare multisystem genomic disorder (0.7/100.000), X-linked and lethal in males, affecting the skin and other ectodermal tissues including the teeth, hair, nails, eyes, and Central Nervous System (CNS) in females. Beside the skin lesions that are always present in IP, other tissues can be differently affected and the most severe effect of the disease are those related to neurological and/or ocular impairment. In most patients, cutaneous manifestations are present at birth or occur within the first 2 weeks of life. The cutaneous manifestations usually appear in a characteristic, chronologic sequence. Other systemic manifestations, including ocular defects, CNS abnormalities, and dental abnormalities, may not be recognized until infancy or early childhood. Investigations and diagnostic evaulation are necessary for the phenotypic characterization of IP patient. Each tissue survey is related to early identification of damage due to pathology that if early detected can be treated. To implement good practice we aim: 1) to made availability of clinical and molecular diagnosis through Europe; 2) to establish the State of the art in European countries; 3) to establish health care standard and teaching related to compatible schemes/protocols; 4) to improve Patient Education, Patient registry/biobank and the use a diagnostic algorithm for clinical management.

Ectodermal dysplasias (ED) are a large group of diseases characterized by the involvement of at least two of the four ectodermal following derivates: nails, teeth, hair and sweat glands. More than 200 diseases belong to this group of diseases. Ectodermal dysplasias are divided in two groups: Pure ED involving the ectodermal derivates only and syndromic ED in which other organs might be involved such as breast (nipples and ductal growth and branching anomalies), clefts and ectrodactyly…. Syndromic ED are, in turn, divided in two groups : ED with PPK and ED with other anomalies. Anhidrotic/hypohidrotic ED remain the more frequent forms.

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