ESID Registry – Working Definitions for Clinical Diagnosis of PID

These criteria are only for patients with **no genetic diagnosis***.
*Exceptions: Atypical SCID, DiGeorge syndrome – a known genetic defect and confirmation of criteria is mandatory

Available entries (Please click on an entry to see the criteria.) **Page**

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Acquired angioedema	Sofia Grigoriadou, Matthew Buckland	At least one of the following - Recurrent angioedema without urticarial rash - History of predisposing disorder (e.g. autoimmune, lymphoreticular malignancy) **AND** No family history to suggest HAE or an alternative diagnosis **AND** Low complement C4 (< 2.S.D of the mean) between or during angioedema attacks **AND** absent C1 esterase protein or absent C1 esterase inhibitor function **AND** (Low C1q level **OR** anti-C1Q antibodies **OR** anti-C1E antibodies)	
Agammaglobulinaemia	Annarosa Soresina, Nizar Mahlaoui, Hans Ochs, Isabella Quinti	Fewer than 2% circulating B cells (CD19 and CD20), preferably in two separate determinations and a normal number of T cells (CD3, CD4 and CD8) **AND** serum IgG levels below: -200 mg/dl in infants aged < 12 months -500 mg/dl in children aged > 12 months **OR** normal IgG levels with IgA and IgM below 2SD **AND** onset of recurrent infections before 5 years of age **OR** positive maternal family history of agammaglobulinaemia	For patients with normal B cells and agammaglobulinaemia, please consider "**Unclassified antibody deficiency"**.
Asplenia syndrome (Ivemark syndrome)	Nizar Mahlaoui David Edgar Stephan Ehl, Capucine Picard, Jean-Laurent Casanova	Asplenia or hyposplenia **AND** Documentation of Howell-Jolly bodies on blood smears **AND** radiological findings evidencing asplenia (US, CT scan, scintigraphy) **AND** heterotaxia defects (dextrocardia, situs inversus, other…) or other heart and great vessel defects	
Ataxia telangiectasia (ATM)	Nizar Mahlaoui David Edgar Stephan Ehl, Richard Gatti, Dominique Stoppa-Lyonnet	Ataxia **AND at least two of the following :** • Oculocutaneous telangiectasia • Elevated alphafetoprotein (tenfold the upper limit of normal) • Lymphocyte A-T caryotype (translocation 7;14) • Cerebellum hypoplasia on MRI	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Atypical Severe Combined Immunodeficiency (Atypical SCID)	Drafted by Stephan Ehl and reviewed by Alain Fischer	Mutation in a SCID-causing gene **AND** >100 T cells/µl **AND** Absence of characteristic SCID-associated infections (PCJ, symptomatic CMV, persistent respiratory or gastrointestinal virus infection) ***in the first year of life*** **AND** Does not fulfil the criteria for Omenn syndrome	Combined immunodeficiency

Autoimmune lymphoproliferative syndrome (ALPS)	David Edgar, Stephan Ehl, Frederic Rieux-Laucat and Benedicte Neven	**At least one of the following:**
		• splenomegaly
		• lymphadenopathy (>3 nodes, >3 months, non-infectious, non-malignant)
		• autoimmune cytopenia (>/= 2 lineages)
		• history of lymphoma
		• affected family member
		AND at least one of the following:
		• TCRab+CD3+CD4-CD8- of TCRab+CD3+ T cells > 6%
		• elevated biomarkers (at least 2 of the following):
		  • sFASL > 200pg/ml
		  • Vitamin B12 > 1500ng/L
		  • IL-10 > 20pg/ml
		  • Impaired FAS mediated apoptosis
			For patients with lymphoproliferation and/or autoimmunity who do not fulfil these criteria, please consider the following diagnoses:
			• CVID
			• Unclassified combined immunodeficiencies
			• Unclassified disorders of immune dysregulation

APECED / APS1 with CMC - Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED)	Nizar Mahlaoui, Frank.vandeVeerdonk (Radboud), Desa Lilic	**Look for at least 2 of the following:** • chronic mucocutaneous candidiasis (oral, oesophageal (difficulty swallowing) genital, skin, nails) – confirm with culture • autoimmune hypoparathyroidism / hypocalcemia • autoimmune adrenocortical failure (Addison's disease) • other autoimmune: hypergonadotropic hypogonadism, alopecia, vitiligo, autoimmune hepatitis, type 1 diabetes, gastrointestinal dysfunction • other: ectodermal dystrophy: dental enamel hypoplasia, nail dystrophy **Diagnostic tests (specific for APECED / APS1):** • organ-specific autoantibodies (parathyroid, adrenal, gonads, islet cell) • anti-cytokine autoantibodies (IFNα & ω and/or IL17A /IL17F/ IL22) [comment: sensitivity & specificity >95% (Kisand et al, Eur J Immunol 2011), can replace AIRE genotyping as >70 known mutations]	

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Barth syndrome	Nizar Mahlaoui, Jean Donadieu, Ch. Klein	Male **AND** Cardiac features (Heart failure, dilated cardiomyopathy, left ventricular non-compaction, endocardial fibroelastosis, and serious disturbances of heart rhythm such as ventricular fibrillation or tachycardia **AND** Chronic Neutropenia **AND at least one of the following** • Neuromuscular features such as skeletal myopathy, hypotonia, delayed motor milestones, exercise intolerance, and abnormal fatigability. • Distinctive facial gestalt (most evident in infancy) • Growth delay is common in childhood	
Bloom syndrome	Markus Seidel, Beata Wolska, Corry Waemes, Andy Gennery	Short stature **AND** • immunodeficiency (hypogammaglobulinemia, variably reduced lymphocyte proliferation, lower respiratory tract infections) • Cytogenetics: high sister-chromatid exchange rate, chromosomal breaks **AND at least one of the following** • Skin: photosensitivity, butterfly erythema, café-au-lait maculae • Head: microcephaly, dolichocephaly, prominent ears and nose • Hands: syndactyly, polydactyly, fifth finger clinodactyly • Malignoma: leukemia, lymphoma, adenocarcinoma, squamous cell carcinoma	
Cartilage hair hypoplasia (CHH)	Nizar Mahlaoui, Bobby Gaspar, Andrew Gennery	Short stature **AND** immunodeficiency (combined immunodeficiency (variable T and B cell lymphopenia), **AND AT LEAST one of the following:** • radiographical manifestations of CHH (metaphyseal chondrodysplasia, • light-coloured hypoplastic hair / fine silky hair • gastrointestinal malabsorption or Hirschsprung's , • hematological abnormalities (bone marrow dysplasia, pure red cell aplasia), • granulomatous inflammation (skin lesions,…), • EBV driven lymphoproliferative disease • Malignancies **AND** no sign of other immune-osseous dysplasia (Schimke disease)	

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CD8 deficiency	Nizar Mahlaoui, Matthew Buckland, Sofia Grigoriadou	**CD8+ cells:** less than 350/µl if age less than 2 years less than 250/µl if age betweeen 2 and 4 years less than 150/µl if age greater than 4 years **AND** Recurrent and/or severe infections **AND** Normal or increased CD4, CD19 and CD56 **AND** normal class HLA-class 1 expression **AND** Other primary causes of lymphopenia excluded	
Chronic mucocutaneous candidiasis (CMC)	Nizar Mahlaoui, Frank.vandeVeerdonk (Radboud), Desa Lilic	**Look for:** • chronic, persistent or recurrent non-invasive mucocutaneous Candida or dermatophyte infections (oral, oesophageal (difficulty swallowing, oesophageal cancer) genital, skin, nails) – confirm with culture • other infections: skin (boils, abscesses, eczema, rosacea) lungs (chest infections, bronchiectasis) eyes (styes, blepharitis, conjunctivitis) • autoimmunity: hypothyroidism, vitiligo, alopecia, autoimmune hepatitis • vasculopathy (intracranial aneurisms, brain vascular anomalies) • family history / early age of onset **Exclude secondary causes:** • predisposing conditions: HIV, diabetes, iron deficiency, neutropenia, dentures • predisposing treatments: antibiotics, immunosuppressive drugs, inhaled steroids, PPIs • exclude isolated recurrent vulvo-vaginal candidiasis (RVVC) [Comment: Informative tests (where available): i. Th-17 & Th-22 cells and production ii. Low CD4 and B cell counts (combined immune deficiency) iii. Low iron]	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Complement component 2 deficiency	Matthew Buckland, Ania Manson, Sofia Grigoriadou	**At least one of the following;** • Increased susceptibility to infections (recurrent pyogenic) • Discoid lupus • SLE • Family history of symptomatic C2 Deficiency **AND** CH50 or CH100 activity less than 10% of control activity **AND** Absent C2 with normal C3 and C4 complement levels	
Complement component 3 deficiency (C3)	Matthew Buckland, Ania Manson, Sofia Grigoriadou	**At least one of the following;** • Increased susceptibility to infections (Neisseria or streptococcal) • Glomerulonephritis • Family history of symptomatic C3 Deficiency **AND** CH50/CH100 and AP50/AP100 less than 10% of control activity **AND** Absent immunochemical C3 with normal Factor H and I levels	
CSR defects and HIGM syndromes	Stephan Ehl, Anne Durandy, Teresa Espanol	**At least one of the following:** • increased susceptibility to infections (recurrent and/or opportunistic, including cryptosporidium) • immune dysregulation (autoimmunity, lymphoproliferation, sclerosing cholangitis) • cytopenia (neutropenia or autoimmune) • malignancy (lymphoma) • affected family member **AND** marked decrease of IgG (measured at least twice) **AND** normal or elevated IgM (measured at least twice) **AND** defined causes of hypogammaglobulinemia have been excluded **AND** no evidence of profound T-cell deficiency, defined as 2/3 of the following (mo=month, y=year of life): • CD4 numbers/microliter: 0-6mo <1000, 6mo-1y <800, 1-2y <500, 2-6y <300, 6-12y <250, >12y <200 • % naive CD4: 0-2y <30%, 2-6y <25%, 6-16y <20%, >16y 10% • T cell proliferation absent **AND** no evidence of Ataxia telangiectasia (cafe-au lait spots, ataxia, telangiectasia, raised AFP)	

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Chediak Higashi syndrome (CHS)	Nizar Mahlaoui, David Edgar Stephan Ehl, Genevieve de Saint Basile, Despina Moshous	**At least one of:** • recurrent bacterial infections • episode of hemophagocytic lymphohistiocytosis (HLH) • Neutropenia • reduced lymphocyte degranulation/cytotoxicity • affected family member **AND one of:** • Typical hair shaft abnormalities • Presence of intracytoplasmic typical giant granules on blood or bone marrow smears	Immunodeficiency with partial albinism
Chronic granulomatous disease (CGD)	Maria Kanariou, Reinhard Seger	**At least one of the following:** • deep seated infection due to bacteria and/or fungi (abscesses, osteomyelitis, lymphadenitis) • recurrent pneumonia • lymphadenopathy and/or hepatomegaly and/or splenomegaly • obstructing/diffuse granulomata (gastrointestinal or urogenital tract) • chronic inflammatory manifestations (colitis, liver abscess and fistula formation) • failure to thrive • affected family member **AND** absent/significantly decreased respiratory burst (NBT or DHR, measured at least twice)	
Clericuzio-type poikiloderma with neutropenia syndrome	Nizar Mahlaoui, Jean Donadieu, Ch. Klein	Chronic neutropenia, **AND** Poikiloderma, **AND** Recurrent infections, **AND** Pachyonychia, **OR** Palmo-plantar hyperkeratosis	

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COHEN syndrome	Nizar Mahlaoui, Jean Donadieu, Ch. Klein	Chronic neutropenia. **AND at least 2 of the followings:** • intellectual deficiency (ID), • microcephaly, • facial dysmorphism, • slender extremities, • obesity, • progressive chorioretinal dystrophy	
Combined immunodeficiency (CID)	Stephan Ehl, Maria Kanariou, Alain Fischer	**At least one of:** • at least one severe infection (requiring hospitalization) • one manifestation of immune dysregulation (autoimmunity, IBD, severe eczema, lymphoproliferation, granuloma) • malignancy • affected family member **AND** 2 of 4 T cell criteria fulfilled: • reduced CD3 or CD4 or CD8 T cells (using age-related reference values) • reduced naive CD4 and/or CD8 T cells • elevated g/d T cells • reduced proliferation to mitogen or TCR stimulation **AND** HIV excluded **AND** exclusion of clinical diagnosis associated with CID (e.g. defined syndromic diseases, DKC, AT, CHH)	

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Common variable immunodeficiency disorders (CVID)	Vojtech Thon, Natalia Martinez, Maria Kanariou, Klaus Warnatz, Isabella Quinti, Helen Chapel	**At least one of the following:** • increased susceptibility to infection • autoimmune manifestations • granulomatous disease • unexplained polyclonal lymphoproliferation • affected family member with antibody deficiency **AND** marked decrease of IgG and marked decrease of IgA with or without low IgM levels (measured at least twice; <2SD of the normal levels for their age); **AND** at least one of the following: • poor antibody response to vaccines (and/or absent isohaemagglutinins); i.e. absence of protective levels despite vaccination where defined • low switched memory B cells (<70% of age-related normal value) **AND** secondary causes of hypogammaglobulinaemia have been excluded (see separate list) **AND** diagnosis is established after the 4th year of life (but symptoms may be present before) **AND** no evidence of profound T-cell deficiency, defined as 2 out of the following (y=year of life): • CD4 numbers/microliter: 2-6y <300, 6-12y <250, >12y <200 • % naive CD4: 2-6y <25%, 6-16y <20%, >16y <10% • T cell proliferation absent	For patients <4 years old or patients with incomplete criteria please consider "**Unclassified antibody deficiency"**. For patients with evidence of profound T-cell deficiency, please consider **Unclassified combined immunodeficiencies**.
Congenital neutropenia	Nizar Mahlaoui, Jean Donadieu	Neutropenia below 0.5 g/L measured on at least 3 occasions **OR** Neutropenia below 1 g/L measured on at least 3 occasions with at least one of the following: • deep seated infection due to bacteria and/or fungi • recurrent pneumonia • buccal and/or genital aphtous lesions or ulcerations • omphalitis • affected family member **AND e**xclusion of secondary causes of neutropenia	For other patients with chronic neutropenia, please consider **Unclassified phagocytic disorders**.
Cyclic neutropenia	Nizar Mahlaoui David Edgar Stephan Ehl, Jean Donadieu	Cyclic fluctuation of Neutrophil counts (every 16 to 28 days) During these neutropenic episodes, symptoms are **at least one of the following**: • Increased susceptibility to infections • Oral apthae • Abdominal pain episodes	

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Defects of TLR/NFkappa-B signalling	Nizar Mahlaoui, Capucine Picard, Jacinta Bustamante	Recurrent and/or severe infections **AND at least 2 of the following:** • normal T- and B-cell responses • mild inflammatory reaction • polysaccharide-specific serum antibodies deficiency • anhidrotic ectodermal dysplasia features in some patients	
Defects with susceptibility to mycobacterial infection (MSMD)	Nizar Mahlaoui, Capucine Picard, Jacinta Bustamante	Infections caused by weakly virulent mycobacteria, such as BCG vaccines and environmental mycobacteria, tuberculosis, salmonellosis, candidiasis, other intramacrophagic bacteria, fungi, or parasites, **AND** Altered IFN-γ mediated immunity tests or Altered IL-12 mediated immunity tests **AND** no IFN-γ auto-antibodies	
Deficiency of specific IgG (Specific antibody deficiency - SPAD)	Nizar Mahlaoui David Edgar, Stephan Ehl, Helen Chapel, Isabella Quinti, Esther de Vries	Infections (recurrent or severe bacterial) **AND** normal serum/plasma IgG, A and M and IgG subclass levels **AND** Profound alteration of the antibody responses to *S.* pneumoniae (or other polysaccharide vaccine) either after documented invasive infection or after test immunization. **AND** Exclusion of T cell defect	**Unclassified antibody deficiencies**
DiGeorge syndrome	Nizar Mahlaoui David Edgar Stephan Ehl	Documented microdeletion 22q11 or 10p **AND** signs of immunodeficiency, i.e. infections (recurrent or severe bacterial) and/or immune dysregulation	
Dyskeratosis congenita	Nizar Mahlaoui David Edgar Stephan Ehl, Inderjeet Dokal	**At least two of the following:** • Skin pigmentation abnormalities • Nail dystrophy • Mucosal leucoplakia • Bone marrow failure **AND** Very short telomeres	

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Early-onset inflammatory bowel disease	Drafted by Joris van Montfrans, reviewed by Christoph Klein and Nicolette Moes	Histologically proven inflammatory bowel disease (IBD) diagnosed with an onset at pediatric age. The following differentiation in age of onset applies (Uhlig et al Gastroenterologie 2014, PMID 25058236): - Infant Onset IBD: onset < 0-2 yrs - Neonatal onset IBD: onset < 28 days **AND** exclusion of infectious cause (bacterial, viral, parasitic) **AND at least one of the following:** • Failure to thrive • Increased values of calprotectine in stool	
Early-onset multi-organ autoimmune disease	Drafted by Joris van Montfrans and reviewed by Andrew Cant and Mario Abinun	This disease is featured by a variable set of presenting symptoms. These presenting symptoms may be “ALPS like” or “IPEX like”. **At least:** The onset of at least 2 separate auto immune diseases <18 yrs (such as: autoimmune cytopenias, IDDM, autoimmune thyroiditis, or organ specific autoimmunity including lung-, gastrointestinal-, hepatic- autoimmune disease, and/or other endocrine dysfunction) **AND at least one of the following:** • Lymphadenopathy > 6 months in >1 region • Hepatosplenomegaly • Recurrent viral infections / reactivations such as mollusca and zoster reactivations • Skin features (eczema or vasculopathy) • Auto immune arthritis	
Epidermodysplasia verruciformis	Drafted by Joris van Montfrans, reviewed by Jean-Laurent Casanova and Capucine Picard	Extensive flat wart-like papules, usually on extremities, trunk or neck **AND at least one of the following:** • pityriasis versicolor-like macules on skin • development of cutaneous carcinomas	

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Factor D deficiency	Matthew Buckland, Ania Manson, Sofia Grigoriadou	**At least one of the following;** • Increased susceptibility to infections (recurrent pyogenic including Neisseria) • Family History of symptomatic Factor D Deficiency **AND** AP50/AP100 activity less than 10% of control value with normal CH50/CH100 activity **Or** Absent Factor D activity in serum in functional or immunochemical assessment	
Familial hemophagocytic lymphohistiocytosis syndromes (FHLH)	Stephan Ehl, Genevieve de Saint Basile, Gritta Janka	**At least one of the following:** • at least 1 episode of HLH (at least 5/8 criteria as defined by the Histiocyte Society) • affected family member **AND at least one of the following:** • recurrent disease (>4 weeks after initiating treatment for first episode) • persistent disease (no full remission can be achieved) • partial albinism • absent or significantly decreased Perforin expression in flow cytometry • at least one assay with absent degranulation (NK or CTL) or two assays with reduced degranulation • at least 2 assays with absent NK cell cytotoxicity	For patients with incomplete criteria, please consider **Unclassified disorders of immune dysregulation**.
FOXP3 deficiency (IPEX)	Nizar Mahlaoui David Edgar Stephan Ehl, Hans Ochs, Benedicte Neven	**At least one of** • Severe and protracted enteropathy with villous atrophy in a male infant • Severe, often multiple endocrinopathies **AND** Exclusion of hypogammaglobulinaemia **AND at least one of the following:** • Low or absent Foxp3 expression by CD4+CD25+ on flow analysis • No overt T cell defect (proliferations are normal) • Elevated IgA and IgE levels • Normal CD25 expression	Combined immunodeficiency

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Glycogen storage disease type 1b (GS1b)	Nizar Mahlaoui David Edgar Stephan Ehl, Jean Donadieu	Recurrent infections **AND** Fasting intolerance **AND** Hypoglycaemic attacks **AND** Hyperlactacidemia **AND** Glycogen accumulation in the liver **AND** colitis mimicking Crohn's disease **AND one of:** • neutrophil function alterations • neutropenia	
Griscelli syndrome type 2	Nizar Mahlaoui, David Edgar Stephan Ehl, Genevieve de Saint Basile, Despina Moshous	**At least one of the following:** • episode of hemophagocytic lymphohistiocytosis (HLH) • reduced lymphocyte degranulation/cytotoxicity • affected family member **AND** Typical hair shaft abnormalities **AND** Absence of giant granules on blood smear	Immunodeficiency with partial albinism
Hereditary Angioedema (C1inh)	Matthew Buckland, Ania Manson, Sofia Grigoriadou	**At least one of the following;** • Recurrent angioedema without urticaria • Recurrent abdominal pain and vomiting • Laryngeal oedema • Family history of angioedema **AND** Low complement C4 (< 2.S.D of the mean) between or during angioedema attacks **AND** Absent C1 esterase protein (Type 1 HAE) or absent C1 esterase inhibitor function (Type 2 HAE) **AND** Normal C1q level	

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Herpetic encephalitis (HSE)	Nizar Mahlaoui, Jean-Laurent Casanova, Isabelle Meyts, Shen-Yin Zhang	**Sporadic Herpes Simplex virus 1 (HSV-2 are excluded) encephalitis in otherwise healthy individuals, wide spectrum of clinical features ranging from necrosis of brain tissue (of the forebrain in 95%, of the brainstem in 5%), fever, altered behavior and disturbed consciousness, with brain image data suggesting brain lesions, and with at least one of the four following virological criteria fulfilled:** **1) HSV-1 PCR positive in CSF,** **OR** **2) HSV-1 antigen positive in CSF** **OR,** **3) anti-HSV-1 antibodies in CSF,** **OR** **4) sero-conversion of anti-HSV-1 antibodies in blood.**	
Hermansky-Pudlak syndrome (type 2)	Nizar Mahlaoui, Stephan Ehl	Oculocutaneous albinism **AND** Chronic neutropenia **AND at least one of the following:** • bleeding diathesis • recurrent infections • hemophagocytic lymphohistiocytosis (HLH) **AND** Defective cytotoxicity caused by impaired degranulation	
HLA class I deficiency	Matthew Buckland, Ania Manson, Sofia Grigoriadou	**At least one of the following:** • Predisposition to recurrent and/or opportunistic infections • Granulomatous skin lesions **AND at least one of the following:** • Predisposition to recurrent and/or opportunistic infections • Necrotizing granulomatous skin lesions • Low T-CD8 or lymphopenia • Absence of Ab production in response to antigens • Absence of T cell proliferation in response to antigens **AND** Reduced or absent HLA A,B,C expression at the surface of resting and PHA/Cytokine activated T-cells	

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HLA class II deficiency (MHC2)	Nizar Mahlaoui, David Edgar Stephan Ehl, Capucine Picard, Amos Etzioni	**One of the following:** • Recurrent and/or opportunistic infections • Autoimmunity **AND one of the following:** • Hypogammaglobulinaemia • Lymphopenia • Low T-CD4 count • absence of Ab production in response to antigens or absence of T cell proliferations in response to antigens **AND** Reduced or absent HLA DR expression at the surface of B cells and/or monocytes	Combined immunodeficiency
Hoyeraal-Hreidarsson syndrome	Nizar Mahlaoui David Edgar Stephan Ehl, Inderjeet Dokal	**At least four of the following criteria:** • Microcephaly and/or neurocognitive impairment • Cerebellar hypoplasia • Bone marrow failure • Immune deficiency including B cell lymphopenia • Severe enteropathy • Severe failure to thrive This can be substantiated by undertaking telomere length analysis (usually very short)	
Hyper IgE syndrome (HIES)	Beata Wolska, David Edgar, Bodo Grimbacher, Steven Holland	IgE > 10 times the norm for age **AND** pathologic susceptibility to infectious diseases **AND** no evidence of T-cell deficiency (low T cell numbers, low naive T cells, reduced proliferation) **AND** no evidence of B cell deficiency (low B cell numbers, hypogammaglobulinaemia)	• For patients with evidence of T-cell deficiency, please consider: **Unclassified combined immunodeficiencies**. • For patients with evidence of B-cell deficiency, please consider **Unclassified antibody deficiency**. • For other patients, please consider **Unclassified immunodeficiencies**.

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IgA with IgG subclass deficiency	Nizar Mahlaoui David Edgar, Stephan Ehl, Helen Chapel, Isabella Quinti, Esther de Vries	Infections (recurrent or severe bacterial) **AND** Undetectable serum/plasma IgA level (with normal/lowish IgG and IgM levels) **AND** Low levels in one or more IgG subclass (documented twice) **AND** normal IgG antibody response to some vaccinations **AND** Exclusion of T cell defect	**Unclassified antibody deficiencies**
Immunodeficiency centromeric instability facial anomalies syndrome (ICF)	Markus Seidel, Beata Wolska, Corry Waemes, Capucine Picard	Immunodeficiency (variable hypogammaglobulinemia, variably reduced T, B, and NK cells, bacterial and opportunistic infections) **AND** • Head: microcephaly, hypertelorism, epicanthal folds, flat face, micrognathia, macroglossia, tongue protrusion, small upturned nose • Cytogenetics: Centromeric instability of chromosomes 1, 9 and 16 with increased somatic recombination and formation of multibranched/-radial configurations **AND at least two of the following** • Short stature • Neurologic: variable mental retardation • Malabsorption, diarrhea • Sinusitis, upper and lower respiratory tract infections	
IPEX-like disease	Nizar Mahlaoui David Edgar Stephan Ehl, Hans Ochs, Benedicte Neven	**At least one of** • Severe and protracted enteropathy with villous atrophy in a male infant • Severe, often multiple endocrinopathies **AND** Exclusion of hypogammaglobulinaemia **AND at least one of the following:** • Normal Foxp3 expression by CD4+CD25+ on flow analysis • No overt T cell defect (proliferations are normal) • Elevated IgA and IgE levels	Combined immunodeficiency

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Isolated IgG subclass deficiency	Nizar Mahlaoui David Edgar, Stephan Ehl, Helen Chapel, Isabella Quinti, Esther de Vries	Infections (recurrent or severe bacterial) **AND** normal IgG, A and M serum/plasma levels **AND** Low levels in one or more IgG subclass (documented twice) **AND** Normal IgG antibody response to some vaccinations **AND**Exclusion of T cell defect	**Unclassified antibody deficiencies**
Isolated congenital asplenia	Nizar Mahlaoui David Edgar Stephan Ehl, Capucine Picard, Jean-Laurent Casanova	Asplenia or hyposplenia **AND** Documentation of Howell-Jolly bodies on blood smears **AND** radiological findings evidencing asplenia (US, CT scan, scintigraphy) **AND** exclusion of any over developmental defect such as heterotaxia (dextrocardia, situs inversus, other…) or other heart and great vessel defects	
Mannose-binding lectin deficiency (MBL)	Matthew Buckland, Sofia Grigoriadou, Ania Manson	Infections (severe recurrent bacterial) **AND one of the following:** Mannose binding lectin <75 µg/L: Correlates with homozygous variant alleles and non-functional MBL which is associated with the greatest risk of infection. **OR** 75 - 399.9 µg/L: Correlates with functional MBL deficiency associated with increased risk of infection. **OR** 400 - 1300 µg/L: Correlates with heterozygous varient alleles and may show mild deficiency associated with some increased risk of infection. **NB: Patients should be classified as Homozygous, Functional or Heterozygous Deficient as appropriate.**	

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MonoMAC (WILD)	Isabella Quinti, Andrew Cant	**At least one of the following:** • disseminated non-tubercolous mycobacterial infections • opportunistic fungal, and viral infections • familial myelodysplastic syndrome / acute myelogenous leukemia • pulmonary alveolar proteinosis • erythema nodosum • lymphedema • disseminated warts • anogenital dysplasia **AND** Monocytopenia, dendritic cell, B and NK lymphocytes lymphopenia **AND** Bone marrow hypocellularity, fibrosis, and multilineage dysplasia	
Netherton syndrome	Drafted by Joris van Montfrans reviewed by E. Renner, Hans Ochs and Nizar Mahlaoui	**At least two of the following:** • generalized ichthyosis (erythroderma covered by fine scales) with an onset < 2 months of age • short hair due to broken off distal shaft, specific hair shaft abnormality called trichorrhexis invaginata or "bamboo hair" • atopic manifestations, including food allergies or elevated serum levels of IgE. **AND at least one of the following:** • failure to thrive in the first years of life • recurrent infections (skin and other locations) • intermittent diarrhea	
Nijmegen breakage syndrome	Markus Seidel, Beata Wolska, Corry Waemes, Andy Gennery	Microcephaly **AND** reduced T cell number and/or elevated percentage of memory CD4 and CD8 cells and/or reduced T cell function **AND at least two of the following** • Typical facial appearance • Variable hypogammaglobulinemia, dysgammaglobulinemia and/or reduction of B cells - opportunistic and/or chronic, recurrent infections, predominantly of the respiratory tract • Skin: Café-au-lait spots and/or hypopigmented areas and/or skin granulomas • lymphoma/leukemia or other malignancy • Chromosomal instability (especially chrom. 7 and 14), increased sensitivity towards ionizing radiation and alkylating agents	

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Omenn syndrome	Nizar Mahlaoui, Annarosa Soresina, Anna Villa, Alain Fischer	Desquamating erythroderma in the first year of life **AND** one of the following: • lymphoproliferation • failure to thrive • chronic diarrhoea • recurrent pneumonia **AND** eosinophilia or elevated IgE **AND** T-cell deficiency (low naïve cells, reduced proliferation, oligoclonality) **AND** maternal engraftment excluded **AND** HIV excluded	For other patients with severe erythroderma, please consider: • SCID • IPEX • Unclassified disorders of immune dysregulation • Unclassified defects in innate immunity.
Other immunoglobulin gene deletions		Please specify affected gene	
Other DNA-breakage disorder		Please specify affected gene	
Papillon-Lefevre syndrome	Isabella Quinti, Steven Holland, Nizar Mahlaoui	Palmoplantar hyperkeratosis **AND** severe early onset periodontitis affecting both the deciduous and permanent teeth **AND at least one of the following:** • mild mental retardation • pyogenic infections • hyperhidrosis • intracranial calcifications • abnormal neutrophil function tests Differential diagnosis includes: allelic variants of PLS, such as Haim-Munk syndrome and prepubertal/aggressive periodontitis. Other diseases with similar dermatologic features include localized epidermolytic palmoplantar keratoderma, Howel-Evans syndrome, Greither's disease, and keratosis punctate.	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Partial albinism and immunodeficiency syndrome	Nizar Mahlaoui, Stephan Ehl	Partial oculo-cutaneous albinism **AND at least one of of the following:** • recurrent bacterial infections • episode of hemophagocytic lymphohistiocytosis (HLH) • reduced lymphocyte degranulation/cytotoxicity • affected family member **AND** Exclusion of Chediak Higashi Syndrome and Griscelli Syndrome type 2	
Properdin P factor complement deficiency (PFC)	Matthew Buckland, Ania Manson, Sofia Grigoriadou	**At least one of the following;** • Increased susceptibility to infections (recurrent pyogenic including Neisseria) • Family History (X-linked inheritance pattern **AND** AP50/AP100 activity in at least the bottom 10% of control value with normal CH50/CH100 activity **AND** Absent Properdin (type I/II) or activity (type III) in serum in functional or immunochemical assessment	
Schimke disease	Nizar Mahlaoui David Edgar Stephan Ehl	Predominantly T cell defects (low T cell counts, low T cell proliferations) **AND** osseous dysplasia (metaphyseal usually) **AND** kidney dysfunction	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Seckel syndrome	Markus Seidel, Beata Wolska, Corry Waemes, Andy Gennery	Short stature (pre- and postnatal growth retardation), severe microcephaly **AND at least three of the following:** • Head: downward slanting palpebral fissures, sloping forehead, face asymmetry, prominent beaked nose, selective tooth agenesis • Hematology: pancytopenia • Cytogenetics: increased sister chromatid exchange • Neurology: mental retardation, seizures, and CNS structural abnormalities • Skeletal: fifth finger clinodactyly, hip and radius head dislocation, hypoplasia of proximal radius and proximal fibula, 11 ribs, scoliosis	
Selective CD4 cell deficiency	Matthew Buckland, Ania Manson, Sofia Grigoriadou	$CD4^+$ T cell less than 350/µl (patient more than 4 years of age) or less than 20% of circulating T-lymphocytes at any age **AND** OKT4 Deficiency Excluded **AND** Normal or increased CD8, CD19 and CD56 **AND** HIV Negative **And** Other primary causes of lymphopenia excluded	
Selective IgA deficiency	Vojtech Thon, Natalia Martinez, Maria Kanariou, Klaus Warnatz, Isabella Quinti	**At least one of the following:** • increased susceptibility to infection • autoimmune manifestations • affected family member **AND** diagnosis after 4th year of life **AND** undetectable serum IgA (when measured with nephelometry less than 0.07 g/L) but normal serum IgG and IgM (measured at least twice) **AND** secondary causes of hypogammaglobulinaemia have been excluded. **AND** normal IgG antibody response to all vaccinations **AND** Exclusion of T-cell defect	• For patients with abnormal vaccine responses, please consider **Deficiency of specific IgG (SPAD)**. • For other patients, please consider **Unclassified antibody deficiency**.

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Selective IgM deficiency	Nizar Mahlaoui David Edgar, Stephan Ehl, Helen Chapel, Isabella Quinti, Esther de Vries	Infections (either invasive or recurrent, usually bacterial) **AND** Low IgM serum/plasma level (with normal IgG and IgG subclasses and IgA plasma level) **AND** Normal IgG antibody response to all vaccinations **AND** Exclusion of T-cell defect	**Unclassified antibody deficiencies**
Severe combined immunodeficiency (SCID)	Stephan Ehl, Alain Fischer	**At least one of the following:** • invasive bacterial, viral or fungal/opportunistic infection • persistent diarrhoea and failure to thrive • affected family member **AND** manifestation in the first year of life **AND** HIV excluded **AND** 2 of 4 T cell criteria fulfilled : • low or absent CD3 or CD4 or CD8 T cells • reduced naive CD4 and/or CD8 T cells • elevated g/d T cells • reduced or absent proliferation to mitogen or TCR stimulation	For other (e.g. older) patients with T-cell deficiency, consider **Unclassified combined IDs**.
Shwachman-Diamond-syndrome	Nizar Mahlaoui, Jean Donadieu	Neutropenia **AND** Exocrine pancreatic failure **AND at least one of the following:** • enlargement of metaphyseal zones on bone X-rays • cognitive retardation or Behavioral problems	
Thymoma with immunodeficiency	David Edgar, Helen Chapel	Presence of thymoma **AND** reduced serum IgG (< 2SD below the mean reference for age)	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Transient hypogammaglobulinaemia of infancy	David Edgar, Maria Kanariou, Esther de Vries	IgG below age-related normal value detected in the first three years of life (measured at least twice) **AND** defined causes of hypogammaglobulinaemia have been excluded **AND** spontaneous resolution approx. after the 4th birthday NB: Patients will initially be registered as **Unclassified antibody deficiency,** in the registry and moved to **THI**, if there is spontaneous resolution before age 4.	
Warts hypogammaglobulinemia infections and myelokathexis (WHIM)	Jean Donadieu, Sarah, Beaussant Cohen, Bodo Grimbacher	Neutropenia **AND** lymphopenia **AND** monocytopenia **AND** Evidence of myelokathexis on bone marrow smear; **AND at least one of the following:** • Recurrent and severe HPV infections • Recurrent bacterial infections • Mycobacterial infection(s). • Mild hypogammagobulinemia	
Wiskott-Aldrich syndrome (XLT/WAS)	Annarosa Soresina, Natalia Martinez, Michael Albert, Adrian Thrasher	**At least one of the following:** • eczema • recurrent bacterial or viral infections • autoimmune diseases (incl. vasculitis) • malignancy • reduced WASP expression in a fresh blood sample • abnormal antibody response to polysaccharide antigens and/or low isohaemagglutinins • positive maternal family history of XLT/WAS **AND** male patient with thrombocytopenia (less than 100,000 platelets/mm3) (measured at least twice) **AND** small platelets (platelet volume < 7,5 fl)	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
X-linked lymphoproliferative syndrome (XLP)	Nizar Mahlaoui, Stephan Ehl	Male individual (or female with severely skewed X-chromosome inactivation) **AND two of the following:** • at least 1 episode of HLH (according to the Histiocyte Society criteria) • affected family member • abnormal EBV response • Hypogammaglobulinemia • Inflammatory Bowel Disease • Vasculitis • Lymphoid Neoplasm, especially if EBV-associated **AND at least one of the following minor criteria:** • decreased or absent SAP (for XLP1) or XIAP (for XLP2) expression assessed by Flow Cytometry • reduced frequency of iNKT cells (< 0.02% of T cells) • Normal Perforin expression in flow cytometry • Normal degranulation (NK or CTL) assays or Normal NK cell cytotoxicity assays **AND** No partial albinism **AND** Normal work-up for metabolic diseases	
Unclassified antibody deficiency	Esther de Vries, Nizar Mahlaoui, David Edgar, Isabella Quinti, Helen Chapel	**At least 1 of the following 4:** • Recurrent or severe bacterial infections • Autoimmune phenomena (especially cytopenias) • Polyclonal lymphoproliferation • Affected family member **AND at least one of the following**: • marked decrease of at least one of total IgG, IgG1, IgG2, IgG3, IgA or IgM levels • failure of IgG antibody response(s) to vaccines **AND** secondary causes of hypogammaglobulinaemia have been excluded (infection, protein loss, medication, malignancy) **AND** no clinical signs of T-cell related disease **AND** does not fit **any** of the other working definitions (**ex**cluding 'unclassified immunodeficiencies')	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Unclassified phagocytic disorders	Nizar Mahlaoui, Capucine Picard, Jacinta Bustamante	**At least one of the following:** • deep seated infection due to bacteria and/or fungi • recurrent severe pneumonia • buccal and/or genital aphtous lesions or ulcerations • omphalitis • chronic inflammatory manifestations (e.g. colitis, fistula formation) • affected family member • BCGitis or BCGosis **AND** normal to subnormal respiratory burst (NBT or DHR, assessed at least twice)	
Unclassified disorders of immune dysregulation	Stephan Ehl, Maria Kanariou	**At least one of the following:** • autoimmune manifestations • lymphoproliferation • severe eczema • inflammatory bowel disease • granuloma • vasculitis • HLH-like disease **AND** at least one numeric or functional abnormal finding upon immunological investigation **AND** no evidence of profound T-cell deficiency, defined as 2 out of the following (y=year of life): • CD4 numbers/microliter: 0-6mo <1000, 6mo-1y <800, 1-2y <500, 2-6y <300, 6-12y <250, >12y <200 • % naive CD4: 0-2y <30%, 2-6y <25%, 6-16y <20%, >16y 10% • T cell proliferation absent **AND** no evidence of B-cell deficiency (low B cell numbers, hypogammaglobulinaemia	• For patients with evidence of profound T-cell deficiency, please register these as **Unclassified combined immunodeficiencies**. • For patients with evidence of B-cell deficiency, please register as **Unclassified antibody deficiency**.
Unclassified defects in innate immunity	Nizar Mahlaoui, Maria Kanariou, Capucine Picard, Jacinta Bustamante	**At least one of the following:** • onset of disease before 5 y of age • pyogenic bacterial infections • unusual infections and/or atypical clinical course **AND** the dominant abnormal immunological finding concerns the innate immune system (excluding defects in phagocyte number or function) i.e. NF-κB-dependent TLR and IL-1R immunity **AND** functional spleen (no Howell-Jolly bodies on blood smears)	For patients with evidence of profound defect of phagocytes, please consider **Unclassified phagocytic disorders**.

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
Unclassified complement deficiencies	Annarosa Soresina, Matthew Buckland, David Edgar	**At least one of the following:** • one episode of bacteraemia, meningitis or systemic Neisserial infection • recurrent respiratory infections **AND** persistent defect of CH50 or AP50 (in three determinations in 6 months) **AND** no evidence of other conventional immunological defects	
Unclassified autoinflammatory diseases	David Edgar, Beata Wolska, Helen Lachmann	Recurrent fever (temperature >38 degrees Celsius) having occurred on at least 6 occasions. **AND** exclusion of other known infective / inflammatory autoimmune disorders **AND** documented evidence of increased inflammatory markers (ESR/CRP) **AND** age of onset under 40 years **AND** predominantly but not exclusively systemic symptoms	
Unclassified syndromic immunodeficiencies	Drafted by Stephan Ehl and reviewed by Alain Fischer	**At least one of the following:** • dysmorphic features such as short stature, facial abnormalities, microcephaly, skeletal abnormalities • other organ manifestations such as albinism, hair or tooth abnormalities, heart or kidney defects, hearing abnormalities, primary neurodevelopmental delay, seizures **AND** at least one numeric or functional abnormal finding upon immunological investigation **AND** exclusion of secondary causes for immunological abnormalities (infection, malignancy)	
Unclassified immunodeficiencies	Stephan Ehl, Alain Fischer	**At least one of the following:** • at least one major infection • abnormal course or frequency of minor infections • at least one manifestation of immune dysregulation • failure to thrive • affected family member **AND** at least one numeric or functional abnormal finding upon immunological investigation **AND** exclusion of secondary causes for immunological abnormalities (infection, protein loss, medication, malignancy) **AND** does not fit **any** of the other working definitions (**in**cluding 'unclassified syndromic immunodeficiencies')	For patients with syndromic manifestations, consider **Unclassified syndromic IDs**.