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 and OMIM number for disease entry (examples)	IUIS category	OMIM number for disease-associated genes (examples)	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis classification)	Suggestions for alternative diagnosis (i.e., if these criteria are not completely fulfilled)
Acquired angioedema	9. Phenocopies of inborn errors of immunity		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)	
Agammaglobulinemia 300310, 300755, 601495, 613500, 612692, 613501, 613502, 613506, 616941, 615214	3. Predominantly antibody deficiencies	300300, 147020, 146770, 112205, 147245, 604515, 171833, 147141, *608360*	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 agammaglobulinemia	For patients with normal B cells and agammaglobulinaemia, please consider **"Unclassified antibody deficiency"**
Asplenia syndrome (Ivemark syndrome) 208530	6. Defects in intrinsic and innate immunity	*602880*	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) 208900	2. Combined immunodeficiencies with associated or syndromic features	607585	Nizar Mahlaoui, David Edgar, Stephan Ehl, Richard Gatti, Dominique Stoppa-Lyonnet	Ataxia **AND at least two of the following :** • Oculocutaneous telangiectasia • Elevated alpha-fetoprotein (tenfold the upper limit of normal) • Lymphocyte A-T karyotype (translocation 7;14) • Cerebellum hypoplasia on MRI	

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Atypical Severe Combined Immunodeficiency (Atypical SCID)	1. Immunodeficiencies affecting cellular and humoral immunity	*179615.0016*, *608958.0031*, *308380.0010*, *308380.0013*	Stephan Ehl, Alain Fischer	Mutation in a SCID-causing gene **AND** >100 T cells/µl **AND** Absence of characteristic SCID-associated infections (PCP, 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)
 	
601859, 603909, 607271, 616100, 615559, 614470
	4. Diseases of immune dysregulation	134637, 134638, 601762, 601763, 602457, *123890, 176977, 164790*	David Edgar, Stephan Ehl, Frederic Rieux-Laucat, 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
					• Combined immunodeficiencies
					• Unclassified disorders of immune dysregulation

APECED / APS1 with CMC - Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) 240300	4. Diseases of immune dysregulation	607358	Nizar Mahlaoui, Frank van de Veerdonk, 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)	

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				• 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]	
Barth syndrome 302060	5. Congenital defects of phagocyte number or function	300394	Nizar Mahlaoui, Jean Donadieu, Christoph 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 210900	2. Combined immunodeficiencies with associated or syndromic features	604610	Markus Seidel, Beata Wolska, Corry Weemaes, 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	

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Cartilage hair hypoplasia (CHH) 250250	2. Combined immunodeficiencies with associated or syndromic features	157660	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)	
CD8 deficiency 608957	1. Immunodeficiencies affecting cellular and humoral immunity	186910	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)	9. Phenocopies of inborn errors of immunity	607358	Nizar Mahlaoui, Frank van de Veerdonk, Desa Lilic	**Look for:** • chronic, persistent or recurrent non-invasive mucocutaneous Candida or dermatophyte infections (oral, esophageal (difficulty swallowing, esophageal cancer) genital, skin, nails) – confirm with culture • other infections: skin (boils, abscesses, eczema, rosacea) lungs (chest infections, bronchiectasis) eyes (stye, blepharitis, conjunctivitis) • autoimmunity: hypothyroidism, vitiligo, alopecia,	

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				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]	
Complement component 1q deficiency (C1q deficiency) 613652	8. Complement deficiencies	120550, 120570, 120575	Matthew Buckland, Ania Manson, Sofia Grigoriadou	**At least one of the following;** • Increased susceptibility to infections with encapsulated organisms • SLE like syndrome • Family history of symptomatic C1q deficiency **AND** CH50/CH100 activity less than 10% of control value with normal AP50/AP100 activity	
Complement component 1r deficiency (C1r deficiency) 216950	8. Complement deficiencies	613785	Matthew Buckland, Ania Manson, Sofia Grigoriadou	**At least one of the following;** • Increased susceptibility to infections with encapsulated organisms • SLE like syndrome • Ehler's Danlos Phenotype • Family history of symptomatic C1r deficiency **AND** CH50/CH100 activity less than 10% of control value with normal AP50/AP100 activity	

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Complement component 1s deficiency (C1s deficiency) 613783	8. Complement deficiencies	120580	Matthew Buckland, Ania Manson, Sofia Grigoriadou	**At least one of the following;** • Increased susceptibility to infections with encapsulated organisms • SLE like syndrome • Multiple autoimmune diseases • Ehler's Danlos Phenotype • Family history of symptomatic C1s deficiency **AND** CH50/CH100 activity less than 10% of control value with normal AP50/AP100 activity	
Complement component 2 deficiency 217000	8. Complement deficiencies	*613927*	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) 613779	8. Complement deficiencies	120700	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	
Complement component 4 deficiency (C4A, C4B) 614380, 614379	8. Complement deficiencies	120810, *120820*	Matthew Buckland, Ania Manson, Sofia Grigoriadou	**At least one of the following;** • Increased susceptibility to infections (Neisserial) • Family history of recurrent Neisserial disease **AND** CH50 (or CH100) and AP50 (or AP100) activity less than 5% of control activity **AND**	

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				Low immunochemical C4 protein or reduced bactericidal activity	
Complement component 5 deficiency 609536	8. Complement deficiencies	120900	Matthew Buckland, Ania Manson, Sofia Grigoriadou	**At least one of the following;** • Increased susceptibility to infections (Neisserial) • Family history of recurrent Neisserial disease **AND** CH50 (or CH100) and AP50 (or AP100) activity less than 5% of control activity **AND** Low immunochemical C5 protein or reduced bactericidal activity	
Complement component 6 deficiency 612446	8. Complement deficiencies	217050	Matthew Buckland, Ania Manson, Sofia Grigoriadou	**At least one of the following;** • Increased susceptibility to infections (Neisserial) • Family history of recurrent Neisserial disease **AND** CH50 (or CH100) and AP50 (or AP100) activity less than 5% of control activity **AND** Low immunochemical C6 protein or reduced bactericidal activity	
Complement component 7 deficiency 610102	8. Complement deficiencies	217070	Matthew Buckland, Ania Manson, Sofia Grigoriadou	**At least one of the following;** • Increased susceptibility to infections (Neisserial) • Family history of recurrent Neisserial disease **AND** CH50 (or CH100) and AP50 (or AP100) activity less than 5% of control activity **AND** Low immunochemical C7 protein or reduced bactericidal activity	
Complement component 8 deficiency (C8A, C8B, C8G) 613790, 613789	8. Complement deficiencies	120950, 120960, 120930	Matthew Buckland, Ania Manson, Sofia Grigoriadou	**At least one of the following;** • Increased susceptibility to infections (Neisserial) • Family history of recurrent Neisserial disease **AND** CH50 (or CH100) and AP50 (or AP100) activity less than 5% of control activity **AND** Low immunochemical C8 protein or reduced bactericidal activity	

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Complement component 9 deficiency 613825	8. Complement deficiencies	120940	Matthew Buckland, Ania Manson, Sofia Grigoriadou	**At least one of the following;** • Increased susceptibility to infections (Neisserial) • Family history of recurrent Neisserial disease **AND** CH50 (or CH100) and AP50 (or AP100) activity less than 5% of control activity **AND** Absent immunochemical C9 protein or reduced bactericidal activity	
CSR defects and HIGM syndrome 608106, 605258, 608184	3. Predominantly antibody deficiencies	600678, *191525*, *605257*	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) 214500	4. Diseases of immune dysregulation	606897	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) 306400, 233700, 233690, 233710, 613960	5. Congenital defects of phagocyte number or function	300481, 608508, 608512, 608515, 601488	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 604173	5. Congenital defects of phagocyte number or function	613276	Nizar Mahlaoui, Jean Donadieu, Christoph Klein	Chronic neutropenia, **AND** Poikiloderma, **AND** Recurrent infections, **AND** Pachyonychia, **OR** Palmo-plantar hyperkeratosis	

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COHEN syndrome 216550	5. Congenital defects of phagocyte number or function	607817	Nizar Mahlaoui, Jean Donadieu, Christoph 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) 616433, 615607, 615897, 312863, 615468, 614172, 616098, 616740, 618131, 233600	1. Immunodeficiencies affecting cellular and humoral immunity	603122, 300386, 109535, 186740, 186910, 176947, 170260, 170261, 601962, 109700, 600005, 603200, 601863, 601861, 602037, 604655, 604758, *300715*, *153390*, *604011*, *611432*, *604965*, *309845*, *186880*, *606558*, *600315*, *602354*, *607210*, *603517*, *603258*, *190010*, *605383*, *604860, 308380*	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 naïve CD4 and/or CD8 T cells • elevated g/d T cells • reduced proliferation to mitogen or TCR stimulation **AND** HIV excluded **AND** exclusion of a clinical diagnosis associated with CID (e.g., defined syndromic diseases, DKC, AT, CHH)	
Common variable immunodeficiency disorders (CVID) 607594, 240500, 613493, 613494, 613495, 613496, 614699, 614700, 615577, 615767, 616576, 616873, 617765	3. Predominantly antibody deficiencies	*604558*, *604907*, *107265*, *606269*, *112210*, *186845*, *120650*, *606453*, *164012*, *605384*, *164011*, *603023*, *615332*	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:	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 **Combined immunodeficiencies**.

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				• poor antibody response to vaccines (and/or absent isohemagglutinins); 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 hypogammaglobulinemia have been excluded (e.g., infection, protein loss, medication, malignancy) **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=years of life): • CD4 numbers/microliter: 2-6y <300, 6-12y <250, >12y <200 • % naive of CD4: 2-6y <25%, 6-16y <20%, >16y <10% T cell proliferation absent	
Congenital neutropenia 202700, 613107, 610738, 612541, 615285, 616022, 617014, 300392	5. Congenital defects of phagocyte number or function	130130, 600871, 605998, 611045, 610035, 602671, 300392, 610389, *604592*, *138971*, *146928*, *616012*	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 162800	5. Congenital defects of phagocyte number or function	130130	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 aphthae • Abdominal pain episodes	
Defects of TLR/NFkappa-B signaling 610799, 607676, 300640,	6. Defects in intrinsic and innate immunity; *OR* categories 2, 3, 7.	*602170*, *606883*, *300248*, *603258*, *164008*, *603029*, *608204*, *601896*, *604834*	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	

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300584, 300636, 300301, 618204, 615592, 612132				• polysaccharide-specific serum antibodies deficiency • anhidrotic ectodermal dysplasia features in some patients	
Defects with susceptibility to mycobacterial infection (MSMD) 614891, 614890, 209950, 615978, 614889, 614892, 613796, 300645, 614893, 611521, 616126, 616622	6. Defects in intrinsic and innate immunity	601604, 161561, 107470, 147569, 600555, 300481, 601565, 176941, 147571, 602943, 147795,	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)	3. Predominantly antibody deficiencies	102582	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 188400	2. Combined immunodeficiencies with associated or syndromic features	602054, *602269*, *138720*, *116790*, *600237*, *601754*	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 congenital 305000, 127550, 613989, 613990, 615190, 616553, 613987, 224230, 613988, 616353	2. Combined immunodeficiencies with associated or syndromic features	300126, *612661*, *604319*, *187270*, *602322*, *608833*, *604212*, *606471*, *606470, 609377*	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 615767, 613148, 612567	Categories 1, 4, 7.	*605384*, *124092*, *146933*, *123889*	Joris van Montfrans, Christoph Klein, 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 615952, 617006, 613385	Categories 1, 4, 7.	*102582*, *176947*, *606409*	Joris van Montfrans, Andrew Cant, 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 226400, 618231, 305350	6. Defects in intrinsic and innate immunity	605828, 605829, 162643	Joris van Montfrans, Jean-Laurent Casanova, 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 B Deficiency 615561	8. Complement deficiencies	138470	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 B Deficiency **AND** AP50/AP100 activity less than 10% of control value with normal CH50/CH100 activity **Or** Absent Factor B activity in serum in functional or immunochemical assessment	
Factor D deficiency 613912	8. Complement deficiencies	134350	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	
Factor H Deficiency 609814	8. Complement deficiencies	134370	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 H Deficiency (Recessive or Dominant Inheritance) • Pre-eclampsia **AND** Reduced serum C3 (due to spontaneous activation) **AND/OR** Reduced AP50/AP100 and CH50/CH100 due to reduced serum C3 **Or** Absent Factor H by immunochemical assessment	
Factor H Related Protein Deficiency 235400, 614809	8. Complement deficiencies	134371, 600889, 605336, 605337, 608593	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 H Deficiency (Recessive or Dominant Inheritance) **AND/OR**	

Disease and OMIM number for disease entry (examples)	IUIS category	OMIM number for disease-associated genes (examples)	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis classification)	Suggestions for alternative diagnosis (i.e., if these criteria are not completely fulfilled)
				Normal AP50/AP100 and CH50/CH100 **And** Antibodies to Factor H	
Factor I Deficiency 610984	8. Complement deficiencies	217030	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 I Deficiency (Recessive or Dominant Inheritance) • Pre-eclampsia **AND** Reduced serum C3 (due to spontaneous activation) **AND/OR** Reduced AP50/AP100 and CH50/CH100 due to reduced serum C3 **Or** Absent Factor I by immunochemical assessment	
Ficolin 3 Deficiency (FC3RN) 613860	8. Complement deficiencies	604973	Matthew Buckland, Ania Manson, Sofia Grigoriadou	**At least one of the following;** • Increased susceptibility to infections • Glomerulonephritis • Multiple Abscesses **AND** Absent Ficollin dependent complement activation **AND/OR** Absent FC3RN	
Familial hemophagocytic lymphohistiocytosis syndromes (FHLH) 267700, 603553, 608898, 603552, 613101	4. Diseases of immune dysregulation	170280, 608897, 605014, 601717, 610884,	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	For patients with incomplete criteria, please consider **Unclassified disorders of immune dysregulation**.

Disease and OMIM number for disease entry (examples)	IUIS category	OMIM number for disease-associated genes (examples)	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis classification)	Suggestions for alternative diagnosis (i.e., if these criteria are not completely fulfilled)
				• at least 2 assays with absent NK cell cytotoxicity	
FOXP3 deficiency (IPEX) 304790	4. diseases of immune dysregulation	300292	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
Glycogen storage disease type 1b (GS1b) 232220	5. Congenital defects of phagocyte number or function	602671	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 607624	4. Diseases of immune dysregulation	603868	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

Disease and OMIM number for disease entry (examples)	IUIS category	OMIM number for disease-associated genes (examples)	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis classification)	Suggestions for alternative diagnosis (i.e., if these criteria are not completely fulfilled)
Hereditary Angioedema (C1inh) 106100, 610618	8. Complement deficiencies	606860, 610619	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	
Herpetic encephalitis (HSE) 613002, 610551, 614849, 614850, 617900, 616532, 608033	6. Defects in intrinsic and innate immunity	603029, 608204, 601896, 607601, 604834, 603734, *601181*, *600650*	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) 608233	4. Diseases of immune dysregulation	603401	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	

Disease and OMIM number for disease entry (examples)	IUIS category	OMIM number for disease-associated genes (examples)	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis classification)	Suggestions for alternative diagnosis (i.e., if these criteria are not completely fulfilled)
HLA class I deficiency 604571	1. Immunodeficiencies affecting cellular and humoral immunity	170260, 170261, 601962, 109700	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	
HLA class II deficiency (MHC2) 209920	1. Immunodeficiencies affecting cellular and humoral immunity	600005, 603200, 601863, 601861	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 305000	2. Combined immunodeficiencies with associated or syndromic features	300126, *609377*, *604212*, *608833*, *187270*, *604319*	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)	

Disease and OMIM number for disease entry (examples)	IUIS category	OMIM number for disease-associated genes (examples)	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis classification)	Suggestions for alternative diagnosis (i.e., if these criteria are not completely fulfilled)
Hyper IgE syndrome (HIES) 147060, 243700, 611521	2. Combined immunodeficiencies with associated or syndromic features	102582, *611432*, *176941*	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: **Combined immunodeficiencies**. • For patients with evidence of B-cell deficiency, please consider **Unclassified antibody deficiency**. • For other patients, please consider **Unclassified immunodeficiencies**.
IgA with IgG subclass deficiency	3. Predominantly antibody deficiencies		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) 242860, 614069, 616910, 616911	2. Combined immunodeficiencies with associated or syndromic features	602900, 614064, 609937, 603946	Markus Seidel, Beata Wolska, Corry Weemaes, 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	

Disease and OMIM number for disease entry (examples)	IUIS category	OMIM number for disease-associated genes (examples)	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis classification)	Suggestions for alternative diagnosis (i.e., if these criteria are not completely fulfilled)
				• Sinusitis, upper and lower respiratory tract infections	
IPEX-like disease 614162	4. Diseases of immune dysregulation	*600555*	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
Isolated IgG subclass deficiency	3. Predominantly antibody deficiencies	*147110*	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 271400	6. Defects in intrinsic and innate immunity	150370, 141250	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	

Disease and OMIM number for disease entry (examples)	IUIS category	OMIM number for disease-associated genes (examples)	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis classification)	Suggestions for alternative diagnosis (i.e., if these criteria are not completely fulfilled)
Mannose-binding lectin deficiency (MBL) 614372	6. Defects in intrinsic and innate immunity	*154545*	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. note: patients should be classified as homozygous, functional or heterozygous deficient as appropriate.	
Membrane CoFactor Protein (CD46) Deficiency	8. Complement deficiencies	120920	Matthew Buckland, Ania Manson, Sofia Grigoriadou	**At least one of the following;** Increased susceptibility to infections • Glomerulonephritis • Recurrent pyogenic infections • Pre-eclampsia **AND** AP50/AP100 activity less than 10% of control value with normal CH50/CH100 activity **AND/OR** Evidence of absent C3b binding by competitive immunoassay	
MonoMAC (WILD) 614172	5. Congenital defects of phagocyte number or function	137295	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	

Disease and OMIM number for disease entry (examples)	IUIS category	OMIM number for disease-associated genes (examples)	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis classification)	Suggestions for alternative diagnosis (i.e., if these criteria are not completely fulfilled)
				AND Bone marrow hypocellularity, fibrosis, and multilineage dysplasia	
Netherton syndrome 256500	2. Combined immunodeficiencies with associated or syndromic features	605010	Joris van Montfrans Ellen Renner, Hans Ochs, 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 251260	2. Combined immunodeficiencies with associated or syndromic features	602667	Markus Seidel, Beata Wolska, Corry Weemaes, 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	

Disease and OMIM number for disease entry (examples)	IUIS category	OMIM number for disease-associated genes (examples)	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis classification)	Suggestions for alternative diagnosis (i.e., if these criteria are not completely fulfilled)
Omenn syndrome 603554	Categories 1, 2, 4.	*605988*, *179615*, *179616*, *607210*, *601837*, *146661*	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.
Papillon-Lefevre syndrome 245000	5. Congenital defects of phagocyte number or function	602365	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.	
Partial albinism and immunodeficiency syndrome	4. Diseases of immune dysregulation		Nizar Mahlaoui, Stephan Ehl	Partial oculo-cutaneous albinism **AND at least one of the following:** • recurrent bacterial infections • episode of hemophagocytic lymphohistiocytosis (HLH) • reduced lymphocyte degranulation/cytotoxicity • affected family member **AND** Exclusion of Chediak Higashi Syndrome, Griscelli Syndrome type 2, and Hermansky-Pudlak Syndrome type 2	

Disease and OMIM number for disease entry (examples)	IUIS category	OMIM number for disease-associated genes (examples)	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis classification)	Suggestions for alternative diagnosis (i.e., if these criteria are not completely fulfilled)
Properdin P factor complement deficiency (PFC) 312060	8. Complement deficiencies	300383	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 242900	2. Combined immunodeficiencies with associated or syndromic features	606622	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	
Seckel syndrome 210600, 606744, 613676, 613529, 614728, 614851, 615807, 616777, 617253		*606605*, *601215*, *601810*, *604124*, *613529*, *609279*, *605925*, *605958*, *614724*, *608684*, *617246*	Markus Seidel, Beata Wolska, Corry Weemaes, 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	

Disease and OMIM number for disease entry (examples)	IUIS category	OMIM number for disease-associated genes (examples)	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis classification)	Suggestions for alternative diagnosis (i.e., if these criteria are not completely fulfilled)
Selective CD4 cell deficiency 615518		*604011*	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 *137100,* 609529	3. Predominantly antibody deficiencies	*604907*	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 hypogammaglobulinemia 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**.
Selective IgM deficiency	3. Predominantly antibody deficiencies		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**

Disease and OMIM number for disease entry (examples)	IUIS category	OMIM number for disease-associated genes (examples)	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis classification)	Suggestions for alternative diagnosis (i.e., if these criteria are not completely fulfilled)
Severe combined immunodeficiency (SCID) 300400, 600802, 608971, 102700, 601457, 602450, 611291, 615617, 615615, 615617, 617237	1. Immunodeficiencies affecting cellular and humoral immunity	308380, 600173, 146661, 151460, 186790, 186830, 186780, 605000, 602354, 179615, 179616, 605988, 611290, 601837, 103020, 608958, *600899*, *600838*, *176947*, *607210*	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 **Combined IDs**.
Shwachman-Diamond-syndrome 260400, 617941	5. Congenital defects of phagocyte number or function	607444, *617048*, *617538*, *604857*	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 behavioural problems	
Thymoma with immunodeficiency			David Edgar, Helen Chapel	Presence of thymoma **AND** reduced serum IgG (< 2SD below the mean reference for age)	
Transient hypogammaglobulinaemia of infancy	3. Predominantly antibody deficiencies		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) 193670	6. Defects in intrinsic and innate immunity	162643	Jean Donadieu, Sarah, Beaussant Cohen, Bodo Grimbacher	Neutropenia **AND** lymphopenia **AND** monocytopenia **AND** Evidence of myelokathexis on bone marrow smear;	

Disease and OMIM number for disease entry (examples)	IUIS category	OMIM number for disease-associated genes (examples)	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis classification)	Suggestions for alternative diagnosis (i.e., if these criteria are not completely fulfilled)
				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) 301000, 614493	2. Combined immunodeficiencies with associated or syndromic features	300392, *602357*	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 isohemagglutinins • 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)	
X-linked lymphoproliferative syndrome (XLP) 308240, 300635	4. Diseases of immune dysregulation	300490, 300079	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	

Disease and OMIM number for disease entry (examples)	IUIS category	OMIM number for disease-associated genes (examples)	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis classification)	Suggestions for alternative diagnosis (i.e., if these criteria are not completely fulfilled)
				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 one of the following:** • 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 hypogammaglobulinemia have been excluded (e.g., 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')	
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	• For patients with evidence of profound T-cell deficiency, please register these as **Combined immunodeficiencies**.

Disease and OMIM number for disease entry (examples)	IUIS category	OMIM number for disease-associated genes (examples)	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis classification)	Suggestions for alternative diagnosis (i.e., if these criteria are not completely fulfilled)
				• 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 • % naïve 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, hypogammaglobulinemia)	• 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**.
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	

Disease and OMIM number for disease entry (examples)	IUIS category	OMIM number for disease-associated genes (examples)	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis classification)	Suggestions for alternative diagnosis (i.e., if these criteria are not completely fulfilled)
Unclassified syndromic immunodeficiencies			Stephan Ehl, 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**.