ESID Registry – Working Definitions for Clinical Diagnosis of PID

These criteria are only for patients with **no genetic diagnosis**.

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

Agammaglobulinaemia 3
Asplenia syndrome (Ivemark syndrome) 3
Ataxia telangiectasia (ATM) 3
Autoimmune lymphoproliferative syndrome (ALPS) 3
CSR defects and HIGM syndromes 4
Chediak Higashi syndrome (CHS) 4
Chronic granulomatous disease (CGD) 5
Combined immunodeficiency (CID) 5
Common variable immunodeficiency disorders (CVID) 6
Congenital neutropenia 7
Cyclic neutropenia 7
Deficiency of specific IgG (Specific antibody deficiency - SPAD) 7
DiGeorge syndrome 7
Dyskeratosis congenita 7
Familial hemophagocytic lymphohistiocytosis syndromes (FHLH) 8
FOXP3 deficiency (IPEX) 8
Glycogen storage disease type 1b (GS1b) 8
Griscelli syndrome type 2 9
HLA class II deficiency (MHC2) 9
Hoyeraal-Hreidarsson syndrome 9
Hyper IgE syndrome (HIES) 10
IgA with IgG subclass deficiency 10
IPEX-like disease 10
Isolated IgG subclass deficiency 11
Isolated congenital asplenia 11
Selective IgM deficiency 11
Omenn syndrome 11
Schimke disease 12
Selective IgA deficiency 12
Severe combined immunodeficiency (SCID) 12

Thymoma with immunodeficiency 12
Transient hypogamma-globulinaemia of infancy 12
Wiskott-Aldrich syndrome (XLT/WAS) 13
Unclassified antibody deficiency 13
Unclassified phagocytic disorders 13
Unclassified disorders of immune dysregulation 14
Unclassified defects in innate immunity 14
Unclassified complement deficiencies 14
Unclassified autoinflammatory diseases 15
Unclassified syndromic immunodeficiencies 15
Unclassified immunodeficiencies 15

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
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	

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 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

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
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)	
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

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
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)	
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)	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
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 below) **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**.

Differential diagnosis of hypogammaglobulinaemia

ADULTS AND (CHILDREN) - *Drug Induced:* Antimalarial agents, Captopril, Carbamazepine, Glucocorticoids, Fenclofenac, Gold salts, Penicillamine, Phenytoin, Sulfasalazine
CHILDREN AND (ADULTS) - *Genetic Disorders:* Ataxia Telangiectasia, Autosomal forms of SCID, Hyper IgM Immunodeficiency, Transcobalamin II deficiency and hypogammaglobulinemia, X-linked agammaglobulinemia, X-linked lymphoproliferative disorder (EBV associated), X-linked SCID, Some metabolic disorders, Chromosomal Anomalies, Chromosome 18q- Syndrome, Monosomy 22, Trisomy 8, Trisomy 21
CHILDREN - *Infectious Diseases:* HIV, Congenital Rubella, Congenital infection with CMV, Congenital infection with Toxoplasma gondii, Epstein-Barr Virus
ADULTS - *Malignancy:* Chronic Lymphocytic Leukemia, Immunodeficiency with Thymoma, Non Hodgkin's lymphoma, B cell malignancy
CHILDREN AND ADULTS - *Systemic Disorders:* Immunodeficiency caused by hypercatabolism of immunoglobulin, Immunodeficiency caused by excessive loss of immunoglobulins (nephrosis, severe burns, lymphangiectasia, severe diarrhea)

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
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	
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 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	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
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
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	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
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
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)	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
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**.
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**
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

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
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	
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**
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.

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
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	
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**.
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**.
Thymoma with immunodeficiency	David Edgar, Helen Chapel	Presence of thymoma **AND** reduced serum IgG (< 2SD below the mean reference for age)	
Transient hypogamma-globulinaemia 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.	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
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)	
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')	
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)	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
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**.
Unclassified complement deficiencies	Annarosa Soresina	**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	

Disease	Contributors	Clinical criteria for a probable diagnosis (= clinical diagnosis)	Suggestions for alternative diagnosis (i.e. if these criteria are not completely fulfilled)
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	Stephan Ehl	**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**.