ESID Registry - Working definitions for clinical diagnosis of PID

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

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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 hypogammaglobulinaemias”
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

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CSR defects and HIGM syndromes with unknown genetic cause	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)	
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)	

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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 hypogammaglobulinaemias” 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** Exclusion of secondary causes of neutropenia	For other patients with chronic neutropenia, please consider “Unclassified phagocytic disorders”

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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, consider "Unclassified disorders of immune dysregulation"
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 hypogammaglobulinaemias" For other patients, please consider "Unclassified immunodeficiencies"
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

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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 vaccination	For patients with abnormal vaccine responses, consider “Deficiency of specific IgG (SPAD)”; For other patients, consider “Unclassified hypogammaglobulinaemias”
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 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 the 4th birthday NB: patients will initially be registered as “hypogammaglobulinaemia, unclassified" in the registry and moved to THI, if there is spontaneous resolution before age 4.	

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Wiskott-Aldrich syndrome (XLT/WAS)	Annarosa Soresina, Natalia, 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 hypogammaglobulinaemias	Vojtech Thon, Natalia Martinez, Maria Kanariou, Klaus Warnatz, Isabella Quinti	**One of the following:** *Recurrent infections *Autoimmune phenomena (especially cytopenias) *lymphoproliferation/lymphoma **AND** marked decrease of at least one of IgG ,IgG subclass(es), IgA or IgM levels (measured at least twice) **AND** secondary causes of hypogammaglobulinaemia have been excluded **AND** Normal isohaemagglutinins or/and antibody response to vaccines **AND** Normal T-cells and normal naive T cells	Marked decrease of only IgA otherwise fulfilling this definition should be classified as selective IgA deficiency
Unclassified combined immunodeficiencies	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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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 hypogammaglobulinaemias”
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”

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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	
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, malignancy) **AND** absence of syndromic manifestations	For patients with syndromic manifestations, consider "Unclassified syndromic IDs"