[i]2025 Inborn Errors of Immunity Practice Parameters:

Guidance from the American Academy of Allergy, Asthma, and Immunology; American College of Allergy, Asthma, and Immunology; and the Clinical Immunology Society

Authors:

Editors: Jordan S. Orange[a], Javier Chinen[b], Caroline C. Horner[c], Lisa J. Kobrynski[d]

Section Editors: Mark Ballow[e], Manish J. Butte[f], Shanmuganathan Chandrakasan[g], Ivan K. Chinn[a], Lisa Forbes Satter[a], Alexandra F. Freeman[h], Jennifer R. Heimall[i], Vijaya Knight[j], Monica G. Lawrence[k], Heather K. Lehman[l], Paul J. Maglione[m], Elena E. Perez[n], Kimberley A. Risma[o], Jolan E. Walters[e].

Workgroup Members: Roshini S. Abraham[p], Sara Barmettler[q], Christopher C. Chang[r], Alice Chan[s], Karin Chen[t], Jim Connelly[u], Lara A. Danziger-Isakov[v], M. Teresa de la Morena[t], Daniel DiGiacomo[w], Victoria R. Dimitriades[x], Morna Dorsey[s], Daniel E. Dulek[y], Cullen M. Dutmer[d], Christopher Dvorak[s], Jocelyn R. Farmer[q], Ashley Frazer-Abel[z], Avni Y. Joshi[aa], Michael D. Keller[bb], Yasmin W. Khan[cc], Maleewan Kitcharoensakkul[c], Jennifer W. Leiding[e], Kasiani C. Myers[dd], Vijayalakshmi Nandakumar[z], Craig D. Platt[ee], Sung-Yun Pai[ff], Niraj C. Patel[gg], Tamara C. Pozos[hh], Jennifer M. Puck[s], Nicholas L. Rider[ii], Keith A. Sacco[h], Kelli W. Williams[jj].

JTF Members. Jay A. Lieberman,[kk] Matthew A. Rank,[ll] Marcus S. Shaker,[mm] Elissa M. Abrams,[nn] Jonathan A. Bernstein[oo], Derek K. Chu[pp], Anne K. Ellis[qq], David B. K. Golden [rr], Matthew Greenhawt, [j] Dennis K Ledford, [ss] Caroline C. Horner [c], Gisselle Mosnaim [tt], Julie Wang. [uu]

Author's Institutions:

[a] Division of Allergy, Immunology and Rheumatology, Department of Pediatrics. Columbia University, New York, NY

[b] Division of Immunology, Allergy and Retrovirology. Department of Pediatrics. Baylor College of Medicine, Houston and The Woodlands, TX

[c] Division of Allergy, Immunology and Pulmonary Medicine. Department of Pediatrics. Washington University. St. Louis. MO

d Division of Allergy and Immunology, Department of Pediatrics. Emory University, Atlanta, GA

e Division of Allergy and Immunology, Department of Pediatrics. University of South Florida, St. Petersburg, FL.

f Division of Allergy, Immunology and Rheumatology, Department of Pediatrics. University of California, Los Angeles. Los Angeles, CA.

g Division of Hematology and Oncology, Department of Pediatrics. Emory University. Atlanta, GA

h Laboratory of Clinical Immunology and Microbiology. National Institutes of Allergy and Infectious Diseases. Bethesda, MD

i Division of Allergy and Immunology, Department of Pediatrics. University of Pennsylvania. Philadelphia, PA

j Division of Allergy and Immunology, Department of Pediatrics. University of Colorado. Aurora, CO

k Division of Asthma, Allergy and Immunology. Department of Medicine. University of Virginia. Charlottesville, VA

l Division of Allergy, Immunology and Rheumatology, Department of Pediatrics. State University of New York at Buffalo. Buffalo, NY

m Pulmonary Center, Section of Pulmonary, Allergy, Sleep & Critical Care Medicine, Department of Medicine, Boston University Chobanian & Avedisian School of Medicine, Boston, MA

n Institute for Asthma and Allergy. North Palm Beach, FL

o Division of Allergy and Immunology, Department of Pediatrics. University of Cincinnati, Cincinnati, OH

p Department of Pathology. Ohio State University. Columbus, OH

q Allergy and Clinical Immunology Unit. Department of Medicine. Harvard Medical School, Boston, MA

r Department of Allergy and Immunology. Joe DiMaggio Children's Hospital. Hollywood, FL

s Division of Allergy, Immunology and Rheumatology, Department of Pediatrics. University of California San Francisco. San Francisco, CA

t Division of Immunology, Department of Pediatrics. University of Washington, Seattle, WA

u Division of Hematology and Oncology, Department of Pediatrics. Vanderbilt University. Nashville, TN

v Division of Allergy and Immunology, Department of Pediatrics. University of Cincinnati, Cincinnati, OH

w Pediatric Allergy and Immunology. Jersey Shore University Medical Center. Neptune, NJ

x Division of Allergy, Immunology and Rheumatology, Department of Pediatrics. University of California Davis. Sacramento, CA

y Division of Infectious Diseases. Department of Pediatrics. Vanderbilt University. Nashville, TN

z Division of Rheumatology, Department of Medicine. University of Colorado. Aurora, CO

aa Division of Allergy and Immunology. Department of Pediatrics and Adolescent Medicine. Mayo Clinic, Rochester, MN

bb Division of Allergy and Immunology. Department of Pediatrics. George Washington University. Washington, DC

cc Division of Allergy and Immunology. Department of Pediatrics. Vanderbilt University. Nashville, TN

dd Division of Hematology and Oncology, Department of Pediatrics. University of Cincinnati, Cincinnati, OH

ee Division of Immunology. Department of Pediatrics. Harvard Medical School, Boston, MA

ff Immune Deficiency Cellular Therapy Program. National Cancer Institute. Bethesda, MD

gg Division of Allergy and Immunology. Department of Pediatrics. Duke University. Durham, NC

hh Immunology Program. Children's Minnesota Hospital. Minneapolis, MN

ii Department of Health Systems & Implementation Science, Virginia Tech Carillion School of Medicine. Roanoke, VA

jj Division of Allergy and Immunology. Department of Pediatrics. Medical University of South Carolina. Charleston. SC

kk Division of Allergy and Immunology. Department of Pediatrics. University of Tennessee. Memphis, TN

ll Division of Allergy, Asthma and Clinical Immunology. Mayo Clinic School of Medicine. Scottsdale and Phoenix, AZ

mm Section of Allergy and Immunology. Department of Medicine. Darmouth School of Medicine. Lebanon, NH

nn Section of Allergy and Immunology. Department of Pediatrics and Child Health. University of Mannitoba, Winnipeg, MB, Canada

oo Division of Immunology, Department of Medicine. University of Cincinnati, Cincinnati, OH

pp Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada

qq Division of Allergy and Immunology, Department of Medicine, Queen's University, Kingston, ON, Canada

rr Division of Allergy and Clinical Immunology, Johns Hopkins University School of Medicine, Baltimore, MD

ss Morsani College of Medicine, University of South Florida and James A. Haley Veterans' Affairs Hospital, Tampa, FL

tt Director of Allergy and Immunology Research. NorthShore University HealthSystem. Evanston, IL

uu Division of Pediatric Allergy and Immunology, Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York City, NY

Conflict of Interest:

Work Group Disclosures:

Dr. Abraham: Grant support from Amgen; Honoraria from ClinGen, NIH, and ClearView; Deputy Editor of Journal of Immunology; and Clinical Immunology Society committee member. Dr. Ballow: Consultant for Pharming, Green Cross, Immune Deficiency Foundation, CSL Behring; Honorarium from UpToDate; Syneos Health Data Safety Monitoring Board for Glaxo Smith Kline; Speaker for CSL Behring, ADMA. Dr. Barmettler: Consultant for CSL Behring; Advisory Board for CSL Behring, OctaPharma; Speaker for OctaPharma; Grant support from Bristol Myers Squibb. Dr. Broderick: Clinical trial support from Novartis; Speaker for SOBI. Dr. Butte: Advisory board for ADMA; Grant support from X4, Pharming; Consultant for Pharming; Speaker for Grifols. Dr. Chan: Advisory board for SOBI; Grant support from NIH, Jeffrey Modell Foundation. Dr. Chandrakasan: Advisory board and honoraria from SOBI, Pharming, Amgen, X4; Speaker for X4. Dr. Chen: Consultant for Immune Deficiency Foundation; Advisory board for Amgen, Pharming. Dr. Chinen: Associate Editor for Journal of Allergy and Clinical Immunology. Dr. Chinn: Consultant for UpToDate; Working Group and Expert Panel Co-Chair for Clinical Genome Resource. Dr. Connelly: Advisory Board for Pharming; Honorarium from Elsevier. Dr. Danziger-Isakov: Royalties from Elsevier; Consultant for Astellas, Kamada; Clinical research support (institution) from Ansun BiPharma, AiCuris, Merck, Takeda; Past Chair of Disease Transmission Advisory Committee of Organ Procurement and Transplantation Network. Dr. Dorsey: Contributor to UpToDate. Dr. Dulek: Non-salary grant support from Eurofins-Viracor. Dr. Dutmer: Advisory Board for Amgen, Pharming; Executive Committee of Colorado Allergy & Asthma Society; Treasurer Aspen Allergy Conference; RSL Regional Governor AAAAI. Dr. Dvorak: Consultant for Alexion, UpToDate. Dr. Farmer: Consultant for Pharming. Grant support from Pharming, Bristol Myers Squibb. Dr. Forbes Satter: Consultant for Sanofi, Takeda, Grifols, Teva; Advisory Board for CSL,Takeda, Grifols; Grant support from Grifols, Immune Deficiency Foundation; CIS President-Elect. Dr. Frazer-Abel: Consultant for Adverum. Dr. Heimall: Royalties from UpToDate; Grant support from CSL Behring, Sumitomo, ADMA, Regeneron; Speaker for CSL Behring; Consultant for CSL Behring, Sumitomo; Medical Advisory Board for Jobs Research Foundation. Dr. Horner: AAAAI ITE, ADCT, and PDT committees. Dr. Keller: Consultant for Chiesi, M3 Global Research, Wolters-Kluwer; Honoraria from Chiesi, M3 Global Research, Wolters-Kluwer. Dr. Knight: Consultant for ICON, Cerus; Speaker for Beckman Coulter; Past President Association of Medical Laboratory Immunologists; CIS member; Editor Journal of Allergy and Clinical Immunology; Section Editor UpToDate; Education Committee American Association of Immunologists. Dr. Lawrence: Advisory Board for Pharming, Pharmacosmos; Grant support (institution) from NIH/NIAID, Regeneron, Takeda, Jeffrey Modell Foundation; CIS Councilor, Secretary/Treasurer; AAAAI Primary Immunodeficiency Committee Member; ACAAI Clinical Immunology & Autoimmune Diseases Committee, Special Advisor. Dr. Lehman: Advisory board for Sanofi; Grant support (institution) from Sanofi, Novartis; AAAAI ITE and PID committee member, Program Directors Assembly Councilor. Dr. Leiding: Stock in Bluebird Bio; Speaker for Grifols, SOBI; Consultant for Rocket Pharma, Prime Medicine; DSMB for Prime Medicine; Advisory board for SOBI, Amgen; Grant support from SOBI. Dr. Maglioni: Speaker for Takeda; Advisory board for Pharming. Dr. Myers: Clinical trial support from Incyte, Elixirgen Therapeutics; Medical advisory board for Team Telomere, Shwachman Diamond Syndrome Foundation; Co-Director Shwachman Diamond Syndrome Registry. Dr. Nandakumar: Secretary-Elect, Association of Medical Laboratory Immunologists; Executive officer, Association for Diagnostics & Laboratory Medicine. Dr. Orange: Consultant for Grifols, Takeda; Scientific advisory board for ADMA Biologics; Editor/Author UpToDate; Grant support

(institution) ADMA Biologics; Medical Advisor Jeffrey Modell Foundation. Dr. Patel: Consultant for Takeda, Janssen; Advisory board for Amgen; Speaker for Grifols, AAP, ACAAI, Amgen, Pharming, Takeda, X4 Pharma; Grant support from Takeda, ACAAI. Dr. Perez: Consultant for Grifols, CSL Behring, ADMA; Advisory board for Grifols, CSL Behring, ADMA; Speaker for Grifols, CSL Behring, ADMA; Member of AAAAI, FAAIS, CIS. Dr. Platt: Royalties from UpToDate; Expert witness for Department of Justice Vaccine Injury Compensation Program; Employment (spouse) by Quest Diagnostics; Executive committee member of Immunology Clinical Domain Working Group - Antibody Deficiencies and Primary Immune Regulatory Disorders for Clin Gen. Dr. Puck: Consultant (spouse) for Illumina; Contributor/Editor for UpToDate; Expert for California Dept of Public Health; Educational grant support (institution) from NIH; Grant support (institution) from NIH, CA Institute for Regenerative Medicine. Dr. Rider: Royalties from Wolters Kluwer; Associate Editor Journal of Clinical Immunology; Consultant for Takeda, Grifols, Pharming, X4 Pharmaceuticals; Grant support from NIH/NIAID, CDC/Jeffrey Modell Foundation, Takeda. Dr. Sacco: Speaker for Pharming. Dr. Walter: Consultant for Takeda, Cheisi, Pharming, GenPharm; Advisory Board for Takeda, Cheisi, Pharming; Speaker for Pharming, Takeda, GenPharm; Grant support from X4 Pharmaceuticals, Orca Bio, Takeda, Grifols, Cheisi, ADMA, Octapharma, Bristol-Myers Squibb. Dr. Williams: Consultant for Blueprint, Amgen, ADMA Biologics; Advisory Board for Blueprint, Genentech; Speaker for Pharming, Amgen; Advisory board for Pharming; Clinical trial grant support (institution) from Glaxo Smith Kline, ADMA Biologics, Cogent, AstraZeneca.

Nothing to disclose: Drs. Chang, de la Morena, DiGiacomo, Dimitriades, Freeman, Joshi, Khan, Kitcharoensakkul, Kobrynski, Pai, and Risma.

The JTFPP members' conflict of interest disclosure forms can be found at www.allergyparameters.org

Dr. Abrams: Nothing to disclose. Dr. Bernstein: Consultant for Novartis, Genentech, Sanofi Regeneron, Allakos, Celldex, Jasper, Escient/Incyte, Blueprint, Cogent, ARS, Guidepoint; Advisory Board for Novartis, Genentech, Sanofi Regeneron, Celldex; Grant support from Novartis, Genentech, Sanofi Regeneron, Allakos, Celldex, Jasper, Escient/Incyte, Blueprint, Cogent; AAAAI Board of Directors, AAAAI Foundation Chair, AFI Executive Vice President, Interama Vice President, WAO Board of Directors, ACARE/UCARE/ADCARE/ANACARE Director of COE, GINA Council Member, AIM COE Co-director. Dr. Chu: Grant support from AAAAI Foundation Faculty Development Award; Grant support (institution) from Canadian Institutes of Health Research, Ontario Ministry of Health and Long-Term Care/Ontario Medical Association, Health Canada (Government of Canada); GRADE Working Group Member. Dr. Ellis: Speaker for ALK Abello, AstraZeneca, Glaxo Smith Kline, Novartis, Amgen, Bausch Health, Regeneron, Sanofi; Consultant for Regeneron. Dr. Golden: Consultant for Kokua, ThermoFisher, CellDex, Aquestive, Novartis; Speaker for ARS; Royalties from UpToDate; Editorial Board for Journal of Allergy Clinical Immunology In Practice, Annals of Allergy Asthma Immunology. Dr. Greenhawt: Consultant for Aquestive; Advisory board for DBV Technologies, Takeda, Griffols, Nutricia, Novartis, Aquestive, Allergy Therapeutics, AstraZeneca, ALK-Abello, Bryn, Genentech, Prota; Speaker for Genentech, ARS; Unpaid member of scientific advisory council for National Peanut Board and medical advisory board of International Food Protein Induced Enterocolitis Syndrome Association; Brighton Collaboration Criteria Vaccine Anaphylaxis 2.0 working group member; Senior associate editor Annals of

Allergy, Asthma, and Immunology; Honoraria from Red Nucleus, Medscape, MJH Communications, Paradigm Medical Communications, Kaplan, Food Allergy Research and Education, and multiple state/local allergy societies. Dr. Ledford: Consultant for Amgen, AstraZeneca; Honoraria from AAAAI, Wolters Kluwer, ECHO CME; Grant support from AstraZeneca; Legal testimony fees; Speaker for Regeneron, Sanofi, Glaxo Smith Kline, AstraZeneca. Dr. Lieberman: Consultant for ARS, Aquestive, Bryn, Celldex, Abbvie, Amgen, Novartis, Genentech, Theravia; Advisory Board for Aquestive, Bryn; Grant support (institution) from DBV; Author for ARS, Aquestive, Bryn, DBV; Associate Editor of Annals of Allergy, Asthma, and Immunology; ACAAI Annual Meeting Program Committee Chair, Food Allergy Chair, Yardstick Committee Chair; ABAI Executive Board Member. Dr. Mosnaim: ABAI Board of Directors Member, Co-Chair Continuous Assessment Program Examination Committee, Chair Nominating Committee; Advisory Board for Chiesi, Jasper, Novartis, Sanofi, Regeneron, Astra Zeneca, Genentech; Consultant for Chiesi, Jasper, Novartis, Sanofi, Regeneron, Astra Zeneca, Genentech; Grant support (institution) from Aretia, Incyte, Teva, Glaxo Smith Kline, Novartis, Sanofi, Regeneron, Astra Zeneca, Genentech; Fellow of AAAAI, ACAAI, Illinois Society of Allergy Asthma and Immunology Dr. Rank: Royalties from UpToDate, Mayo Ventures; AAAAI Committee Member, FDA PADAC Committee Member. Dr. Shaker: Speaker for Local and Regional Allergy Society; Honoraria from Local and Regional Allergy Society; Associate Editor ACAAI; AAAAI Board of Directors; Editorial Board for Journal of Food Allergy, Journal of Allergy and Clinical Immunology In Practice.Dr. Wang: Advisory Board for FARE, Novartis; Clinical trial support (institution) from Aimmune, DBV, Siolta, NIH; Author for UpToDate; AAAAI AMPC Chair.

Resolving Conflicts of Interest: The JTFPP is committed to ensuring that the Practice Parameters are based on the best scientific evidence at the time of publication and that such evidence is free of commercial bias to the greatest extent possible. (https://www.allergyparameters.org/parameter-and-guideline-development-process/) The JTFPP recognizes that experts in a field may have interests that could create a potential conflict of interest (COI) with the development of a completely unbiased and objective practice parameter. To take advantage of their expertise, a process has been developed to acknowledge potential COI and attempt to prevent them from influencing the final document in a negative way. The disclosure and management of potential conflicts for all participants were conducted in accordance with JTFPP policies. To preserve the greatest transparency regarding potential COI, all members of the JTFPP and the practice parameters workgroups complete a standard potential COI disclosure form before the development of each document. During the review process, there are additional measures to avoid bias. At the workgroup level, all the sections are reviewed by all workgroup members to ensure that content is appropriate and without apparent bias. In addition, the entire document is then reviewed by the JTFPP, and any apparent bias is removed at that level. At the time of appointment, there were not any workgroup members with conflicts of interest as defined and judged by JTFPP (ie, no current material interest in any commercial entity with a product that could be affected by the guidelines). No new disclosure of new interests or relationships occurred during the development process. The final document and all recommendations are reviewed and approved by the workgroup and JTFPP. In a final stage of review, the practice parameter is sent to invited expert reviewers, selected by the AAAAI and the American College of Allergy, Asthma, and Immunology (ACAAI). The document is also posted on the AAAAI and ACAAI (and CIS for this parameter) websites for general membership and

the public-at-large to review and offer comment. Reviewers are also asked to provide statements of potential COI. Although the JTFPP has the final responsibility for the content of the documents submitted for publication, each reviewer's comment is discussed, and reviewers receive written responses to comments when appropriate.

PREFACE. What is New

The Joint Task Force on Practice Parameters (JTFPP) was commissioned by the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) in 1989 to develop guidelines for the clinical practice of allergy and clinical immunology reflecting current evidence-based practices and clinical consensus, and to provide periodic updates. The first practice parameter for primary immunodeficiencies was developed and published in 1995.[1] The publication was 13 printed pages long with 47 references. It focused on the assessment of immunological function with management limited to intravenous immunoglobulins for antibody deficiencies and bone marrow transplantation for severe cellular immunodeficiencies. Subsequent updates were published in 2005 and 2015 and were 63 and 98 printed pages, respectively with 530 and 768 references.[2, 3] These versions expanded upon the diagnosis and care of patients with primary immunodeficiencies.

Reports of several genetic defects resulting primarily in autoimmunity and inflammatory symptoms with or without immune deficiency provided the justification for the International Union of Immunological Societies (IUIS) committee to coin the term Inborn Errors of Immunity (IEI) for all congenital disorders that primarily affect immune function, including primary immunodeficiencies. The field of IEI has grown substantively over the past decade and continues to expand. Considering the large number of publications related to the care of patients with IEI, it would be unwieldly to provide all available information in a practice parameter. The guiding principle for this practice parameter update was to present the best evidence-based recommendations to support practice, while avoiding being encyclopedic or becoming a textbook. In this update, several sections utilize tables to outline some disease specific recommendations rather than discussing each one individually in the text, while providing key references. This conveys guidelines for diagnosis and management highlighting specific examples, as well as exceptions. Broadly, the document is divided into diagnostic (1-7) and management (8-14) sections.(**Figure 1**)

New topics of importance to improving the care of patients with IEI are included. Since the last practice parameters in 2015, there have been significant advances in genetic testing and identification of novel pathogenic gene variants causing IEI. Genetic testing has also become widely available, in part due to its decreasing cost.

As in previous practice parameters on IEI, the current sections on diagnosis and management of antibody deficiencies include statements more specific than those discussed for other IEI disorders, consistent with the larger proportion of patients in these categories and the high number of available publications relative to other IEI. Because of the implementation of universal newborn screening for severe combined immunodeficiency (SCID), guidance for prompt management of infants with abnormal

screening tests is included. Specific protein antibody deficiency with recurrent infections is being introduced as a diagnosis for those patients with adequate serum IgG levels and absent response to antigens other than polysaccharides. Targeted therapy or precision medicine for IEI based on immunopathogenesis has changed the landscape of therapies for these disorders over the last decade. Thus, Section 13 is focused upon therapies that have been shown to be effective for many IEI. The last section discusses the use of tools to measure patient reported outcomes and quality of life (QoL). Several statements refer to the importance of consulting a clinician with expertise in the care of IEI. Expertise is defined as clinical training in IEI and providing care to patients with IEI. Of note, the JTFPP has developed a focused practice parameter for hereditary angioedema[4] and this condition is not included in the present document. Secondary immunodeficiencies constitute a growing area of clinical knowledge, with an increasing use of different therapeutic applications that modulate the immune response. Other than referring to their diagnostic evaluation, secondary immunodeficiencies are not discussed in depth in this practice parameter.

ABBREVIATIONS

AAAAI, American Academy of Allergy, Asthma and Immunology

ACAAI, American College of Allergy, Asthma and Immunology

ACIP, Advisory Committee on Immunization Practices

AD, autosomal dominant

ADA; adenosine deaminase

ALPS; autoimmune lymphoproliferative syndrome

APDS; activated phosphoinositide 3-kinase delta syndrome

AR, autosomal recessive

AT; ataxia-telangiectasia

BCG; bacillus Calmette-Guerin

CAPS; cryopyrin associated periodic fever

CDC, Center for Disease Control and Prevention

CFH; complement Factor H

CGD, chronic granulomatous disease

CH50; complement hemolytic activity 50%

CID, combined immunodeficiency

CMV, cytomegalovirus

CNV, copy number variation

CTTI, cultured thymus tissue implantation

CVID; common variable immune deficiency

DIRA; deficiency of IL-1 receptor antagonist

DNT, double negative T cells

EBV; Epstein-Barr virus

FCAS; familial cold autoinflammatory syndrome

FMF; familial mediterranean fever

GOF, gain of function

GRADE, Grading of Recommendations, Assessment, Development, and Evaluation

GvHD; graft versus host disease

HIV; human immunodeficiency virus

HCT/HSCT; hematopoietic stem cell transplant

HLH, hemophagocytic lymphohistiocytosis

IEI, Inborn Error(s) of Immunity
IgRT; immunoglobulin replacement therapy
INF; interferon
IPEX; immunodeficiency, polyendocrinopathy, enteropathy, X-linked
IUIS; International Union of Immunological Societies
IVIG, intravenous immunoglobulins
HIDS; hyper IgD syndrome
JTFPP, Joint Task Force on Practice Parameters
KREC; kappa restriction excision circle
LAD; leukocyte adhesion deficiency
LOF, loss of function
MHC; major histocompatibility syndrome
MPS, massive parallel sequencing
MSMD; Mendelian susceptibility to mycobacterial disease
NBS, newborn screening
NTM, non-tuberculous mycobacteria
PAP; pulmonary alveolar proteinosis
PAPA; pyogenic arthritis pyoderma gangrenosum and acne
PHA; phytohemagglutinin
PID, primary immunodeficiency
PIDTC; Primary Immune Deficiency Treatment Consortium
PIRD; primary immune dysregulatory disorders
PRO, patient related outcome
QoL, quality of life
RTE; recent thymic emigrant
SAD; specific antibody deficiency
SCID, severe combined immunodeficiency
SCIG; subcutaneous immunoglobulin
SNP; single nucleotide polymorphism
SNV; single nucleotide variant
TRAPS; TNF receptor associated periodic syndrome
WAS; Wiskott-Aldrich syndrome
WES; whole exome sequencing

WGS; whole genome sequencing

WHIM; warts, hypogammaglobulinemia, infections and myelokathexis

XLP; X-linked lymphoproliferative syndrome

GLOSSARY

Antibody deficiency. A condition characterized by impaired quantitative or functional antibodies.

Combined immune deficiency. A condition characterized by impaired T and B cell functions.

Chromosomal microarray (CMA). A genetic test that identifies deletions or duplications of DNA regions in the genome, also known as copy number variants (CNV).

Immune dysregulation. A defect in the immune system to control its reaction to microbes, other foreign substances and body tissues, resulting in excessive and/or insufficient response.

Immunodeficiency. A condition characterized by impaired immune responses.

Immunorestorative therapy. A term referring to treatments that correct the immune response, including hematopoietic stem cell transplantation (HSCT), cultured thymus tissue implantation (CTTI) and gene therapy.

Inborn errors of immunity (IEI). A group of genetic disorders that result in increased occurrence of infections, immunodysregulation (autoimmunity, autoinflammation and allergy) and cancer

Leaky SCID. A form of severe combined immunodeficiency (SCID), also known as atypical SCID, that presents with a small number of T cells, usually oligoclonal and with impaired function. These T cells may be autoreactive and produce inflammation in the skin, liver and lymphadenopathy, a condition known as Omenn syndrome.

Jakinib. A class of small molecules that inhibit JAK/STAT signal transduction pathways, with application in the management of allergic and inflammatory conditions. Also referred as Jak inhibitor.

Massive parallel sequencing. (MPS), A number of high throughput methods of DNA sequencing using simultaneous reactions in micro platforms. Also known as next-generation sequencing (NGS)

Newborn screening. Also known as Universal Newborn Screening (NBS), it is a public health program that identifies treatable disorders in newborns, mostly metabolic and hereditary. The goal of NBS is to diagnose and treat infants early to prevent or reduce severe medical outcomes.

Non-coding region, DNA sequences that do not code for a protein aminoacid sequence. Examples are introns and regulatory elements

Precision medicine. In IEI, refers to a medical approach of using therapeutic agents that address the specific molecular defect of the patient's condition.

Somatic mosaicism. The presence of a genetically distinct group of cells within tissues, secondary to a gene variant occurring after a fertilized oocyte starts dividing.

Quality of Life. A subjective measure of how a patient is doing at a particular point of time. It is multidimensional, including physical, mental, and social health. This information comes directly from the patient (patient-reported outcome), usually in the form of a questionnaire (patient's perception of their health). It aims to capture the well-being, whether of a population or individual, regarding both positive and negative elements within the entirety of their existence at a specific point in time.

Whole exome sequencing. A laboratory method aimed to sequence exons of all known genes, using massive parallel sequencing.

METHODS

Systematic appraisal of the evidence and using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology[5] is internationally accepted as the optimal way to inform clinical decision making. While this Practice Parameter document does not formally employ all aspects of GRADE, we strive to adopt as many qualities as possible and present recommendations with a clear separation of strength of recommendation and Certainty of Evidence (informed by the formal GRADE domains) as possible.

The JTFPP conceived the project, obtained approvals from the parent organizations, recruited a workgroup of clinical experts and Chairs and provided overall oversight, including document review, feedback, and approval of the parameter. Within the membership of ACAAI and AAAAI, experts in the field of IEI were selected based on recent accomplishments, expertise, and leadership. The team reviewed the published scientific literature and provided concise summary recommendations. Workgroup discussions of recommendations were conducted twice a year. Simple vote and majority consensus were adopted to make decisions when differences of opinion occurred.

Recommendations are rated based on the strength of recommendation and the certainty of evidence. The paucity of controlled studies or trials combined with the relative rarity of some IEI presents a challenge for the GRADE system's use. Nonetheless, the statements have undergone extensive review by the authors, members of the JTF and the AAAAI, ACAAI and CIS, and given opportunities for all members to provide comments and feedback.

Each summary statement provides terms denoting the strength of recommendation and an assessment of the certainty of evidence following these definitions.

Strength of Recommendation

Strong = Recommended
Desirable effects outweigh undesirable effects
Most patients would want this course of action Most clinicians would implement these recommendations in patient care Most policy makers would agree to follow these recommendations
Conditional = Suggested
Most patients would want this course of action, but many may not Most clinicians would consider this course of action, but would review the case to see if other options are also appropriate and involve the patient in shared decision making Policy makers will likely require additional information from many stakeholders

Adapted from Chu DK[5]

Certainty of Evidence

High	Further research is very unlikely to change the confidence in the recommendation.
Moderate	Further research is likely to affect the confidence of the balance of effects and may change the recommendation.
Low	Further research is likely to change the recommendation.
Very Low	The estimate of the effect is very uncertain.

Adapted from Dykewicz M. et al.[6]

EXECUTIVE SUMMARY

Since the publication of the previous practice parameter in 2015, many advances in the care and diagnosis of patients with primary immune deficiency disorders (now also known as inborn errors of immunity (IEI)) have occurred. This practice parameter will discuss and highlight some of these changes, including the use of genetic testing in the diagnosis and in guiding treatment of IEI, newborn screening for severe T cell lymphopenia, and the use of targeted therapies and precision medicine, based on the identification of the immunopathology of the disorder. This practice parameter discusses groups of disorders based on the most recent disease classification system set out by the International Union of Immunology Societies (IUIS).[7]

Section and number	RECOMMENDATION	Strength	Certainty of Evidence
SECTION 1: Clinical Approach to the Diagnosis Of IEI			
1.1	**We recommend** investigating for IEI diagnosis in patients with recurrent, severe, or rare infections, autoinflammation, autoimmunity, severe atopy, atypical malignancy, bone marrow failure or combinations of these conditions.	Strong	High
1.2	**We recommend** obtaining a detailed family history to support the IEI diagnosis and to identify undiagnosed affected relatives.	Strong	Moderate
1.3	**We recommend** an integrated approach for the diagnosis of a suspected IEI: clinical, immunological and genetic components.	Strong	Moderate
1.4	**We recommend** that the evaluation of immunodeficiency should include testing for secondary causes of immunodeficiency**.**	Strong	Moderate
1.5	**We suggest** consultation with a clinical immunology expert and multidisciplinary care for the evaluation and follow up of suspected or diagnosed patients with IEI.	Conditional	Moderate
1.6	**We suggest** the provision of supportive resources (e.g., social, educational, emotional) for patients and families diagnosed with IEI.	Conditional	Low
SECTION 2: Newborn screening for Severe Combined Immunodeficiency and Athymia- Diagnostic and Initial Approach			
2.1	**We recommend** TREC quantitation for newborn population-based screening for the early identification of newborns with severe combined immunodeficiency (SCID) and complete athymia.	Strong	High

2.2	**We recommend** the urgent confirmation of an abnormal NBS for SCID with complete blood counts with differential and flow cytometric measurement of peripheral blood lymphocyte subset populations, including assessment of numbers of T, B and NK subsets and naïve T cells.	Strong	High
2.3	**We recommend** that diagnostic evaluation for SCID and athymia include genetic testing, ascertainment of maternal T cell engraftment, IgE levels, eosinophilia, T cell oligoclonality, T cell proliferation and adenosine deaminase enzyme activity.	Strong	High
2.4	**We recommend** urgent referral to centers with expertise in the care of severe immunodeficiency after SCID or athymia diagnosis is confirmed.	Strong	High
2.5	**We recommend** referral to clinicians with expertise in IEI for assessment and diagnosis of patients with non-SCID T cell lymphopenia detected by NBS.	Strong	Moderate
SECTION 3 – Genetic Evaluation of IEI			
3.1	**We recommend** single gene sequencing to test patients with suspected IEI who have a similarly affected family member with a known genetic defect or who present with a condition with a defect in a gene that might not be reliably analyzed using high-throughput massively parallel sequencing.	Strong	High
3.2	**We recommend** targeted gene panel sequencing including genes associated with IEI or exome sequencing as an initial step for genetic diagnosis, when a familial gene defect does not explain the patient's condition.	Strong	High
3.3	**We suggest** whole genome sequencing of individuals with suspected IEI and non-immunologic traits or with high suspicion for a non-coding genetic defect.	Conditional	Low

3.4	**We recommend** DNA copy number variant testing in patients with IEI with a suspected gene(s) deletion or duplication.	Strong	High
3.5	**We recommend** the American College of Medical Genetics and Genomics (ACMG) guidelines for evaluating gene variant pathogenicity.	Strong	High
3.6	**We recommend** familial genetic testing to aid in gene variant pathogenicity resolution.	Strong	High
3.7	**We suggest** familial genetic testing to ascertain risk of disease in currently unaffected relatives.	Conditional	Low
3.8	**We recommend** investigating multiple genetic diagnoses when a monogenetic diagnosis does not explain the patient's clinical characteristics.	Strong	Moderate
3.9	**We recommend** that genetic testing for patients with IEI can be ordered by clinicians with expertise in IEI and not limited to geneticists.	Strong	Moderate
SECTION 4. Immunologic diagnosis of predominantly antibody deficiencies			
4.1	**We recommend** that patients with suspected antibody deficiencies be evaluated with immunoglobulin measurement, antigen-specific antibody responses and lymphocyte phenotyping and exclusion of secondary causes of antibody deficiency.	Strong	High
4.2	**We recommend** the diagnosis of agammaglobulinemia for patients with low or undetectable serum immunoglobulin concentrations ***and*** low or undetectable circulating B lymphocytes *and* normal total CD3+ T cell numbers.	Strong	High
4.3	**We recommend** the diagnosis of CVID for patients with low serum IgG ***and*** low serum IgA and/or low IgM levels ***and*** demonstrated	Strong	High

	impaired antibody response to infection or immunization.		
4.4	**We recommend** the diagnosis of selective IgA deficiency (SIGAD) for patients older than 4 years of age with serum IgA below the limit of detection ***and*** normal serum IgG and IgM levels.	Strong	High
4.5	**We suggest** the diagnosis of IgG subclass deficiency for patients with recurrent infections ***and*** low levels of one or more serum IgG subclass levels (IgG1, IgG2 or IgG3 excluding IgG4) ***and*** normal serum total IgG levels.	Conditional	Moderate
4.6	**We suggest** the diagnosis of specific antibody deficiency (SAD) to polysaccharides for patients with recurrent respiratory infections ***and*** impaired antibody responses to polysaccharides ***and*** normal serum total IgG levels.	Conditional	Moderate
4.7	**We suggest** the diagnosis of specific antibody deficiency (SAD) to protein antigen for patients with recurrent infections ***and*** impaired antibody responses to protein antigen immunizations ***and*** normal serum total IgG levels.	Conditional	Low
4.8	**We recommend** that patients with low serum IgG and IgA levels ***and*** normal or elevated serum IgM level be given the diagnosis of immunoglobulin class-switch defects **after ruling out** combined immunodeficiencies that present with similar laboratory findings.	Strong	High
4.9	**We recommend** considering the diagnosis of transient hypogammaglobulinemia of infancy (THI), for infants and children with low serum IgG level ***and*** normal antibody response to immunizations ***and*** absent evidence of secondary causes.	Strong	High
4.10	**We suggest** considering the diagnosis of unspecified primary hypogammaglobulinemia for patients with significant morbidity from infections ***and*** low serum IgG level ***and*** normal cellular	Conditional	Moderate

	immunity AND absent evidence of secondary causes of low IgG levels ***and*** who do not fulfill diagnostic criteria for the above antibody deficiency disorders.		
SECTION 5. Immunology Diagnosis of Combined Immunodeficiencies, Neutrophil Defects, Innate Immune Defects and Complement Deficiencies			
Combined immunodeficiencies less severe than SCID and syndromic immunodeficiencies			
5.1	**We recommend** immunological investigations in patients with infectious manifestations, autoimmunity, malignancy, or organ-specific pathologies, suggesting cellular and humoral immunodeficiency.	Strong	High
5.2	**We recommend** the diagnosis of CID for patients with impairment (quantitative or functional) of both cellular and antibody immune functions.	Strong	High
5.3	**We recommend** immunological investigations and testing of diagnostic biological markers in patients with suspicion of CID ***and*** certain specific clinical findings in non-immunological organs and systems (syndromic features).	Strong	High
5.4	**We suggest** periodic assessments of immunological function in patients with CID and syndromic features.	Conditional	Low
Neutrophil Defects			
5.5	**We recommend** that patients with suspected quantitative neutrophil defects be screened with serial CBCs with differential.	Strong	High
5.6	**We recommend** that patients with suspected Leukocyte Adhesion Deficiency (LAD) be tested with flow cytometry analysis of relevant phagocyte surface molecules for LAD I and II, and targeted genetic testing for LAD I, II, III and IV.	Strong	High
5.7	**We recommend** that patients with suspected chronic granulomatous disease (CGD) have measurement of phagocyte	Strong	High

	oxidase activity ***and*** genetic testing for CGD associated gene defects.		
5.8	**We recommend** that patients with pulmonary alveolar proteinosis (PAP) be tested for pathogenic variants in the genes encoding the GM-CSF receptor and for autoantibodies to GM-CSF.	Strong	High
Defects of Innate Immunity			
5.9	**We recommend** that patients with suspected inherited susceptibility to a specific pathogen(s) be investigated for associated gene defects of innate immunity in addition to exclusion of adaptive immune defects and secondary causes of immune defects.	Strong	Moderate
Defects of the Complement System			
5.10	**We recommend** that patients with recurrent or severe infections by encapsulated bacteria ***and*** with normal antibody responses be evaluated for complement deficiency.	Strong	High
5.11	**We recommend** that patients presenting with thrombocytopenia, microangiopathic hemolytic anemia, ***and*** acute renal failure be screened for abnormalities of complement regulatory proteins and/or autoantibodies against complement Factor H (CFH) and related proteins 1 and 3 (CFHR1/CFHR3).	Strong	High
5.12	**We recommend** genetic testing when complement function screening is abnormal.	Strong	Moderate
SECTION 6: Immunologic diagnosis of immune dysregulation disorders (PIRD) and autoinflammatory disorders			
6.1	**We recommend** evaluation for IEI in patients with clinical manifestations of immune dysregulation, such as immunodeficiency, autoimmunity, lymphoproliferation and autoinflammation.	Strong	High

6.2	**We recommend** the assessment of cellular and humoral immunological functions in patients with suspected immune dysregulation disorders.	Strong	High
6.3	**We recommend** that patients with periodic fevers and chronic systemic inflammation should be evaluated for IEI and secondary causes such as infection, autoimmune disease, or malignancy.	Strong	High
6.4	**We recommend** that patients who exhibit lymphoproliferation and autoimmunity be evaluated for primary and secondary immune dysregulation syndromes.	Strong	High
Section 7. Surveillance of potential clinical manifestations in IEI			
7.1	**We suggest** the evaluation of growth (pediatrics) and nutritional status in patients with IEI.	Conditional	Moderate
7.2	**We suggest** testing for specific pathogen infections in patients with IEI known to be associated with high morbidity and mortality to these infections.	Conditional	Moderate
7.3	**We recommend** the assessment of complete blood cell counts with differential in patients with IEI.	Strong	High
7.4	**We recommend *against*** routine screening for autoantibodies, given the high proportion of asymptomatic patients with autoantibodies in circulation.	Strong	Moderate
7.5	**We recommend** the evaluation for major organ system functions and screening for cancer and mental health disorders in patients with IEI.	Strong	High
Section 8. Immunoglobulin Replacement			
8.1	**We recommend** immunoglobulin replacement therapy for patients with IEI with IgG antibody deficiency.	Strong	High

8.2	**We recommend** that initial dosing of immunoglobulin for replacement therapy be at 400 mg/kg-600 mg/kg per month, followed by dose adjustment, if necessary	Strong	Moderate
8.3	**We recommend** the monitoring of serum IgG levels, complete blood cell counts, with differential and serum chemistry for patients on immunoglobulin replacement therapy**.**	Strong	Moderate
8.4	**We recommend** maintaining serum IgG levels at > 800 mg/dl to improve outcomes.	Strong	Moderate
8.5	**We recommend** that immunoglobulin replacement therapy is indicated as a continuous therapy for IEI.	Strong	Low
8.6	**We recommend** that a low or absent IgA, in the setting of low IgG levels, is not a contraindication for immunoglobulin replacement therapy.	Strong	Moderate
8.7	**We suggest** that the route of immunoglobulin replacement therapy be determined based on patient tolerance or preference.	Conditional	Moderate
SECTION 9. Infection Prevention in IEI			
9.1	**We recommend** targeted antimicrobial prophylaxis for patients with IEI and increased susceptibility to infections.	Strong	High
9.2	**We recommend** using only irradiated, cytomegalovirus (CMV)–negative, lymphocyte-depleted blood products for administration to patients with cellular or combined IEI.	Strong	Moderate
9.3	**We recommend** educating patients regarding environmental exposures that may increase the risk of infections for patients with IEI.	Strong	Moderate
9.4	**We suggest** prompt diagnostic testing in patients with IEI with acute infection symptoms and the use of antimicrobial regimens with duration longer than	Conditional	Low

	recommended for immunocompetent patients.		
SECTION 10. Management of co-morbidities in IEI			
10.1	**We suggest** that systemic comorbidities in patients with IEI should be evaluated and managed with a multidisciplinary team with expertise in IEI-related comorbidities.	Conditional	Moderate
10.2	**We recommend** prompt management of cytopenia(s) or malignancies in patients with IEI.	Strong	Moderate
SECTION 11- Immunizations in the Management of IEI			
11.1	**We recommend the** use of vaccine recommendations provided by local government agencies (e.g., CDC) for patients with IEI.	Strong	Low
SECTION 12- Immune Reconstitution Therapy for IEI			
12.1	**We suggest** that allogeneic HSCT for patients with IEI be performed at a center with experience in HSCT for IEI	Conditional	Moderate
12.2	**We recommend** that patients with typical SCID or leaky/atypical SCID receive definitive therapy with allogeneic HSCT or gene therapy.	Strong	High
12.3	**We recommend** that patients with congenital athymia disorders be treated with cultured thymus tissue implantation (CTTI).	Strong	High
12.4	**We recommend** that patients with CID disorders who have severe cellular immune defects or who manifest severe or refractory disease complications be considered for allogeneic HSCT**.**	Strong	Moderate
12.5	**We recommend** that patients with primary HLH disorders and patients with X-linked	Strong	High

	lymphoproliferative disease type 1 be evaluated for HSCT.		
12.6	**We suggest** that patients with immune dysregulation who manifest severe or refractory disease complications be evaluated for allogeneic HSCT.	Conditional	Moderate
12.7	**We recommend** HSCT for patients with defects in neutrophil number or function associated with severe clinical phenotypes**.**	Strong	High
12.8	**We suggest** HSCT in patients with innate immune defects affecting hematopoietic cell lineages and who manifest with recurrent, persistent severe infections.	Conditional	Moderate
12.9	**We recommend** that any patient with IEI who receives definitive treatment with HSCT, CTTI, or gene therapy receive life-long follow-up by clinicians experienced in evaluating immune reconstitution and monitoring for long-term complications of these procedures.	Strong	Moderate
SECTION 13. Precision Medicine in IEI			
13.1	**We recommend** the use of targeted therapies to treat IEI based on either an identified molecular defect or a clinical phenotype suggestive of a defective immune function.	Conditional to Strong	Low to High
SECTION 14. Quality of Life in IEI			
14.1	**We recommend** performing quality of life (QoL) measurements in patients with IEI, inclusive of patient reported outcome measurements (PRO) conducted with a validated tool.	Strong	Moderate
14.2	**We suggest** that patient reported outcomes (PROs) should be measured serially and at important management changes in the patient's clinical journey.	Conditional	Low

14.3	**We suggest** that patients with IEI have perceived health assessed at each clinical encounter.	Conditional	Low
14.4	**We suggest** that patients with IEI be assessed for fatigue at each clinical encounter.	Conditional	Low
14.5	**We suggest** implementing shared decision making between the provider and the patient as part of clinical care to improve QoL and patient satisfaction.	Conditional	Low

Section 1. Clinical Evaluation of IEI.

RECOMMENDATION 1.1. We recommend investigating for IEI diagnosis in patients with recurrent, severe, or rare infections, autoinflammation, autoimmunity, severe atopy, atypical malignancy, bone marrow failure or combinations of these conditions.

Strength of Recommendation **– Strong**

Certainty of Evidence **– High**

Our understanding of the role of the immune system has broadened from defense of the host to include roles in inflammation, regeneration, metabolism, and development.

IEI are suspected in patients who have an unusual presentation of infections, which includes severe outcomes following infection, recurrence of infections, or infection with organisms that are deemed opportunistic (i.e., do not occur in any significant frequency in those with normal immunity).[8] IEI are considered in patients who have atypical presentations of autoimmune diseases, which includes onset at early age, severe manifestations, multiple autoimmune diseases, and those refractory to treatment.[8-10] IEI are also considered in patients with chronic inflammatory processes, which includes autoinflammation, granulomas, severe or prolonged inflammation after infection, or tissue injury.[11, 12] IEI may be diagnosed in patients with very-early onset inflammatory bowel disease, especially under age 6 years.[13, 14] IEI may be considered in patients with severe atopy, with unusual chronicity or refractory to treatment.[15, 16] **Sections 2, 3, 4, 5 and 6** of the Practice Parameter provide guidelines for the diagnostic approach for specific IEI.

IEI are classified according to the principal immunologic mechanisms that are disrupted or dysregulated. Nine broad categories are updated by the International Union of Immunological Societies (IUIS) every 2 years.[7, 17] IEI are presented in tables with associated defective genes and the reported clinical and immunological characteristics. (**Table 1.1**) Disorders affecting T cell function are in IUIS Tables I and II (**see Section 2**

and 5.1) Primary antibody disorders are classified in IUIS Table III (**see Section 4**). Immunodysregulation disorders, characterized by autoimmunity and inflammation, with and without susceptibility to infections, are included in IUIS Table IV (**see Section 6)** Primary neutrophil disorders are in IUIS Table V (**see Section 5.2**), while complement deficiencies are in IUIS Table VIII (**see Section 5.4**). IUIS Table VI groups innate immunity defects conferring high risk of infection by specific microorganisms. (**see Section 5.3**). Autoinflammatory disorders related and not related to inflammasome dysfunction are classified in IUIS Table VII (**see Section 6**). The IUIS Table IX lists primary bone marrow failure conditions, which may manifest with increased frequency of infections and are commonly managed by hematology/oncology specialists. The IUIS classification includes Table X to compile phenocopies of inborn errors of immunity for clinician awareness and to be considered when a genetic diagnostic is uncertain. These conditions have clinical presentations similar (phenocopies) to IEI and are caused by an acquired disease process, such as the development of neutralizing anti-cytokine antibodies or somatic pathogenic gene variants. Table IX and X disorders are not addressed in detail in this practice parameter.

Table 1.1. IUIS Classification of Human Inborn Errors of Immunity 2024

Table I	Immunodeficiencies affecting cellular and humoral immunity 1. T-B+ Severe combined immunodeficiencies (SCID) 2. T-B- SCID 3. Combined immunodeficiencies. Generally less profound than SCID.
Table II	Combined immunodeficiencies with associated or syndromic features 1. Immunodeficiency with Congenital thrombocytopenia 2. DNA repair defects 3. Thymic Defects with additional congenital anomalies 4. ImmunoOsseus Dysplasias 5. Hyper IgE syndromes 6. Defects of vitamin B12 and folate metabolism 7. Anhydrotic ectodermal dysplasia with immunodeficiency 8. Calcium channel defects 9. Other
Table III	Predominantly antibody deficiencies 1. Severe reduction of all serum immunoglobulins with profoundly decreased B cell numbers. 2. Severe reduction of at least 2 serum immunoglobulin isotypes with normal or low B cell numbers, CVID. 3. Severe reduction in serum IgG and IgA with normal/elevated IgM and normal B cell numbers, hyper IgM.

	4. Isotype, light chain or functional deficiencies with generally normal B cell numbers
Table IV	Diseases of immune dysregulation 1. Familial Hemophagocytic lymphohystiocytosis (FHLH). 2. FHLH syndromes with hypopigmentation. 3. Regulatory T cell defects. 4. Autoimmunity with or without lymphoproliferation. 5. Immune dysregulation with colitis. 6. Autoimmune lymphoproliferative syndrome. 7. Susceptibility to EBV and lymphoproliferative conditions
Table V	Congenital defects of phagocyte number or function 1. Congenital neutropenia. 2. Defects of motility. 3. Defects of respiratory burst. 4. Other non-lymphoid defects.
Table VI	Defects in intrinsic and innate immunity 1. Mendelian Susceptibility to Mycobacterial Disease (MSMD) 2. Epidermodysplasia verruciformis (HPV) 3. Predisposition to severe viral infections 4. Herpes Simplex encephalitis 5. Predisposition to invasive fungal disease 6. Predisposition to mucocutaneous candidiasis 7. TLR signaling pathway deficiency 8. Other IEI related to non-hematopoietic tissues 9. Other IEI related to leukocytes
Table VII	Autoinflammatory disorders 1. Type I interferonopathies. 2. Defects affecting the inflammasome. 3. Non-inflammasome related conditions.
Table VIII	Complement deficiencies
Table IX	Bone marrow failures
Table X	*Phenocopies of inborn errors of immunity.*

RECOMMENDATION 1.2. We <u>recommend</u> obtaining a detailed family history to support the IEI diagnosis and to identify undiagnosed affected relatives.

Strength of recommendation **- Strong**

Certainty of evidence **– Moderate**

A family history that reveals manifestations of IEI and high frequency of infections as compared to other household members is suggestive of an IEI. Beyond infections, family history should inquire the presence of autoimmunity, inflammatory features (e.g., vasculitis, colitis, fevers, rashes), cancers, and severe atopy. A detailed family history might identify relatives that are also affected by the patient's condition. Around 1.5% of patients in a large cohort of patients with IEI were diagnosed because of a family history,[8] while another reports 26% having positive family history at initial presentation.[18]

Because IEI are genetic disorders, a detailed understanding of the family history, including consanguinity, can suggest potential patterns of inheritance (e.g., autosomal dominant, X-linked). The inheritance pattern of symptoms could be useful for defining the pathogenicity of identified gene variants. Furthermore, an awareness of inheritance patterns guides genetic counseling regarding the probability of disease in future descendants.

RECOMMENDATION 1.3. We <u>recommend</u> an integrated approach for the diagnosis of a suspected IEI: clinical, immunological, and genetic components.

Strength of recommendation**- Strong**

Certainty of evidence **- Moderate**

The evaluation for the diagnosis of suspected IEIs requires a synthesis of three important components:[19, 20] 1) clinical findings obtained from history and physical exam; 2) supporting immunological findings obtained from laboratory studies; and 3) genetic findings. Screening with a detailed history is necessary, eliciting frequency and severity of infections, autoimmunity, episodes of fever or inflammation, malignancy, and severe atopy.[17] As discussed in **RECOMMENDATION 1.2**, the family history is often helpful.[18] Physical exam should focus on features of syndromes with characteristic dysmorphisms (e.g., face features in DiGeorge syndrome), stigmata of recurrent infections (e.g., warts, bronchiectasis), autoimmunity (e.g., alopecia, vitiligo), lymphoproliferative phenotypes (e.g., lymphadenopathy, splenomegaly), and severe atopy (e.g., generalized lichenified and infected eczema). Based on clinical findings, immunological tests should focus on assessing parameters of the molecular and cellular pathways most likely to be implicated in the suspected clinical syndrome.[21] For example, disseminated warts prompt an evaluation of T cells and NK cells. The IUIS phenotypical classification tables are useful to guide diagnostic investigations.[17] Because IEI might present with atypical manifestations or an incomplete clinical picture, genetic testing is recommended from the start of the workup – details of specific diagnostic tests to order are covered in other Sections. (**Sections 2-7**).

RECOMMENDATION 1.4. We <u>recommend</u> that the evaluation of immunodeficiency should include testing for secondary causes of immunodeficiency.

Strength of recommendation **– Strong**

Certainty of evidence**- Moderate**

In patients where susceptibility to infection is among the chief concerns, a broader consideration should be given to secondary immunodeficiencies, (**Table 1.2**) which are more prevalent as a group than IEI, particularly in adult patients.[22, 23] There are microscopic or macroscopic anatomic causes of recurrent infections. For example, structural and functional defects of the respiratory epithelial cilia increase the risk of recurrent pneumonias, as observed in cystic fibrosis, primary ciliary dyskinesia, or from chemical damage due to second-hand smoke.[24] Macroscopic anatomic defects of the nose and paranasal sinuses and adenoidal hypertrophy can mechanically block mucus flow and drainage, favoring infection. Allergic mucosal inflammation also reduces pathogen clearance.[24] Infectious diseases that target the immune system (such as human immunodeficiency virus (HIV) infection) lead to a deficient immune response.

Secondary immunodeficiency conditions arise with the use of immunosuppressive medications in autoimmunity and blood cancers. A few medications can impair immune cells in a non-predictable manner, such as anti-epileptic drugs.[25, 26]

Disorders where immune cells and immunoglobulins are lost from the gut, respiratory tract, or lymphatic vessels such as hydrops, protein-losing enteropathy, intestinal lymphangiectasis, lympho-venous malformations, and chylothorax. also result in immunodeficiency,

Some extremes of physiological states can result in immune deficiency or dysregulation, including malnutrition, extreme heat or cold, and sleep deprivation. Aging individuals may develop immune defects that predispose them to infections.[27, 28] Neonates also have immune impairment of both innate and adaptive immunity compared to older children, which increase their risk for infections and are exacerbated by premature birth.[29-31]

The presence of autoantibodies against cytokines can result in clinical phenocopies of IEI with infection susceptibility and autoimmunity.[32-34] Thymus malignancies and some IEI are associated with development of elevated levels of autoantibodies to cytokines, including RAG1/2 deficiency, IPEX, AIRE deficiency, NFKB2 deficiency, and NEMO deficiency.[34, 35]

Table.1.2. Examples of secondary causes of immunodeficiency:

-	Anatomical: nasal polyposis, deviated septum, adenoidal hypertrophy.

-	Defective epithelial barriers: primary ciliary dyskinesia, cystic fibrosis.
-	Malnutrition.
-	Infections targeting immune cells: HIV infection, measles, EBV infection.
-	Use of immunosuppressive medication: corticosteroids, cyclosporine, rituximab
-	Lymphatic system malformations
-	Prematurity and advanced age

*HIV, human immunodeficiency virus; EBV, Epstein-Barr virus.

RECOMMENDATION 1.5. We <u>suggest</u> consultation with a clinical immunology expert and multidisciplinary care for the evaluation and follow up of suspected or diagnosed patients with IEI.

Strength of recommendation: **Conditional**

Certainty of evidence**: Moderate**

Primary care physicians and other health care professionals conduct screening evaluations for IEI.[36-38] However, consultation with a clinical immunology expert is recommended to confirm IEI diagnosis, interpretation of abnormal test results and management.[39] For patients with established IEI diagnoses, evaluations should be conducted regularly (every 4 to 12 months, depending on the diagnosis) by a health care professional with training and experience in the care of patients with IEI (**see Section 7**).

The multisystem nature of IEI necessitates an integrated multidisciplinary approach to management. This approach provides significant cost savings, improved quality of life, and improved outcomes.[40-42] Such an approach optimizes medical treatments and permits integration of health and social care professionals and physical and occupational therapy into the patient's overall care. Different patient comorbidities require the involvement of different clinical teams. For example, early onset inflammatory bowel disease clinics may require a clinical immunologist and a gastroenterologist, as well as pharmacists and geneticists.[43] Within the same concept, a clinic focusing on patients with 22q11 deletion syndrome additionally requires experts in otorhinolaryngology, endocrinology, cardiology, and speech therapy.[44]

RECOMMENDATION 1.6: We <u>suggest</u> the provision of support resources (e.g., educational, emotional) for patients and families diagnosed with IEI.

Strength of recommendation **- Conditional**

Certainty of evidence**- Low**

IEI are considered rare conditions and are unfamiliar to most people. Thus, when faced with an IEI diagnosis, most patients do not have familial or cultural examples to help guide their understanding of disease process and management. Patients and families need to be given sufficient educational material in the appropriate language and level of detail so that they understand the inheritance, causes, manifestations, and natural histories of their IEI.[45]

Receiving an IEI diagnosis can be distressing and may elicit depression in adult patients[46, 47] and in parents of children with IEI.[48] When the IEI diagnosis is made in the neonatal period, there is added risk of postpartum depression. Screening for depression in patients and their immediate relatives might be considered.[49-51]

Patient-based organizations are additional resources for advocacy and support from other patients and families, education regarding new developments and treatments, and government or private support of research programs. Patients and families may establish long-term relationships with health care professionals, including physicians, nurses, and social workers to help obtain the best outcomes for their diseases.

SECTION 2. Newborn Screening (NBS) for severe combined immunodeficiency and athymia- diagnosis and initial approach.

Infants born with severe combined immunodeficiency (SCID) or with congenital athymia have absent or very few naïve T cells in their blood. This deficiency can be quantitatively detected via PCR amplification of T cell receptor excision circles (TRECs), a byproduct of T cell receptor rearrangement, which occurs in the thymus during T cell maturation. NBS for SCID allows early diagnosis and treatment of SCID and congenital athymia.[52]

SCID meets the key criteria for NBS as a public health initiative: (1) absence of TRECs constitutes a reliable biomarker to identify asymptomatic infants with SCID and athymia, (2) use of NBS decreases morbidity and mortality, and (3) effective therapies are available, in the form of hematopoietic stem cell transplantation (HSCT) and gene therapy.

RECOMMENDATION 2.1: We recommend TREC quantitation for newborn population-based screening for the early identification of newborns with severe combined immunodeficiency (SCID) and complete athymia.

Strength of recommendation**: Strong**

Certainty of evidence**: High**

In the United States, initial pilot programs in Massachusetts, Wisconsin and the Navajo Nation using TREC-based screening for SCID started in 2008.[53] Early identification of

SCID-affected infants in these groups, as well as cost effectiveness modelling,[54-56] led to the addition of SCID to the Department of Human Health Services Recommended Uniform Screening Panel (RUSP) in 2010. By 2018, all 50 US states had adopted TREC-based NBS for SCID (SCID NBS).[57] SCID NBS allowed the determination of the SCID incidence in the US population to be 1/65,000 live births, higher than previous estimates.[58] Nearly all infants are diagnosed with SCID in the US through SCID NBS.[59] Importantly, post-transplant survival has improved with the implementation of SCID NBS.[60] Harmonization of interpretation of TREC results, including consensus language to describe abnormal results and urgent results for all US States is being pursued.[61]

SCID NBS via the TREC assay identifies typical SCID, almost all cases of atypical and leaky SCID (including Omenn Syndrome), and congenital athymia as the primary targets of screening.[58, 62-64] Moreover, a proportion of cases with combined immunodeficiency (CID) and syndromic immunodeficiency also have abnormal SCID NBS if total naïve T cell numbers are low; such disorders include ataxia telangiectasia, 22q11 deletion syndrome without complete athymia and others.[58, 64, 65] Patients with these conditions exhibit widely variable T cell lymphopenia and are not uniformly detected by SCID NBS. Certain severe cellular immune deficiencies (such as MHC Class II) or, rarely, pathogenic variants causing late-onset SCID, (such as hypomorphic adenosine deaminase (*ADA*) defects), are not detected via SCID NBS.[66, 67] Therefore, if concern arises for an immune disorder based on history or clinical presentation, diagnostic testing should be pursued, despite normal SCID NBS.

In the case of SCID due to ADA deficiency, concomitant use of tandem mass spectrometry may improve upon detection provided by TREC alone.[68] The use of kappa light chain receptor excision circle (KREC) quantitation for B cell deficiency may be adopted by NBS programs to identify additional patients with IEI.[69] Genetic sequencing to detect other IEI is being evaluated for NBS.[70] Population-based genome sequencing programs for treatable IEI could be both comprehensive and cost effective.[71, 72]

RECOMMENDATION 2.2: We <u>recommend</u> the urgent confirmation of an abnormal NBS for SCID with complete blood counts with differential and flow cytometric measurement of peripheral blood lymphocyte subset populations, including assessment of numbers of T, B and NK subsets and naïve T cells.

Strength of recommendation**: Strong**

Certainty of evidence **High**.

Approximately 1/15,000 live births in the US are born with clinically significant lymphopenia.[73] While SCID NBS is highly sensitive to screen for the primary targets of SCID and complete athymia, it is not a diagnostic test. Indeed, only about 15% of patients with a positive SCID NBS are ultimately diagnosed with SCID, while others have secondary causes of T cell lymphopenia (e.g., prematurity) or have normal

lymphocyte populations.[58, 73] Therefore, it is important for newborn screening programs to collaborate with clinical immunology experts to ensure prompt confirmatory testing, which includes enumeration of absolute counts of T cell subsets (CD3, CD4, CD8), naïve CD4 T cells (defined by CD45RA expression alone or in conjunction with other markers, such as CCR7and CD62L) or CD4+ recent thymic emigrants (CD4 RTE, as identified by expression of CD31, CD45RA and CD4).[74, 75]

Unless the above laboratory tests are sufficient to rule out SCID or a T cell lymphopenia disorder, infants require a complete birth history, family history and physical exam by a physician with expertise in pediatric immunology. A diagnosis of SCID or congenital athymia should be suspected if the Primary Immune Deficiency Treatment Consortium (PIDTC) criteria for SCID diagnosis are met (**See Table 2.1**).[76] The threshold for clinically significant T cell lymphopenia may vary, but in general, lower than 1,000 cells/uL with lower than 20% of naïve CD4 T cells suggests an increased risk for infection for newborns. Other concerning features are low B cell or NK cell counts, dysmorphisms associated with immunodeficiency, and family history of T cell deficiency. While patients with an abnormal SCID NBS but normal clinical and laboratory evaluation can be discharged from immunologic care, it is recommended for these infants to be reassessed within 3 to 6 months.[74, 77]

Prematurity and low birth weight can be associated with T cell lymphopenia that improves with age and weight gain.[78] However, 10% of infants with SCID are premature and/or have low birthweight; therefore, it is recommended to maintain a high level of suspicion for SCID in premature infants with an abnormal SCID NBS and abnormal T cell counts.[79] Other causes of abnormal SCID NBS are due to maternal conditions during pregnancy, such as the use of immunosuppressive therapies (e.g., azathioprine) and diabetes mellitus.[80]

Table 2.1: PIDTC 2022 Definitions for SCID[76]

SCID subtype	Criterion 1	Criterion 2	Criterion 3	Criterion 4
Typical SCID Criteria 1 & 2 OR criteria 1 & 3 OR criteria 4	Very low T cells (<0.05 x 10^3/L	Pathogenic variant in SCID-associated gene	No alternate explanation for low T cell count AND, EITHER: Undetectable or low TREC OR <20% naïve CD4 T cells	Presence of maternal T cells engraftment
Leaky/atypical SCID Criteria 1 & 2 & 4 OR criteria 1 & 3 & 4	Two or more of: -Low T cell number for age -Oligoclonal T cells	Pathogenic variant in SCID-associated gene	Reduced T cell proliferation	Does not have: -Other SCID subtype -CID with known phenotype -Thymic disorder -Other disorder with low T cell number

	-Abnormal TREC OR <20% naïve CD4 T cells			
Omenn syndrome All 4 criteria	>80% of CD4 T cells have CD45RO memory phenotype	Pathogenic variant in SCID-associated gene	Generalized rash AND absence of maternal T cell engraftment	Two or more of: -Eosinophilia -Elevated IgE -Abnormal TREC - Lymphadenopathy -Hepatomegaly and/or splenomegaly -Oligoclonal T cells

RECOMMENDATION 2.3: We recommend that diagnostic evaluation for SCID and athymia include genetic testing, ascertainment of maternal T cell engraftment, IgE levels, eosinophilia, T cell oligoclonality, T cell proliferation and adenosine deaminase enzyme activity.

Strength of recommendation**: Strong**

Certainty of evidence **High.**

Once SCID or athymia is suspected, urgent follow up testing is needed to confirm a diagnosis and optimize management. Diagnostic criteria for typical SCID, leaky/atypical SCID and Omenn syndrome were updated in 2022 by the PIDTC based on review of clinical presentation of 379 infants with SCID (**Table 2.1**).[76] Omenn syndrome presents with eosinophilia and elevated serum IgE level. Choice of immune reconstitution treatment is influenced by specific genotypes, some of which are associated with radiosensitivity, and the presence of oligoclonal T cells (**see Section 12).** Assessment of T cell oligoclonality by evaluating the T cell receptor repertoire diversity is available in immunology laboratories. Transplacental maternal T cell engraftment can be tested in patients with T cell counts > 50 cell/uL, by comparing HLA markers expressed in T cells and non-T cells (e.g., neutrophils). In cases where adenosine deaminase deficiency is suspected (i.e., patients with very low numbers of T and B cells), measuring adenosine deaminase enzyme activity is indicated.[81]

RECOMMENDATION 2.4: We recommend urgent referral to centers with expertise in the care of severe immunodeficiency after a SCID or athymia diagnosis is confirmed.

Strength of recommendation: **Strong**

Certainty of evidence**: High**

Infants with SCID and complete athymia are at high risk for the development of infection and other life-threatening complications.[77] The implementation of SCID NBS has

resulted in improved survival and clinical outcomes, due to early diagnosis and management, decreasing the risk of infections, organ damage, and increasing survival.[60, 82, 83] Therefore, urgent follow-up with a clinician with expertise in the evaluation and management of infants with SCID or athymia is important to achieve the best outcomes for these complex patients.[84] Measures to reduce morbidity and mortality due to CMV infection are recommended.[85, 86] Live vaccines should be avoided.[87, 88] **Table 2.2** summarizes recommendations for surveillance of infections and antibiotic prophylaxis in patients with SCID. (**Also see Sections 8-11**)

Table 2.2. Recommendations for the care of infants with SCID diagnosis (*)

Recommendation	Frequency	Comment
Test CMV PCR in urine and in blood	Baseline and every 3 to 4 months	If present, treat CMV infection (Valganciclovir, 16 mg/Kg/dose, orally twice a day or Ganciclovir, 6 mg/kg/dose, intravenously twice a day). Alternatives are cidofovir and foscarnet.
Test serum anti-CMV IgG in patient's mother	Baseline	If suspected or confirmed maternal CMV infection, avoid breastfeeding
Test EBV PCR in blood	Baseline and every 3 to 4 months	If present, treat EBV infection (valganciclovir or ganciclovir, dose similar to EBV).
Test HIV PCR or antigen tests in blood	Baseline	Treat HIV infection
Test PCR-based respiratory viral pathogen panel (e.g., Influenza A and B, Parainfluenza 1, 2 and 3, adenovirus, rhinovirus, human metapneumovirus).	When there is an increase of nasal secretions or respiratory symptoms such as cough and shortness of breath	Treat respiratory viral infection: oxygen support, beta-agonists, antiviral drugs (e.g., Oseltamivir) if indicated.
Environment with reduced exposure to infections	At all times	Inpatient (with reverse isolation) or outpatient (close distance to a medical center)
Prophylaxis for PJP	Daily, starting at one month of age	Trimetroprim/sulfamethoxazole 2.5 mg (of trimethoprim component)/Kg/day

Prophylaxis for Candidiasis	Daily	Fluconazole 3 mg/Kg/day oral
Prophylaxis for herpes infection	Daily	Acyclovir 12.5 mg/kg/day oral
Prophylaxis for RSV infection	Monthly during RSV season	palivizumab or nirsevimab-alip
Immunoglobulin replacement therapy	Monthly or weekly	Intravenous or subcutaneous routes (400 mg/Kg/month)
Avoid live viral vaccines		Includes: rotavirus, MMR, BCG, oral polio. Household members are encouraged to receive all scheduled vaccines

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HIV, human immunodeficiency virus; PJP, Pneumocystis jiroveci pneumonia; RSV, respiratory syncytial virus

(*) From Dorsey MJ, et al.[77]

RECOMMENDATION 2.5: We <u>recommend</u> referral to clinicians with expertise in IEI for assessment and diagnosis of patients with non-SCID T cell lymphopenia detected by NBS.

Strength of recommendation**: Strong**

Certainty of evidence **Moderate**

Infants with non-SCID T cell lymphopenia should be monitored longitudinally.[74, 78] These infants may be immunologically defined by having CD3+ T cell count >50 but <1,000 cells/uL, with naïve CD4+ T cells comprising most of the population and without maternal T cell engraftment or Omenn syndrome. Once these criteria are met, clinical history should carefully assess for evidence of secondary loss of T cells (e.g., chylous loss), prematurity and/or dysmorphic features consistent with other syndromic conditions (e.g., chromosome 22q11.2 deletion syndrome).[74, 78]

Diagnostic testing in this setting includes quantitative assessment of serum levels of IgG, IgA, IgM and IgE; and genetic testing, including for 22q11.2 deletion syndrome (**see Section 3**). Inactivated vaccines of the routine primary series should be administered, and antibody responses to these immunizations be monitored to assess overall immune function.

We suggest the following schedule for ongoing immunologic evaluation and monitoring based on reported trajectories for resolution of non-SCID T cell lymphopenia[74, 78, 89] **(See Section 4 and 5):**

- At 3 months of age: reassess lymphocyte subsets including naïve T cell populations, IgG, IgA, IgM, IgE levels, genetic testing for IEI for lymphopenia that is unexplained and persistent.
- At 6-7 months of age: reassess lymphocyte subsets including naïve T cell populations, T cell proliferation responses, IgG, IgA, IgM, IgE levels, response to inactivated vaccines if not started on immunoglobulin replacement.
- Continue clinical and immunological reassessment every 3 to 6 months. May increase time between evaluations if immuno competence is achieved.

SECTION 3 - Genetic Evaluation of IEI

Determination of an underlying genetic diagnosis assists in the evaluation and treatment of patients with suspected IEI.[90] IEI are caused by defects in over 505 genes, underscoring the need for genetic evaluation.[7] The application of massively parallel sequencing (MPS) for genetic testing (e.g. exome sequencing) and decreasing costs have contributed to the availability of genetic tests in clinical settings. Genetic testing has led to the broadening of clinical phenotypes (*e.g.*, very early onset inflammatory bowel disease as a manifestation of chronic granulomatous disease) and selection of targeted therapies based on the identified disease mechanism (*e.g.*, JAK inhibition for *STAT1* or *STAT3* gain of function). A variety of testing methods are available (**Table 3.1),** and depending on the question being pursued, some are preferred over others.

Genetic counseling before and after genetic testing is recommended and includes the nature of gene defects, inheritance patterns, disease penetrance and implications for family planning.

This can be performed by a genetic counselor or an immunologist with expertise in IEI. Informed consent for genetic testing is required, because of the potential impact of the results on the patient's health, family relationships and future decisions. Patients need to understand the limitations of genetic testing and every effort should be made to address psychological distress associated with genetic diagnoses. Sensitive genetic information should be protected from unauthorized disclosure.

Table 3.1. Detection capabilities of genetic testing platforms for various genomic findings

Genetic defect	Sanger sequencing	IEI targeted gene panel sequencing	Exome sequencing	Whole genome sequencing	Chromosomal microarray analysis

Coding SNV	YES(a)	YES	YES	YES	No
Non-coding SNV	YES(a)	YES(b)	YES(b)	YES	No
CNV	No	YES(b)	YES(b)	YES	YES(b)
Mosaicism	YES	YES	YES(b)	YES(b)	No
High genomic homology	YES	No	No	YES	No
Non-IEI gene defects	No	No	YES	YES	YES

SNV, single nucleotide variant; CNV, copy number variation. (a) if SNV is known. (b) sensitivity varies with test protocol design

RECOMMENDATION 3.1: We <u>recommend</u> single gene sequencing to test patients with suspected IEI who have a similarly affected family member with a known genetic defect or who present with a condition due to a defect in a gene that might not be reliably analyzed using high-throughput massively parallel sequencing.

Strength of recommendation**: Strong**

Certainty of evidence**: High**

Single gene sequencing, also known as Sanger sequencing, is based on polymerase chain reaction (PCR) amplification.[91]Another approach is the use of MPS-based test focused entirely on one large gene or a gene for which high read-depth sequence coverage is needed. (**See RECOMMENDATION 3.2 and 3.3)**. A strength of Sanger sequencing is its high accuracy and has been considered the gold standard for gene testing. This method was used to confirm gene variants identified by MPS-based tests. However, with MPS accuracy improving and approaching that of Sanger sequencing over time,[92] this practice is becoming unnecessary,[93-96] with exception of genes for which MPS-based tests have difficulty producing high-quality data.[96] Examples include genes with pseudogenes or repetitive regions and genes with established pathogenic variants in non-coding regions, intronic or untranslated regions (UTRs). Sanger sequencing may distinguish genes from pseudogenes, which are non-functional genetic segments that evolutionarily arose from duplication of existing genes. Genes linked to known IEI that have pseudogenes include *IKBKG* (encoding the NEMO protein), *NCF1* (encoding the p47phox protein), *ATAD3A, C4A, CFB, IRAK1, SBDS, and USP18*.[97]

Single gene sequencing is indicated when IEI is suspected in a patient for whom a specific gene variant is known to be responsible for the same IEI in one or more direct

relatives of the patient. Single gene sequencing can also be used to establish carrier status for apparently unaffected family members (**see RECOMMENDATION 3.6**). Single gene sequencing should not be used when multiple candidate genes are associated with the clinical presentation (notably, almost all IEI fall into this situation). Single gene sequencing cannot detect copy number or structural variants.

Single gene sequencing has been used if somatic mosaicism is suspected. Somatic mosaicism is a term to describe the presence of more than one genetically defined cell populations in one individual. For example, somatic mosaicism has been reported in patients with variants in genes such as *FAS*[98] and *NLRP3*[99] (**Table 3.2**). While Sanger sequencing samples of different tissues or cells has been used to evaluate mosaicism, it is not sensitive below a threshold of 15%–20%.[100] In contrast, MPS-based tests with very high read depth can detect variant allele frequencies below 1% in one sample.[101]

Table 3.2: Examples of IEI genes associated with mosaicism

CYBB	*KRAS*	*NLRC4*	*TNFRSF1A*
FAS	*NOD2*	*PIK3R1*	*TMEM173*
IL6ST	*NRAS*	*STAT3*	*TLR8*
JAK1	*NLRP3*	*STAT5B*	*UBA1*

RECOMMENDATION 3.2: We <u>recommend</u> targeted gene panel sequencing including genes associated with IEI or exome sequencing as an initial step for genetic diagnosis, when a familial gene defect does not explain the patient's condition.

Strength of recommendation**: Strong**

Certainty of evidence**: High**

Because exome sequencing and comprehensive IEI gene targeted panel sequencing are similar in diagnostic yield for detecting pathogenic gene variants,[102] the choice between these two test methods is based on availability, turnaround time, sequencing depth, copy number variation (CNV) reporting, and cost. These factors will be specific for the clinical needs of each patient.

Exome sequencing aims to sequence all coding regions within the genome. In contrast, targeted gene panels evaluate coding and selected non-coding regions of a selected group of genes associated with a particular patient phenotype. The number of genes in these panels can vary from relatively few (*e.g.*, a SCID panel may analyze 24 genes), to panels of over 500 genes that encompass the most known IEI as well as additional genes for which defects may mimic IEI.[102-104] Both targeted gene panels and exome sequencing use a library of DNA or RNA capture probes, which hybridize with complementary target sequences to allow for isolation of the specific regions of genomic

DNA. Targeted gene panels may include PCR based amplicons for sequencing. In addition to the coding regions, the immediately adjacent intronic regions are sequenced to account for variants that impact splicing. Some targeted panels capture non-coding regions known to harbor pathogenic variants of certain genes (*e.g.*, *GATA2*). Of note, some targeted gene panels use exome sequencing capture probes and limit the analysis and reporting to disease-associated genes. Such panels are also called "focused exome sequencing," "exome slicing," or "virtual gene panels."[102-104]

DNA is sequenced using MPS high-throughput technologies. Sequencing data are then aligned to a reference genome, and variants are identified and annotated. The depth of coverage (the number of unique sequencing reads per nucleotide in the reconstructed sequence) will vary based on the technology used. Average read depth for a targeted gene panel may be 500x or higher, while the average read depth for exome sequencing is typically around 100x.[102-104] These technologies are limited in their ability to analyze genes associated when pseudogenes are present.

Targeted gene panel sequencing is expected to have the lowest cost and fastest turnaround time among MPS-based tests because of the small number of gene variants that are identified and annotated. Additionally, the increased depth of coverage obtained with targeted gene panels allows for detection of somatic variants with low allele frequencies.[102-104]

For CNV detection, targeted gene panels exhibit higher sensitivity and reliability than exome sequencing tests due to the higher read-depth provided in panel tests.[105-107] Small CNVs may not be identified (**see RECOMMENDATION 3.4**). Because many computational tools are newly developed and require validation for clinical reporting, CNV detection is best evaluated by a chromosomal microarray test.

Targeted panels based on "focused exome sequencing" lose the advantages of higher read depth and potential inclusion of high-yield non-coding regions of relevant genes that are provided by "true" targeted panels. However, if initial testing does not reveal a plausible candidate variant, reflex testing to include the entire exome may be pursued.[102-104] Exome sequencing allows for the identification of variants in genes that can cause a phenotype that may mimic an IEI by clinical presentation (*e.g.*, primary ciliary dyskinesia).[108,109]

Exome and whole genome sequencing (**see RECOMMENDATION 3.3)** are preferentially considered over targeted gene panels in two situations. First, for evaluation of patients with IEI and additional phenotypic features that do not involve the immune system (*e.g.*, cardiac malformations, neurologic deficits). These patients may have a higher pre-test probability of immune defects caused by variants in genes not associated with an IEI. As an example, patients with Rubinstein-Taybi syndrome are known to have increased susceptibility to infections and immunologic abnormalities, but the disease is not considered an IEI, and targeted IEI gene panels do not include

CREBBP, the gene associated with this condition. Second, exome and genome sequencing are preferred for patients from parents with a high likelihood of consanguinity. Multiple studies suggest that use of broader sequencing platforms in such patients increases the diagnostic yield and may be more cost-effective over targeted gene panel testing.[102, 108, 109]

RECOMMENDATION 3.3: We <u>suggest</u> whole genome sequencing of individuals with suspected IEI and non-immunologic traits or with high suspicion for a non-coding genetic defect.

Strength of recommendation: **Conditional**

Certainty of evidence: **Low**

Whole genome sequencing (WGS) is an MPS-based test that sequences the entire genome without an initial capture step. Sequencing data are then aligned to a reference genome, and gene variants are identified and annotated. Based on the vast amounts of data generated, the analysis pipeline may include initially limiting variant evaluation to "panel-like analysis" or "exome-like analysis." If no plausible candidates are identified in this manner, analysis can be expanded to include non-coding regions.[102-104, 110]

WGS sequencing includes introns and gene regulatory regions that may contain pathogenic variants, and are not covered by targeted panels and exome sequencing. Examples of IEI genes with known pathogenic variants in such non-coding regions include *LRBA*, *DOCK8*, and *ARPC1B*.[110, 111] (**Table 3.3**) The absence of an initial capture step allows for uniform read depth (average read depth approximately 20x-30x), although the limited read depth of WGS does not identify variants with low allele frequencies (*i.e.*, somatic mosaicism). WGS has an enhanced ability to detect CNVs compared to gene panels or exomes.[112] Overall, studies have shown that WGS provides an increase in diagnostic yield over exome sequencing.[113, 114]

WGS is indicated when a patient with suspected IEI remains without genetic diagnosis despite targeted gene panel or exome sequencing, as well as those patients with suspected IEI presenting with non-immunological traits, such as cardiac defect, skeletal malformations and neurological deficits.

Table 3.3: Examples of IEI genes reported to contain non-coding pathogenic variants

ADA	*CTPS1*	*GINS1*	*NLRP3*	*SPINK5*
ADA2	*CTSC*	*IKBKG*	*PALB2*	*STAT1*
AIRE	*CYBB*	*IL10RB*	*PARN*	*STAT3*
AP3B1	*DCLRE1C*	*IL2RA*	*PNP*	*STX11*

ATM	*DKC1*	*IL2RG*	*POLA1*	*STXBP2*
BRCA1	*DNMT3B*	*IL7R*	*POLR3A*	*TBX1*
BRCA2	*DOCK8*	*IRAK4*	*PRF1*	*TCIRG1*
BRIP1	*FADD*	*ITGB2*	*PRKDC*	*TCN2*
BTK	*FANCA*	*ITK*	*PTEN*	*TERC*
C1QB	*FANCC*	*JAK3*	*RAB27A*	*TERT*
C7	*FANCD2*	*LAMTOR2*	*RAG2*	*TGFBR2*
CD27	*FANCI*	*LRBA*	*RMRP*	*THBD*
CD40LG	*TNFRSF6*	*LYST*	*RNASEH2B*	*TNFRSF1A*
CD70	*TNFSF6*	*MAGT1*	*RPSA*	*TP53*
CFTR	*FERMT1*	*MEFV*	*SERPING1*	*TRNT1*
CHD7	*FOXP3*	*MSH6*	*SH2D1A*	*TTC7A*
CLCN7	*GATA2*	*MVK*	*SKIV2L*	
CORO1A	*GFI1*	*NLRC4*	*SLC7A7*	

RECOMMENDATION 3.4: We <u>recommend</u> DNA copy number variant (CNV) testing in patients with IEI with a suspected gene(s) deletion or duplication.

Strength of recommendation: **Strong**

Certainty of evidence**: High**

Detection of gains and losses in DNA can be important for identifying IEI, such as the 22q11 deletion syndrome.[115, 116] CNVs include deletions, duplications, or complex rearrangements of DNA and range in size from 50 to several million base pairs. CNVs account for approximately 12% of the human genome diversity[117] and it is highest in patients with developmental delays.[118] Karyotyping or chromosomal analysis using the G-banding technique with trypsin and Giemsa stain can evaluate large CNVs.[119] This technique is best to identify balanced translocations, unless the translocation breakpoints are known. Chromosomal microarray analysis (CMA), by comparative genomic hybridization (CGH) arrays or single nucleotide polymorphism (SNP) arrays detect small CNVs of at least 400 kb.[120]. In general, these methods label genomic DNA from a patient or probes and hybridize them to a control DNA sample. The relative amount of labeled DNA hybridization compared to the control sample is used to determine gains or losses of DNA regions. CMA testing is recommended over fluorescence *in situ* hybridization (FISH) since it has a higher sensitivity to detect microdeletions, such as 22q11.2 microdeletion. As a separate advantage, while karyotyping and FISH are dependent on culturing cells, CMA and MPS based methods can be applied to DNA extracted from any tissue.

MPS-based tests are less sensitive than CMA for detecting changes in one to two exons.[121,122] CMA and MPS-based CNV testing are limited in their ability to detect balanced rearrangements, certain types of repeat expansions, and low levels of mosaicism. CNV testing may yield incidental findings, since entire genomic regions are investigated.[123] CMA also evaluates consanguinity based on the absence of heterozygosity, for regions of homozygosity, or for uniparental disomy.[116]

CNV testing is recommended as a first-tier genetic test for evaluating patients who have developmental delays, intellectual disabilities, or congenital anomalies.[124] It should be performed in a patient with a suspected IEI known to present with gene deletions or duplications. We suggest use of CNV testing to help exclude or confirm pathogenic variation in the opposite allele in patients who have one pathogenic variant in a gene that causes disease in an autosomal recessive manner.[102]

RECOMMENDATION 3.5: We <u>recommend</u> the American College of Medical Genetics and Genomics (ACMG) guidelines for evaluating gene variant pathogenicity.

Strength of recommendation: **Strong**

Certainty of evidence: **High**

The ACMG publishes guidelines for gene variant classification and interpretation with improvements, modifications, and updates.[102, 123, 125] These guidelines are meant to serve as a framework for evaluating gene variant pathogenicity rather than as stringent criteria.

Using ACMG guidelines, gene variants are classified as one of five categories: benign, likely benign, variant of uncertain significance, likely pathogenic, and pathogenic. Criteria for classification are determined by evidence including population frequency, laboratory testing of patient samples, and *in silico* prediction algorithms. Because genetic conditions differ mechanistically, molecularly and clinically, gene-specific interpretations are recommended.[126] Although such specifications are being developed for many genes, few currently exist for IEI.[127,128] One caveat is that the ACMG criteria for pathogenicity favor the identification of loss-of-function rather than gain-of-function genetic mechanisms. For example, nonsense, frameshift, canonical splice site, and exonic deletions are favored for asserting pathogenicity, because these types of variants most often generate loss of function diseases.

Providers should note that a gene variant classification in a clinical report may not account for gene-specific factors.[102] A distinction must be made between variant classification and clinical interpretation.[129] Clinical interpretation of a variant may be understood in terms of pre-test probability and likelihood ratio, which together determine post-test probability (as depicted by Fagan's nomogram).[130] Pre-test probability reflects

how likely a gene defect specified by the test report explains the phenotype of the patient. Such estimations are based on clinical expertise and information from scientific and medical resources. The assessment must account for potential or known heterogeneity in disease presentations associated with the gene, particularly when diverse pathogenesis models (*e.g.*, gain-of-function, haploinsufficiency, dominant-negative loss-of-function, or neomorphic molecular function) are possible. The likelihood ratio of pathogenicity is determined by the ACMG-based variant classification. Reclassification by the clinical provider may be necessary due to information not considered by the laboratory or in accordance with application of gene-specific modifications to the ACMG guidelines.[130] The post-test probability is then ascertained from the pre-test probability and likelihood ratio to provide a clinical interpretation of the variant.

For example, when genetic testing in a male infant with agammaglobulinemia and absent B cells reveals the presence of a variant in *BTK*, clinical expertise suggests a high pre-test probability that this patient has *BTK* deficiency. If the variant is reported as a variant of uncertain significance, likely pathogenic, or pathogenic, the post-test probability remains high, supporting that the variant is responsible for the phenotype. If it is classified as benign or likely benign, it follows that the *BTK* variant is not likely to explain the disease. In a female infant with SCID, a monoallelic pathogenic variant in *JAK3* (a known gene associated with AR- SCID) would be clinically important because of the high pre-test probability given the diagnosis, suggesting an undetected pathogenic variant on the other allele. In another example, a likely pathogenic variant in *COPA* identified incidentally in a completely healthy adult would be interpreted as unlikely to be clinically relevant for that individual, because the pre-test probability is low. This interpretation is with the caveat that a person can be asymptomatic (or "pre-symptomatic") at the time of evaluation but develop disease later.

RECOMMENDATION 3.6: We recommend familial genetic testing to aid in gene variant pathogenicity resolution.

Strength of recommendation: **Strong**

Certainty of evidence**: High**

The sequencing of both biological parents together with the proband (known as "trio analysis") defines maternal-, paternal-inherited or *de novo* variants, and may help to determine whether potentially compound heterozygous gene variants are located in *cis* or *trans*.[102-104] For example, if two variants are identified in a gene that causes IEI due to biallelic defects (i.e., autosomal recessive), these may not be located on opposite alleles. In situations when a parent is unavailable, testing of a parental relative or an offspring of the patient may be informative. Because penetrance of gene defects might

not be 100%, segregation of candidate variants with disease in affected family members should not be assumed.[131]

Genetic testing for X-linked IEI disorders should also be considered in females. Extreme skewing towards the X chromosome carrying the pathogenic allele can lead to disease, and has been described in CGD, WAS, XLA and other IEI.[132-136] In some X-linked IEI, female carriers can have health issues even without X-chromosome skewing.[137,138]

RECOMMENDATION 3.7: We <u>suggest</u> familial genetic testing to ascertain risk of disease in currently unaffected relatives.

Strength of recommendation**: Conditional**

Certainty of evidence**: Low**

Some IEI are known to have variable penetrance and clinical presentation in different individuals carrying the same pathogenic gene variant, such as *CTLA4* haploinsufficiency and *STAT1* gain of function.[139, 140] Awareness of a genetic diagnosis in unaffected relatives can facilitate monitoring for possible future development of the disease in family members who are healthy at the time of genetic testing.[131]

For unaffected minors, decisions for genetic testing should weigh whether the results will have an immediate beneficial impact on their health or whether testing can be delayed until adulthood for consent of testing. In IEI disorders mediated by biallelic and X-linked variants, carrier testing is useful to determine recurrence risk and to assist with family planning.[141]

RECOMMENDATION 3.8: We <u>recommend</u> investigating multiple genetic diagnoses when a monogenic diagnosis does not explain the patient's clinical characteristics.

Strength of recommendation**: Strong**

Certainty of evidence**: Moderate**

Multiple genetic diagnoses can be present within an individual and produce a blended phenotype consisting of completely distinct, partially, or completely overlapping features.[142] For genetic diseases overall, additional genetic defects are found in approximately 5% of patients with one genetic diagnosis.[143] In patients with IEI, the multiple molecular diagnosis rate is higher, ranging from 9% to 11% of diagnosed patients.[90, 116] Broad genetic testing is indicated when the initial identified gene defect does not explain all of the patient's clinical presentation. Providers should especially weigh the potential for a blended phenotype in patients who appear to have an "atypical" or "expanded" presentation of a single genetic condition.

RECOMMENDATION 3.9: We <u>recommend</u> that genetic testing for patients with IEI can be ordered by clinicians with expertise in IEI diagnosis.

Strength of recommendation: **Strong**

Certainty of evidence: **Moderate**

Clinical immunologists have dedicated training in recognizing both the clinical phenotypes related to IEI and defects of genes and pathways of the immune system that can cause disease. Clinicians trained in IEI have the necessary expertise to determine appropriate genetic testing for patients with suspected IEI and provide appropriate genetic counseling.[19, 90, 102-104, 110, 116] Collaboration with a geneticist or genetic counselor is helpful but not required for obtaining such testing, and testing restrictions could delay diagnosis and treatment, with occurrence of comorbidities.

<u>SECTION 4. Immunologic diagnosis of predominantly antibody deficiencies.</u>

RECOMMENDATION 4.1: We <u>recommend</u> that patients with suspected antibody deficiencies be evaluated with immunoglobulin measurement, antigen- specific antibody responses and lymphocyte phenotyping, and exclusion of secondary causes.

Strength of recommendation **– Strong.**

Certainty of evidence**- High**

Assessment of serum immunoglobulin levels (IgG, IgA, and IgM) is recommended as first-tier in the diagnostic work-up of patients with suspected antibody deficiency. The interpretation of these test results should take into consideration age-specific and laboratory specific normal reference ranges and whether there are secondary causes of antibody deficiency.

An IgG level less than 2 standard deviations below the age-appropriate reference mean for 2 measurements more than 3 weeks apart is considered by international consensus guidelines to be low.[144-146] If the IgG level is very low at time of first measurement (<100-300 mg/dL depending on age), then a single measurement may be appropriate in terms of expediting the subsequent clinical testing and management.[144]

Secondary causes of antibody deficiency include medication-induced (e.g., concomitant use of corticosteroids at the time of testing and prolonged effects from B cell depleting therapeutic agents), and neoplastic disease, particularly in patients with adulthood-onset history of frequent infections.[147] Causes of protein and antibody losses, such as nephrotic syndromes, protein-loss enteropathies, lymphangiectasias, or inflammatory bowel disease with low serum IgG and low serum IgM have been well described.[148] Supporting laboratory evidence for protein loss includes low serum albumin level,

proteinuria, and/or protein losses in the stool (e.g., a positive stool alpha-1-antitrypsin level).

An assessment of total peripheral blood counts of CD19+ B cells, CD3+ T cells, CD4+ T cells, CD8+ T cells, and CD16/56+CD3- NK cells is necessary to identify combined immune deficiency (**see Section 5**) and congenital agammaglobulinemia (**see RECOMMENDATION 4.2**). This diagnostic clarity has direct implications on patient clinical management.

An assessment of peripheral blood B cell subsets, in particular class-switched memory (CD27+IgD-/IgM-) B cells, is recommended for patients with antibody deficiencies. Absent memory B cells is a component diagnostic criterion for common variable immune deficiency (CVID) using the European Society for Immunodeficiency (ESID) guidelines.[146] Patients with low class-switched memory B cells (defined as <2% of total CD19+ B cells) do not produce protective antibody levels following vaccination, including to the COVID mRNA vaccines,[149] and are at high risk for the development of auto-inflammatory disease co-morbidities,[150] and death.[150, 151] Expansions of early transitional B cells (defined as IgD+CD27-CD10+ or IgD+CD27-CD24hiCD38hi) or activated CD21lo B cells are associated with the occurrence of autoimmune and end-organ inflammatory disease.[150, 152]

An assessment of peripheral blood T cell subsets may contribute to the diagnostic evaluation of antibody deficiency. T-cell abnormalities in number and function are frequently found in patients with CVID.[153-155] The diagnosis of some of these patients may be revised after genetic testing to other IEI, in particular several forms of T regulatory cell dysfunction (Tregopathy) syndromes (e.g., CTLA4 deficiency)[156, 157]

Normal serum immunoglobulin levels do not rule out a diagnosis of humoral immune dysfunction. **RECOMMENDATION 4.6 and 4.7** detail specific antibody deficiency (SAD), a condition in which patient antibody levels (total IgG) are normal, however, antigen-specific antibody response to immunization is decreased. Patients with SAD are susceptible to frequent infections - predominantly at ears, sinuses, lung, and/or gastrointestinal locations - similarly to patients with low serum IgG levels.

Vaccines do not uniformly elicit high serum antibody titers, and some are not recommended for routine clinical assessment of vaccine responsiveness, such as the hepatitis B vaccine.[158] Testing of antigen-specific antibody response to immunization has historically centered around testing of both T-dependent vaccine responses (e.g., HiB and tetanus toxoid) and T-independent vaccine responses (e.g., pneumococcal 23 serotype polysaccharide vaccine).[159] With use of the new 15-, 20- and 21-valent conjugated pneumococcal vaccines becoming widespread in routine clinical care, testing of vaccine responsiveness is evolving (**RECOMMENDATION 4.6 and 4.7**).

Guidelines for the analysis of anti-pneumococcal antibody responses suggest using 1.3 ug/mL following a polysaccharide pneumococcal vaccine and 0.35 ug/mL following a pneumococcal conjugate vaccine as thresholds to determine protective pneumococcal serotype-specific antibody levels against invasive pneumococcal infections. These testing are measured at baseline, 4-week post-vaccination, and, to assess persistence of immunological memory, at 6 months post-vaccination.[159] Testing pre- to post-immunization antibody titers to pneumococcus serotypes should be performed by the same clinical laboratory for diagnostic accuracy. Results vary widely by reference laboratory with discordance in micrograms per milliliter reported.[160]

RECOMMENDATION 4.2: We recommend the diagnosis of agammaglobulinemia for patients with low or undetectable serum immunoglobulin concentrations *and* low or undetectable circulating B cells *and* normal total CD3+ T cell numbers.

Strength of recommendation**- Strong**

Certainty of evidence **– High.**

Patients with agammaglobulinemia present with recurrent bacterial respiratory tract infections, particularly otitis media, sinusitis, and pneumonia in the first 2 years of life.[161-163] The most common organisms isolated are *S. pneumoniae* and *H. influenzae*. Other reported infections in agammaglobulinemia include those by enterocytopathic human orphan (ECHO) viruses and ecthyma or pyoderma gangrenosum caused by species of *Helicobacter* and *Campylobacter*. Rarely, patients present with pneumocystis pneumonia or vaccine strain poliovirus infection.[164, 165] *Ureaplasma* or *Mycoplasma* species–related arthritis and bacteremia or regional enteritis associated with enterovirus are also seen.[165-167] Some patients are not recognized to have agammaglobulinemia until after 5 years of age.[167, 168]

The physical examination of patients with agammaglobulinemia usually reveals absence of lymph nodes and tonsils distinct from other forms of antibody deficiency. There are no other consistent physical findings in patients with agammaglobulinemia.[161]

Agammaglobulinemia is characterized by a serum IgG level of usually less than 100 mg/dL, low or undetectable serum IgM and serum IgA levels, and peripheral blood CD19+ B-cell counts of less than 2%.[161, 162] The differential diagnosis of agammaglobulinemia include secondary causes and severe CVID (see below) with serum immunoglobulins levels and B cells in the agammaglobulinemic range. It can be difficult to distinguish agammaglobulinemia from CVID without molecular testing. Measurement of antigen-specific antibodies titers is not necessary in patients with IgG levels less than 150 mg/dL.

Genetic evaluation is recommended in the diagnosis of agammaglobulinemia (**see Section 3**). Approximately 85% of patients with agammaglobulinemia patients have the

X-linked form (XLA), associated with variants in *BTK* encoding Bruton's tyrosine kinase (BTK).[161, 169] The absence of BTK protein in monocytes or platelets can be demonstrated by Western blotting or flow cytometry. Patients with certain *BTK* variants can have milder clinical and immunologic phenotypes with higher concentrations of serum immunoglobulins suggestive of CVID or even specific antibody deficiency (SAD).[162] A family history of affected maternal male cousins, uncles, or nephews suggestive of X-linked inheritance may be present, although sporadic cases are common. Pathogenic variants in one of several genes that regulate B-cell maturation cause autosomal recessive agammaglobulinemia.[169-172] These genes encode components of the pre–B-cell immunoglobulin receptor, including IgM heavy chain (*IGHM*), the surrogate light chain (*IGLL1*), the immunoglobulin receptor–associated signal transducing chains Igα and Igβ (*CD79A*, *CD79B*), the cytoplasmic adapter molecule B-cell linker protein (*BLNK*), and the downstream PI3K signaling pathway. Autosomal dominant monogenic agammaglobulinemias are reported associated with variants in *TCF3*, *TOP2B*, and *SPI1*.[173-175]

RECOMMENDATION 4.3: We <u>recommend</u> the diagnosis of CVID for patients with low serum IgG *and* low serum IgA and/or low serum IgM levels *and* demonstrated impaired antibody response to infection or immunization.

Strength of recommendation**: Strong**

Certainty of evidence: **High**.

CVID may be the most frequently encountered symptomatic IEI, affecting an estimated 1:30,000 individuals, though prevalence among specific populations may vary with a particularly high prevalence described in Northern Europe.[176, 177] The typical clinical presentation for these patients is recurrent sinopulmonary infections, but CVID may be diagnosed after recurrent autoimmune cytopenias, benign lymphoid hyperplasia, or chronic gastrointestinal disease.[144] Patients with hypogammaglobulinemia and thymoma should be given a diagnosis of Good syndrome.[178]

Bacterial infections are frequent in CVID, including common respiratory infections caused by *S. pneumoniae* and non-typeable *H. influenzae* as well as atypical pneumonia caused by *Mycoplasma* and *Ureaplasma* species that also include joint involvement.[179] Respiratory tract infections with viruses are common.[180] Gastrointestinal infections may be frequent and refractory to treatment, including parasitic (such as Giardia) and viral (such as norovirus) infections (**Section 9**).[181]

In addition to infections, CVID patients may present with autoimmunity, chronic gastrointestinal, liver, and lung disease and malignancy. Autoimmunity most frequently manifests as cytopenias, though other forms, such as arthritis, also occur.[182] Frequent chronic gastrointestinal complications include gastritis and enteritis, which may have pathological appearance of autoimmune inflammation but absent autoantibodies

typically found in these diagnoses.[183, 184] Liver disease shows nodular regenerative hyperplasia on biopsy, a condition with unclear etiology and challenging clinical course.[185] Chronic lung disease in CVID presents as asthma, chronic obstructive pulmonary disease, or bronchiectasis.[186] Interstitial lung disease may be present, characteristically displaying benign lymphoid hyperplasia pathology together with granulomatous inflammation and thus described as granulomatous-lymphocytic interstitial lung disease (GLILD).[187] Lymphoproliferation in the lung often coincides with lymphoproliferation elsewhere, such as the lymph nodes or spleen.[188]

It is now estimated that around 30% of CVID cases have identifiable genetic etiology.[189, 190] Widespread availability of clinical genetic testing is at the forefront of CVID clinical care. As examples, heterozygous pathogenic variants of *CTLA4* and homozygous pathogenic variants of *LRBA* both reduce expression of CTLA-4, a key regulator of T cell responses, leading to an autoimmune and lymphoproliferative disease as well as varying degrees of antibody deficiency consistent with CVID.[191, 192] Also, heterozygous gain-of-function variants of *PIK3CD* and loss of function variants of *PIK3R1* result in similar immune disorders marked by a CVID-like clinical presentation of autoimmune cytopenias, lymphoid hyperplasia, and antibody deficiency termed activated phosphoinositide 3-kinase delta syndrome (APDS).[193] IgG replacement therapy (**Section 8**) should be initiated in those diagnosed with CVID.

RECOMMENDATION 4.4: We <u>recommend</u> the diagnosis of selective IgA deficiency (SIGAD) for patients older than 4 years of age with serum IgA below the limit of detection *and* normal serum IgG and IgM levels.

Strength of recommendations**: Strong**

Certainty of evidence: **High**.

SIGAD is relatively common with a prevalence of about 1:500 in Caucasians and appears to be less common in Asian populations, where the prevalence is reported between 1:3000 to 1:18000.[194, 195] Assays at most clinical laboratories have not been sensitive enough to measure IgA levels below 7 mg/dL, and about one third of SIGAD patients are thought to have completely absent serum IgA.[3] Four years of age is considered the time when most children reach the normal range for serum IgA level. SIGAD patients may evolve into CVID later in life.[196, 197]

Genetic determinants of SIGAD are not well defined; it has been associated with variants in MHC loci, *TNFSRF13B*, and in other genes.[198] Patients with SIGAD can be asymptomatic; however, a subset of them may present with frequent infections (27%), atopy (23%) or autoimmunity (14%).[199] SIGAD should be considered in the evaluation of celiac disease as it can give false negative results on IgA-based antibody tests. Presence of SIGAD may increase the likelihood of an alternative cause for villus atrophy

other than celiac disease, such as Giardia infection or small intestinal bacterial overgrowth.[200]

RECOMMENDATION 4.5: We <u>suggest</u> the diagnosis of IgG subclass deficiency for patients with recurrent infections *and* low levels of one or more serum IgG subclass levels (IgG1, IgG2 or IgG3 and excluding IgG4) *and* normal serum total IgG level.

Strength of recommendation**: Conditional**

Certainty of evidence**: Moderate.**

Patients with recurrent infections may present with normal total IgG level with low serum levels of one or more of the four IgG subclasses. IgG1 is the most abundant subclass (70-80% of total IgG), and IgG1 serum levels correlate with total IgG serum levels. IgG2 follows in abundance with 20-30% of total IgG levels. IgG3 represents about 10% of total IgG and has the shortest half-life at 7 days, compared to 21 days for the other subclasses. IgG4 is the least abundant (less than 1% of total IgG), and its role against infections has not been defined.

The genetic and molecular basis of IgG subclass deficiencies have not yet been defined, although associations with IEI have been reported. IgA deficiency infrequently occurs concurrently with IgG2 subclass deficiency, and such individuals may have worse clinical course than those with either immunological finding alone.[201] More than half of activated PI3K delta syndrome (APDS) patients with normal total IgG levels may have IgG2 subclass deficiency.[202] A prospective study of 49 children with IgG2 subclass deficiency, predominantly boys, showed increased frequency of respiratory infections, compared with age-matched healthy controls.[203] Healthy children may have IgG2 subclass deficiency without presenting with increased frequency of infections.[204]

RECOMMENDATION 4.6: We <u>suggest</u> the diagnosis of specific antibody deficiency (SAD) to polysaccharides for patients with recurrent respiratory infections *and* impaired antibody responses to polysaccharides *and* normal serum IgG levels.

Strength of recommendation**: Conditional**

Certainty of evidence: **Moderate.**

Patients with SAD to polysaccharides have recurrent infections and normal antibody responses to protein antigens and have normal responses to conjugate polysaccharide vaccines, but the antibody response to a booster dose of the 23-valent unconjugated pneumococcal polysaccharide vaccine is impaired, defined as non-protective antibody levels when measured after 4 weeks after immunization. The molecular and immunological mechanisms for this condition have not been defined.

In patients who already have protective levels to some pneumococcal serotypes due to prior vaccination with conjugated polysaccharide vaccines, serotypes present in the unconjugated pneumococcal polysaccharide vaccine but not in the conjugated vaccine are used for diagnostic evaluation. Widespread pediatric use of the most recently approved 20-valent conjugated pneumococcal vaccine limits the utility of diagnostic challenge with the 23-valent unconjugated pneumococcal polysaccharide vaccine, as only 4 serotypes are present in the 23-valent vaccine that are not in the 20-valent vaccine (serotypes 2, 9N, 17F, 20). Serotype 6A is included in the 20-valent conjugated vaccine but not in the 23-valent unconjugated polysaccharide vaccine. Usage of the unconjugated *Salmonella* vaccine has been proposed as an alternative vaccine for diagnosis of SAD to polysaccharide antigens, but it's unclear diagnostic value limits clinical utility.[205]

Results of anti-pneumococcal antibody testing, including percentage of positive results, can vary between clinical laboratories.[160, 206] Previous guidelines with regards to protective antibody levels against invasive pneumococcal infection recommended using anti-pneumococcal serotype specific capsular antibody titers of 1.3 µg/mL or greater after unconjugated polysaccharide vaccine and 0.35 ug/mL for response to conjugated vaccine.[159] A response to immunization of less than 50% of the measured anti-serotype antibodies at protective levels is a cut-off for diagnosis of SAD.

It is suggested to use first the unconjugated pneumococcal vaccine (PSV23) to evaluate T cell-independent antibody responses then, if the response is suboptimal administer one of the conjugated vaccines. As an alternative, the evaluation of SAD may be accelerated by moving directly to conjugated pneumococcal vaccine after assessing pre-vaccination pneumococcal antibody levels. While this approach will not identify those who have inadequate antibody responses to the unconjugated vaccine, it provides with an intervention that might result in a decrease in the frequency of infections, other than antibiotic prophylaxis and IgG replacement (**see Sections 8 and 9),** and may allow for diagnosis of SAD to protein antigen (**see RECOMMENDATION 4.7**)**.**

RECOMMENDATION 4.7: We <u>suggest</u> the diagnosis of specific antibody deficiency (SAD) to protein antigen for patients with recurrent infections *and* impaired antibody responses to protein antigen immunizations *and* normal serum total IgG levels.

Strength of recommendation: **Conditional**

Certainty of evidence: **Low**.

While SAD has historically referred to patients with recurrent infections and antibody deficiency for pneumococcal polysaccharide antigens, the increased use of 20-valent conjugated pneumococcal vaccination and greater awareness of immune defects

necessitate broader consideration of SAD diagnosis. Inability to respond to specific antigens other than pneumococcal polysaccharides in the context of normal serum immunoglobulin levels is not well recognized.

Individuals with recurrent infections and normal total serum IgG levels who have impaired antibody responses to highly immunogenic vaccines but no other immunological defects may receive the diagnosis of SAD to those protein antigens. Examples of highly immunogenic vaccines include those for tetanus or diphtheria, in which nearly 100% of immunocompetent individuals immunized develop protective antitoxin antibodies, and varicella, which has 98% or more seroconversion in individuals who have completed the vaccine series. In contrast, hepatitis B vaccination has significantly lower immunogenicity.[207]

RECOMMENDATION 4.8: We <u>recommend</u> that patients with low serum IgG and IgA levels *and* normal or elevated serum IgM level be given the diagnosis of immunoglobulin class-switch defects *after* ruling out combined immunodeficiencies that present with similar laboratory findings

Strength of recommendation**: Strong**

Quality of evidence: **High**.

Immunoglobulin class-switch defects have been known as hyper-IgM syndromes (HIGM), because often, but not always, serum IgM is elevated. Deficiencies of activation-induced cytidine deaminase (AID), uracil nucleoside glycosylase (UNG), and mutator S homolog 6 (MSH6) clinically present similarly to other forms of antibody deficiency, with recurrent upper and lower respiratory tract infections in childhood.[209-211] These patients may also develop nonmalignant lymphoid hyperplasia, which occurs in approximately 70%.[211] Autoimmune and inflammatory disorders (e.g., autoimmune hemolytic anemia and inflammatory bowel disease) can be seen in approximately 20% of patients with a deficiency of AID.[212]

The total numbers of B cells and non-switched memory B cells (CD27+IgD+IgM+) are normal, whereas numbers of class-switched memory B cells (CD27+IgM-IgD-) are reduced.[211] Expansion of germinal centers occurs in peripheral lymphoid tissue from these patients.[208] T cells counts and T cell proliferation are typically normal and are helpful to rule out combined immunodeficiencies (CID), such as CD40 ligand deficiency and NEMO deficiency (**See Section 5.1).** We recommend genetic testing because of potential implications in prognosis. IEI presenting with similar screening laboratory findings also include CVID (**RECOMMENDATION 4.3**) and, in adults, monoclonal gammopathy of uncertain significance (MGUS) should be considered as a masquerading secondary immunodeficiency, as approximately 15% of MGUS presents with elevated IgM.[213]

RECOMMENDATION 4.9: We <u>recommend</u> the diagnosis of transient hypogammaglobulinemia of infancy (THI), for infants and children with low serum IgG level *and* normal antibody response to immunizations *and* absent evidence of secondary causes

Strength of recommendation**: Strong**

Certainty of evidence: **High**.

Infants have transplacentally-acquired maternal IgG for the first 3 to 6 months of life until it is metabolized. In some infants, production of IgG (and in some cases IgA and IgM) does not reach normal levels until early childhood. Prematurity might result in limited maternal IgG transplacental transfer and contribute to low serum IgG levels in the infant or toddler. This period of hypogammaglobulinemia can be associated with recurrent respiratory infections.[214-216] THI is a diagnosis of exclusion made in the absence of other immune deficiency diagnoses, and in retrospect once serum IgG levels reach normal range. Antigen-specific antibody responses and cellular immunity are usually preserved but may be incomplete. In one prospective study of 18 patients with THI, IgG levels spontaneously corrected to normal at a mean age of 27 months, with all patients at normal levels by 59 months.[217]

There is no known genetic basis for THI, although an increased incidence is reported in families with other immunodeficiencies, particularly *IGLL1* deficiency.[218] Some THI patients have reduced memory B-cell counts.[219, 220] We recommend measuring serum IgG levels every six months until these levels are in normal range for age. Although most children with THI spontaneously recover their IgG levels and have a benign clinical course, some of them do not recover and are diagnosed with CVID, or other forms of antibody deficiency.[214-217]

RECOMMENDATION 4.10: We <u>suggest</u> the diagnosis of unspecified primary hypogammaglobulinemia for patients with significant morbidity from infections *and* low serum IgG level *and* normal cellular immunity *and* no evidence of secondary causes of low IgG levels *and* not fulfilling diagnostic criteria for the above antibody deficiency disorders.

Strength of recommendations**: Conditional**

Certainty of evidence: **Moderate**.

A diagnosis of unspecified primary hypogammaglobulinemia can be given to patients who have (1) low levels of serum immunoglobulins not conforming to any of the diagnoses above, (2) significant morbidity from infections, (3) normal cellular immunity, (4) no other potential immune deficiency diagnosis, and (5) no other conditions predisposing to humoral immunodeficiency, including secondary immunodeficiencies (**See RECOMMENDATION 4.1**).[147, 216, 217]

SECTION 5. **Combined Immunodeficiencies, Neutrophil Defects, Innate Immune Defects and Complement Deficiencies.**

RECOMMENDATION 5.1: We recommend immunological investigations in patients with infectious manifestations, autoimmunity, malignancy, *or* organ-specific pathologies suggesting cellular and humoral immunodeficiency.

Strength of recommendation**: Strong**

Certainty of evidence**: High.**

General evaluation of immune phenotype and function is necessary to support detailed clinical history and physical exam for the assessment of suspected combined immunodeficiency (CID). While clinical presentation of CIDs can be variable and include infectious manifestations, autoimmunity, malignancy, and organ-specific pathologies, they share the common feature of presenting with both cellular and antibody defects. It is essential that immunology test results are reported with appropriate age-specific reference intervals.[220] The following testing is indicated in IEI, depending on clinical presentation. The list is not exhaustive and both additional testing and new applications of current testing are likely to be established in the future. A list of laboratories performing specialized immunology testing is available at URL: https://cis/clinimmsoc.org/dli/test-directory.php

Complete Blood Count with Differential (CBCd): CBCd is informative in all patients with suspected CID. Lymphopenia, defined as an absolute lymphocyte count (ALC) below the normal range for age (e.g., <1000 cells/μL in adults or <2500 cells/μL in infants), is characteristically found in CIDs. Cytopenias are frequently part of the clinical spectrum of CIDs [e.g., neutropenia in CD40 Ligand (CD40L)[222] and thrombocytopenia in Wiskott Aldrich Syndrome (WAS)].[223]

Serum immunoglobulin levels and quantitative specific antibody titers: Abnormal immunoglobulin levels and low or absent antibody responses to immunizations are frequent in CIDs. Serum immunoglobulin levels must be interpreted in the context of age-appropriate reference intervals **(see Section 4).** Reference intervals represent the mid-95 percentile of a healthy population and therefore 5% of this population will have values below or above the middle 95%, and thus, clinical significance may not be based only on numerical cut-offs.

Lymphocyte subset phenotyping: A hallmark of most CIDs is low percentages of T and sometimes B cells, both of which can vary depending on the specific underlying genetic cause and degree of immune activation at the time of blood sampling. Additionally, lymphocyte counts are influenced by age, sex, circadian rhythms and diurnal variation.[225, 226] Lymphocyte subset (T/B/NK) phenotyping includes quantification

of the relative percentages and absolute numbers of T cells (CD3+, CD3+CD4+, CD3+CD8+), B cells (CD19+, CD20+), and natural killer (NK) cells (CD16+CD56+) by flow cytometry. Markers for T/B/NK panels may include (1) CD45 for identification of nucleated blood cells and for accurate discrimination of lymphocyte, monocyte, and neutrophil populations, (2) CD14 for identifying monocytes, (3) CD3, CD4 and CD8 for T cell subset identification and enumeration, (4) CD19 and/or CD20 for identification of B cells, and (5) CD56 and CD16 for the identification of NK cells. The ratio of CD4:CD8 T cells may also be reported. Significant discrepancies between the percentage of CD3+ T cells and the sum of CD4 and CD8 T cells percentages should be investigated for increases in double-negative T cells (DNTs), which may express either T cell receptor (TCR) αβ+, seen in certain lymphoproliferative conditions including Autoimmune Lymphoproliferative Syndrome (ALPS),[227] or TCR γδ+, which occur with viral and mycobacterial infections, and is associated with CID (e.g., Ataxia Telangiectasia [A-T]).[228] A low CD4:CD8 ratio may be indicative of MHC Class I or ZAP70 deficiency,[229, 230] where CD8 T cells are significantly low or MHC Class II deficiency where CD4 T cells are significantly low.[231] B cell counts are low in a variety of CIDs (e.g., ICOS deficiency, NBS1 deficiency).[231, 232]

Naïve and memory T cells, and recent thymic emigrant (RTE) phenotyping. The percentage of naïve T cells (CD4+CD45RA+ and CD8+CD45RA+) and RTEs (CD4+CD31+CD45RA+ and CD8+CD31+CD45RA+) is highest in newborns (>80%) and decreases with age. Conversely, activated/memory T cells (CD4+CD45RO+ and CD8+CD45RO+) increase with age, reflecting antigen exposure and development of T cell memory response. T cell phenotyping panels include a variety of markers to differentiate naive, memory, effector memory T cells (Tem), central memory T cells (Tcm), and terminally differentiated memory T cells re-expressing CD45RA (TemRA). Quantification of these populations is useful for assessing an ongoing T cell mediated immune process (e.g., an unexpected increase in effector memory T cells may indicate a T-cell mediated reactive or autoreactive process) TemRA cells are a heterogeneous subset and represent preformed effector cells with high expression of effector molecules. If they express CD57 they can represent a “pre-exhaustion” or senescent phenotype. CD8+ TemRA cells can expand with age and are also increased in chronic viral infections and chronic antigenic stimulation. CD4+TemRA cells have been implicated in protective immunity against viral pathogens. Defective T cell memory development is observed in a variety of CIDs.[233, 234] RTEs correlate with TREC levels (**See Section 2),** and are reduced in severe CIDs and in congenital athymia.[65, 235]

B cell phenotyping: B cell phenotyping panels include markers (CD19 and/or CD20, IgD, CD27, IgM, CD24, CD21, CD38, CD10, IgG, IgA), to assess the relative frequencies of naïve, memory, class-switched and non- class-switched (marginal zone) memory, transitional, CD21-/low(or dim) B cells and plasmablasts.[236] Additional phenotyping may include quantification of IgM, IgD, IgG and IgA-expressing B cells, as

well as CD10+ immature B cells. These analyses are useful for assessment and diagnosis of CIDs with perturbation of immunoglobulin levels or defective antibody responses, such as decreased class-switched memory B cells (CD40L, CD40 deficiency),[237] or increased CD21-/low B cells as a correlate of autoimmune complications in CIDs.[187-189]

Quantification of regulatory T cells (Treg): Tregs (CD4+CD127loFOXP3+CD25hi) constitute approximately 5-10% of peripheral blood CD4+ T cells.[238] Although low in frequency, Tregs are a crucial component of immune regulation. Low Treg numbers are associated with immune dysregulation (lymphoproliferation, autoimmune cytopenias, organ-specific autoimmunity) in a variety of CIDs (e.g., *DOCK8* pathogenic variants).[239] Treg function testing is not clinically available. Of note, the CD4+CD25hiCD127lo phenotype (without measuring FOXP3 expression) may not accurately identify Tregs[240] and FOXP3 can be transiently expressed in activated T cells that are not Tregs.[241]

Quantification of T Follicular Helper Cells (Tfh): Tfh (CD4+CXCR5+PD1hi ICOS+BCL6+) are orchestrators of long-lived antibody responses.[242] These cells are classically found in germinal centers (GC) of secondary lymphoid organs with a small population (~10%) found in peripheral circulation. IEI resulting in defective GC formation (e.g., *CD40L*, *ICOS*, *IL-10R*, *NEMO*)[243] are associated with low frequencies of Tfh. Elevated numbers of Tfh may occur in CID with autoantibody production,[244] including those with autoimmune cytopenias.[245]

Quantification of activated, exhausted, senescent T cells: CIDs associated with an underlying dysregulated immune process or impaired T cell responses may present with an increase in activated, exhausted and/or senescent T cells. A variety of cell surface markers are used to quantify these cell populations including but not limited to, HLA-DR and a combination of HLA-DR and CD38 for activated T cells, CD57 for senescent T cells, and PD-1 for exhausted T cells. Activated T cells may be increased in CIDs with decreased Treg function (e.g., STAT5b deficiency)[246] and immune dysregulated processes (e.g., DOCK8 deficiency).[247] Patients with CIDs associated with chronic or refractory viral infections may have increased HLADR+CD38+ activated T cells. Expansion of senescent CD8+ T cells is observed in patients with activated p110-delta syndrome (APDS).[248] T cell exhaustion can be observed in the context of chronic antigenic stimulation, especially persistent viral infections.[249] Monitoring the relative frequencies of these cell populations is useful for diagnosis and when assessing responses to therapy.

Assays for T cell proliferation to mitogens and antigens: The capacity of T cells to respond and proliferate when exposed to an antigen in the presence of either MHC class I or class II on antigen-presenting cells (APCs) is crucial for an effective adaptive immune response. Due to limited exposure to foreign antigens, and prior to immunization with routine childhood vaccines (before two months of life), evaluation of

the antigen-specific T cell response in newborns may not be informative. Pan- T cell stimulants, or mitogens, such as the plant lectins phytohemagglutinin (PHA), concanavalin A (ConA) and pokeweed mitogen (PWM) are used to test T cell capacity to proliferate. In addition to these mitogens, T cells can be stimulated to proliferate via antibody crosslinking of the CD3 complex and costimulation with anti-CD28 antibody, or the addition of exogenous IL-2. Anti-CD3 stimulation with IL-2 or CD28 is particularly useful when assessing signaling defects downstream of the T cell receptor, or due to defective IL-2 production or response (e.g., WAS).[250] Also, stimulation with anti-CD3 and other costimulants as described above offers a more physiological yet global assessment of the T cell proliferative response compared to mitogen stimulation. T cell proliferative responses to antigens are commonly measured after exposure to tetanus toxoid or candida. Defective T cell proliferation in response to mitogenic stimulation is a feature of several CIDs, including ZAP70 deficiency, MHC Class II deficiency and calcium channel defects, among others.[251]

While the well-established radiometric method based on incorporation of tritiated thymidine is still widely used in many clinical laboratories for T cell proliferation assays, this method may not discriminate between normal and defective T cell function in severely lymphopenic patients. In these patients, the use flow cytometry methods that identify CD3+ T cells and use DNA-intercalating fluorescent dyes to identify dividing cells is most specific for the assessment of T cell proliferation.[252]

RECOMMENDATION *5.2:* We <u>recommend</u> the diagnosis of CID for patients with impairment (quantitative or functional) of both cellular and antibody immune functions.

Strength of recommendation: **Strong**

Quality of evidence: **High.**

CID is characterized by abnormalities in both antibody and cell-mediated immunity. Monogenic disorders with significant T cell lymphopenia, although less severe than SCID, and leading to a CID phenotype, form a separate category within the IUIS classification of IEI, often having their own specific diagnostic laboratory approach in addition to genetic testing (**Table 5.1).** This testing is recommended in addition also to those referred to in **RECOMMENDATION 5.1** Confirmation of a specific underlying genetic cause and diagnosis may enable tailored therapy.

Hypomorphic pathogenic variants of SCID-associated genes may lead to “leaky” forms of SCID and may not always present in infancy. Clinical and immunological presentation is similar to CID, with increased risk of infection, autoimmunity and lymphoproliferative disease.[253-255]

Table 5.1. Examples of specific laboratory testing for CIDs with or without syndromic features.

IEI	Associated genes	Available clinical testing
Hyper IgM Syndrome	*CD40L, CD40*, *UNG, IKBKG, NFKBIA, ATM, NBS1, PMS2, MSH6, PIK3CD, PIK3RI*	CD40L surface expression and function (CD40-mulg) CD40 surface expression B cell subset phenotyping
MHC Class I deficiency	*TAP1, TAP2, TAPBP, B2M*	MHC Class I expression on multiple immune cell types, increased CD4:CD8 ratio
MHC Class II deficiency	*RFXANK, RFX5, RFXAP, CIITA*	MHC Class II expression on B cells and monocytes, inverted CD4:CD8 ratio
CID with syndromic features		
Wiskott Aldrich Syndrome	*WAS*	WASp expression in lymphocytes
DNA repair defects	*ATM, NBS1, BLM, DNMT3B, ZBTB24, PMS2, POLE1, POLE2, LIG4*	Serum AFP levels (>6 mo of age) Flow cytometry analysis of DNA repair
Immunodeficiency, centromeric instability and facial anomalies (ICF) syndrome	*DNMT3B, ZBTB24, CDCA7, HELLS*	Cytogenetic analysis for evaluation of centromeric instability
Thymic insufficiency with congenital/syndromic features	*Chr22q11.2 deletion, TBX1, TBX2, CHD7, FOXN1, PAX1* 11q23del, 10p13-p14 deletion	TREC levels or recent thymic emigrants by flow cytometry Chromosomal analysis (SNP array),
Hyper IgE Syndromes (HIES)	*STAT3, DOCK8, PGM3, CARD11, IL6R, IL6ST, ERBIN, and ZNF431*	Serum IgE, eosinophil count TH17 cells quantification DOCK8 expression
Cartilage Hair Hyperplasia	*RMRP*	Evaluation of compartment-specific telomere length.

Clinical features of selected CIDs are discussed below.

Hyper IgM Syndromes present with low serum levels of IgG and IgA, and normal or elevated serum IgM levels.

Monogenic IEI characterized by normal or elevated serum IgM levels and low serum levels of IgG, IgA, and IgE are collectively classified as Hyper IgM Syndromes (HIGM). The underlying pathology in HIGM is the inability to class-switch immunoglobulins thus resulting in normal or elevated levels of serum IgM and decreased levels of all other immunoglobulin isotypes. HIGM syndromes are caused by pathogenic variants in genes

involved in class-switch recombination (e.g., *CD40L, CD40, AID*)[256-259] (**also see RECOMMENDATION 4.8)** and others that are caused by impaired T-B cell interaction and activation signaling (*IKBKG, NFKBIA, ATM, NBS1, PMS2, MSH6, PIK3CD, PIK3RI*).[260-262] *CD40L* pathogenic variants account for approximately 70% of reported HIGM syndromes.[256]

The clinical presentation may vary depending on the underlying genetic cause and include susceptibility to recurrent bacterial and opportunistic infections, gastrointestinal and pulmonary complications, autoimmune cytopenias, inflammatory bowel disease, lymphoproliferation and malignancies.

Laboratory features of CD40L and CD40 deficiency include low serum IgG levels with normal or elevated serum IgM, and low serum IgA levels. Specific antigen antibody production is impaired. Peripheral blood T, B and NK cell quantification is generally normal, however, memory B cells, specifically class-switched memory B cells (CD27+IgD-IgM-), are significantly decreased. Upregulation of CD40L on stimulated CD4+ T cells, measured by flow cytometry, is significantly low or absent in 80% of cases of XL-HIGM due to CD40L deficiency.[257] *CD40L* pathogenic variants that result in normal expression but non-functional CD40L are not detected with this method. A modification of the flow cytometry assay using the extracellular domain of CD40 fused with murine IgG-Fc (CD40-muIg) enables functional analysis of CD40L and can identify all cases of CD40L deficiency.[258] Female carriers of CD40L deficiency with extreme skewing of lyonization of the X-chromosome may be clinically symptomatic.[259] B cells from patients with AR-HIGM syndrome due to *CD40* null variants lack CD40 expression, which can be demonstrated by flow cytometry.[260] Abnormal test results for CD40L and/or CD40 analysis are confirmed with genetic analysis of *CD40L*.

MHC Class I and II deficiencies present with abnormal CD4:CD8 ratio, or significant CD8 T cell lymphopenia, or CD4 T cell lymphopenia and severe, recurrent infections

MHC Class I and II deficiencies are rare, autosomal recessive CIDs.[261] As interaction with MHC class I and class II in the thymus is crucial for development of CD8 and CD4 T cells, respectively, pathogenic variants of genes involved in peptide loading and transport (*TAP1, TAP2, TAPBP*) or assembly of MHC class I on the cell surface (*B2M*) result in decreased or absent MHC Class I surface expression and consequently significantly low or absent CD8 T cells.[261] Similarly, pathogenic variants of genes that control MHC Class II gene expression (*RFXANK, RFX5, RFXAP, CIITA*) lead to decreased surface MHC Class II expression and therefore low or absent CD4 T cells.[262, 263]

Flow cytometry analysis of peripheral blood for surface expression of MHC Class I (all nucleated cells) and MHC Class II (B cells and antigen-presenting cells) along with genetic analysis for the suspected gene defects is necessary to confirm the diagnosis.

RECOMMENDATION *5.3*: We recommend immunological investigations and testing of diagnostic biological markers in patients with suspicion of CID *and* certain clinical findings in non-immunological organs and systems (syndromic features).

Strength of recommendation**: Strong**

Certainty of evidence**: High**

CIDs with syndromic features form a distinct group of IEI. These patients are susceptible to bacterial, fungal, and/or viral infections and have distinctive non-immunologic features. Patients with syndromic CIDs should undergo targeted immunologic testing when available, in addition to investigation of cellular and humoral immunological compartments (**Table 5.1**).

Wiskott Aldrich Syndrome (WAS) and related disorders present with thrombocytopenia, eczema and increased susceptibility to infection

Wiskott Aldrich Syndrome (WAS) is an X-linked syndromic CID that occurs due to pathogenic variants in *WAS*, resulting in lack of expression or non-functional WAS protein, and pronounced deficits in multiple hematopoietic cell lineages.[264] WAS patients present with micro-thrombocytopenia, bleeding diathesis, eczema, severe and recurrent infections, autoimmune disease, and EBV-associated B cell lymphoma.[265] Allelic variants of WAS include X-linked thrombocytopenia (XLT), which is associated with hypomorphic loss-of-function (LOF) variants,[266, 267] and X-linked neutropenia and myelodysplasia, associated with gain-of-function (GOF) variants).[268, 269]

Laboratory findings in WAS patients include thrombocytopenia with small platelet size, abnormal immunoglobulin levels, and defective antibody responses to specific antigens. T cell numbers are decreased. T cell proliferation in response to anti-CD3 stimulation is significantly low and normalizes with the addition of IL-2.[270] Other immunological abnormalities include impaired chemotaxis of neutrophils and impaired cytotoxicity of NK cells, decreased Treg function, and increased autoreactive B cells. Flow cytometry analysis for intracellular WASP and genetic testing are necessary for confirmation of diagnosis, as WASP is not decreased in all cases.[271] Extreme lyonization of the abnormal X-chromosome in female carriers may result in clinical manifestations of WAS.[272-274]

Biallelic pathogenic variants of *WIPF1*, which encodes WASP interacting protein (WIP) that stabilizes WASP, result in a clinical phenotype resembling WAS.[275]

Defects of DNA repair present with frequent infections in combination with neurological deficits, growth retardation, skeletal, and immunological abnormalities.

DNA repair deficiencies are characterized by cutaneous, neurological, and immunological abnormalities. DNA repair deficiencies occur due to pathogenic variants

of *ATM, NBS1, BLM, DNMT3B, ZBTB24, PMS2, POLE1, POLE2, and LIG4* (and other less frequently encountered genes). Additional clinical features in these patients include frequent infections, skeletal abnormalities, growth retardation, and increased risk of malignancy.[276]

Clinical features of ataxia telangiectasia (A-T, due to pathogenic variants in *ATM*),include cerebellar ataxia, oculocutaneous telangiectasias, growth retardation, increased risk of malignancy and variable immune deficiency.[277, 278] Elevated serum alpha fetal protein (AFP) level is a consistent laboratory finding in A-T patients over 6 months of age.[279] Other findings are T cell lymphopenia and low TREC levels at birth (**see Section 2**), an increase of gamma-delta T cells, impaired T cell proliferative responses, low serum IgG, IgA, and IgE levels with normal or elevated IgM, and impaired antibody responses to specific antigens. HIGM is among the differential diagnoses given the serum immunoglobulin abnormalities in A-T.[277]

Similar immunological findings are seen in other DNA repair syndromes such as *NBN* deficiency and *LIG4* deficiency, therefore genetic sequencing is recommended to confirm the specific genetic defect.

Laboratory evaluation for lymphocyte radiosensitivity is recommended to complement immune and genetic assessment of patients with suspected DNA repair defects.[280] The assay involves measurement of phosphorylation of key proteins (ATM, SMC1 and H2AX) in the non-homologous end joining (NHEJ) and of double-stranded DNA (DNA DSB) breaks after exposure of cells to low-doses of ionizing radiation, with assessment of the temporal course of DNA repair.[281] The pattern of initiation and repair of the DNA DSB pathway is associated with the diagnosis (e.g., *ATM*, *NBN* with defects in DNA DSB damage response initiation vs. radiosensitive SCID, e.g., *DCLRE1C, LIG4, NHEJ1*, which are associated with defects in the DNA DSB repair process). Some of these defects may also be associated with increased cell apoptosis and/or cell death after exposure to radiation, which is also measured in this flow cytometry assay.

Developmental delay, abnormal facies (low-set ears, hypertelorism, epicanthal folds, and flat nasal bridge) are features for the diagnosis of Immunodeficiency, centromeric instability and facial anomalies (ICF) syndromes.

Patients present with abnormal facies, congenital malformations including inguinal hernia and hypospadias, cleft palate, syndactyly, and cardiac defects. Chromosomal methylation is defective in these patients. Approximately 50% of ICF patients have pathogenic variants in *DNMT3B* (ICF1), less frequent in *ZBTB24* (ICF2), *CDCA7* (ICF3), and *HELLS* (ICF4), while some patients with an ICF phenotype have no identified genetic cause.[282]

Immunological laboratory findings include hypogammaglobulinemia or agammaglobulinemia, variable T and B cell absolute numbers ranging from low to normal, and low T cell proliferative responses. Cytogenetic analysis for the evaluation of

centromeric instability may demonstrate breaks, deletions, multibranched configurations, and interchanges between homologous and non-homologous chromosomes, frequently involving chromosomes 1, 16 and 9, and rarely 2 and 10.[283]

DiGeorge Syndrome (DGS) present with congenital conotruncal heart disease, thymic aplasia or hypoplastic thymus, hypoparathyroidism, and midline craniofacial defects.

The underlying genetic etiology of most DGS patients is heterozygosity for Chr22q11.2 deletion (~90% of DGS patients, 1 in 4000 live births).[284] In contrast, Chr22q11.2 deletion accounts for only 38% of congenital athymia cases treated with cultured thymus tissue.

Severity of immunodeficiency in DGS patients varies depending on the degree of lymphopenia with approximately 1% or less of Chr22q11 deletion syndrome patients presenting with athymia and a SCID-like phenotype (**See Section 2**).[285] Clinical features of the syndrome might not be present in all patients. Laboratory findings in thymic insufficiency are T cell lymphopenia and low TRECs, which when severe may be identified by an abnormal newborn screen for SCID. Expanded memory T cells may be detected in cases of severe lymphopenia due to engraftment of maternal T cells or oligoclonal expansion of autologous self-reactive T cells (**See Section 2**). B cell numbers may be normal or low, and serum immunoglobulin levels can be variable with defective antibody responses to pneumococcal polysaccharide vaccine. Testing for copy number variants and gene sequencing analysis is essential for diagnostic confirmation.

Other genetic causes of thymic insufficiency with associated congenital anomalies include pathogenic variants of *TBX1* and *TBX2*, pathogenic variants of *CHD7* resulting in CHARGE syndrome (Coloboma, Heart defects, Atresia, Retarded development, Genital and Ear anomalies), biallelic and monoallelic LOF variants of *FOXN1*, biallelic variants of *PAX1.* Non-genetic etiologies of congenital thymic insufficiency include diabetic embryopathy or maternal retinoic acid exposure during pregnancy.

Hyper IgE Syndrome (HIES) presents with respiratory and skin infections, eczema and elevated serum IgE levels.

Hyper IgE Syndromes (HIES) are characterized by recurrent sinopulmonary infections, eczematous dermatitis, eosinophilia, and elevated serum IgE.[286] Recurrent cutaneous infections with *Staphylococcus aureus* and *Candida albicans* are frequent. Several gene defects cause HIES.[287] The most frequent presentation is AD-HIES due to pathogenic LOF variants of *STAT3* (Job's syndrome). Additional clinical features in STAT3 deficiency include increased risk of infections with fungi, non-tuberculous mycobacteria (NTM), development of bronchiectasis and pneumatoceles, osteoporosis, coarse facies, delayed shedding of primary teeth, and hyperextensible joints. *DOCK8* deficiency, presenting as AR-HIES, is associated with disseminated cutaneous viral infections, commonly due to HSV, HPV or severe *molluscum contagiosum*. These patients may

also present with autoimmune vasculopathies and neurological involvement. Other genetic causes of HIES include pathogenic variants of *PGM3, CARD11, IL6R, IL6ST, ERBIN, and ZNF431*.[287] STK4 deficiency present with polyclonal hypergammaglobulinemia, which includes elevated IgE.[288]

Significantly elevated serum IgE levels with variably low or normal levels of other immunoglobulin isotypes and impaired specific antibody responses are characteristics of HIES. *STAT3* deficiency is associated with low numbers of Th17 and Tfh cells,[289] increased Tregs, and decreased memory B cells. *DOCK8* deficiency presents with T cell lymphopenia in addition to HIES. Flow cytometry for intracellular DOCK8 expression is helpful for confirmation of diagnosis.[290, 291]

Cartilage Hair Hyperplasia (CHH), an immuno-osseus dysplasia, presents with short limbs, short stature, fine sparse hair, and immunodeficiency.

CHH, caused by biallelic pathogenic variants in *RMRP,* is a syndromic CID characterized by short stature, fine, sparse hair, immunodeficiency, Hirschsprung disease, and increased susceptibility to hematologic malignancies, particularly non-Hodgkin lymphoma and basal cell carcinoma.[292-294] CHH is also associated with autoimmune complications. While rare in the general population, CHH has a reported incidence of 1 in 1340 live births in the Amish population and 1 in 23,000 live births in the Finnish population,[295] explained by the presence of founder mutations in these populations. Depending on the severity of T cell lymphopenia, newborns with CHH may have an abnormal newborn screen for SCID (**See Section 2**).

Laboratory testing in CHH may reveal multiple immunologic abnormalities including hypogammaglobulinemia, neutropenia, lymphopenia, particularly T cell lymphopenia, and defective T cell proliferative responses.[296] Shortened telomeres in T and NK cells are diagnostic of CHH when clinical features are suggestive of the syndrome and should be included in the laboratory workup.[297, 298] Telomere length is measured in various leukocyte populations by Flow-FISH technology.[299, 300]

Calcium channel defects present with anhidrotic ectodermal dysplasia, muscular hypotonia, and severe immunodeficiency.

Calcium signals play a key role in activation and function of lymphocytes. Defects of Ca2+ influx from extracellular spaces into lymphocytes through the Calcium Release-Activated Calcium (CRAC) channels, result in severe congenital immunodeficiency. This has been shown in patients with biallelic pathogenic variants of *ORAI1, STIM1*, and *CRACR2A*.[301]

Calcium channel defects result in a clinical phenotype characterized by anhidrotic ectodermal dysplasia, muscular hypotonia, and severe T and B cell immunodeficiency. T cell and B cell numbers may be normal, but T cell proliferative responses to mitogen

stimulation are significantly decreased. Patients with *STIM1* pathogenic variants may also present with low Treg numbers, autoimmunity and lymphoproliferation.

RECOMMENDATION *5.4:* We <u>suggest</u> periodic assessments of immunological function in patients with CID and syndromic features.

Strength of recommendation: **Conditional**

Certainty of evidence: **Low**

As the immune phenotype and associated complications may evolve with age, it is important to perform periodic immune evaluations for patients with CIDs, every six months or more frequently, as determined by the complexity and severity of the CID. Evolving autoimmune complications, progressive lymphopenia, hematological malignancies, or organ-specific disease are documented complications in various CIDs. Thus, establishing a baseline immune phenotype and function at the time of initial evaluation with periodic evaluation for changes in immune phenotype or function is useful for optimal clinical management. (**Sections 8-12**).

<u>Neutrophil defects.</u>

RECOMMENDATION *5.5*: **We <u>recommend</u> that patients with suspected quantitative neutrophil defects be screened with serial CBCs with differential.**

Strength of recommendation**: Strong**

Certainty of evidence: **High.**

Common infections in neutropenic patients include pharyngitis with lymphadenopathy, pneumonia, mastoiditis, and cellulitis. Patients may also experience oral ulceration, gingivitis, and mucosal ulcers in the vaginal or rectal area.[302] The severity of infections correlates with the severity of neutropenia.[303]

Severe congenital neutropenia (SCN) can be cyclic or persistent and is associated with pathogenic variants of genes involved in neutrophil development: SCN1 (*ELANE*), SCN2 (*GFI1*), SCN3 (*HAX1*), SCN4 (*G6PC3*), and SCN5 (*VPS45*). (**Table 5.2**) Wiskott Aldrich Syndrome (WAS) variant X-linked neutropenia should also be considered, particularly if neutropenia is associated with increased bleeding tendency (**See RECOMMENDATION 5.3**).[304, 305]

Serial CBCd measurements may be performed up to 2-3 times weekly for 6-8 weeks to identify cyclic from persistent or chronic neutropenia. Cyclic neutropenia usually follows a periodicity of about 21 days, but it can range from 14 to 36 days.[303, 304] Infections occur during the nadirs of neutrophil count, but there may be a delay between nadirs and the onset of symptoms. Neutrophil morphology is useful for the differential

diagnosis of neutropenia (e.g., giant cytoplasmic granules within neutrophils may be indicative of Chediak-Higashi Syndrome (*LYST)*). Persistent neutrophilia suggests leukocyte adhesion deficiency (**RECOMMENDATION 5.6**)

The bone marrow aspirate in SCN due to pathogenic variants of *ELANE*, *HAX1*, *WAS*, *G6PC3*, and *G-CSFR* typically reveals hypocellularity with early myeloid arrest, whereas hypocellularity with decreased myeloid precursors is seen in SCN due to Schwachman-Diamond Syndrome, GSD1b, WHIM syndrome (Warts, Hypogammaglobulinemia, recurrent bacterial Infections and Myelokathexis) (*CXCR4*-GOF), Cohen syndrome, and Hermansky-Pudlak syndrome.

Table 5.2. Defects of neutrophil numbers and function

Neutrophil defect	Genes associated	Recommended laboratory testing
Congenital neutropenia	*ELANE, HAX1, WAS, G6PC3, SLC37A4, TAZ, VPS13B, JAGN1, CSF3R, CEBPE, SMARCD2, HYOU1, SBDS, DNAJC21, EFL1, USB1, SRP54, CXCR2, WAS*	Serial CBC with differential Bone marrow aspirate
Leukocyte Adhesion Defect I	*ITGB2* (AR)	Flow cytometry to assess CD18
Leukocyte Adhesion Defect II	*SLC35C1* (AR)	Flow cytometry to evaluate sialyl Lewis X (CD15s) expression on leukocytes.
Leukocyte Adhesion Defect III	*FERMT3* (AR)	Platelet function
Leukocyte Adhesion Defect IV	*RAC2* (AR)	Assessment of neutrophil chemotaxis DHR with fMLP for oxidative burst assessment
XL-Chronic Granulomatous Disease	*CYBB*	DHR test for neutrophil oxidative burst
AR-Chronic Granulomatous Disease	*CYBA, CYBC1, NCF1, NCF2 and NCF4*	DHR test for neutrophil oxidative burst Flow cytometry for individual NAPDH oxidase complex proteins
Pulmonary Alveolar Proteinosis	*CSF2RA, GATA2*	Analysis of anti-GM-CSF autoantibodies

*DHR, dihydrorhodamine oxidation assay; XL, X-linked; AR, autosomal recessive

RECOMMENDATION *5.6:* We recommend that patients with suspected leukocyte adhesion deficiency (LAD) be tested with flow cytometry analysis of relevant phagocyte surface molecules for LAD I and II and targeted genetic testing for LAD I, II, III and IV.

Strength of recommendation**: Strong**

Certainty of evidence: **High**

Leukocyte adhesion deficiency (LAD) can present as distinct types: LAD-I, LAD-II, LAD-III, and LAD-IV, each associated with different gene defects and distinct clinical features **(Table 5.2)**. LAD should be suspected in patients with recurrent cellulitis, severe gingivitis, chronic abscesses, or respiratory tract infections along with increased white blood cell counts, mimicking myeloid leukemia or leukemoid reactions.[306, 307]

LAD-I (CD18 deficiency) patients experience severe infectious complications early in life, with omphalitis and delayed (over 3 weeks of age) umbilical cord separation. In milder cases, infections are limited to impaired wound healing with reduced pus formation at wound sites and severe periodontitis.[308] LAD-II (SLC35c1 deficiency) patients present with pulmonary infections, chronic severe periodontitis, growth and developmental delay, and a unique facial appearance.[307] LAD-III (kindlin 3 deficiency) patients exhibit dysfunctional platelet aggregation, leading to bleeding complications, similar to Glanzmann thrombasthenia, including cerebral hemorrhage at birth.[306, 307] LAD-IV (Rac2 deficiency) patients present with delayed umbilical cord separation, recurrent infections and impaired wound healing.[309]

A baseline elevated complete blood cell count (CBC) with differential is the first diagnostic finding.[306, 306] Flow cytometry supports a diagnosis of LAD-I/II: LAD-I is characterized by the absence or reduced expression of CD18 on the surface of neutrophils and monocytes. LAD-II is identified by the absence of sialyl Lewis-X/CD15s on myeloid cells, and Bombay (hh) blood group. LAD-III diagnosis relies on demonstrating impaired platelet function and requires genetic analysis for pathogenic variants in *FERMT3*.[307] LAD-IV patients have decreased neutrophil chemotaxis and normal neutrophil oxidative burst when stimulated with phorbol myristate acetate (PMA) but diminished oxidative burst when stimulated with fMLP, a physiological activator of neutrophils.[309, 310]

RECOMMENDATION *5.7:* We <u>recommend</u> that patients with suspected chronic granulomatous disease (CGD) have measurement of phagocyte oxidase activity and genetic testing for CGD-associated gene defects.

Strength of recommendation**: Strong**

Certainty of evidence: **High.**

CGD should be suspected in patients with deep-seated infections with bacteria and fungi, particularly *Pseudomonas spp*, *Serratia* spp and *Aspergillus spp*, regardless of age of onset.[311] CGD should also be suspected in patients with very-early onset inflammatory bowel disease, which presents before age 6 years.[312] Pathogenic variants of *CYBB* cause X-linked CGD and biallelic pathogenic variants of *CYBA*, *CYBC1*, *NCF1*, *NCF2* and *NCF4* cause autosomal recessive (AR) CGD.

The initial screening test for CGD is the measurement of phagocyte oxidase activity, preferably using the dihydrorhodamine 123 (DHR) oxidative burst assay rather than the nitroblue tetrazolium (NBT) reduction assay.[313] The DHR assay, a flow cytometric assay, is objective and quantitative, whereas the NBT assay provides a microscopic visual readout, which is qualitative and subjective with higher false-negative results and a lower ability to detect AR forms of CGD. It is important to consider that the neutrophil oxidative burst test results may be compromised if time from sample collection to testing is prolonged over 24 hrs, due to spontaneous neutrophil degranulation.[314] Neutrophil oxidative burst test is reported as a Stimulation Index (SI), which represents the increase in oxidative burst activity following *in vitro* stimulation of the patient sample. Neutrophils from patients with X-linked CGD show little to absent oxidative burst activity (i.e., SI is 1), whereas neutrophils from patients with AR-CGD may have marginal to moderate oxidative burst activity. Female carriers of X-linked CGD have a population of neutrophils with normal oxidative burst and a population with little to no oxidative burst. Rarely, female carriers of XL-CGD may present with severe infections typical of XL-CGD when their neutrophils are heavily skewed towards the abnormal population.[134] About one-third of female carriers may also present with autoimmune manifestations.[315]

While decreased oxidative burst is typical of CGD patients, neutrophil oxidative burst may be decreased in other monogenic defects including *MPO* deficiency,[316] *G6PD* deficiency,[317] *RAC2* deficiency,[309] Protein kinase C δ deficiency[318] and GSD1b deficiency.[319]

Gene testing provides ultimate confirmation and may be performed concurrently with analysis of neutrophil oxidative burst when clinical findings and/or family history are strongly suggestive of a neutrophil defect. (**See Section 3**) Analysis of *NCF1* is not commonly included in CGD targeted gene panels due to sequencing difficulties posed by presence of pseudogenes.[311] Flow cytometry for detection of specific NADPH oxidase complex proteins may help to rapidly diagnose CGD genetic subtypes and identify patients with *NCF1* variants that may be missed on exome or targeted gene panels.[313, 320]

RECOMMENDATION *5.8:* We <u>recommend</u> that patients with pulmonary alveolar proteinosis (PAP) be tested for pathogenic variants in the genes encoding the GM-CSF receptor and for autoantibodies to GM-CSF.

Strength of recommendations**: Strong**

Certainty of evidence: **High**.

PAP is a rare and progressive chronic lung disease caused by defective alveolar macrophages needed for surfactant homeostasis.[321, 322] Patients with PAP exhibit increased risk for both common respiratory infections and opportunistic infections, which are primarily controlled by phagocytes in immunocompetent individuals. These include

nontuberculous mycobacteria, as well as fungi such as *Aspergillus*, *Cryptococcus*, *Histoplasma*, *Nocardia*, and *Proteus* species, causing infections in the lungs, central nervous system, joints, and disseminate throughout the body.[323]

PAP is caused by defects in the GM-CSF receptor a and b subunits or GATA2 haploinsufficiency or arise secondary to hematologic malignancy, immunosuppressive medication use, or toxin inhalation.[323, 324] Most adult patients diagnosed with PAP do not have a germline genetic defect; instead, they have neutralizing autoantibodies against GM-CSF.[325, 326] Analysis of neutralizing autoantibodies to GM-CSF is recommended to identify an underlying autoimmune cause of PAP.[327]

Defects of innate immunity.

RECOMMENDATION 5.9: We recommend that patients with suspected inherited susceptibility to a specific pathogen(s) be investigated for associated gene defects of innate immunity, in addition to exclusion of adaptive immune defects and secondary causes of immune defects.

Strength of recommendation**: Strong**

Certainty of evidence**: Moderate**

Increased susceptibility to viruses particularly herpes simplex encephalitis (HSE) outside of the neonatal period or severe/recurrent/sustained HSE, and to human papilloma virus (HPV) including severe, or extensive, or therapy-resistant cutaneous warts, and epidermodysplasia verruciformis (EV).

IEI involving the toll-like receptor (TLR)3 or interferon (IFN) pathways[328] have been associated with increased susceptibility to HSE. Approximately 5% of children with HSE and with high rates of HSE recurrence due to viral reactivation might have TLR3 deficiency.[329] NK cell defects can be associated with recurrent HSE.[330] Several monogenic disorders associated with HSE have broad susceptibility to infections, such as mycobacterial infection in STAT1 deficiency.[331] **(See Table 5.3)** Diagnosis of these monogenic disorders in patients with HSE is critical for prophylaxis, disease surveillance, and genetic counseling. As many of these conditions have an AD inheritance pattern, it is important to screen family members once the diagnosis is established. Currently no clinical testing is available for TLR3 function and other defects in the TLR3 pathway, and genetic testing is required for diagnosis of these conditions.

Regarding IEI associated with HPV infection, the majority of WHIM syndrome due to GOF *CXCR4* variants and more than half of GATA2 haploinsufficiency patients develop warts following α-HPV infection.[332] Biallelic LOF variants of EV-associated genes (*TMC6* and *TMC8*) can be identified in about half of EV patients. AD and X-linked recessive

forms of EV have also been reported. Approximately two-thirds of EV patients develop non-melanoma skin cancer.[333]

Defects of the type I IFN pathway, including presence of neutralizing anti-type I IFN autoantibodies present with severe viral infections (including COVID-19 and disseminated infections with vaccine strains (e.g., measles, yellow fever)).

Approximately 15-20% of adults with severe COVID-19 pneumonia had deficiencies of type I IFN immunity due to either presence of neutralizing autoantibodies against type I IFN, or pathogenic variants of genes involved in type I IFN immunity.[334] Patients with autosomal recessive complete or partial LOF pathogenic variants in *STAT1* have increased susceptibility to broad types of viral illnesses and mycobacterial disease, while patients with heterozygous LOF variants in *STAT1* exhibit increased susceptibility to mycobacterial infection, and not to viral infections.[335] Patients with type I IFN defects including STAT2 deficiency have increased risk of disseminated infections with live-attenuated viral vaccine strains.[336]

Congenital asplenia may present with a family history of asplenia or sepsis caused by encapsulated bacteria, most frequently S. pneumoniae.

Abdominal imaging to evaluate spleen anatomy and the assessment of pitted red cell count on peripheral blood are common diagnostic tests. There is not an established method to accurately assess splenic function.[337, 338] IgM memory B cells are depleted in asplenia patients. Blood smear for Howell-Jolly bodies is sensitive to detect moderate to severe hyposplenic function. Scintigraphy using ^{99m}Technetium labeled heat-damaged erythrocytes is used to assess spleen clearance of abnormal erythrocytes.

Toll-like receptor (TLR) deficiencies present with recurrent serious infections with gram-positive bacteria.

Patients with deficiencies in the TLR pathways have normal levels of immunoglobulins and vaccine antibody titers, normal complement, and normal phagocytic capacity. They might not have signs of inflammation despite active infection. Infections in TLR, IRAK4 or MyD88 deficiency are limited to pyogenic bacteria in the form of sepsis, abscesses, cellulitis, arthritis, osteomyelitis, and meningitis. Patients with IKBKG and IKBA deficiencies have increased susceptibility to pyogenic bacteria, mycobacteria, viruses, fungi and parasites. Defects of TLR signaling are diagnosed by demonstrating decreases of TLR responses *in vitro*[339] and genetic defects of relevant genes. TLR3 deficiency is singular for its association with HSV encephalitis.

Chronic mucocutaneous candidiasis (CMC) presents with recurrent Candida species infection of the nails, skin, and mucous membranes,

The laboratory testing for suspected CMC should include evaluation of NK cell numbers, T cell responses to *C. albicans*, Th17 cells,[340] IFN-γ responses, and genetic analysis of relevant genes (*STAT1, AIRE, RORC, ACT1, CARD9* and genes encoding proteins of the IL-17 pathway).

The presence of neutralizing autoantibodies to Th17-related cytokines in APECED patients[341] and dysregulation of INF-γ responses.[342] are associated with CMC. CMC was reported in siblings associated with a homozygous LOF variant of *Dectin1*, however pathogenicity remains uncertain because this variant allele is common in the reported population.[343]

Mendelian Susceptibility to Mycobacterial Disease (MSMD) present with severe tuberculous or atypical mycobacterial infections, Salmonella species infections, or herpesvirus infections, and normal results on screening studies of humoral and cellular adaptive immunity

The clinical penetrance and severity of MSMD depend on genetic etiology and increase with decreasing level of IFN-γ activity.[344] AD partial IFNGR1 deficiency presents in childhood later with more localized infections than AR IFNGR deficiency,[345] and typically presents with mycobacterial osteomyelitis. IL12B and IL12RB1 deficiencies have variable penetrance, which might be related to degree of pathogen exposure.[345] Patients with anti-IFN γ autoantibodies also present with increased susceptibility to mycobacterial infections and have been reported mostly in Southeast and East Asian countries.[346, 347]

Testing for MSMD includes measuring STAT4 phosphorylation and IL12 secretion in lymphocytes stimulated with IL12, STAT1 phosphorylation induced by IFN-γ , and cell surface expression of IFN-γR1 and IL12βR.[345]

Table 5.3: Examples of diagnostic assays for defects of innate immune system based on infection susceptibility. (Complement defects not included)

Infection susceptibility	Genes associated	Recommended diagnostic assays other than genetic testing
HSV encephalitis	*TLR3*; *UNC93B1; STAT1; IKBKG; IFNAR1*; *DOCK8*	MSMD testing for IFNAR1, IFNAR2, or STAT1 deficiency
		Phenotyping and functional assessments of NK cells
		Toll-like receptor (TLR) assay
		Flow cytometric evaluation of IFN-γR (CD119) surface expression
		Flow cytometry for DOCK8 protein expression

HPV **Alpha-HPV (**muco-cutaneous warts and HPV-related cancers) **Beta-HPV (**epidermody splasia verruciformis EV)	**Alpha-HPV** *CXCR4;* *DOCK8*; *GATA2* **Beta-HPV** *TMC6* (*EVER1*) *TMC8* (*EVER2*) *STK4*; *RHOH*; *MST1*; *CORO1A*	Phenotyping and functional assessments of NK cells
Severe viral infections	*IKBKG; TLR3; GATA2; STAT1*; *TYK2*; *IFNAR1; IRF8*; *IRF7*; *IRF9; MDA5; ZNFX1*.	Phenotyping and functional assessments of NK cells Targeted cytokine assays Autoantibodies to type 1 IFNs
Disseminated vaccine-strain measles and /or yellow fever	*IFNAR1*; *IFNAR2*; *TYK2*; *STAT1; STAT2*; *IRF9*; *IKBKG*	Phenotyping and functional assessments of NK cells Targeted cytokine assays
Recurrent invasive pyogenic bacterial infection	*IRAK4; MYD88; IKBKG; NFKBIA*	TLR-4 response to LPS
	Hypo/asplenia (for encapsulated bacteria)	Peripheral blood erythrocytes for pitted red cell count and/or IgM memory B cell count for hyposplenism Blood smear for Howell-Jolly bodies Abdominal imaging for asplenia. Scintigraphy with ^{99m}Technetium labeled heat-damaged erythrocytes
Chronic muco-cutaneous candidiasis	*AIRE*; *IL17RA*; *IL17RC*; *IL17F; STAT3*; *DOCK8; STAT1*; *CARD9*	Enumeration of Th17 cells by flow cytometry
		Autoantibodies against IL-17A or IL17F for acquired CMC
Mycobacterial disease (MSMD)	*IFNGR1; IFNGR2*; *IKBKG*; *IL12RB1*; *IL12B1*;	Targeted cytokine assays

	IL12RB2; *IL23R* ; STAT1 ; *JAK1*; *IFNG*; *GATA2*	Flow cytometry of IFNGR1 (CD119) and IL12RB1 (CD212) Autoantibodies against IFN-γ, for acquired MSMD

(*) A list of immunology testing laboratories is available at URL: https://cis.clinimmsoc.org/dli/test-directory.php

Complement deficiency

Inherited complement defects can result in recurrent infections, autoimmunity, and disorders related to complement hyperactivation. The latter includes thrombotic microangiopathies, renal disorders, age related macular degeneration and hereditary angioedema. (**Table 5.4**) Hereditary angioedema is not addressed in this practice parameter.

RECOMMENDATION 5.10*:* We recommend that patients with recurrent or severe infections by encapsulated bacteria AND with normal antibody responses be evaluated for complement deficiency.

Strength of recommendation**: Strong**

Certainty of evidence**: High**

Patients with complement deficiencies have increased susceptibility to infection.[348, 349] Almost 50% are prone to bacteremia or severe infections such as pneumonia, meningitis, septicemia, or osteomyelitis, caused by encapsulated bacteria (e.g., *H. influenzae, N. meningitidis, S. pneumoniae).* Deficiency of the early components of the classical pathway also predisposes to autoimmune diseases such as systemic lupus erythematosus (SLE), juvenile rheumatoid arthritis, glomerulonephritis, Henoch-Schönlein purpura and dermatomyositis.[350, 351] C1s/C1r deficiencies are commonly inherited together. More than 50% of these patients and 90% of patients with deficiency of C1q are reported to have SLE or lupus-like syndrome. The leading cause of mortality in patients with C1q or C2 deficiencies experiencing infection or autoimmunity is complications related to their vascular system.[352] There is a 1% prevalence of non-functional *C2* gene variants in the Caucasian population, and females with this deficiency have a higher risk of SLE.[352] C4 deficiency is rare and is strongly related to SLE.[351] Individuals with monoallelic pathogenic variants in *C2* or *C4* are asymptomatic.[353]

In addition to recurrent infections, patients with C3 deficiency can develop conditions such as membranous glomerulonephritis, SLE, atypical hemolytic uremic syndrome (aHUS) and age-related macular degeneration (AMD).[353-355]

Deficiency in the components of the terminal pathway[348, 353] have increased risk of meningococcal meningitis. Repeated *Neisseria* infections or family history of meningococcal infections suggest terminal component deficiency.

Patients with deficiency in the alternate pathway complement components such as regulators Factor H, Factor I and properdin have also been reported to have severe bacterial infections.6 Properdin deficiency is an X-linked complement deficiency, which presents with increased susceptibility to severe *Neisseria* infections including sepsis, often during adolescence.[356, 357] Patients with Factor B and Factor D deficiencies have been reported to have recurrent pneumococcal and meningococcal infections.[358, 359]

Deficiency of lectin pathway components such as collectin and ficolin has not been clearly associated with a clinical phenotype. Mannose binding lectin (MBL) deficiency is observed in about 5-7% of Caucasian populations.[360] MBL deficiency has been reported with increased susceptibility to meningococcal meningitis, human immunodeficiency virus (HIV) infection, hepatitis C virus (HCV) infection and severe bacterial and fungal infections producing sepsis. However, MBL deficiency is not a major risk factor for infections by itself, and the severity of the infection may be due to the presence of other immune system abnormalities.[361] MBL-associated serine protease 2 (MASP2) insufficiency in combination with the anti-C1q autoantibody presence has been associated with recurring pneumonia, pulmonary fibrosis, and ulcerative colitis[361] and with febrile neutropenia in pediatric cancer patients.[362]

Initial tests for evaluating complement function are CH50 and AH50, which help to narrow down the specific affected complement component(s).[353, 363-365] Because complement proteins are not stable, attention should be given to blood sample collection and handling. Complement activation is temperature-dependent so serum must be obtained from samples as soon as possible and stored at -80°C. If CH50 is low with normal AH50 results, deficiencies in the classical pathway should be suspected; if AH50 is low with normal CH50 results, it suggests a deficiency in the alternative pathway. When both assays show low results, deficiency in the terminal pathway, including regulatory proteins factors H and I, is likely. This approach should lead to evaluation of specific pathway components.[365]

Serum complement levels are maintained as a balance between production and consumption through activation. Multiple complement components are decreased when there is chronic over-activation of the pathway. Causes may include the presence of autoantibody against a complement protein, deficiency in a complement control protein, protein-losing enteropathies, chronic infection, or malnutrition.[351, 366] An increase in the levels of activation fragments amidst multiple complement components helps distinguish low results due to excessive consumption versus reduced production.[366] Measurement of activation fragments also indicates the extent of involvement of the respective

pathways and the degree of inhibition when a patient is being treated with complement-targeted therapeutics.

RECOMMENDATION *5.11:* We <u>recommend</u> that patients presenting with thrombocytopenia, microangiopathic hemolytic anemia, and acute renal failure be screened for abnormalities of complement regulatory proteins and/or autoantibodies against complement Factor H (CFH) and related proteins 1 and 3 (CFHR1/CFHR3).

Strength of recommendation**: Strong**

Certainty of evidence**: High**

Deficiency of complement regulatory proteins presents with recurrent infections, inflammatory disorders, protein-losing enteropathies, thrombotic microangiopathies or renal disorders, which include conditions such as age-related macular degeneration (AMD), atypical Hemolytic Uremic Syndrome (aHUS) and paroxysmal nocturnal hemoglobinuria (PNH).[355, 367, 368] aHUS is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury. The clinical findings of aHUS require exclusion of idiopathic thrombotic thrombocytopenic purpura (TTP), Shiga toxin-producing Escherichia coli (STEC) induced HUS, pregnancy related conditions and other causes of thrombotic microangiopathy.[369]

Deficiency of complement regulatory proteins in the kidney endothelium can result in uncontrolled amplification of the cascade, complement-mediated inflammation, secondary consumption of circulating complement factors, deposition of C3b on the kidney microvasculature and tissue injury,[368] leading to aHUS.[369, 370] About 20-30% of aHUS cases have pathogenic variants in Factor H, 5-10% in Factor I, 1-4% in Factor B, 10-15% in membrane cofactor protein (MCP)/CD46 and 3-5% have pathogenic variants in thrombomodulin.[369, 371-373] Ten percent of aHUS cases are due to autoantibodies against Factor H, and autoantibodies against complement Factor H-related proteins 1 and 3 have been reported (CFHR1/CFHR3).[353, 374]

GOF gene variants in *C3* and *C5* increase the stability of their respective convertases and similarly lead to aHUS.[369, 370, 374] Not all carriers of pathogenic variants in aHUS-associated complement genes show disease manifestations.[375]

C3 glomerulopathy (C3G) is also a rare kidney disease characterized by complement dysregulation of the alternative pathway due to mutations in Factor H, Factor I, and MCP.[376] C3G occurs in the fluid phase of the glomerular microenvironment causing C3 deposition and tissue injury. C3 nephritic factors, autoantibodies that bind to the C3 convertase, stabilizing and increase its half-life are, is seen in 50-80% of C3G cases. There have also been reports of C4 nephritic factors, which act through a similar mechanism on classical and lectin pathway C3 convertases in membranoproliferative

glomerulonephritis, meningitis, and sepsis.[377] In addition, presence of anti-Factor B antibodies has also been associated with C3G.[377, 378] Polymorphisms in genes encoding Factor H, Factor I, and C3 and dysregulation of the alternative pathway have also been associated with AMD, with retinal deposits of complement proteins and vision loss in elderly individuals.[379, 380] Decay accelerating factor (CD55) and CD59 are membrane-bound inhibitors that bind to anchoring structures encoded by the phosphatidylinositol glycan class A (PIG-A) gene to protect red blood cells. In Paroxysmal Nocturnal Hemoglobinuria (PNH), somatic mutations in *PIGA* leads to the premature death and impaired production of red blood cells.[381] Isolated CD55 deficiency has been associated with protein losing enteropathy,[382] and isolated CD59 deficiency has been associated with Guillain-Barré-like neurological symptoms.[383] Similarly, mutations in Factor H, MCP and Factor I have also been reported in conditions such as pre-eclampsia, hemolysis, elevated liver enzyme levels and low platelet levels (HELLP) syndrome, urinary infections, otitis, pyelonephritis, meningitis, and sepsis.[384-386]

RECOMMENDATION 5.12: We recommend genetic testing when complement function is abnormal.

Strength of recommendation**: Strong**

Certainty of evidence: **Moderate**

When complement deficiency is suspected, genetic testing should be pursued in addition to protein level and functional assays.[353, 386] (**See Section 3**) Genetic polymorphisms of Factor H, CFHR1–5, C3 and rare variants of Factor I genes are associated with AMD or serve as risk predictors for AMD.[388] Disease specific targeted gene panels with specificity for complement-mediated TMA, aHUS, and C3G are now available.[389] Individuals' responses to complement-targeted therapeutics can vary in the context of their genetic background.[390] Genetic variants in C5 and rare polymorphisms of the complement receptor 1 gene may determine response to eculizumab therapy in PNH patients.[390, 391]

Table 5.4 Complement Deficiencies and Associated Infection and Diseases

Component	Infection	Other Diseases
Classical Pathway		
C1q, C1r and C1s, C2, C4	Encapsulated bacteria	SLE, Vasculitis, RA, SS, SSC Glomerulonephritis
Lectin Pathway		

MBL	Bacterial, fungal, protozoal, viral infections when with other immunological abnormalities	SLE, Inflammatory arthritis, cardiovascular
Ficolins (M, L, H)	Bacterial infections when with other immunological abnormalities	Pneumonia, Ulcerative colitis
MASPs	Bacterial infections when with other immunological abnormalities	Pneumonia, Pulmonary fibrosis, and Ulcerative colitis
Alternate Pathway		
Properdin, Factor B, Factor D	Meningococcus	aHUS, Glomerulonephritis
Terminal Pathway		
C3	Severe bacterial, Respiratory tract	Glomerulonephritis, SLE, RA, aHUS, AMD
C5, C6, C7, C8, C9	Meningococcus, Neisseria	SLE, glomerulonephritis Vasculitis, APS, Myasthenia Gravis, TMA
Regulatory proteins		
Factor H	Bacterial	ITP, aHUS, Glomerulonephritis, SLE, AMD
Factor I	Encapsulated Bacterial	aHUS, Glomerulonephritis, scleroderma, RA, Vasculitis
CD46		aHUS
CD59, CD55		PNH

SLE Systemic Lupus Erythematosus, RA Rheumatoid arthritis, SS Sjogren's syndrome, SSc Systemic sclerosis, ITP Immune thrombocytopenic purpura, aHUS Atypical Uremic Syndrome, PBC Primary Biliary Cholangitis, APS Antiphospholipid Syndrome, AMD Age-related macular degeneration, PNH Paroxysmal nocturnal hemoglobinuria; HAE, hereditary angioedema; AAE acquired angioedema.

Section 6. Immunologic diagnosis of immune dysregulation disorders (PIRD) and autoinflammatory disorders

RECOMMENDATION 6.1. We recommend evaluation for IEI in patients with clinical manifestations of immune dysregulation, such as immunodeficiency, autoimmunity, lymphoproliferation and autoinflammation.

Strength of recommendation**: Strong**

Certainty of evidence: **High**

Patients with manifestations of immune dysregulation should be evaluated for underlying genetic causes and for the presence of biomarkers of hyperinflammation, autoimmunity and immunodeficiency.[8, 392] Both humoral and cellular mechanisms are involved in immune dysregulation, including cytokines and chemokines, T and B cell subsets, NK cells, macrophages and the inflammasome.[393, 394]

Classification of immune dysregulation syndromes according to the type of response and the involvement of specific molecular and cellular mechanisms has been proposed. (See **Table 1.1- subtable IV**) Some of the common clinical presentations include cytokine release syndromes (CRS), hemophagocytic lymphohistiocytosis (HLH), systemic inflammatory response syndrome (SIRS), multisystem inflammatory syndrome related to COVID-19 in adults and children (MIS-A and MIS-C) and the interferonopathies. Classification can also be based on affected cellular phenotypes such as Treg cells, double negative T cells, T and B cell subsets, and innate immune cells such as macrophages and neutrophils.[17]

There is genetic predisposition to developing immune dysregulation.[395-397] While primary HLH is associated with pathogenic gene variants, there is also a genetic contribution that leads to increased risk of secondary HLH. Genetic defects in immune dysregulation disorders may involve germline or somatic variants, lyonization, mosaicism and epigenetic modifications. (**Section 3**)

RECOMMENDATION 6.2. We <u>recommend</u> the assessment of cellular and humoral immunological function in patients with suspected immune dysregulation disorders.

Strength of recommendation**: Strong**

Certainty of evidence**: Moderate**

When evaluating suspecting immune dysregulation syndromes, it is important to be able to identify markers of inflammation. These include common non-specific markers such as ESR and CRP. Other markers include ferritin, triglycerides, fibrinogen, and clotting studies. Cytokine and chemokine serum levels may be useful in identifying the underlying mechanism of inflammation, such as distinguishing between an interleukin-1 mediated process versus an interferonopathy.[398] Examples of these tests are serum levels of IL-2Ra (soluble CD25) and CXCL9, which are elevated in IFNg-mediated inflammation. Immune dysregulation may present with abnormal lymphocyte sub-populations: regulatory T cells (Treg), Th17 cells, TCRαβ DN T cells, follicular helper T cells (Tfh); B cell subsets (e.g., transitional B cells) and NK cells. **(see RECOMMENDATION 5.1)**

RECOMMENDATION 6.3. We recommend that patients with periodic fevers and chronic systemic inflammation be evaluated for IEI and for secondary causes such as infection, autoimmune disease, or malignancy.

Strength of recommendation: **Strong**

Certainty of evidence**: High**

An inflammatory condition is suspected when the patient presents with typical signs of inflammation: fever, pain, rashes and joint swelling.[395-397] Other signs can be present, including neurologic, gastrointestinal or pulmonary symptoms. A chronic inflammatory state may be suspected if the patient has recurrent or episodic symptoms, in addition to elevated C reactive protein and erythrocyte sedimentation rate in peripheral blood. Because of the variety of ways that inflammation can present, a high index of suspicion must be maintained. Diagnostic evaluation for both IEI and secondary causes should be performed in these chronic cases. The evaluation of autoinflammatory disorders requires a multidisciplinary approach with involvement of experts in Immunology and Rheumatology to differentiate clinical subtypes. Patients suspected of having an autoinflammatory disorder should undergo genetic testing early in the diagnostic process.

Autoinflammatory disorders are classified by the IUIS as: 1. Type I Interferonopathy; 2. Recurrent inflammatory syndromes, with or without skin findings; 3. Systemic inflammation predominantly in bone and joints; 4. Other systemic inflammatory syndromes. (Fig 7 in Bousfiha et al, 2022[17]).

Cryopyrin related disorders

Cryopyrin-associated periodic syndrome (CAPS) is suspected in patients presenting with episodes of systemic inflammation manifested by rash, fevers, arthritis, neurological deficits, hearing loss and amyloidosis.[399] Patients suspected of CAPS are screened for persistent systemic signs of inflammation in the absence of demonstrable infection, autoimmune disease, or malignancy. There is abnormal inflammasome activation with release of the pro-inflammatory cytokines IL-1β and IL-18. Patients presenting at or soon after birth with a pustular rash, joint swelling, and profound osteopenia and bone lesions may have deficiency of IL-1 receptor antagonist (DIRA). Patients presenting with generalized pustular psoriasis may have deficiency of IL-36 receptor antagonist (DITRA). Patients with phospholipase Cg2–associated antibody deficiency and immune dysregulation (PLAID) may present with atypical cold urticaria.

Periodic fever syndromes

Familial Mediterranean fever (FMF) or TNF receptor–associated periodic syndrome (TRAPS) present with recurrent and often prolonged fever attacks associated with serosal, cutaneous, and synovial manifestations.[400] Periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA) should be suspected in young children

presenting with the namesake features and is a diagnosis of exclusion. Hyper-IgD syndrome (HIDS) presents fevers with lymphadenopathy, abdominal pain, diarrhea, vomiting, arthralgia, rash, aphthous ulcers, and splenomegaly. It represents a mild form of mevalonic kinase deficiency. Patients with suspected HIDS are screened by measuring serum IgD and urine mevalonic acid levels. Proteasome catalytic subunit b type 8 (*PSMB8*) and *TMEM173* defects are suspected in patients with early-onset fevers, systemic inflammation, and purpuric plaques caused by cutaneous leukocytoclastic vasculitis. Generalized pustular psoriasis and familial pityriasis rubra pilari are present in patients with pathogenic variants in *CARD14.*

RECOMMENDATION 6.4. We <u>recommend</u> that patients who exhibit lymphoproliferation and autoimmunity should be evaluated for IEI and for secondary causes, such as infection, autoimmune disease and malignancy.

Strength of recommendation: **Strong**

Certainty of evidence**: High**

Patients with immune dysregulation syndromes present with unexplained lymphoproliferation (defined as a pathologic accumulation of lymphocytes within secondary lymphoid organs and/or end-organs), autoimmune cytopenias (affecting at least two cell lineages), and other severe, recurrent or early onset autoimmunity. The evaluation of these conditions includes blood cell counts and auto-antibodies according to the tissue and organ affected.

The International Union of Immunological Societies (IUIS) classifies immune dysregulation into 4 broad phenotypes as follows: 1. Familial Hemophagocytic lymphohistiocytosis (HLH), with or without hypopigmentation, 2. disorders that confer Epstein-Barr Virus (EBV) susceptibility, including EBV associated HLH, 3. autoimmunity with or without lymphoproliferation including ALPS and Tregopathies, and 4. Immune dysregulation with colitis. (Fig 4 in Bousfiha et al, 2022[17]).

<u>Familial HLH</u>

The evaluation of HLH requires a multidisciplinary approach with involvement of experts in Immunology, Rheumatology, Infectious Disease and Hematology Oncology and Genetics and other services to differentiate subtypes of HLH.

Familial lymphohistiocytosis (FLH) is suspected in patients with fever, hepatosplenomegaly, and neurological symptoms. For primary HLH, testing should include perforin/granzyme by flow cytometry, and soluble CD25 levels. Secondary HLH can be triggered by malignancy, autoimmunity, infection, and iatrogenic causes. The underlying etiology of HLH may not be apparent in the disease's initial stages. The evaluation of suspected secondary HLH includes the diagnostic tools of primary HLH. Patients with IEI may develop HLH-like disease without meeting the HLH-2024

criteria.[401] These atypical forms of HLH should still be evaluated and treated as an immune dysregulation syndrome. These patients may need repeated and ongoing evaluation for humoral and cellular markers and genetic analysis to guide management. The diagnosis of FHL can be established if at least 1 of either 1, 2, or 3 below is fulfilled.

1) A molecular diagnosis consistent with FHL in a patient with signs/symptoms suggestive of HLH
2) Functional cellular findings consistent with FHL in a patient with signs/symptoms suggestive of HLH
3) Clinical diagnostic criteria for FHL with at least 5 of the 7 criteria below fulfilled∗
4) Fever ≥38.5°C
    a. splenomegaly (≥2 cm below the costal margin)
    b. cytopenias (affecting ≥2/3 lineages in the peripheral blood: hemoglobin <90 g/L; platelets <100 × 109/L; neutrophils <1.0 × 109/L [in infants aged <4 wk: hemoglobin <100 g/L])
    c. hypertriglyceridemia and/or hypofibrinogenemia:
    d. fasting triglycerides ≥3.0 mmol/L and fibrinogen ≤1.5 g/L
    e. hemophagocytosis
    f. ferritin ≥500 µg/L
    g. sCD25 (i.e., soluble interleukin-2 receptor) ≥2400 U/mL

Tregopathies

Disorders in Treg cell function (called “Tregopathies”) often accompany IEI with other T cell subset abnormalities. This can lead to an autoimmune diathesis in which the balance of Treg cells with other T-cell types may dictate a concurrent immune deficiency with autoimmunity phenotype.[157, 402] A representative disorder in this group is IPEX.[403] In addition to Tregopathies, immune dysfunction leading to autoimmunity can occur through other immune mechanisms such as molecular mimicry, bystander activation, and cross-reactivity.

Autoimmune lymphoproliferative syndromes (ALPS)

Chronic non-malignant lymphoproliferation, autoimmune cytopenias, and lymphoma are associated with autoimmune lymphoproliferative syndrome (ALPS),[404, 405] although many other IEI may present with an ALPS-like phenotype.[405] Patients with ALPS typically have elevated soluble FAS ligand (sFASL) and elevated serum levels of vitamin B12 and IL-10. Genetic testing may demonstrate pathogenic variants in *FAS*, associated with ALPS. ALPS and ALPS-like manifestations have recently been grouped into autoimmune lymphoproliferative immunodeficiency (ALPID) disorders, the most common of which include ALPS, CTLA-4 haploinsufficiency, LRBA deficiency, STAT3 gain of function (GOF) and activated phosphoinositide 3-kinase (PI3k) delta syndrome (APDS).[406, 407] ALPID disorders have increased double-negative T-cells (DNT), and other markers of immune dysregulation such as increased transitional B-cells, an atypical expansion of CD21lo B-cells, and decreased naïve CD4+ T-cells.

APECED (Autoimmune polyglandular syndromes)

Autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED), is one of the autoimmune polyglandular syndromes (APS), specifically APS-1. Clinical manifestations of APS-1 include hypoparathyroidism, Addison's disease and chronic mucocutaneous candidiasis (CMC).[408] APS-1 results from pathogenic variants in the Autoimmune Regulator (*AIRE*) gene. About 60 variants have been identified to cause APECED. Other clinical manifestations can occur, including associated with autoimmune involvement, such as type 1 diabetes mellitus, primary hypogonadism, and pituitary failure, etc. Diagnosis of APECED is made by identification of two or the 3 clinical components of APS1 or the presence of a pathogenic variant in the *AIRE* gene.

Immune dysregulation with colitis

Colitis is a common feature of primary immune regulation disorders. There are several monogenic IEI associated with immune dysregulation and colitis presenting at an early age.[409] Inflammatory bowel diseases such as Crohn's disease or ulcerative colitis can accompany chronic granulomatous disease or adenosine deaminase (ADA) deficiency and may be manifestations of primary PIRDs. One mechanism involves loss of interleukin-10 (IL-10) or its receptor (IL-10R).[410] Clinical features may include diarrhea, abdominal pain, fever, weight loss or anemia or rectal bleeding. Severe cases may present with hemorrhage, perforation or toxic megacolon.

Section 7. Surveillance of potential clinical manifestations in IEI

RECOMMENDATION 7.1: We suggest evaluation of growth (in Pediatrics) and nutritional status in patients with IEI.

Strength of recommendation**- Conditional**

Certainty of evidence**- Moderate**

Patients with IEI are at risk for malnutrition,[411-414] and children with IEI are at risk for associated growth delay.[414, 415] Those with inflammatory or infectious gastrointestinal complications of IEI are especially at risk for nutritional deficiencies.[416] We recommend nutritional assessment every 6 to 12 months in patients with IEI and concerns for growth/nutritional deficiencies.

Height, weight, and BMI (percentiles for pediatric patients) should be reviewed at each visit to monitor for malnutrition or overnutrition and trends over time. Nutritional status may be monitored with serum albumin/prealbumin and additional micronutrient testing.

Referral to a dietician for patients with IEI and weight/nutritional abnormalities, especially in those with immune-mediated or chronic infectious enteropathy, is helpful for providing and accessing optimal dietary intake.

RECOMMENDATION 7.2: We <u>suggest</u> testing for specific pathogen infections in patients with IEI known to be associated with high morbidity and mortality to these infections.

Strength of recommendation**- Conditional**

Certainty of evidence**- Moderate**

Surveillance and monitoring for viral infections, including EBV and CMV in blood should be performed periodically in patients with IEI susceptible to these viral infections, every three months or in the presence of symptoms. Adequate T and NK cell function is particularly important in controlling viral infections, thus deficiency and/or dysfunction in these cells confer high risk for recurrent or persistent viral infections, especially with EBV and CMV.[417, 418] (**Table 7.1**). Signs and symptoms concerning infection should guide the indications for infectious disease evaluation. PCR or antigen testing, rather than serology, is used in patients receiving immunoglobulin replacement therapy or those with impaired antibody responses. Patients with IEI have higher incidence, prolonged shedding, and higher recurrence rates of gastrointestinal infections than immunocompetent individuals, because of frequent antibiotic use, nutritional deficiencies, increased exposure to healthcare settings, and immunocompromised state. Patients with IEI who develop gastrointestinal symptoms should be screened for intestinal infections including *Clostridium difficile, Giardia lamblia, Cryptosporidium, Salmonella,* norovirus, and parasitic infections.[419-421] Gastrointestinal pathogen panel testing by PCR or antigen testing in stools should be considered when evaluating IEI patients. (**See Sections 9 and 10**)

Table 7.1 – Examples of IEI associated with chronic viral infections and specific non-viral infections that may warrant evaluation or monitoring

Infectious Susceptibility	IEI	Associated genes	References
Herpesvirus family	SCID	*IL2RG, RAG1, RAG2, ADA, JAK3, IL7R, DCLRE1C, NHEJ1, LIG4, RMRP*	331 330 422
	FHL	*PRF1, UNC13CD, STX11, STXBP2*	423
	NK deficiencies	*MCM4, GATA2, IRF8, RTEL1, FCGR3A*	424
	CTLA4 haploinsufficiency	*CTLA4*	
	LRBA deficiency	*LRBA*	

	APDS1, 2	*PIK3CD, PIK3R1*	
	DOCK8 deficiency	*DOCK8*	
	DOCK2 deficiency	*DOCK2*	
EBV	XLP1, 2	*SH2D1A, BIRC4/XIAP*	423
	ITK deficiency	*ITK*	424
	CD27 deficiency	*CD27*	425
	CD70 deficiency	*CD70*	331
	XMEN	*MAGT1*	
	Coronin 1A deficiency	*CORO1A*	
	STK4 deficiency	*STK4*	
	STAT1 deficiency	*STAT1*	
	BENTA	*CARD11*	
	CARMIL2 deficiency	*CARMIL2*	
	PRKCD deficiency	*PRKCD*	
	RASGRP1 deficiency	*RASGRP1*	
	CTPS1 deficiency	*CTPS1*	
	CD137 deficiency	*TNFRSF9*	
	COPG1 deficiency	*COPG1*	
	HELIOS, AIOLOS	*IKZF2, IKZF3*	
	CHH	*RMRP*	
CMV	C2 deficiency	*C2*	424
	Properdin deficiency	*PFC*	423
	Late complement deficiency	*C5/C6/C7/C8/C9*	
	CGD	*CYBA, CYBB, CYBC1, NCF1/2/4*	426
		CXCR4	
	WHIM syndrome	*SH2D1A, BIRC4/XIAP*	
	XLP1, XLP2	*ITK*	
	ITK deficiency	*CD27*	
	CD27 deficiency	*MAGT1*	
	XMEN	*RASGRP1*	
	RASGRP1 deficiency	*CTPS1*	
	CTPS1 deficiency	*CD8*	
	CD8 deficiency	*WAS*	
	WAS	*BTK*	
	XLA	*COPG1*	
	COPG1 deficiency	*MCM10*	
	MCM10 deficiency	*NOS2*	
	NOS2 deficiency	*SP110*	
	VODI	*RMRP*	
	CHH		
HSV	TLR3 deficiency	*TLR3*	331
	D6R1 deficiency	*D6R1*	424
	UNC93B1 deficiency	*UNC93B1*	
	TRAF3 deficiency	*TRAF3*	
	TICAM1/TRIF deficiency	*TICAM1/TRIF*	

	TBK1 deficiency IRF3 deficiency SNORA31 deficiency ATG4A deficiency MAP11C382 deficiency CHH	*TBK1* *IRF3* *SNORA31* *ATG4A* *MAP11C382* *RMRP*	
VZV	WAS Ataxia telangiectasia RNA Polymerase III deficiency TLR3 deficiency WHIM syndrome STAT5B deficiency GINS1 deficiency Moesin deficiency CTPS1 deficiency CHH	*WAS* *ATM* *POLR3A, 3C, 3F* *TLR3* *CXCR4* *STAT5B* *GINS1* *MSN* *CTPS1* *RMRP*	331 427 424
HPV	WHIM syndrome Epidermodysplasia verruciformis C1B1 deficiency STK4 deficiency Ataxia telangiectasia RHOH deficiency CD28 deficiency LAD1 CD28 deficiency NEMO WAS Comel-Netherton syndrome	*CXCR4* *EVER1, EVER2* *C1B1* *STK4* *ATM* *RHOH* *CD28* *ITGB2* *CD28* *NFKB1A* *WAS* *SPINK5*	428 429 424
Cryptosporidium	NIK deficiency Hyper IgM syndrome IL21, IL21R deficiency	*MAP3K14* *CD40LG, CD40* *IL21, IL21R*	430
Mycobacterium spp.	Mendelian Susceptibility to Mycobacterial Diseases (MSMD)	*IL12RB1, IL12B, IL12RB2, IL23R, IFNGR1, IFNGR2, STAT1* LOF*, IFNG, IRF8, CYBB, ISG15, TYK2, SPPL2A, IKBKG, JAK1, RORC*	345 346

RECOMMENDATION *7.3:* **We <u>recommend</u> the assessment of complete blood cell counts with differential in patients with IEI.**

Strength of recommendation**- Strong**

Certainty of evidence**- High**

Patients with antibody deficiencies and immune dysregulation disorders have a high incidence of autoimmune cytopenias, including ITP, AIHA, and AN, and hematologic malignancy (**Table 7.2**). While autoimmune cytopenias are typically an early finding in many of these IEI,[431-434] they can also develop after initial disease presentation. Therefore, close monitoring with complete blood cell counts with WBC differential (CBCd) to identify cytopenias or myelodysplasia at an early stage is appropriate. Routine CBCd should be checked every 3 to 12 months in patients with antibody

deficiencies and immune regulatory disorders to monitor for autoimmune cytopenias and myelodysplasia (as well as complications of Ig replacement therapy). Patients with longstanding IEI diagnosis and no cytopenias may require only annual testing **(See RECOMMENDATION 5.1).**

Table 7.2 – Examples of IEI associated with autoimmune cytopenias

IEI	Associated gene	Prevalence of autoimmune cytopenias	Reference
Common Variable Immunodeficiency (CVID)	Various (e.g., *NFKB1, NFKB2*)	10-18% prevalence ITP>AIHA>AN, First episode of immune cytopenia may occur before CVID diagnosis	435 151 153 436
Autoimmune Lymphoproliferative Syndrome (ALPS)	*TNFRSF6, TNFSF6, CASP8, CASP10*	52-70% prevalence AIHA>ITP>AN Multilineage cytopenias>single lineage cytopenias	437 432 438
Immune Polyendocrinopathy X-linked (IPEX)	*FOXP3*	22-42% prevalence	402 439
Hyper IgM Syndrome	*CD40LG, CD40, AID, UNG*	Immune cytopenias may occur. Neutropenia is common in HyperIgM due to defects in *CD40LG/CD40*	161 222 210
CTLA4 haploinsufficiency	*CTLA4*	62-68% prevalence ITP=AIHA>AN	440 192
LRBA deficiency	*LRBA*	70% prevalence	192
Activated PI3K-delta Syndrome	*PIK3CD, PIK3R1*	17-30% prevalence late onset of cytopenias compared to other disease manifestations	202 441
XMEN	*MAGT1*	35% prevalence	442
Kabuki syndrome	*KMT2D, KDM6A*	2-8% prevalence ITP>AIHA	443 444
STAT1 GOF	*STAT1*	4% prevalence	445
STAT3 GOF	*STAT3*	67% prevalence Multilineage cytopenias>single lineage cytopenias	446 447
Wiskott Aldrich syndrome	*WAS*	AIHA>ITP>AN onset in infancy	448 449

		differentiate ITP vs baseline microthrombocytopenia	
DiGeorge Syndrome	*del22q11*	4-8% prevalence ITP>AIHA single lineage cytopenias>multilineage cytopenias	[450] [451]
RAS-associated Autoimmune Leukoproliferative Disorder (RALD)	*KRAS, NRAS* (somatic mutations)	94% prevalence Multilineage cytopenias>single lineage cytopenias	[452]

ITP, immune thrombocytopenia; AIHA, autoimmune hemolytic anemia; AN, autoimmune neutropenia

RECOMMENDATION *7.4:* We <u>recommend</u> *against* routine screening for autoantibodies, given the high proportion of asymptomatic patients with autoantibodies in circulation.

Strength of recommendation**- Strong**

Certainty of evidence**- Moderate**

There is a growing list of IEI that are associated with increased rates of autoimmunity and immune-mediated pathology, especially in primary immune dysregulatory disorders where multiorgan autoimmunity is common.[453, 454] Additionally, non-specific autoantibodies have been identified in other acquired disease states, such as COVID-19 pneumonia, multisystem inflammatory syndrome in children, and Kawasaki's disease.[455-457] Broad autoantibody panels should not be ordered routinely. Instead, use of autoantibody testing should be guided by clinical symptoms. Autoimmune cytopenias are the most reported autoimmune condition in patients with IEI,[453, 458] but laboratory confirmation may be challenging as there is low sensitivity in anti-platelet and anti-neutrophil antibody testing and variability in laboratory testing methods.[458-460] Given the low positive and negative predictive values of autoantibody panel testing in patients with IEI, these tests should be reserved for confirmation in the setting of signs or symptoms suggestive of autoimmune or rheumatologic disease.[458-460]

Patients who are receiving antibody replacement therapy may have false-positive testing to some types of autoantibodies that are present in the donor population plasma pool.[461-464]

RECOMMENDATION *7.5:* We <u>recommend</u> the evaluation of major organ system functions and screening for cancer and mental health disorders in IEI patients.

Strength of recommendation**- Strong**

Certainty of evidence**- High**

It is critical to periodically assess for major organ system involvement in patients with IEI**.** Infectious complications are commonly brought to clinical attention, but non-infectious complications are associated with higher mortality[8, 465] and may be missed if not screened at during visits. Early identification of non-infectious complications is possible through diverse laboratory tests, imaging, and procedures. However, the precise frequency and extent of surveillance of such interventions may vary with the clinical complexity of each patient.[465]

Clinical Exam: A thorough (at least yearly) clinical exam by a physician with expertise in IEI should be integral to routine monitoring in patients with IEI.[435, 466] A skilled clinical examination may prompt effective decision making leading to targeted laboratory assessments.[467]

Pulmonary: Clinical pulmonary assessment, inclusive of complete lung function testing with diffusion capacity (DLCO) should be performed at baseline and at least on a yearly basis in patients with IEI at risk for parenchymal lung disease or with a history of recurrent lower respiratory tract infections.[145, 466, 468-472] This evaluation includes CT of the chest for early detection of lung disease progression.[145, 468, 471-474] Repeated imaging with low dose CT or MRI to decrease the cumulative radiation risk is recommended in IEI with increased radiosensitivity.[475, 476] Pulse oximetry at rest and with exercise may be helpful in patients with chronic lung disease to determine the need for oxygen therapy.[477] The six-minute walk test is a simple cardiopulmonary functional testing modality to assess aerobic capacity and endurance.[478]

Gastrointestinal: Annual clinical exam should include assessment for hepato-splenomegaly and presence of ascites. Serum liver enzymes should be assessed yearly and undertaken more frequently if there is a high risk for autoimmune complications or use of medications associated with hepatic toxicities.[468] In patients with IEI and symptoms suggestive of gastrointestinal reflux, screening for *H. pylori* infection is recommended.[479-481] Noninvasive screening for gastrointestinal infection (gastrointestinal pathogen PCR panel) and inflammation (fecal calprotectin) should be performed in patients with chronic lower gastrointestinal symptoms or weight loss.[481, 482] For patients with a history suggestive of protein losing enteropathy (PLE), we recommend stool alpha 1 antitrypsin (A1AT) testing.[483] Random A1AT fecal assessments have proven to be as reliable as 24-hour A1AT assessments. Endoscopy is recommended based on clinical presentation. Liver imaging with elastography provides an assessment of liver stiffness (cirrhosis).

Cardiac-Circulatory: Clinical cardiac and lymphatic examination should be performed at least annually, assessing for pallor, petechiae, pedal edema, lymphadenopathy and splenomegaly.[468, 472, 480]

Nephrologic: Fluid retention and facial edema prompt evaluation of renal function. Standard kidney function tests (i.e., serum creatinine as a surrogate marker) are

adequate and undertaken at least once a year if there is a high risk for autoimmune complications or medications associated with nephrotoxicity are used.[468] Serum cystatin C has a high sensitivity for identifying early kidney dysfunction. Known associations of kidney disease and IEI include IgA nephropathy in WAS[484] and aHUS seen in complement deficiencies.[381]

Dermatologic: Skin examinations should be performed at least annually, to screen for skin conditions associated with IEI including malignancies, skin infections, and vaccine-strain rubella granulomas. Skin biopsies and microbiological investigations are recommended for diagnosis accuracy.[485-487]

Endocrine and Bone Health: We recommend monitoring for signs/symptoms of immune endocrinopathies for patients with IEI, in particular immune regulatory disorders.[488] Targeted laboratory testing should be ordered directed by history and clinical examination.

Osteoporosis is often an overlooked complication in chronic care of IEI.[489] Bone density studies (DEXA scan) may be useful if there are concerns about chronic inflammation, height loss or evidence of malabsorption. Patients with abnormalities in IL-6 and IL-11 signaling, including STAT3-HIES, are at increased risk for reduced bone mineral density (BMD) and minimal trauma fractures.[490] We recommend screening for osteoporosis via bone densitometry starting at age 8 years old for those with a history of fractures.

Malignancy: Malignancy may be the initial manifestation or may develop after initial disease presentation of an IEI.[491-493] Patients with IEI have an increased risk for malignancy, with a reported prevalence between 4-25% depending on the underlying disorder.[492, 494] Hematologic malignancies are more common than solid tumors and Non-Hodgkin and Hodgkin lymphomas occur most frequently.[493] Therefore, close monitoring includes at least yearly physical exams. Significant unintended changes in body weight and systemic symptoms such as fevers should warrant a more in-depth evaluation for potential malignancy.[468, 495] Targeted biopsy and pathology examination may be indicated in cases of persistent or increasing lymphadenopathy or splenomegaly, to differentiate lymphoma from non-malignant lymphoproliferation. Tc-labeled splenic scan and PET scan may be useful in patients with concerns of asplenia or lymphoproliferation.[337] For IEI with increased radiosensitivity, imaging modalities that do not use radiation are preferred.[476, 496]

The clinician may encourage patients with IEI to adhere to United States Preventive Services Task Force (USPSTF) guidelines for cancer screenings (**Table 7.3**). All patients with IEI should be counseled to reduce their risk of cancer by choosing a healthy lifestyle including avoidance of known carcinogens, implementing regular exercise and a healthy diet, education on their risk of malignancy, cancer signs and symptoms, and self-examination, reducing both UVB and UVA exposure (i.e. use of sunscreen) and following recommended screening for skin cancer.[497]

The development of non-melanoma skin cancer occurs in two thirds of patients with epidermodysplasia verruciformis (EV).[333] Patients with deficient immunity to HPV are at increased risk for HPV-driven epithelial cancers.[498] We recommend that patients with IEI disorders at risk for HPV infection (e.g., EV) and IEI with cellular deficiencies be vaccinated against HPV[499] (**See Sections 10 and 11**). Patients should be educated on safe sex practices and females should undergo regular cervical cancer screening.

Myeloid disease, including myelodysplastic syndrome (MDS) and acute myeloid leukemia, are a common complication of many IEI with defects in hematopoiesis (e.g. *ELANE, SBDS, GATA2*). Current guidelines recommend regular surveillance of peripheral blood counts and annual bone marrow evaluation to include morphology, cytogenetics, and molecular investigation of clonal hematopoiesis.[500]

IEI associated with both non-malignant lymphoproliferation and increased risk of lymphoma (e.g., ALPS) may be difficult to manage in terms of cancer surveillance as imaging modalities will not differentiate between benign and malignant proliferation.[501] Concerns for malignancy in a lymph node should be confirmed with targeted biopsy and pathology examination.

Table 7.3 – Examples of IEIs associated with increased cancer risk:

IEI	Type of cancer and risk	Reference
DNA repair defects	Ataxia-telangiectasia: Leukemia (70-500-fold) and lymphoma (200-750-fold) Bloom syndrome: Intestinal cancer, leukemia, and lymphoma (150-300-fold)	502 503
Common variable immunodeficiency	Mucosa-associated lymphoid tissue (MALT) lymphoma Non-Hodgkin lymphoma (30-400-fold) Gastric cancer (10-fold)	504
Defects in *GATA2*, *CXCR4*, *STK4*	HPV-, EBV-associated cancers Chronic myeloid leukemia Acute myeloid leukemia Myelodysplastic syndrome Melanoma (*GATA2*)	505 502 506
Epidermodysplasia verruciformis	Non-melanoma skin cancers	333
Wiskott Aldrich Syndrome	Lymphoma	502

Combined immune deficiencies: IL10R deficiency; AD-HIES	B cell lymphoma	502
Familial HLH (*PRF1*)	Lymphoma	502
NK cell deficiency	EBV and hematologic malignancies	330
X-Linked Hyper IgM syndrome	Pancreatic and liver cancers	502

Neurologic and psychologic: Developmental milestones and behavioral concerns should be reviewed at each visit to monitor for developmental delay and behavioral disorders, which may occur in patients with IEIs, especially SCID,[507, 508] as a consequence of the genetic defect, HSCT or secondary to an infection.

Patients with chronic diseases are at higher risk for depression and other mental health concerns.[509] Studies of patients with IEI have shown up to 40% rates of psychiatric symptoms, particularly anxiety and depression,[510-513] as well as formal psychiatric diagnoses (odds ratio 1.91; 95% CI 1.66-2.01) and suicidal behavior (odds ratio 1.84 95% CI 1.81-2.01),[514, 515] when compared to the general population. Patients with IEI also have high rates of fatigue,[516-518] which may be a somatic symptom of depression. Simple screening mental health questionnaires exist for adult and adolescent patients[519, 520] and may be incorporated into IEI patient visits.

PART II; MANAGEMENT

Section 8. Immunoglobulin replacement

RECOMMENDATION 8.1: We recommend immunoglobulin replacement therapy (IgRT) for IEI with IgG antibody deficiency.

Strength of recommendation**: Strong**

Certainty of evidence: **High**

Immunoglobulin replacement therapy (IgRT) provides passive immunity in the form of polyclonal IgG to patients with IEI whose humoral immune response is absent or impaired, and who are at increased risk of serious bacterial infections. Early diagnosis and therapy are the keys to survival and improved quality of life for these patients. Delays in initiating IgRT can result in permanent organ damage or death from overwhelming infection. IgRT is indicated for the treatment of patients with hypogammaglobulinemia and impaired humoral immunity and have been shown to prevent serious bacterial infections in these patients, inclusive of bacterial pneumonia, sepsis, bacterial meningitis, visceral abscesses, and osteomyelitis/septic arthritis.[3, 522, 523]

Adverse events associated with IgRT include fever, chills, malaise, fatigue, anxiety, rash, flushing, nausea, vomiting, headache, myalgia, back pain, arthralgia, tingling of extremities, hypo- or hypertension, tachycardia, fluid overload, and infusion site pain/swelling/erythema (for SCIG). These are generally mild, and rate or dose related, occurring in 5-15% of IVIG infusions, and more frequent in patients with active inflammation.[522, 524. 525] Severe adverse events are infrequent, usually occurring at the end of or post-infusion, and can include renal impairment, thrombosis, aseptic meningitis, hemolytic anemia, arrhythmia, and acute transfusion related lung injury (TRALI). Strategies that mitigate adverse events include slowing the rate of infusion (for intravenous administration) and administering premedication (**see below).** Slowing or stopping the IVIG infusion for 15-30 minutes will reverse many reactions.[522] Infusions can often be restarted at the last tolerated rate and then increased again. Another option frequently employed is switching to subcutaneous immunoglobulin (SCIG) IgRT, which is associated with fewer systemic adverse events. [522, 526, 527]

Premedication before IgG product infusions. If a patient experiences an infusion related adverse event with IVIG, pretreatment with ibuprofen or acetaminophen, and diphenhydramine or a nonsedating antihistamine (anti-H1) and/or hydrocortisone one hour before the infusion may prevent adverse reactions. Oral (or IV) hydration prior to the infusion is often used to prevent hypotension. A survey by the Immune Deficiency Foundation found that 34% of reactions occurred during the first infusion of an IVIG

product. After three treatments with the same product, additional infusion reactions become less likely.[522] Certain high-risk conditions such as renal failure, congestive heart disease, and diabetes mellitus need to be considered when evaluating the premedication with fluids because of the risk for fluid overload; or corticosteroids prior to each infusion because of the risk for hyperglycemia and hypertension.

Caution with central venous access devices. Benefits of ease of venous access provided using indwelling venous catheters for IVIG administration should be weighed against the thrombotic and infectious risks inherent in these devices which may be further amplified in patients with IEI and their use for the sole purpose of providing IVIG is not recommended. For patients with difficult venous access, consideration of administration of IgRT via the subcutaneous route is advised.[2, 3, 522] Significant adverse complications of IVIG administration include thromboembolic events, such as myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism. These adverse events are rare but have been reported in patients with IEI. Risk factors for these reactions include preexisting cardiovascular disease, diabetes mellitus, dehydration, age >65 years, sepsis, paraproteinemia, increased blood viscosity, hypercholesterolemia, and hypertension.[522, 528]

IgG products may not be equally tolerated. The AAAAI developed the Eight Guiding Principles for Effective Use of IVIG for Patients with Primary Immunodeficiency.[522] One of the Guiding Principles regarding product choice discusses that IVIG is not a generic drug and IVIG products are not interchangeable. To ensure patient safety, a change of IVIG product should occur only with the active participation of the prescribing physician. IVIG products have distinct characteristics including sodium content, osmolality, stabilizers and pH that should be considered in patients at risk for adverse effects. Long-term tolerance of one IVIG product does not necessarily equate to tolerance to another product. When switching IVIG products, adverse reactions during IgG infusion were reported in approximately 15-18% of patients.[529] A retrospective review analyzed 802 switches between immunoglobulin products between 2017-2018 due to supply issues,[530] twelve reactions were reported, none of which required admission to the hospital; one was treated with oral corticosteroids, and others required no treatment or treatment with oral antihistamines alone. These results contradicted the established guidelines regarding adverse reactions linked to product changes in the context of IEI with antibody deficiency, suggesting that there may be flexibility regarding immunoglobulin product switches for most patients; although safety of this practice is not predictable.

Pooled plasma for IgRT products is obtained from thousands of donors, inclusive of all ABO blood groups, therefore, plasma for IgRT products can contain various antibodies to blood cell antigens, including anti-A and anti-B IgG, which can lead to hemolysis. Although this is a rare occurrence, monitoring of blood cell counts is recommended for

this reason.[531] A higher incidence of IVIG-related hemolysis was consistently reported in patients with blood groups A and AB, occurred more frequently in patients treated with high dose IVIG for conditions such as Kawasaki disease, and the incidence was lower in studies using IVIG products whose manufacturing processes included steps to reduce isoagglutinin levels.[532]

The prescribing information for every IVIG product includes a warning about renal dysfunction, acute renal failure, osmotic nephrosis, and death. These renal complications were reported more commonly in patients receiving IVIG products containing sucrose.[533] Currently, in the US there are no IVIG products containing sucrose on the market. Incidences of renal impairment with sucrose-free IVIGs are similar between products and much lower than those seen with sucrose-stabilized IVIGs.[533, 534] In a case control study from 1996 to 2009, predictors of renal failure associated with IVIG included use of angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, use of diuretics, and age > 70 yrs, male gender, chronic kidney disease, hypertension, and diabetes mellitus.[535] Monitoring BUN and creatinine over time alert the clinician regarding adverse events related to kidney function during therapy.

Between 1983 and 1987 clusters of non-A, non-B hepatitis (i.e., hepatitis C) were reported after IVIG treatment, and in February 1994, one manufacturer instituted a worldwide recall of its brand of IVIG, because of reports of ten cases of possible transmission of hepatitis C. At that time, the production process for several IVIG products did not include steps for viral inactivation.[536] This led to the recommendation by the FDA to add solvent/detergent (S/D) to the manufacturing process to inactivate lipid envelope viruses. In the late 1990's Mad Cow Disease (a variant of Creutzfeldt-Jakob disease) emerged in Europe. To address this pathogen safety, all immunoglobulin products utilize nanofiltration to remove possible prion contamination in donor plasma.[537] There have been no further reports of transmission of hepatitis or other infectious agents from IVIG products since the addition of additional pathogen inactivation/exclusion steps. Nonetheless, monitoring of liver function tests is often routine in the management of patients on IgRT.

RECOMMENDATION 8.2: We <u>recommend</u> that initial dosing of immunoglobulin for replacement therapy be at 400 mg/kg-600 mg/kg per month, followed by dose adjustment if necessary.

Strength of recommendation: **Strong**

Certainty of evidence**: Moderate**

IgRT dosing is recommended to start at 400 mg/kg-600 mg/kg every 3-4 weeks, when given intravenously, followed by dose adjustment to obtain clinical efficacy, and for changes in body weight >5% of baseline. When the subcutaneous route is used, this

dose is given in divided weekly or biweekly infusions. This dosing range achieves adequate serum IgG trough levels resulting in prevention of serious bacterial infections. However, serum IgG levels required for improved infection control vary among patients.[538, 539] In one study using an IgRT dosing range from 200 to 1200 mg/kg/month, patients with XLA required trough serum levels from 800-1300 mg/uL to stay infection free, while a cohort of CVID patients required a range of trough levels from 500-1700 mg/uL to prevent breakthrough bacterial infections (**see RECOMMENDATION 8.4**).[538]

RECOMMENDATION 8.3: We recommend monitoring of serum IgG levels, complete blood counts with differential, and serum chemistry levels for patients on immunoglobulin replacement therapy.

Strength of recommendation**: Strong**

Certainty of evidence**: Moderate**

Regular monitoring of trough or steady state serum IgG levels allows clinicians to assess patient compliance with therapy, monitor potential adverse effects, and define the IgG level at which their risk of infection is best controlled.[538-541] Serum IgG levels during IgRT provide supporting evidence of the ongoing therapeutic effect and need for IgRT to maintain these levels. A declining trend of serum IgG levels suggests the need of increasing IgRT dosing.

When patients on IgRT consistently receive infusions at recommended intervals (usually every 3-4 weeks for IVIG and every 1-2 weeks for SCIG) the serum IgG level is expected to vary depending on the pharmacokinetics and dose of the product. For IV administration, the IgG level is highest hours after infusion and levels drop steadily over 3-4 weeks. With SC administration, maximum IgG levels occur around 3-5 days post-infusion and decrease slowly. After 4-6 months of weekly or biweekly SC infusions serum IgG levels are consistent with steady state kinetics.[542-544] Due to differences in the kinetics of absorption as well as the distribution in extravascular spaces, dose adjustments are recommended by some U.S. manufacturers in initiating therapy. The recommendations vary from increasing dosing of SCIG from 1.35 to 1.53 times the calculated IVIG dose. These recommendations are intended to provide IgG levels that approximate the same bioavailability for SCIG and IVIG.[543, 545]

We recommend checking the serum IgG levels every 6 months to every year, in clinically stable patients receiving IgRT. However, a more frequent (i.e., monthly) monitoring of IgG levels is appropriate in patients who continue to have breakthrough bacterial infections, have underlying comorbidities (such as protein losing conditions), take immunosuppressive therapies, have significant weight changes, or who may not be adherent with therapy.

RECOMMENDATION 8.4: We <u>recommend</u> maintaining serum IgG levels at >800mg/dl to improve outcomes.

Strength of recommendation: **Strong**

Certainty of evidence**: High**

The goal of IgRT therapy is to improve clinical outcomes and prevent serious bacterial infections. In addition, individualization of dose according to patient response to therapy is important, given the variability between patients. This is illustrated by the concept of a "biologic trough" referring to the IgG trough level above which patients are infection free.[546] The biologic trough IgG level varies between individuals depending on the underlying disorder and comorbidities.[538] A meta-analysis of IVIG studies concluded that serum trough IgG levels 800 mg/dl – 1000 mg/dl are associated with significantly less occurrence of pneumonia.[547] Incidence of pneumonia declined by 27% with each 100 mg/dl increment in trough IgG, and the incidence of pneumonia with a maintenance trough IgG level of 500 mg/dl was 5-fold higher than with trough IgG levels of 1000 mg/dl (0.113 cases per patient year vs 0.023 cases per patient year respectively). No benefit was seen at trough IgG levels higher than 1000 mg/dL. An analysis of available SCIG studies reported a similar inverse correlation between the annual rate of infection and the serum trough IgG concentrations.[548]

RECOMMENDATION 8.5: We <u>recommend</u> that immunoglobulin replacement therapy is indicated as a continuous therapy for IEI

Strength of recommendation**: Strong**

Certainty of evidence**: Low**

Continuous and uninterrupted immunoglobulin replacement therapy is indicated for IEI with defects in humoral immunity. Immunoglobulin therapy *with polyvalent human IgG* is an essential, life-saving therapy for these patients. Only in selected cases, (such as specific antibody deficiency in children or transient hypogammaglobulinemia of infancy) it may be clinically appropriate to stop immunoglobulin therapy temporarily to determine if the antibody deficiency has resolved over time. This strategy should not be repeated if the trial indicates a persistent deficit of IgG production.[522, 549]

RECOMMENDATION 8.6: We <u>recommend</u> that low or absent IgA, in the setting of low IgG levels, is not a contraindication for immunoglobulin replacement therapy.

Strength of recommendation**: Strong**

Certainty of evidence**: Moderate**

Intravenous administration of IgRT has been associated with a risk for anaphylaxis in IgA-deficient patients who have anti-IgA IgE antibodies and a risk of reactions due to

complement activation if IgG anti-IgA antibodies are present. However; most patients who have low serum IgA, with or without IgG anti-IgA antibodies, receive IVIG without difficulty, regardless of the IgA content.[522, 550-552]

A retrospective and prospective observational study evaluated the possible association of IgG and/or IgE anti-IgA with adverse reactions in a subgroup of IgA-deficient patients receiving immunoglobulin replacement and was unable to conclude any increased risk for adverse reactions associated with IgA deficiency. The investigators suggested that in an individual patient, the presence of IgG anti-IgA might be a biomarker of increased risk for non–IgE-mediated anaphylactoid reactions to immunoglobulin infusion containing IgA, but studies are needed to determine whether class- or subclass-specific IgG anti-IgA antibodies have any clinical relevance.[552]

Regardless of IgA level, in any patient who is having significant systemic symptoms with IVIG, switching to SCIG or use of IgA-depleted IgRT product should be considered.[522, 550-552]

RECOMMENDATION 8.7: We <u>suggest</u> that the route of immunoglobulin administration be determined based on patient tolerance and preference.

Strength of recommendation: **Conditional**

Certainty of evidence**: Moderate**

Many studies support equivalence of effectiveness and safety between SCIG and IVIG therapy for the management of antibody deficiencies.[522] The decision to infuse immunoglobulins in a hospital, hospital outpatient, community office, or home-based setting and the route of immunoglobulin administration whether IV, SC must be based upon the clinical characteristics of the patient.[522]

There is a reduced incidence of systemic adverse events with SCIG, increased flexibility in scheduling and shorter infusion times as compared with IVIG, but requires independence and good adherence on the part of the patient or parent, the confidence of the physician and the nurse, and more frequent dosing as well as increased number of needle sticks.[522, 553] A form of SCIG is “facilitated SCIG”, using the addition of hyaluronidase to the IgRT product to increase the amount of volume of immunoglobulins (up to four times) infused at once into the subcutaneous tissue, allowing to reduce the frequency of infusions, SCIG therapy may be preferred in select patient populations, including children, pregnant women, and patients with difficult intravenous access.[553] Studies have shown enhanced quality of life in patients receiving SCIG compared with IVIG therapy, mostly due to the freedom to administer SCIG at home and at the patient’s convenience.[522] This benefit results in greater patient satisfaction and fewer missed days of work or school for infusion-clinic appointments.[522, 554, 555] Initial infusions are done under supervision by a health care professional,

providing training for subsequent self-infusions at home.[555] Patients with reduced manual dexterity, who cannot self-administer, or who prefer less frequent treatments may have most success with IVIG administration by medical staff in a clinic, infusion center or at home. A useful and comprehensive algorithm based on individual clinical outcomes and patient-related factors relating to immunoglobulin therapy may assist in shared decision making.[555]

Section 9. Infection Prevention in IEI

RECOMMENDATION 9.1: We recommend targeted antimicrobial prophylaxis for IEI patients with increased susceptibility to infections.

Strength of recommendation**: Strong**

Quality of evidence**: High**

Prophylaxis for Selected IEI:

CGD

Trimethoprim-sulfamethoxazole (TMP/SMX) is an ideal antibiotic for prophylaxis in CGD as it covers the most common bacterial infections, namely *Staphylococcus aureus, Burkholderia cepacia, Serratia marscens*, and *Nocardia* species (**Table 9.1**).[556] Retrospective studies demonstrated a decrease of bacterial infections by approximately 50% with the use of TMP/SMX prophylaxis.[556-558] Drug desensitization is suggested when there is concern for hypersensitivity to TMP/SMX. Alternatives, which have gaps in the CGD pathogen coverage, are second or third generation cephalosporins or trimethoprim alone.

Antifungal prophylaxis with itraconazole decreased the frequency of fungal infections in a placebo-controlled crossover study: seven patients were diagnosed with invasive fungal infection while on placebo compared to one invasive fungal infection on itraconazole.[559] Liquid itraconazole has better absorption than tablets but may pose adherence concerns. Itraconazole tablets should be taken with a meal, and ideally with an acidic food such as orange juice. It is important to note that itraconazole and other azoles have many drug interactions; itraconazole can inhibit the metabolism of corticosteroids (**Table 9.2**). Other antifungal triazoles, including posaconazole, voriconazole and isavuconazole have not been studied, but are likely effective for prophylaxis. Voriconazole can be associated with photosensitivity and increased risk of skin malignancies[560] as well as fluorosis.[561]

Prophylactic interferon gamma (IFN γ) is frequently used in addition to antimicrobial prophylaxis in CGD. A randomized placebo-controlled study performed in the early

1990s showed that IFN γ reduced the rate of serious infections by two-thirds and decreased the frequency and length of hospitalization.[562] Importantly, this study was performed prior to standard use of prophylactic antifungals for CGD patients; therefore, the impact of IFN γ is not known when given with itraconazole and TMP/SMX. A meta-analysis of published literature identified 3 case-control studies reports the risk ratio for serious infection was 0.56 (95%CI 0.35-0.90) when using IFN-γ.[563] Some patients experience flu-like side effects with IFN γ doses, which can be ameliorated with night-time dosing and antipyretics. IFN γ is typically not used during treatment of acute infections, due to side effects of fever and elevated inflammatory markers that may confuse the assessment of therapeutic response to antimicrobials.

SCID/athymia prior to immune reconstitution.

Infections prior to immune reconstitution with definitive therapy (HSCT, gene therapy, or cultured thymic tissue implantation) are associated with increased morbidity and mortality.[59, 77] TMP/SMX is recommended as first-line Pneumocystis prophylaxis, starting at one month of age due to case reports of drug-induced liver injury and hyperbilirubinemia in the neonatal period. (**Table 9.2**) Alternative agents include pentamidine (typically intravenous in infants and inhaled in adults), oral atovaquone, and dapsone (assuming normal G6PD levels). **(see Section 2)**

Candida infections are the most common fungal infections in SCID, typically causing mucocutaneous disease. Prophylaxis is recommended with fluconazole.[77] Nystatin topical suspension can be utilized in the neonatal period in lieu of fluconazole.

HSV prophylaxis is recommended only if the patient has risk factors for HSV infection, such as maternal active disease.[77] Acyclovir should not be given if the patient is currently receiving ganciclovir or valganciclovir. CMV prophylaxis is discussed under **Section 2.4**, and **Table 9.1.**

Prophylaxis with azithromycin or clarithromycin has been suggested for patients with athymia who received thymus implantation as three cases of disseminated NTM were reported in these infants.[564]

Antibody deficiencies.

Antibody deficiencies, such as CVID and XLA, are characterized by recurrent sinopulmonary infections, predominantly with encapsulated bacteria such as *S. pneumoniae* and *H. influenzae,* and less frequently with *S. aureus* or other organisms. The airway flora may change if bronchiectasis develops, with more Gram-negative bacteria including *Pseudomonas*. IgRT is the mainstay of therapy to replace the IgG deficit.[547] However, if patients continue to have breakthrough bacterial infections despite optimal dosing of IgRT, then antibiotic prophylaxis, such as azithromycin, amoxicillin, or TMP/SMX should be considered as an additional preventive therapy.[565-567] If chronic lung disease such as bronchiectasis is present, azithromycin is recommended as the

antibiotic prophylaxis of choice due to antimicrobial and anti-inflammatory properties.[568] In a randomized placebo-controlled study involving adult patients with primary antibody deficiencies and chronic lung disease on IgRT, azithromycin decreased the frequency of lung exacerbations, hospitalizations, and antibiotic courses.[569] Azithromycin can be dosed either 3 days/week at 250 mg as in the randomized study, at 500 mg 3 days/week as in cystic fibrosis, or daily at 250 mg.

Patients with XLA are at risk for disseminated infections with typically gastro-intestinal restricted bacteria including *Campylobacter* and *Helicobacter* species[570]; some of these organisms are azithromycin sensitive, and thus prophylaxis may decrease the disseminated infections. *Mycoplasma* infections can also cause disseminated infections, such as arthritis, and may be targeted with azithromycin prophylaxis.

Specific antibody deficiencies, transient hypogammaglobulinemia of infancy, and mild hypogammaglobulinemia may be associated with recurrent sinopulmonary infections. In these settings, a retrospective experience showed a trial of antibiotic prophylaxis is an alternative first line approach, with benefit in converting to IgRT there is not an improvement.[566, 571, 572]

Complement defects and asplenia.

Terminal complement defects and asplenia are associated with severe and disseminated infection with encapsulated bacteria including *S. pneumoniae, N. meningitidis*, and *H. influenzae*. Vaccination against these organisms are the mainstay for prevention of infection. (**See Section 11**). In addition, antibiotic prophylaxis, amoxicillin or penicillin, is recommended for children through at least 5 years of age, but can be considered lifelong, especially for those with a history of sepsis.[573, 574] For those with penicillin allergy, cephalosporins such as cephalexin, or azithromycin, are the alternatives. An evaluation for penicillin allergy may be preferred prior to considering the second-line drugs.[573, 574]

Hyper IgE syndrome due to STAT3/IL-6 signaling pathway defects and recurrent infections.

Hyper IgE syndromes caused by defects in STAT3 and IL-6 signaling are characterized by recurrent skin and lung infections as well as eczematoid dermatitis. Recurrent *S. aureus* pneumonia results in pneumatoceles and bronchiectasis.[575, 576] Prophylaxis against S. *aureus* is recommended, typically with TMP/SMX. In addition, if atopic dermatitis is present, use of antiseptics for bathing (e.g., dilute bleach baths or chlorhexidine) can decrease the colonization of skin by *S. aureus,* decreasing skin infections and improving eczema. Antifungal prophylaxis for HIES is discussed below.

Prophylaxis for Specific Pathogens and Settings:

Anti-*Pneumocystis jirovecii* pneumonia (PJP) prophylaxis.

Patients with T cell deficiencies and combined immune defects (CID) such as CD40L/CD40 deficiency, DOCK8 deficiency, and Wiskott-Aldrich syndrome, are at risk for PJP, and prophylaxis should be provided with TMP/SMX or alternatively, pentamidine (IV or inhaled), atovaquone, or dapsone (in G6PD sufficient patients).[577-579] In addition, PJP prophylaxis is recommended in IEI with immune dysregulation with decreased cellular immunity due to immune suppression.

Antiviral prophylaxis.

Various IEI, including SCID/athymia, CID, and certain innate defects, have increased risk for viral infections. Viral prophylaxis for SCID/athymia are discussed in **section 2.4**. Antivirals are limited in oral formulations and anti-viral activity. Acyclovir or valacyclovir are used for HSV and VZV prophylaxis for IEI at risk for recurrent or severe infections, such as defects of the TLR3 pathway.[331, 580] After high risk VZV exposure, varicella immune globulin can be considered for varicella-susceptible patients at risk for disseminated disease. As an alternative, a dose of immune globulin (400 mg/kg) can be considered within 10 days of exposure (if the patient is not on IgRT) or acyclovir or valacyclovir prophylaxis for 7 days starting 7-10 days after exposure.[581]

Patients with innate defects along the IFNα signaling pathway are at high risk for certain infections such as influenza and SARS-CoV-2.[582-584] Inactivated vaccines for viral respiratory tract infections (e.g., influenza, SARS-CoV-2) are recommended to patients and household contacts. The use of live viral vaccines should be avoided by these patients. Influenza antiviral prophylaxis is recommended after high-risk exposure to Influenza, typically with oseltamivir (oral) or zanamivir (inhaled).[585]

Seasonal RSV prophylaxis is recommended for patients with SCID or congenital athymia prior to immune reconstitution, and for patients with other IEI up to 24 months of age.[77]

Nontuberculous mycobacteria (NTM) infection prophylaxis.

Defects affecting the IL-12/IFN γ /STAT1 pathway, defects affecting NF-kB activation (NEMO, IkBa), and other MSMD defects are at high risk for disseminated NTM and BCG infection.[345, 586] Neonates born to families with history of these defects should not receive BCG vaccination until diagnostic studies confirm absence of IEI. Antibiotic prophylaxis against NTM, such as azithromycin, should be provided after exclusion of active mycobacterial infection, primarily by clinical assessment, AFB cultures, and/or imaging.

Antifungal prophylaxis.

Certain IEI predispose to chronic mucocutaneous candidiasis (CMC), including STAT3 HIES, STAT1 GOF, APECED, CARD9 deficiency and defects of IL-17 and its receptor.[335, 587, 588] For patients with frequent candidal infections, antifungal prophylaxis

with fluconazole is recommended. For patients with STAT1 GOF treated with JAK inhibitors, the CMC may improve, and azole prophylaxis may be stopped.[589] Certain IEI, namely STAT3 HIES and STAT1 GOF can be associated with severe disseminated coccidiodomycosis, therefore antifungal prophylaxis is recommended in endemic regions (i.e., southwestern United States and Northern Mexico).[590] In addition, STAT3 HIES is associated with pneumatoceles that can be secondarily infected with Aspergillus or other molds; therefore, when pneumatoceles are present, a mold-specific antifungal (e.g., itraconazole) should be used as prophylaxis. CARD9 deficiency is associated with disseminated Candida infections, including meningitis, and anti-fungal prophylaxis is suggested.[591]

Peri-operative *S. aureus* prophylaxis.

Surgery can be associated with impaired wound healing and post-operative infections in patients with IEI.[592, 593] For IEI susceptible to *S. aureus* infections, such as neutrophil defects (e.g., CGD, LAD) or STAT3 and IL-6 related HIES, we suggest measures to decrease bacterial burden pre-operatively, such as with nasal mupirocin and/or chlorhexidine or dilute bleach baths. Peri-operative antibiotics directed against *S. aureus* are also suggested in these cases.

Airway clearance peri-operatively

Patients with IEI complicated by bronchiectasis or other forms of chronic lung disease may have increased risk during surgeries due to decreased airway clearance associated with anesthesia and decreased activity. Communication between the surgeons and the IEI expert to optimize airway clearance peri-operatively is suggested. Methods to improve airway clearance post-operatively include increased activity to diminish time in bed, hypertonic saline nebulizations, airway clearance devices, and consideration of inhaled medications (e.g., tobramycin) for those with chronic Pseudomonas colonization.

Dental procedures in IEI patients.

Dental work is inherently associated with disturbance of the oral flora, typically with streptococcal species and anaerobes. Individuals with neutropenia or functional neutrophil defects are at greater risk for infections from these organisms. Other IEI such as STAT3/IL-6 HIES are associated with dental abscesses. With extensive dental work, such as extractions, root canals, deep scaling and implant placement, we suggest antibiotic prophylaxis such as with amoxicillin/clavulanate or clindamycin. Patients with other forms of immunodeficiency, particularly isolated antibody deficiencies, do not typically require antibiotic prophylaxis for invasive dental work.[594]

Caution with use of multiple antimicrobials.

Patients with IEI often receive multiple antimicrobials and are at increased risk of adverse drug reactions. Involving a pharmacist may be helpful for close review of antimicrobials, facilitate drug monitoring, dosing and therapeutic optimization.[595]

Table: 9.1 Antibiotic Prophylaxis for Selected IEI

IEI	Indication for prophylaxis	Drug regimen	Organisms covered	Strength of recommendation	Certainty of evidence	References
CGD	Severe bacterial infection: pneumonia, skin abscess	TMP/SMX (5 mg/kg max dose 160 mg TMP component twice daily). Alternatives: cephalosporins, doxycycline.	*S. aureus,* Burkholderia spp, Nocardia spp, Serratia spp	Strong	High	557
	Invasive Aspergillus (lung, bone)	Itraconazole 5 mg/kg daily, max daily dose 100 mg (< 50kg), 200 mg (>50kg)	*Aspergillus spp*	Strong	Moderate	559
	All infections	IFN γ 50 ug/m^2 (min 1.5 ug) SC injection 3 days/week		Strong	Moderate	562 563
SCID, congenital athymia	*Pneumocystis* pneumonia	TMP/SMX (5 mg/kg max dose 160 mg TMP component twice daily). Alternatives: pentamidine, atovaquone, dapsone	*Pneumocystis jirovecii*	Strong	High	59 77
	Candidiasis, fungal infection	Fluconazole 5 mg/kg	*Candida* spp	Strong	High	59 77
	Prevention/ Treatment of CMV viremia, pneumonia, hepatitis, CNS infection	Acyclovir 5 mg/kg Ganciclovir Valganciclovir 16 mg/kg/day Treat until infant is CMV PCR negative weekly x 4	CMV, HSV infection.	Strong	Low	59 77
Antibody Deficiencies	Respiratory infections	Azithromycin (5 mg/kg/day. max of 250 mg daily or	*S. aureus, S pneumoniae, H. influenzae, M. catarrhalis*	Conditional	Low	567 569

		500 mg 3 days/week) Alternatives: Amoxicillin TMP/SMX				
Terminal Complement defects or asplenia	Sepsis, meningitis with encapsulated bacteria	Amoxicillin or Penicillin daily or through 5 years of age May continue lifelong	*S. pneumoniae, Haemophilus influenzae* *N meningitides*	Strong	moderate	573 574
STAT3/IL-6 related HIES	Bacterial Infection	TMP/SMX dose: 5-6 mg/kg/day (divided BID)	*S. aureus*	Conditional	Low	575 576
	Chronic muco-cutaneous Infection	Fluconazole (if not on itraconazole or other triazoles) 5 mg/kg	*Candida* species CMC Coccidioides if endemic region	Conditional	Low	590
	Prophylaxis against Aspergilloma	Itraconazole 5 mg/kg daily, (max 100 mg/day < 50kg, 200 mg day >50kg) Treat if pneumatocele present	*Aspergillus* spp.	Conditional	Low	575
Chronic Muco-cutaneous Candidiasis (STAT1 GOF, APECED, CARD9, IL17 and IL17R defects)	Disseminated candidiasis or Coccidioidomycosis	Fluconazole 5 mg/kg	*Candida* spp; Coccidioides	Conditional	Low	589
MSMD	Myco-bacterial infections	Azithromycin (5 mg/kg/day. max of 250 mg daily or 500 mg 3 days/week)	Environmental mycobacteria	Conditional	Moderate	586 345

CID with severe T cell defects	*Pneumocystis* pneumonia	TMP/SMX (5 mg/kg max dose 160 mg TMP component twice daily). Alternatives: pentamidine, atovaquone, dapsone	*Pneumocystis jirovecii*	Conditional	Low	[578] [579]
	Chronic viral infection	Acyclovir 5 mg/kg Ganciclovir Valganciclovir 16 mg/kg/day	HSV/VZV	Conditional	Low	[580]
	GI infection	Azithromycin (5 mg/kg/day. max of 250 mg daily or 500 mg 3 days/week)	*Crypto-sporidium*	Conditional	Very Low	None

TMP/SMX Trimethoprim sulfamethoxazole; CGD Chronic Granulomatous Disease; Tx treatment; PJP Pneumocystis jirovecii pneumonia; CMC Chronic Mucocutaneous Candidiasis; CMV cytomegalovirus; PCR polymerase chain reaction; WAS Wiskott Aldrich Syndrome; PAD Primary Antibody Deficiency; HIES Hyper IgE Syndrome; HSV Herpes Simplex Virus ; VZV Varicella Zoster Virus ; NTM Non Tuberculous Mycobacteria; DN Double Negative

Table 9.2: Special considerations for antibiotic treatment in at risk individuals

Special Antimicrobial Considerations	
Neonates	TMP/SMX can cause hyperbilirubinemia in neonates; prophylaxis may be delayed until approximately 4 weeks of age.
Pregnancy	Many antimicrobials used in IEI bear increased risks including but not limited to TMP/SMX, azoles, tetracyclines and fluoroquinolones, and require risk/benefit discussions
Photosensitivity	Voriconazole and doxycycline, and less frequently TMP/SMX can cause photosensitivity, and long-term voriconazole has been associated with skin cancers.
EKG abnormalities	Several antimicrobials used in IEI can be associated with prolonged QTc such as azithromycin, fluoroquinolones, certain azoles, and need monitoring for this arrhythmia.

RECOMMENDATION 9.2: We <u>recommend</u> using only irradiated, cytomegalovirus (CMV)–negative, lymphocyte-depleted blood products for administration to patients with cellular or combined IEI.

Strength of recommendation**: Strong**

Certainty of evidence: **Moderate**

For patients with SCID, congenital athymia or CID, care should be taken not to avoid CMV infection by using CMV negative, lymphocyte depleted irradiated blood products. Patients with suspected or known SCID or athymia as well as their mothers should be evaluated for CMV status, breastfeeding withheld, and formula given, if feasible until maternal CMV status is known[77] (**see RECOMMENDATION 2.4**). Newborns should be screened with blood and urine CMV PCR and the mother's CMV serostatus should be evaluated. If the newborn is found to be infected with CMV or develops symptoms consistent with CMV infection while PCR is pending, ganciclovir (6 mg/Kg IV twice daily) or valganciclovir (16 mg/Kg IV twice daily) therapy should be started and subsequently continued until immune reconstitution. If the mother is found to be CMV seropositive, ganciclovir or valganciclovir should be started until weekly patient's urine and blood PCRs are negative for CMV for 4 weeks. CMV disease is seen much less commonly in other IEI, but asymptomatic viremia can be present in CID patients. In this setting, examination for signs of disease, such as hepatitis, pneumonitis, chorioretinitis, or enteritis, is prudent, and suppression of viremia prior to HSCT is recommended if HSCT is planned.

RECOMMENDATION 9.3: We <u>recommend</u> educating patients regarding environmental exposures that may increase the risk of infections for patients with IEI.

Strength of recommendation**: Strong**

Certainty of evidence**: Moderate**

Large inhalational exposures of mold can cause overwhelming pulmonary fungal infection. In patients with CGD, this condition is referred to as "mulch pneumonitis" and causes diffuse infiltrates on chest imaging and potentially significant hypoxemia.[596] Treatment involves antifungal medications, the addition of antibiotics for a mixed pathogen infection, and systemic corticosteroids. In STAT3-HIES, pneumatoceles can become infected with *Aspergillus* (e.g., aspergillomas) or other molds that can lead to chronic infection and significant hemoptysis.[597] Large mold inhalations can lead to ABPA-type presentations. Examples of activities with high risk for mold exposure include hayrides, playing or working with mulch, and marijuana smoking.

Endemic fungi, such as *Histoplasma*, *Blastomyces*, *Coccidioides*, and *Cryptococcus* can cause disseminated infection in certain IEI. These infections are seen with STAT3-associated HIES, STAT1 GOF, and less frequently with IFNγ R defects and CIDs.[335, 598] Patients should be counseled regarding high-risk exposures to mold. Those at high risk for disseminated *Coccidioides* should be placed on prophylaxis when visiting endemic regions (i.e., Southwestern United States and northern Mexico). High risk activities for histoplasmosis include exploring caves with bat exposures and construction work.

Cryptococcus can be acquired from soil, particularly when contaminated with bird droppings.

Fresh and salt water can be contaminated with parasites or bacteria that cause significant infection in patients with IEI. Patients with neutrophil defects, such as CGD, are susceptible to uncommon infections by water-based bacteria, such as *Chromobacterium violaceum*.[599] Therefore, patients with CGD are encouraged to swim only in chlorinated or saltwater swimming pools.

Some CIDs, including CD40 ligand deficiency, DOCK8 deficiency and IL-21R deficiency are susceptible to chronic *Cryptosporidium* infections that can lead to significant biliary disease and potentially portal hypertension.[600-602] Treatment requires immune reconstitution, typically with HSCT, which can be challenging if liver disease is present. Avoiding high risk exposures such as water parks or public water fountains and drinking safe (filtered or boiled) water are helpful, along with screening patients with diarrhea and/or signs of cholestatic disease.

Antibody deficiencies are associated with giardiasis and other bacterial intestinal infections such as *Campylobacter*.[570, 603] Ensuring access to safe water, avoiding drinking from streams, lakes, or creeks, and using good hand washing and cooking techniques can minimize these infections.

RECOMMENDATION 9.4: We <u>suggest</u> prompt diagnostic testing in patients with IEI presenting with acute infection symptoms and treatment with antimicrobial regimens with duration longer than recommended for immunocompetent patients.

Strength of recommendation**: Conditional**

Certainty of evidence**: Low**

Patients with severe IEI may lack cardinal signs of inflammation and infection, such as fever or elevated white blood cell counts or inflammatory markers. Therefore, subtle changes in clinical status or inflammatory markers should lead to in depth evaluation and/or closer clinical follow-up than for patients without IEI. TLR pathway defects or STAT3/IL-6 associated HIES are examples of diseases that fall into this group. Patients should be educated on signs of infection and when to seek medical attention. Health care practitioners should have a low threshold to look for infections in patients with IEI and focus on the typical infections associated with the specific IEI. Cultures or other microbiologic techniques, such as viral pathogen multiplex PCR assays, should be performed whenever possible to identify the type of infection and to allow antibiotic sensitivities when feasible. As some infections can progress quickly in the setting of severe IEI (such as CID, quantitative neutrophil deficiency, or SCID), and thereby lead to significant morbidity and mortality, practitioners should have a low threshold to initiate

empiric antimicrobials, with cultures and definitive diagnosis obtained as quickly as feasible. Choice of antibiotic therapy should consider development of resistance to antibiotics and drug hypersensitivity. The antimicrobial drug spectrum is then narrowed based on culture results when it becomes available. Certain infections may require a longer course of therapy to reduce the risk of recurrence. Repeat imaging studies are suggested for severe pneumonias to guide length of therapy and to assess for development of bronchiectasis. Disseminated fungal and mycobacterial infections require longer courses of treatment with guidance from repeat imaging and laboratory markers. Some patients may continue to be treated with antimicrobials for secondary prophylaxis once therapy has concluded.

SECTION 10: Management of co-morbidities in IEI

RECOMMENDATION 10.1: We suggest that systemic comorbidities in patients with IEI be evaluated and managed with a multidisciplinary team with expertise in IEI-related comorbidities.

Strength of recommendation: **Conditional.**

Certainty of evidence**: Moderate.**

Management of patients with IEI and systemic comorbidities should be provided by a multidisciplinary team knowledgeable of IEI. Depending on the specific manifestations, cross-specialty involvement can include dermatologists, endocrinologists, gastroenterologists, hematologists, infectious disease specialists, oncologists, pulmonologists, rheumatologists as well as a variety of other specialists.

Immunosuppressive, anti-inflammatory, and cytotoxic therapies are all used for the treatment of non-infectious manifestations and have been demonstrated to be effective. When choosing among therapeutic options for a particular complication in patients with IEI, the degree of immune suppression associated with treatment and underlying IEI-specific susceptibilities to infection are deciding factors (**Tables 10.1-10.4**).

Solid organ transplantation outcomes in IEI patients are mixed.[604-606] When possible, organ transplants should occur at centers with experience in treating patients with IEI.

*Lung Disease (**Table 10.1**)*

Pulmonary complications of IEI are common, including infections and morbidity secondary to infection, (e.g., bronchiectasis). Antimicrobial prophylaxis for patients with bronchiectasis is discussed in **Section 9**. In addition, maintaining higher trough serum IgG levels in patients with bronchiectasis receiving IgRT may be helpful in preventing infection and slowing progression of disease (**see Section 8, RECOMMENDATION 8.2**).[607]

Granulomatous-lymphocytic interstitial lung disease (GLILD), a non-infectious complication, occurs at increased rates in patients with primary antibody deficiency (PAD). Although high dose glucocorticoids may be used to induce disease remission in GLILD, maintenance corticosteroids may result in relapse.[608] One effective approach for GLILD is the treatment with B cell depleting therapy (e.g., rituximab) or equivalent, in combination with maintenance anti-metabolite therapy (mycophenolate mofetil or azathioprine).[609] Duration of therapy is typically 12-18 months, with ongoing clinical, radiologic and laboratory monitoring. Relapse occurs in a subset of patients and the approach to therapy in these patients is similar to initial therapy.

Patients with STAT-3 HIES are prone to the development of pneumatocele following pneumonia.[610] These pneumatoceles may become colonized with pathogens including *Pseudomonas aeruginosa* or *Aspergillus*. Antimicrobial therapy is needed to avoid a cycle of re-infection (**see Section 9**). Surgical interventions may result in complications following thoracic surgery compared to other patients, the most commonly reported as bronchopleural fistula formation.[593]

Table 10.1. Management of lung disease

Manifestation	Associated IEI	Intervention/ management	Strength of recommendation	Certainty of Evidence	References
Granulomatous and lymphocytic interstitial lung disease (GLILD)	Antibody deficiency	Combination treatment: B cell depleting therapy (e.g., rituximab) + anti-metabolite therapy (mycophenolate mofetil or azathioprine)	Strong	Moderate	609
		High dose corticosteroids	Conditional	Moderate	608
Pneumatocele following lung infection	STAT3-HIES	Antimicrobial treatment Avoid surgical approach if possible	Strong	Moderate	610
Bronchiectasis	Antibody deficiencies	Avoid surgical approach if possible Periodic, at least annual, imaging of lungs with high resolution CT scan Maintain high trough serum IgG levels Airway secretion clearance measures	Strong	Moderate	610 611 608 607

Abbreviations: GLILD – Granulomatous and lymphocytic interstitial lung disease; HIES – Hyper IgE syndrome

*Gastrointestinal Disease (**Table 10.2**)*

As many as 30% of patients with IEI have gastrointestinal involvement including enteric and hepatic disease,[612] the treatment of which in general is similar to that of immune competent patients but with some special considerations outlined below.

Patients with antibody deficiencies may develop immune-mediated villous atrophy of the upper gastrointestinal tract that pathologically mimics gluten-sensitive enteropathy (celiac disease). It can be challenging to differentiate these two entities as serologies are unreliable in patients with antibody deficiencies. However, gluten avoidance is not helpful for patients who are negative for celiac-associated HLA markers.[613, 614] Instead, immunomodulatory therapy (e.g., enteral or systemic corticosteroids) is the mainstay of therapy.[615]

Chronic norovirus infection is associated with chronic diarrhea in patients with IEI and can lead to significant morbidity. There is no consensus regarding effective treatment. Suggested therapies include a trial of antimicrobials (e.g., nitazoxanide, ribavirin) and/or anti-inflammatory drugs (e.g., enteral steroids, enteral immunoglobulin, or biologics).[181, 615-617]

Inflammatory bowel disease associated with CGD (also referred to as CGD colitis) is treated with standard therapy including 5-aminosalicylates, corticosteroids, and ustekinumab.[618] Caution is advised with the use of TNF-α inhibitors in patients with CGD colitis due to the increased risk of infection observed in a small case series of patients.[619-621] CGD patients undergoing HSCT have demonstrated remission of CGD colitis.[622]

Liver abscesses are a common manifestation of CGD, the management of which includes both initial treatment with culture/biopsy directed antimicrobials in addition to systemic corticosteroids.[623] Surgical management with debridement or resection may be required.[624]

Nodular regenerative hyperplasia (NRH) is a difficult to treat cause of non-cirrhotic portal hypertension in patients with IEI. Aggressive medical and surgical management is required to prevent variceal bleeding and minimize complications.[625-627] End-stage disease is associated with significant morbidity and mortality, and liver transplantation may be followed by disease recurrence.[605, 606]

Autoimmune hepatitis occurs with increased frequency in patients with IEI.[627] Treatment with corticosteroids and non-specific immunomodulators such as azathioprine is often effective but where possible, precision therapy based on the underlying molecular defect is preferred. For example, abatacept has been shown to be effective in patients with CTLA4 haplo-insufficiency[628] and jakinibs have demonstrated efficacy in patients with STAT3 GOF.[447]

Table 10.2. Management of gastrointestinal disease

Manifestation	Associated IEI	Intervention/management	Strength of Recommendation	Certainty of Evidence	References

Villous atrophy of the upper gastrointestinal tract	Antibody deficiency	Immunomodulatory therapy, first-line (e.g., enteral or systemic steroids)	Strong	Moderate	614 615
		Do not avoid gluten unless patients have celiac-associated HLA markers	Strong	Moderate	613
Chronic norovirus infection	Antibody deficiency, CID	Antimicrobials (e.g., nitazoxanide, ribavirin) and/or diverse drugs (e.g., enteral steroids, enteral immunoglobulin)	Conditional	Very low	616 617
Inflammatory bowel disease	CGD	5-aminosalicylates, corticosteroids, ustekinumab	Conditional	Low	618
		Use TNF-alpha inhibitors with caution of risk of severe infection	Conditional	Moderate	619 620
		HSCT	Conditional	Moderate	622
Liver abscess	CGD	Initial treatment with culture and biopsy directed antimicrobials and systemic corticosteroids	Strong	High	623
		Surgical management with debridement or resection if medical management is inadequate	Strong	Moderate	624
Nodular regenerative hyperplasia of liver	Antibody deficiency, CGD	Medical and surgical management of non-cirrhotic portal hypertension to prevent variceal bleeding	Conditional	Low	625 626
		Liver transplantation is discouraged	Conditional	Low	605 606
Autoimmune Hepatitis	Antibody deficiency, PIRD	Corticosteroids, immunomodulators	Conditional	Low	627
		Precision therapy based on underlying molecular defect (e.g., abatacept, jakinibs)	Conditional	Low	628 447

Abbreviations: CGD – Chronic granulomatous disease; HLA – Human leukocyte antigen; HSCT – Hematopoietic stem cell transplant; PAD – Primary antibody deficiency; TNF – Tumor necrosis factor

*Dermatologic Disease (**Table 10.3**)*

Cutaneous disease occurs in patients with IEI in several different forms. For a rash not responsive to empiric therapy, diagnostic skin biopsy with bacterial, fungal and mycobacterial cultures should be performed to guide treatment.

Granulomatous skin disease can occur in CID, CGD, and CVID. Granulomas can also be found in other organs, including lymph nodes, spleen, liver, lung, and the GI tract. Vaccine strain rubella has been isolated by PCR from skin granulomas in patients with SCID, CID (notably those with DNA repair defects), and has also been reported in

patients with hypogammaglobulinemia and defects of innate immunity.[629] Once attenuated rubella or other infection has been ruled out, first line therapy for skin granulomas is oral corticosteroids, followed by TNF-alpha inhibitors if refractory or unresponsive to corticosteroid therapy[630] with the caveat that TNF-alpha inhibitors should be used with caution in patients with CGD and other IEI with increased susceptibility to mycobacteria and fungal infections (**see Table 10.2**).

Atopic dermatitis is associated with many IEI and can be quite severe. It can also predispose patients to skin infections. Initial management should focus on improvement of skin barrier with emollient therapy and control of inflammation with topical corticosteroids.[631] For some patients, particularly those who have had recurrent bacterial skin infections, dilute bleach baths or swimming in chlorinated pools 2-3 times per week can be beneficial to decrease bacterial colonization on skin. However, this strategy has not been studied specifically in patients with IEI.[632] For severe or refractory disease, immunosuppression is a consideration, but increased risk for infection must be balanced carefully. Biologic therapy, specifically dupilumab, has been used successfully in patients with IEI, notably STAT3-related HIES, with improvement in skin disease and good safety.[633]

Cutaneous warts can be found in various SCID or CID due to inability to control human papilloma virus (HPV) infection. Anti-wart treatment in patients with IEI is challenging as some therapies rely on activation of the immune system to clear the warts and may require multiple strategies, including destructive therapies, topical immunostimulants, surgical excision, or ablation. Response to systemic therapies, including immunomodulation, is inconsistent. Mavorixafor has been approved for the treatment of WHIM (**see Section 13**).[634] Treatment is also imperative as lesions can progress to malignancy.[429] The role of HPV vaccination for prevention of disease in patients with immunodeficiency is not clear but should be considered (**see section 11**).

Table 10.3. Management of dermatologic disease

Manifestation	Associated IEI	Intervention/management	Strength of Recommendation	Certainty of Evidence	References
Rash not responsive to therapy	Various IEI	Use diagnostic skin biopsy with cultures as guidance for treatment	Strong	Very low	None
Granulomatous skin disease	CID, CVID, CGD	PCR/immunohistochemistry for attenuated vaccine strain rubella virus.	Strong	Moderate	[629]
		Topical corticosteroids for non-infectious rash	Strong	Moderate	[630]
		TNF-alpha inhibitors to treat progressive or refractory disease	Conditional	Very low	[630]

		imaging for extra-cutaneous granulomatous disease	Strong	Very low	[629]
Moderate-to-severe atopic dermatitis	HIES, WAS	Biologic/targeted molecular therapy for refractory disease	Strong	Moderate	[631]
		Adjunct measures to reduce colonization with *S. aureus*	Conditional	Moderate	[632]
Refractory warts	CID	Topical cytotoxic therapies (e.g., cryoablation, salicylic acid or 5-flurouracil) and topical immunostimulants (e.g. imiquimod) Mavorixafor (for WHIM)	Conditional Strong	Very low Moderate	[429] [634]

Abbreviations: CGD – Chronic granulomatous disease; CID – Combined immunodeficiency disorder; CVID – Common variable immunodeficiency; HIES – Hyper IgE syndrome; TNF – Tumor necrosis factor; WAS – Wiskott-Aldrich syndrome

Neurodevelopmental disorders

Speech, gross and fine motor delays are associated with many IEI, therefore, early intervention with physical, occupational and speech therapy is essential.[635-637]

*Rheumatologic and musculoskeletal disease (**Table 10.4**)*

Bone health optimization should be considered with vitamin D replacement, if needed, and adequate calcium intake.[490] Treatment with bisphosphonates may not reduce fracture risk but is considered when there are recurrent fractures and osteoporosis. Patients with STAT3-HIES also frequently have retained primary teeth, and consultation with a dentist regarding the timing of extraction of retained incisors and molars is recommended.[638]

Inflammatory myopathy, connective tissue disease, and non-infectious arthritis occur in patients with antibody deficiencies and WAS. Physical activity has been shown to reduce symptoms such as fatigue and pain, and improve function and mental health.[639] Patients are more likely to adopt better health practices when recommended by their physician[640] and thus physical activity should be routinely recommended by physicians caring for patients with IEI.

Pharmacologic treatment of rheumatologic disease should be approached similarly to patients without immune issues, inclusive of NSAIDs, corticosteroids, and corticosteroid-sparing agents such as methotrexate, sulfasalazine, cyclosporine or biologics.[449, 641-643]

Relatives of patients with CVID and CGD who are carriers of pathogenic variants in disease-associated genes may develop SLE and SLE-like symptoms, secondary to the inflammatory response and the impaired clearance of apoptotic cells. Lupus-like autoimmunity has been reported with increased frequency in STAT3-HIES patients.[315,

[643-645] These symptoms should be treated like SLE even in the absence of classic serologic findings since serology is not confirmatory in many patients and carriers.[315, 644]

Patients with WAS have a high incidence of small vessel vasculitis which affects the skin, gastrointestinal system, and kidney.[449] Aortic aneurysms were reported in five cases.[646] Treatment of vasculitis includes standard therapies such as corticosteroids, methotrexate, cyclophosphamide, azathioprine, rituximab as well as high dose IVIg.[647, 648]

Table 10.4. Management of rheumatologic and musculoskeletal disease

Manifestation	Associated IEI	Intervention/management	Strength of Recommendation	Certainty of Evidence	References
Reduced bone mineral density and minimal trauma fractures	STAT3-HIES	Vitamin D replacement, if needed, adequate calcium dietary intake and/or supplementation, bisphosphonate therapy	Conditional	Moderate	490
Retained primary teeth	STAT3-HIES	Consultation with dentist for extraction of retained incisors and molars	Strong	Moderate	638
SLE and SLE-like symptoms	Antibody deficiencies, CGD, CGD carriers,	Treat SLE	Conditional	Moderate	644 315
Small-medium vessel vasculitis	Complement deficiency, WAS	NSAIDs, corticosteroids, methotrexate, cyclophosphamide, azathioprine, rituximab	Strong	Low	449
		High dose IVIG	Conditional	Low	647, 648
Inflammatory myopathy. Persistent non-infectious oligo- or poly-articular arthritis	Antibody deficiencies, WAS	NSAIDs, corticosteroids, and steroid-sparing agents such as methotrexate, sulfasalazine, cyclosporine, or biological agents	Strong	Moderate	641 642 643
		Physical therapy and exercise therapy	Strong	Moderate	639

Abbreviations: CGD – Chronic granulomatous disease; CNS – Central nervous system; HLH – Hemophagocytic lymphohistiocytosis; HSCT – Hematopoietic stem cell transplant; IVIG – Intravenous immunoglobulin; MAS – Macrophage activation syndrome; NSAID – non-steroidal anti-inflammatory drug; PAD – Primary antibody deficiency; TNF – Tumor necrosis factor; WAS – Wiskott-Aldrich syndrome

RECOMMENDATION 10.2: We <u>recommend</u> prompt management of cytopenias and malignancies in patients with IEI

Strength of recommendation**: Strong.**

Certainty of evidence**: Moderate.**

Patients with certain IEI have increased risk for hematologic and oncologic complications, including immune cytopenias, malignancy, cancer susceptibility, lymphoproliferation, and HLH/MAS (**see Tables 7.2 and 7.3)**.[649] Malignancy development in individual IEIs can occur secondary to defects in DNA repair, cellular maturation, signaling or apoptosis; impaired cancer immunosurveillance; and recurrent infections with viruses such as EBV and HPV which can cause oncogenic transformation.[650] The development of manifestations such as cytopenias and malignancies warrants prompt treatment in patients with IEI. (**see Table 10.5**)

Cytopenias

Autoimmune cytopenias occur commonly in IEI[10] secondary to self-reacting T- and B-cells. Patients can present with a range of symptoms including emergent, life-threatening anemia or hemorrhage to mild, asymptomatic cytopenias to chronic, refractory/recurrent disease.

Blood product transfusion is indicated for the management of critical cytopenias.[651] Interventions to increase the safety of blood product transfusions in patients with IEI include the use of leukocyte-depletion and irradiation. Leukocyte-depletion with leukocyte filters is critical for removing cells that serve as a reservoir for latent CMV infection in donors and has been demonstrated to reduce the risk of CMV transfusion-transmission. (**see RECOMMENDATION 9.2**). Although leukocyte-depletion is common practice in most blood centers, the use of irradiation is reserved for cases where the recipient is at risk for transfusion-associated graft-versus-host disease (TA-GvHD), a complication resulting from allogeneic attack from passenger donor T-cells.[652] TA-GvHD risk is increased when the recipient has compromised T-cell function and when the donor has shared HLA-haplotypes with the recipient. These recommendations apply to whole blood, packed red blood cells, platelets, and fresh plasma products, but irradiation is not required for cryoprecipitate, fresh frozen plasma, or fractionated plasma products.[652]

Glucocorticoids represent the first line therapy for autoimmune anemia and for autoimmune thrombocytopenia. Second line therapies for refractory cases or in patients who require prolonged high doses of glucocorticoids, include immunosuppressive agents, monoclonal antibody targeting B cells and splenectomy. B cell depletion has demonstrated good initial response rates but high rates of relapse.[653, 654] Use of serotherapy against B cells may result in prolonged B cell aplasia or hypofunction,[655, 656] with increased risk for infections. Splenectomy was widely used to treat refractory cytopenias, but given the risk for sepsis and the growing list of less invasive options, removal of the spleen is rarely used in modern clinical practice.[657]

Most patients with autoimmune neutropenia are asymptomatic despite having very low levels of circulating neutrophils. A minority of patients with autoimmune neutropenia will develop recurrent or severe infections or stomatitis from impaired mucosal surveillance.

In these clinical scenarios, G-CSF administration has shown clinical benefit in retrospective registry analyses and is well tolerated.[658] As myelopoiesis is partially or fully intact in autoimmune neutropenia, clinical benefit can be achieved by small doses of 0.5-3 µg/kg/day of G-CSF given every 1-3 days to increase the ANC to a target maintenance of 1000-1500 cells/uL.[659] Immune suppression to treat primary autoimmune neutropenia has very limited success and is not recommended secondary to risk of infection with additional immune modulation.[660] Secondary autoimmune neutropenia associated with autoimmune syndromes rarely requires immune suppression solely for the low neutrophil count.

Management of Malignancy

Current recommendations based on reports of patient cohorts do not alter standard treatment regimens in patients with IEI but consider standard regimens of shorter duration to avoid extensive periods of high infectious risk.[502] Patients with IEI and DNA radiation sensitivity require adjustment to standard dosing of chemotherapy and irradiation, which can cause significant short- and long-term toxicity, including later development of therapy related malignancy.[661] For patients with IEI but no genetic diagnosis, we recommend performing a radiation sensitivity assay prior to initiating treatment of malignancy.[281]

Outcomes for malignancy in IEI based on case reports and case series are inferior to immunocompetent patients and are due to advanced disease at presentation, higher risk of infections during treatment, and modifications of chemotherapy based on real or perceived risk of toxicity.[650] To minimize risk of infections, we suggest early consultation with infectious disease experts in immunocompromised patients and incorporation of multi-prophylactic antimicrobials and surveillance strategies, depending on the underlying IEI and oncologic therapy.

HLH/MAS

We recommend evaluation for HLH/MAS in patients with prolonged or high fever, development or rapid progression of lymphoproliferation, unexplained rash or respiratory compromise, neurologic changes, unexplained elevation of liver enzymes or cytopenias, primary or reactivation of herpetic viral infections. Initial evaluation should include a complete blood count, complete metabolic panel, coagulation studies (PT/PTT/fibrinogen), ferritin, sIL2R, CXCL9, IL18, bone marrow biopsy, flow cytometry for perforin, CD107a mobilization, SAP and XIAP, quantitative immunoglobulins, T/B/NK cell subsets, brain MRI, and a comprehensive genetic panel for IEI and in fulfillment of the HLH2024 criteria.[401]

Development of extreme hyperinflammation including HLH and MAS in patients with IEI can be difficult to manage given the severity of presentation and frequent presence of other comorbidities such as infections or underlying organ dysfunction. A multi-disciplinary care team including immunology, hematology/oncology, rheumatology, infectious disease, and other specialists can lead to improved patient care.[662, 663]

Depending on the etiology of hyperinflammation, optimal treatment may include antimicrobials, glucocorticoids, biologics, chemotherapy, and/or HSCT. For stable patients, we recommend deferring therapy until after complete evaluation for malignancy (imaging, bone marrow or other tissue biopsy where appropriate) and infection. Treatment of hyperinflammation without knowledge of an underlying malignancy may delay this diagnosis, while use of immune suppression in the setting of severe infection may lead to overwhelming illness. Stable patients should therefore be treated with supportive measures including antimicrobials, intravenous fluids, and close monitoring until malignancy and infection are confirmed or excluded.

Table 10.5. Management of hematologic/oncologic disease

Manifestation	Associated IEI	Intervention/management	Strength of Recommendation	Certainty of Evidence	References
Severe Anemia or thrombocyto-penia	SCID, CID	Only irradiated, leukocyte-depleted cellular blood products	Strong	Moderate	652
Autoimmune anemia or thrombocyto-penia	Antibody deficiencies, immunodysregulatory disorders	Systemic glucocorticoids	Strong	Moderate	436
		B-cell depleting therapy for severe refractory cytopenias, control of EBV-infected B cells, or significant lymphoproliferation High Dose IVIG	Strong	Low	436 656 654
		Do not use splenectomy, unless splenic sequestration or severe, refractory cytopenias	Conditional	Moderate	657
Autoimmune neutropenia	Antibody deficiencies, immunodysregulatory disorders	Granulocyte-colony stimulating factor (G-CSF) to achieve an ANC of 1000-1500 cells/ul for patients with recurrent and severe infections	Conditional	Low	658 659
		Do not treat autoimmune neutropenia without infections	Strong	Moderate	660
Lymphoproliferative disorders	CID with EBV susceptibility or risk of EBV-driven malignancies	Do not treat isolated benign lymphoproliferation without organ compromise, discomfort, or significant impact on quality of life	Conditional	Very Low	662
Malignancies	All IEI	Radiation sensitivity testing prior to cancer therapy in patients with IEI without molecular diagnosis	Conditional	Low	281

		Standard treatment regimens of shorter duration	Conditional	Low	[494]
HLH/MAS	All IEI	Coordinated treatment by a multidisciplinary team with expertise in hyperinflammation. Defer HLH treatment in stable patients until associated malignancy and infection have been ruled out	Strong	Low	[663] [662]

Abbreviations: AT – Ataxia-telangiectasia; CID – Combined immunodeficiency disorder; CVID – Common variable immunodeficiency; EBV – Epstein-Barr virus; PCR – Polymerase chain reaction; PET – Positron emission tomography; SCID = Severe combined immunodeficiency disorder

SECTION 11: Immunizations in the Management of IEI

RECOMMENDATION 11.1: We recommend the use of vaccine recommendations from local government agencies (e.g., CDC) for patients with IEI.

Strength of Recommendation**: Strong to Conditional**

Certainty of Evidence**: Low to Very Low**

Vaccine schedules and recommendations in the United States evolve rapidly in response to emerging pathogens, review of published research, and newly available agents. Since the 2015 IEI practice parameter, novel vaccines against new pathogens and expanded serotypes have been approved by the FDA, impacting individuals with IEI and their household contacts. These include vaccines for the prevention of COVID-19, Respiratory Syncytial Virus, Herpes Zoster virus, Human Papillomavirus, *Neisseria meningococcus*, *Streptococcus pneumoniae*, and MPox. Providers are urged to refer to guidelines from local government agencies (in the US, to include the Centers for Disease Control or CDC) as the recommendations may supersede the practice parameter guidelines. The CDC works in real time via the Advisory Committee on Immunization Practices (ACIP) recommendations which includes specific guidance for individuals with IEI.

IEI patients with severe immune defects (cellular, phagocytic, and/or humoral) should not receive live, replicating vaccines **(Table 11.1).**

Live vaccines should be avoided in all infants with SCID or complete athymia.[87] Unfortunately, vaccine-strain infections following administration of live attenuated rotavirus to newborns with SCID have been reported, occurring prior to the implementation of routine newborn screening.[87-88] BCG vaccination, which is still recommended in countries with high-prevalence of tuberculosis, has also caused disseminated or localized granulomatous disease in infants with SCID, interferon gamma pathway defects, or chronic granulomatous disease.[664] Vaccine strain rubella

virus has been detected in skin granulomas in patients with IEI, including AT, CID, and even patients with humoral immunity defects.[629]

It is not necessary for household contacts to avoid administration of live vaccines, other than live oral poliovirus vaccine and live, replication competent ACAM2000 for MPox/Smallpox.[85, 87] If an immunocompetent infant in the household has received oral rotavirus vaccination, handwashing is recommended for one month after diaper changes to prevent from transmitting live rotavirus to household siblings with IEI. Patients with IEI should avoid direct contact with an individual's affected skin if they are suffering from a blistering rash after VZV vaccination or shingles outbreak.

Individuals with isolated T cell lymphopenia and preserved cellular and humoral function may receive live viral vaccines.

This includes infants with abnormal newborn screens indicating T cell lymphopenia (but not SCID) and pediatric patients with idiopathic T cell lymphopenia, DiGeorge Syndrome (DGS), or CHARGE syndrome.

Infants with abnormal newborn screens for SCID who do not meet criteria for SCID diagnosis are at risk for preventable infectious disease prior to routine vaccination with rotavirus, MMR, or VZV. Prolonged avoidance of vaccination in these infants may lead to undesirable outcomes as measles outbreaks continue to occur because of vaccine hesitancy,[665] and VZV vaccination can prevent 97% of infections in children annually in the United States.[666] Rotavirus infection following vaccination has only been described in infants with SCID; widespread vaccination has led to a significant decrease in hospital visits for rotavirus infections in children less than 3 years of age.[667]

The recommended time for administration of the first dose of rotavirus vaccine is 15 weeks of age at the latest. At this age, some infants with persistent T cell lymphopenia may have convincing evidence for intact thymic function, increasing IgA and IgG production, and normal lymphocyte proliferation studies. Genetic testing may also provide an explanation for T cell lymphopenia arising from partial defects in thymic function such as DGS, CHARGE syndrome, or heterozygous carriers of FOXN1 defects.[668]

Recent guidelines for children without SCID, however with T cell lymphopenia recommends administering live viral vaccines if CD4 T cells > 400 cell/uL AND CD8 T cells > 200 cells/uL AND naïve CD4 T cells > 20% of CD4 T cells.[284]

For patients receiving IgRT, vaccines may be considered when there is a potential gain of T cell immunity and/or lack of seroprotection in available immunoglobulin preparations.

Recent examples include mRNA based COVID-19 vaccines under emergency use authorization, and attenuated, non-replicating Mpox vaccines in at risk individuals.

During the COVID-19 pandemic patients on IgRT were given COVID-19 vaccines (prior to the emergence of serologic immunity in the IgRT products) and T cell responses and serologic responses were measurable and found to be surprisingly robust.[669] As such patients with IEI are strongly recommended to receive COVID-19 vaccination and consider ongoing boosters. Pemgarda® (Pemibart) is a monoclonal antibody indicated for COVID-19 prophylaxis in immunocompromised patients, ages 12 years and older, every 3 months.

A live, non-replicating, attenuated orthopoxvirus (also referred to as modified vaccinia Ankara) was approved in 2019 for protection against smallpox/mpox in individuals with high risk of infection, including those with acquired immunodeficiency from HIV. There is currently no contra-indication for immunocompromised individuals. There have not been reports of use of this vaccine in patients with IEI, but it is certainly a vaccine to consider in at risk individuals with preserved capacity for generating a T cell response to vaccination such as 22q11 deletion syndrome with T cell cytopenia.

HPV vaccination is recommended in all patients with IEI 9 to 45 years of age, including patients on IgRT, due to theoretical gain in cellular mediated immunity. About 80% of sexually active individuals will acquire genital HPV infection in their lifetime.[670] Protection prior to exposure through vaccination is recommended. Three doses are currently recommended for immunocompromised persons regardless of age. IgRT products do not contain adequate specific antibody titers to prevent genital HPV infection and CD4 responses rather than serologic responses are associated with clearance of primary infection. The quadrivalent vaccine is effective for stimulating T cell function against HPV.[671] Patients with T cell lymphopenia from a variety of causes are at risk for viral persistence.[428]

Seasonal influenza vaccination is recommended in patients with IEI due to the safety of influenza vaccination and the COVID-19 vaccination data indirectly supporting this recommendation. Pre-emptive administration of antiviral medications is effective for influenza, and we suggest that patients (3 months or older) with IEI and exposure to influenza receive a prescription for on demand chemoprophylaxis[672] in addition to vaccination.

In 2023, routine vaccination for RSV has been recommended for “at risk” adults 60-74 years, all individuals older than 75 years-old,[673] and pregnant women to prevent infection in infants.[674] In the same year, RSV monoclonal antibody infusions for toddlers were approved up to 24 months of age.[675] The approach to vaccinate pregnant women or administer monoclonal antibody infusions in non-protected infants also applies for families affected by IEI.

For patients with IEI that do not require IgRT, vaccinations with conjugate vaccines may be recommended outside of the typical vaccination schedule. Patients with asplenia, TLR pathway defects, or complement deficiency require confirmation of childhood

vaccination followed by administration of booster vaccines against pneumococcal (PCV20 or PPSV23) and meningococcal (A, C, Y, W135 and B) infections. Administration of meningitis vaccines are recommended at diagnosis for asplenia and complement deficiency.

Because of the complexity and rapid evolution of recommendations for pneumococcal vaccination of the general population including those with special healthcare needs, the CDC has developed algorithmic tools to assist providers with decision making around pneumococcal vaccines. (**See RECOMMENDATION 4.6**)

We recommend that patients with IEI who no longer require IgRT (i.e., THI) receive live viral vaccines according to catchup schedule, at least 4 weeks after their last IgG infusion.

Shingles prevention:

Since 2017, a recombinant subunit varicella zoster vaccine (RZV) has replaced an attenuated live viral vaccine to prevent shingles in adults 50 years and older with up to 97% efficacy; in 2021, the recombinant subunit varicella zoster vaccine (RZV) was approved for administration to immunocompromised adults 19 and older. Immunologists should routinely check guidelines for the lowering of this age as immunocompromised teenagers with a history of prior live viral varicella vaccination or wild-type varicella infection may benefit.[676, 677] The effectiveness of the RZV in individuals with IEI is unknown; however, those who have received a previous live viral vaccine in childhood or had wild-type varicella infection are at higher risk for reactivation which may be preventable with the RZV administration. Thus, RZV is recommended for adult patients with IEI (particularly defects in NK or CTL function) that may still have preserved humoral and/or $CD4^+$ T cell function.[87]

The RZV vaccine is not approved at the current time for the prevention of primary varicella infection in patients who have been exposed to live varicella zoster virus from a community outbreak of varicella or direct contact with a person experiencing a shingles outbreak. For these exposures, patients with IEI may receive passive immunization via Varicella Zoster Immune Globulin (VZIG).[678] Patients receiving IgRT are likely protected if IVIG is given within 3 weeks of exposure.[679]

Table 11.1. Vaccination considerations in IEI

Vaccination approaches	Associated IEI	Vaccines of relevance	Strength of recommendation	Certainty of evidence	References

CONTRA-INDICATED	Severe IEI - including SCID, CID, IFN- α deficiency, IFN- γ deficiency, IL-12 axis deficiencies, antibody deficiencies and CGD	All live viral vaccines, live attenuated Influenza vaccination (LAIV), Dengue All live bacterial (BCG, typhoid)	Strong	Low	87 664 384
Active vaccination while receiving IgRT: Target vaccine preventable diseases	Patients with IEI with adequate T cell function AND receiving IgRT	mRNA vaccines, e.g., COVID-19 emerging strains	Conditional	Low	669
		HPV vaccines	Conditional	Very Low	671
		Seasonal inactivated vaccines, e.g., Influenza	Conditional	Low	680
		Recombinant zoster vaccine for shingles	Conditional	Very Low	676 677
Vaccination and boosters with conjugated vaccines for patients at risk for severe bacterial infections	Complement deficiencies Asplenia/Hypospleni a TLR defects	Early administration of MenACWY (less than 5 yrs); followed by boosters with MenACWY + MenB vaccination, or pentavalent meningococcal vaccine Primary vaccination or completion of primary series with conjugated pneumococcal vaccines	Strong	Low	87
Catch up and "booster" vaccines for patients at risk for serious and/or chronic viral infections	Defects in cytotoxic T cells; NK cell deficiencies	HPV vaccines	Conditional	Very Low	330
		Recombinant zoster vaccine for shingles	Strong	Very Low	676 677
Vaccination of household contacts of	Household contacts of any patient with IEI	Scheduled routine vaccinations are encouraged, including routine live viral vaccines, except oral polio vaccine	Strong	Low	85 87 284

patients with IEI		and ACAM2000 Mpox vaccine			

SECTION 12: Immune Reconstitution Therapy for IEI

RECOMMENDATION 12.1: We suggest that allogeneic HSCT for patients with IEI be performed at a center with experience in HSCT for IEI.

Strength of recommendation**: Conditional**

Certainty of evidence**: Moderate**

Since 1968, allogeneic HSCT has become a widely used definitive treatment for patients with severe forms of IEI. The 5-year overall survival (OS) for patients with IEI receiving allogeneic HSCT can be approximated at 80%,[681] but this estimate varies depending on the underlying IEI, donor-patient human leukocyte antigen (HLA) match, myeloablation approach, stem cell source, patient age, performance status and co-morbidities. The indication for specific genetic disorders and the approaches and timing of HSCT are variable depending on individual IEI. For example, allogeneic HSCT is universally recommended for patients with SCID, and transplant outcomes are superior for patients transplanted before 3.5 months of age to minimize the risk of acquiring infection prior to HSCT.[82] In contrast, patients with diseases of immune dysregulation such as *LRBA* deficiency or *CTLA4* haploinsufficiency are typically only considered for allogeneic HSCT once the disease expression in patients has proven to be severe.[682] HSCT for IEI associated with radiation sensitivity and chemosensitivity necessitate the use of minimal-intensity conditioning regimens to reduce risk of toxicity.

An in-depth knowledge and active clinical practice in IEI are required for treating clinicians and HSCT teams to remain abreast of currently accepted or preferred practices for patients with IEI as they evolve.[683]

RECOMMENDATION 12.2: We recommend that patients with typical SCID or leaky/atypical SCID receive definitive therapy with allogeneic HSCT or gene therapy.

Strength of recommendation**: Strong**

Certainty of evidence**: High**

Patients with SCID require definitive treatment with allogeneic HSCT or gene therapy to survive beyond 1-2 years of age.[56] HSCT outcomes are optimal for patients diagnosed by newborn screening with greater than 90% overall survival (OS).[60] Survival has repeatedly been demonstrated to be superior for patients transplanted before the age of 3.5 months, which can be considered as a surrogate for lack of infection.[59, 82, 684]

For patients with SCID, the decision to proceed to allogeneic HSCT is straight-forward. (**See Section 2**).[82] HSCT for patients with severe T cell lymphopenia without a genetic diagnosis may be deferred because of the potential improvement of T cell numbers over time. Patients with congenital athymia should be treated with cultured thymus tissue implantation (CTTI) (**see RECOMMENDATION 12.3**).[83]

For SCID patients undergoing allogeneic HSCT, the use of pretransplant myeloablative conditioning regimen is associated with improved B cell reconstitution,[684] but other factors should be considered regarding the treatment approach such as the presence of active infection, donor and recipient HLA-matching, graft type, and underlying genetic disorder. Importantly, SCID patients who have genetic variants associated with radiation and chemotherapy sensitivity should receive treatment with reduced doses of alkylator-based conditioning agents, in order to decrease the risk of late effects such as poor growth, failure of development of secondary dentition, autoimmunity and malignancy.

Gene therapy is another option for SCID patients with pathogenic variants in certain genes, for example *ADA*, *IL2RG*, *DCLRE1C* and *RAG1,* through enrollment in open clinical trials. Gene therapy offers immune reconstitution without the risk of graft versus host disease (GVHD) associated with allogeneic HSCT. SCID is ideally suited to gene therapy given the survival advantage of T cells expressing the normal gene. The first gene therapy trials for SCID were performed in patients with X-linked SCID and used gammaretroviral vectors. Despite early successes in T cell reconstitution and patient survival, the development of T-cell acute lymphoblastic leukemia due to insertional mutagenesis tempered early successes, and these vectors were abandoned.[685] Self-inactivating (SIN) gammaretroviral and lentiviral vectors were later developed, with modification of viral promoters and enhancers to reduce the risk of malignancy.[686] Recent clinical trials have incorporated low-exposure/non-myeloablative conditioning to facilitate the engraftment of hematopoietic stem cells and the development of immune cells other than T cells. The numbers of gene-corrected stem cells and the vector copy number influence T cell reconstitution and are being optimized. At the time of writing, clinical trials utilizing lentiviral vectors were open for X-linked SCID (NCT03601286, NCT04286815), ADA-SCID (NCT05432310), Artemis SCID (NCT03538899), and RAG1 SCID (NCT04797260) patients who lack an HLA-matched related donor. Some trials also exclude patients with an HLA-matched unrelated donor. Remarkably, 5-year OS for healthy patients with ADA SCID treated with gene therapy or allogeneic HSCT after the year 2000 are similar, both greater than 90%.[81]

RECOMMENDATION 12.3: We <u>recommend</u> that patients with congenital athymia disorders be treated with cultured thymus tissue implantation (CTTI).

Strength of recommendation**: Strong**

Certainty of evidence**: Moderate**

The treatment of patients with congenital athymia with cultured thymus tissue implantation (CTTI) at the time of writing is clinically available at Duke Health Center (North Carolina, US) and Great Ormond Street Hospital (London, UK). T cell reconstitution, sufficient to prevent overwhelming infections, typically develops 6 to 12 months following CTTI. Two-year survival among 95 patients with congenital athymia treated with CTTI was 76%.[83, 687] CTTI should be pursued, when possible, in all patients with severe congenital athymia disorders (e.g.,22q11 deletion syndrome, CHD7 deficiency, TBX1 deficiency, FOXN1 deficiency, and PAX1 deficiency). BMT with a matched sibling donor, when available, has been suggested as a temporary alternative form of immune reconstitution; however, evidence is limited.[688-690]

RECOMMENDATION 12.4: We recommend that patients with CID disorders who have severe cellular immune defects or who manifest severe or refractory disease complications be considered for allogeneic HSCT.

Strength of recommendation**: Strong**

Certainty of evidence**: Moderate**

Decisions regarding allogeneic HSCT for CID are made based on both the genetic disorder and individual presentation. CID disorders are heterogeneous, and patient phenotypes can range from mild to severe. Clinicians should gauge the pathogenicity of the genetic variant for CID disorders that have multiple mechanisms of disease and the range of phenotypes, such as *IKZF1* deficiency.[691, 692] Additionally, care should be given to whether CID disease manifestations can be corrected by replacement of hematopoietic stem cells and derived lymphocyte populations.[693] Allogeneic HSCT decisions should be directed by physicians experienced in the care of patients with IEI. Shared decision making with families and patients is also needed given the diversity of management options for most CID disorders. Recent experience suggests that allogeneic HSCT outcomes are better for patients treated at young ages, without severe disease complications, than older patients. Among 130 patients with CD40L deficiency studied, 5-year OS for patients transplanted after the year 2000 was 90% or higher for patients less than 5 years of age and for patients without organ damage, liver disease, or *Cryptosporidium* species infection. Survival for patients older than 10 years of age or with these comorbidities ranged from approximately 40-60%.[694] For DOCK8 deficiency, a multicenter cohort of 81 patients exhibited 2-year OS of 84%. Patients transplanted after 2010 had an improved 2-year OS of 92%, and there was a trend towards better survival for patients who received HSCT before 8 years of age, 96% versus 78% in older patients.[695] Over 100 patients with MHC Class II deficiency have been treated with allogeneic HSCT with OS ranging between 66–100% in more recent years, and outcomes appear better in patients transplanted before the age of 2 years.[696]

Allogeneic HSCT can be curative for patients with WAS, and HSCT is recommended to prevent the severe disease complications of WAS. Survival outcomes following

allogeneic HSCT are highest for patients transplanted at a young age, usually less than 2-5 years of age. Five-year OS in patients transplanted younger than 5 years of age is reported to be greater than 90%.[697] Patients should be treated with conditioning regimens that achieve myeloablation, such as reduced toxicity busulfan-containing regimens, with the goal of obtaining stable myeloid donor chimerism >50% as lower levels are associated with increased risk of thrombocytopenia and the development of autoimmunity following HSCT.[697]

Allogeneic HSCT is often considered for patients with CID disorders when they present severe disease manifestations, such as NEMO deficiency and cartilage-hair hypoplasia (CHH).[698, 699] OS after HSCT in a cohort of 29 patients with NEMO deficiency was 74%, with greater than 90% survival for patients who received grafts from matched sibling donors and for patients who did not have mycobacterial infection. HSCT may not cure colitis because of cell-intrinsic abnormalities of epithelial cells. Reported survival outcomes following allogeneic HSCT in patients with CHH from several case series range from 63 to100%.[699]

RECOMMENDATION 12.5: We <u>recommend</u> that patients with primary HLH disorders, and patients with X-linked lymphoproliferative disease type 1 be evaluated for allogeneic HSCT.

Strength of recommendation**: Strong**

Certainty of evidence**: Moderate**

Patients with familial HLH due to pathogenic variants in *PRF1, UNC13D, STX11*, and *STXBP2* should be offered allogeneic HSCT due to the clinical severity.[700] Patients with HLH associated with Griscelli syndrome type 2 due to pathogenic variants in *RAB27A*, are often treated with allogeneic HSCT, even without obvious pigmentary defects.[701] Decision to HSCT in patients with Chediak-Higashi syndrome should take results of genetic testing and cytotoxicity assay results into account along with the clinical phenotype.[702] The risk of HLH is low in patients with Hermansky-Pudlak syndrome type 2, and HSCT is typically not justified.[703] Patients with XLP1 are offered allogeneic HSCT due to the high risks of fatal HLH associated with EBV infection along with the risks of lymphoma, humoral deficiency, vasculitis, and other rare complications.[704] Patients with XIAP deficiency have a wide phenotypic variability and allogeneic HSCT should be reserved for patients who manifest severe recurrent or refractory HLH, IBD, or other serious complications.[705] Of note, deficiency of XIAP confers higher risk of severe GVHD, and aggressive measures should be taken to prevent GVHD.[706]

For all patients, allogeneic HSCT is ideally performed once HLH is in remission, as active HLH confers a negative effect on survival. However, allogeneic HSCT should not be delayed if complete remission seems unlikely. Allogeneic HSCT should be performed in patients with isolated central nervous system HLH.[708] Asymptomatic siblings identified due to family history should be offered HSCT, as outcomes are

superior prior to onset of HLH symptoms.[709, 710] Fully myeloablative conditioning regimens (such as full myeloablative busulfan and cyclophosphamide) are avoided in patients with HLH because of a high risk of complications such as hepatic veno-occlusive disease, pulmonary hemorrhage, and low survival.[711] Reduced intensity conditioning regimens incorporating melphalan or treosulfan and fludarabine were implemented as an alternative with greater than 80% survival but have fallen out of favor due to high rates of mixed chimerism and eventual secondary graft failures.[712] A European study reported 100% OS at a median follow up of 36 months for patients treated with busulfan and fludarabine.[713]

RECOMMENDATION 12.6: We <u>suggest</u> that patients with immune dysregulation who manifest severe or refractory disease complications be evaluated for allogeneic HSCT

Strength of recommendation**: Conditional**

Certainty of evidence**: Moderate**

Patients with IEI classified by the IUIS as diseases of immune dysregulation with autoimmunity can be challenging to treat with allogeneic HSCT due to the significant pre-treatment complications, the potential need to control the underlying immune dysregulation prior to HSCT and variability in the tissue expression of causative genes. There is currently limited experience for most immune dysregulation disorders, and the outcomes are variable. Approaches to HSCT should be discussed with an understanding of the underlying genetic disorder and whether allogeneic HSCT would correct it, along with knowledge of the success of allogeneic HSCT versus conventional treatments.

Despite the limited number of patients reported, patients with IL-10R and IL-10 deficiencies appear to do well following allogeneic HSCT, which may relate to the relatively young age at transplant, having disease generally limited to the GI tract, and predominantly more recent years of transplant.[714, 715] Of note, it is important to identify a genetic etiology in patients with very early onset IBD and early onset IBD, as allogeneic HSCT would not be indicated in patients with epithelial defects that are responsible for disease.[312]

Survival for patients with immune dysregulatory disorders is variable and, in some cases, long-term OS after allogeneic HSCT can appear similar to that reported for conventional therapies. A study of long-term outcomes for IPEX patients observed a 15-year survival rate of 73% for patients treated with allogeneic HSCT (N=58) and 86% for patients treated with immune suppression only (N=34).[716] However, new autoimmune problems continued to develop in 51% of patients treated with immune suppression compared to only 17% of transplanted patients. Notably, patients with low disease scores had significantly better survival, greater than 80%. Reported allogeneic HSCT survival among 18 patients with CTLA-4 haploinsufficiency was 73%,[682] and among 23

patients with STAT3 GOF was 62%.[447] While reported outcomes are not high, outcomes are likely to improve with time as pre-HSCT targeted treatments and conditioning approaches are being tailored for these disorders, and allogeneic HSCT being performed at younger ages before accumulation of co-morbidities.

Not all immune dysregulatory disorders should be considered for allogeneic HSCT. For instance, allogeneic HSCT is not indicated in patients with pathogenic variants in *AIRE*. *AIRE* is expressed in the thymus and is involved in the expression of tissue-restricted antigens that are essential for negative selection and elimination of autoreactive T cells.[408] Patients with ALPS are usually manageable with sirolimus or other treatments and are not typically considered for allogeneic HSCT.[717]

Allogeneic HSCT may be indicated in a small subset of autoinflammatory disorders that are severe and not refractory to conventional treatment. Outcomes for patients with ADA2 deficiency appear excellent, with 2-year OS of 97% and GVHD-free, rejection-free survival of 73%.[718] Notably, allogeneic HSCT prevented new vascular complications.

RECOMMENDATION 12.7: We <u>recommend</u> allogeneic HSCT for patients with defects in neutrophil number and function associated with severe clinical phenotypes

Strength of recommendation**: Strong**

Certainty of evidence**: Moderate**

Most patients with LAD Types I and III and with CGD are considered for allogeneic HSCT due to the severity of disease complications and long-standing HSCT experience. The largest multi-center retrospective cohort analysis of outcomes in LAD Types I (N=69) and III (N=11) reported 83% 3-year OS.[719] Survival was greater than >90% for patients with a fully matched related or unrelated donor and for patients transplanted in infancy.[719] Data from the Inborn Errors Working Party (IEWP) of the European Society for Blood and Marrow Transplantation (EBMT) on 712 patients with CGD demonstrated a 3-year OS of 85.7%.[720] Survival was greater for patients transplanted before the age of 18 years and for patients with HLA-matched donors.[720] Data from the PIDTC also demonstrated excellent outcomes among 400 patients with CGD, with 3-year OS of 82% and superior survival with HLA-matched donors.[721]

Definitive treatment of patients with other congenital defects of phagocyte number or function is more variable. Many patients may be managed with conservative treatments such as G-CSF and prophylactic antimicrobials.

RECOMMENDATION 12.8: We <u>suggest</u> allogeneic HSCT in patients with innate immunity defects affecting hematopoietic cell lineages and who manifest with recurrent and persistent severe infections.

Strength of recommendation**: Conditional**

Certainty of evidence**: Low**

Patients with disorders classified as defects in intrinsic and innate immunity who have severe disorders or severe phenotypes can be considered for treatment with allogeneic HSCT. Patients with severe forms of Mendelian Susceptibility to Mycobacterial Disease including complete *IFNGR1* and *IFNGR2* deficiencies are usually considered for allogeneic HSCT however; mortality and graft failure are relatively high in these patients, often related to disseminated mycobacterial disease and to high levels of endogenous interferon gamma that contribute to graft rejection.[722] A review of 12 cases of IFN-γR1 deficiency noted only four successful transplantations,[723] and a single center series of 7 patients with IFN-γR2 deficiency reported 71% event-free survival.[724] Similarly, patients with STAT1 GOF may have severe disease that is indication for allogeneic HSCT, but current experience suggests challenges related to inflammation, graft failure, and suboptimal outcomes in these patients.[725] Strategies to mitigate the effects of interferon gamma may improve transplant outcomes in these patients.[726]

Patients with congenital neutropenia or Schwachman-Diamond syndrome who develop myelodysplastic syndrome (MDS), leukemia, or other bone marrow diseases can be treated with allogeneic HSCT. 5-10% of MDS patients will develop aplastic anemia, 20-33% will develop cytogenetic abnormalities or MDS, and 12% to 25% will transform into leukemia and require allogeneic HSCT.[727, 728] Several studies have reported superior survival for patients with marrow failure (70-80%) versus those with MDS/AML (15-40%).[729, 730] Outcomes also appear superior for patients with MDS compared with AML, suggesting that marrow surveillance for identification of early stages of clonal evolution may be indicated.[731] Patients with GATA2 deficiency can be treated with HSCT based on the development of severe infectious complications or bone marrow abnormalities including MDS. A series of 22 patients treated at a single center for MDS or AML; reported 2-year OS of 86%,[732] and a series of 65 patients with MDS reported 5-year OS of 75%.[733]

RECOMMENDATION 12.9: We recommend that any patient with IEI who receives definitive treatment with allogeneic HSCT, CTTI, or gene therapy receive life-long follow-up by clinicians experienced in evaluating immune reconstitution and monitoring for long-term complications of these procedures.

Strength of recommendation**: Strong**

Certainty of evidence**: Moderate**

Survivors of allogeneic HSCT and other definitive therapies require continued care beyond the first year following definitive treatment. Evaluation of immune reconstitution during the first 2 years following treatment is critical. Even patients without IEI who receive allogeneic HSCT may have impaired immune function following HSCT.[734] Evaluation of immune reconstitution facilitates decisions regarding ending isolation practices, withdrawing prophylactic antimicrobial medications, and beginning routine

post-HSCT vaccinations. Complete immune reconstitution following allogeneic HSCT is estimated to occur within 1-2 years, or sooner, in the absence of GVHD. Recommendations exist regarding vaccination strategies for HSCT patients in general and for patients with specific IEI, such as SCID. Initiation of vaccine schedules is guided by time post-HSCT or, preferably, by immunology evaluation.[735-737] Patients may have prolonged deficient adaptive immunity and therefore live vaccines should not be given to patients after HSCT without confirmation of their immune competence. T cell reconstitution sufficient to prevent infections typically develops by a year following CTTI, and guidance regarding vaccination of patients who received CTTI is available.[83, 738]

Patients who receive definitive treatments require continued clinical monitoring throughout their lifetime for late effects of allogeneic HSCT and for underlying disease-specific complications not addressed by the definitive therapy. Late deaths more than 2 years post HSCT can occur in patients with IEI, highlighting the need for lifetime follow-up.[739-741]

SECTION 13: PRECISION MEDICINE

RECOMMENDATION 13.1: We recommend the use of targeted therapies to treat IEI based on an identified molecular defect or a clinical phenotype suggestive of a defect in host immune responses.

Strength of recommendation**: Conditional to Strong**

Quality of evidence**: Low to High**

Advances in the immunopathogenic mechanisms of IEI have led to the development of targeted therapies, which is also referred as Precision Medicine. (**Table 13.1**) Several of these medications are currently approved by the FDA. (**Table 13.2**)

JAK inhibitor therapy for patients with JAK/STAT gain of function mutations.

Evidence supporting the use of JAK inhibitors for IEI is limited, and there are no clinical trials to date. However, for monogenic JAK/STAT disorders, early introduction of JAK inhibitor therapy can be essential for partial or complete resolution of disease. JAK/STAT signaling pathway causes engagement of one of four JAK proteins, which phosphorylate and recruit one of seven STAT proteins (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, STAT6). Once phosphorylated, dimerized STAT translocates to the nucleus and regulates gene expression. JAK inhibitors are now approved for a variety of disorders including myelofibrosis, polycythemia vera, rheumatoid arthritis, inflammatory bowel disease, psoriasis and psoriatic arthritis, eczema, alopecia, and acute graft vs. host disease. Mechanistic studies and cohort case reports have shown partial or complete response to treatment in JAK/STAT GOF disorders, specifically STAT1 GOF and STAT3 GOF.[447, 587, 742-751] JAK inhibitors have also shown clinical efficacy in cohort studies and case reports in treating interferonopathies (**Table 13.1**).[752-757]

JAK inhibitors are administered starting with the recommended dose for FDA approved indications and titrated every 4-6 weeks based on clinical response. There are no prospective studies to indicate optimal dosing for each JAK inhibitor, and dosing regimens are limited to cohort and case reports. Based on the retrospective experiences, ruxolitinib treatment is started at a dose of 15 mg/m^2/dose twice daily and increased to 30 mg/m^2/dose twice daily, maximal dose is 25 mg twice a day. 50 mg/m^2/dose has been tolerated in children, but the long-term data on high dose is not adequate to recommend this dose longitudinally.[758] Baricitinib may be used 2 mg daily and increased to 4 mg daily within 4-6 weeks, again according to clinical response and tolerance. In children under 9 years, use 2 mg per day[759] Dose escalation of 25% weekly until goal dose is achieved is suggested.[589] Given the increased risk for herpes virus Infections, prophylaxis with acyclovir is suggested.[589] Clinical assessments should be taken every 4 to 6 months for opportunistic infections,[447, 589] cardiovascular disease, thromboembolic disease, malignancy, or severe liver disease.[447]

ADA-ERT for patients with ADA deficiency

Elepegademenase is an FDA-approved recombinant, polyethylene-glycol conjugated bovine adenosine deaminase enzyme replacement therapy (ADA-ERT) and has been successfully used in ADA deficient patients, resulting in improvement in lymphocyte counts, absolute neutrophil counts, and reduction in infections. Elepegademenase has a half-life of 3 days and has been demonstrated to reduce plasma deoxyadenosine levels to <0.02 mmol/L within 3-6 months.[760-762] Rare adverse reactions include cough, vomiting, diarrhea, and minor injection site reactions. Initiation of ADA-ERT should be prompt upon diagnosis of ADA deficiency and does not require waiting for genetic diagnosis, if absence of enzyme activity is demonstrated. Initial dosing is 0.4 mg/kg/week intramuscularly in infants with ADA-SCID, which is divided into two doses per week. Longitudinal monitoring of plasma ADA levels, erythrocyte deoxyAXP levels, as well as blood counts and lymphocyte subsets should be performed at least every six months to ensure adequate response. Up dosing by 0.033 mg/kg/week is recommended if trough plasma ADA level remains <30 mmol/hr/L or if trough dAXP exceeds 0.02mmol/L. In patients with ADA deficiency-associated pulmonary alveolar proteinosis or idiopathic hepatitis, higher doses of ADA-ERT may be needed for clinical responses. In older children and adolescents, dosing of 0.2 mg/kg/week is recommended to maintain trough plasma ADA levels >30 mmol/hr/L, which may be given in a single dose weekly. There are no contraindications to ADA-ERT therapy. Known medication interactions include vidarabine, which is a substrate for ADA, and 2-dexycoformycin, which is a potent inhibitor of ADA. As ADA-ERT does not result in full immune reconstitution, antimicrobial prophylaxis and IgRT might also be used for patients on ADA-ERT. Restoration of antibody function was demonstrated in patients receiving bovine-derived ADA-ERT, and waning of antibody function and B cell oligoclonality has been described in patients on long-term therapy. Furthermore,

reduced efficacy has been observed with long-term therapy with bovine-derived ADA-ERT, which may be due in part to development of neutralizing antibodies. Serious events including EBV-associated lymphoproliferative disease, thyroid carcinoma, and lymphomas have also been described in patients on long-term ADA-ERT. Accordingly, ADA-ERT should be a bridging therapy prior to curative treatments such as allogeneic HSCT.

CTLA4-Immunoglobulin for patients with CTLA4 haploinsufficiency and LRBA deficiency.

CTLA4 is an inhibitor checkpoint protein that works in competition with the costimulatory molecule CD28 for the ligands CD80 and CD86. LRBA is essential for intracellular recycling of proteins, including CTLA4. Abatacept and belatacept are recombinant fusion proteins of CTLA-4 and human IgG1 that stop T cell activation by blocking CD28 engagement and T cell activation.[763] Abatacept has been shown to induce improvement in symptoms in patients with CTLA4 haploinsufficiency.[682, 764] A case series of subjects with LRBA deficiency showed that 3 of the subjects who experienced severe interstitial lung disease, refractory to other medications, experienced an improvement in pulmonary function after abatacept treatment, apparent within 6 months of starting treatment.[763] Long term follow up of patients with LRBA deficiency on abatacept showed improvement in chronic diarrhea, lymphoproliferation, and autoimmune cytopenia. Circulating T follicular helper cells (cTfh) and soluble CD25 were reliable biomarkers, decreasing while on abatacept in most patients.[764]

IL-1 inhibition

Three drugs targeting the IL-1 pathway are currently approved by the FDA: anakinra (recombinant form of IL-1R antagonist), rilonacept (recombinant IL-1R that binds to IL-1α, IL-1β and IL-1RA), and canakinumab (human monoclonal antibody that binds to IL-1β). All have been shown to reduce symptoms, inflammatory markers, serum amyloid A and neutrophil counts in patients with IEI due to excess IL-1 signaling. The therapies differ by international disease indications and regulatory approvals, as well as cost and availability. These drugs have different half-lives that may affect clinical and patient preference: anakinra has a terminal half-life of 4-6 hours, rilonacept has a half-life of approximately 7 days, and canakinumab is the longest at 22.9 to 25.7 days. Anakinra may have improved central nervous system penetration.[765] For all IL-1 targeted therapies, higher doses may be required in pediatric subjects. In addition, data on safety and efficacy in pregnant or breastfeeding patients is limited. To avoid delays associated with achieving a molecular diagnosis and the associated morbidity, a trial of IL-1 blockade with anakinra, rilonacept, or canakinumab may aid in the diagnosis of IL-1 mediated disorders.[766]

IL-1 inhibitors are used for treatment of patients with periodic fever syndromes with increased inflammation due to cryopyrin associated periodic syndrome, hyper IgD, or

familial mediterranean fever (FMF) unresponsive to colchicine, or TNF receptor associated periodic syndrome (TRAPS) which is also associated with increased IL-1 release. Therapeutic targeting and dosing based on severity of disease may improve efficacy. Patients with severe phenotypes require higher doses than patients with mild disease.[767,768] Long term studies of each of the therapies independently demonstrate a favorable safety profile, reduction in symptoms, and improved quality of life in children and adults.[767-772]

Randomized controlled trials of canakinumab in FMF showed resolution of baseline flares in greater than 80% of patients, with approximately 60% showing complete resolution. Increased dosing from 150 mg every 4 weeks to 300 mg every 4 weeks led to complete response in greater than 70% of participants.[768] Notably anti-IL-1 blockade is efficacious in reducing proteinuria.[768] Long-term efficacy of both anakinra and canakinumab has been reported for patients with colchicine-resistant FMF.[771, 772] A randomized controlled trial of canakinumab in mevalonate kinase deficiency showed resolution of baseline flares in 60% of patients, with 35% showing complete resolution. Increased dosing led to resolution in 57% of participants.[768] In 8 patients with less severe disease and normal inflammatory markers between inflammatory episodes, on-demand anakinra was effective for reducing frequency or length of episodes by greater than 50%.[773] A randomized controlled trial of canakinumab in TRAPS showed resolution of baseline flares in >60% of patients, with 45% showing complete resolution. Increased dosing led to clinical responses in greater than 73% of participants.[767] Long term studies of canakinumab demonstrate a favorable safety profile, reduction in symptoms, and improved quality of life in children and adults.[768-774]

Anakinra and canakinumab have been effective in patients with certain variants in *PSTPIP1,* causing PAPA syndrome.[775, 776] Homozygous mutations in *LPIN2* are associated with Majeed syndrome, a chronic recurrent multifocal osteomyelitis phenotype with congenital dyserythropoietic anemia and interventions, primarily with anakinra, have been shown to reduce systemic inflammatory markers and sterile osteomyelitis in affected individuals.[777-779] IL-1 treatment for patients with missense mutations in *NLRP12* has led to improvement in febrile episodes, though some patients experienced relapse of symptoms.[780, 781] IL-1 blockade with canakinumab or anakinra has been effective in patients with FCAS4, or mild NLRC4-AID with symptoms to cold stimuli.[782, 783] Treatment with anakinra reduces inflammatory episodes associated with Neonatal-Onset Cytopenia, Autoinflammation, and Recurrent Hemophagocytic lymphohistiocytosis (NOCARH).[784] Patients showed improvement in systemic inflammatory markers including CRP and ferritin, fever, rash, hepatosplenomegaly, and growth. The cytopenias may be less responsive to IL-1 blockade. Patients with more severe disease and features of HLH may require additional therapies or HSCT.[784] Use of rilonacept produces similar anti-inflammatory efficacy in patients with cryopyrin-associated syndromes.[785]

G-CSF in neutropenia

The administration of G-CSF to patients with neutropenia is summarized in **Table 13.1**.[785-792] Recombinant granulocyte-colony stimulating factor (rG-CSF) stimulates neutrophil mobilization and delays neutrophil apoptosis.[791] A randomized controlled phase 3 trial of 173 patients with severe chronic neutropenia (ANC <500 cells/uL) showed an increase in ANC (median 1500 cells/uL), increased proportion of maturing neutrophils within the bone marrow, and significant reduction in infection-related events.[792]

Plerixafor and Mavorixafor for patients with WHIM syndrome as initial therapy.

Plerixafor is a small molecule antagonist of CXCR4 and has shown efficacy in treating patients with WHIM syndrome. In clinical trials, plerixafor has been shown to reverse panleukopenia within 1-2 weeks of initiation and reduce the burden of infections including skin and anogenital warts due to HPV.[793, 794] In a phase 3 randomized cross-over study, plerixafor was non-superior to G-CSF for reduction of infection severity scores, but superior for resolution of leukopenia.[795, 796] Adverse reactions include injection site reactions, but unlike higher dose plerixafor as used in bone marrow transplant donors, cardiovascular and GI reactions have not been reported. Plerixafor is teratogenic in animals and contraindicated during pregnancy. Plerixafor is administered as a twice daily subcutaneous injection, and initial recommended dosing is 0.02-0.04 mg/kg/dose. Longitudinal monitoring of blood counts should be performed regularly to ensure adequate response. Up dosing of 0.01 mg/kg/dose may be undertaken if, within 2-3 weeks of starting therapy, inadequate responses are seen. Antimicrobial prophylactic therapy including IgRT is often indicated. Though restoration of IgA production has been reported in patients receiving G-CSF therapy, no notable changes in serum immunoglobulin levels were seen in 3 patients after 3 months of plerixafor therapy, and antibody responses to pneumococcal and tetanus/diphtheria vaccinations were highly variable. Mavorixafor is an oral CXCR4 antagonist approved by the FDA for patients 12 years and older with WHIM syndrome. [793] Dosing is based on weight >50kg is 400mg daily and <50kg is 300 mg daily based on the package insert. As with plerixafor, longitudinal monitoring of blood counts should be performed regularly to ensure adequate response. Need for IgRT should therefore be evaluated on a case-by-case basis in patients with WHIM syndrome who are receiving plerixafor therapy.

Cobalamin and folate for patients with IEI caused by defects in vitamin B12 and folate metabolism.

These defects include transcobalamin II (TCN2), solute carrier family 46 (SLC46A1; also called the proton-coupled folate transporter), and methylenetetrahydrofolate dehydrogenase (NADP1 dependent) 1 (MTHFD1). They present with clinical and laboratory features of SCID including low or absent T cell proliferation following mitogen stimulation, hypogammaglobulinemia and impaired antibody responses. These

abnormalities return to normal with folate therapy.[797-800] A case report of a patient with a defect in *LMBRD1*, a gene encoding a lysosomal membrane protein, also known as cblF, was described with recurrent infections, otitis media, bronchiolitis, urinary tract infections, oral candidiasis, giardiasis who had resolution of infections after treatment with cobalamin therapy.[800]

IFN-γ in the treatment of mycobacterial infections in patients with IL-12p40, IL-12RB2 and IL-23R deficiency, AD partial IFN-γR1 or R2, TYK2 deficiency, IRF8 and ISG15 deficiency.

In vitro data show reduced production of IFN-*γ* in multiple gene defects leading to increased susceptibility to invasive *Mycobacterium* spp. infections. Disorders include lack of response to IL-12 or IL-23.[345, 801] Patients with disseminated mycobacterial infections showed improvement after treatment with IFN-γ;[802] several of these patients were identified as having NEMO deficiency. Treatment with IFN-γ at 50mcg/m^2 in addition to anti-mycobacterial therapy have led to improvement of disseminated BCG and other mycobacterial infections in patients with IL-12RB2 deficiency and IFNgR1 deficiencies.[803-805]

Fucose for treatment of lymphocyte adhesion deficiency, type II (LAD-II).

LAD-II is a defect of fucosylation leading to loss of selectin ligands, leukocytosis, recurrent infections, as well as short stature and developmental delay. Supplementation with oral fucose has led to re-expression of selectin ligands on neutrophils with normalization of white blood cells and improvement in infections in some patients.[806] Discontinuation has led to loss of selectin ligands and leukocytosis.[807, 808]

Leniolisib for patients with activated phosphoinositide 3-kinase delta syndrome (APDS).

Leniolisib is a small molecule inhibitor that selectively targets hyperactive PI3K delta signaling. Leniolisib was studied in 31 patients aged 12-75 years age in an international phase 3, triple-blinded, placebo controlled with randomization 2:1 clinical trial.[809] Results of this trial led to FDA approval of leniolisib for the treatment of patients 12 years of age or older in 2023. Treatment with leniolisib significantly reduced lymphadenopathy and spleen size. Also noted was a decrease in elevation of transitional B cells and CD38+ plasmablasts, switched and non-switched memory B cell populations, CD8+ senescent CD57+ T cells, and CD8+ T cells including terminally differentiated effector memory ($CD8+_{TEMRA}$) T cells. Overall CD4+ T cell quantities increased with reduction in $CD4+_{TEMRA}$ cells. Treatment with leniolisib also greatly reduced serum IgM, which is often elevated in patients with APDS.[809, 810]

TABLE 13.1. Key examples of precision medicine in IEI

Associated IEI	Therapeutic agent	Biomarkers*	Strength of recommendation	Certainty of Evidence	Reference
JAK/STAT Gain of Function Disorders					
STAT1 Gain of Function	Ruxolitinib baricitinib	CXCL9 Th17	Conditional	Moderate	[743] [589] [742] [745] [744]
STAT3 Gain of Function	Ruxolitinib tofacitinib	Double negative T cells	Strong	Moderate	[447] [847] [748] [655] [847]
STAT4 Gain of Function	Ruxolitinib	IL-6	Conditional	Very low	[751]
STAT5b Gain of Function	Ruxolitinib	eosinophilia	Conditional	Low	[750]
SOCS1 deficiency	Baricitinib Tofacitinib	CXCL9	Strong	Low	[749]
Interferonopathies					
USP18 deficiency, SAVI, Aicardi-Goutières syndrome, CANDLE	Ruxolitinib Baricitinib Tofacitinib	Interferon activity	Strong	Low	[752] [756] [755] [753] [754]
SCID due to ADA deficiency					
ADA deficiency	Elepegademenase	Plasma ADA activity, ddNDP	Strong	High	[760] [761]
CVID with complications					
CTLA4 haploinsufficiency LRBA deficiency	Abatacept or belatacept (CTLA4-Ig)	$cT_{FH,}$ soluble CD25	Strong	Moderate	[763] [764]
Inflammasome related disorders					

CAPS (FCAS1, MWS, NOMID/CINCA; NLRP3)	anakinra rilonacept canakinumab	WBC (ANC), CRP, SAA, proteinuria	Strong	High	768
TRAPS (TNFRSF1A) FMF (MEFV) MKD (MVK)	canakinumab	WBC (ANC), CRP, SAA, proteinuria	Strong	High	769
DIRA (IL1RN)	anakinra rilonacept	CRP, SAA CRP, SAA	Strong	Moderate	785
PAPA syndrome (PSTPIP1) FCAS2 (NLRP12) Majeed syndrome (LPIN2)	anakinra canakinumab	CRP, SAA CRP, SAA	Conditional	Low	775 778 777 779
NOCARH (CDC42)	anakinra	CRP, SAA, ferritin	Conditional	Low	784
FCAS4 (NLRC4)	canakinumab	CRP, SAA, ferritin	Conditional	Low	783
Non-Syndromic Severe Congenital Neutropenia (SCN)					
SCN Type 1 SCN Type 2 SCN Type 3 SCN Type 4 XL Congenital Neutropenia, CXCR2 deficiency	G-CSF	ANC	Strong	High	786 787
Miscellaneous Syndromes that include Neutropenia					
Glycogen storage disease type IB Barth Syndrome Cartilage Hair Hypoplasia Pearson's Syndrome Schwachman-Diamond Syndrome Reticular dysgenesis CD40L deficiency BTK deficiency WHIM syndrome	G-CSF	ANC	Strong	High	788 796 727 793 794 790 791 577
IEI with SCN and hypopigmentation					
Chediak-Higashi Syndrome Hermansky-Pudlak	G-CSF	ANC	Strong	High	727 793

Syndrome type 2 Griscelli Syndrome type 2					
WHIM syndrome					
WHIM Syndrome	Plerixafor Mavorixafor	CBC	Strong	Moderate	794 795 796
Disorders of Vitamin B12 and Folate metabolism					
TCN2 deficiency	Cyanocobalamin Hydroxycobalamin	Vitamin B12 Folate	Strong	Low	797
SLC46A1 deficiency	High dose intravenous folinic acid				798 799
MTHFD1 deficiency, CblF LBMRD1	Hydroxycobalamin Folinic acid				800
Innate Immune disorders of Interferon gamma signaling					
IL-12 IL-23RB1 IL-12p40 IL-12RB2 deficiency AD partial IFN-gR1 or R2 deficiency STAT1 LOF IRF8 deficiency	IFN-gamma		Strong	Very low	803 804
IFN-g deficiency	IFN-gamma		Strong	Very low	805
Leukocyte Adhesion Disorder					
LAD-II	Fucose	CBC with differential	Strong	Low	806 807
Activate PI3K Delta Syndrome					
APDS1 APDS2	Leniolisib	IgM; Transitional B cells $CD8+_{TEMRA}$ $CD4+_{TEMRA}$ cells	Strong	High	809

*Biomarkers are recommended but are not included in the strength of recommendation and are only provided as a guide to therapeutic efficacy.

Table 13.2 FDA approved precision agents with applications in IEI

Therapy	Use in IEI	Adverse Events	Monitoring	Duration	Reference
JAK inhibitors	JAK/STAT GOF disorders, interferonopathies	Viral infections Cytopenias Liver enzyme elevations, elevated triglycerides	CBC w diff, liver panel, chem 10, viral PCR	Lifelong or until transplant	589
Elapega-demase	ADA deficiency SCID*	Medication interactions	Whole blood ADA level, CBC, lymphocyte subsets	Until transplant	762
Anakinra	NOMID*, DIRA*	injection site reactions, infection	CRP, ESR, SAA	Lifelong	766
Canakin-umab	FCAS*, MWS,* NOMID*, FMF, TRAPS, HIDS/MKD	injection site reactions, infection	CRP, ESR, SAA	Lifelong	766
Rilonacept	FCAS*/MWS*	injection site reactions, infection	CRP, ESR, SAA	Lifelong	785
Abatacept	CTLA4 haploinsufficiency LRBA deficiency	Live vaccines should not be given concurrently or within 3 months of discontinuation Do not give with TNF inhibitors	None	Lifelong	764
Plerixafor Mavorixafor	WHIM syndrome WHIM Syndrome*	Teratogenic	CBC CBC	Lifelong Lifelong	795 634
Cyanocobal amin Hydroxycob alamin	TCN2 deficiency	None	CBC, Vitamin B12 Folate	Lifelong	797
Folinic Acid	SLC46A1 deficiency MTHFD1 deficiency	None	CBC, Vitamin B12 Folate	Lifelong	798 800
Interferon gamma 1-b	CGD* and Immune disorders of Interferon signaling	Liver enzyme elevations Renal toxicity, fever	Liver enzymes Chem 10 CBC w diff	Lifelong or until transplant	811
Fucose	LAD II	None	CBC	Lifelong	808
Leniolisib	APDS*	Possible fetal harm Medication interactions	CBC Immunoglobulin	Lifelong	810

*FDA approved indication

Section 14- Quality of Life in IEI

RECOMMENDATION 14.1: **We recommend performing quality of life (QoL) measurements in patients with IEI, inclusive of patient reported outcome measurements (PRO) conducted with a validated tool.**

Strength of recommendation: **Strong**

Certainty of Evidence: **Moderate**

Patient-reported outcome (PRO) instruments are a means to capture health-related quality of life (HR-QoL) information as a measure of treatment benefits. This information comes directly from the patient, usually in the form of a questionnaire. In clinical trials, a PRO instrument can be used to measure the effect of a medical intervention on one or more *concepts* (i.e., the *thing* being measured, such as a symptom or group of symptoms, effects on a particular function or group of functions, or a group of symptoms or functions shown to measure the severity of a health condition). There are several variables (domains) in PRO instruments for measuring a person's physical health, psychological state, level of independence, social relationships, and their relationship to their environment's features. These domains in the survey instrument and the content, e.g., specific questions make the survey instrument unique for a disease category. An example is PROMIS® (Patient-Reported Outcomes Measurement Information System), a free instrument that can be used in adults and children (www.healthmeasures.net).

HR-QoL instruments are usually used in clinical trials to assess changes in the patient's perspective related to any treatment effect. QoL instruments can be global such as the 36 item Short Form survey (SF-36) while others are disease specific HR-QoL instruments such as the validated Primary Antibody Deficiency-Quality of Life (PAD-QoL)[812] and the Common Variable Immunodeficiency Quality of Life (CVID-QoL)[813] instruments. The latter instruments were developed to assess disease specific associated domains that may not be captured by generic QoL instruments. The CVID-QoL survey highlighted GI and skin issues, and levels of activity, pain and discomfort.[813]

Many patient-reported surveys have been published examining treatment satisfaction and the comparison between IVIG and SCIG replacement therapy in patients with IEI. Most surveys have used a generic HR-QoL instrument, e.g. the Medical Outcomes Study 36-item Short Form Health Survey (SF-36), a Life Quality Index and Treatment Satisfaction Question Survey. (**Table 14.1**) Several studies have shown more favorable patient QoL among patients receiving Ig therapy at home compared to hospital or infusion center-based IgRT particularly if the IgRT Is given subcutaneously (SC).[814-816] Patients reported greater convenience, comfort, and treatment schedule flexibility. Using the SF-36 general health questionnaire, and the Toronto Alexithymia Scale questionnaire, it was shown that the health status of adult patients with CVID was lower than those of normal subjects. Most patients (88%) were receiving IVIG every 2 or 3

weeks in a hospital setting. Overall, physical and general health scales correlated with lower clinical status, especially in females and older patients. Limitations in daily activities due to lower physical health was a major problem facing patients.[816] Using the SF-36 and the LQI instruments, patients showed significant improvement regardless of the form of administration of IgRT and preference for home SCIG infusions.[817] Prior to IgRT, CVID patients experienced diminished HR-QoL vs. the general population and a chronic disease control group.[818] The SF-36 and the General Health Questionnaire (GHQ-12) were used to show that almost 1/3 of CVID patients were at risk for anxiety and depression at all time points and affected two-thirds of females.[512] Over 6 years using the GHQ, patients perceived that their disease was getting worse over time which correlated with lower mean values of all SF-36 scales.

Using the PedsQL questionnaire, QoL was reduced in CGD patients receiving conservative management, while transplanted patients had QoL comparable to healthy children on PedsQL survey instrument.[819]

RECOMMENDATION *14.2:* We <u>suggest</u> that patient reported outcomes (PROs) should be measured using a disease-specific QoL instrument and at relevant important management changes in the patient's clinical journey.

Strength of Recommendation**: Conditional**

Certainty of Evidence**: Low**

Health-related QoL instruments may be disease specific and change temporally with respect to treatment interventions. Some IEI such as CVID,[820] Ataxia-Telangiectasia,[821] X-linked agammaglobulinemia,[822] and antibody deficiencies in general[823] have been studied with respect to patient HR-QoL. However, many distinct IEI have not; thus, it is possible that disease-specific HR-QoL patterns of measurement will be defined to optimize care and shared decision making. Future studies investigating HR-QoL for specific IEI are warranted.

Specific interventions and diagnostic elements of relevance may include HSCT, immunoglobulin route of delivery and time from symptom onset to diagnosis.[824, 825] In some cases, HSCT has been reported to improve HR-QoL;[824, 826] however, this is not universally noted across all studies.

Delays in IEI diagnosis are expected contributors to impaired HR-QoL. Explanations for this are incomplete; however, increased organ-specific impairment is a logical and reported consequence of undiagnosed IEI.[827] In addition, long-term follow up by expert clinicians improves QoL. Taken together, these and other reports suggest that early and precise diagnosis can improve QoL, which has been linked to improved survival among persons with IEI.[828] Co-occurrence of auto-inflammatory disease has also been related to low QoL in patients with IEI and should be captured over temporal periods of disease onset and/or treatment intervention.[829]

RECOMMENDATION 14.3: We <u>suggest</u> that IEI patients have perceived health assessed at each clinical encounter.

Strength of Recommendation: **Conditional**

Certainty of Evidence: **Low**

Perceived health (PH) status relates to the global sense of well-being by an individual which includes physical, mental and social well-being.[830] Typically, PH is measured on a 5-point scale as assessed by a single question ranging from poor to excellent and is both simple and inexpensive to measure. PH is an important measure owing to the close association with overall mortality as an independent factor in a variety of disease states.[831] Within the realm of IEI, determinants of PH have been studied and include sleep quality,[832] route of immunoglobulin replacement,[833] hematopoietic stem cell transplant status,[834] and cognitive status.[513]

RECOMMENDATION 14.4: We <u>suggest</u> that IEI patients be assessed for fatigue at each clinical encounter.

Strength of Recommendation**: Conditional**

Certainty of Evidence**: Low**

Patients with a primary antibody deficiency[517] and those with CVID[518] commonly report fatigue as a subjective concern. Additionally, pediatric patients with IEI suffer fatigue at rates ranging from approximately 19%-65%,[835] which appears to be unrelated to disease activity. Clear drivers of fatigue are not evident; however, the symptom is widely found among studies examining IEI QoL,[835, 836] and it may be a useful prognostic feature. Since the etiology of fatigue among persons with IEI is unclear, treatment is similarly not well defined: tailored exercise prescriptions,[837] optimization of IgRT,[838] and therapeutic options for subtypes and complications of IEI[839] offer opportunities for improving IEI-associated fatigue.

RECOMMENDATION 14.5: We <u>suggest</u> implementing shared decision making between the provider and the patient as part of clinical care to improve QoL and patient satisfaction.

Strength of Recommendation**: Conditional**

Certainty of Evidence**: Low**

Different routes of IgRT affect HR-QoL and patient reported outcomes. Many of the HR-QoL studies comparing IVIG with SCIG suggested the latter was more acceptable to patients and improved certain aspects of HR-QoL parameters. Pulvirenti and colleagues[840] addressed the impact of the route of IgRT on HR-QoL using shared decision making. The first 6 months of IgRT was devoted to the education and training of CVID patients that included possible choices of IgRT administration covering such items as setting (home or infusion center), route, interval, possible adverse reactions, and interference with lifestyle patterns or needs. Patients were allowed to shift to an

alternative regimen. There was no difference on the HR-QoL with each delivery method, indicating that extensive educational attention for the patients leading to shared decision-making and individualizing patient wishes achieve the best therapeutic approach.

Table 14.1. QoL Tools Used in IEI

Tool	Description	Reference
Short-form 36 (SF-36) version 2.0	Generic measure of health-related QoL with 8 domains. Not specific for any disease or population.	828
Child Health Questionnaire Parent Form 50 (CHQ-PF50)	Generic measure of health-related QoL with 15 domains. Specifically designed for children 5-13 years of age.	817
Pediatric quality of Life Inventory (PedsQL 4.0)	23 item instrument for children ages 2 to 18. Scales are multidimensional for child self-report and parent proxy-report scales for healthy and acute and chronic health conditions.	819
Life Quality Index (LQI)	Measure of treatment preferences relative to enhancement of life with 4 domains. Developed for IEI patients receiving IgG.	817
General Health Questionnaire (GHQ-12)	12-item questionnaire designed to measure psychological stress and to detect depression and anxiety.	828
Treatment Satisfaction Questionnaire for Medication (TSQM)	Generic measure of treatment satisfaction with 4 domains.	838
PROMIS-29	Assess fatigue in patients with CVID	838
CVID-QoL	32 item validated HR-QOL instrument for adult patients with CVID	813
PADQOL-16	16 item validated HR-QOL instrument for adult patients with primary antibody deficiency.	812

REFERENCES

1. Shearer WT, Buckley RH, Engler RJ, Finn AF, Jr., Fleisher TA, Freeman TM, et al. Practice parameters for the diagnosis and management of immunodeficiency. The Clinical and Laboratory Immunology Committee of the American Academy of Allergy, Asthma, and Immunology (CLIC-AAAAI). Ann Allergy Asthma Immunol 1996;76:282-94
2. Bonilla FA, Bernstein IL, Khan DA, Ballas ZK, Chinen J, Frank MM, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol 2005;94:S1-63
3. Bonilla FA, Khan DA, Ballas ZK, Chinen J, Frank MM, Hsu JT, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol 2015;136:1186-205.e1-78
4. Zuraw BL, Bernstein JA, Lang DM, Craig T, Dreyfus D, Hsieh F, et al. A focused parameter update: hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor-associated angioedema. J Allergy Clin Immunol 2013;131:1491-3
5. Chu DK, Golden DBK, Guyatt GH. Translating evidence to optimize patient care using GRADE. J Allergy Clin Immunol Pract. 2021; 9: 4221-4230
6. Dykewicz MS, Wallace DV, Amrol DJ, Baroody FM, Bernstein JA, Craig TJ, et al. Rhinitis 2020: A practice parameter update. J Allergy Clin Immunol 2020;146:721-767
7. Poli MC, Aksentijevich I, Bousfiha A, Cunningham-Rundles C, Hambleton S, et al. Human inborn errors of immunity: 2024 update on the classification from the International Union of Immunological Societies Expert Committee. Available from URL https://iuis.org/committees/iei/. Accessed November 15, 2024
8. Thalhammer J, Kindle G, Nieters A, Rusch S, Seppänen MRJ, Fischer A, et al. Initial presenting manifestations in 16,486 patients with inborn errors of immunity include infections and noninfectious manifestations. J Allergy Clin Immunol 2021;148:1332-1341.e5
9. Carneiro-Sampaio M and Coutinho A. Early-onset autoimmune disease as a manifestation of primary immunodeficiency. Front Immunol 2015;6:185
10. Fischer A, Provot J, Jais JP, Alcais A and Mahlaoui N. Autoimmune and inflammatory manifestations occur frequently in patients with primary immunodeficiencies. J Allergy Clin Immunol 2017;140:1388-1393.e8
11. Kačar M, Markelj G and Avčin T. Autoimmune and autoinflammatory manifestations in inborn errors of immunity. Curr Opin Allergy Clin Immunol 2022;22:343-351
12. Sacco KA, Gazzin A, Notarangelo LD and Delmonte OM. Granulomatous inflammation in inborn errors of immunity. Front Pediatr 2023;11:1110115
13. Azabdaftari A, Jones KDJ, Kammermeier J and Uhlig HH. Monogenic inflammatory bowel disease-genetic variants, functional mechanisms and personalised medicine in clinical practice. Hum Genet 2023;142:599-611
14. Uhlig HH, Charbit-Henrion F, Kotlarz D, Shouval DS, Schwerd T, Strisciuglio C, et al. Clinical Genomics for the Diagnosis of Monogenic Forms of Inflammatory Bowel Disease: A Position Paper From the Paediatric IBD Porto Group of European Society of

Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2021;72:456-473
15. Nelson RW, Geha RS and McDonald DR. Inborn Errors of the Immune System Associated With Atopy. Front Immunol 2022;13:860821
16. Vaseghi-Shanjani M, Snow AL, Margolis DJ, Latrous M, Milner JD, Turvey SE, et al. Atopy as Immune Dysregulation: Offender Genes and Targets. J Allergy Clin Immunol Pract 2022;10:1737-1756
17. Bousfiha A, Moundir A, Tangye SG, Picard C, Jeddane L, Al-Herz W, et al. The 2022 Update of IUIS Phenotypical Classification for Human Inborn Errors of Immunity. J Clin Immunol 2022;42:1508-1520
18. Kido T, Hosaka S, Imagawa K, Fukushima H, Morio T, Nonoyama S, et al. Initial manifestations in Patients with Inborn Errors of Immunity Based on Onset Age: a Study from a Nationwide Survey in Japan. J Clin Immunol 2023;43:747-755
19. Abraham RS and Butte MJ. The New "Wholly Trinity" in the Diagnosis and Management of Inborn Errors of Immunity. J Allergy Clin Immunol Pract 2021;9:613-625
20. Khan YW, Minnicozzi SC and Lawrence MG. Navigating diagnostic options for inborn errors of immunity in children: a case-based illustration. Curr Opin Pediatr 2022;34:589-594
21. Ma CS, Tangye AF and Fleisher TA. Inborn Errors of Immunity: A Role for Functional Testing and Flow Cytometry in Aiding Clinical Diagnosis. J Allergy Clin Immunol Pract 2023;11:1579-1591
22. Patel SY, Carbone J and Jolles S. The Expanding Field of Secondary Antibody Deficiency: Causes, Diagnosis, and Management. Front Immunol 2019;10:33
23. Tuano KS, Seth N and Chinen J. Secondary immunodeficiencies: An overview. Ann Allergy Asthma Immunol 2021;127:617-626
24. Bustamante-Marin XM and Ostrowski LE. Cilia and Mucociliary Clearance. Cold Spring Harb Perspect Biol 2017;9
25. Ponsford MJ, Steven R, Bramhall K, Burgess M, Wijellileka S, Carne E, et al. Clinical and laboratory characteristics of clozapine-treated patients with schizophrenia referred to a national immunodeficiency clinic reveals a B-cell signature resembling common variable immunodeficiency (CVID) J Clin Pathol. 2020; 73: 587-592
26. Knight AK, Cunninham-Rundles. Oxcarbazepine-induced immunoglobulin deficiency. Clin Digan Lab Immunol. 2005; 12: 560-561
27. Zhang H, Weyand CM and Goronzy JJ. Hallmarks of the aging T-cell system. FEBS J. 2021;288:7123-7142
28. Teissier T, Boulanger E, Cox LS. Interconnections between inflammageing and immunosenescence during ageing. Cells. 2022; 11:359
29. Lawrence SM, Corriden R and Nizet V. Age-Appropriate Functions and Dysfunctions of the Neonatal Neutrophil. Front Pediatr 2017;5:23
30. Rudd BD. Neonatal T Cells: A Reinterpretation. Annu Rev Immunol 2020;38:229-247
31. Levy O, Martin S, Eichenwald E, Ganz T, Valore E, Carroll SF, et al. Impaired innate immunity in the newborn: newborn neutrophils are deficient in bactericidal/permeability-increasing protein. Pediatrics 1999;104:1327-33
32. Sadighi Akha AA and Kumánovics A. Anti-cytokine autoantibodies and inborn errors of immunity. J Immunol Methods 2022;508:113313

33. Knight V. Immunodeficiency and Autoantibodies to Cytokines. J Appl Lab Med 2022;7:151-164
34. Cheng A and Holland SM. Anti-cytokine autoantibodies: mechanistic insights and disease associations. Nat Rev Immunol 2024;24:161-177
35. Burbelo PD, Browne SK, Sampaio EP, Giaccone G, Zaman R, Kristosturyan E, et al. Anti-cytokine autoantibodies are associated with opportunistic infection in patients with thymic neoplasia. Blood 2010;116:4848-58
36. Lehman H, Hernandez-Trujillo V and Ballow M. Diagnosing primary immunodeficiency: a practical approach for the non-immunologist. Curr Med Res Opin 2015;31:697-706
37. O'Keefe AW, Halbrich M, Ben-Shoshan M and McCusker C. Primary immunodeficiency for the primary care provider. Paediatr Child Health 2016;21:e10-4
38. Orange JS, Seeborg FO, Boyle M, Scalchunes C and Hernandez-Trujillo V. Family Physician Perspectives on Primary Immunodeficiency Diseases. Front Med (Lausanne) 2016;3:12
39. Routes J, Abinun M, Al-Herz W, Bustamante J, Condino-Neto A, De La Morena MT, et al. ICON: the early diagnosis of congenital immunodeficiencies. J Clin Immunol 2014;34:398-424
40. Stirling RG. Primary immunodeficiency: a call for multidisciplinary care. Lancet 2008;372:1877-1878
41. Yeung CH, Santesso N, Zeraatkar D, Wang A, Pai M, Sholzberg M, et al. Integrated multidisciplinary care for the management of chronic conditions in adults: an overview of reviews and an example of using indirect evidence to inform clinical practice recommendations in the field of rare diseases. Haemophilia 2016;22 Suppl 3:41-50
42. Ward AJ, Murphy D, Marron R, McGrath V, Bolz-Johnson M, Cullen W, et al. Designing rare disease care pathways in the Republic of Ireland: a co-operative model. Orphanet J Rare Dis 2022;17:162
43. Wren AA and Maddux MH. Integrated Multidisciplinary Treatment for Pediatric Inflammatory Bowel Disease. Children (Basel) 2021;8
44. Meneses Z, Durant J and Ale H. The Unique Experience of a New Multidisciplinary Program for 22q Deletion and Duplication Syndromes in a Community Hospital in Florida: A Reaffirmation That Multidisciplinary Care Is Essential for Best Outcomes in These Patients. Genes (Basel) 2022;13
46. Fasshauer M, Schuermann G, Gebert N, Bernuth HV, Bullinger M, Goldacker S, et al. A patient empowerment program for primary immunodeficiency improves quality of life in children and adolescents. Immunotherapy 2024;16:813-819
47. Heath J, Lehman E, Saunders EF and Craig T. Anxiety and depression in adults with primary immunodeficiency: How much do these patients experience and how much do they attribute to their primary immunodeficiency? Allergy Asthma Proc 2016;37:409-15
48. Kaplan Sarıkavak S, Sarıkavak T, Türkyılmaz Uçar Ö, Aydoğmuş Ç and Celiksoy MH. Life quality, depression, and anxiety levels in parents of children with primary immunodeficiency. Pediatr Allergy Immunol 2024;35:e14068
49. Blom M, Bredius RGM, Jansen ME, Weijman G, Kemper EA, Vermont CL, et al. Parents' Perspectives and Societal Acceptance of Implementation of Newborn Screening for SCID in the Netherlands. J Clin Immunol 2021;41:99-108

50. Raspa M, Lynch M, Squiers L, Gwaltney A, Porter K, Peay H, et al. Information and Emotional Support Needs of Families Whose Infant Was Diagnosed With SCID Through Newborn Screening. Front Immunol 2020;11:885
51. Raspa M, Kutsa O, Andrews SM, Gwaltney AY, Mallonee E, Creamer A, et al. Uncertainties experienced by parents of children diagnosed with severe combined immunodeficiency through newborn screening. Eur J Hum Genet 2024;32:392-398
52. Puck JM. Laboratory technology for population-based screening for severe combined immunodeficiency in neonates: the winner is T-cell receptor excision circles. J Allergy Clin Immunol 2012;129:607-16
53. Verbsky J, Thakar M and Routes J. The Wisconsin approach to newborn screening for severe combined immunodeficiency. J Allergy Clin Immunol 2012;129:622-7
54. Chan K, Davis J, Pai SY, Bonilla FA, Puck JM and Apkon M. A Markov model to analyze cost-effectiveness of screening for severe combined immunodeficiency (SCID). Mol Genet Metab 2011;104:383-9
55. McGhee SA, Stiehm ER and McCabe ER. Potential costs and benefits of newborn screening for severe combined immunodeficiency. J Pediatr 2005;147:603-8
56. Kubiak C, Jyonouchi S, Kuo C, Garcia-Lloret M, Dorsey MJ, Sleasman J, et al. Fiscal implications of newborn screening in the diagnosis of severe combined immunodeficiency. J Allergy Clin Immunol Pract 2014;2:697-702
57. Puck JM, Routes J, Filipovich AH and Sullivan K. Expert commentary: practical issues in newborn screening for severe combined immune deficiency (SCID). J Clin Immunol 2012;32:36-8
58. Kwan A, Abraham RS, Currier R, Brower A, Andruszewski K, Abbott JK, et al. Newborn screening for severe combined immunodeficiency in 11 screening programs in the United States. Jama 2014;312:729-38
59. Heimall J, Logan BR, Cowan MJ, Notarangelo LD, Griffith LM, Puck JM, et al. Immune reconstitution and survival of 100 SCID patients post-hematopoietic cell transplant: a PIDTC natural history study. Blood 2017;130:2718-2727
60. Thakar MS, Logan BR, Puck JM, Dunn EA, Buckley RH, Cowan MJ, et al. Measuring the effect of newborn screening on survival after haematopoietic cell transplantation for severe combined immunodeficiency: a 36-year longitudinal study from the Primary Immune Deficiency Treatment Consortium. Lancet 2023;402:129-140
61. Blom M, Zetterström RH, Stray-Pedersen A, Gilmour K, Gennery AR, Puck JM, et al. Recommendations for uniform definitions used in newborn screening for severe combined immunodeficiency. J Allergy Clin Immunol 2022;149:1428-1436
62. Rota IA and Dhalla F. FOXN1 deficient nude severe combined immunodeficiency. Orphanet J Rare Dis 2017;12:6
63. Collins C, Sharpe E, Silber A, Kulke S and Hsieh EWY. Congenital Athymia: Genetic Etiologies, Clinical Manifestations, Diagnosis, and Treatment. J Clin Immunol 2021;41:881-895
64. Mallott J, Kwan A, Church J, Gonzalez-Espinosa D, Lorey F, Tang LF, et al. Newborn screening for SCID identifies patients with ataxia telangiectasia. J Clin Immunol 2013;33:540-9
65. Barry JC, Crowley TB, Jyonouchi S, Heimall J, Zackai EH, Sullivan KE, et al. Identification of 22q11.2 Deletion Syndrome via Newborn Screening for Severe Combined Immunodeficiency. J Clin Immunol 2017;37:476-485

66. Damoiseaux M, Damoiseaux J, Pico-Knijnenburg I, van der Burg M, Bredius R and van Well G. Lessons learned from the diagnostic work-up of a patient with the bare lymphocyte syndrome type II. Clin Immunol 2022;235:108932
67. Kahwash BM, Yonkof JR, Abraham RS, Mustillo PJ, Abu-Arja R, Rangarajan HG, et al. Delayed-Onset ADA1 (ADA) Deficiency Not Detected by TREC Screen. Pediatrics 2021;147
68. la Marca G, Giocaliere E, Malvagia S, Funghini S, Ombrone D, Della Bona ML, et al. The inclusion of ADA-SCID in expanded newborn screening by tandem mass spectrometry. J Pharm Biomed Anal 2014;88:201-6
69. Hiroki H, Moriya K, Uchiyama T, hirose F, Endo A, Sato I, et al. A high-throughput TREC- and KREC-based newborn screening for severe inborn errors of immunity. Pediatr Int. 2025; 67:e15872
70. Borte S, Wang N, Oskarsdóttir S, von Döbeln U and Hammarström L. Newborn screening for primary immunodeficiencies: beyond SCID and XLA. Ann N Y Acad Sci 2011;1246:118-30
71. King JR, Grill K and Hammarström L. Genomic-Based Newborn Screening for Inborn Errors of Immunity: Practical and Ethical Considerations. Int J Neonatal Screen 2023;9
72. Kingsmore SF, Smith LD, Kunard CM, Bainbridge M, Batalov S, Benson W, et al. A genome sequencing system for universal newborn screening, diagnosis, and precision medicine for severe genetic diseases. Am J Hum Genet 2022;109:1605-1619
73. Amatuni GS, Currier RJ, Church JA, Bishop T, Grimbacher E, Nguyen AA, et al. Newborn Screening for Severe Combined Immunodeficiency and T-cell Lymphopenia in California, 2010-2017. Pediatrics 2019;143
74. Knight V, Heimall JR, Wright N, Dutmer CM, Boyce TG, Torgerson TR, et al. Follow-Up for an Abnormal Newborn Screen for Severe Combined Immunodeficiencies (NBS SCID): A Clinical Immunology Society (CIS) Survey of Current Practices. Int J Neonatal Screen 2020;6
75. Blom M, Bredius RGM and van der Burg M. Efficient screening strategies for severe combined immunodeficiencies in newborns. Expert Rev Mol Diagn 2023;23:815-825
76. Dvorak CC, Haddad E, Heimall J, Dunn E, Buckley RH, Kohn DB, et al. The diagnosis of severe combined immunodeficiency (SCID): The Primary Immune Deficiency Treatment Consortium (PIDTC) 2022 Definitions. J Allergy Clin Immunol 2023;151:539-546
77. Dorsey MJ, Wright NAM, Chaimowitz NS, Dávila Saldaña BJ, Miller H, Keller MD, et al. Infections in Infants with SCID: Isolation, Infection Screening, and Prophylaxis in PIDTC Centers. J Clin Immunol 2021;41:38-50
78. Kubala SA, Sandhu A, Palacios-Kibler T, Ward B, Harmon G, DeFelice ML, et al. Natural history of infants with non-SCID T cell lymphopenia identified on newborn screen. Clin Immunol 2022;245:109182
79. Frazer LC and O'Connell AE. Primary immunodeficiency testing in a Massachusetts tertiary care NICU: persistent challenges in the extremely premature population. Pediatr Res 2021;89:549-553
80. Carol HA, Ochfeld EN and Ahmed A. In-utero exposure to immunosuppressive medications resulting in abnormal newborn screening for severe combined immunodeficiency: a case series on natural history and management. Immunol Res 2022;70:561-56

81. Cuvelier GDE, Logan BR, Prockop SE, Buckley RH, Kuo CY, Griffith LM, et al. Outcomes following treatment for ADA-deficient severe combined immunodeficiency: a report from the PIDTC. Blood 2022;140:685-705
82. Pai SY, Logan BR, Griffith LM, Buckley RH, Parrott RE, Dvorak CC, et al. Transplantation outcomes for severe combined immunodeficiency, 2000-2009. N Engl J Med 2014;371:434-46
83. Markert ML, Gupton SE and McCarthy EA. Experience with cultured thymus tissue in 105 children. J Allergy Clin Immunol 2022;149:747-757
84. Kutsa O, Gwaltney A, Creamer A and Raspa M. Severe Combined Immunodeficiency: Knowledge and Information Needs Among Healthcare Providers. Front Pediatr 2022;10:804709
85. Dergousoff BA, Vayalumkal JV and Wright NAM. Survey of Infection Control Precautions for Patients with Severe Combined Immune Deficiency. J Clin Immunol 2019;39:753-761
86. Hernandez-Alvarado N, Shanley R, Schleiss MR, Ericksen J, Wassenaar J, Webo L, et al. Clinical, Virologic and Immunologic Correlates of Breast Milk Acquired Cytomegalovirus (CMV) Infections in Very Low Birth Weight (VLBW) Infants in a Newborn Intensive Care Unit (NICU) Setting. Viruses 2021;13
87. Shearer WT, Fleisher TA, Buckley RH, Ballas Z, Ballow M, Blaese RM, et al. Recommendations for live viral and bacterial vaccines in immunodeficient patients and their close contacts. J Allergy Clin Immunol 2014;133:961-6
88. Bakare N, Menschik D, Tiernan R, Hua W and Martin D. Severe combined immunodeficiency (SCID) and rotavirus vaccination: reports to the Vaccine Adverse Events Reporting System (VAERS). Vaccine 2010;28:6609-12
89. Thorsen J, Kolbert K, Joshi A, Baker M and Seroogy CM. Newborn Screening for Severe Combined Immunodeficiency: 10-Year Experience at a Single Referral Center (2009-2018). J Clin Immunol 2021;41:595-602
90. Stray-Pedersen A, Sorte HS, Samarakoon P, Gambin T, Chinn IK, Coban Akdemir ZH, et al. Primary immunodeficiency diseases: Genomic approaches delineate heterogeneous Mendelian disorders. J Allergy Clin Immunol 2017;139:232-245
91. Sanger F, Nicklen S and Coulson AR. DNA sequencing with chain-terminating inhibitors. Proc Natl Acad Sci U S A 1977;74:5463-7
92. Beck TF, Mullikin JC and Biesecker LG. Systematic Evaluation of Sanger Validation of Next-Generation Sequencing Variants. Clin Chem 2016;62:647-54
93. Strom SP, Lee H, Das K, Vilain E, Nelson SF, Grody WW, et al. Assessing the necessity of confirmatory testing for exome-sequencing results in a clinical molecular diagnostic laboratory. Genet Med 2014;16:510-5
94. Baudhuin LM, Lagerstedt SA, Klee EW, Fadra N, Oglesbee D and Ferber MJ. Confirming Variants in Next-Generation Sequencing Panel Testing by Sanger Sequencing. J Mol Diagn 2015;17:456-61
95. Fridman H, Bormans C, Einhorn M, Au D, Bormans A, Porat Y, et al. Performance comparison: exome sequencing as a single test replacing Sanger sequencing. Mol Genet Genomics 2021;296:653-663
96. Arteche-López A, Ávila-Fernández A, Romero R, Riveiro-Álvarez R, López-Martínez MA, Giménez-Pardo A, et al. Sanger sequencing is no longer always necessary based on

a single-center validation of 1109 NGS variants in 825 clinical exomes. Sci Rep 2021;11:5697
97. Mandelker D, Schmidt RJ, Ankala A, McDonald Gibson K, Bowser M, Sharma H, et al. Navigating highly homologous genes in a molecular diagnostic setting: a resource for clinical next-generation sequencing. Genet Med 2016;18:1282-1289
98. Dowdell KC, Niemela JE, Price S, Davis J, Hornung RL, Oliveira JB, et al. Somatic FAS mutations are common in patients with genetically undefined autoimmune lymphoproliferative syndrome. Blood 2010;115:5164-9
99. Tanaka N, Izawa K, Saito MK, Sakuma M, Oshima K, Ohara O, et al. High incidence of NLRP3 somatic mosaicism in patients with chronic infantile neurologic, cutaneous, articular syndrome: results of an International Multicenter Collaborative Study. Arthritis Rheum 2011;63:3625-32
100. Rohlin A, Wernersson J, Engwall Y, Wiklund L, Björk J and Nordling M. Parallel sequencing used in detection of mosaic mutations: comparison with four diagnostic DNA screening techniques. Hum Mutat 2009;30:1012-20
101. Aluri J and Cooper MA. Genetic Mosaicism as a Cause of Inborn Errors of Immunity. J Clin Immunol 2021;41:718-728
102. Chinn IK and Orange JS. A 2020 update on the use of genetic testing for patients with primary immunodeficiency. Expert Rev Clin Immunol 2020;16:897-909
103. Heimall JR, Hagin D, Hajjar J, Henrickson SE, Hernandez-Trujillo HS, Tan Y, et al. Use of Genetic Testing for Primary Immunodeficiency Patients. J Clin Immunol 2018;38:320-329
104. Chinn IK, Chan AY, Chen K, Chou J, Dorsey MJ, Hajjar J, et al. Diagnostic interpretation of genetic studies in patients with primary immunodeficiency diseases: A working group report of the Primary Immunodeficiency Diseases Committee of the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol 2020;145:46-69
105. Yoon S, Xuan Z, Makarov V, Ye K and Sebat J. Sensitive and accurate detection of copy number variants using read depth of coverage. Genome Res 2009;19:1586-92
106. Singh AK, Olsen MF, Lavik LAS, Vold T, Drabløs F and Sjursen W. Detecting copy number variation in next generation sequencing data from diagnostic gene panels. BMC Med Genomics 2021;14:214
107. Quenez O, Cassinari K, Coutant S, Lecoquierre F, Le Guennec K, Rousseau S, et al. Detection of copy-number variations from NGS data using read depth information: a diagnostic performance evaluation. Eur J Hum Genet 2021;29:99-109
108. Platt CD, Zaman F, Bainter W, Stafstrom K, Almutairi A, Reigle M, et al. Efficacy and economics of targeted panel versus whole-exome sequencing in 878 patients with suspected primary immunodeficiency. J Allergy Clin Immunol 2021;147:723-726
109. Rudilla F, Franco-Jarava C, Martínez-Gallo M, Garcia-Prat M, Martín-Nalda A, Rivière J, et al. Expanding the Clinical and Genetic Spectra of Primary Immunodeficiency-Related Disorders With Clinical Exome Sequencing: Expected and Unexpected Findings. Front Immunol 2019;10:2325
110. Thaventhiran JED, Lango Allen H, Burren OS, Rae W, Greene D, Staples E, et al. Whole-genome sequencing of a sporadic primary immunodeficiency cohort. Nature 2020;583:90-95

111. Hagl B, Spielberger BD, Thoene S, Bonnal S, Mertes C, Winter C, et al. Somatic alterations compromised molecular diagnosis of DOCK8 hyper-IgE syndrome caused by a novel intronic splice site mutation. Sci Rep 2018;8:16719
112. Austin-Tse CA, Jobanputra V, Perry DL, Bick D, Taft RJ, Venner E, et al. Best practices for the interpretation and reporting of clinical whole genome sequencing. NPJ Genom Med 2022;7:27
113. Ewans LJ, Minoche AE, Schofield D, Shrestha R, Puttick C, Zhu Y, et al. Whole exome and genome sequencing in mendelian disorders: a diagnostic and health economic analysis. Eur J Hum Genet 2022;30:1121-1131
114. Vorsteveld EE, Hoischen A and van der Made CI. Next-Generation Sequencing in the Field of Primary Immunodeficiencies: Current Yield, Challenges, and Future Perspectives. Clin Rev Allergy Immunol 2021;61:212-225
115. Wan R, Schieck M, Caballero-Oteyza A, Hofmann W, Cochino AV, Shcherbina A, et al. Copy Number Analysis in a Large Cohort Suggestive of Inborn Errors of Immunity Indicates a Wide Spectrum of Relevant Chromosomal Losses and Gains. J Clin Immunol 2022;42:1083-1092
116. Similuk MN, Yan J, Ghosh R, Oler AJ, Franco LM, Setzer MR, et al. Clinical exome sequencing of 1000 families with complex immune phenotypes: Toward comprehensive genomic evaluations. J Allergy Clin Immunol 2022;150:947-954
117. Redon R, Ishikawa S, Fitch KR, Feuk L, Perry GH, Andrews TD, et al. Global variation in copy number in the human genome. Nature 2006;444:444-54
118. Cooper GM, Coe BP, Girirajan S, Rosenfeld JA, Vu TH, Baker C, et al. A copy number variation morbidity map of developmental delay. Nat Genet 2011;43:838-46
119. Bayani J and Squire JA. Traditional banding of chromosomes for cytogenetic analysis. Curr Protoc Cell Biol 2004;Chapter 22:Unit 22.3
120. Kearney HM, South ST, Wolff DJ, Lamb A, Hamosh A and Rao KW. American College of Medical Genetics recommendations for the design and performance expectations for clinical genomic copy number microarrays intended for use in the postnatal setting for detection of constitutional abnormalities. Genet Med 2011;13:676-9
121. Marchuk DS, Crooks K, Strande N, Kaiser-Rogers K, Milko LV, Brandt A, et al. Increasing the diagnostic yield of exome sequencing by copy number variant analysis. PLoS One 2018;13:e0209185
122. Retterer K, Scuffins J, Schmidt D, Lewis R, Pineda-Alvarez D, Stafford A, et al. Assessing copy number from exome sequencing and exome array CGH based on CNV spectrum in a large clinical cohort. Genet Med 2015;17:623-9
123. Riggs ER, Andersen EF, Cherry AM, Kantarci S, Kearney H, Patel A, et al. Technical standards for the interpretation and reporting of constitutional copy-number variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics (ACMG) and the Clinical Genome Resource (ClinGen). Genet Med 2020;22:245-257
124. Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet 2010;86:749-64
125. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation

of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17:405-24
126. Harrison SM, Biesecker LG and Rehm HL. Overview of Specifications to the ACMG/AMP Variant Interpretation Guidelines. Curr Protoc Hum Genet 2019;103:e93
127. Ross JE, Zhang BM, Lee K, Mohan S, Branchford BR, Bray P, et al. Specifications of the variant curation guidelines for ITGA2B/ITGB3: ClinGen Platelet Disorder Variant Curation Panel. Blood Adv 2021;5:414-431
128. Rehm HL, Berg JS, Brooks LD, Bustamante CD, Evans JP, Landrum MJ, et al. ClinGen--the Clinical Genome Resource. N Engl J Med 2015;372:2235-42
129. Giles HH, Hegde MR, Lyon E, Stanley CM, Kerr ID, Garlapow ME, et al. The Science and Art of Clinical Genetic Variant Classification and Its Impact on Test Accuracy. Annu Rev Genomics Hum Genet 2021;22:285-307
130. Fagan TJ. Letter: Nomogram for Bayes's theorem. N Engl J Med 1975;293:257
131. Delavari S, Rasouli SE, Fekrvand S, Chavoshzade Z, Mahdaviani SA, Shirmast P, et al. Clinical heterogeneity in families with multiple cases of inborn errors of immunity. Clin Immunol 2024;259:109896
132. Takada H, Kanegane H, Nomura A, Yamamoto K, Ihara K, Takahashi Y, et al. Female agammaglobulinemia due to the Bruton tyrosine kinase deficiency caused by extremely skewed X-chromosome inactivation. Blood 2004;103:185-7
133. de Saint Basile G, Tabone MD, Durandy A, Phan F, Fischer A and Le Deist F. CD40 ligand expression deficiency in a female carrier of the X-linked hyper-IgM syndrome as a result of X chromosome lyonization. Eur J Immunol 1999;29:367-73
134. Anderson-Cohen M, Holland SM, Kuhns DB, Fleisher TA, Ding L, Brenner S, et al. Severe phenotype of chronic granulomatous disease presenting in a female with a de novo mutation in gp91-phox and a non familial, extremely skewed X chromosome inactivation. Clin Immunol 2003;109:308-17
135. Mou W, Zhao Z, Gao L, Fu L, Li J, Jiao A, et al. An Atypical Incontinentia Pigmenti Female with Persistent Mucocutaneous Hyperinflammation and Immunodeficiency Caused by a Novel Germline IKBKG Missense Mutation. J Clin Immunol 2023;43:2165-2180
136. Russell SJ and Nisen PD. Random X chromosome inactivation in a female with a variant of Wiskott-Aldrich syndrome. Br J Haematol 1995;90:210-2
137. Patel NC, Younger MEM, Williams K, Matias Lopes JP, Kuhns DB, Patel MN, et al. Severe clinical phenotypes of heterozygous females with X-linked chronic granulomatous disease. J Allergy Clin Immunol Pract. 2024; 12: 3452-3456
138. Miranda MA, Tsalatsanis A, Trotter JR, Arnold DE, Squire JD, Kidd S, et al. High symptom burden in female X-linked chronic granulomatous disease carriers. Clin Immunol. 2024; 268: 110364
139. Schwab C, Gabrysch A, Olbrich P, Patiño V, Warnatz K, Wolff D, et al. Phenotype, penetrance, and treatment of 133 cytotoxic T-lymphocyte antigen 4-insufficient subjects. J Allergy Clin Immunol. 2018;142:1932-1946.
140. Stewart O, Gruber C, Randolph HE, Patel R, Ramba M, Calzoni E, et al. Monoallelic expression can govern penetrance of inborn errors of immunity. Nature. 2025;637:1186-1197.

141. Davidson HR, Jamal L, Mueller R, Similuk M and Owczarzak J. Renegotiation, uncertainty, imagination: Assemblage perspectives on reproductive and family planning with an Inborn Error of immunity. Soc Sci Med 2024;360:117303.
142. Posey JE, Harel T, Liu P, Rosenfeld JA, James RA, Coban Akdemir ZH, et al. Resolution of Disease Phenotypes Resulting from Multilocus Genomic Variation. N Engl J Med. 2017;376:21-31.
143. Yang Y, Muzny DM, Xia F, Niu Z, Person R, Ding Y, et al. Molecular findings among patients referred for clinical whole-exome sequencing. JAMA. 2014;312:1870-9.
144. Lee TK, Gereige JD and Maglione PJ. State-of-the-art diagnostic evaluation of common variable immunodeficiency. Ann Allergy Asthma Immunol 2021;127:19-27
145. Bonilla FA, Barlan I, Chapel H, Costa-Carvalho BT, Cunningham-Rundles C, de la Morena MT, et al. International Consensus Document (ICON): Common Variable Immunodeficiency Disorders. J Allergy Clin Immunol Pract 2016;4:38-59
146. Seidel MG, Kindle G, Gathmann B, Quinti I, Buckland M, van Montfrans J, et al. The European Society for Immunodeficiencies (ESID) Registry Working Definitions for the Clinical Diagnosis of Inborn Errors of Immunity. J Allergy Clin Immunol Pract 2019;7:1763-1770.
147. Otani IM, Lehman HK, Jongco AM, Tsao LR, Azar AE, Tarrant TK, et al. Practical guidance for the diagnosis and management of secondary hypogammaglobulinemia: A Work Group Report of the AAAAI Primary Immunodeficiency and Altered Immune Response Committees. J Allergy Clin Immunol 2022;149:1525-1560.
148. Rai T, Wu X and Shen B. Frequency and risk factors of low immunoglobulin levels in patients with inflammatory bowel disease. Gastroenterol Rep (Oxf) 2015;3:115-21.
149. Barmettler S, DiGiacomo DV, Yang NJ, Lam T, Naranbhai V, Dighe AS, et al. Response to Severe Acute Respiratory Syndrome Coronavirus 2 Initial Series and Additional Dose Vaccine in Patients With Predominant Antibody Deficiency. J Allergy Clin Immunol Pract 2022;10:1622-1634.
150. Warnatz K, Denz A, Dräger R, Braun M, Groth C, Wolff-Vorbeck G, et al. Severe deficiency of switched memory B cells (CD27(+)IgM(-)IgD(-)) in subgroups of patients with common variable immunodeficiency: a new approach to classify a heterogeneous disease. Blood 2002;99:1544-51
151. Resnick ES, Moshier EL, Godbold JH and Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. Blood 2012;119:1650-7
152. Farmer JR, Ong MS, Barmettler S, Yonker LM, Fuleihan R, Sullivan KE, et al. Common Variable Immunodeficiency Non-Infectious Disease Endotypes Redefined Using Unbiased Network Clustering in Large Electronic Datasets. Front Immunol 2017;8:1740
153. Gathmann B, Mahlaoui N, Gérard L, Oksenhendler E, Warnatz K, Schulze I, et al. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. J Allergy Clin Immunol 2014;134:116-26
154. Bateman EA, Ayers L, Sadler R, Lucas M, Roberts C, Woods A, et al. T cell phenotypes in patients with common variable immunodeficiency disorders: associations with clinical phenotypes in comparison with other groups with recurrent infections. Clin Exp Immunol 2012;170:202-11
155. Genre J, Errante PR, Kokron CM, Toledo-Barros M, Câmara NO and Rizzo LV. Reduced frequency of CD4(+)CD25(HIGH)FOXP3(+) cells and diminished FOXP3 expression in

patients with Common Variable Immunodeficiency: a link to autoimmunity? Clin Immunol 2009;132:215-21
156. Kuehn HS, Ouyang W, Lo B, Deenick EK, Niemela JE, Avery DT, et al. Immune dysregulation in human subjects with heterozygous germline mutations in CTLA4. Science 2014;345:1623-1627
157. Schubert D, Bode C, Kenefeck R, Hou TZ, Wing JB, Kennedy A, et al. Autosomal dominant immune dysregulation syndrome in humans with CTLA4 mutations. Nat Med 2014;20:1410-1416
158. Raven SFH, Hoebe C, Vossen A, Visser LG, Hautvast JLA, Roukens AHE, et al. Serological response to three alternative series of hepatitis B revaccination (Fendrix, Twinrix, and HBVaxPro-40) in healthy non-responders: a multicentre, open-label, randomised, controlled, superiority trial. Lancet Infect Dis 2020;20:92-101
159. Orange JS, Ballow M, Stiehm ER, Ballas ZK, Chinen J, De La Morena M, et al. Use and interpretation of diagnostic vaccination in primary immunodeficiency: a working group report of the Basic and Clinical Immunology Interest Section of the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol 2012;130:S1-24
160. Allan CLM, Keating PE, Smith SM, Spellerberg MB and O'Donnell JL. Anti-pneumococcal antibody measurement: implications of discordance between second and third generation assays. Pathology 2020;52:375-377
161. Winkelstein JA, Marino MC, Lederman HM, Jones SM, Sullivan K, Burks AW, et al. X-linked agammaglobulinemia: report on a United States registry of 201 patients. Medicine (Baltimore) 2006;85:193-202
162. Hernandez-Trujillo V, Zhou C, Scalchunes C, Ochs HD, Sullivan KE, Cunningham-Rundles C, et al. A registry study of 240 patients with X-linked agammaglobulinemia living in the USA. J Clin Immunol. 2023;43:1468-1477
163 O'Toole D, Groth D, Wright H, Bonilla FA, Fuleihan RL, Cunningham-Rundles C, et al. X-linked agammaglobulinemia: infection frequency and infection-related mortality in the USIDNET Registry. J Clin Immunol. 2022;42:827-836.
164. Kanegane H, Nakano T, Shimono Y, Zhao M and Miyawaki T. Pneumocystis jiroveci pneumonia as an atypical presentation of X-linked agammaglobulinemia. Int J Hematol 2009;89:716-7
165. Fiore L, Plebani A, Buttinelli G, Fiore S, Donati V, Marturano J, et al. Search for poliovirus long-term excretors among patients affected by agammaglobulinemia. Clin Immunol 2004;111:98-102
168. Sabnis GR, Karnik ND, Chavan SA and Korivi DS. Recurrent pyogenic meningitis in a 17-year-old: a delayed presentation of X-linked agammaglobulinemia with growth hormone deficiency. Neurol India 2011;59:435-7
169. Conley ME, Broides A, Hernandez-Trujillo V, Howard V, Kanegane H, Miyawaki T, et al. Genetic analysis of patients with defects in early B-cell development. Immunol Rev 2005;203:216-34
170. Ferrari S, Zuntini R, Lougaris V, Soresina A, Sourková V, Fiorini M, et al. Molecular analysis of the pre-BCR complex in a large cohort of patients affected by autosomal-recessive agammaglobulinemia. Genes Immun 2007;8:325-33
171. Lougaris V, Ferrari S and Plebani A. Ig beta deficiency in humans. Curr Opin Allergy Clin Immunol 2008;8:515-9

172. Conley ME, Dobbs AK, Quintana AM, Bosompem A, Wang YD, Coustan-Smith E, et al. Agammaglobulinemia and absent B lineage cells in a patient lacking the p85α subunit of PI3K. J Exp Med 2012;209:463-70
173. Boisson B, Wang YD, Bosompem A, Ma CS, Lim A, Kochetkov T, et al. A recurrent dominant negative E47 mutation causes agammaglobulinemia and BCR(-) B cells. J Clin Invest 2013;123:4781-5
174. Broderick L, Yost S, Li D, McGeough MD, Booshehri LM, Guaderrama M, et al. Mutations in topoisomerase IIβ result in a B cell immunodeficiency. Nat Commun 2019;10:3644
175. Le Coz C, Nguyen DN, Su C, Nolan BE, Albrecht AV, Xhani S, et al. Constrained chromatin accessibility in PU.1-mutated agammaglobulinemia patients. J Exp Med 2021;218:e20201750
176. Weifenbach N, Schneckenburger AAC and Lötters S. Global Distribution of Common Variable Immunodeficiency (CVID) in the Light of the UNDP Human Development Index (HDI): A Preliminary Perspective of a Rare Disease. J Immunol Res 2020;2020:8416124
177. Selenius JS, Martelius T, Pikkarainen S, Siitonen S, Mattila E, Pietikäinen R, et al. Unexpectedly High Prevalence of Common Variable Immunodeficiency in Finland. Front Immunol 2017;8:1190
178. Kabir A, Alizadehfar R and Tsoukas CM. Good's Syndrome: Time to move on from reviewing the past. Front Immunol 2021;12:815710
179. Bloom KA, Chung D and Cunningham-Rundles C. Osteoarticular infectious complications in patients with primary immunodeficiencies. Curr Opin Rheumatol 2008;20:480-5
180. Sperlich JM, Grimbacher B, Workman S, Haque T, Seneviratne SL, Burns SO, et al. Respiratory Infections and Antibiotic Usage in Common Variable Immunodeficiency. J Allergy Clin Immunol Pract 2018;6:159-168.e3
181. Sanchez DA, Rotella K, Toribio C, Hernandez M, Cunningham-Rundles C. Characterization of infectious and non-infectious gastrointestinal disease in common variable immunodeficiency: analysis of 114 patient cohort. Front Immunol. 2023 Aug 30:14:1209570.
182. Gereige JD and Maglione PJ. Current Understanding and Recent Developments in Common Variable Immunodeficiency Associated Autoimmunity. Front Immunol 2019;10:2753
183. Daniels JA, Lederman HM, Maitra A and Montgomery EA. Gastrointestinal tract pathology in patients with common variable immunodeficiency (CVID): a clinicopathologic study and review. Am J Surg Pathol 2007;31:1800-12
184. Daza-Cajigal V, Segura-Guerrero M, López-Cueto M, Robles-Marhuenda Á, Camara C, Gerra-Galán T, et al. Clinical manifestations and approach to the management of patients with common variable immunodeficiency and liver disease. Front Immunol 2023;14:1197361
185. DiGiacomo DV, Shay JE, Crotty R, Yang N, Bloom P, Corey K, et al. Liver Stiffness by Transient Elastography Correlates With Degree of Portal Hypertension in Common Variable Immunodeficiency Patients With Nodular Regenerative Hyperplasia. Front Immunol 2022;13:864550

186. Maglione PJ. Chronic Lung Disease in Primary Antibody Deficiency: Diagnosis and Management. Immunol Allergy Clin North Am 2020;40:437-459
187. Bintalib HM, van de Ven A, Jacob J, Davidsen JR, Fevang B, Hanitsch LG, et al. Diagnostic testing for interstitial lung disease in common variable immunodeficiency: a systematic review. Front Immunol 2023;14:1190235
188. Maglione PJ. Autoimmune and Lymphoproliferative Complications of Common Variable Immunodeficiency. Curr Allergy Asthma Rep 2016;16:19
189. de Valles-Ibáñez G, Esteve-Solé A, Piquer M, González-Navarro EA, Hernandez-Rodriguez J, Laayouni H, et al. Evaluating the Genetics of Common Variable Immunodeficiency: Monogenetic Model and Beyond. Front Immunol 2018;9:636
190. Maffucci P, Filion CA, Boisson B, Itan Y, Shang L, Casanova JL, et al. Genetic Diagnosis Using Whole Exome Sequencing in Common Variable Immunodeficiency. Front Immunol 2016;7:220
191. Lo B, Fritz JM, Su HC, Uzel G, Jordan MB and Lenardo MJ. CHAI and LATAIE: new genetic diseases of CTLA-4 checkpoint insufficiency. Blood 2016;128:1037-42
192. Jamee M, Hosseinzadeh S, Sharifinejad N, Zaki-Dizaji M, Matloubi M, Hasani M, et al. Comprehensive comparison between 222 CTLA-4 haploinsufficiency and 212 LRBA deficiency patients: a systematic review. Clin Exp Immunol 2021;205:28-43
193. Cant AJ, Chandra A, Munro E, Rao VK and Lucas CL. PI3Kδ Pathway Dysregulation and Unique Features of Its Inhibition by Leniolisib in Activated PI3Kδ Syndrome and Beyond. J Allergy Clin Immunol Pract 2024;12:69-78
194. Yazdani R, Azizi G, Abolhassani H, Aghamohammadi A. Selective IgA deficiency: epidemiology, pathogenesis, clinical phenotype, diagnosis, prognosis and management. Scand J Immunol. 2017; 85: 3-12
195. Feng ML, Zhao YL, Shen T, Huang H, Yin B, Liu RZ, et al. Prevalence of immunoglobulin A deficiency in Chinese blood donors and evaluation of anaphylactic transfusion reaction risk. Transfus Med 2011;21:338-43
196. Español T, Catala M, Hernandez M, Caragol I and Bertran JM. Development of a common variable immunodeficiency in IgA-deficient patients. Clin Immunol Immunopathol 1996;80:333-5
197. Aghamohammadi A, Mohammadi J, Parvaneh N, Rezaei N, Moin M, Espanol T, et al. Progression of selective IgA deficiency to common variable immunodeficiency. Int Arch Allergy Immunol 2008;147:87-92
198. Abolhassani H, Aghamohammadi A and Hammarström L. Monogenic mutations associated with IgA deficiency. Expert Rev Clin Immunol 2016;12:1321-1335
199. Lougaris V, Sorlini A, Monfredini C, Ingrasciotta G, Caravaggio A, Lorenzini T, et al. Clinical and laboratory features of 184 Italian pediatric patients affected with selective IgA deficiency (IgA): a longitudinal single-center study. J Clini Immunol. 2019; 39: 470-475
200. Lopez RV, Cid CM, Garcia GR, Romero RG, Cilleruelo ML, Riechman ER, et al. Influence of the 2012 European guidelines in diagnosis and follow up of coeliac children with selective IgA deficiency. J Pediatr Gastroenterol Nutr. 2020; 71: 59-63
201. Björkander J, Bake B, Oxelius VA and Hanson LA. Impaired lung function in patients with IgA deficiency and low levels of IgG2 or IgG3. N Engl J Med 1985;313:720-4

202. Coulter TI, Chandra A, Bacon CM, Babar J, Curtis J, Screaton N, et al. Clinical spectrum and features of activated phosphoinositide 3-kinase δ syndrome: A large patient cohort study. J Allergy Clin Immunol 2017;139:597-606.e4
203. Schatone EJ, DeJong E, Van Hout RW, Garcia Vivas Y, de Vries Y. The challenge of immunoglobulin G subclass deficiency and specific antibody deficiency- a dutch pediatric cohort study. J Clin Immunol. 2016; 36: 141-148
204. Shackelford PG, Granoff DM, Madassery JV, Scott MG and Nahm MH. Clinical and immunologic characteristics of healthy children with subnormal serum concentrations of IgG2. Pediatr Res 1990;27:16-21
205. Bucciol G, Schaballie H, Schrijvers R, Bosch B, Proesmans M, De Boeck K, et al. Defining Polysaccharide Antibody Deficiency: Measurement of Anti-Pneumococcal Antibodies and Anti-Salmonella typhi Antibodies in a Cohort of Patients with Recurrent Infections. J Clin Immunol 2020;40:105-113
206. Lawrence MG and Borish L. Specific antibody deficiency: pearls and pitfalls for diagnosis. Ann Allergy Asthma Immunol 2022;129:572-578
207. Raven SFH, Hoebe C, Vossen A, Visser LG, Hautvast JLA, Roukens AHE, et al. Serological response to three alternative series of hepatitis B revaccination (Fendrix, Twinrix, and HBVaxPro-40) in healthy non-responders: a multicentre, open-label, randomised, controlled, superiority trial. Lancet Infect Dis 2020;20:92-101
208. Revy P, Muto T, Levy Y, Geissmann F, Plebani A, Sanal O, et al. Activation-induced cytidine deaminase (AID) deficiency causes the autosomal recessive form of the Hyper-IgM syndrome (HIGM2). Cell 2000;102:565-75
209. Minegishi Y, Lavoie A, Cunningham-Rundles C, Bédard PM, Hébert J, Côté L, et al. Mutations in activation-induced cytidine deaminase in patients with hyper IgM syndrome. Clin Immunol 2000;97:203-10
210. Quartier P, Bustamante J, Sanal O, Plebani A, Debré M, Deville A, et al. Clinical, immunologic and genetic analysis of 29 patients with autosomal recessive hyper-IgM syndrome due to Activation-Induced Cytidine Deaminase deficiency. Clin Immunol 2004;110:22-9
211. Notarangelo LD, Lanzi G, Peron S and Durandy A. Defects of class-switch recombination. J Allergy Clin Immunol 2006;117:855-64
212. Durandy A, Cantaert T, Kracker S, Meffre E. Potential roles of activation induced cytidine deaminase in promotion or prevention of autoimmunity in humans. Autoimmunity. 2013; 46: 148-156
213. Kyle RA, Therneau TM, Rajkumar SV, Offord JR, Larson DR, Plevak MF, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. N Engl J Med 2002;346:564-9
214. Moschese V, Graziani S, Avanzini MA, Carsetti R, Marconi M, La Rocca M, et al. A prospective study on children with initial diagnosis of transient hypogammaglobulinemia of infancy: results from the Italian Primary Immunodeficiency Network. Int J Immunopathol Pharmacol 2008;21:343-52
215. Keles S, Artac H, Kara R, Gokturk B, Ozen A and Reisli I. Transient hypogammaglobulinemia and unclassified hypogammaglobulinemia: 'similarities and differences'. Pediatr Allergy Immunol 2010;21:843-51

216. Ozen A, Baris S, Karakoc-Aydiner E, Ozdemir C, Bahceciler NN and Barlan IB. Outcome of hypogammaglobulinemia in children: immunoglobulin levels as predictors. Clin Immunol 2010;137:374-83
217. Ricci G, Piccinno V, Giannetti A, Miniaci A, Specchia F and Masi M. Evolution of hypogammaglobulinemia in premature and full-term infants. Int J Immunopathol Pharmacol 2011;24:721-6
218. Soomann M, Bily V, Elgizouli M, Kraemer D, Akgül G, von Bernuth H, et al. Variants in IGLL1 cause a broad phenotype from agammaglobulinemia to transient hypogammaglobulinemia. J Allergy Clin Immunol 2024;154:1313-1324.e7
219. Bukowska-Straková K, Kowalczyk D, Baran J, Siedlar M, Kobylarz K and Zembala M. The B-cell compartment in the peripheral blood of children with different types of primary humoral immunodeficiency. Pediatr Res 2009;66:28-34
220. Artac H, Kara R, Gokturk B and Reisli I. Reduced CD19 expression and decreased memory B cell numbers in transient hypogammaglobulinemia of infancy. Clin Exp Med 2013;13:257-63
221. Simon AK, Hollander GA and McMichael A. Evolution of the immune system in humans from infancy to old age. Proc Biol Sci 2015;282:20143085
222. Levy J, Espanol-Boren T, Thomas C, Fischer A, Tovo P, Bordigoni P, et al. Clinical spectrum of X-linked hyper-IgM syndrome. J Pediatr 1997;131:47-54
223. Aldrich RA, Steinberg AG and Campbell DC. Pedigree demonstrating a sex-linked recessive condition characterized by draining ears, eczematoid dermatitis and bloody diarrhea. Pediatrics 1954;13:133-9
224. Yan J, Greer JM, Hull R, O'Sullivan JD, Henderson RD, Read SJ, et al. The effect of ageing on human lymphocyte subsets: comparison of males and females. Immun Ageing 2010;7:4
225. Abdullah M, Chai PS, Chong MY, Tohit ER, Ramasamy R, Pei CP, et al. Gender effect on in vitro lymphocyte subset levels of healthy individuals. Cell Immunol 2012;272:214-9
226. Haspel JA, Anafi R, Brown MK, Cermakian N, Depner C, Desplats P, et al. Perfect timing: circadian rhythms, sleep, and immunity - an NIH workshop summary. JCI Insight 2020;5
227. Rieux-Laucat F and Magerus-Chatinet A. Autoimmune lymphoproliferative syndrome: a multifactorial disorder. Haematologica 2010;95:1805-7
228. Carbonari M, Cherchi M, Paganelli R, Giannini G, Galli E, Gaetano C, et al. Relative increase of T cells expressing the gamma/delta rather than the alpha/beta receptor in ataxia-telangiectasia. N Engl J Med 1990;322:73-6
229. Zimmer J, Andrès E, Donato L, Hanau D, Hentges F and de la Salle H. Clinical and immunological aspects of HLA class I deficiency. QJM 2005;98:719-27
230. Sharifinejad N, Jamee M, Zaki-Dizaji M, Lo B, Shaghaghi M, Mohammadi H, et al. Clinical, immunological, and genetic features in 49 patients with ZAP-70 deficiency: A systematic review. Front Immunol. 2020 May 5;11:831
231. Aluri J, Gupta M, Dalvi A, Mhatre S, Kulkarni M, Hule G, et al. Clinical, Immunological, and Molecular Findings in Five Patients with Major Histocompatibility Complex Class II Deficiency from India. Front Immunol 2018;9:188

231. Schepp J, Chou J, Skrabl-Baumgartner A, Arkwright PD, Engelhardt KR, Hambleton S, et al. 14 Years after Discovery: Clinical follow-up on 15 patients with Inducible Co-Stimulator deficiency. Front Immunol. 2017 Aug 16;8:964.
232. Wolska-Kuśnierz B, Gregorek H, Chrzanowska K, Piątosa B, Pietrucha B, Heropolitańska-Pliszka E, et al. Nijmegen Breakage Syndrome: Clinical and Immunological Features, Long-Term Outcome and Treatment Options - a Retrospective Analysis. J Clin Immunol 2015;35:538-49
233. Courtois G, Smahi A, Reichenbach J, Döffinger R, Cancrini C, Bonnet M, et al. A hypermorphic IkappaBalpha mutation is associated with autosomal dominant anhidrotic ectodermal dysplasia and T cell immunodeficiency. J Clin Invest 2003;112:1108-15
234. Cardinez C, Miraghazadeh B, Tanita K, da Silva E, Hoshino A, Okada S, et al. Gain-of-function IKBKB mutation causes human combined immune deficiency. J Exp Med 2018;215:2715-2724
235. Lima K, Abrahamsen TG, Foelling I, Natvig S, Ryder LP and Olaussen RW. Low thymic output in the 22q11.2 deletion syndrome measured by CCR9+CD45RA+ T cell counts and T cell receptor rearrangement excision circles. Clin Exp Immunol 2010;161:98-107
236. Kumánovics A and Sadighi Akha AA. Flow cytometry for B-cell subset analysis in immunodeficiencies. J Immunol Methods 2022;509:113327
237. Renner ED, Krätz CE, Orange JS, Hagl B, Rylaarsdam S, Notheis G, et al. Class Switch Recombination Defects: impact on B cell maturation and antibody responses. Clin Immunol 2021;222:108638
238. Sakaguchi S, Mikami N, Wing JB, Tanaka A, Ichiyama K and Ohkura N. Regulatory T cells and human disease. Annu Rev Immunol 2020;38:541-566
239. Singh AK, Eken A, Hagin D, Komal K, Bhise G, Shaji A, et al. DOCK8 regulates fitness and function of regulatory T cells through modulation of IL-2 signaling. JCI Insight 2017;2:e94275
240. Del Pozo-Balado Mdel M, Leal M, Méndez-Lagares G and Pacheco YM. CD4(+)CD25(+/hi)CD127(lo) phenotype does not accurately identify regulatory T cells in all populations of HIV-infected persons. J Infect Dis 2010;201:331-5
241. Wang J, Ioan-Facsinay A, van der Voort EI, Huizinga TW and Toes RE. Transient expression of FOXP3 in human activated nonregulatory CD4+ T cells. Eur J Immunol 2007;37:129-38
242. Vinuesa CG, Linterman MA, Yu D and MacLennan IC. Follicular Helper T Cells. Annu Rev Immunol 2016;34:335-68
243. Tangye SG and Ma CS. Molecular regulation and dysregulation of T follicular helper cells - learning from inborn errors of immunity. Curr Opin Immunol 2021;72:249-261
244. Walker LSK. The link between circulating follicular helper T cells and autoimmunity. Nat Rev Immunol 2022;22:567-575
245. Kumar D, Prince C, Bennett CM, Briones M, Lucas L, Russell A, et al. T-follicular helper cell expansion and chronic T-cell activation are characteristic immune anomalies in Evans syndrome. Blood 2022;139:369-383
246. Kanai T, Jenks J and Nadeau KC. The STAT5b Pathway Defect and Autoimmunity. Front Immunol 2012;3:234
247. Su HC, Jing H and Zhang Q. DOCK8 deficiency. Ann N Y Acad Sci 2011;1246:26-33

248. Wentink MWJ, Mueller YM, Dalm V, Driessen GJ, van Hagen PM, van Montfrans JM, et al. Exhaustion of the CD8(+) T Cell compartment in patients with mutations in Phosphoinositide 3-Kinase Delta. Front Immunol 2018;9:446
249. Saeidi A, Zandi K, Cheok YY, Saeidi H, Wong WF, Lee CYQ, et al. T-cell exhaustion in chronic infections: reversing the state of exhaustion and reinvigorating optimal protective immune responses. Front Immunol 2018;9:2569
250. Ngoenkam J, Paensuwan P, Wipa P, Schamel WWA and Pongcharoen S. Wiskott-Aldrich Syndrome Protein: Roles in Signal Transduction in T Cells. Front Cell Dev Biol 2021;9:674572
251. Latour S. Inherited immunodeficiencies associated with proximal and distal defects in T cell receptor signaling and co-signaling. Biomed J 2022;45:321-333
252. Heider S, Strobel J, Mempel W, Eckstein R, Weisbach V. Measuring Lymphocyte Proliferation in Response to Specific Antigen and Mitogen Stimuli Using Flow Cytometry. Clin Lab. 2016 ;62(10):1857-1878
253. Schuetz C, Gerke J, Ege M, Walter J, Kusters M, Worth A, et al. Hypomorphic RAG deficiency: impact of disease burden on survival and thymic recovery argues for early diagnosis and HSCT. Blood 2023;141:713-724
254. Cifaldi C, Cotugno N, Di Cesare S, Giliani S, Di Matteo G, Amodio D, et al. Partial T cell defects and expanded CD56(bright) NK cells in an SCID patient carrying hypomorphic mutation in the IL2RG gene. J Leukoc Biol 2020;108:739-748
255. Lee PP, Woodbine L, Gilmour KC, Bibi S, Cale CM, Amrolia PJ, et al. The many faces of Artemis-deficient combined immunodeficiency - Two patients with DCLRE1C mutations and a systematic literature review of genotype-phenotype correlation. Clin Immunol 2013;149:464-74
256. Etzioni A and Ochs HD. The hyper IgM syndrome--an evolving story. Pediatr Res 2004;56:519-25
257. Karaca NE, Durandy A, Gulez N, Aksu G and Kutukculer N. Study of patients with Hyper-IgM type IV phenotype who recovered spontaneously during late childhood and review of the literature. Eur J Pediatr 2011;170:1039-47
258. Della Mina E and Tangye SG. Atypical Autosomal Recessive AID Deficiency-Yet Another Piece of the Hyper-IgM Puzzle. J Clin Immunol 2022;42:713-715
259. Kavli B, Andersen S, Otterlei M, Liabakk NB, Imai K, Fischer A, et al. B cells from hyper-IgM patients carrying UNG mutations lack ability to remove uracil from ssDNA and have elevated genomic uracil. J Exp Med 2005;201:2011-21
260. Jain A, Ma CA, Lopez-Granados E, Means G, Brady W, Orange JS, et al. Specific NEMO mutations impair CD40-mediated c-Rel activation and B cell terminal differentiation. J Clin Invest 2004;114:1593-602
261. Morio T. Recent advances in the study of immunodeficiency and DNA damage response. Int J Hematol 2017;106:357-365
262. Yazdani R, Hamidi Z, Babaha F, Azizi G, Fekrvand S, Abolhassani H, et al. PIK3R1 Mutation Associated with Hyper IgM (APDS2 Syndrome): A Case Report and Review of the Literature. Endocr Metab Immune Disord Drug Targets 2019;19:941-958
257. O'Gorman MR, Zaas D, Paniagua M, Corrochano V, Scholl PR and Pachman LM. Development of a rapid whole blood flow cytometry procedure for the diagnosis of X-linked hyper-IgM syndrome patients and carriers. Clin Immunol Immunopathol 1997;85:172-81

258. Abraham RS and Aubert G. Flow Cytometry, a Versatile Tool for Diagnosis and Monitoring of Primary Immunodeficiencies. Clin Vaccine Immunol 2016;23:254-71
259. Hollenbaugh D, Wu LH, Ochs HD, Nonoyama S, Grosmaire LS, Ledbetter JA, et al. The random inactivation of the X chromosome carrying the defective gene responsible for X-linked hyper IgM syndrome (X-HIM) in female carriers of HIGM1. J Clin Invest 1994;94:616-22
260. Ferrari S, Giliani S, Insalaco A, Al-Ghonaium A, Soresina AR, Loubser M, et al. Mutations of CD40 gene cause an autosomal recessive form of immunodeficiency with hyper IgM. Proc Natl Acad Sci U S A 2001;98:12614-9
261. Hanna S and Etzioni A. MHC class I and II deficiencies. J Allergy Clin Immunol 2014;134:269-75
262. Ouederni M, Vincent QB, Frange P, Touzot F, Scerra S, Bejaoui M, et al. Major histocompatibility complex class II expression deficiency caused by a RFXANK founder mutation: a survey of 35 patients. Blood 2011;118:5108-18
263. Villard J, Reith W, Barras E, Gos A, Morris MA, Antonarakis SE, et al. Analysis of mutations and chromosomal localisation of the gene encoding RFX5, a novel transcription factor affected in major histocompatibility complex class II deficiency. Hum Mutat 1997;10:430-5
264. Ochs HD, Slichter SJ, Harker LA, Von Behrens WE, Clark RA and Wedgwood RJ. The Wiskott-Aldrich syndrome: studies of lymphocytes, granulocytes, and platelets. Blood 1980;55:243-52
265. Imai K, Nonoyama S and Ochs HD. WASP (Wiskott-Aldrich syndrome protein) gene mutations and phenotype. Curr Opin Allergy Clin Immunol 2003;3:427-36
266. Zhu Q, Zhang M, Blaese RM, Derry JM, Junker A, Francke U, et al. The Wiskott-Aldrich syndrome and X-linked congenital thrombocytopenia are caused by mutations of the same gene. Blood 1995;86:3797-804
267. Villa A, Notarangelo L, Macchi P, Mantuano E, Cavagni G, Brugnoni D, et al. X-linked thrombocytopenia and Wiskott-Aldrich syndrome are allelic diseases with mutations in the WASP gene. Nat Genet 1995;9:414-7
268. Ancliff PJ, Blundell MP, Cory GO, Calle Y, Worth A, Kempski H, et al. Two novel activating mutations in the Wiskott-Aldrich syndrome protein result in congenital neutropenia. Blood 2006;108:2182-9
269. Devriendt K, Kim AS, Mathijs G, Frints SG, Schwartz M, Van Den Oord JJ, et al. Constitutively activating mutation in WASP causes X-linked severe congenital neutropenia. Nat Genet 2001;27:313-7
270. Orange JS, Roy-Ghanta S, Mace EM, Maru S, Rak GD, Sanborn KB, et al. IL-2 induces a WAVE2-dependent pathway for actin reorganization that enables WASp-independent human NK cell function. J Clin Invest 2011;121:1535-48
271. Chiang SCC, Vergamini SM, Husami A, Neumeier L, Quinn K, Ellerhorst T, et al. Screening for Wiskott-Aldrich syndrome by flow cytometry. J Allergy Clin Immunol 2018;142:333-335.e8
272. Cazzola M and Bergamaschi G. X-linked Wiskott-Aldrich syndrome in a girl. N Engl J Med 1998;338:1850; author reply 1851
273. Boonyawat B, Dhanraj S, Al Abbas F, Zlateska B, Grunenbaum E, Roifman CM, et al. Combined de-novo mutation and non-random X-chromosome inactivation causing

Wiskott-Aldrich syndrome in a female with thrombocytopenia. J Clin Immunol 2013;33:1150-5
274. Daza-Cajigal V, Martínez-Pomar N, Garcia-Alonso A, Heine-Suñer D, Torres S, Vega AK, et al. X-linked thrombocytopenia in a female with a complex familial pattern of X-chromosome inactivation. Blood Cells Mol Dis 2013;51:125-9
275. Schwinger W, Urban C, Ulreich R, Sperl D, Karastaneva A, Strenger V, et al. The Phenotype and Treatment of WIP Deficiency: Literature Synopsis and Review of a Patient With Pre-transplant Serial Donor Lymphocyte Infusions to Eliminate CMV. Front Immunol 2018;9:2554
276. Yilmaz Demirdag Y and Gupta S. Infections in DNA Repair Defects. Pathogens 2023;12
277. Gatti RA, Berkel I, Boder E, Braedt G, Charmley P, Concannon P, et al. Localization of an ataxia-telangiectasia gene to chromosome 11q22-23. Nature 1988;336:577-80
278. Amirifar P, Ranjouri MR, Lavin M, Abolhassani H, Yazdani R and Aghamohammadi A. Ataxia-telangiectasia: epidemiology, pathogenesis, clinical phenotype, diagnosis, prognosis and management. Expert Rev Clin Immunol 2020;16:859-871
279. Waldmann TA and McIntire KR. Serum-alpha-fetoprotein levels in patients with ataxia-telangiectasia. Lancet 1972;2:1112-5
280. Barmettler S, Coffey K, Smith MJ, Chong HJ, Pozos TC, Seroogy CM, et al. Functional Confirmation of DNA Repair Defect in Ataxia Telangiectasia (AT) Infants Identified by Newborn Screening for Severe Combined Immunodeficiency (NBS SCID). J Allergy Clin Immunol Pract 2021;9:723-732.e3
281. Buchbinder D, Smith MJ, Kawahara M, Cowan MJ, Buzby JS and Abraham RS. Application of a radiosensitivity flow assay in a patient with DNA ligase 4 deficiency. Blood Adv 2018;2:1828-1832
282. Weemaes CM, van Tol MJ, Wang J, van Ostaijen-ten Dam MM, van Eggermond MC, Thijssen PE, et al. Heterogeneous clinical presentation in ICF syndrome: correlation with underlying gene defects. Eur J Hum Genet 2013;21:1219-25
283. Tuck-Muller CM, Narayan A, Tsien F, Smeets DF, Sawyer J, Fiala ES, et al. DNA hypomethylation and unusual chromosome instability in cell lines from ICF syndrome patients. Cytogenet Cell Genet 2000;89:121-8
284. Mustillo PJ, Sullivan KE, Chinn IK, Notarangelo LD, Haddad E, Davies EG, et al. Clinical practice guidelines for the immunological management of chromosome 22q11.2 deletion syndrome and other defects in thymic development. J Clin Immunol 2023;43:247-270
285. McDonald-McGinn DM and Sullivan KE. Chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). Medicine (Baltimore) 2011;90:1-18
286. Minegishi Y. Hyper-IgE syndrome, 2021 update. Allergol Int 2021;70:407-414
287. Al-Shaikhly T and Ochs HD. Hyper IgE syndromes: clinical and molecular characteristics. Immunol Cell Biol 2019;97:368-379
288. Abdollahpour H, Appaswamy G, Kotlarz D, Diestelhorst J, Beier R, Schäffer AA, et al. The phenotype of human STK4 deficiency. Blood 2012;119:3450-7
289. Ma CS, Chew GY, Simpson N, Priyadarshi A, Wong M, Grimbacher B, et al. Deficiency of Th17 cells in hyper IgE syndrome due to mutations in STAT3. J Exp Med 2008;205:1551-7

290. Pai SY, de Boer H, Massaad MJ, Chatila TA, Keles S, Jabara HH, et al. Flow cytometry diagnosis of dedicator of cytokinesis 8 (DOCK8) deficiency. J Allergy Clin Immunol 2014;134:221-3
291. Meshaal SS, El Hawary RE, Eldash A, Grimbacher B, Camacho-Ordonez N, Abd Elaziz DS, et al. Diagnosis of DOCK8 deficiency using Flow cytometry Biomarkers: an Egyptian Center experience. Clin Immunol 2018;195:36-44
292. Thiel CT, Horn D, Zabel B, Ekici AB, Salinas K, Gebhart E, et al. Severely incapacitating mutations in patients with extreme short stature identify RNA-processing endoribonuclease RMRP as an essential cell growth regulator. Am J Hum Genet 2005;77:795-806
293. Mäkitie O, Heikkinen M, Kaitila I and Rintala R. Hirschsprung's disease in cartilage-hair hypoplasia has poor prognosis. J Pediatr Surg 2002;37:1585-8
294. Kukkola HL, Utriainen P, Huttunen P, Taskinen M, Mäkitie O and Vakkilainen S. Lymphomas in cartilage-hair hypoplasia - A case series of 16 patients reveals advanced stage DLBCL as the most common form. Front Immunol 2022;13:1004694
295. Mäkitie O. Cartilage-hair hypoplasia in Finland: epidemiological and genetic aspects of 107 patients. J Med Genet 1992;29:652-5
296. Vakkilainen S, Taskinen M and Mäkitie O. Immunodeficiency in cartilage-hair hypoplasia: Pathogenesis, clinical course and management. Scand J Immunol 2020;92:e12913
297. Aubert G, Strauss KA, Lansdorp PM and Rider NL. Defects in lymphocyte telomere homeostasis contribute to cellular immune phenotype in patients with cartilage-hair hypoplasia. J Allergy Clin Immunol 2017;140:1120-1129.e1
298. Kostjukovits S, Degerman S, Pekkinen M, Klemetti P, Landfors M, Roos G, et al. Decreased telomere length in children with cartilage-hair hypoplasia. J Med Genet 2017;54:365-370
299. Alder JK, Hanumanthu VS, Strong MA, DeZern AE, Stanley SE, Takemoto CM, et al. Diagnostic utility of telomere length testing in a hospital-based setting. Proc Natl Acad Sci U S A 2018;115:E2358-e2365
300. Aubert G, Hills M and Lansdorp PM. Telomere length measurement-caveats and a critical assessment of the available technologies and tools. Mutat Res 2012;730:59-67
301. Lacruz RS and Feske S. Diseases caused by mutations in ORAI1 and STIM1. Ann N Y Acad Sci 2015;1356:45-79
302. Spoor J, Farajifard H and Rezaei N. Congenital neutropenia and primary immunodeficiency diseases. Crit Rev Oncol Hematol 2019;133:149-162
303. Sullivan KE. Neutropenia as a sign of immunodeficiency. J Allergy Clin Immunol 2019;143:96-100
304. Skokowa J, Dale DC, Touw IP, Zeidler C and Welte K. Severe congenital neutropenias. Nat Rev Dis Primers 2017;3:17032
305. Rydzynska Z, Pawlik B, Krzyzanowski D, Mlynarski W and Madzio J. Neutrophil Elastase Defects in Congenital Neutropenia. Front Immunol 2021;12:653932
306. Harris ES, Weyrich AS and Zimmerman GA. Lessons from rare maladies: leukocyte adhesion deficiency syndromes. Curr Opin Hematol 2013;20:16-25
307. Hanna S and Etzioni A. Leukocyte adhesion deficiencies. Ann N Y Acad Sci 2012;1250:50-5

308. Almarza Novoa E, Kasbekar S, Thrasher AJ, Kohn DB, Sevilla J, Nguyen T, et al. Leukocyte adhesion deficiency-I: A comprehensive review of all published cases. J Allergy Clin Immunol Pract 2018;6:1418-1420.e10
309. Ambruso DR, Knall C, Abell AN, Panepinto J, Kurkchubasche A, Thurman G, et al. Human neutrophil immunodeficiency syndrome is associated with an inhibitory Rac2 mutation. Proc Natl Acad Sci U S A 2000;97:4654-9
310. Pai SY, Kim C and Williams DA. Rac GTPases in human diseases. Dis Markers 2010;29:177-87
311. Zerbe CS, Holland SM. Functional neutrophil disorders: chronic granulomatous disease and beyond. Immunol Rev. 2024; 322: 71-80
312. Ouahed J, Spencer E, Kotlarz D, Shouval DS, Kowalik M, Peng K, et al. Very Early Onset Inflammatory Bowel Disease: A Clinical Approach With a Focus on the Role of Genetics and Underlying Immune Deficiencies. Inflamm Bowel Dis 2020;26:820-842
313. Priel DP, Lau K, Fink DL, Kuhns DB. Functional assays for the diagnosis of Chronic Granulomatous Disease. J Immunol Methods. 2025 Feb;537:113820
314. Knight V, Heimall JR, Chong H, Nandiwada SL, Chen K, Lawrence MG, et al. A Toolkit and Framework for Optimal Laboratory Evaluation of Individuals with Suspected Primary Immunodeficiency. J Allergy Clin Immunol Pract 2021;9:3293-3307.e6
315. Battersby AC, Braggins H, Pearce MS, Cale CM, Burns SO, Hackett S, et al. Inflammatory and autoimmune manifestations in X-linked carriers of chronic granulomatous disease in the United Kingdom. J Allergy Clin Immunol 2017;140:628-630.e6
316. Mauch L, Lun A, O'Gorman MR, Harris JS, Schulze I, Zychlinsky A, et al. Chronic granulomatous disease (CGD) and complete myeloperoxidase deficiency both yield strongly reduced dihydrorhodamine 123 test signals but can be easily discerned in routine testing for CGD. Clin Chem 2007;53:890-6
317. Siler U, Romao S, Tejera E, Pastukhov O, Kuzmenko E, Valencia RG, et al. Severe glucose-6-phosphate dehydrogenase deficiency leads to susceptibility to infection and absent NETosis. J Allergy Clin Immunol 2017;139:212-219.e3
318. Neehus AL, Moriya K, Nieto-Patlán A, Le Voyer T, Lévy R, Özen A, et al. Impaired respiratory burst contributes to infections in PKCδ-deficient patients. J Exp Med 2021;218
319. Wortmann SB, Van Hove JLK, Derks TGJ, Chevalier N, Knight V, Koller A, et al. Treating neutropenia and neutrophil dysfunction in glycogen storage disease type Ib with an SGLT2 inhibitor. Blood 2020;136:1033-1043
320. Sacco KA, Smith MJ, Bahna SL, Buchbinder D, Burkhardt J, Cooper MA, et al. NAPDH Oxidase-Specific Flow Cytometry Allows for Rapid Genetic Triage and Classification of Novel Variants in Chronic Granulomatous Disease. J Clin Immunol 2020;40:191-202
321. McCarthy C, Bonella F, O'Callaghan M, Dupin C, Alfaro T, Fally M, et al. European Respiratory Society guidelines for the diagnosis and management of pulmonary alveolar proteinosis. Eur Respir J. 2024;64:2400725.
322. Kelly A and McCarthy C. Pulmonary Alveolar Proteinosis Syndrome. Semin Respir Crit Care Med 2020;41:288-298
323. Punatar AD, Kusne S, Blair JE, Seville MT and Vikram HR. Opportunistic infections in patients with pulmonary alveolar proteinosis. J Infect 2012;65:173-9

324. Trapnell BC, Nakata K, Bonella F, Campo I, Griese M, Hamilton J, et al. Pulmonary alveolar proteinosis. Nat Rev Dis Primers 2019;5:16
325. McCarthy C, Carey BC and Trapnell BC. Autoimmune Pulmonary Alveolar Proteinosis. Am J Respir Crit Care Med 2022;205:1016-1035
326. Ataya A, Knight V, Carey BC, Lee E, Tarling EJ and Wang T. The Role of GM-CSF Autoantibodies in Infection and Autoimmune Pulmonary Alveolar Proteinosis: A Concise Review. Front Immunol 2021;12:752856
327. Merkel PA, Lebo T and Knight V. Functional Analysis of Anti-cytokine Autoantibodies Using Flow Cytometry. Front Immunol 2019;10:1517
328. Esteve-Solé A, Sologuren I, Martínez-Saavedra MT, Deyà-Martínez À, Oleaga-Quintas C, Martinez-Barricarte R, et al. Laboratory evaluation of the IFN-γ circuit for the molecular diagnosis of Mendelian susceptibility to mycobacterial disease. Crit Rev Clin Lab Sci 2018;55:184-204
329. Lim HK, Seppänen M, Hautala T, Ciancanelli MJ, Itan Y, Lafaille FG, et al. TLR3 deficiency in herpes simplex encephalitis: high allelic heterogeneity and recurrence risk. Neurology 2014;83:1888-97
330. Abdalgani M, Hernandez ER, Pedroza LA, Chinn IK, Forbes Satter LR, Rider NL, et al. Clinical, immunologic and genetic characteristics of 148 patients with NK cell deficiency. J Allergy Clin Immunol 2025 Feb 4:S0091-6749(25)00119-8 Online ahead of print
331. Zhang SY. Herpes simplex virus encephalitis of childhood: inborn errors of central nervous system cell-intrinsic immunity. Hum Genet 2020;139:911-918
332. Béziat V and Jouanguy E. Human inborn errors of immunity to oncogenic viruses. Curr Opin Immunol 2021;72:277-285
333. de Jong SJ, Imahorn E, Itin P, Uitto J, Orth G, Jouanguy E, et al. Epidermodysplasia Verruciformis: Inborn Errors of Immunity to Human Beta-Papillomaviruses. Front Microbiol 2018;9:1222
334. Casanova JL and Anderson MS. Unlocking life-threatening COVID-19 through two types of inborn errors of type I IFNs. J Clin Invest 2023;133
335. Toubiana J, Okada S, Hiller J, Oleastro M, Lagos Gomez M, Aldave Becerra JC, et al. Heterozygous STAT1 gain-of-function mutations underlie an unexpectedly broad clinical phenotype. Blood. 2016;127:3154-64
336. Bucciol G, Moens L, Ogishi M, Rinchai D, Matuozzo D, Momenilandi M, et al. Human inherited complete STAT2 deficiency underlies inflammatory viral diseases. J Clin Invest 2023;133
337. Lenti MV, Luu S, Carsetti R, Osier F, Ogwang R, Nnodu OE, et al. Asplenia and spleen hypofunction. Nat Rev Dis Primers 2022;8:71
338. Saba TG, Geddes GC, Ware SM, Schidlow DN, Del Nido PJ, Rubalcava NS, et al. A multi-disciplinary, comprehensive approach to management of children with heterotaxy. Orphanet J Rare Dis 2022;17:351
339. Deering RP and Orange JS. Development of a clinical assay to evaluate toll-like receptor function. Clin Vaccine Immunol 2006;13:68-76
340. Dhalla F, Fox H, Davenport EE, Sadler R, Anzilotti C, van Schouwenburg PA, et al. Chronic mucocutaneous candidiasis: characterization of a family with STAT-1 gain-of-function and development of an ex-vivo assay for Th17 deficiency of diagnostic utility. Clin Exp Immunol 2016;184:216-27

341. Puel A, Döffinger R, Natividad A, Chrabieh M, Barcenas-Morales G, Picard C, et al. Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I. J Exp Med 2010;207:291-7
342. Oikonomou V, Smith G, Constantine GM, Schmitt MM, Ferré EMN, Alejo JC, et al. The Role of Interferon-γ in Autoimmune Polyendocrine Syndrome Type 1. N Engl J Med 2024;390:1873-1884
343. Maródi L, Erdös M. Dectin-1 deficiency and mucocutaneous fungal infections. N Engl J Med. 2010;362(4):367.
344. Tangye SG and Puel A. The Th17/IL-17 Axis and Host Defense Against Fungal Infections. J Allergy Clin Immunol Pract 2023;11:1624-1634
345. Bustamante J, Boisson-Dupuis S, Abel L and Casanova JL. Mendelian susceptibility to mycobacterial disease: genetic, immunological, and clinical features of inborn errors of IFN-γ immunity. Semin Immunol 2014;26:454-70
346. Patel SY, Ding L, Brown MR, Lantz L, Gay T, Cohen S, et al. Anti-IFN-gamma autoantibodies in disseminated nontuberculous mycobacterial infections. J Immunol 2005;175:4769-76
347. Hong GH, Ortega-Villa AM, Hunsberger S, Chetchotisakd P, Anunnatsiri S, Mootsikapun P, et al. Natural History and Evolution of Anti-Interferon-γ Autoantibody-Associated Immunodeficiency Syndrome in Thailand and the United States. Clin Infect Dis 2020;71:53-62
348. Figueroa JE and Densen P. Infectious diseases associated with complement deficiencies. Clin Microbiol Rev 1991;4:359-95
349. Sarma JV and Ward PA. The complement system. Cell Tissue Res 2011;343:227-35
350. Stegert M, Bock M and Trendelenburg M. Clinical presentation of human C1q deficiency: How much of a lupus? Mol Immunol 2015;67:3-11
351. Macedo AC and Isaac L. Systemic Lupus Erythematosus and Deficiencies of Early Components of the Complement Classical Pathway. Front Immunol 2016;7:55
352. Jönsson G, Truedsson L, Sturfelt G, Oxelius VA, Braconier JH and Sjöholm AG. Hereditary C2 deficiency in Sweden: frequent occurrence of invasive infection, atherosclerosis, and rheumatic disease. Medicine (Baltimore) 2005;84:23-34
353. Brodszki N, Frazer-Abel A, Grumach AS, Kirschfink M, Litzman J, Perez E, et al. European Society for Immunodeficiencies (ESID) and European Reference Network on Rare Primary Immunodeficiency, Autoinflammatory and Autoimmune Diseases (ERN RITA) Complement Guideline: Deficiencies, Diagnosis, and Management. J Clin Immunol 2020;40:576-591
354. Schramm EC, Clark SJ, Triebwasser MP, Raychaudhuri S, Seddon J and Atkinson JP. Genetic variants in the complement system predisposing to age-related macular degeneration: a review. Mol Immunol 2014;61:118-125
355. Loirat C and Frémeaux-Bacchi V. Atypical hemolytic uremic syndrome. Orphanet J Rare Dis 2011;6:60
356. Lee JX, Yusin JS and Randhawa I. Properdin deficiency-associated bronchiectasis. Ann Allergy Asthma Immunol 2014;112:557-9
357. Hourcade DE. The role of properdin in the assembly of the alternative pathway C3 convertases of complement. J Biol Chem 2006;281:2128-32

358. Gauthier A, Wagner E, Thiebault R, Lavoie A. A novel case of complement Factor B deficiency. J Clin Immunol. 2021; 41:277-279
359. Hiemstra PS, Langeler E, Compier B, Keepers Y, Leijh PC, van den Barselaar MT, et al. Complete and partial deficiencies of complement factor D in a Dutch family. J Clin Invest 1989;84:1957-61
360. Dahl M, Tybjaerg-Hansen A, Schnohr P and Nordestgaard BG. A population-based study of morbidity and mortality in mannose-binding lectin deficiency. J Exp Med 2004;199:1391-9
361. Swierzko AS, Cedzynski M. The influence of the lectin complement activation on infections of the respiratory system. Front Immunol 2020 Oct 21; 11:585243
362. Schlapbach LJ, Aebi C, Otth M, Leibundgut K, Hirt A and Ammann RA. Deficiency of mannose-binding lectin-associated serine protease-2 associated with increased risk of fever and neutropenia in pediatric cancer patients. Pediatr Infect Dis J 2007;26:989-94
363. Shih AR and Murali MR. Laboratory tests for disorders of complement and complement regulatory proteins. Am J Hematol 2015;90:1180-6
364. Prohászka Z, Nilsson B, Frazer-Abel A and Kirschfink M. Complement analysis 2016: Clinical indications, laboratory diagnostics and quality control. Immunobiology 2016;221:1247-58
365. Grumach AS and Kirschfink M. Are complement deficiencies really rare? Overview on prevalence, clinical importance and modern diagnostic approach. Mol Immunol 2014;61:110-7
366. Wehling C, Amon O, Bommer M, Hoppe B, Kentouche K, Schalk G, et al. Monitoring of complement activation biomarkers and eculizumab in complement-mediated renal disorders. Clin Exp Immunol 2017;187:304-315
367. Zipfel PF and Skerka C. Complement regulators and inhibitory proteins. Nat Rev Immunol 2009;9:729-40
368. Liszewski MK and Atkinson JP. Complement regulators in human disease: lessons from modern genetics. J Intern Med 2015;277:294-305
369. Schaefer F, Ardissino G, Ariceta G, Fakhouri F, Scully M, Isbel N, et al. Clinical and genetic predictors of atypical hemolytic uremic syndrome phenotype and outcome. Kidney Int 2018;94:408-418
370. Noris M, Mescia F and Remuzzi G. STEC-HUS, atypical HUS and TTP are all diseases of complement activation. Nat Rev Nephrol 2012;8:622-33
371. Szarvas N, Szilágyi Á, Csuka D, Takács B, Rusai K, Müller T, et al. Genetic analysis and functional characterization of novel mutations in a series of patients with atypical hemolytic uremic syndrome. Mol Immunol 2016;71:10-22
372. Vyse TJ, Morley BJ, Bartok I, Theodoridis EL, Davies KA, Webster AD, et al. The molecular basis of hereditary complement factor I deficiency. J Clin Invest 1996;97:925-33
373. Heurich M, Preston RJ, O'Donnell VB, Morgan BP and Collins PW. Thrombomodulin enhances complement regulation through strong affinity interactions with factor H and C3b-Factor H complex. Thromb Res 2016;145:84-92
374. Nester CM, Barbour T, de Cordoba SR, Dragon-Durey MA, Fremeaux-Bacchi V, Goodship TH, et al. Atypical aHUS: State of the art. Mol Immunol 2015;67:31-42

375. Bresin E, Rurali E, Caprioli J, Sanchez-Corral P, Fremeaux-Bacchi V, Rodriguez de Cordoba S, et al. Combined complement gene mutations in atypical hemolytic uremic syndrome influence clinical phenotype. J Am Soc Nephrol 2013;24:475-86
376. Michels M, van de Kar N, Okrój M, Blom AM, van Kraaij SAW, Volokhina EB, et al. Overactivity of Alternative Pathway Convertases in Patients With Complement-Mediated Renal Diseases. Front Immunol 2018;9:612
377. Sethi S, Smith RJ, Dillon JJ and Fervenza FC. C3 glomerulonephritis associated with complement factor B mutation. Am J Kidney Dis 2015;65:520-1
378. Marinozzi MC, Roumenina LT, Chauvet S, Hertig A, Bertrand D, Olagne J, et al. Anti-Factor B and Anti-C3b Autoantibodies in C3 Glomerulopathy and Ig-Associated Membranoproliferative GN. J Am Soc Nephrol 2017;28:1603-1613
379. Kavanagh D, Yu Y, Schramm EC, Triebwasser M, Wagner EK, Raychaudhuri S, et al. Rare genetic variants in the CFI gene are associated with advanced age-related macular degeneration and commonly result in reduced serum factor I levels. Hum Mol Genet 2015;24:3861-70
380. Reis ES, Falcão DA and Isaac L. Clinical aspects and molecular basis of primary deficiencies of complement component C3 and its regulatory proteins factor I and factor H. Scand J Immunol 2006;63:155-68
381. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. Blood 2014;124:2804-11
382. Ozen A, Comrie WA, Ardy RC, Domínguez Conde C, Dalgic B, Beser Ö F, et al. CD55 Deficiency, Early-Onset Protein-Losing Enteropathy, and Thrombosis. N Engl J Med 2017;377:52-61
383. Ardicli D, Taskiran EZ, Kosukcu C, Temucin C, Oguz KK, Haliloglu G, et al. Neonatal-Onset Recurrent Guillain-Barré Syndrome-Like Disease: Clues for Inherited CD59 Deficiency. Neuropediatrics 2017;48:477-481
384. Salmon JE, Heuser C, Triebwasser M, Liszewski MK, Kavanagh D, Roumenina L, et al. Mutations in complement regulatory proteins predispose to preeclampsia: a genetic analysis of the PROMISSE cohort. PLoS Med 2011;8:e1001013
385. Vaught AJ, Braunstein EM, Jasem J, Yuan X, Makhlin I, Eloundou S, et al. Germline mutations in the alternative pathway of complement predispose to HELLP syndrome. JCI Insight 2018;3
386. Grumach AS, Leitão MF, Arruk VG, Kirschfink M and Condino-Neto A. Recurrent infections in partial complement factor I deficiency: evaluation of three generations of a Brazilian family. Clin Exp Immunol 2006;143:297-304
387. Blazina Š, Debeljak M, Košnik M, Simčič S, Stopinšek S, Markelj G, et al. Functional Complement Analysis Can Predict Genetic Testing Results and Long-Term Outcome in Patients With Complement Deficiencies. Front Immunol 2018;9:500
388. Geerlings MJ, de Jong EK and den Hollander AI. The complement system in age-related macular degeneration: A review of rare genetic variants and implications for personalized treatment. Mol Immunol 2017;84:65-76
389. Prohászka Z, Varga L and Füst G. The use of 'real-time' complement analysis to differentiate atypical haemolytic uraemic syndrome from other forms of thrombotic microangiopathies. Br J Haematol 2012;158:424-5
390. Nishimura J, Yamamoto M, Hayashi S, Ohyashiki K, Ando K, Brodsky AL, et al. Genetic variants in C5 and poor response to eculizumab. N Engl J Med 2014;370:632-9

391. Rondelli T, Risitano AM, Peffault de Latour R, Sica M, Peruzzi B, Ricci P, et al. Polymorphism of the complement receptor 1 gene correlates with the hematologic response to eculizumab in patients with paroxysmal nocturnal hemoglobinuria. Haematologica 2014;99:262-6
392. Costagliola G and Consolini R. Lymphadenopathy at the crossroad between immunodeficiency and autoinflammation: An intriguing challenge. Clin Exp Immunol 2021;205:288-305
393. Seidel MG, Tesch VK, Yang L, Hauck F, Horn AL, Smolle MA, et al. The Immune Deficiency and Dysregulation Activity (IDDA2.1 'Kaleidoscope') Score and Other Clinical Measures in Inborn Errors of Immunity. J Clin Immunol 2022;42:484-498
394. Mauracher AA, Gujer E, Bachmann LM, Güsewell S and Pachlopnik Schmid J. Patterns of Immune Dysregulation in Primary Immunodeficiencies: A Systematic Review. J Allergy Clin Immunol Pract 2021;9:792-802
395. Walter JE, Ayala IA and Milojevic D. Autoimmunity as a continuum in primary immunodeficiency. Curr Opin Pediatr 2019;31:851-862
396. Ren A, Yin W, Miller H, Westerberg LS, Candotti F, Park CS, et al. Novel Discoveries in Immune Dysregulation in Inborn Errors of Immunity. Front Immunol 2021;12:725587
397. Chandrakasan S, Chandra S, Davila Saldana BJ, Torgerson TR and Buchbinder D. Primary immune regulatory disorders for the pediatric hematologist and oncologist: A case-based review. Pediatr Blood Cancer 2019;66:e27619
398. Mayer-Barber KD and Yan B. Clash of the Cytokine Titans: counter-regulation of interleukin-1 and type I interferon-mediated inflammatory responses. Cell Mol Immunol 2017;14:22-35
399. Welzel T, Kuemmerle-Deschner JB. Diagnosis and management of the cryopyrin-associated periodic syndromes (CAPS): what do we know today? J Clin Med. 2021; 10: 128
400. Gattorno M, Hofer M, Federici S, Vanoni F, Bovis F, Aksentijevich I, et al. Classification criteria for autoinflammatory recurrent fevers. Ann Rheum Dis 2019; 78: 1025-1032
401. Henter JI, Sieni E, Eriksson J, Bergsten E, Hed Myrberg I, Canna SW, et al. Diagnostic guidelines for familial hemophagocytic lymphohistiocytosis revisited. Blood 2024;144:2308-2318
402. Jamee M, Zaki-Dizaji M, Lo B, Abolhassani H, Aghamahdi F, Mosavian M, et al. Clinical, Immunological, and Genetic Features in Patients with Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX) and IPEX-like Syndrome. J Allergy Clin Immunol Pract 2020;8:2747-2760.e7
403. Bacchetta R and Roncarolo MG. IPEX syndrome from diagnosis to cure, learning along the way. J Allergy Clin Immunol 2024;153:595-605
404. Oliveira JB, Bleesing JJ, Dianzani U, Fleisher TA, Jaffe ES, Lenardo MJ, et al. Revised diagnostic criteria and classification for the autoimmune lymphoproliferative syndrome (ALPS): report from the 2009 NIH International Workshop. Blood 2010;116:e35-40
405. López-Nevado M, González-Granado LI, Ruiz-García R, Pleguezuelo D, Cabrera-Marante O, Salmón N, et al. Primary Immune Regulatory Disorders With an Autoimmune Lymphoproliferative Syndrome-Like Phenotype: Immunologic Evaluation, Early Diagnosis and Management. Front Immunol 2021;12:671755

406. Hägele P, Staus P, Scheible R, Uhlmann A, Heeg M, Klemann C, et al. Diagnostic evaluation of paediatric autoimmune lymphoproliferative immunodeficiencies (ALPID): a prospective cohort study. Lancet Haematol 2024;11:e114-e126
407. Magerus A, Rensing-Ehl A, Rao VK, Teachey DT, Rieux-Laucat F and Ehl S. Autoimmune lymphoproliferative immunodeficiencies (ALPIDs): A proposed approach to redefining ALPS and other lymphoproliferative immune disorders. J Allergy Clin Immunol 2024;153:67-76
408. Ferre EMN, Schmitt MM, Lionakis MS. Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. Front Pediatr. 2021; Nov 1;9:723532
409. Kelsen JR and Sullivan KE. Inflammatory Bowel Disease in Primary Immunodeficiencies. Curr Allergy Asthma Rep 2017;17:57
410. Sharifinejad N, Zaki-Dizaji M, Sepahvandi R, Fayyaz F, Dos Santos Vilela MM, ElGhazali G, et al. The clinical, molecular, and therapeutic features of patients with IL10/IL10R deficiency: a systematic review. Clin Exp Immunol 2022;208:281-291
411. Ruffner MA and Sullivan KE. Complications Associated with Underweight Primary Immunodeficiency Patients: Prevalence and Associations Within the USIDNET Registry. J Clin Immunol 2018;38:283-293
412. Ardeniz O, Avci CB, Sin A, Ozgen G, Gunsar F, Mete N, et al. Vitamin D deficiency in the absence of enteropathy in three cases with common variable immunodeficiency. Int Arch Allergy Immunol 2008;147:74-83
413. dos Santos-Valente EC, da Silva R, de Moraes-Pinto MI, Sarni RO and Costa-Carvalho BT. Assessment of nutritional status: vitamin A and zinc in patients with common variable immunodeficiency. J Investig Allergol Clin Immunol 2012;22:427-31
414. Pieniawska-Śmiech K, Bar K, Babicki M, Śmiech K and Lewandowicz-Uszyńska A. Assessment of weight and height of patients with primary immunodeficiency disorders and group of children with recurrent respiratory tract infections. BMC Immunol 2020;21:42
415. Kouhkan A, Pourpak Z, Moin M, Dorosty AR, Safaralizadeh R, Teimorian S, et al. A study of malnutrition in Iranian patients with primary antibody deficiency. Iran J Allergy Asthma Immunol 2004;3:189-96
416. Agarwal S and Mayer L. Diagnosis and treatment of gastrointestinal disorders in patients with primary immunodeficiency. Clin Gastroenterol Hepatol 2013;11:1050-63
417. Chung BK, Tsai K, Allan LL, Zheng DJ, Nie JC, Biggs CM, et al. Innate immune control of EBV-infected B cells by invariant natural killer T cells. Blood 2013;122:2600-8
418. Picarda G and Benedict CA. Cytomegalovirus: Shape-Shifting the Immune System. J Immunol 2018;200:3881-3889
419. Khan R, Habbal M, Scaffidi MA, Bukhari AA, Rumman A, Al Ghamdi S, et al. Gastrointestinal Disease in Patients with Common Variable Immunodeficiency: A Retrospective Observational Study. J Can Assoc Gastroenterol 2020;3:162-168
420. Haessler S and Granowitz EV. Norovirus gastroenteritis in immunocompromised patients. N Engl J Med 2013;368:971
421. Revolinski SL and Munoz-Price LS. Clostridium difficile in Immunocompromised Hosts: A Review of Epidemiology, Risk Factors, Treatment, and Prevention. Clin Infect Dis 2019;68:2144-2153
422. Mace EM and Orange JS. Emerging insights into human health and NK cell biology from the study of NK cell deficiencies. Immunol Rev 2019;287:202-225

423. Cohen JI. Herpesviruses in the Activated Phosphatidylinositol-3-Kinase-δ Syndrome. Front Immunol 2018;9:237
424. Mogensen TH. Genetic susceptibility to viral disease in humans. Clin Microbiol Infect 2022;28:1411-1416
425. Hoshino A, Tanita K, Kanda K, Imadome KI, Shikama Y, Yasumi T, et al. High frequencies of asymptomatic Epstein-Barr virus viremia in affected and unaffected individuals with CTLA4 mutations. Clin Immunol 2018;195:45-48
426. Godsell J, Chan S, Slade C, Bryant V, Douglass JA, Sasadeusz J, et al. Cytomegalovirus in primary immunodeficiency. Curr Opin Infect Dis 2021;34:663-671
427. Ansari R, Rosen LB, Lisco A, Gilden D, Holland SM, Zerbe CS, et al. Primary and Acquired Immunodeficiencies Associated With Severe Varicella-Zoster Virus Infections. Clin Infect Dis 2021;73:e2705-e2712
428. Leiding JW and Holland SM. Warts and all: human papillomavirus in primary immunodeficiencies. J Allergy Clin Immunol 2012;130:1030-48
429. Zampella J and Cohen B. Consideration of underlying immunodeficiency in refractory or recalcitrant warts: A review of the literature. Skin Health Dis 2022;2:e98
430. Wolska-Kusnierz B, Bajer A, Caccio S, Heropolitanska-Pliszka E, Bernatowska E, Socha P, et al. Cryptosporidium infection in patients with primary immunodeficiencies. J Pediatr Gastroenterol Nutr 2007;45:458-64
431. Michel M, Chanet V, Galicier L, Ruivard M, Levy Y, Hermine O, et al. Autoimmune thrombocytopenic purpura and common variable immunodeficiency: analysis of 21 cases and review of the literature. Medicine (Baltimore) 2004;83:254-263
432. Price S, Shaw PA, Seitz A, Joshi G, Davis J, Niemela JE, et al. Natural history of autoimmune lymphoproliferative syndrome associated with FAS gene mutations. Blood 2014;123:1989-99
433. Taskin RB, Topyıldız E, Edeer Karaca N, Aksu G, Yılmaz Karapınar D, Kutukculer N. Autoimmune Cytopenias Are Highly Associated with Inborn Errors of Immunity and They May Be the Initial Presentations in Cases without Severe Infections. Int Arch Allergy Immunol. 2024;185:392-401
434. Schiavo E, Martini B, Attardi E, Consonni F, Ciullini Mannurita S, Coniglio ML, et al. Autoimmune Cytopenias and Dysregulated Immunophenotype Act as Warning Signs of Inborn Errors of Immunity: Results From a Prospective Study. Front Immunol. 2022 Jan 4;12:790455.
435. Chapel H, Lucas M, Lee M, Bjorkander J, Webster D, Grimbacher B, et al. Common variable immunodeficiency disorders: division into distinct clinical phenotypes. Blood 2008;112:277-86
436. Feuille EJ, Anooshiravani N, Sullivan KE, Fuleihan RL and Cunningham-Rundles C. Autoimmune Cytopenias and Associated Conditions in CVID: a Report From the USIDNET Registry. J Clin Immunol 2018;38:28-34
437. Neven B, Magerus-Chatinet A, Florkin B, Gobert D, Lambotte O, De Somer L, et al. A survey of 90 patients with autoimmune lymphoproliferative syndrome related to TNFRSF6 mutation. Blood 2011;118:4798-807
438. Palmisani E, Miano M, Micalizzi C, Calvillo M, Pierri F, Terranova P, et al. Clinical features and therapeutic challenges of cytopenias belonging to alps and alps-related (ARS) phenotype. Br J Haematol 2019;184:861-864

439. Gambineri E, Ciullini Mannurita S, Hagin D, Vignoli M, Anover-Sombke S, DeBoer S, et al. Clinical, Immunological, and Molecular Heterogeneity of 173 Patients With the Phenotype of Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-Linked (IPEX) Syndrome. Front Immunol 2018;9:2411
440. Schwab C, Gabrysch A, Olbrich P, Patiño V, Warnatz K, Wolff D, et al. Phenotype, penetrance, and treatment of 133 cytotoxic T-lymphocyte antigen 4-insufficient subjects. J Allergy Clin Immunol 2018;142:1932-1946
441. Elkaim E, Neven B, Bruneau J, Mitsui-Sekinaka K, Stanislas A, Heurtier L, et al. Clinical and immunologic phenotype associated with activated phosphoinositide 3-kinase δ syndrome 2: A cohort study. J Allergy Clin Immunol 2016;138:210-218.e9
442. Ravell JC, Matsuda-Lennikov M, Chauvin SD, Zou J, Biancalana M, Deeb SJ, et al. Defective glycosylation and multisystem abnormalities characterize the primary immunodeficiency XMEN disease. J Clin Invest 2020;130:507-522
443. Margot H, Boursier G, Duflos C, Sanchez E, Amiel J, Andrau JC, et al. Immunopathological manifestations in Kabuki syndrome: a registry study of 177 individuals. Genet Med 2020;22:181-188
444. Murakami H, Tsurusaki Y, Enomoto K, Kuroda Y, Yokoi T, Furuya N, et al. Update of the genotype and phenotype of KMT2D and KDM6A by genetic screening of 100 patients with clinically suspected Kabuki syndrome. Am J Med Genet A 2020;182:2333-2344
445. Toubiana J, Okada S, Hiller J, Oleastro M, Lagos Gomez M, Aldave Becerra JC, et al. Heterozygous STAT1 gain-of-function mutations underlie an unexpectedly broad clinical phenotype. Blood 2016;127:3154-64
446. Fabre A, Marchal S, Barlogis V, Mari B, Barbry P, Rohrlich PS, et al. Clinical Aspects of STAT3 Gain-of-Function Germline Mutations: A Systematic Review. J Allergy Clin Immunol Pract 2019;7:1958-1969.e9
447. Leiding JW, Vogel TP, Santarlas VGJ, Mhaskar R, Smith MR, Carisey A, et al. Monogenic early-onset lymphoproliferation and autoimmunity: Natural history of STAT3 gain-of-function syndrome. J Allergy Clin Immunol 2023;151:1081-1095
448. Mahlaoui N, Pellier I, Mignot C, Jais JP, Bilhou-Nabéra C, Moshous D, et al. Characteristics and outcome of early-onset, severe forms of Wiskott-Aldrich syndrome. Blood 2013;121:1510-6
449. Dupuis-Girod S, Medioni J, Haddad E, Quartier P, Cavazzana-Calvo M, Le Deist F, et al. Autoimmunity in Wiskott-Aldrich syndrome: risk factors, clinical features, and outcome in a single-center cohort of 55 patients. Pediatrics 2003;111:e622-7
450. Cancrini C, Puliafito P, Digilio MC, Soresina A, Martino S, Rondelli R, et al. Clinical features and follow-up in patients with 22q11.2 deletion syndrome. J Pediatr 2014;164:1475-80.e2
451. Montin D, Marolda A, Licciardi F, Robasto F, Di Cesare S, Ricotti E, et al. Immunophenotype Anomalies Predict the Development of Autoimmune Cytopenia in 22q11.2 Deletion Syndrome. J Allergy Clin Immunol Pract 2019;7:2369-2376
452. Neven Q, Boulanger C, Bruwier A, de Ville de Goyet M, Meyts I, Moens L, et al. Clinical Spectrum of Ras-Associated Autoimmune Leukoproliferative Disorder (RALD). J Clin Immunol 2021;41:51-58
453. Chan AY and Torgerson TR. Primary immune regulatory disorders: a growing universe of immune dysregulation. Curr Opin Allergy Clin Immunol 2020;20:582-590

454. Cepika AM, Sato Y, Liu JM, Uyeda MJ, Bacchetta R and Roncarolo MG. Tregopathies: Monogenic diseases resulting in regulatory T-cell deficiency. J Allergy Clin Immunol 2018;142:1679-1695
455. Damoiseaux J, Dotan A, Fritzler MJ, Bogdanos DP, Meroni PL, Roggenbuck D, et al. Autoantibodies and SARS-CoV2 infection: The spectrum from association to clinical implication: Report of the 15th Dresden Symposium on Autoantibodies. Autoimmun Rev 2022;21:103012
456. Bastard P, Rosen LB, Zhang Q, Michailidis E, Hoffmann HH, Zhang Y, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. Science 2020;370
456. Sakurai Y. Autoimmune Aspects of Kawasaki Disease. J Investig Allergol Clin Immunol 2019;29:251-261
457. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. N Engl J Med 2020;383:334-346
458. Tahiat A, Yagoubi A, Ladj MS, Belbouab R, Aggoune S, Atek L, et al. Diagnostic and Predictive Contribution of Autoantibodies Screening in a Large Series of Patients With Primary Immunodeficiencies. Front Immunol 2021;12:665322
459. Vrbensky JR, Moore JE, Arnold DM, Smith JW, Kelton JG and Nazy I. The sensitivity and specificity of platelet autoantibody testing in immune thrombocytopenia: a systematic review and meta-analysis of a diagnostic test. J Thromb Haemost 2019;17:787-794
460. Soto ME, Hernández-Becerril N, Perez-Chiney AC, Hernández-Rizo A, Telich-Tarriba JE, Juárez-Orozco LE, et al. Predictive value of antinuclear antibodies in autoimmune diseases classified by clinical criteria: Analytical study in a specialized health institute, one year follow-up. Results Immunol 2015;5:13-22
461. Burbelo PD, Castagnoli R, Shimizu C, Delmonte OM, Dobbs K, Discepolo V, et al. Autoantibodies Against Proteins Previously Associated With Autoimmunity in Adult and Pediatric Patients With COVID-19 and Children With MIS-C. Front Immunol 2022;13:841126
462. Grüter T, Ott A, Meyer W, Jarius S, Kinner M, Motte J, et al. Effects of IVIg treatment on autoantibody testing in neurological patients: marked reduction in sensitivity but reliable specificity. J Neurol 2020;267:715-720
463. Salib MM, Morkos M, Yu C, D'Souza M, Yosar J, Potter JM, et al. Intravenous immunoglobulin as a source of passively acquired thyroid autoantibodies. Pathology 2024;56:129-130
464. Miyamoto T, Fukunaga Y, Ogasawara A, Munakata A and Murai K. Autoantibody profiles in intravenous immunoglobulin preparations: A possible cause of mistaken autoimmunity diagnosis. Transfusion 2024;64:597-605
465. Lee EY, Betschel S and Grunebaum E. Monitoring patients with uncomplicated common variable immunodeficiency: a systematic review. Allergy Asthma Clin Immunol 2022;18:21
466. Cunningham-Rundles C. How I treat common variable immune deficiency. Blood 2010;116:7-15
467. Cook C. The lost art of the clinical examination: an overemphasis on clinical special tests. J Man Manip Ther 2010;18:3-4

468. Bethune C, Egner W, Garcez T, Huissoon A, Jolles S, Karim Y, et al. British Society for Immunology/United Kingdom Primary Immunodeficiency Network consensus statement on managing non-infectious complications of common variable immunodeficiency disorders. Clin Exp Immunol 2019;196:328-335
469. Salvator H, Mahlaoui N, Catherinot E, Rivaud E, Pilmis B, Borie R, et al. Pulmonary manifestations in adult patients with chronic granulomatous disease. Eur Respir J 2015;45:1613-23
470. Schussler E, Beasley MB and Maglione PJ. Lung Disease in Primary Antibody Deficiencies. J Allergy Clin Immunol Pract 2016;4:1039-1052
471. Maglione PJ, Overbey JR, Radigan L, Bagiella E and Cunningham-Rundles C. Pulmonary radiologic findings in common variable immunodeficiency: clinical and immunological correlations. Ann Allergy Asthma Immunol 2014;113:452-9
472. Maglione PJ, Ko HM, Beasley MB, Strauchen JA and Cunningham-Rundles C. Tertiary lymphoid neogenesis is a component of pulmonary lymphoid hyperplasia in patients with common variable immunodeficiency. J Allergy Clin Immunol 2014;133:535-42
473. Scarpa R, Cinetto F, Milito C, Gianese S, Soccodato V, Buso H, et al. Common and Uncommon CT Findings in CVID-Related GL-ILD: Correlations with Clinical Parameters, Therapeutic Decisions and Potential Implications in the Differential Diagnosis. J Clin Immunol 2023;43:1903-1915
474. Smits BM, Boland SL, Hol ME, Dandis R, Leavis HL, de Jong PA, et al. Pulmonary Computed Tomography Screening Frequency in Primary Antibody Deficiency. J Allergy Clin Immunol Pract 2024;12:1037-1048.e3
475. Bhatt JM, Bush A, van Gerven M, Nissenkorn A, Renke M, Yarlett L, et al. ERS statement on the multidisciplinary respiratory management of ataxia telangiectasia. Eur Respir Rev 2015;24:565-81
476. Serra G, Milito C, Mitrevski M, Granata G, Martini H, Pesce AM, et al. Lung MRI as a possible alternative to CT scan for patients with primary immune deficiencies and increased radiosensitivity. Chest 2011;140:1581-1589
477. Khor YH, Goh NS, Glaspole I, Holland AE and McDonald CF. Exertional Desaturation and Prescription of Ambulatory Oxygen Therapy in Interstitial Lung Disease. Respir Care 2019;64:299-306
478. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-7
479. Motta-Raymundo A, Rosmaninho P, Santos DF, Ferreira RD, Silva SP, Ferreira C, et al. Contribution of Helicobacter pylori to the Inflammatory Complications of Common Variable Immunodeficiency. Front Immunol 2022;13:834137
480. Quinti I, Soresina A, Spadaro G, Martino S, Donnanno S, Agostini C, et al. Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. J Clin Immunol 2007;27:308-16
481. Pikkarainen S, Martelius T, Ristimäki A, Siitonen S, Seppänen MRJ and Färkkilä M. A High Prevalence of Gastrointestinal Manifestations in Common Variable Immunodeficiency. Am J Gastroenterol 2019;114:648-655
482. Khare R, Espy MJ, Cebelinski E, Boxrud D, Sloan LM, Cunningham SA, et al. Comparative evaluation of two commercial multiplex panels for detection of gastrointestinal pathogens by use of clinical stool specimens. J Clin Microbiol 2014;52:3667-73

483. Levitt DG and Levitt MD. Protein losing enteropathy: comprehensive review of the mechanistic association with clinical and subclinical disease states. Clin Exp Gastroenterol 2017;10:147-168
484. Shimizu M, Nikolov NP, Ueno K, Ohta K, Siegel RM, Yachie A, Candotti F. Development of IgA nephropathy-like glomerulonephritis associated with Wiskott-Aldrich syndrome protein deficiency. Clin Immunol 2012; 142: 160-166
485. Lehman H. Skin manifestations of primary immune deficiency. Clin Rev Allergy Immunol 2014;46:112-9
486. Wanat KA, Perelygina L, Chen MH, Hao L, Abernathy E, Bender NR, et al. Association of Persistent Rubella Virus With Idiopathic Skin Granulomas in Clinically Immunocompetent Adults. JAMA Dermatol 2022;158:626-633
487. Cagdas D, Ayasun R, Gulseren D, Sanal O and Tezcan I. Cutaneous Findings in Inborn Errors of Immunity: An Immunologist's Perspective. J Allergy Clin Immunol Pract 2023;11:3030-3039
488. Takasawa K, Kanegane H, Kashimada K, Morio T. Endocrinopathies in Inbron Errors of Immunity. Front Immunol. 2021 Nov 23: 12:786241
489. Baris S, Ozen A, Ercan H, Karakoc-Aydiner E, Cagan H, Ozdemir C, et al. Osteoporosis: an ignored complication of CVID. Pediatr Allergy Immunol 2011;22:676-83
490. Sowerwine KJ, Shaw PA, Gu W, Ling JC, Collins MT, Darnell DN, et al. Bone density and fractures in autosomal dominant hyper IgE syndrome. J Clin Immunol 2014;34:260-4
491. Ballow M, Sánchez-Ramón S and Walter JE. Secondary Immune Deficiency and Primary Immune Deficiency Crossovers: Hematological Malignancies and Autoimmune Diseases. Front Immunol 2022;13:928062
492. Mayor PC, Eng KH, Singel KL, Abrams SI, Odunsi K, Moysich KB, et al. Cancer in primary immunodeficiency diseases: Cancer incidence in the United States Immune Deficiency Network Registry. J Allergy Clin Immunol 2018;141:1028-1035
493. Chua I, Quinti I and Grimbacher B. Lymphoma in common variable immunodeficiency: interplay between immune dysregulation, infection and genetics. Curr Opin Hematol 2008;15:368-74
494. Tiri A, Masetti R, Conti F, Tignanelli A, Turrini E, Bertolini P, et al. Inborn Errors of Immunity and Cancer. Biology (Basel) 2021;10
495. Chinen J, Anmuth D, Franklin AR and Shearer WT. Long-term follow-up of patients with primary immunodeficiencies. J Allergy Clin Immunol 2007;120:795-7
496. Pollard JM and Gatti RA. Clinical radiation sensitivity with DNA repair disorders: an overview. Int J Radiat Oncol Biol Phys 2009;74:1323-31
497. Sander M, Sander M, Burbidge T and Beecker J. The efficacy and safety of sunscreen use for the prevention of skin cancer. CMAJ 2020;192:E1802-e1808
498. Hewavisenti RV, Arena J, Ahlenstiel CL and Sasson SC. Human papillomavirus in the setting of immunodeficiency: Pathogenesis and the emergence of next-generation therapies to reduce the high associated cancer risk. Front Immunol 2023;14:1112513
499. Handisurya A, Schellenbacher C, Reininger B, Koszik F, Vyhnanek P, Heitger A, et al. A quadrivalent HPV vaccine induces humoral and cellular immune responses in WHIM immunodeficiency syndrome. Vaccine 2010;28:4837-41
500. Connelly JA and Walkovich K. Diagnosis and therapeutic decision-making for the neutropenic patient. Hematology Am Soc Hematol Educ Program 2021;2021:492-503

501. Carrasquillo JA, Chen CC, Price S, Whatley M, Avila NA, Pittaluga S, et al. 18F-FDG PET Imaging Features of Patients With Autoimmune Lymphoproliferative Syndrome. Clin Nucl Med 2019;44:949-955
502. Mortaz E, Tabarsi P, Mansouri D, Khosravi A, Garssen J, Velayati A, et al. Cancers Related to Immunodeficiencies: Update and Perspectives. Front Immunol 2016;7:365
503. Cunniff C, Bassetti JA and Ellis NA. Bloom's Syndrome: Clinical Spectrum, Molecular Pathogenesis, and Cancer Predisposition. Mol Syndromol 2017;8:4-23
504. Yakaboski E, Fuleihan RL, Sullivan KE, Cunningham-Rundles C and Feuille E. Lymphoproliferative Disease in CVID: a Report of Types and Frequencies from a US Patient Registry. J Clin Immunol 2020;40:524-530
505. Cohen JI. GATA2 Deficiency and Epstein-Barr Virus Disease. Front Immunol 2017;8:1869
506. Nguyen J, Alexander T, Jiang H, Hill N, Abdullaev Z, Pack SD, et al. Melanoma in patients with GATA2 deficiency. Pigment Cell Melanoma Res 2018;31:337-340
507. Kose H, Karali Z, Bodur M, Cekic S and Kilic SS. Neurological involvement in patients with primary immunodeficiency. Allergol Immunopathol (Madr) 2024;52:85-92
508. Titman P, Pink E, Skucek E, O'Hanlon K, Cole TJ, Gaspar J, et al. Cognitive and behavioral abnormalities in children after hematopoietic stem cell transplantation for severe congenital immunodeficiencies. Blood 2008;112:3907-13
509. Chapman DP, Perry GS and Strine TW. The vital link between chronic disease and depressive disorders. Prev Chronic Dis 2005;2:A14
510. Campbell M, Clarke A, Symes A, Workman S, Stauss H and Webster AD. Investigating the Effectiveness, Acceptability and Impact on Healthcare Usage of Providing a Cognitive-Behavioural Based Psychological Therapy Service for Patients with Primary Antibody Deficiency. J Clin Immunol 2018;38:214-220
511. Manusama OR, van Beveren NJM, van Hagen PM, Drexhage HA and Dalm V. Psychological Symptoms in Primary Immunodeficiencies: a Common Comorbidity? J Clin Immunol 2022;42:695-698
512. Tabolli S, Giannantoni P, Pulvirenti F, La Marra F, Granata G, Milito C, et al. Longitudinal study on health-related quality of life in a cohort of 96 patients with common variable immune deficiencies. Front Immunol 2014;5:605
513. Sowers KL, Gayda-Chelder CA and Galantino ML. Self-reported cognitive impairment in individuals with Primary Immunodeficiency Disease. Brain Behav Immun Health 2020;9:100170
514. Isung J, Williams K, Isomura K, Gromark C, Hesselmark E, Lichtenstein P, et al. Association of Primary Humoral Immunodeficiencies With Psychiatric Disorders and Suicidal Behavior and the Role of Autoimmune Diseases. JAMA Psychiatry 2020;77:1147-1154
515. De Almeida BI, Smith TL, Delic A, Esquibel L, Galli J, Millsap L, et al. Neurologic Manifestations of Common Variable Immunodeficiency: Impact on Quality of Life. Neurol Neuroimmunol Neuroinflamm 2023;10
516. Nijhof LN, van Brussel M, Pots EM, van Litsenburg RRL, van de Putte EM, van Montfrans JM, et al. Severe Fatigue Is Common Among Pediatric Patients with Primary Immunodeficiency and Is Not Related to Disease Activity. J Clin Immunol 2021;41:1198-1207

517. Hajjar J, Kutac C, Rider NL, Seeborg FO, Scalchunes C and Orange J. Fatigue and the wear-off in adult patients with common variable immunodeficiency. Clin Exp Immunol 2018;194:327-338
518. Hajjar J, Guffey D, Minard CG and Orange JS. Increased Incidence of Fatigue in Patients with Primary Immunodeficiency Disorders: Prevalence and Associations Within the US Immunodeficiency Network Registry. J Clin Immunol 2017;37:153-165
519. Spitzer RL, Kroenke K, Williams JB and Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166:1092-7
520. Johnson JG, Harris ES, Spitzer RL and Williams JB. The patient health questionnaire for adolescents: validation of an instrument for the assessment of mental disorders among adolescent primary care patients. J Adolesc Health 2002;30:196-204
522. Perez EE, Orange JS, Bonilla F, Chinen J, Chinn IK, Dorsey M, et al. Update on the use of immunoglobulin in human disease: A review of evidence. J Allergy Clin Immunol 2017;139:S1-s46
523. Hernandez-Trujillo HS, Chapel H, Lo Re V, 3rd, Notarangelo LD, Gathmann B, Grimbacher B, et al. Comparison of American and European practices in the management of patients with primary immunodeficiencies. Clin Exp Immunol 2012;169:57-69
524. Brennan VM, Salomé-Bentley NJ and Chapel HM. Prospective audit of adverse reactions occurring in 459 primary antibody-deficient patients receiving intravenous immunoglobulin. Clin Exp Immunol 2003;133:247-51
525. Ballow M. Safety of IGIV therapy and infusion-related adverse events. Immunol Res 2007;38:122-32
526. Stiehm ER. Adverse effects of human immunoglobulin therapy. Transfus Med Rev 2013;27:171-8
527. Cherin P, Marie I, Michallet M, Pelus E, Dantal J, Crave JC, et al. Management of adverse events in the treatment of patients with immunoglobulin therapy: A review of evidence. Autoimmun Rev 2016;15:71-81
528. Brown HC and Ballas ZK. Acute thromboembolic events associated with intravenous immunoglobulin infusion in antibody-deficient patients. J Allergy Clin Immunol 2003;112:797-9
529. Feldmeyer L, Benden C, Haile SR, Boehler A, Speich R, French LE, et al. Not all intravenous immunoglobulin preparations are equally well tolerated. Acta Derm Venereol 2010;90:494-7
530. Bethune C, Herriot R. Switching immunoglobulin products, what are the implications? Result of 2018 census of immunology centres. Clin Med (Lond) 2019;19:201-204
531. Cicha A, Fischer MB, Wesinger A, Haas S, Bauer WM, Wolf HM, et al. Effect of intravenous immunoglobulin administration on erythrocyte and leucocyte parameters. J Eur Acad Dermatol Venereol 2018;32:1004-1010
532. Cuesta H, El Menyawi I, Hubsch A, Hoefferer L, Mielke O, Gabriel S, et al. Incidence and risk factors for intravenous immunoglobulin-related hemolysis: A systematic review of clinical trial and real-world populations. Transfusion 2022;62:1894-1907
533. Dantal J. Intravenous immunoglobulins: in-depth review of excipients and acute kidney injury risk. Am J Nephrol 2013;38:275-84
534. Lin RY, Rodriguez-Baez G, Bhargave GA and Lin H. Intravenous gammaglobulin-associated renal impairment reported to the FDA: 2004 - 2009. Clin Nephrol 2011;76:365-72

535. Moulis G, Sailler L, Sommet A, Lapeyre-Mestre M and Montastruc JL. Exposure to inhibitors of the renin-angiotensin system is a major independent risk factor for acute renal failure induced by sucrose-containing intravenous immunoglobulins: a case-control study. Pharmacoepidemiol Drug Saf 2012;21:314-9
536. Centers for Disease Control and Prevention (CDC). Outbreak of hepatitis C associated with intravenous immunoglobulin administration--United States, October 1993-June 1994. MMWR Morb Mortal Wkly Rep.1994;43:505-509
537. Poelsler G, Berting A, Kindermann J, Spruth M, Hämmerle T, Teschner W, et al. A new liquid intravenous immunoglobulin with three dedicated virus reduction steps: virus and prion reduction capacity. Vox Sang. 2008;94(3):184-192.
538. Lucas M, Lee M, Lortan J, Lopez-Granados E, Misbah S and Chapel H. Infection outcomes in patients with common variable immunodeficiency disorders: relationship to immunoglobulin therapy over 22 years. J Allergy Clin Immunol 2010;125:1354-1360.e4
539. Quinti I, Soresina A, Guerra A, Rondelli R, Spadaro G, Agostini C, et al. Effectiveness of immunoglobulin replacement therapy on clinical outcome in patients with primary antibody deficiencies: results from a multicenter prospective cohort study. J Clin Immunol 2011;31:315-22767.
540. Shrestha P, Karmacharya P, Wang Z, Donato A and Joshi AY. Impact of IVIG vs. SCIG on IgG trough level and infection incidence in primary immunodeficiency diseases: A systematic review and meta-analysis of clinical studies. World Allergy Organ J 2019;12:100068
541. Ballow M. Optimizing immunoglobulin treatment for patients with primary immunodeficiency disease to prevent pneumonia and infection incidence: review of the current data. Ann Allergy Asthma Immunol 2013;111:S2-5
542. Berger M. Choices in IgG replacement therapy for primary immune deficiency diseases: subcutaneous IgG vs. intravenous IgG and selecting an optimal dose. Curr Opin Allergy Clin Immunol 2011;11:532-8
543. Landersdorfer CB, Bexon M, Edelman J, Rojavin M, Kirkpatrick CM, Lu J, et al. Pharmacokinetic modeling and simulation of biweekly subcutaneous immunoglobulin dosing in primary immunodeficiency. Postgrad Med 2013;125:53-61
544. Sidhu J, Rojavin M, Pfister M and Edelman J. Enhancing Patient Flexibility of Subcutaneous Immunoglobulin G Dosing: Pharmacokinetic Outcomes of Various Maintenance and Loading Regimens in the Treatment of Primary Immunodeficiency. Biol Ther 2014;4:41-55
545. Berger M, Jolles S, Orange JS and Sleasman JW. Bioavailability of IgG administered by the subcutaneous route. J Clin Immunol 2013;33:984-90
546. Bonagura VR. Using intravenous immunoglobulin (IVIG) to treat patients with primary immune deficiency disease. J Clin Immunol 2013;33 Suppl 2:S90-4
547. Orange JS, Grossman WJ, Navickis RJ and Wilkes MM. Impact of trough IgG on pneumonia incidence in primary immunodeficiency: A meta-analysis of clinical studies. Clin Immunol 2010;137:21-30
548. Orange JS, Belohradsky BH, Berger M, Borte M, Hagan J, Jolles S, et al. Evaluation of correlation between dose and clinical outcomes in subcutaneous immunoglobulin replacement therapy. Clin Exp Immunol 2012;169:172-81
549. Stiehm ER, Orange JS, Ballow M and Lehman H. Therapeutic use of immunoglobulins. Adv Pediatr 2010;57:185-218

550. Burks AW, Sampson HA and Buckley RH. Anaphylactic reactions after gamma globulin administration in patients with hypogammaglobulinemia. Detection of IgE antibodies to IgA. N Engl J Med 1986;314:560-4
551. Collet A, de Chambure DP, Moitrot E, Breyne G, Mirgot F, Rogeau S, et al. Non-allergic hypersensitivity reactions to immunoglobulin preparations in antibody deficiencies: what role for anti-IgA IgG and complement activation. Clin Rev Allergy Immunol 2024; 67: 47-57
552. Rachid R and Bonilla FA. The role of anti-IgA antibodies in causing adverse reactions to gamma globulin infusion in immunodeficient patients: a comprehensive review of the literature. J Allergy Clin Immunol 2012;129:628-34
553. Jolles S, Orange JS, Gardulf A, Stein MR, Shapiro R, Borte M, et al. Current treatment options with immunoglobulin G for the individualization of care in patients with primary immunodeficiency disease. Clin Exp Immunol 2015;179:146-60
554. Fasth A and Nyström J. Quality of life and health-care resource utilization among children with primary immunodeficiency receiving home treatment with subcutaneous human immunoglobulin. J Clin Immunol 2008;28:370-8
555. Duff C and Ballow M. Nuts and Bolts of Subcutaneous Therapy. Immunol Allergy Clin North Am 2020;40:527-537
556. Slack MA, Thomsen IP. Prevention of Infectious Complications in Patients With Chronic Granulomatous Disease. J Pediatric Infect Dis Soc 2018;7:S25-S30
557. Margolis DM, Melnick DA, Alling DW and Gallin JI. Trimethoprim-sulfamethoxazole prophylaxis in the management of chronic granulomatous disease. J Infect Dis 1990;162:723-6
558. Weening RS, Kabel P, Pijman P and Roos D. Continuous therapy with sulfamethoxazole-trimethoprim in patients with chronic granulomatous disease. J Pediatr 1983;103:127-30
559. Gallin JI, Alling DW, Malech HL, Wesley R, Koziol D, Marciano B, et al. Itraconazole to prevent fungal infections in chronic granulomatous disease. N Engl J Med 2003;348:2416-22
560. Tang H, Shi W, Song Y and Han J. Voriconazole exposure and risk of cutaneous squamous cell carcinoma among lung or hematopoietic cell transplant patients: A systematic review and meta-analysis. J Am Acad Dermatol 2019;80:500-507.e10
561. Guarascio AJ, Bhanot N and Min Z. Voriconazole-associated periostitis: Pathophysiology, risk factors, clinical manifestations, diagnosis, and management. World J Transplant 2021;11:356-371
562. International Chronic Granulomatouse Disease Cooperative Disease Study GroupA controlled trial of interferon gamma to prevent infection in chronic granulomatous disease. N Engl J Med 1991;324:509-16
563. Lugo Reyes SO, González Garay A, González Bobadilla NY, Rivera Lizárraga DA, Madrigal Paz AC, Medina-Torres EA, et al. Efficacy and Safety of Interferon-Gamma in Chronic Granulomatous Disease: a Systematic Review and Meta-analysis. J Clin Immunol 2023;43:578-584
564. Hicks ED, Agada NO, Yates TR, Kelly MS, Tam JS, Ferdman RM, et al. Case Report: Nontuberculous mycobacterial infections in children with complete DiGeorge anomaly. Front Immunol 2023;14:1078976
565. Freeman AF and Holland SM. Antimicrobial prophylaxis for primary immunodeficiencies. Curr Opin Allergy Clin Immunol 2009;9:525-30

566. Yong PL, Boyle J, Ballow M, Boyle M, Berger M, Bleesing J, et al. Use of intravenous immunoglobulin and adjunctive therapies in the treatment of primary immunodeficiencies: A working group report of and study by the Primary Immunodeficiency Committee of the American Academy of Allergy Asthma and Immunology. Clin Immunol 2010;135:255-63
567. Ballow M, Paris K and de la Morena M. Should Antibiotic Prophylaxis Be Routinely Used in Patients with Antibody-Mediated Primary Immunodeficiency? J Allergy Clin Immunol Pract 2018;6:421-426
568. Haworth CS, Bilton D and Elborn JS. Long-term macrolide maintenance therapy in non-CF bronchiectasis: evidence and questions. Respir Med 2014;108:1397-408
569. Milito C, Pulvirenti F, Cinetto F, Lougaris V, Soresina A, Pecoraro A, et al. Double-blind, placebo-controlled, randomized trial on low-dose azithromycin prophylaxis in patients with primary antibody deficiencies. J Allergy Clin Immunol 2019;144:584-593.e7
570. Romo-Gonzalez C, Bustamante-Ogando JC, Yamazaki-Nakashimada MA, Aviles-Jimenez F, Otero-Mendoza F, Espinosa-Rosales FJ, et al. Infections With Enterohepatic Non-H. pylori Helicobacter Species in X-Linked Agammaglobulinemia: Clinical Cases and Review of the Literature. Front Cell Infect Microbiol 2021;11:807136
571. Ameratunga R, Ahn Y, Steele R and Woon ST. Transient hypogammaglobulinaemia of infancy: many patients recover in adolescence and adulthood. Clin Exp Immunol 2019;198:224-232
572. Hajjar J, Nguyen AL, Constantine G, Kutac C, Syed MN, Orange JS, et al. Prophylactic Antibiotics Versus Immunoglobulin Replacement in Specific Antibody Deficiency. J Clin Immunol 2020;40:158-164
573. Lee GM. Preventing infections in children and adults with asplenia. Hematology Am Soc Hematol Educ Program 2020;2020:328-335
574. Ram S, Lewis LA and Rice PA. Infections of people with complement deficiencies and patients who have undergone splenectomy. Clin Microbiol Rev 2010;23:740-80
575. Tsilifis C, Freeman AF and Gennery AR. STAT3 Hyper-IgE Syndrome-an Update and Unanswered Questions. J Clin Immunol 2021;41:864-880
576. Chandesris MO, Melki I, Natividad A, Puel A, Fieschi C, Yun L, et al. Autosomal dominant STAT3 deficiency and hyper-IgE syndrome: molecular, cellular, and clinical features from a French national survey. Medicine (Baltimore) 2012;91:e1-e19
577. Leven EA, Maffucci P, Ochs HD, Scholl PR, Buckley RH, Fuleihan RL, et al. Hyper IgM Syndrome: a Report from the USIDNET Registry. J Clin Immunol 2016;36:490-501
578. Aydin SE, Kilic SS, Aytekin C, Kumar A, Porras O, Kainulainen L, et al. DOCK8 deficiency: clinical and immunological phenotype and treatment options - a review of 136 patients. J Clin Immunol 2015;35:189-98
579. Candotti F. Clinical Manifestations and Pathophysiological Mechanisms of the Wiskott-Aldrich Syndrome. J Clin Immunol 2018;38:13-27
580. Skouboe MK, Werner M and Mogensen TH. Inborn Errors of Immunity Predisposing to Herpes Simplex Virus Infections of the Central Nervous System. Pathogens 2023;12: 310
581. Gans H, Chemaly RF. Varicella zoster immune globulin (human) (VARIZIG) in immunocompromised patients: a subgroup analysis for safety and outcomes from a large, expanded-access program. BMC Infect Dis. 2021;21(1):46

582. Dupuis S, Jouanguy E, Al-Hajjar S, Fieschi C, Al-Mohsen IZ, Al-Jumaah S, et al. Impaired response to interferon-alpha/beta and lethal viral disease in human STAT1 deficiency. Nat Genet 2003;33:388-91
583. Campbell TM, Liu Z, Zhang Q, Moncada-Velez M, Covill LE, Zhang P, et al. Respiratory viral infections in otherwise healthy humans with inherited IRF7 deficiency. J Exp Med 2022;219
584. Zhang Q, Bastard P, Cobat A and Casanova JL. Human genetic and immunological determinants of critical COVID-19 pneumonia. Nature 2022;603:587-598
585. Chan KKP and Hui DSC. Antiviral therapies for influenza. Curr Opin Infect Dis 2023;36:124-131
586. Wu UI and Holland SM. Host susceptibility to non-tuberculous mycobacterial infections. Lancet Infect Dis 2015;15:968-80
587. Egri N, Esteve-Solé A, Deyà-Martínez À, Ortiz de Landazuri I, Vlagea A, García AP, et al. Primary immunodeficiency and chronic mucocutaneous candidiasis: pathophysiological, diagnostic, and therapeutic approaches. Allergol Immunopathol (Madr) 2021;49:118-127
588. van de Veerdonk FL and Netea MG. Treatment options for chronic mucocutaneous candidiasis. J Infect 2016;72 Suppl:S56-60
589. Forbes LR, Vogel TP, Cooper MA, Castro-Wagner J, Schussler E, Weinacht KG, et al. Jakinibs for the treatment of immune dysregulation in patients with gain-of-function signal transducer and activator of transcription 1 (STAT1) or STAT3 mutations. J Allergy Clin Immunol 2018;142:1665-1669
590. Odio CD, Milligan KL, McGowan K, Rudman Spergel AK, Bishop R, Boris L, et al. Endemic mycoses in patients with STAT3-mutated hyper-IgE (Job) syndrome. J Allergy Clin Immunol 2015;136:1411-3.e1-2
591. Glocker EO, Hennigs A, Nabavi M, Schäffer AA, Woellner C, Salzer U, et al. A homozygous CARD9 mutation in a family with susceptibility to fungal infections. N Engl J Med 2009;361:1727-35
592. Eckert JW, Abramson SL, Starke J and Brandt ML. The surgical implications of chronic granulomatous disease. Am J Surg 1995;169:320-3
593. Freeman AF, Renner ED, Henderson C, Langenbeck A, Olivier KN, Hsu AP, et al. Lung parenchyma surgery in autosomal dominant hyper-IgE syndrome. J Clin Immunol 2013;33:896-902
594. Squire JD, Gardner PJ, Moutsopoulos NM and Leiding JW. Antibiotic Prophylaxis for Dental Treatment in Patients with Immunodeficiency. J Allergy Clin Immunol Pract 2019;7:819-823
595. Viswanathan M, Kahwati LC, Golin CE, Blalock SJ, Coker-Schwimmer E, Posey R, et al. Medication therapy management interventions in outpatient settings: a systematic review and meta-analysis. JAMA Intern Med 2015;175:76-87
596. Siddiqui S, Anderson VL, Hilligoss DM, Abinun M, Kuijpers TW, Masur H, et al. Fulminant mulch pneumonitis: an emergency presentation of chronic granulomatous disease. Clin Infect Dis 2007;45:673-81
597. Freeman AF and Holland SM. Clinical manifestations, etiology, and pathogenesis of the hyper-IgE syndromes. Pediatr Res 2009;65:32r-37r
598. Zerbe CS and Holland SM. Disseminated histoplasmosis in persons with interferon-gamma receptor 1 deficiency. Clin Infect Dis 2005;41:e38-41

599. Meher-Homji Z, Mangalore RP, P DRJ and K YLC. Chromobacterium violaceum infection in chronic granulomatous disease: a case report and review of the literature. JMM Case Rep 2017;4:e005084
600. Ben Yakov G, Sharma D, Cho MH, Shah NN, Hickstein D, Urban A, et al. Cryptosporidium infection in dedicator of cytokinesis 8 (DOCK 8) deficiency. J Allergy Clin Immunol Pract 2020;8:3663-3666.e1
601. de la Morena MT, Leonard D, Torgerson TR, Cabral-Marques O, Slatter M, Aghamohammadi A, et al. Long-term outcomes of 176 patients with X-linked hyper-IgM syndrome treated with or without hematopoietic cell transplantation. J Allergy Clin Immunol 2017;139:1282-1292
602. Cagdas D, Mayr D, Baris S, Worley L, Langley DB, Metin A, et al. Genomic Spectrum and Phenotypic Heterogeneity of Human IL-21 Receptor Deficiency. J Clin Immunol 2021;41:1272-1290
603. Oksenhendler E, Gérard L, Fieschi C, Malphettes M, Mouillot G, Jaussaud R, et al. Infections in 252 patients with common variable immunodeficiency. Clin Infect Dis 2008;46:1547-54
604. Rademacher J, Ringshausen FC, Suhling H, Fuge J, Marsch G, Warnecke G, et al. Lung transplantation for non-cystic fibrosis bronchiectasis. Respir Med 2016;115:60-5
605. Azzu V, Elias JE, Duckworth A, Davies S, Brais R, Kumararatne DS, et al. Liver transplantation in adults with liver disease due to common variable immunodeficiency leads to early recurrent disease and poor outcome. Liver Transpl 2018;24:171-181
606. Bonatti HJR, Roman AL, Krebs E, Sifri CD, Hagspiel KD, Sawyer RG, et al. Good Long-Term Outcome Following Liver Transplant in a Patient With Common Variable Immunodeficiency Syndrome Despite Multiple Infections and Recurrent Nodular Regenerative Hyperplasia. Exp Clin Transplant 2023;21:66-69
607. Janssen WJM, Mohamed Hoesein F, Van de Ven A, Maarschalk J, van Royen F, de Jong PA, et al. IgG trough levels and progression of pulmonary disease in pediatric and adult common variable immunodeficiency disorder patients. J Allergy Clin Immunol 2017;140:303-306.e4
608. Smits B, Goldacker S, Seneviratne S, Malphettes M, Longhurst H, Mohamed OE, et al.The efficacy and safety of systemic corticosteroids as first line treatment for granulomatous lymphocytic interstitial lung disease. J Allergy Clin Immunol. 2023 Aug;152(2):528-537
609. Verbsky JW, Hintermeyer MK, Simpson PM, Feng M, Barbeau J, Rao N, et al. Rituximab and antimetabolite treatment of granulomatous and lymphocytic interstitial lung disease in common variable immunodeficiency. J Allergy Clin Immunol 2021;147:704-712.e17
610. Kröner C, Neumann J, Ley-Zaporozhan J, Hagl B, Meixner I, Spielberger BD, et al. Lung disease in STAT3 hyper-IgE syndrome requires intense therapy. Allergy 2019;74:1691-1702
611. Lamers OAC, Smits BM, Leavis HL, de Bree GJ, Cunningham-Rundles C, Dalm V, et al. Treatment Strategies for GLILD in Common Variable Immunodeficiency: A Systematic Review. Front Immunol 2021;12:606099
612. Hartono S, Ippoliti MR, Mastroianni M, Torres R and Rider NL. Gastrointestinal Disorders Associated with Primary Immunodeficiency Diseases. Clin Rev Allergy Immunol 2019;57:145-165

613. Venhoff N, Emmerich F, Neagu M, Salzer U, Koehn C, Driever S, et al. The role of HLA DQ2 and DQ8 in dissecting celiac-like disease in common variable immunodeficiency. J Clin Immunol 2013;33:909-16
614. Malamut G, Verkarre V, Suarez F, Viallard JF, Lascaux AS, Cosnes J, et al. The enteropathy associated with common variable immunodeficiency: the delineated frontiers with celiac disease. Am J Gastroenterol 2010;105:2262-75
615. Franzblau LE, Fuleihan RL, Cunningham-Rundles C and Wysocki CA. CVID-Associated Intestinal Disorders in the USIDNET Registry: An Analysis of Disease Manifestations, Functional Status, Comorbidities, and Treatment. J Clin Immunol 2023;44:32
616. van Kampen JJA, Dalm V, Fraaij PLA, Oude Munnink BB, Schapendonk CME, Izquierdo-Lara RW, et al. Clinical and In Vitro Evidence Favoring Immunoglobulin Treatment of a Chronic Norovirus Infection in a Patient With Common Variable Immunodeficiency. J Infect Dis 2022;226:1781-1789
617. Brown LK, Clark I, Brown JR, Breuer J and Lowe DM. Norovirus infection in primary immune deficiency. Rev Med Virol 2017;27:e1926
618. Bhattacharya S, Marciano BE, Malech HL, Quezado M, Holland SM, De Ravin SS, et al. Safety and Efficacy of Ustekinumab in the Inflammatory Bowel Disease of Chronic Granulomatous Disease. Clin Gastroenterol Hepatol 2022;20:461-464.e2
619. Uzel G, Orange JS, Poliak N, Marciano BE, Heller T and Holland SM. Complications of tumor necrosis factor-α blockade in chronic granulomatous disease-related colitis. Clin Infect Dis 2010;51:1429-34
620. Conrad A, Neven B, Mahlaoui N, Suarez F, Sokol H, Ruemmele FM, et al. Infections in Patients with Chronic Granulomatous Disease Treated with Tumor Necrosis Factor Alpha Blockers for Inflammatory Complications. J Clin Immunol 2021;41:185-193
621. Lehman HK and Davé R. Candida Glabrata Lymphadenitis Following Infliximab Therapy for Inflammatory Bowel Disease in a Patient With Chronic Granulomatous Disease: Case Report and Literature Review. Front Pediatr 2021;9:707369
622. Marsh RA, Leiding JW, Logan BR, Griffith LM, Arnold DE, Haddad E, et al. Chronic Granulomatous Disease-Associated IBD Resolves and Does Not Adversely Impact Survival Following Allogeneic HCT. J Clin Immunol 2019;39:653-667
623. Leiding JW, Freeman AF, Marciano BE, Anderson VL, Uzel G, Malech HL, et al. Corticosteroid therapy for liver abscess in chronic granulomatous disease. Clin Infect Dis 2012;54:694-700
624. Chen LE, Minkes RK, Shackelford PG, Strasberg SM, Kuo EY and Langer JC. Cut it out: Managing hepatic abscesses in patients with chronic granulomatous disease. J Pediatr Surg 2003;38:709-13
625. Nunes-Santos CJ, Koh C, Rai A, Sacco K, Marciano BE, Kleiner DE, et al. Nodular regenerative hyperplasia in X-linked agammaglobulinemia: An underestimated and severe complication. J Allergy Clin Immunol 2022;149:400-409.e3
626. Fuss IJ, Friend J, Yang Z, He JP, Hooda L, Boyer J, et al. Nodular regenerative hyperplasia in common variable immunodeficiency. J Clin Immunol 2013;33:748-58
627. Sharma D, Ben Yakov G, Kapuria D, Viana Rodriguez G, Gewirtz M, Haddad J, et al. Tip of the iceberg: A comprehensive review of liver disease in Inborn errors of immunity. Hepatology 2022;76:1845-1861

628. Lanz AL, Riester M, Peters P, Schwerd T, Lurz E, Hajji MS, et al. Abatacept for treatment-refractory pediatric CTLA4-haploinsufficiency. Clin Immunol 2021;229:108779
629. Perelygina L, Faisthalab R, Abernathy E, Chen MH, Hao L, Bercovitch L, et al. Rubella Virus Infected Macrophages and Neutrophils Define Patterns of Granulomatous Inflammation in Inborn and Acquired Errors of Immunity. Front Immunol 2021;12:796065
630. Lin JH, Liebhaber M, Roberts RL, Dyer Z and Stiehm ER. Etanercept treatment of cutaneous granulomas in common variable immunodeficiency. J Allergy Clin Immunol 2006;117:878-82
631. Chu DK, Schneider L, Asiniwasis RN, Boguniewicz M, De Benedetto A, Ellison K, et al. Atopic dermatitis (eczema) guidelines: 2023 American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Joint Task Force on Practice Parameters GRADE- and Institute of Medicine-based recommendations. Ann Allergy Asthma Immunol 2024;132:274-312
632. Bakaa L, Pernica JM, Couban RJ, Tackett KJ, Burkhart CN, Leins L, et al. Bleach baths for atopic dermatitis: A systematic review and meta-analysis including unpublished data, Bayesian interpretation, and GRADE. Ann Allergy Asthma Immunol 2022;128:660-668.e9
633. Nihal A, Comstock JR, Holland KE, Singh AM, Seroogy CM and Arkin LM. Clearance of atypical cutaneous manifestations of hyper-IgE syndrome with dupilumab. Pediatr Dermatol 2022;39:940-942
634. Badolato R, Alsina L, Azar A, Bertrand Y, Bolyard AA, Dale D, et al. A phase 3 randomized trial of mavorixafor, a CXCR4 antagonist, for WHIM syndrome. Blood 2024;144:35-45
635. Van Aken K, De Smedt B, Van Roie A, Gewillig M, Devriendt K, Fryns JP, et al. Motor development in school-aged children with 22q11 deletion (velocardiofacial/DiGeorge syndrome). Dev Med Child Neurol 2007;49:210-3
636. Gerdes M, Solot C, Wang PP, Moss E, LaRossa D, Randall P, et al. Cognitive and behavior profile of preschool children with chromosome 22q11.2 deletion. Am J Med Genet 1999;85:127-33
637. O'Driscoll M, Cerosaletti KM, Girard PM, Dai Y, Stumm M, Kysela B, et al. DNA ligase IV mutations identified in patients exhibiting developmental delay and immunodeficiency. Mol Cell 2001;8:1175-85
638. Meixner I, Hagl B, Kröner CI, Spielberger BD, Paschos E, Dückers G, et al. Retained primary teeth in STAT3 hyper-IgE syndrome: early intervention in childhood is essential. Orphanet J Rare Dis 2020;15:244
639. Björk M, Dragioti E, Alexandersson H, Esbensen BA, Boström C, Friden C, et al. Inflammatory Arthritis and the Effect of Physical Activity on Quality of Life and Self-Reported Function: A Systematic Review and Meta-Analysis. Arthritis Care Res (Hoboken) 2022;74:31-43
640. Katz P, Andonian BJ and Huffman KM. Benefits and promotion of physical activity in rheumatoid arthritis. Curr Opin Rheumatol 2020;32:307-314
641. Patiroglu T, Akar HH, Gunduz Z, Sisko S and Ng YY. X-linked agammaglobulinemia in two siblings with a novel mutation in the BTK gene who presented with polyarticular juvenile idiopathic arthritis. Scand J Rheumatol 2015;44:168-70

642. Verbruggen G, De Backer S, Deforce D, Demetter P, Cuvelier C, Veys E, et al. X linked agammaglobulinaemia and rheumatoid arthritis. Ann Rheum Dis 2005;64:1075-8
643. Mucke J, Cornet A, Witte T and Schneider M. Association of common variable immunodeficiency and rare and complex connective tissue and musculoskeletal diseases. A systematic literature review. Clin Exp Rheumatol 2022;40 Suppl 134:40-45
644. Cale CM, Morton L and Goldblatt D. Cutaneous and other lupus-like symptoms in carriers of X-linked chronic granulomatous disease: incidence and autoimmune serology. Clin Exp Immunol 2007;148:79-84
645. Goel RR, Nakabo S, Dizon BLP, Urban A, Waldman M, Howard L, et al. Lupus-like autoimmunity and increased interferon response in patients with STAT3-deficient hyper-IgE syndrome. J Allergy Clin Immunol 2021;147:746-749.e9
646. Pellier I, Dupuis Girod S, Loisel D, Benabidallah S, Proust A, Malhlaoui N, et al. Occurrence of aortic aneurysms in 5 cases of Wiskott-Aldrich syndrome. Pediatrics 2011;127:e498-504
647. Shimizu T, Morita T and Kumanogoh A. The therapeutic efficacy of intravenous immunoglobulin in anti-neutrophilic cytoplasmic antibody-associated vasculitis: a meta-analysis. Rheumatology (Oxford) 2020;59:959-967
648. Hellmich B, Sanchez-Alamo B, Schirmer JH, Berti A, Blockmans D, Cid MC, Holle JU, et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. Ann Rheum Dis. 2024 Jan 2;83(1):30-47
649. Riaz IB, Faridi W, Patnaik MM and Abraham RS. A Systematic Review on Predisposition to Lymphoid (B and T cell) Neoplasias in Patients With Primary Immunodeficiencies and Immune Dysregulatory Disorders (Inborn Errors of Immunity). Front Immunol 2019;10:777
650. Bomken S, van der Werff Ten Bosch J, Attarbaschi A, Bacon CM, Borkhardt A, Boztug K, et al. Current Understanding and Future Research Priorities in Malignancy Associated With Inborn Errors of Immunity and DNA Repair Disorders: The Perspective of an Interdisciplinary Working Group. Front Immunol 2018;9:2912
651. Carson JL, Stanworth SJ, Guyatt G, Valentine S, Dennis J, Bakhtary S, et al. Red Blood Cell Transfusion: 2023 AABB International Guidelines. JAMA 2023;330:1892-1902
652. Foukaneli T, Kerr P, Bolton-Maggs PHB, Cardigan R, Coles A, Gennery A, et al. Guidelines on the use of irradiated blood components. Br J Haematol 2020;191:704-724
653. Gobert D, Bussel JB, Cunningham-Rundles C, Galicier L, Dechartres A, Berezne A, et al. Efficacy and safety of rituximab in common variable immunodeficiency-associated immune cytopenias: a retrospective multicentre study on 33 patients. Br J Haematol 2011;155:498-508
654. Kim JJ, Thrasher AJ, Jones AM, Davies EG and Cale CM. Rituximab for the treatment of autoimmune cytopenias in children with immune deficiency. Br J Haematol 2007;138:94-6
655. Ottaviano G, Marinoni M, Graziani S, Sibson K, Barzaghi F, Bertolini P, et al. Rituximab Unveils Hypogammaglobulinemia and Immunodeficiency in Children with Autoimmune Cytopenia. J Allergy Clin Immunol Pract 2020;8:273-282
656. Labrosse R, Barmettler S, Derfalvi B, Blincoe A, Cros G, Lacombe-Barrios J, et al. Rituximab-induced hypogammaglobulinemia and infection risk in pediatric patients. J Allergy Clin Immunol 2021;148:523-532.e8

657. Wong GK, Goldacker S, Winterhalter C, Grimbacher B, Chapel H, Lucas M, et al. Outcomes of splenectomy in patients with common variable immunodeficiency (CVID): a survey of 45 patients. Clin Exp Immunol 2013;172:63-72
658. Sicre de Fontbrune F, Moignet A, Beaupain B, Suarez F, Galicier L, Socié G, et al. Severe chronic primary neutropenia in adults: report on a series of 108 patients. Blood 2015;126:1643-50
659. Dale DC. How I diagnose and treat neutropenia. Curr Opin Hematol 2016;23:1-4
660. Dungarwalla M, Marsh JC, Tooze JA, Lucas G, Ouwehand W, Pettengell R, et al. Lack of clinical efficacy of rituximab in the treatment of autoimmune neutropenia and pure red cell aplasia: implications for their pathophysiology. Ann Hematol 2007;86:191-7
661. Upadhyaya SA, Mody R, Walkovich K, Hutchinson RJ, Sandlund JT and Connelly JA. Ataxia Telangiectasia and Cancer Predisposition: Challenges in Management. J Pediatr Hematol Oncol 2018;40:483-486
662. Halyabar O, Chang MH, Schoettler ML, Schwartz MA, Baris EH, Benson LA, et al. Calm in the midst of cytokine storm: a collaborative approach to the diagnosis and treatment of hemophagocytic lymphohistiocytosis and macrophage activation syndrome. Pediatr Rheumatol Online J 2019;17:7
663. Watts S, Diaz M, Teller C, Hamby T, Guirola R, Perez M, et al. Pediatric Hemophagocytic Lymphohistiocytosis: Formation of an Interdisciplinary HLH Working Group at a Single Institution. J Pediatr Hematol Oncol 2023;45:e328-e333
664. Fekrvand S, Yazdani R, Olbrich P, Gennery A, Rosenzweig SD, Condino-Neto A, et al. Primary Immunodeficiency Diseases and Bacillus Calmette-Guérin (BCG)-Vaccine-Derived Complications: A Systematic Review. J Allergy Clin Immunol Pract 2020;8:1371-1386
665. Tiller EC, Masters NB, Raines KL, Mathis AD, Crooke SN, Zwickl RC, et al. Notes from the Field: Measles Outbreak - Central Ohio, 2022-2023. MMWR Morb Mortal Wkly Rep 2023;72:847-849
666. Marin M, Leung J, Anderson TC and Lopez AS. Monitoring Varicella Vaccine Impact on Varicella Incidence in the United States: Surveillance Challenges and Changing Epidemiology, 1995-2019. J Infect Dis 2022;226:S392-s399
667. Staat MA, Payne DC, Halasa N, Weinberg GA, Donauer S, Wikswo M, et al. Continued Evidence of the Impact of Rotavirus Vaccine in Children Less Than 3 Years of Age From the United States New Vaccine Surveillance Network: A Multisite Active Surveillance Program, 2006-2016. Clin Infect Dis 2020;71:e421-e429
668. Bosticardo M and Notarangelo LD. Human thymus in health and disease: Recent advances in diagnosis and biology. Semin Immunol 2023;66:101732
669. Paris R. SARS-CoV-2 Infection and Response to COVID-19 Vaccination in Patients With Primary Immunodeficiencies. J Infect Dis 2023;228:S24-s33
670. Chesson HW, Dunne EF, Hariri S and Markowitz LE. The estimated lifetime probability of acquiring human papillomavirus in the United States. Sex Transm Dis 2014;41:660-4
671. de Gruijl TD, Bontkes HJ, Walboomers JM, Coursaget P, Stukart MJ, Dupuy C, et al. Immune responses against human papillomavirus (HPV) type 16 virus-like particles in a cohort study of women with cervical intraepithelial neoplasia. I. Differential T-helper and IgG responses in relation to HPV infection and disease outcome. J Gen Virol 1999;80 (Pt 2):399-408

672. Uyeki TM, Bernstein HH, Bradley JS, Englund JA, File TM, Fry AM, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenzaa. Clin Infect Dis 2019;68:895-902
673. Britton A, Roper LE, Kotton CN, Hutton DW, Fleming-Dutra KE, Godfrey M, et al. Use of Respiratory Syncytial Virus Vaccines in Adults Aged ≥60 Years: Updated Recommendations of the Advisory Committee on Immunization Practices - United States, 2024. MMWR Morb Mortal Wkly Rep 2024;73:696-702
674. Fleming-Dutra KE, Jones JM, Roper LE, Prill MM, Ortega-Sanchez IR, Moulia DL, et al. Use of the Pfizer Respiratory Syncytial Virus Vaccine During Pregnancy for the Prevention of Respiratory Syncytial Virus-Associated Lower Respiratory Tract Disease in Infants: Recommendations of the Advisory Committee on Immunization Practices - United States, 2023. MMWR Morb Mortal Wkly Rep 2023;72:1115-1122
675. Jones JM, Fleming-Dutra KE, Prill MM, Roper LE, Brooks O, Sánchez PJ, et al. Use of Nirsevimab for the Prevention of Respiratory Syncytial Virus Disease Among Infants and Young Children: Recommendations of the Advisory Committee on Immunization Practices - United States, 2023. MMWR Morb Mortal Wkly Rep 2023;72:920-925
676. Weinmann S, Chun C, Schmid DS, Roberts M, Vandermeer M, Riedlinger K, et al. Incidence and clinical characteristics of herpes zoster among children in the varicella vaccine era, 2005-2009. J Infect Dis 2013;208:1859-68
677. Hwang JH, Kim KH, Han SB, Kim HH, Kim JH, Lee SY, et al. A clinico-epidemiological multicenter study of herpes zoster in immunocompetent and immunocompromised hospitalized children. Clin Exp Vaccine Res 2019;8:116-123
678. Levin MJ, Duchon JM, Swamy GK and Gershon AA. Varicella zoster immune globulin (VARIZIG) administration up to 10 days after varicella exposure in pregnant women, immunocompromised participants, and infants: Varicella outcomes and safety results from a large, open-label, expanded-access program. PLoS One 2019;14:e0217749
679. Paryani SG, Arvin AM, Koropchak CM, Wittek AE, Amylon MD, Dobkin MB, et al. Varicella zoster antibody titers after the administration of intravenous immune serum globulin or varicella zoster immune globulin. Am J Med 1984;76:124-7
680. Hanitsch LG, Löbel M, Mieves JF, Bauer S, Babel N, Schweiger B, et al. Cellular and humoral influenza-specific immune response upon vaccination in patients with common variable immunodeficiency and unclassified antibody deficiency. Vaccine 2016;34:2417-2423
681. Marsh RA, Hebert KM, Keesler D, Boelens JJ, Dvorak CC, Eckrich MJ, et al. Practice pattern changes and improvements in hematopoietic cell transplantation for primary immunodeficiencies. J Allergy Clin Immunol 2018;142:2004-2007
682. Egg D, Rump IC, Mitsuiki N, Rojas-Restrepo J, Maccari ME, Schwab C, et al. Therapeutic options for CTLA-4 insufficiency. J Allergy Clin Immunol 2022;149:736-746
683. Shaw P, Shizuru J, Hoenig M and Veys P. Conditioning Perspectives for Primary Immunodeficiency Stem Cell Transplants. Front Pediatr 2019;7:434
684. Lankester AC, Neven B, Mahlaoui N, von Asmuth EGJ, Courteille V, Alligon M, et al. Hematopoietic cell transplantation in severe combined immunodeficiency: The SCETIDE 2006-2014 European cohort. J Allergy Clin Immunol 2022;149:1744-1754.e8

685. Hacein-Bey-Abina S, Garrigue A, Wang GP, Soulier J, Lim A, Morillon E, et al. Insertional oncogenesis in 4 patients after retrovirus-mediated gene therapy of SCID-X1. J Clin Invest 2008;118:3132-42
686. Blanco E, Izotova N, Booth C and Thrasher AJ. Immune Reconstitution After Gene Therapy Approaches in Patients With X-Linked Severe Combined Immunodeficiency Disease. Front Immunol 2020;11:608653
687. Davies EG, Cheung M, Gilmour K, Maimaris J, Curry J, Furmanski A, et al. Thymus transplantation for complete DiGeorge syndrome: European experience. J Allergy Clin Immunol 2017;140:1660-1670.e16
688. Chitty-Lopez M, Duff C, Vaughn G, Trotter J, Monforte H, Lindsay D, et al. Case Report: Unmanipulated Matched Sibling Donor Hematopoietic Cell Transplantation In TBX1 Congenital Athymia: A Lifesaving Therapeutic Approach When Facing a Systemic Viral Infection. Front Immunol. 2022;12:721917
689. Sonoda M, Ishimura M, Inoue H, Eguchi K, Ochiai M, Sakai Y, et. al. Non-conditioned cord blood transplantation for infection control in athymic CHARGE syndrome. Pediatr Blood Cancer. 2024;71(3):e30809.
690. Land MH, Garcia-Lloret MI, Borzy MS, Rao PN, Aziz N, McGhee SA, et. al. Long-term results of bone marrow transplantation in complete DiGeorge syndrome. J Allergy Clin Immunol. 2007;120(4):908-15
691. Kuehn HS, Nunes-Santos CJ and Rosenzweig SD. Germline IKZF1 mutations and their impact on immunity: IKAROS-associated diseases and pathophysiology. Expert Rev Clin Immunol 2021;17:407-416
692. Kellner ES, Krupski C, Kuehn HS, Rosenzweig SD, Yoshida N, Kojima S, et al. Allogeneic hematopoietic stem cell transplant outcomes for patients with dominant negative IKZF1/IKAROS mutations. J Allergy Clin Immunol 2019;144:339-342
693. Tsilifis C, Moreira D, Marques L, Neves E, Slatter MA and Gennery AR. Stem cell transplantation as treatment for major histocompatibility class I deficiency. Clin Immunol 2021;229:108801
694. Ferrua F, Galimberti S, Courteille V, Slatter MA, Booth C, Moshous D, et al. Hematopoietic stem cell transplantation for CD40 ligand deficiency: Results from an EBMT/ESID-IEWP-SCETIDE-PIDTC study. J Allergy Clin Immunol 2019;143:2238-2253
695. Aydin SE, Freeman AF, Al-Herz W, Al-Mousa HA, Arnaout RK, Aydin RC, et al. Hematopoietic Stem Cell Transplantation as Treatment for Patients with DOCK8 Deficiency. J Allergy Clin Immunol Pract 2019;7:848-855
696. Lum SH, Neven B, Slatter MA and Gennery AR. Hematopoietic Cell Transplantation for MHC Class II Deficiency. Front Pediatr 2019;7:516
697. Burroughs LM, Petrovic A, Brazauskas R, Liu X, Griffith LM, Ochs HD, et al. Excellent outcomes following hematopoietic cell transplantation for Wiskott-Aldrich syndrome: a PIDTC report. Blood 2020;135:2094-2105
698. Miot C, Imai K, Imai C, Mancini AJ, Kucuk ZY, Kawai T, et al. Hematopoietic stem cell transplantation in 29 patients hemizygous for hypomorphic IKBKG/NEMO mutations. Blood 2017;130:1456-1467
699. Fitch T, Bleesing J, Marsh RA and Chandra S. Reduced Intensity Conditioning Allogeneic Transplant for SCID Associated with Cartilage Hair Hypoplasia. J Clin Immunol 2022;42:1604-1607

700. Zhang K, Meyer LK, Machowicz R, Coniglio ML, Sieni E, Nichols KE. Genetics of familial hemophagocytic lymphohistiocytosis. Hematol Oncol Clin North Am. 2025 Apr 7:S0889-8588(25)00017-6
701. Cetica V, Hackmann Y, Grieve S, Sieni E, Ciambotti B, Coniglio ML, et al. Patients with Griscelli syndrome and normal pigmentation identify RAB27A mutations that selectively disrupt MUNC13-4 binding. J Allergy Clin Immunol 2015;135:1310-8.e1
702. Nagai K, Ochi F, Terui K, Maeda M, Ohga S, Kanegane H, et al. Clinical characteristics and outcomes of Chédiak-Higashi syndrome: a nationwide survey of Japan. Pediatr Blood Cancer 2013;60:1582-6
703. Jessen B, Bode SF, Ammann S, Chakravorty S, Davies G, Diestelhorst J, et al. The risk of hemophagocytic lymphohistiocytosis in Hermansky-Pudlak syndrome type 2. Blood 2013;121:2943-51
704. Booth C, Gilmour KC, Veys P, Gennery AR, Slatter MA, Chapel H, et al. X-linked lymphoproliferative disease due to SAP/SH2D1A deficiency: a multicenter study on the manifestations, management and outcome of the disease. Blood 2011;117:53-62
705. Mudde ACA, Booth C and Marsh RA. Evolution of Our Understanding of XIAP Deficiency. Front Pediatr 2021;9:660520
706. Arnold DE, Nofal R, Wakefield C, Lehmberg K, Wustrau K, Albert MH, et al. Reduced-Intensity/Reduced-Toxicity Conditioning Approaches Are Tolerated in XIAP Deficiency but Patients Fare Poorly with Acute GVHD. J Clin Immunol 2022;42:36-45
708. Blincoe A, Heeg M, Campbell PK, Hines M, Khojah A, Klein-Gitelman M, et al. Neuroinflammatory Disease as an Isolated Manifestation of Hemophagocytic Lymphohistiocytosis. J Clin Immunol 2020;40:901-916
709. Lucchini G, Marsh R, Gilmour K, Worth A, Nademi Z, Rao A, et al. Treatment dilemmas in asymptomatic children with primary hemophagocytic lymphohistiocytosis. Blood 2018;132:2088-2096
710. Tomomasa D, Booth C, Bleesing JJ, Isoda T, Kobayashi C, Koike K, et al. Preemptive hematopoietic cell transplantation for asymptomatic patients with X-linked lymphoproliferative syndrome type 1. Clin Immunol 2022;237:108993
711. Marsh RA, Vaughn G, Kim MO, Li D, Jodele S, Joshi S, et al. Reduced-intensity conditioning significantly improves survival of patients with hemophagocytic lymphohistiocytosis undergoing allogeneic hematopoietic cell transplantation. Blood 2010;116:5824-31
712. Marsh RA, Hebert K, Kim S, Dvorak CC, Aquino VM, Baker KS, et al. Comparison of hematopoietic cell transplant conditioning regimens for hemophagocytic lymphohistiocytosis disorders. J Allergy Clin Immunol 2022;149:1097-1104.e2
713. Felber M, Steward CG, Kentouche K, Fasth A, Wynn RF, Zeilhofer U, et al. Targeted busulfan-based reduced-intensity conditioning and HLA-matched HSCT cure hemophagocytic lymphohistiocytosis. Blood Adv 2020;4:1998-2010
714. Engelhardt KR, Shah N, Faizura-Yeop I, Kocacik Uygun DF, Frede N, Muise AM, et al. Clinical outcome in IL-10- and IL-10 receptor-deficient patients with or without hematopoietic stem cell transplantation. J Allergy Clin Immunol 2013;131:825-30
715. Karaca NE, Aksu G, Ulusoy E, Aksoylar S, Gozmen S, Genel F, et al. Early Diagnosis and Hematopoietic Stem Cell Transplantation for IL10R Deficiency Leading to Very Early-Onset Inflammatory Bowel Disease Are Essential in Familial Cases. Case Reports Immunol 2016;2016:5459029

716. Barzaghi F, Amaya Hernandez LC, Neven B, Ricci S, Kucuk ZY, Bleesing JJ, et al. Long-term follow-up of IPEX syndrome patients after different therapeutic strategies: An international multicenter retrospective study. J Allergy Clin Immunol 2018;141:1036-1049.e5
717. Paskiewicz A, Niu J, Chang C. Autoimmune lymphoproliferative syndrome: A disorder of immune dysregulation. Autoimmun Rev. 2023 Nov;22(11):103442.
718. Hashem H, Bucciol G, Ozen S, Unal S, Bozkaya IO, Akarsu N, et al. Hematopoietic Cell Transplantation Cures Adenosine Deaminase 2 Deficiency: Report on 30 Patients. J Clin Immunol 2021;41:1633-1647
719. Bakhtiar S, Salzmann-Manrique E, Blok HJ, Eikema DJ, Hazelaar S, Ayas M, et al. Allogeneic hematopoietic stem cell transplantation in leukocyte adhesion deficiency type I and III. Blood Adv 2021;5:262-273
720. Chiesa R, Wang J, Blok HJ, Hazelaar S, Neven B, Moshous D, et al. Hematopoietic cell transplantation in chronic granulomatous disease: a study of 712 children and adults. Blood 2020;136:1201-1211
721. Leiding JW, Arnold DE, Parikh S, Logan B, Marsh RA, Griffith LM, et al. Genotype, oxidase status, and preceding infection or autoinflammation do not affect allogeneic HCT outcomes for CGD. Blood 2023;142:2105-2118
722. Merli P, Caruana I, De Vito R, Strocchio L, Weber G, Del Bufalo F, et al. Role of interferon-γ in immune-mediated graft failure after allogeneic hematopoietic stem cell transplantation. Haematologica 2019;104:2314-2323
723. Tovo PA, Garazzino S, Saglio F, Scolfaro C, Bustamante J, Badolato R, et al. Successful Hematopoietic Stem Cell Transplantation in a Patient with Complete IFN-γ Receptor 2 Deficiency: a Case Report and Literature Review. J Clin Immunol 2020;40:1191-1195
724. Nazir HF, Rawas AA, Tamemi SA, Zadjali SA, Hosni SA, Tauro M, et al. Hematopoietic Stem Cell Transplantation for Patients with Autosomal Recessive Complete INF-λ Receptor 2 Deficiency: Experience in Oman. Transplant Cell Ther 2021;27:881.e1-881.e5
725. Leiding JW, Okada S, Hagin D, Abinun M, Shcherbina A, Balashov DN, et al. Hematopoietic stem cell transplantation in patients with gain-of-function signal transducer and activator of transcription 1 mutations. J Allergy Clin Immunol 2018;141:704-717.e5
726. Kunvarjee B, Bidgoli A, Madan RP, Vidal E, McAvoy D, Hosszu KK, et al. Emapalumab as bridge to hematopoietic cell transplant for STAT1 gain-of-function mutations. J Allergy Clin Immunol 2023;152:815-817
727. Donadieu J, Leblanc T, Bader Meunier B, Barkaoui M, Fenneteau O, Bertrand Y, et al. Analysis of risk factors for myelodysplasias, leukemias and death from infection among patients with congenital neutropenia. Experience of the French Severe Chronic Neutropenia Study Group. Haematologica 2005;90:45-53
728. Furutani E, Liu S, Galvin A, Steltz S, Malsch MM, Loveless SK, et al. Hematologic complications with age in Shwachman-Diamond syndrome. Blood Adv 2022;6:297-306
729. Cesaro S, Pillon M, Sauer M, Smiers F, Faraci M, de Heredia CD, et al. Long-term outcome after allogeneic hematopoietic stem cell transplantation for Shwachman-Diamond syndrome: a retrospective analysis and a review of the literature by the Severe Aplastic Anemia Working Party of the European Society for Blood and Marrow Transplantation (SAAWP-EBMT). Bone Marrow Transplant 2020;55:1796-1809

730. Myers K, Hebert K, Antin J, Boulad F, Burroughs L, Hofmann I, et al. Hematopoietic Stem Cell Transplantation for Shwachman-Diamond Syndrome. Biol Blood Marrow Transplant 2020;26:1446-1451
731. Myers KC, Furutani E, Weller E, Siegele B, Galvin A, Arsenault V, et al. Clinical features and outcomes of patients with Shwachman-Diamond syndrome and myelodysplastic syndrome or acute myeloid leukaemia: a multicentre, retrospective, cohort study. Lancet Haematol 2020;7:e238-e246
732. Parta M, Shah NN, Baird K, Rafei H, Calvo KR, Hughes T, et al. Allogeneic Hematopoietic Stem Cell Transplantation for GATA2 Deficiency Using a Busulfan-Based Regimen. Biol Blood Marrow Transplant 2018;24:1250-1259
733. Bortnick R, Wlodarski M, de Haas V, De Moerloose B, Dworzak M, Hasle H, et al. Hematopoietic stem cell transplantation in children and adolescents with GATA2-related myelodysplastic syndrome. Bone Marrow Transplant 2021;56:2732-2741
734. Bunin N, Small T, Szabolcs P, Baker KS, Pulsipher MA and Torgerson T. NCI, NHLBI/PBMTC first international conference on late effects after pediatric hematopoietic cell transplantation: persistent immune deficiency in pediatric transplant survivors. Biol Blood Marrow Transplant 2012;18:6-15
735. Heimall J, Buckley RH, Puck J, Fleisher TA, Gennery AR, Haddad E, et al. Recommendations for Screening and Management of Late Effects in Patients with Severe Combined Immunodeficiency after Allogenic Hematopoietic Cell Transplantation: A Consensus Statement from the Second Pediatric Blood and Marrow Transplant Consortium International Conference on Late Effects after Pediatric HCT. Biol Blood Marrow Transplant 2017;23:1229-1240
736. Haynes AS, Curtis DJ, Campbell K, Giller RH, Quinones RR, Verneris MR, et al. An Immune Recovery-Based Revaccination Protocol for Pediatric Hematopoietic Stem Cell Transplant Recipients: Revaccination Outcomes Following Pediatric HSCT. Transplant Cell Ther 2021;27:317-326
737. Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant 2009;15:1143-238
738. Gupton SE, McCarthy EA and Markert ML. Care of Children with DiGeorge Before and After Cultured Thymus Tissue Implantation. J Clin Immunol 2021;41:896-905
739. Majhail NS, Rizzo JD, Lee SJ, Aljurf M, Atsuta Y, Bonfim C, et al. Recommended screening and preventive practices for long-term survivors after hematopoietic cell transplantation. Bone Marrow Transplant 2012;47:337-41
740. Eissa H, Thakar MS, Shah AJ, Logan BR, Griffith LM, Dong H, et al. Posttransplantation late complications increase over time for patients with SCID: A Primary Immune Deficiency Treatment Consortium (PIDTC) landmark study. J Allergy Clin Immunol 2024;153:287-296
741. Eapen M, Ahn KW, Orchard PJ, Cowan MJ, Davies SM, Fasth A, et al. Long-term survival and late deaths after hematopoietic cell transplantation for primary immunodeficiency diseases and inborn errors of metabolism. Biol Blood Marrow Transplant 2012;18:1438-45
742. Deyà-Martínez A, Rivière JG, Roxo-Junior P, Ramakers J, Bloomfield M, Guisado Hernandez P, et al. Impact of JAK Inhibitors in Pediatric Patients with STAT1 Gain of

Function (GOF) Mutations-10 Children and Review of the Literature. J Clin Immunol 2022;42:1071-1082
743. Kayaoglu B, Kasap N, Yilmaz NS, Charbonnier LM, Geckin B, Akcay A, et al. Stepwise Reversal of Immune Dysregulation Due to STAT1 Gain-of-Function Mutation Following Ruxolitinib Bridge Therapy and Transplantation. J Clin Immunol 2021;41:769-779
744. Moriya K, Suzuki T, Uchida N, Nakano T, Katayama S, Irie M, et al. Ruxolitinib treatment of a patient with steroid-dependent severe autoimmunity due to STAT1 gain-of-function mutation. Int J Hematol 2020;112:258-262
745. Meesilpavikkai K, Dik WA, Schrijver B, Nagtzaam NMA, Posthumus-van Sluijs SJ, van Hagen PM, et al. Baricitinib treatment in a patient with a gain-of-function mutation in signal transducer and activator of transcription 1 (STAT1). J Allergy Clin Immunol 2018;142:328-330.e2
746. Tanita K, Sakura F, Nambu R, Tsumura M, Imanaka Y, Ohnishi H, et al. Clinical and Immunological Heterogeneity in Japanese Patients with Gain-of-Function Variants in STAT3. J Clin Immunol 2021;41:780-790
747. Sarfati E, Hadjadj J, Fusaro M, Klifa R, Grimaud M, Berteloot L, et al. Life-Saving, Dose-Adjusted, Targeted Therapy in a Patient with a STAT3 Gain-of-Function Mutation. J Clin Immunol 2021;41:807-810
748. Silva-Carmona M, Vogel TP, Marchal S, Guesmi M, Dubus JC, Leroy S, et al. Successful Treatment of Interstitial Lung Disease in STAT3 Gain-of-Function Using JAK Inhibitors. Am J Respir Crit Care Med 2020;202:893-897
749. Michniacki TF, Walkovich K, DeMeyer L, Saad N, Hannibal M, Basiaga ML, et al. SOCS1 Haploinsufficiency Presenting as Severe Enthesitis, Bone Marrow Hypocellularity, and Refractory Thrombocytopenia in a Pediatric Patient with Subsequent Response to JAK Inhibition. J Clin Immunol 2022;42:1766-1777
750. Eisenberg R, Gans MD, Leahy TR, Gothe F, Perry C, Raffeld M, et al. JAK inhibition in early-onset somatic, nonclonal STAT5B gain-of-function disease. J Allergy Clin Immunol Pract 2021;9:1008-1010.e2
751. Baghdassarian H, Blackstone SA, Clay OS, Philips R, Matthiasardottir B, Nehrebecky M, et al. Variant STAT4 and Response to Ruxolitinib in an Autoinflammatory Syndrome. N Engl J Med 2023;388:2241-2252
752. Frémond ML, Rodero MP, Jeremiah N, Belot A, Jeziorski E, Duffy D, et al. Efficacy of the Janus kinase 1/2 inhibitor ruxolitinib in the treatment of vasculopathy associated with TMEM173-activating mutations in 3 children. J Allergy Clin Immunol 2016;138:1752-1755
753. Vanderver A, Adang L, Gavazzi F, McDonald K, Helman G, Frank DB, et al. Janus Kinase Inhibition in the Aicardi-Goutières Syndrome. N Engl J Med 2020;383:986-989
754. Meesilpavikkai K, Dik WA, Schrijver B, van Helden-Meeuwsen CG, Versnel MA, van Hagen PM, et al. Efficacy of Baricitinib in the Treatment of Chilblains Associated With Aicardi-Goutières Syndrome, a Type I Interferonopathy. Arthritis Rheumatol 2019;71:829-831
755. Cetin Gedik K, Lamot L, Romano M, Demirkaya E, Piskin D, Torreggiani S, et al. The 2021 European Alliance of Associations for Rheumatology/American College of Rheumatology points to consider for diagnosis and management of autoinflammatory type I interferonopathies: CANDLE/PRAAS, SAVI and AGS. Ann Rheum Dis 2022;81:601-613

756. Patel PN, Hunt R, Pettigrew ZJ, Shirley JB, Vogel TP and de Guzman MM. Successful treatment of chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome with tofacitinib. Pediatr Dermatol 2021;38:528-529
757. Sanchez GAM, Reinhardt A, Ramsey S, Wittkowski H, Hashkes PJ, Berkun Y, et al. JAK1/2 inhibition with baricitinib in the treatment of autoinflammatory interferonopathies. J Clin Invest 2018;128:3041-3052
758. Loh ML, Tasian SK, Rabin KR, Brown P, Magoon D, Reid JM, et al. A phase 1 dosing study of ruxolitinib in children with relapsed or refractory solid tumors, leukemias, or myeloproliferative neoplasms: A Children's Oncology Group phase 1 consortium study (ADVL1011). Pediatr Blood Cancer 2015;62:1717-24
759. Simpson EL, Lacour JP, Spelman L, Galimberti R, Eichenfield LF, Bissonnette R, et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. Br J Dermatol 2020;183:242-255
760. Dorsey MJ, Rubinstein A, Lehman H, Fausnight T, Wiley JM and Haddad E. PEGylated Recombinant Adenosine Deaminase Maintains Detoxification and Lymphocyte Counts in Patients with ADA-SCID. J Clin Immunol 2023;43:951-964
761. Murguia-Favela L, Suresh S, Wright NAM, Alvi S, Tehseen S, Hernandez-Trujillo V, et al. Long-Term Immune Reconstitution in ADA-Deficient Patients Treated With Elapegademase: A Real-World Experience. J Allergy Clin Immunol Pract 2023;11:1725-1733
762. Hicks ED, Hall G, Hershfield MS, Tarrant TK, Bali P, Sleasman JW, et al. Treatment with Elapegademase Restores Immunity in Infants with Adenosine Deaminase Deficient Severe Combined Immunodeficiency. J Clin Immunol 2024;44:107
763. Lo B, Zhang K, Lu W, Zheng L, Zhang Q, Kanellopoulou C, et al. Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy. Science 2015;349:436-40
764. Taghizade N, Babayeva R, Kara A, Karakus IS, Catak MC, Bulutoglu A, et al. Therapeutic modalities and clinical outcomes in a large cohort with LRBA deficiency and CTLA4 insufficiency. J Allergy Clin Immunol 2023;152:1634-1645
765. Sjöström EO, Culot M, Leickt L, Åstrand M, Nordling E, Gosselet F, et al. Transport study of interleukin-1 inhibitors using a human in vitro model of the blood-brain barrier. Brain Behav Immun Health 2021;16:100307
766. Romano M, Arici ZS, Piskin D, Alehashemi S, Aletaha D, Barron KS, et al. The 2021 EULAR/American College of Rheumatology points to consider for diagnosis, management and monitoring of the interleukin-1 mediated autoinflammatory diseases: cryopyrin-associated periodic syndromes, tumour necrosis factor receptor-associated periodic syndrome, mevalonate kinase deficiency, and deficiency of the interleukin-1 receptor antagonist. Ann Rheum Dis 2022;81:907-921
767. Kuemmerle-Deschner JB, Hofer F, Endres T, Kortus-Goetze B, Blank N, Weißbarth-Riedel E, et al. Real-life effectiveness of canakinumab in cryopyrin-associated periodic syndrome. Rheumatology (Oxford) 2016;55:689-96
768. Kuemmerle-Deschner JB, Hachulla E, Cartwright R, Hawkins PN, Tran TA, Bader-Meunier B, et al. Two-year results from an open-label, multicentre, phase III study evaluating the safety and efficacy of canakinumab in patients with cryopyrin-associated

periodic syndrome across different severity phenotypes. Ann Rheum Dis 2011;70:2095-102
769. De Benedetti F, Gattorno M, Anton J, Ben-Chetrit E, Frenkel J, Hoffman HM, et al. Canakinumab for the Treatment of Autoinflammatory Recurrent Fever Syndromes. N Engl J Med 2018;378:1908-1919
770. Lachmann HJ, Lauwerys B, Miettunen P, Kallinich T, Jansson A, Rosner I, et al. Canakinumab improves patient-reported outcomes in children and adults with autoinflammatory recurrent fever syndromes: results from the CLUSTER trial. Clin Exp Rheumatol 2021;39 Suppl 132:51-58
771. Ozen S, Ben-Cherit E, Foeldvari I, Amarilyo G, Ozdogan H, Vanderschueren S, et al. Long-term efficacy and safety of canakinumab in patients with colchicine-resistant familial Mediterranean fever: results from the randomised phase III CLUSTER trial. Ann Rheum Dis 2020;79:1362-1369
772. Atas N, Eroglu GA, Sodan HN, Ozturk BO, Babaoglu H, Satis H, et al. Long-term safety and efficacy of anakinra and canakinumab in patients with familial Mediterranean fever: a single-centre real-life study with 101 patients. Clin Exp Rheumatol 2021;39 Suppl 132:30-36
773. Bodar EJ, Kuijk LM, Drenth JP, van der Meer JW, Simon A and Frenkel J. On-demand anakinra treatment is effective in mevalonate kinase deficiency. Ann Rheum Dis 2011;70:2155-8
774. Jeyaratnam J, Simon A, Calvo I, Constantin T, Shcherbina A, Hofer M, et al. Long-term efficacy and safety of canakinumab in patients with mevalonate kinase deficiency: results from the randomised Phase 3 CLUSTER trial. Rheumatology (Oxford) 2022;61:2088-2094
775. Brenner M, Ruzicka T, Plewig G, Thomas P and Herzer P. Targeted treatment of pyoderma gangrenosum in PAPA (pyogenic arthritis, pyoderma gangrenosum and acne) syndrome with the recombinant human interleukin-1 receptor antagonist anakinra. Br J Dermatol 2009;161:1199-201
776. Omenetti A, Carta S, Caorsi R, Finetti M, Marotto D, Lattanzi B, et al. Disease activity accounts for long-term efficacy of IL-1 blockers in pyogenic sterile arthritis pyoderma gangrenosum and severe acne syndrome. Rheumatology (Oxford) 2016;55:1325-35
777. Bhuyan F, de Jesus AA, Mitchell J, Leikina E, VanTries R, Herzog R, et al. Novel Majeed Syndrome-Causing LPIN2 Mutations Link Bone Inflammation to Inflammatory M2 Macrophages and Accelerated Osteoclastogenesis. Arthritis Rheumatol 2021;73:1021-1032
778. Herlin T, Fiirgaard B, Bjerre M, Kerndrup G, Hasle H, Bing X, et al. Efficacy of anti-IL-1 treatment in Majeed syndrome. Ann Rheum Dis 2013;72:410-3
779. Roy NBA, Zaal AI, Hall G, Wilkinson N, Proven M, McGowan S, et al. Majeed syndrome: description of a novel mutation and therapeutic response to bisphosphonates and IL-1 blockade with anakinra. Rheumatology (Oxford) 2020;59:448-451
780. Borghini S, Tassi S, Chiesa S, Caroli F, Carta S, Caorsi R, et al. Clinical presentation and pathogenesis of cold-induced autoinflammatory disease in a family with recurrence of an NLRP12 mutation. Arthritis Rheum 2011;63:830-9
781. Wang HF. NLRP12-associated systemic autoinflammatory diseases in children. Pediatr Rheumatol Online J 2022;20:9

782. Kitamura A, Sasaki Y, Abe T, Kano H and Yasutomo K. An inherited mutation in NLRC4 causes autoinflammation in human and mice. J Exp Med 2014;211:2385-96
783. Bardet J, Laverdure N, Fusaro M, Picard C, Garnier L, Viel S, et al. NLRC4 GOF Mutations, a Challenging Diagnosis from Neonatal Age to Adulthood. J Clin Med 2021;10
784. Gernez Y, de Jesus AA, Alsaleem H, Macaubas C, Roy A, Lovell D, et al. Severe autoinflammation in 4 patients with C-terminal variants in cell division control protein 42 homolog (CDC42) successfully treated with IL-1β inhibition. J Allergy Clin Immunol 2019;144:1122-1125.e6
785. Hoffman HM, Throne ML, Amar NJ, Cartwright RC, Kivitz AJ, Soo Y, et al. Long-term efficacy and safety profile of rilonacept in the treatment of cryopryin-associated periodic syndromes: results of a 72-week open-label extension study. Clin Ther 2012;34:2091-2103
786. Donini M, Fontana S, Savoldi G, Vermi W, Tassone L, Gentili F, et al. G-CSF treatment of severe congenital neutropenia reverses neutropenia but does not correct the underlying functional deficiency of the neutrophil in defending against microorganisms. Blood 2007;109:4716-23
787. Pogozhykh D, Yilmaz Karapinar D, Klimiankou M, Gerschmann N, Ebetsberger-Dachs G, Palmblad J, et al. HAX1-related congenital neutropenia: Long-term observation in paediatric and adult patients enrolled in the European branch of the Severe Chronic Neutropenia International Registry (SCNIR). Br J Haematol 2023;202:393-411
788. Boztug K, Rosenberg PS, Dorda M, Banka S, Moulton T, Curtin J, et al. Extended spectrum of human glucose-6-phosphatase catalytic subunit 3 deficiency: novel genotypes and phenotypic variability in severe congenital neutropenia. J Pediatr 2012;160:679-683.e2
789. McCawley LJ, Korchak HM, Douglas SD, Campbell DE, Thornton PS, Stanley CA, et al. In vitro and in vivo effects of granulocyte colony-stimulating factor on neutrophils in glycogen storage disease type 1B: granulocyte colony-stimulating factor therapy corrects the neutropenia and the defects in respiratory burst activity and Ca2+ mobilization. Pediatr Res 1994;35:84-90
790. Steward CG, Groves SJ, Taylor CT, Maisenbacher MK, Versluys B, Newbury-Ecob RA, et al. Neutropenia in Barth syndrome: characteristics, risks, and management. Curr Opin Hematol 2019;26:6-15
791. Ammann RA, Duppenthaler A, Bux J and Aebi C. Granulocyte colony-stimulating factor-responsive chronic neutropenia in cartilage-hair hypoplasia. J Pediatr Hematol Oncol 2004;26:379-81
792. Lord BI, Bronchud MH, Owens S, Chang J, Howell A, Souza L, et al. The kinetics of human granulopoiesis following treatment with granulocyte colony-stimulating factor in vivo. Proc Natl Acad Sci U S A 1989;86:9499-503
793. Dale DC, Cottle TE, Fier CJ, Bolyard AA, Bonilla MA, Boxer LA, et al. Severe chronic neutropenia: treatment and follow-up of patients in the Severe Chronic Neutropenia International Registry. Am J Hematol 2003;72:82-93
794. McDermott DH and Murphy PM. WHIM syndrome: Immunopathogenesis, treatment and cure strategies. Immunol Rev 2019;287:91-102

795. McDermott DH, Liu Q, Velez D, Lopez L, Anaya-O'Brien S, Ulrick J, et al. A phase 1 clinical trial of long-term, low-dose treatment of WHIM syndrome with the CXCR4 antagonist plerixafor. Blood 2014;123:2308-16
796. McDermott DH, Velez D, Cho E, Cowen EW, DiGiovanna JJ, Pastrana DV, et al. A phase III randomized crossover trial of plerixafor versus G-CSF for treatment of WHIM syndrome. J Clin Invest 2023;133
797. Trakadis YJ, Alfares A, Bodamer OA, Buyukavci M, Christodoulou J, Connor P, et al. Update on transcobalamin deficiency: clinical presentation, treatment and outcome. J Inherit Metab Dis 2014;37:461-73
798. Gök V, Erdem Ş, Haliloğlu Y, Bişgin A, Belkaya S, Başaran KE, et al. Immunodeficiency associated with a novel functionally defective variant of SLC19A1 benefits from folinic acid treatment. Genes Immun 2023;24:12-20
799. Kishimoto K, Kobayashi R, Sano H, Suzuki D, Maruoka H, Yasuda K, et al. Impact of folate therapy on combined immunodeficiency secondary to hereditary folate malabsorption. Clin Immunol 2014;153:17-22
800. Huemer M, Diodato D, Schwahn B, Schiff M, Bandeira A, Benoist JF, et al. Guidelines for diagnosis and management of the cobalamin-related remethylation disorders cblC, cblD, cblE, cblF, cblG, cblJ and MTHFR deficiency. J Inherit Metab Dis 2017;40:21-48
801. Boisson-Dupuis S. The monogenic basis of human tuberculosis. Hum Genet. 2020 Jun;139(6-7):1001-1009
802. Holland SM, Eisenstein EM, Kuhns DB, Turner ML, Fleisher TA, Strober W, et al. Treatment of refractory disseminated nontuberculous mycobacterial infection with interferon gamma. A preliminary report. N Engl J Med 1994;330:1348-55
803. Alroqi F, Almutairi A, Alhammadi M and Alhamdi S. Successful treatment of invasive mycobacterium infection with interferon beta in a patient with Interferon-Gamma Receptor 1 deficiency. J Infect Public Health 2024;17:102468
804. Ulrichs T, Fieschi C, Nevicka E, Hahn H, Brezina M, Kaufmann SH, et al. Variable outcome of experimental interferon-gamma therapy of disseminated Bacillus Calmette-Guerin infection in two unrelated interleukin-12Rbeta1-deficient Slovakian children. Eur J Pediatr 2005;164:166-72
805. Rosain J, Kiykim A, Michev A, Kendir-Demirkol Y, Rinchai D, Peel JN, et al. Recombinant IFN-γ1b Treatment in a Patient with Inherited IFN-γ Deficiency. J Clin Immunol 2024;44:62
806. Marquardt T, Lühn K, Srikrishna G, Freeze HH, Harms E and Vestweber D. Correction of leukocyte adhesion deficiency type II with oral fucose. Blood 1999;94:3976-85
807. Lühn K, Marquardt T, Harms E and Vestweber D. Discontinuation of fucose therapy in LADII causes rapid loss of selectin ligands and rise of leukocyte counts. Blood 2001;97:330-2
808. Tahata S, Raymond K, Quade M, Barnes S, Boyer S, League S, et al. Defining the mild variant of leukocyte adhesion deficiency type II (SLC35C1-congenital disorder of glycosylation) and response to l-fucose therapy: Insights from two new families and review of the literature. Am J Med Genet A 2022;188:2005-201
809. Rao VK, Webster S, Šedivá A, Plebani A, Schuetz C, Shcherbina A, et al. A randomized, placebo-controlled phase 3 trial of the PI3Kδ inhibitor leniolisib for activated PI3Kδ syndrome. Blood 2023;141:971-983

810. Rao VK, Kulm E, Grossman J, Buchbinder D, Chong H, Bradt J, et al. Long-term treatment with selective PI3Kδ inhibitor leniolisib in adults with activated PI3Kδ syndrome. Blood Adv 2024;8:3092-3108
811. Marciano BE, Wesley R, De Carlo ES, Anderson VL, Barnhart LA, Darnell D, et al. Long-term interferon-gamma therapy for patients with chronic granulomatous disease. Clin Infect Dis 2004;39:692-98
812. Ballow M, Conaway MR, Sriaroon P, Rachid RA, Seeborg FO, Duff CM, et al. Construction and validation of a novel disease-specific quality-of-life instrument for patients with primary antibody deficiency disease (PADQOL-16). J Allergy Clin Immunol 2017;139:2007-2010.e8
813. Quinti I, Pulvirenti F, Giannantoni P, Hajjar J, Canter DL, Milito C, et al. Development and Initial Validation of a Questionnaire to Measure Health-Related Quality of Life of Adults with Common Variable Immune Deficiency: The CVID_QoL Questionnaire. J Allergy Clin Immunol Pract 2016;4:1169-1179.e4
814. Jiang F, Torgerson TR and Ayars AG. Health-related quality of life in patients with primary immunodeficiency disease. Allergy Asthma Clin Immunol 2015;11:27
815. Peshko D, Kulbachinskaya E, Korsunskiy I, Kondrikova E, Pulvirenti F, Quinti I, et al. Health-Related Quality of Life in Children and Adults with Primary Immunodeficiencies: A Systematic Review and Meta-Analysis. J Allergy Clin Immunol Pract 2019;7:1929-1957.e5
816. Daly PB, Evans JH, Kobayashi RH, Kobayashi AL, Ochs HD, Fischer SH, et al. Home-based immunoglobulin infusion therapy: quality of life and patient health perceptions. Ann Allergy 1991;67:504-10
817. Gardulf A, Borte M, Ochs HD, Nicolay U; Vivaglobin Clinical Study Group. Prognostic factors for health-related quality of life in adults and children with primary antibody deficiencies receiving SCIG home therapy. Clin Immunol. 2008 Jan;126(1):81-8
818. Nicolay U, Kiessling P, Berger M, Gupta S, Yel L, Roifman CM, et al. Health-related quality of life and treatment satisfaction in North American patients with primary immunedeficiency diseases receiving subcutaneous IgG self-infusions at home. J Clin Immunol 2006;26:65-72
819. Cole T, McKendrick F, Titman P, Cant AJ, Pearce MS, Cale CM, et al. Health related quality of life and emotional health in children with chronic granulomatous disease: a comparison of those managed conservatively with those that have undergone haematopoietic stem cell transplant. J Clin Immunol 2013;33:8-13
820. Rider NL, Kutac C, Hajjar J, Scalchunes C, Seeborg FO, Boyle M, et al. Health-Related Quality of Life in Adult Patients with Common Variable Immunodeficiency Disorders and Impact of Treatment. J Clin Immunol 2017;37:461-475
821. McGlashan HL, Blanchard CV, Luscombe C, Prasad M, Chow G, Auer DP, et al. Quality of life and neurological disability in children and young people with ataxia telangiectasia. Eur J Paediatr Neurol 2022;40:34-39
822. Altman K, Zhou C, Hernandez-Trujillo V, Scalchunes C, Rawlings DJ and de la Morena MT. Health-Related Quality of Life in 91 Patients with X-Linked Agammaglobulinemia. J Clin Immunol 2022;42:811-818
823. Berg AK, Diseth TH, Abrahamsen TG, Halvorsen K, Reinfjell T and Erichsen HC. Primary antibody deficiency: The impact on the quality of life and mental health of affected children and their parents. Acta Paediatr 2021;110:1645-1652

824. Nicholson B, Goodman R, Day J, Worth A, Carpenter B, Sandford K, et al. Quality of Life and Social and Psychological Outcomes in Adulthood Following Allogeneic HSCT in Childhood for Inborn Errors of Immunity. J Clin Immunol 2022;42:1451-1460
825. Kan AKC, Leung GMK, Chiang V, Au EYL, Lau CS and Li PH. Ten-year population trends of immunoglobulin use, burden of adult antibody deficiency and feasibility of subcutaneous immunoglobulin (SCIg) replacement in Hong Kong Chinese. Front Immunol 2022;13:984110
826. Abd Hamid IJ, Slatter MA, McKendrick F, Pearce MS and Gennery AR. Long-term outcome of hematopoietic stem cell transplantation for IL2RG/JAK3 SCID: a cohort report. Blood 2017;129:2198-2201
827. Joshi AY, Iyer VN, Hagan JB, St Sauver JL and Boyce TG. Incidence and temporal trends of primary immunodeficiency: a population-based cohort study. Mayo Clin Proc 2009;84:16-22
828. Tabolli S, Giannantoni P, Pulvirenti F, La Marra F, Granata G, Milito C, et al. Longitudinal study on health-related quality of life in a cohort of 96 patients with common variable immune deficiencies. Front Immunol 2014;5:605
829. Elmoursi A, Zhou B, Ong MS, Hong JS, Pak A, Tandon M, et al. A Cross-Sectional Study of Health-Related Quality of Life in Patients with Predominantly Antibody Deficiency. J Clin Immunol 2024;44:173
830. Heiestad H, Gjestvang C and Haakstad LAH. Investigating self-perceived health and quality of life: a longitudinal prospective study among beginner recreational exercisers in a fitness club setting. BMJ Open 2020;10:e036250
831. Barger SD, Cribbet MR and Muldoon MF. Participant-Reported Health Status Predicts Cardiovascular and All-Cause Mortality Independent of Established and Nontraditional Biomarkers: Evidence From a Representative US Sample. J Am Heart Assoc 2016;5
832. Sowers KL, Sawaged A and Bowen B. Perceived Sleep Quality in Individuals with Inborn Errors of Immunity. J Clin Immunol 2023;43:1221-1228
833. Mallick R, Solomon G, Bassett P, Zhang X, Patel P and Lepeshkina O. Immunoglobulin replacement therapy in patients with immunodeficiencies: impact of infusion method on patient-reported outcomes. Allergy Asthma Clin Immunol 2022;18:110
834. Lee AY, Frith K, Schneider L and Ziegler JB. Haematopoietic stem cell transplantation for severe combined immunodeficiency: Long-term health outcomes and patient perspectives. J Paediatr Child Health 2017;53:766-770
835. Ridao-Manonellas S, Fábregas-Bofill A, Núñez-Rueda G, González-Amores M, García-Prat M, López-Seguer L, et al. Health-Related Quality of Life and Multidimensional Fatigue Scale in Children with Primary Immunodeficiencies. J Clin Immunol 2020;40:602-609
836. Janssen LMA, van den Akker K, Boussihmad MA and de Vries E. Which triggers could support timely identification of primary antibody deficiency? A qualitative study using the patient perspective. Orphanet J Rare Dis 2021;16:289
837. Sowers KL, Litwin BA, Lee ACW and Galantino MLA. Exercise Perception and Behaviors in Individuals Living with Primary Immunodeficiency Disease. J Clin Immunol 2018;38:174-184
838. Mallick R, Henderson T, Lahue BJ, Kafal A, Bassett P and Scalchunes C. Subcutaneous immunoglobulin in primary immunodeficiency - impact of training and infusion characteristics on patient-reported outcomes. BMC Immunol 2020;21:47

839. von Spee-Mayer C, Echternach C, Agarwal P, Gutenberger S, Soetedjo V, Goldacker S, et al. Abatacept Use Is Associated with Steroid Dose Reduction and Improvement in Fatigue and CD4-Dysregulation in CVID Patients with Interstitial Lung Disease. J Allergy Clin Immunol Pract 2021;9:760-770.e10
840. Pulvirenti F, Cinetto F, Pecoraro A, Carrabba M, Crescenzi L, Neri R, et al. Health-Related Quality of Life in Patients with CVID Under Different Schedules of Immunoglobulin Administration: Prospective Multicenter Study. J Clin Immunol 2019;39:159-170