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Practice Parameters

2025 Inborn errors of immunity practice parameter

Guidance from the Joint Task Force on Practice Parameters, the American Academy of Allergy, Asthma & Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI) and the Clinical Immunology Society (CIS)

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Preface. What Is New

The Joint Task Force on Practice Parameters (JTFPP) was commissioned by the American Academy of Allergy, Asthma & 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 immunologic 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 with 530 and 768 references, respectively.[2,3] These versions expanded on 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 in the past decade and continues to expand. Considering the large number of publications related to the care of patients with IEI, it would be unwieldy 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 use 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 and exceptions. Broadly, the document is divided into diagnostic (1-7) and management (8-14) sections (Fig. 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 higher

SUMMARY TO THE 2025 INBORN ERRORS OF IMMUNITY PRACTICE PARAMETER

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

For more information, visit www.allergyparameters.org

Certainty of Evidence: High, Moderate, Low, Very Low

Summary Statement 3.1

Strength of Recommendation: "Recommend" = Strong; "Suggest" = Conditional

- **Strong in Favor:** Offer to Almost All
- **Conditional in Favor:** Appropriate for Most
- **Conditional Against:** Use Only in Select Cases
- **Strong Against:** Do Not Use

DIAGNOSIS

ABNORMAL SCID NEWBORN SCREEN

ALL PATIENTS: INITIAL WORK UP

Recommend urgent confirmation with: 2.2
- CBC/differential
- Lymphocyte subsets (T/B/NK)
- Naive T cells

SUSPECTED OR CONFIRMED SCID

Recommend obtaining: 2.3
- History and physical exam
- Genetic testing
- If T cell count >50 cells/μL:
  - T cell oligoclonality
  - Maternal T cell engraftment
  - Lymphocyte proliferation assay
- If rash is present:
  - IgE level and eosinophil count
- ADA activity

Recommend urgent referral to SCID transplant center 2.4

NON-SCID LYMPHOPENIA

Recommend referral to an IEI specialist for follow up testing at 3 months, including: 2.5
- Lymphocyte subsets (T/B/NK)
- Naive T cells
- Immunoglobulins
- Genetic testing if lymphopenia persists

SUSPICIOUS CLINICAL HISTORY FOR IEI

Recurrent, severe, or rare infections; autoinflammation; severe autoimmunity; severe atopy; atypical malignancy; bone marrow failure; or a combination of these conditions

ALL PATIENTS: INITIAL WORK UP

Recommend evaluation for secondary causes such as allergies, infections, medications, and malignancy 1.4

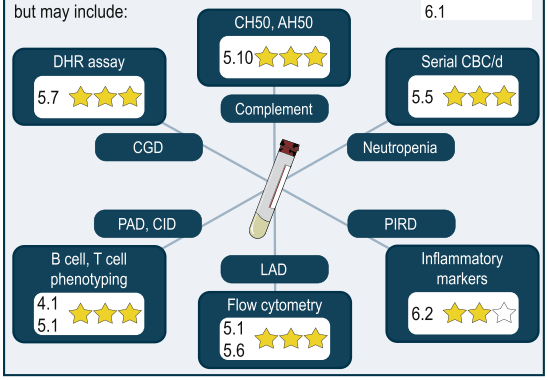
Recommend laboratory testing with: 4.1, 5.1
- CBC/differential
- Immunoglobulins
- Specific antibody titers (HiB, tetanus, diphtheria, pneumococcus*)
- Lymphocyte subsets (T/B/NK)

Recommend genetic testing early in the work up for all suspected IEIs 1.3

Known Familial Variant:	**Recommend** single gene sequencing	3.1
No Familial Variant:	**Recommend** IEI gene panel or WES	3.2
Congenital Anomalies, Developmental Delays:	**Recommend** copy number variant (CNV) testing	3.4

SOME PATIENTS: TARGETED TESTING

Recommend additional testing targeted to suspected deficiency. See practice parameters for further details, but may include: 4.1, 5.1, 6.1



MANAGEMENT

MONITORING

GENERAL MONITORING

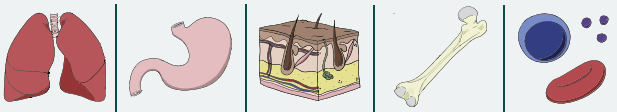
Recommend: 7.3, 7.5
- Thorough history and physical exam yearly
- CBC/d every 3-12 months
- CMP yearly
- Lung function test and imaging

Recommend AGAINST: 7.4
- Routine autoantibody screening

Suggest assessing: 7.1
- Growth (pediatric), nutritional status

Recommend performing quality of life measurements with a validated tool 14.1

MONITORING FOR COMMON COMORBIDITIES



LUNG	GI	SKIN	MSK	BLOOD
• chronic lung disease • bronchiectasis	• IBD • enteropathy • liver disease • malignancy	• atopic dermatitis • malignancy	• osteoporosis • rheumatologic disease	• cytopenias • malignancy • lympho-proliferation

Suggest systemic comorbidities be evaluated and managed by a multidisciplinary team with IEI expertise 10.1

ABBREVIATIONS:
ADA: adenosine deaminase
SCID: severe combined immune deficiency
IEI: inborn error of immunity
WES: whole exome sequencing
CH50: classical complement activity assay
AH50: alternative complement activity assay
DHR: dihydrorhodamine
CGD: chronic granulomatous disease
LAD: leukocyte adhesion deficiency
PAD: predominantly antibody deficiency
CID: combined immune deficiency
PIRD: primary immune dysregulation disorders
HiB: *Haemophilus influenzae* type B
PFT: pulmonary function testing
DLCO: diffusing capacity
GI: gastrointestinal
IBD: inflammatory bowel disease
MSK: musculoskeletal

*Normal response: >50% of titers protective 4-6 weeks after vaccination. Protective titer: >=0.35 μg/mL after protein conjugate vaccine or >=1.3 μg/mL after polysaccharide vaccine, unless assay specifies otherwise

Infographic by EL Reigh, MD

Fig 1. Infographic summary of the 2025 IEI practice parameter summarizing in three parts the approach to diagnosis (sections 1-7), management (sections 8-14) and with greater specificity to predominatly antibody deficiency (sections 4 and 8). Please see corresponding text sections for further detail.

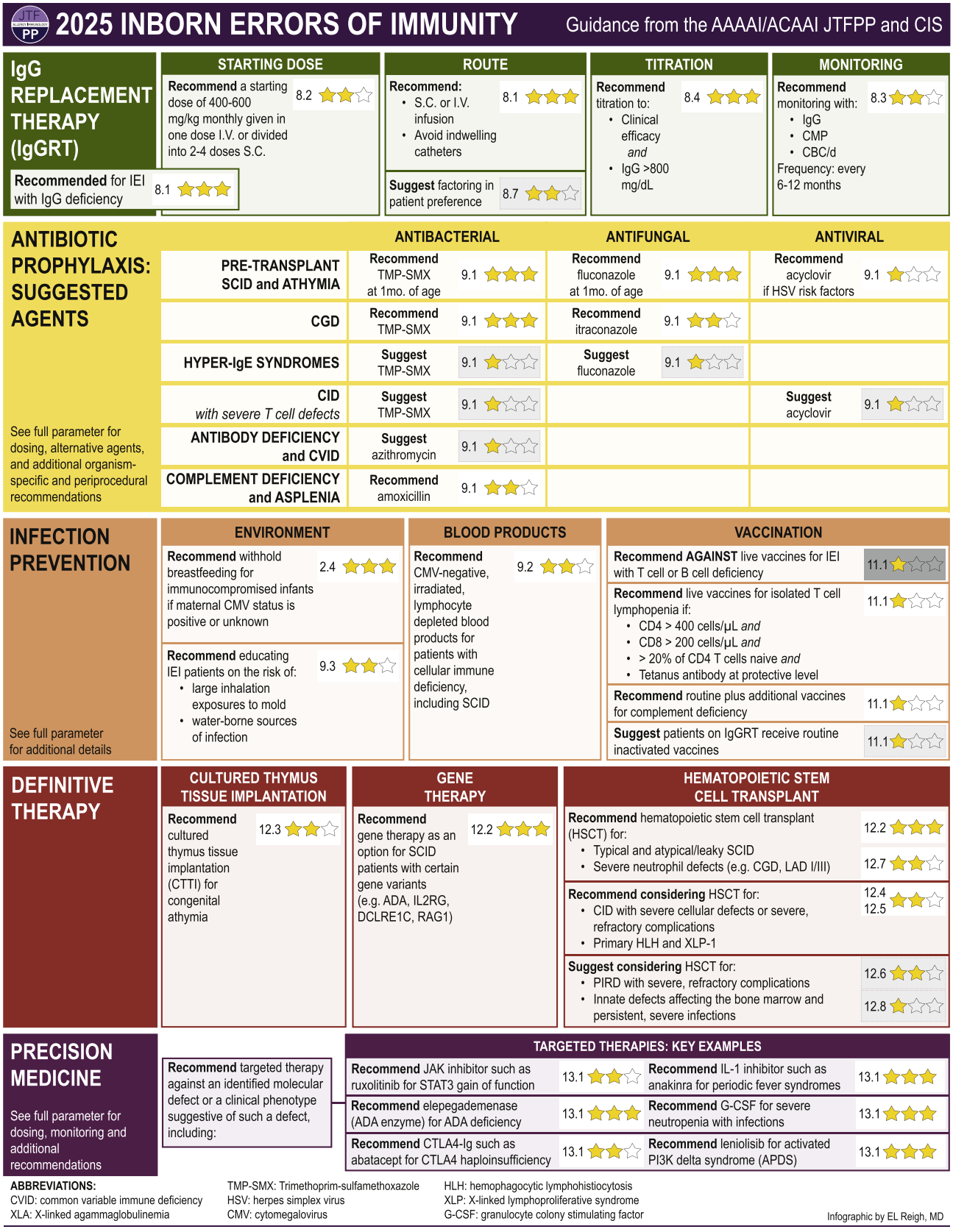


Fig 1. Continued.

SUMMARY TO THE 2025 INBORN ERRORS OF IMMUNITY PRACTICE PARAMETER

DIAGNOSIS AND TREATMENT OF PREDOMINANTLY ANTIBODY DEFICIENCY

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

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Certainty of Evidence: High, Moderate, Low, Very Low

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Strength of Recommendation: "Recommend" = Strong; "Suggest" = Conditional

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- **Strong Against:** Do Not Use

DIAGNOSIS

EVALUATION OF SUSPECTED ANTIBODY DEFICIENCY

INITIAL TESTING

Recommend evaluation for secondary causes, including medications, malignancy, and protein-losing states — 4.1

Recommend obtaining: — 4.1
- Serum IgG, IgM, and IgA levels
  - IgG <2 SD below the mean 2 times >3 weeks apart is low
- Specific antibody titers (e.g. HiB, tetanus, pneumococcus*) to assess antibody function
- Lymphocyte subsets (T/B/NK) to screen for CID

FOLLOW UP TESTING

Recommend assessing peripheral blood B cell subsets, with particular attention to: — 4.1
- Class-switched memory B cells: if <2%, high risk for autoinflammatory disease and death
- Transitional and CD21lo B cells: if elevated, associated with autoimmune complications

Recommend genetic testing early in the work up for all suspected IEIs — 1.3

DIAGNOSTIC CRITERIA

	SERUM IMMUNOGLOBULINS	SPECIFIC ANTIBODIES	OTHER CRITERIA	
Recommend diagnosis of AGAMMAGLOBULINEMIA if:	Low or undetectable IgG, IgM, and IgA	Not required when IgG <150 mg/dL	Peripheral B cells (<2%) Normal CD3+ T cells	4.2
Recommend diagnosis of COMMON VARIABLE (CVID) if:	Low IgG *plus* Low IgA *and/or* IgM	Impaired*	May present with infections and/or autoimmunity/inflamm.	4.3
Recommend diagnosis of SELECTIVE IgA DEFICIENCY if:	Undetectable IgA *plus* Normal IgG and IgM		Age > 4 years	4.4
Suggest diagnosis of IgG SUBCLASS DEFICIENCY if:	Normal IgG *plus* IgG1, IgG2 *and/or* IgG3 low		Recurrent respiratory infections	4.5
Suggest diagnosis of SAD *to polysaccharides* if:	Normal IgG	Impaired to polysaccharides*	Recurrent respiratory infections	4.6
Suggest diagnosis of SAD *to protein antigens* if:	Normal IgG	Impaired to protein antigens	Recurrent infections	4.7
Recommend diagnosis of Ig CLASS-SWITCH DEFECTS if:	Low IgG *and* low IgA *plus* normal or high IgM		Rule out CIDs with similar lab findings	4.8
Recommend considering diagnosis of THI if:	Low IgG	Normal	Age < 5 years *and* other causes excluded	4.9
Suggest diagnosis of unspecified 1° hypogammaglobulinemia if:	Low IgG with significant infections *and* normal cellular immunity *plus* other causes excluded (including potential primary and secondary immune deficiencies)			4.10

See full parameter for additional details on diagnostic criteria, including interpretation of specific antibody function

*For pneumococcus: a normal response is >50% of titers protective 4-6 weeks after vaccination. *Protective titer* defined as ≥0.35 μg/mL after protein conjugate vaccine or ≥1.3 μg/mL after polysaccharide vaccine, unless assay specifies otherwise

TREATMENT

IgG REPLACEMENT THERAPY (IgGRT)

Recommended for IEI with IgG deficiency — 8.1

STARTING DOSE

Recommend a starting dose of 400-600 mg/kg monthly given in one dose I.V. or divided into 2-4 doses S.C. — 8.2

ROUTE

Recommend: — 8.1
- S.C. or I.V. infusion
- Avoid indwelling catheters

Suggest factoring in patient preference — 8.7

TITRATION

Recommend titration to: — 8.4
- Clinical efficacy *and*
- IgG >800 mg/dL

MONITORING

Recommend monitoring with: — 8.3
- IgG
- CMP
- CBC/d

Frequency: every 6-12 months

OTHER

ANTIBIOTIC PROPHYLAXIS

Suggest antibiotic prophylaxis with azithromycin in mild antibody deficiency or in addition to IgGRT if experiencing breakthrough infections. See parameter for alternatives. — 9.1

PRECISION MEDICINE

Recommend targeted therapy against an identified molecular defect or a clinical phenotype suggestive of such a defect. See parameter for examples. — 13.1 (Low to High)

ABBREVIATIONS:
SD: standard deviation
HiB: *Haemophilus influenzae* type B
CID: combined immune deficiency
IEI: inborn error of immunity
CVID: common variable immune deficiency
SAD: specific antibody deficiency
THI: transient hypogammaglobulinemia of infancy
PAD: predominantly antibody deficiency

Infographic by EL Reigh, MD

Fig 1. Continued.

number of available publications. Because of the implementation of universal newborn screening for severe combined immunodeficiency (SCID), guidance for prompt management of infants with abnormal screening test results 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 in the last decade. Thus, Section 13 is focused on therapies found to be effective for many IEI. The last section discusses the use of tools to measure patient-reported outcomes (PRO) 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 this 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.

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. Although this practice parameter document does not formally use 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 to the greatest degree 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 Clinical Immunology Society (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

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

In some cases in this parameter a range for strength of recommendation is listed as the individual statement refers to a table that contains multiple recommendations associated with different strengths of recommendation.
Adapted from Chu et al.[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 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 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, NBS 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 IUIS.[7]

List of Recommendations

Section and number	Recommendation	Strength	Certainty of evidence
Section 1. Clinical Approach to the Diagnosis of Inborn Errors of Immunity			
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, immunologic, 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 (eg, 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 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	Strong	High

(*continued*)

(*Continued*)

Section and number	Recommendation	Strength	Certainty of evidence
	peripheral blood lymphocyte subset populations, including assessment of numbers of T, B, and NK subsets and naive T cells.		
2.3	**We recommend** that diagnostic evaluation for SCID and athymia includes 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 Inborn Errors of Immunity			
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 noncoding 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 monogenic 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.	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.	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 impaired antibody response to infection or immunization ***and*** other causes of hypogammaglobulinemia have been excluded	Strong	High
4.4	**We recommend** the diagnosis of selective IgA deficiency (SIGAD) for patients older than 4 years of age with serum IgA level 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 1 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 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** 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** the diagnosis of unspecified primary hypogammaglobulinemia for patients with recurrent infections ***and*** low serum IgG level ***and*** normal cellular immunity ***and*** absent evidence of secondary causes of low IgG levels ***and*** not fulfilling diagnostic criteria for the above-mentioned antibody deficiency disorders.	Conditional	Moderate
Section 5. Diagnosis of Combined Immunodeficiencies, Phagocyte Defects, Innate Immune Defects, and Complement Deficiencies			
Combined Immunodeficiencies Less Severe Than SCID and Syndromic Immunodeficiencies			
5.1	**We recommend** immunologic 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** immunologic investigations and testing of diagnostic biological markers in patients with suspicion of CID ***and*** certain specific clinical findings in non-immunologic organs and systems (syndromic features).	Strong	High

(*continued*)

(*Continued*)

Section and number	Recommendation	Strength	Certainty of evidence
5.4	**We suggest** periodic assessments of immunologic function in patients with CID and syndromic features.	Conditional	Low
Phagocyte 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 oxidase activity ***and*** genetic testing for CGD associated gene defects.	Strong	High
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).	Strong	High
5.12	**We recommend** genetic testing when complement function screening is abnormal.	Strong	Moderate
Section 6. Immunologic Diagnosis of Primary Immune Dysregulation Disorders 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 immunologic functions in patients with suspected primary 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 Inborn Errors of Immunity			
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 infectious pathogens 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 to 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 panel for patients on immunoglobulin replacement therapy**.**	Strong	Moderate
8.4	**We recommend** maintaining serum IgG levels at more than 800 mg/dL to improve outcomes.	Strong	High
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 level, 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 Inborn Errors of Immunity			
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 combined immunodeficiencies or athymia.	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 recommended for immunocompetent patients.	Conditional	Low
Section 10. Management of Co-Morbidities in Inborn Errors of Immunity			
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 to strong	Low to moderate

(*continued*)

(*continued*)

(*Continued*)

Section and number	Recommendation	Strength	Certainty of evidence
10.2	**We recommend** prompt management of cytopenia(s) or malignancies in patients with IEI.	Strong	Moderate
Section 11. Immunizations in the Management of Inborn Errors of Immunity			
11.1	**We recommend** the use of vaccine recommendations from public agencies (eg, WHO and CDC) and professional medical organizations (eg, AAAAI, ACAAI, and CIS) for patients with IEI.	Strong	Low
Section 12. Immune Reconstitution Therapy for Inborn Errors of Immunity			
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	Moderate
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 lymphoproliferative disease type 1 be evaluated for allogeneic HSCT.	Strong	Moderate
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	Low
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 Inborn Errors of Immunity			
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 Inborn Errors of Immunity			
14.1	**We recommend** performing quality-of-life (QoL) measurements in patients with IEI, inclusive of patient-reported outcome (PRO) measurements conducted with a validated tool.	Strong	Moderate
14.2	**We suggest** that PROs should be measured using a disease-specific QoL instrument 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

*Note that these recommendations are associated with a range of strength and certainty of evidence as they refer to a table that contain multiple examples that differ in their strenght and certainty. Please do refer specifically to the linked tables for these statements.

Part I: Diagnosis

Section 1. Clinical Evaluation of Inborn Errors of Immunity

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 after infection, recurrence of infections, or infection with organisms that are deemed opportunistic (ie, 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 IUIS every 2 years.[7,17] In the IUIS classification document, IEI are presented in subtables with associated defective genes and the reported clinical and immunologic characteristics (summarized in Table 1A). Disorders affecting T-cell function are in IUIS subtables I and II (Sections 2 and 5.1). Primary antibody disorders are classified in IUIS subtable III (Section 4). Immunodysregulation disorders, characterized by autoimmunity and inflammation, with and without susceptibility to infections, are included in IUIS subtable IV (Section 6). Primary neutrophil disorders are in IUIS subtable V (Sections 5.5-5.8). IUIS subtable VI groups innate immunity defects conferring high risk of infection by specific microorganisms (Section 5.9). Autoinflammatory disorders related and not related to inflammasome dysfunction are classified in IUIS subtable VII (Section 6), whereas complement deficiencies are in IUIS subtable VIII (Sections 5.10-12). The IUIS subtable IX lists primary bone marrow failure conditions, which may manifest with increased frequency of infections and are often managed by hematology/oncology specialists. The IUIS classification includes subtable X to compile phenocopies of IEI for clinician awareness and to be considered when a genetic diagnostic is uncertain. These conditions have clinical presentations similar

Table 1A
IUIS Classification of Human IEI 2024

Subtable I	Immunodeficiencies affecting cellular and humoral immunities 1. T-B+ SCID 2. T-B− SCID 3. Combined immunodeficiencies. Generally less profound than SCID
Subtable 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. Immuno-osseus 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 defects
Subtable 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 levels with normal/elevated IgM level and normal B-cell numbers, hyper IgM 4. Isotype, light chain, or functional deficiencies with generally normal B-cell numbers
Subtable IV	Diseases of immune dysregulation 1. 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
Subtable V	Congenital defects of phagocyte number or function 1. Congenital neutropenia 2. Defects of motility 3. Defects of respiratory burst 4. Other nonlymphoid defects
Subtable VI	Defects in intrinsic and innate immunities 1. 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
Subtable VII	Autoinflammatory disorders 1. Type I interferonopathies 2. Defects affecting the inflammasome 3. Non–inflammasome-related conditions
Subtable VIII	Complement deficiencies
Subtable IX	Bone marrow failures
Subtable X	Phenocopies of IEI

Abbreviations: CVID, common variable immune deficiency; EBV, Epstein-Barr virus; FHLH, familial hemophagocytic lymphohystiocytosis; HPV, human papilloma virus; IEI, inborn error(s) of immunity; IUIS, International Union of Immunological Societies; MSMD, Mendelian susceptibility to mycobacterial disease; SCID, severe combined immunodeficiency; TLR, toll-like receptor.

(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. IUIS subtable IX and X disorders are not addressed in detail in this practice parameter.

Recommendation 1.2: We recommend 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 with other household members is suggestive of an IEI. Beyond infections, family history should inquire the presence of autoimmunity, inflammatory features (eg, vasculitis, colitis, fevers, rashes), cancers, and severe atopy. A detailed family history might identify relatives that are also affected by the patient's condition. Approximately 1.5% of patients in a large cohort of patients with IEI were diagnosed because of a family history,[8] whereas 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 (eg, 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 recommend an integrated approach for the diagnosis of a suspected IEI: clinical, immunologic, and genetic components.

Strength of recommendation: **Strong**

Certainty of evidence: **Moderate**

The evaluation for the diagnosis of suspected IEIs requires a synthesis of the following 3 important components[19,20]: (1) clinical findings obtained from history and physical examination; (2) supporting immunologic 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 examination should focus on features of syndromes with characteristic dysmorphisms (eg, face features in DiGeorge syndrome), stigmata of recurrent infections (eg, warts, bronchiectasis), autoimmunity (eg, alopecia, vitiligo), lymphoproliferative phenotypes (eg, lymphadenopathy, splenomegaly), and severe atopy (eg, generalized lichenified and infected eczema). Based on clinical findings, immunologic 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, presence of disseminated warts prompts an evaluation of T 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 recommend that the evaluation of immunodeficiency should include testing for secondary causes of immunodeficiency.

Strength of recommendation: **Strong**

Certainty of evidence: **Moderate**

In patients in which susceptibility to infection is among the chief concerns, a broader consideration should be given to secondary immunodeficiencies (Table 1B), 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 chemical damage due to secondhand 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

Table 1B
Examples of Secondary Causes of Immunodeficiency

Anatomical: nasal polyposis, deviated septum, adenoidal hypertrophy, CSF leak
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

Abbreviations: CSF, cerebrospinal fluid; EBV, Epstein-Barr virus.

inflammation also reduces pathogen clearance.[24] Infectious diseases that target the immune system (such as HIV infection) lead to a deficient immune response.

Secondary immunodeficiency conditions arise with the use of immunosuppressive medications in autoimmunity and cancers. A few medications can impair immune cells in a nonpredictable manner, such as antiepileptic drugs.[25,26]

Disorders in which immune cells and immunoglobulins are lost from the gut, respiratory tract, or lymphatic vessels such as hydrops, protein-losing enteropathy, intestinal lymphangiectasis, lymphovenous 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 immunities compared with 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, and NFKB2 deficiency.[34,35]

Recommendation 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.

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 (Section 7).

The multisystem nature of IEI necessitates an integrated multidisciplinary approach to management. This approach provides significant cost savings, improved QoL, and improved outcomes.[40–42] Such an approach optimizes medical treatments and permits integration of health and social care professionals and physical and occupational therapies 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, gastroenterologist, pharmacists, and geneticists.[43] Within the same concept, a clinic focusing on patients with 22q11 deletion syndrome also requires experts in otorhinolaryngology, endocrinology, cardiology, and speech therapy.[44]

Recommendation 1.6: We suggest the provision of support resources (eg, 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 for Severe Combined Immunodeficiency and Athymia—Diagnosis and Initial Approach

Infants born with SCID or with congenital athymia have absent or very few naive T cells in their blood. This deficiency can be quantitatively detected through polymerase chain reaction (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 for 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 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 modeling,[54–56] led to the addition of SCID to the Department of Human and Health Services Recommended Uniform Screening Panel (RUSP) in 2010. By 2018, all 50 US states and Puerto Rico 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 of 65,000 live births, higher than previous estimates.[58] Nearly all infants are diagnosed with SCID in the United States 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 naive 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 TREC-based 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 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 naive T cells.

Strength of recommendation: **Strong**

Certainty of evidence **High**.

Approximately 1 of 15,000 live births in the United States are born with clinically significant lymphopenia.[73] Although SCID NBS is highly sensitive to screen for the primary targets of SCID and complete athymia, it is not a diagnostic test. Indeed, only approximately 15% of patients with an abnormal SCID NBS are ultimately diagnosed with SCID, whereas others have secondary causes of T-cell lymphopenia (eg, prematurity) or have normal lymphocyte populations.[58,73] Therefore, it is important for NBS 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), naive 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-mentioned laboratory tests are sufficient to rule out SCID or a T-cell lymphopenia disorder, infants require a complete birth history, family history, and physical examination 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 (Table 2A).[76] The threshold for clinically significant T-cell lymphopenia may vary, but in general, lower than 1000 cells/μL T-cells with lower than 20% of naive 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. Although 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 (eg, azathioprine) and diabetes mellitus.[80]

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 2A).[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 (Section 12). Assessment of T-cell oligoclonality by evaluating the T-cell receptor repertoire diversity is commercially available in immunology laboratories. Transplacental maternal T-cell engraftment can be tested in patients with T-cell counts more than 50 cells/μL, by comparing HLA markers expressed in T cells and non-T cells (eg, neutrophils). In cases in which adenosine deaminase deficiency is suspected (ie, patients with very low numbers of T, B, and NK 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

Table 2A
PIDTC 2022 Definitions for SCID[76]

SCID subtype	Criterion 1	Criterion 2	Criterion 3	Criterion 4
Typical SCID Criteria 1 and 2 OR criteria 1 and 3 OR criterion 4	Very low T cells ($<0.05 \times 10^3$/L)	Pathogenic variant in SCID-associated gene	No alternate explanation for low T-cell count AND, EITHER: Undetectable or low TREC OR <20% naive CD4 T cells	Presence of maternal T-cell engraftment
Leaky/atypical SCID Criteria 1 and 2 and 4 OR criteria 1 and 3 and 4	Two or more of: -Low T-cell number for age -Oligoclonal T cells -Abnormal TREC OR <20% naive CD4 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
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 level -Abnormal TREC - Lymphadenopathy -Hepatomegaly and/or splenomegaly -Oligoclonal T cells

Abbreviations: PIDTC, Primary Immune Deficiency Treatment Consortium; SCID, severe combined immunodeficiency; TREC, T-cell receptor excision circle.

Table 2B
Recommendations for the Care of Infants With SCID Diagnosis[a]

Recommendation	Frequency	Comment
Test CMV PCR in urine and in blood	Baseline and every 3 to 4 mo	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 mo	If present, treat EBV infection (valganciclovir or ganciclovir, dose similar to CMV).
Test HIV PCR or antigen tests in blood	Baseline	Treat HIV infection
Test PCR-based respiratory viral pathogen panel (eg, 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 (eg, 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	Starting at 1 mo of age	Trimetroprim/sulfamethoxazole 5 mg (of trimethoprim component)/kg/d oral 2 or 3 times a week
Prophylaxis for Candidiasis	Daily	Fluconazole 3 mg/kg/d oral
Prophylaxis for herpes infection	Daily	Acyclovir 12.5 mg/kg/d oral
Prophylaxis for RSV infection	During RSV season	Palivizumab or nirsevimab-alip
Immunoglobulin replacement therapy	Monthly or weekly	Intravenous or subcutaneous routes (400 mg/kg/mo)
Avoid live viral vaccines		Includes: rotavirus, MMR, BCG, oral polio. Household members are encouraged to receive all scheduled vaccines

Abbreviations: BCG, bacillus Calmette-Guerin; CMV, cytomegalovirus; EBV, Epstein-Barr virus; MMR, measles, mumps, rubella; PCR, polymerase chain reaction; PJP, *Pneumocystis jirovecii* pneumonia; RSV, respiratory syncytial virus; SCID, severe combined immunodeficiency.
[a]From Dorsey et al.[77] Not an exhaustive list, alternative recommendations exist.

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] Recommendation 9.2 discusses use of blood products. Table 2B summarizes recommendations for surveillance of infections and antibiotic prophylaxis in patients with SCID (Sections 8-11).

Recommendation 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.

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 more than 50 but less than 1000 cells/μL, with naive 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 (eg, chylous loss), prematurity, and/or dysmorphic features consistent with other syndromic conditions (eg, 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 (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] (Sections 4 and 5):

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

Section 3. Genetic Evaluation of Inborn Errors of Immunity

Determination of an underlying genetic diagnosis assists in the evaluation and treatment of patients with suspected IEI.[90] IEI are caused by defects in more than 505 genes, underscoring the need for genetic evaluation.[7] The application of massively parallel sequencing (MPS), also known as next generation sequencing (NGS), for genetic testing (eg, exome sequencing) and decreasing costs have contributed to the increasing availability of genetic tests in clinical settings. Genetic testing has led to the broadening of clinical phenotypes (eg, very early onset inflammatory bowel disease as a manifestation of chronic granulomatous disease) and selection of targeted therapies based on the identified disease mechanism (eg, JAK inhibition for *STAT1* or *STAT3* gain of function). A variety of testing methods are available (Table 3A), 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.

Recommendation 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 due to a defect in a gene that might not be reliably analyzed using high-throughput massively parallel sequencing.

Strength of recommendation: **Strong**

Table 3A
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
Noncoding 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

Abbreviations: CNV, copy number variation; IEI, inborn error(s) of immunity; SNV, single nucleotide variant.
[a]If SNV is known.
[b]Sensitivity varies with test protocol design.

Certainty of evidence: **High**

Single-gene sequencing, also known as Sanger sequencing, is based on PCR amplification.[91] A strength of Sanger sequencing is its high accuracy, and it 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 noncoding regions, intronic or untranslated regions (UTRs). Sanger sequencing may distinguish genes from pseudogenes, which are nonfunctional 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 1 or more direct relatives of the patient. Single-gene sequencing can also be used to establish carrier status for apparently unaffected family members (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 variations (CNV) 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 1 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 3B). Although Sanger sequencing samples of different tissues or cells has been used to evaluate mosaicism, it is not sensitive below a threshold of 15% to 20%.[100] In contrast, MPS-based tests with very high read depth can detect variant allele frequencies below 1% in 1 sample.[101]

Recommendation 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.

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 2 test methods is based on availability, turnaround time, sequencing depth, CNV reporting, and cost. These factors will be specific for the clinical needs of each patient.

Table 3B
Examples of IEI Genes Associated With Mosaicism

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

Abbreviation: IEI, inborn errors of immunity.

Exome sequencing aims to sequence all coding regions within the genome. In contrast, targeted gene panels evaluate coding and selected noncoding 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 (eg, a SCID panel may analyze 24 genes) to panels of more than 500 genes that encompass the most known IEI and 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 affect splicing. Some targeted panels capture noncoding regions known to harbor pathogenic variants of certain genes (eg, *GATA2*). Of note, some targeted gene panels use exome sequencing to 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 500 reads or higher, whereas the average read depth for exome sequencing is typically approximately 100 reads.[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. In addition, 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 (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 noncoding 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 (eg, primary ciliary dyskinesia).[108,109]

Exome and whole genome sequencing (Recommendation 3.3) are preferentially considered than targeted gene panels in 2 situations. First, for evaluation of patients with IEI and additional phenotypic features that do not involve the immune system (eg, cardiac malformations, neurologic deficits). These patients may have a higher pretest 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. Studies suggest that use of broader sequencing platforms in such patients increases the diagnostic yield and may be more cost-effective than targeted gene panel testing.[102,108,109]

Recommendation 3.3: We suggest whole genome sequencing of individuals with suspected IEI and non-immunologic traits or with high suspicion for a noncoding 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 noncoding 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 noncoding regions include *LRBA, DOCK8*, and *ARPC1B*[110,111] (Table 3C). The absence of an initial capture step allows for uniform read depth (average read depth approximately 20 -30 times), although the limited read depth of WGS does not identify variants with low allele frequencies (ie, somatic mosaicism). WGS has an enhanced ability to detect CNVs compared with gene panels or exomes.[112] Overall, studies have revealed that WGS provides an increase in diagnostic yield than exome sequencing.[113,114]

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

Recommendation 3.4: We recommend DNA CNV testing in patients with IEI with a suspected gene(s) deletion or duplication.

Table 3C
Examples of IEI Genes Reported to Contain Noncoding Pathogenic Variants

ADA	*CTPS1*	*GINS1*	*NLRP3*	*SPINK5*
ADA2	*CTSC*	*IKBKG*	*PALB2*	*STAT1*
AIRE	*CYBB*	*IL10RB*	*PARN*	*STAT3*
ARPC1B	*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*	

Abbreviation: IEI, inborn error(s) of immunity.

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 with the control sample is used to determine gains or losses of DNA regions. CMA testing is recommended than fluorescence in situ hybridization (FISH) because it has a higher sensitivity to detect microdeletions, such as 22q11.2 microdeletion. As a separate advantage, although 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 1 to 2 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, because 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 1 pathogenic variant in a gene that causes disease in an autosomal recessive manner.[102]

Recommendation 3.5: We recommend 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 1 of the following 5 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 (LOF) rather than gain-of-function (GOF) 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 LOF 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 pretest probability and likelihood ratio, which together determine post-test probability (as depicted by Fagan's nomogram).[130] Pretest 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 (eg, GOF, haploinsufficiency, dominant-negative LOF, 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 pretest 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 pretest 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 pretest 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 pretest probability is low. This interpretation is with the caveat that a person can be asymptomatic (or "presymptomatic") 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 2 variants are identified in a gene that causes IEI due to biallelic defects (ie, 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 toward 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 suggest 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 CTLA-4 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 recommend 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 1 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 recommend 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.

Section 4. Immunologic Diagnosis of Predominantly Antibody Deficiencies

Recommendation 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.

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 workup 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.

Low serum IgG level is defined by a value less than 2 SDs below the age-appropriate reference mean for 2 measurements more than 3 weeks apart.[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]

Individuals with undetectable serum levels of IgA, IgM, or IgE have been described. Selective IgA deficiency (SIGAD) is considered the most common IEI (Recommendation 4.4). Selective IgM deficiency (SIgM) and selective IgE deficiency (SIgE) are considered rare, and their association with clinical manifestations is not well established.[147,148]

Secondary causes of antibody deficiency include medication induced (eg, 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. Causes of protein and antibody losses, such as nephrotic syndromes, protein-losing enteropathies, lymphangiectasias, or inflammatory bowel disease with low serum IgG level have been well described.[149] Supporting laboratory evidence for protein loss includes low serum albumin level, proteinuria, and/or protein losses in the stool (eg, a positive result for 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 (Section 5) and congenital agammaglobulinemia (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 or reduced memory B cells is a component of the diagnostic criteria for 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 after vaccination, including to the COVID mRNA vaccines, and are at high risk for the development of autoimmune disease co-morbidities and death.[150,151] Expansions of early transitional B cells (defined as IgD+CD27−CD10+ or IgD+CD27−$CD24^{hi}CD38^{hi}$) or activated $CD21^{lo}$ 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 (eg, CTLA-4 deficiency)[156,157–159]

Normal serum immunoglobulin levels do not rule out a diagnosis of humoral immune dysfunction. Recommendations 4.6 and 4.7 detail SAD, a condition in which patients with recurrent infections present with normal serum IgG levels; however, antigen-specific antibody responses to immunization are decreased. Patients with SAD have respiratory infections 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.[160] Testing of antigen-specific antibody response to immunization has historically centered in testing of both T-dependent vaccine responses (eg, HiB and tetanus toxoid) and T-independent vaccine responses (eg, pneumococcal 23 serotype polysaccharide vaccine).[161] 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 (Recommendations 4.6 and 4.7).

Guidelines for the analysis of anti-pneumococcal antibody responses suggest using 1.3 μg/mL after a polysaccharide pneumococcal vaccine and 0.35 μg/mL after a pneumococcal conjugate vaccine as thresholds to determine protective pneumococcal serotype-specific antibody levels against invasive pneumococcal infections. Demonstration of protective levels to all tested anti-pneumococcal serotype antibodies after vaccination constitutes an optimal response (Recommendation 4.6). These tests are measured at baseline, 4-week post-vaccination, and, to assess persistence of immunologic memory, at 6 months post-vaccination.[161] 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.[161,162]

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 *Streptococcus pneumoniae* and *Haemophilus 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 found.[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.[163]

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%.[163,164] The differential diagnosis of agammaglobulinemia includes secondary causes and severe CVID (see subsequent section) with serum immunoglobulin levels and B cells in the agammaglobulinemic range. It can be difficult to distinguish agammaglobulinemia from CVID without molecular testing. Measurement of antigen-specific antibody titers is not necessary in patients with IgG levels less than 150 mg/dL.

Genetic evaluation is recommended in the diagnosis of agammaglobulinemia (Section 3). Approximately 85% of patients with agammaglobulinemia 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 SAD.[163,164] 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 1 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 recommend 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 and other causes of hypogammaglobulinemia have been excluded

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,* and 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* spp) and viral (such as norovirus) infections (Section 9).[181]

In addition to infections, patients with CVID may present with autoimmunity, chronic gastrointestinal, liver, and lung diseases, 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 pathologic appearance of autoimmune inflammation but absent autoantibodies typically found in these diagnoses.[183,184] Liver disease frequently demonstrates 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 approximately 30% of CVID cases have identifiable genetic etiology.[189,190] Widespread availability of clinical genetic testing is at the forefront of CVID clinical care. Other IEI might present as CVID. 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 and varying degrees of antibody deficiency consistent with CVID.[191,192] Also, heterozygous GOF variants of *PIK3CD* and LOF 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 recommend the diagnosis of 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 approximately 1:500 in Whites and appears to be less common in Asian populations, in which the prevalence is reported between 1:3000 and 1:18000.[194,195] Assays at most clinical laboratories have not been sensitive enough to measure IgA levels below 7 mg/dL, and approximately one-third of patients with SIGAD are thought to have completely absent serum IgA level.[3] Four years of age is considered the time when most children reach the normal range for serum IgA level. Patients with SIGAD 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 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%). Antibiotic prophylaxis might reduce frequency of infections.[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* spp. infection or small intestinal bacterial overgrowth.[200]

Recommendation 4.5: We suggest the diagnosis of IgG subclass deficiency for patients with recurrent infections and low levels of 1 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 1 or more of the 4 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% to 30% of total IgG levels. IgG3 represents approximately 10% of total IgG and has the shortest half-life at 7 days, compared with 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 bases 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 immunologic finding alone.[201] More than half of patients with activated PI3K delta syndrome (APDS) with normal total IgG levels may have IgG2 subclass deficiency.[202] A prospective study of 49 children with IgG2 subclass deficiency, predominantly boys, had 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 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 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 nonprotective antibody levels when measured after 4 weeks after immunization. The molecular and immunologic 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. Use of the unconjugated *Salmonella* vaccine has been proposed as an alternative vaccine for diagnosis of SAD to polysaccharide antigens, although studies to establish sensitivity and specificity are limited.[205]

Results of anti-pneumococcal antibody testing, including percentage of positive results, can vary between clinical laboratories.[162,206] Previous guidelines with regard 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 μg/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 cutoff for diagnosis of SAD.

It is suggested to use first the unconjugated pneumococcal polysaccharide vaccine (PPSV23) to evaluate T-cell–independent antibody responses, then, if the response is suboptimal, administer 1 of the conjugated vaccines. As an alternative, the evaluation of SAD may be accelerated by moving directly to conjugated pneumococcal vaccine after assessing prevaccination pneumococcal antibody levels. Although 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 (Sections 8 and 9), and may allow for diagnosis of SAD to protein antigen (Recommendation 4.7).

Recommendation 4.7: We suggest the diagnosis of 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**

Although 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 immunologic 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.[160,207]

Recommendation 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.

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.[208–211] These patients may also develop nonmalignant lymphoid hyperplasia, which occurs in approximately 70%.[211] Autoimmune and inflammatory disorders (eg, autoimmune hemolytic anemia and inflammatory bowel disease) can be found 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-cell counts and T-cell proliferation are typically normal and are helpful to rule out CID, such as CD40 ligand deficiency and NEMO deficiency (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 level.[213]

Recommendation 4.9: We recommend 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 immunodeficiency 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 1 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 patients with THI have reduced memory B-cell counts.[219,220] We recommend measuring serum IgG levels every 6 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,[221] some do not recover and are diagnosed with CVID or other forms of antibody deficiency.[214–217]

Recommendation 4.10: We suggest the diagnosis of unspecified primary hypogammaglobulinemia for patients with recurrent infections *and* low serum IgG level *and* normal cellular immunity *and* absent evidence of secondary causes of low IgG levels *and* not fulfilling diagnostic criteria for the above-mentioned 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 previously discussed, (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 (Recommendation 4.1).[147,216,217]

Section 5. Combined Immunodeficiencies, Phagocyte Defects, Innate Immune Defects, and Complement Deficiencies

Combined Immunodeficiencies

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

Strength of recommendation: **Strong**

Certainty of evidence: **High**

General evaluation of immune phenotype and function is necessary to support detailed clinical history and physical examination for the assessment of suspected CID. Although 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.[221] The testing described in this Recommendation 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 the following URL: https://cis.clinimmsoc.org/dli/test-directory.php

Complete blood cell 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 (eg, <1000 cells/mL in adults or <2500 cells/mL in infants), is characteristically found in CIDs. Cytopenias are frequently part of the clinical spectrum of CIDs (eg, 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 (Section 4).[224] 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 cutoffs.

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. In addition, 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 NK cells (CD16+CD56+) by flow cytometry. Markers for T/B/NK panels may include the following: (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-cell percentages should be investigated for increases in double-negative T cells (DNTs), which may express either T-cell receptor (TCR) αβ+, found 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 (eg, Ataxia Telangiectasia [A-T]).[228] Abnormal CD4:CD8 ratio may be indicative of MHC Class I or ZAP70 deficiency,[229,230] in which CD8 T cells are significantly low or MHC class II deficiency in which CD4 T cells are significantly low.[231] B-cell counts are low in a variety of CIDs (eg, NBS1 deficiency).[232]

Naive and memory T cells and recent thymic emigrant (RTE) phenotyping: The percentage of naive 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 (eg, 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 (Section 2) and are reduced in severe CIDs and 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 naive, 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 and 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 (Tregs): Tregs (CD4+CD127^{lo}FOXP3+CD25^{hi}) constitute approximately 5% to 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 (eg, *DOCK8* pathogenic variants).[239] Treg function testing is not clinically available. Of note, the CD4+CD25^{hi}CD127^{lo} 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+PD1^{hi}) are orchestrators of long-lived antibody responses.[242] These cells are classically found in germinal centers (GCs) of secondary lymphoid organs with a small population (approximately 10%) found in peripheral circulation. IEI resulting in defective GC formation (eg, *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 (high expression) for activated T cells, CD57 for senescent T cells, and PD-1 and LAG-3 for exhausted T cells. Activated T cells may be increased in CIDs with decreased Treg function (eg, STAT5b deficiency)[246] and immune dysregulated processes (eg, 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 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: These assays are indicated in the evaluation of suspected deficiency of cell-mediated immunity. 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 before immunization with routine childhood vaccines (before 2 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 co-stimulation with anti-CD28 antibody, or the

Table 5A
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 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
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
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)
HIES	*STAT3, DOCK8, PGM3, CARD11, IL6R, IL6ST, ERBIN*, and *ZNF431*	Serum IgE, eosinophil count T_H17 cell quantification DOCK8 expression
Cartilage hair hyperplasia	*RMRP*	Evaluation of compartment-specific telomere length

Abbreviations: CID, combined immunodeficiency; HIES, hyper immunoglobulin E syndrome; ICF, immunodeficiency, centromeric instability, and facial anomalies; IEI, inborn error (s) of immunity; MHC, major histocompatibility complex; SNP, single nucleotide polymorphism; TREC, T-cell receptor excision circle.

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 (eg, WAS).[250] Also, stimulation with anti-CD3 and other co-stimulants as described previously offers a more physiological yet global assessment of the T-cell proliferative response compared with mitogen stimulation. T-cell proliferative responses to antigens are often measured after exposure to tetanus toxoid or candida. Defective T-cell proliferation in response to antigen stimulation is a feature of several CIDs, including ZAP70 deficiency, MHC class II deficiency, and calcium channel defects, among others.[251]

Although 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 patients with severe lymphopenia. 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 recommend 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 5A). 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 immunologic presentation is similar to CID, with increased risk of infection, autoimmunity, and lymphoproliferative disease.[253–255]

Clinical features of selected CIDs are discussed subsequently.

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 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 (eg, *CD40L, CD40, AID*)[256–259] (also 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 level 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.[256] 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.

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 CID.[263] 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.[263] 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.[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 immunologic investigations and testing of diagnostic biological markers in patients with

suspicion of CID *and* certain clinical findings in non-immunologic 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 immunologic compartments (Table 5A).

WAS and Related Disorders Present With Thrombocytopenia, Eczema, and Increased Susceptibility to Infection

WAS is an X-linked syndromic CID that occurs due to pathogenic variants in *WAS*, resulting in lack of expression or nonfunctional WAS protein, and pronounced deficits in multiple hematopoietic cell lineages.[264] Patients with WAS present with microthrombocytopenia, 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 LOF variants,[266,267] and X-linked neutropenia and myelodysplasia, associated with GOF variants.[268,269]

Laboratory findings in patients with WAS 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 immunologic 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 Neurologic Deficits, Growth Retardation, Skeletal, and Immunologic Abnormalities

DNA repair deficiencies are characterized by cutaneous, neurologic, and immunologic abnormalities. DNA repair deficiencies occur due to pathogenic variants of *ATM, NBN, BLM, DNMT3B, ZBTB24, PMS2, POLE1, POLE2, DCLRE1C*, 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 patients with A-T more than 6 months of age.[279] Other findings are T-cell lymphopenia and low TREC levels at birth (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 level, and impaired antibody responses to specific antigens. HIGM is among the differential diagnoses given the serum immunoglobulin abnormalities in A-T.[278]

Similar immunologic findings are found 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 (eg, *ATM, NBN* with defects in DNA DSB damage response initiation vs radiosensitive SCID, eg, *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 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 patients with immunodeficiency, centromeric instability, and facial anomalies (ICF) have pathogenic variants in *DNMT3B* (ICF1), less frequent in *ZBTB24* (ICF2), *CDCA7* (ICF3), and *HELLS* (ICF4), whereas some patients with an ICF phenotype have no identified genetic cause.[282]

Immunologic 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 nonhomologous 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 patients with DGS is heterozygosity for Chr22q11.2 deletion (approximately 90% of patients with DGS, 1 in 4000 live births).[284] In contrast, Chr22q11.2 deletion accounts for only 38% of congenital athymia cases treated with CTTI.

Severity of immunodeficiency in patients with DGS 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 (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 NBS result 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 (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 variation 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, Choanal Atresia, Retarded development, Genital and Ear anomalies), biallelic and monoallelic LOF variants of *FOXN1*, and biallelic variants of *PAX1*.[286] Nongenetic 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 syndrome (HIES) is characterized by recurrent sinopulmonary infections, eczematous dermatitis, eosinophilia, and elevated serum IgE level. 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 (STAT3-HIES) 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, often due to HSV, HPV, or severe *molluscum contagiosum*.[287] These patients may also present with vasculopathies and neurologic involvement. Other genetic causes of HIES include pathogenic variants of *PGM3, CARD11, IL6R, IL6ST, ERBIN*, and *ZNF431*. STK4 deficiency presents with polyclonal hypergammaglobulinemia, which includes elevated IgE level.[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-HIES is associated with low numbers of T_H17 and Tfh cells,[289] increased Tregs, and decreased memory B cells. DOCK8 deficiency presents with T-cell lymphopenia in addition to elevated serum IgE levels. 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's disease, and increased susceptibility to hematologic malignancies, particularly non-Hodgkin lymphoma and basal cell carcinoma.[292–294] CHH is also associated with autoimmune complications. Although 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 NBS result for SCID (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 Ca^{2+} influx from extracellular spaces into lymphocytes through the Calcium Release-Activated Calcium (CRAC) channels result in severe congenital immunodeficiency. This has been found 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 anti-CD3 antibody stimulation are significantly decreased. Patients with *STIM1* pathogenic variants may also present with low Treg numbers, autoimmunity, and lymphoproliferation.

Recommendation 5.4: We suggest periodic assessments of immunologic 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 6 months or more frequently, as determined by the complexity and severity of the CID. Evolving autoimmune complications, progressive lymphopenia, hematologic 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).

Phagocyte Defects

Recommendation 5.5: We recommend 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 5B). WAS variant X-linked neutropenia should also be considered, particularly if neutropenia is associated with increased bleeding tendency (Recommendation 5.3).[304,305]

Serial CBCd measurements may be performed once or twice weekly up to 6 weeks to identify cyclic from persistent or chronic neutropenia. Cyclic neutropenia usually follows a periodicity of approximately 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 (eg, giant cytoplasmic granules within neutrophils may be indicative of

Table 5B
Defects of Phagocyte 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*	Flow cytometry to assess CD18
Leukocyte adhesion defect II	*SLC35C1*	Flow cytometry to evaluate sialyl Lewis X (CD15s) expression on leukocytes.
Leukocyte adhesion defect III	*FERMT3*	Platelet function
Leukocyte adhesion defect IV	*RAC2*	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

Abbreviations: AR, autosomal recessive; CBC, complete blood cell count; DHR, dihydrorhodamine oxidation assay; GM-CSF, granulocyte-macrophage colony-stimulating factor; XL, X-linked.

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 hypercellularity with decreased myeloid precursors is found 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.

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 5B). 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]

Patients with LAD-I (CD18 deficiency) experience severe infectious complications early in life, with omphalitis and delayed (>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] Patients with LAD-II (SLC35c1 deficiency) present with pulmonary infections, chronic severe periodontitis, growth and developmental delay, and a unique facial appearance.[307] Patients with LAD-III (kindlin 3 deficiency) exhibit dysfunctional platelet aggregation, leading to bleeding complications, similar to Glanzmann thrombasthenia, including cerebral hemorrhage at birth.[306,307] Patients with LAD-IV (Rac2 deficiency) present with delayed umbilical cord separation, recurrent infections, and impaired wound healing.[309]

A baseline, elevated neutrophil count in a 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] Patients with LAD-IV 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 recommend 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 *S aureus, Burkholderia* spp., *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 with the use of acetaminophen within 24 hours of blood sample collection, and if time from sample collection to testing is prolonged more than 24 hours, 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 after in vitro stimulation of the patient sample. Neutrophils from patients with X-linked CGD demonstrate little to absent oxidative burst activity (ie, 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 X-linked CGD may present with severe infections typical of X-linked CGD when their neutrophils are heavily skewed toward the abnormal population.[134] Approximately one-third of female carriers may present with autoimmune manifestations[315] and psychiatric conditions, such as anxiety and depression.[138]

Although decreased oxidative burst is typical of patients with CGD, 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 (Section 3). Analysis of *NCF1* is not often included in CGD targeted gene panels due to sequencing difficulties posed by presence of associated 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 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.

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, and joints and disseminating throughout the body.[323]

PAP may be caused by several gene defects such as in ADA deficiency, GM-CSF receptor alpha and beta 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) Are Characteristic of Genetic Innate Immune Defects

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] (Table 5C). 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. Type I IFN testing by flow cytometry can be used to assess TLR3 pathway and related gene defects and is also useful for the diagnosis of type I interferonopathies. Genetic testing is also very useful for diagnosis of these conditions.

Regarding IEI associated with HPV infection, most patients with WHIM syndrome due to GOF *CXCR4* variants and more than half of GATA2 haploinsufficiency patients develop warts after α-HPV infection.[332] Biallelic LOF variants of EV-associated genes (*TMC6* and *TMC8*) can be identified in approximately half of EV patients. AD and X-linked recessive forms of EV have also been reported. Approximately two-thirds of EV patients develop nonmelanoma 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 [eg, Measles, Yellow Fever])

Approximately 15% to 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, whereas 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] The type I IFN test by flow cytometry can be used for the clinical diagnosis of the type I interferonopathies.

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 used in considering asplenia. 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.

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 TLR4, IRAK4, or MyD88 deficiency are limited to those caused by 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

Table 5C
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 TLR assay Flow cytometric evaluation of IFN-γR (CD119) surface expression Flow cytometry for DOCK8 protein expression
HPV Alpha-HPV (mucocutaneous warts and HPV-related cancers) Beta-HPV (epidermodysplasia 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* Hypo/asplenia (for encapsulated bacteria)	TLR-4 response to LPS 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 mucocutaneous candidiasis	*AIRE, IL17RA, IL17RC, IL17F, STAT3, DOCK8, STAT1, CARD9*	Enumeration of T_H17 cells by flow cytometry Autoantibodies against IL-17A or IL17F for acquired CMC
Mycobacterial disease (MSMD)	*IFNGR1, IFNGR2, IKBKG, IL12RB1, IL12B1, IL12RB2, IL23R,* STAT1, *JAK1, IFNG;,GATA2*	Targeted cytokine assays Flow cytometry of IFNGR1 (CD119) and IL12RB1 (CD212) Autoantibodies against IFN-γ, for acquired MSMD

Abbreviations: HPV, human papilloma virus; HSV, herpes simplex virus; IFN, interferon; MSMD, Mendelian susceptibility to mycobacterial disease; NK, natural killer; TLR, toll-like receptor.

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 pronounced 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*, T_H17 cells,[340] IFN-γ responses and genetic analysis of relevant genes (*STAT1, STAT3, AIRE, RORC, ACT1, CARD9*, and genes encoding proteins of the IL-17 pathway).

The presence of neutralizing autoantibodies to T_H17-related cytokines in patients with autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED)[341] and dysregulation of IFN-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 Presents With Severe Tuberculous or Atypical Mycobacterial Infections, Salmonella Species Infections, or Herpesvirus Infections, and Normal Results on Screening Studies of Humoral and Cellular Adaptive Immunities

The severity of MSMD clinical manifestations depends on genetic etiology and increases with decreasing level of IFN-γ activity.[344] AD partial IFNGR1 deficiency presents in late childhood 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 IL-12–induced STAT4 phosphorylation in activated T cells, IFN-γ–induced STAT1 phosphorylation in monocytes, IL12 secretion in stimulated mononuclear cells, and cell surface expression of IFN-γR1 and IL12βR.[345]

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 5D). 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 (eg, *H influenzae, Neisseria 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 and C1r deficiencies may be 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 infection followed by cardiovascular complications.[352] There is a 1% prevalence of nonfunctional *C2* gene variants in the North European 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] is associated with an 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.[356,357] Properdin deficiency is an X-linked complement deficiency, which presents with increased susceptibility to severe *Neisseria* infections, including sepsis, often during adolescence. 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 approximately 5% to 7% of populations of North European ancestry.[360] MBL deficiency has been reported with increased susceptibility to meningococcal meningitis, HIV infection, hepatitis C virus (HCV) infection,

Table 5D
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		
Ficolins (M, L, H)	Bacterial infections when with other immunologic abnormalities	Pneumonia, ulcerative colitis
MASPs	Bacterial infections when with other immunologic 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* spp	SLE, glomerulonephritis vasculitis, APS, myasthenia gravis, TMA
Regulatory proteins		
Factor H	Encapsulated bacteria	ITP, aHUS, glomerulonephritis, SLE, AMD
Factor I	Encapsulated bacteria	aHUS, glomerulonephritis, scleroderma, RA, vasculitis
CD46		aHUS
CD59, CD55		PNH

Abbreviations: AAE, acquired angioedema; aHUS, atypical uremic syndrome, AMD, age-related macular degeneration; APS, antiphospholipid syndrome; HAE, hereditary angioedema; ITP, immune thrombocytopenic purpura; PBC, primary biliary cholangitis; PNH, paroxysmal nocturnal hemoglobinuria; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS Sjogren's syndrome; SSc, systemic sclerosis.

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 patients with cancer.[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 demonstrate 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 overactivation 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 vs 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 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).

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 AMD, 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] Approximately 20% to 30% of aHUS cases have pathogenic variants in Factor H, 5% to 10% in Factor I, 1% to 4% in Factor B, 10% to 15% in membrane cofactor protein (MCP)/CD46, and 3% to 5% have pathogenic variants in thrombomodulin.[369,371–373] Furthermore, 10% of aHUS cases present with autoantibodies against Factor H, with deletion of genes encoding complement Factor H-related proteins 1 and 3 (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 demonstrate 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 are autoantibodies that bind to the C3 convertase, stabilizing and increase its half-life. These are detected in 50% to 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, the presence of anti-Factor B antibodies has 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. Paroxysmal nocturnal hemoglobinuria (PNH) occurs in CD55 and CD59 deficiencies. Also, somatic mutations in *PIGA* lead 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 neurologic symptoms.[383] Similarly, gene variants in Factor H, MCP, and Factor I have also been reported in conditions such as pre-eclampsia, HELLP (hemolysis, elevated liver enzyme levels and low platelet levels) 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[353,386,387] (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 thrombotic microangiopathy, 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 patients with PNH.[390,391]

Section 6. Immunologic Diagnosis of Primary Immune Dysregulation Disorders 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 (Table 1A—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] Although 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 recommend the assessment of cellular and humoral immunologic function in patients with suspected primary immune dysregulation disorders.

Strength of recommendation: **Strong**

Certainty of evidence: **High**

Immune dysregulation may present with abnormal lymphocyte subpopulations: regulatory T cells (Treg), T_H17 cells, TCR$\alpha\beta$ DN T cells, follicular helper T cells (Tfh), B-cell subsets (eg, transitional B cells, switched memory B cells, plasmablasts), and NK cells (Recommendation 5.1). When evaluating suspected primary immune dysregulation syndromes, in addition to genetic testing, it is important to evaluate markers of inflammation. These include common nonspecific markers, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). 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 vs an interferonopathy.[398] Examples of these tests are serum levels of IL-2Ra (soluble CD25) and CXCL9, which are elevated in IFN-γ–mediated inflammation.

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 is suggested by recurrent or episodic symptoms, in addition to persistent elevated ESR and CRP levels in the 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 phenotypically by the IUIS as follows: (1) recurrent inflammation; (2) systemic inflammation with skin findings; (3) type I interferonopathy; (4) sterile inflammation predominantly in bone and joints or skin; and (5) other systemic inflammatory syndromes (Figs 17-19 in Bousfiha et al[17]). Examples of autoinflammatory disorders are the cryopyrin-related disorders and the periodic fever syndromes.

Cryopyrin-Related Disorders

Cryopyrin-associated periodic syndrome (CAPS) is suspected in patients presenting with episodes of systemic inflammation manifested by rash, fevers, arthritis, neurologic 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 proinflammatory cytokines IL-1β and IL-18.

Periodic Fever Syndromes

Familial Mediterranean fever (FMF) and 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) is characterized by febrile episodes 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 during disease flares.

Recommendation 6.4. We recommend 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 2 cell lineages), and other severe, recurrent, or early onset autoimmunity. The evaluation of these conditions includes blood cell counts and autoantibodies according to the tissue and organ affected.

The IUIS classifies immune dysregulation into 4 broad phenotypes as follows: (1) familial hemophagocytic lymphohistiocytosis (HLH), with or without hypopigmentation; (2) disorders that confer EBV susceptibility, including EBV-associated HLH; (3) syndromes with autoimmunity and with or without lymphoproliferation, including ALPS and Tregopathies; and (4) immune dysregulation with colitis (Figs 10-12 in Bousfiha et al[17]).

Familial HLH

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

Familial lymphohistiocytosis (FLH) is suspected in patients with fever, hepatosplenomegaly, and neurologic 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. According to the 2024 criteria, the diagnosis of FHL can be established if at least 1 of either of the following 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 following criteria fulfilled:
   a. Fever more than or equal to 38.5°C
   b. Splenomegaly (≥2 cm below the costal margin)
   c. Cytopenias (affecting ≥2/3 lineages in the peripheral blood: hemoglobin < 90 g/L [in infants aged <4 weeks: hemoglobin < 100 g/L]; platelets < 100×10^9/L; neutrophils < 1.0×10^9/L)
   d. Hypertriglyceridemia and/or hypofibrinogenemia

e. Fasting triglycerides more than or equal to 3.0 mmol/L and fibrinogen less than or equal to1.5 g/L
f. Hemophagocytosis
g. Ferritin more than or equal to 500 μg/L
h. sCD25 (ie, soluble interleukin-2 receptor) more than or equal to 2400 U/mL (Other cut-off values may apply for alternative clinical laboratory tests for assessing sCD25 levels).

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 nonmalignant lymphoproliferation, autoimmune cytopenias, and lymphoma are associated with 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 GOF, and activated phosphoinositide 3-kinase (PI3k) delta syndrome (APDS).[406,407] ALPID disorders have increased Fas-controlled 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 naive CD4+ T cells.

APECED (Autoimmune Polyglandular Syndromes)

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 *AIRE* gene. Approximately 60 variants have been identified to cause APECED. Other clinical manifestations can occur, including autoimmunity, such as type 1 diabetes mellitus, primary hypogonadism, and pituitary failure. Diagnosis of APECED is made by identification of 2 of the 3 clinical components of APS1 or the presence of a pathogenic variant in the *AIRE* gene.

Immune Dysregulation With Inflammatory Bowel Disorder (IBD)

Colitis is a common feature of primary immune regulation disorders. There are several monogenic IEI associated with immune dysregulation and IBD 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 primary immune dysregulation disorders. 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, anemia, or rectal bleeding. Severe cases may present with hemorrhage, perforation, or toxic megacolon. Additional laboratory evaluation should also be considered, based on specific clinical phenotype and genetic defect, for example, quantitation of Tregs along with FOXP3 protein expression in IPEX syndrome.

Section 7. Surveillance of Potential Clinical Manifestations in Inborn Errors of Immunity

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.[412–416] We recommend nutritional assessment every 6 to 12 months in patients with IEI and concerns for growth/nutritional deficiencies.

Height, weight, and body mass index (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/pre-albumin 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 suggest testing for specific infectious pathogens 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, should be performed periodically in patients with IEI susceptible to these viral infections, every 3 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 confers high risk for recurrent or persistent viral infections, especially with EBV and CMV[417,418] (Table 7A). Signs and symptoms concerning for 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 health care settings, and immunocompromised state. Patients with IEI who develop gastrointestinal symptoms should be screened for intestinal infections, including *Clostridium difficile, Giardia lamblia, Cryptosporidium* spp, *Salmonella* spp, norovirus, and parasitic infections.[419–421] Gastrointestinal pathogen panel testing by PCR or antigen testing in stools should be considered when evaluating patients with IEI (Sections 9 and 10).

Recommendation 7.3: We recommend 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 and hematologic malignancy (Table 7B). Although 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 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 (including complications of immunoglobulin replacement therapy). Patients with longstanding IEI diagnosis and no cytopenias may require only annual testing (Recommendation 5.1).

Recommendation 7.4: We recommend *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

Table 7A
Examples of IEI Associated With Chronic Viral Infections and Specific Nonviral 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, 424
	NK deficiencies	*MCM4, GATA2, IRF8, RTEL1, FCGR3A*	
	CTLA-4 haploinsufficiency	*CTLA-4*	
	LRBA deficiency	*LRBA*	
	APDS1, 2	*PIK3CD, PIK3R1*	
	DOCK8 deficiency	*DOCK8*	
	DOCK2 deficiency	*DOCK2*	
EBV	XLP1, 2	*SH2D1A, BIRC4/XIAP*	423, 424, 425, 331
	ITK deficiency	*ITK*	
	CD27 deficiency	*CD27*	
	CD70 deficiency	*CD70*	
	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, 423, 426
	Properdin deficiency	*PFC*	
	Late complement def.	*C5/C6/C7/C8/C9*	
	CGD	*CYBA, CYBB, CYBC1, NCF1/2/4*	
	WHIM syndrome	*CXCR4*	
	XLP1, XLP2	*SH2D1A, BIRC4/XIAP*	
	ITK deficiency	*ITK*	
	CD27 deficiency	*CD27*	
	XMEN	*MAGT1*	
	RASGRP1 deficiency	*RASGRP1*	
	CTPS1 deficiency	*CTPS1*	
	CD8 deficiency	*CD8*	
	WAS	*WAS*	
	XLA	*BTK*	
	COPG1 deficiency	*COPG1*	
	MCM10 deficiency	*MCM10*	
	NOS2 deficiency	*NOS2*	
	VODI	*SP110*	
	CHH	*RMRP*	
HSV	TLR3 deficiency	*TLR3*	331, 424
	D6R1 deficiency	*D6R1*	
	UNC93B1 deficiency	*UNC93B1*	
	TRAF3 deficiency	*TRAF3*	
	TICAM1/TRIF deficiency	*TICAM1/TRIF*	
	TBK1 deficiency	*TBK1*	
	IRF3 deficiency	*IRF3*	
	SNORA31 deficiency	*SNORA31*	
	ATG4A deficiency	*ATG4A*	
	MAP11C382 deficiency	*MAP11C382*	
	CHH	*RMRP*	
VZV	WAS	*WAS*	331, 427, 424
	Ataxia telangiectasia	*ATM*	
	RNA polymerase III def.	*POLR3A, 3C, 3F*	
	TLR3 deficiency	*TLR3*	
	WHIM syndrome	*CXCR4*	
	STAT5B deficiency	*STAT5B*	
	GINS1 deficiency	*GINS1*	
	Moesin deficiency	*MSN*	
	CTPS1 deficiency	*CTPS1*	
	CHH	*RMRP*	
HPV	WHIM syndrome	*CXCR4*	428, 429, 424
	Epidermodysplasia verruciformis	*EVER1, EVER2*	
	C1B1 deficiency	*C1B1*	
	STK4 deficiency	*STK4*	
	Ataxia telangiectasia	*ATM*	
	RHOH deficiency	*RHOH*	
	CD28 deficiency	*CD28*	
	LAD1	*ITGB2*	
	CD28 deficiency	*CD28*	
	NEMO	*NFKB1A*	
	WAS	*WAS*	
	Comel-Netherton syndrome	*SPINK5*	
Cryptosporidium spp	NIK deficiency	*MAP3K14*	430
	Hyper IgM syndrome	*CD40LG, CD40*	
	IL21, IL21R deficiency	*IL21, IL21R*	
	DOCK8 deficiency	*DOCK8*	
Mycobacterium spp.	MSMD	*IL12RB1, IL12B, IL12RB2, IL23R, IFNGR1, IFNGR2, STAT1* LOF, *IFNG, IRF8, CYBB, ISG15, TYK2, SPPL2A, IKBKG, JAK1, RORC*	345, 346
	GATA2 deficiency	*GATA2*	

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HPV, human papilloma virus; HSV, herpes simplex virus; IEI, inborn error(s) of immunity; MSMD, Mendelian susceptibility to mycobacterial disease; VZV, varicella zoster virus.

in primary immune dysregulatory disorders in which multiorgan autoimmunity is common.[451,452] In addition, nonspecific autoantibodies have been identified in other acquired disease states, such as COVID-19 pneumonia, multisystem inflammatory syndrome in children, and Kawasaki's disease.[453–455] 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,[451,456] 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.[456–458] 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.[456–458]

Patients who are receiving immunoglobulin replacement therapy may have false-positive testing to some types of autoantibodies that are present in the donor population plasma pool.[459–462]

Recommendation 7.5: We recommend the evaluation of major organ system functions and screening for cancer and mental health disorders in patients with IEI.

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 often brought to clinical attention, but noninfectious complications are associated with higher mortality[8,463] and may be missed if not screened during visits. Early identification of noninfectious 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.[463]

Clinical Examination: A thorough (at least yearly) clinical examination by a physician with expertise in IEI should be integral to routine monitoring in patients with IEI.[435,464] A skilled clinical examination may prompt effective decision making leading to targeted laboratory assessments.[465]

Table 7B
Examples of IEI Associated With Autoimmune Cytopenias

IEI	Associated gene	Prevalence of autoimmune cytopenias	Reference
CVID	Various (eg, *NFKB1*, *NFKB2*)	10%-18% prevalence	435
		ITP > AIHA > AN,	151
		First episode of immune cytopenia may occur before CVID diagnosis	153
			436
ALPS	*TNFRSF6, TNFSF6, CASP8, CASP10*	52%-70% prevalence	437
		AIHA > ITP > AN	432
		Multilineage cytopenias > single lineage cytopenias	438
IPEX	*FOXP3*	22%-42% prevalence	402
			439
Hyper IgM syndrome	*CD40LG, CD40, AID, UNG*	Immune cytopenias may occur. Neutropenia is common in hyper-IgM due to defects in *CD40LG*/*CD40*	161
			222
			210
CTLA-4 haploinsufficiency	*CTLA-4*	62%-68% prevalence	139
		ITP = AIHA > AN	192
LRBA deficiency	*LRBA*	70% prevalence	192
Activated PI3K-delta Syndrome	*PIK3CD, PIK3R1*	17%-30% prevalence	202
		Late onset of cytopenias compared with other disease manifestations	440
XMEN	*MAGT1*	35% prevalence	441
Kabuki syndrome	*KMT2D, KDM6A*	2%-8% prevalence	442
		ITP > AIHA	443
STAT1 GOF	*STAT1*	4% prevalence	335
STAT3 GOF	*STAT3*	67% prevalence	444
		Multilineage cytopenias > single lineage cytopenias	445
Wiskott-Aldrich syndrome	*WAS*	AIHA > ITP > AN	446
		Onset in infancy	447
		Differentiate ITP vs baseline microthrombocytopenia	
DiGeorge Syndrome	*del22q11*	4%-8% prevalence	448
		ITP > AIHA	449
		Single lineage cytopenias > multilineage cytopenias	
RALD	*KRAS, NRAS* (somatic mutations)	94% prevalence	450
		Multilineage cytopenias > single lineage cytopenias	

Abbreviations: AIHA, autoimmune hemolytic anemia; ALPS, autoimmune lymphoproliferative syndrome; AN, autoimmune neutropenia; CVID, common variable immunodeficiency; def., deficiency; GOF, gain of function; IEI, inborn error(s) of immunity; IPEX, immune polyendocrinopathy X-linked; ITP, immune thrombocytopenia; RALD, RAS-associated autoimmune leukoproliferative disorder.

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.[145,464,466–470] This evaluation includes computed tomography (CT) of the chest for early detection of lung disease progression.[145,466,469–472] Repeated imaging with low-dose CT or magnetic resonance imaging to decrease the cumulative radiation risk is recommended in IEI with increased radiosensitivity.[473,474] Pulse oximetry at rest and with exercise may be helpful in patients with chronic lung disease to determine the need for oxygen therapy.[475] The 6-minute walk test is a simple cardiopulmonary functional testing modality to assess aerobic capacity and endurance.[476]

Gastrointestinal: Annual clinical examination should include assessment for hepatosplenomegaly 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.[466] In patients with IEI and symptoms suggestive of gastrointestinal reflux, screening for *Helicobacter pylori* infection is recommended.[477–479] 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.[479,480] For patients with a history suggestive of protein losing enteropathy (PLE), we recommend stool alpha 1 antitrypsin (A1AT) testing.[481] 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.[466,470,478]

Nephrologic: Fluid retention and facial edema prompt evaluation of renal function. Standard kidney function tests (ie, 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.[466] Serum cystatin C has a high sensitivity for identifying early kidney dysfunction. Known associations of kidney disease and IEI include IgA nephropathy in WAS[482] and aHUS found 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.[483–485]

Endocrine and Bone Health: We recommend monitoring for signs/symptoms of immune endocrinopathies for patients with IEI, in particular immune regulatory disorders.[486] Targeted laboratory testing should be ordered directed by history and clinical examination.

Osteoporosis is often an overlooked complication in chronic care of IEI.[487] 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.[488] 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.[489–491] Patients with IEI have an increased risk for malignancy, with a reported prevalence between 4% and 25% depending on the underlying disorder.[490,492] Hematologic malignancies are more common than solid tumors and non-Hodgkin and Hodgkin lymphomas occur most frequently.[491] Therefore, close monitoring includes at least yearly

Table 7C
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)	500
	Bloom syndrome: Intestinal cancer, leukemia, and lymphoma (150-300-fold)	501
Common variable immunodeficiency	MALT lymphoma	502
	Non-Hodgkin lymphoma (30-400-fold)	
	Gastric cancer (10-fold)	
Defects in *GATA2, CXCR4, STK4*	HPV-, EBV-associated cancers	503
	Chronic myeloid leukemia	500
	Acute myeloid leukemia	504
	Myelodysplastic syndrome	
	Melanoma (*GATA2*)	
Epidermodysplasia verruciformis	Nonmelanoma skin cancers	333
Wiskott-Aldrich Syndrome	Lymphoma	500
Combined immune deficiencies: IL-10R deficiency; AD-HIES	B-cell lymphoma	500
FHLH (*PRF1*)	Lymphoma	500
NK cell deficiency	EBV and hematologic malignancies	330
X-Linked hyper IgM syndrome	Pancreatic and liver cancers	500

Abbreviations: EBV, Epstein-Barr virus; FHLH, familial hemophagocytic lymphohystiocytosis; HPV, human papilloma virus; IEI, inborn error(s) of immunity; MALT, mucosa-associated lymphoid tissue; NK, natural killer.

physical examinations. Significant unintended changes in body weight and systemic symptoms such as fevers should warrant a more in-depth evaluation for potential malignancy.[466,493] Targeted biopsy and pathology examination may be indicated in cases of persistent or increasing lymphadenopathy or splenomegaly, to differentiate lymphoma from nonmalignant lymphoproliferation. Tc-99m–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.[474,494]

The clinician may encourage patients with IEI to adhere to US Preventive Services Task Force (USPSTF) guidelines for cancer screenings (https://www.uspreventiveservicestaskforce.org/uspstf/recommendation-topics) (examples in Table 7C). 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 (ie, use of sunscreen) and following recommended screening for skin cancer.[495]

The development of nonmelanoma 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.[496] We recommend that patients with IEI disorders at risk for HPV infection (eg, EV) and IEI with cellular deficiencies be vaccinated against HPV[497] (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, is a common complication of many IEI with defects in hematopoiesis (eg, *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.[498]

IEI associated with both nonmalignant lymphoproliferation and increased risk of lymphoma (eg, ALPS) may be difficult to manage in terms of cancer surveillance as imaging modalities will not differentiate between benign and malignant proliferation.[499] Concerns for malignancy in a lymph node should be confirmed with targeted biopsy and pathology examination.

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,[505,506] as a consequence of the genetic defect, HSCT, or secondary to an infection. Other examples are neuropsychiatric disease in 22q11.2 deletion syndrome and depression in female carriers of X-linked CGD.

Patients with chronic diseases are at higher risk for depression and other mental health concerns.[507] Studies of patients with IEI have shown up to 40% rates of psychiatric symptoms, particularly anxiety and depression,[508–511] 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),[512,513] when compared with the general population. Patients with IEI also have high rates of fatigue,[514–516] which may be a somatic symptom of depression. Simple screening mental health questionnaires exist for adult and adolescent patients[517,518] 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 QoL 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 found to prevent serious bacterial infections in these patients, inclusive of bacterial pneumonia, sepsis, bacterial meningitis, visceral abscesses, and osteomyelitis/septic arthritis.[3,519,520,521]

Adverse events associated with IgRT are reported during infusions and 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% to 15% of IVIG infusions and more frequent in patients with active inflammation.[520,522,523] 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 subsequent discussion). Slowing or stopping the IVIG infusion for 15 to 30 minutes will reverse many reactions.[520] Infusions can often be restarted at the last tolerated rate and then increased again. Another option frequently used is switching to subcutaneous immunoglobulin (SCIG) IgRT, which is associated with fewer systemic adverse events.[520,524,525]

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-H_1) and/or hydrocortisone 1 hour before the infusion may prevent adverse reactions. Oral (or IV) hydration before 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 3 treatments with the same product, additional infusion reactions become less likely.[520] 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 the use of corticosteroids before 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.[2,3,520] 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 above 65 years, sepsis, paraproteinemia, increased blood viscosity, hypercholesterolemia, and hypertension.[520,526]

IgG Products May Not Be Equally Tolerated. The AAAAI developed the Eight Guiding Principles for Effective Use of IVIG for Patients with Primary Immunodeficiency.[520] 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 1 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% to 18% of patients.[527] A retrospective review analyzed 802 switches between immunoglobulin products between 2017 and 2018 due to supply issues,[528] 12 reactions were reported, none of which required admission to the hospital; 1 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.[529] 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.[530]

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 often in patients receiving IVIG products containing sucrose.[531] Currently, in the United States, 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 found with sucrose-stabilized IVIGs.[531,532] 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, age above 70 years, male sex, chronic kidney disease, hypertension, and diabetes mellitus.[533] Monitoring BUN and creatinine over time alerts the clinician to possible adverse events related to kidney function during therapy.

Between 1983 and 1987, clusters of non-A, non-B hepatitis (ie, hepatitis C) were reported after IVIG treatment, and, in February 1994, 1 manufacturer instituted a worldwide recall of its brand of IVIG, because of reports of 10 cases of possible transmission of hepatitis C. At that time, the production process for several IVIG products did not include steps for viral inactivation.[534] This led to the recommendation by the Food and Drug Administration (FDA) to add solvent/detergent (S/D) to the manufacturing process to inactivate lipid envelope viruses. In the late 1990s, mad cow disease (a variant of Creutzfeldt-Jakob disease) emerged in Europe. To address this pathogen safety, all immunoglobulin products use nanofiltration to remove possible prion contamination in donor plasma.[535] 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 recommend that initial dosing of immunoglobulin for replacement therapy be at 400 mg/kg to 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 to 600 mg/kg every 3 to 4 weeks, when given intravenously, followed by dose adjustment to obtain clinical efficacy, and for changes in body weight more than 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.[536,537] In 1 study using an IgRT dosing range from 200 to 1200 mg/kg/mo, patients with XLA required trough serum levels from 800 to 1300 mg/dL to stay infection free, whereas a cohort of patients with CVID required a range of trough levels from 500 to 1700 mg/dL to prevent breakthrough bacterial infections (Recommendation 8.4).[536]

Recommendation 8.3: We recommend monitoring of serum IgG levels, complete blood counts with differential, and serum chemistry panel 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.[536–539] 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 intravenous administration, the IgG level is highest hours after infusion and levels drop steadily in 3 to 4 weeks. Trough IgG level is obtained with blood samples drawn before the IVIG infusions. With subcutaneous administration, maximum IgG levels occur approximately 3 to 5 days post-infusion and decrease slowly. After 4 to 6 months of weekly or biweekly subcutaneous infusions, serum IgG levels are consistent with steady-state kinetics.[540–542] Due to differences in the kinetics of absorption and the distribution in extravascular spaces, dose adjustments are recommended by some US manufacturers in initiating therapy. The recommendations vary from increasing dosing of SCIG from 1.35 to 1.53 times the calculated IVIG dose to provide IgG levels that approximate the same bioavailability for SCIG and IVIG.[541,543]

We recommend checking the serum IgG levels every 6 months to every year in clinically stable patients receiving IgRT. However, a more frequent (ie, monthly) monitoring of IgG levels is appropriate in patients who continue to have breakthrough bacterial infections, during pregnancy, 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 recommend maintaining serum IgG levels at more than 800 mg/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.[544] The biologic trough IgG level varies between individuals depending on the underlying disorder and comorbidities.[536] A meta-analysis of IVIG studies concluded that serum trough IgG levels 800 mg/dL to 1000 mg/dL are associated with significantly less occurrence of pneumonia.[545] Incidence of pneumonia declined by 27% with each 100 mg/dL increment in trough IgG level, 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 found 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.[546]

Recommendation 8.5: We recommend 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 SAD in children or THI) it may be clinically appropriate to stop immunoglobulin therapy temporarily to determine whether the antibody deficiency has resolved over time. This strategy should not be repeated if the trial indicates a persistent deficit of IgG production.[520,547]

Recommendation 8.6: We recommend that low or absent IgA level, 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.[520,548–550]

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.[550]

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.[520,548–550]

Recommendation 8.7: We suggest 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.[520] The decision to infuse immunoglobulins in a hospital, hospital outpatient, community office, or home-based setting and the route of immunoglobulin administration (ie, whether intravenous, subcutaneous) must be based on the clinical characteristics of the patient.[520]

There is a reduced incidence of systemic adverse events with SCIG, increased flexibility in scheduling, and shorter infusion times as compared with IVIG. SCIG 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 and increased number of needle sticks than IVIG.[520,551] A form of SCIG is "facilitated SCIG," which uses the addition of hyaluronidase to the IgRT product to increase the amount of volume of immunoglobulins (up to 4 times) infused at once into the subcutaneous tissue and reduce the frequency of infusions.

SCIG therapy may be preferred in select patient populations, including children, pregnant women, and patients with difficult intravenous access.[551] Studies have revealed enhanced QoL in patients receiving SCIG compared with IVIG therapy, mostly due to the freedom to administer SCIG at home and at the patient's convenience.[520] This benefit results in greater patient satisfaction and fewer missed days of work or school for infusion-clinic appointments.[520,552,553] Initial infusions are done under supervision by a health care professional, providing training for subsequent self-infusions at home.[553] 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.[553]

Section 9. Infection Prevention in Inborn Errors of Immunity

Recommendation 9.1: We recommend targeted antimicrobial prophylaxis for patients with IEI 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

Table 9A
Antibiotic Prophylaxis for Selected IEI[a]

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.	*S aureus, Burkholderia* spp., *Nocardia* spp., *Serratia* spp.	Strong	High	555
	Invasive Aspergilosis (lung, bone)	Itraconazole 5 mg/kg daily, max daily dose 100 mg (<50 kg), 200 mg (>50 kg)	*Aspergillus* spp.	Strong	Moderate	557
	All infections	IFN-γ 50 μg/m^2 (min 1.5 μg) subcutaneous injection 3 d/wk		Strong	Moderate	560 561
SCID, congenital athymia	*Pneumocystis* pneumonia	TMP/SMX (5 mg/kg max dose 160 mg TMP component 2-3 times/week). Alternatives: pentamidine, atovaquone, dapsone	*Pneumocystis jirovecii*	Strong	High	59 77
	Candidiasis, fungal infection	Fluconazole 3 mg/kg	*Candida* spp.	Strong	High	59 77
	Prevention/treatment of CMV viremia, pneumonia, hepatitis, CNS infection	Acyclovir 12.5 mg/kg/day Ganciclovir Valganciclovir 16 mg/kg/day Treat until infant is CMV PCR negative weekly × 4	CMV, HSV infection	Strong	Low	59 77
Antibody deficiencies	Respiratory infections	Azithromycin (5 mg/kg/d max of 250 mg daily or 500 mg 3 d/wk) Alternatives: Amoxicillin TMP/SMX	*S aureus, S pneumoniae, H influenzae, M catarrhalis*	Conditional	Low	565 567
Terminal complement defects or asplenia	Sepsis, meningitis with encapsulated bacteria	Amoxicillin or penicillin daily or through 5 y of age	*S pneumoniae, H influenzae, N meningitides*	Strong	Moderate	571 572
STAT3/IL-6–related HIES	Bacterial infection	TMP/SMX dose: 5-6 mg/kg/d of TMP componenet (divided BID)	*S aureus*	Conditional	Low	573 574
	Chronic mucocutaneous infection	Fluconazole (if not on itraconazole or other triazoles) 5 mg/kg	*Candida* species CMC Coccidioides if endemic region	Conditional	Low	588
	Prophylaxis against Aspergilloma	Itraconazole 5 mg/kg daily, (max 100 mg/d < 50 kg, 200 mg/d > 50 kg) Treat if pneumatocele present	*Aspergillus* spp.	Conditional	Low	573
Chronic mucocutaneous candidiasis (STAT1 GOF, APECED, CARD9, IL17, and IL17R defects)	Disseminated candidiasis or Coccidioidomycosis	Fluconazole 5 mg/kg	*Candida* spp., coccidioides	Conditional	Low	587
MSMD	Mycobacterial infections	Azithromycin (5 mg/kg/d max of 250 mg daily or 500 mg 3 d/wk)	Environmental mycobacteria	Conditional	Moderate	584 345
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	576 577
	Chronic viral infection	Acyclovir 5 mg/kg valacyclovir, ganciclovir Valganciclovir 16 mg/kg/d	HSV/VZV	Conditional	Low	578
	GI infection	Azithromycin (5 mg/kg/d max of 250 mg daily or 500 mg 3 d/wk)	*Cryptosporidium* spp	Conditional	Very low	None

Abbreviations: CGD, chronic granulomatous disease; CMC, chronic mucocutaneous candidiasis; CMV, cytomegalovirus; DN, double negative; HIES, hyper IgE syndrome; HSV, herpes simplex virus; NTM, non-tuberculous mycobacteria; PAD, primary antibody deficiency; PCR, polymerase chain reaction; PJP, *Pneumocystis jirovecii* pneumonia; TMP/SMX, trimethoprim sulfamethoxazole; Tx, treatment; VZV, varicella zoster virus; WAS, Wiskott-Aldrich syndrome.
[a]not an exhaustive list, alternative recommendations exist

infections, namely *S aureus, Burkholderia cepacia, Serratia marscens*, and *Nocardia* species (Table 9A).[554] Retrospective studies demonstrated a decrease of bacterial infections by approximately 50% with the use of TMP/SMX prophylaxis.[554–556] 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: 7 patients were diagnosed with invasive fungal infection while on placebo compared with 1 invasive fungal infection on itraconazole.[557] Liquid itraconazole has better absorption than tablets but may pose adherence concerns. Itraconazole tablets should be taken with a meal. It is important to note that itraconazole and other azoles have

Table 9B
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 wk 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, and certain azoles, and thus underlies a need monitoring for this arrhythmia.

Abbreviations: EKG, electrocardiogram; IEI, inborn error(s) of immunity; TMP/SMX, trimethoprim-sulfamethoxazole.

many drug interactions; they inhibit the metabolism of corticosteroids (Table 9B). 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[558] and fluorosis.[559]

Prophylactic IFN-γ is frequently used in addition to antimicrobial prophylaxis in CGD. A randomized placebo-controlled study performed in the early 1990s revealed that IFN-γ reduced the rate of serious infections by two-thirds and decreased the frequency and length of hospitalization.[560] Importantly, this study was performed before standard use of prophylactic antifungals for patients with CGD; 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 that report the risk ratio for serious infection was 0.56 (95% CI 0.35-0.90) when using IFN-γ.[561] Some patients experience flu-like adverse 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 adverse effects of fever and elevated inflammatory markers that may confuse the assessment of therapeutic response to antimicrobials.

SCID/Athymia Before Immune Reconstitution

Infections before 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 anti-*Pneumocystis* prophylaxis, starting at 1 month of age due to case reports of drug-induced liver injury and hyperbilirubinemia in the neonatal period (Table 9B). Alternative agents include pentamidine (intravenous or inhaled), oral atovaquone, and dapsone (assuming normal G6PD levels) (Section 2).

Candida spp. infections are the most common fungal infections in SCID, typically causing mucocutaneous disease. Prophylaxis is recommended with fluconazole.[77] Nystatin topical suspension may be used in the neonatal period instead 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 9A.

Prophylaxis with azithromycin or clarithromycin has been suggested for patients with athymia who received thymus implantation as 3 cases of disseminated NTM were reported in these infants.[562]

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* spp. IgRT is the mainstay of therapy to replace the IgG deficit.[545] 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.[563–565] 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.[566] When possible, pulmonary nontuberculous mycobacteria (NTM) infection should be excluded prior to azithromycin initiation so that azithromycin-resistant NTM does not develop. 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.[567] Azithromycin can be dosed either 3 d/wk at 250 mg as in the randomized study, at 500 mg 3 d/wk as in cystic fibrosis, or daily at 250 mg.

Patients with XLA are at risk for disseminated infections with typically gastrointestinal-restricted bacteria, including *Campylobacter* and *Helicobacter* species,[568] and some of these organisms are azithromycin sensitive. *Mycoplasma* infections can also cause disseminated infections, presenting as infectious arthritis, and may also be targeted with azithromycin prophylaxis.

Specific antibody deficiencies, THI, and other hypogammaglobulinemias are associated with recurrent sinopulmonary infections. In these settings, a retrospective experience revealed that a trial of antibiotic prophylaxis is a first-line approach alternative to IgRT.[564,569,570]

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 is the mainstay for prevention of infection (Section 11). In addition, antibiotic prophylaxis, amoxicillin or penicillin, is recommended for children to at least 5 years of age, but it can be considered lifelong, especially for those with a history of sepsis.[571,572] For those with penicillin allergy, cephalosporins such as cephalexin or azithromycin are the alternatives. An evaluation for penicillin allergy may be preferred before considering the second-line drugs.[571,572]

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 and eczematoid dermatitis. Recurrent *S aureus* pneumonia results in pneumatoceles and bronchiectasis.[573,574] Prophylaxis against S *aureus* is recommended, typically with TMP/SMX. In addition, if atopic dermatitis is present, use of antiseptics for bathing (eg, 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 subsequently.

Prophylaxis for Specific Pathogens and Settings

Anti-*Pneumocystis jirovecii* Pneumonia Prophylaxis

Patients with T-cell deficiencies and combined immune defects (CID), such as CD40L/CD40 deficiency, DOCK8 deficiency, and WAS, are at risk for PJP, and prophylaxis should be provided with TMP/SMX or, alternatively, pentamidine (intravenous or inhaled), atovaquone, or dapsone (when G6PD is normal).[575–577] In addition, PJP prophylaxis may be 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 is discussed in Section 2.4. Acyclovir or valacyclovir is used for HSV and varicella zoster virus (VZV) prophylaxis for IEI at risk for recurrent or severe infections, such as defects of the TLR3 pathway.[331,578] After high-risk VZV exposure, anti-varicella immune globulin preparations 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 given within 10 days of exposure (if the patient is not on IgRT) or acyclovir or valacyclovir prophylaxis for 7 days starting 7 to 10 days after exposure.[579]

Patients with innate defects along the IFN-α signaling pathway are at high risk for certain infections, such as influenza and SARS-CoV-2.[580–582] Inactivated vaccines for viral respiratory tract infections (eg, 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).[583]

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

Nontuberculous Mycobacteria 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.[345,584] 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 studies.

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.[335,585,586] For patients with frequent candidal infections, antifungal prophylaxis with fluconazole is recommended. For patients with STAT1 GOF treated with JAK inhibitors, CMC may improve, and azole prophylaxis may be stopped.[587] Certain IEI, namely STAT3 HIES and STAT1 GOF, can be associated with severe disseminated coccidiodomycosis; therefore, antifungal prophylaxis is recommended in endemic regions (ie, southwestern United States and Northern Mexico).[588] In addition, STAT3 HIES is associated with pneumatoceles that can be secondarily infected with *Aspergillus* spp. or other molds; therefore, when pneumatoceles are present, a mold-specific antifungal (eg, itraconazole) should be used as prophylaxis. CARD9 deficiency is associated with disseminated *Candida spp* infections, including meningitis, and antifungal prophylaxis is suggested.[589]

Perioperative *S aureus* Prophylaxis

Surgery can be associated with impaired wound healing and postoperative infections in patients with IEI.[590,591] For IEI susceptible to *S aureus* infections, such as neutrophil defects (eg, CGD, LAD) or STAT3 and IL-6 related HIES, we suggest measures to decrease bacterial burden preoperatively, such as with nasal mupirocin and/or chlorhexidine or dilute bleach baths. Perioperative antibiotics directed against *S aureus* are also suggested in these cases.

Airway Clearance Perioperatively

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 perioperatively is suggested. Methods to improve airway clearance postoperatively include minimizing time lying in bed, hypertonic saline nebulizations, airway clearance devices, and consideration of inhaled medications (eg, tobramycin) for those with chronic *Pseudomonas* spp. colonization.

Dental Procedures in Patients With IEI

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 canal procedures, deep scaling, and implant placement, we suggest antibiotic prophylaxis such as with amoxicillin/clavulanate or clindamycin. Patients with other IEI, particularly isolated antibody deficiencies, do not typically require antibiotic prophylaxis for invasive dental work.[592]

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 and facilitate drug monitoring, dosing, and therapeutic optimization.[593]

Recommendation 9.2: We recommend using only irradiated, cytomegalovirus (CMV)-negative, lymphocyte-depleted blood products for administration to patients with combined immunodeficiencies or athymia.

Strength of recommendation: **Strong**

Certainty of evidence: **Moderate**

For patients with SCID, congenital athymia, or CID, care should be taken to avoid CMV infection by using CMV-negative, lymphocyte-depleted irradiated blood products. Patients with suspected or known SCID or athymia and their mothers should be evaluated for CMV status, breastfeeding withheld, and formula given, if feasible until maternal CMV status is known[77] (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 intravenous twice daily) or valganciclovir (16 mg/kg intravenous twice daily) therapy should be started and subsequently continued until immune reconstitution. If the infant is found to be infected with CMV, ganciclovir or valganciclovir should be started until weekly patient's urine and blood PCR results are negative for CMV for 4 weeks. CMV disease is found much less often in IEI other than SCID or athymia, but asymptomatic viremia can be present in patients with CID. In this setting, examination for signs of disease, such as hepatitis, pneumonitis, chorioretinitis, or enteritis, is prudent, and suppression of viremia before HSCT is recommended if HSCT is planned.

Recommendation 9.3: We recommend 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.[594] 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* (eg, aspergillomas) or other molds that can lead to chronic infection and significant hemoptysis.[595] 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* species, can cause disseminated infection in certain IEI. These infections are found with STAT3-HIES, STAT1 GOF, and less frequently with IFN-γR defects and CIDs.[335,596] Patients should be counseled regarding high-risk exposures to mold. Those at high risk for disseminated *Coccidioides* spp infection should be placed on prophylaxis when visiting endemic regions (ie, Southwestern United States

and northern Mexico). High-risk activities for histoplasmosis include construction work and exploring caves with bat colonies. *Cryptococcus* spp 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*.[597] 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* spp infections that can lead to significant biliary disease and potentially portal hypertension.[598–600] Treatment requires immune reconstitution (ie, 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 by *Campylobacter* spp.[568,601]

Ensuring access to safe water, avoiding drinking from streams, lakes, or creeks, and using good handwashing and cooking techniques can reduce risk for these infections.

Recommendation 9.4: We suggest 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 closer clinical follow-up than for patients without IEI. TLR pathway defects or 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 determine 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 long courses of treatment with guidance from repeat imaging and laboratory markers. Continuation of antimicrobials for secondary prophylaxis may be considered.

Section 10. Management of Co-Morbidities in Inborn Errors of Immunity

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 to strong**

Certainty of evidence: **Low to 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, and rheumatologists, among other medical specialists.

Immunosuppressive, anti-inflammatory, and cytotoxic therapies are all used for the treatment of noninfectious 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 patients with IEI are mixed.[602–604] When possible, organ transplants should occur at centers with experience in treating patients with IEI.

Lung Disease

Pulmonary complications of IEI are common, including infections and morbidity secondary to infection (eg, bronchiectasis) (Table 10A). Antimicrobial prophylaxis for patients with bronchiectasis is discussed in Section 9. In addition, maintaining high trough serum IgG levels in patients with bronchiectasis receiving IgRT may be helpful in preventing infection and slowing progression of disease (Section 8, Recommendation 8.2).[605]

GLILD, a noninfectious complication, occurs at increased rates in patients with primary antibody deficiency. Although high-dose glucocorticoids may be used to induce disease remission in GLILD, maintenance corticosteroids may result in relapse.[606] One effective approach for GLILD is the treatment with B-cell–depleting therapy (eg, rituximab) or equivalent, in combination with maintenance antimetabolite therapy (mycophenolate mofetil or azathioprine).[607] Duration of therapy is typically 12 to 18 months, with ongoing clinical, radiologic, and laboratory monitoring. Relapse occurs in a subset

Table 10A
Management of Lung Disease

Manifestation	Associated IEI	Intervention/management	Strength of recommendation	Certainty of evidence	References
GLILD	Antibody deficiency	Combination treatment: B-cell–depleting therapy (eg, rituximab) + antimetabolite therapy (mycophenolate mofetil or azathioprine)	Strong	Moderate	607
		High-dose corticosteroids	Conditional	Moderate	606
Pneumatocele after lung infection	STAT3-HIES	Antimicrobial treatment Avoid surgical approach if possible	Strong	Moderate	608
Bronchiectasis	Antibody deficiencies	Avoid surgical approach if possible	Strong	Moderate	608
		Periodic, at least annual, imaging of lungs with high-resolution CT scan			609 606
		Maintain high trough serum IgG levels			605
		Airway secretion clearance measures			

Abbreviations: CT, computed tomography; GLILD, granulomatous and lymphocytic interstitial lung disease; HIES, hyper IgE syndrome; IEI, inborn error(s) of immunity.

Table 10B
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 (eg, enteral or systemic steroids)	Strong	Moderate	612, 613
		Do not avoid gluten unless patients have celiac-associated HLA markers	Strong	Moderate	611
Chronic norovirus infection	Antibody deficiency, CID	Antimicrobials (eg, nitazoxanide, ribavirin) and/or diverse drugs (eg, enteral steroids, enteral immunoglobulin)	Conditional	Very low	614, 615
Inflammatory bowel disease	CGD	5-Aminosalicylates, corticosteroids, ustekinumab	Conditional	Low	616
		Use TNF-α inhibitors with caution of risk of severe infection	Conditional	Moderate	617, 618
		HSCT	Conditional	Moderate	620
Liver abscess	CGD	Initial treatment with culture and biopsy-directed antimicrobials and systemic corticosteroids	Strong	High	621
		Surgical management with debridement or resection if medical management is inadequate	Strong	Moderate	622
Nodular regenerative hyperplasia of liver	Antibody deficiency, CGD	Medical and surgical management of non-cirrhotic portal hypertension to prevent variceal bleeding	Conditional	Low	623, 624
		Liver transplantation is discouraged	Conditional	Low	603, 604
Autoimmune hepatitis	Antibody deficiency, PIRD	Corticosteroids, immunomodulators	Conditional	Low	625
		Precision therapy based on underlying molecular defect (eg, abatacept, jakinibs)	Conditional	Low	626, 445

Abbreviations: CGD, chronic granulomatous disease; HSCT, hematopoietic stem cell transplant; IEI, inborn error(s) of immunity; PIRD, primary immune dysregulatory disorders; TNF, tumor necrosis factor.

of patients, and the approach to therapy in these patients is similar to initial therapy.

Patients with STAT3-HIES are prone to the development of pneumatocele after pneumonia.[608] These pneumatoceles may become colonized with pathogens including *Pseudomonas aeruginosa* or *Aspergillus* spp. Antimicrobial therapy is needed to avoid a cycle of re-infection (Section 9). Surgical interventions may result in high rate of complications after thoracic surgery compared with other patients; the most frequently reported is bronchopleural fistula formation.[591]

Gastrointestinal Disease

As many as 30% of patients with IEI have gastrointestinal involvement including enteric and hepatic diseases,[610] the treatment of which is similar to that of immune-competent patients but with some special considerations outlined in the following paragraphs (Table 10B).

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 2 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.[611,612] Instead, immunomodulatory therapy (eg, enteral or systemic corticosteroids) is the mainstay of therapy.[613]

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 (eg, nitazoxanide, ribavirin) and/or anti-inflammatory drugs (eg, enteral steroids, enteral immunoglobulin, or biologics).[181,613–615]

Inflammatory bowel disease associated with CGD (also referred to as CGD colitis) is treated with standard therapy including 5-aminosalicylates, corticosteroids, and ustekinumab.[616] Caution is advised with the use of TNF-α inhibitors in patients with CGD colitis due to the increased risk of severe infection observed in a small case series of patients.[617–619] Patients with CGD undergoing HSCT have demonstrated remission of CGD colitis.[620]

Liver abscesses are a common manifestation of CGD and are treated with culture/biopsy-directed antimicrobials in addition to systemic corticosteroids.[621] Surgical management with debridement or resection may be required.[622]

Nodular regenerative hyperplasia (NRH) is a difficult-to-treat cause of non-cirrhotic portal hypertension in patients with IEI. Medical and surgical management is required to prevent variceal bleeding and minimize complications.[623–625] End-stage disease is associated with significant morbidity and mortality, and liver transplantation may be followed by disease recurrence.[603,604]

Autoimmune hepatitis occurs with increased frequency in patients with IEI.[625] Treatment with corticosteroids and nonspecific immunomodulators such as azathioprine is often effective, but where possible, treatment based on the underlying molecular defect is preferred. For example, abatacept has been found to be effective in patients with CTLA-4 haploinsufficiency[626] and jakinibs have demonstrated efficacy in patients with STAT3 GOF.[445]

Dermatologic Disease

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 (Table 10C).

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 and CID (notably those with DNA repair defects), and it has also been reported in patients with hypogammaglobulinemia and defects of innate immunity.[627] Once attenuated rubella or other infection has been ruled out, first-line therapy for skin granulomas is oral corticosteroids, followed by TNF-α inhibitors if refractory or unresponsive to corticosteroid therapy[628] with the caveat that TNF-α inhibitors should be used with caution in patients with CGD and other IEI with increased susceptibility to mycobacteria and fungal infections (Table 10B).

Atopic dermatitis is associated with many IEI and can be quite severe. It also predisposes patients to skin infections. Initial

Table 10C
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	627
		Topical corticosteroids for noninfectious rash	Strong	Moderate	628
		TNF-α inhibitors to treat progressive or refractory disease	Conditional	Very low	628
		Imaging for extracutaneous granulomatous disease	Strong	Very low	627
Moderate-to-severe atopic dermatitis	HIES, WAS	Biologic/targeted molecular therapy for refractory disease	Strong	Moderate	629
		Adjunct measures to reduce colonization with *S aureus*	Conditional	Moderate	630
Refractory warts	CID	Topical cytotoxic therapies (eg, cryoablation, salicylic acid or 5-flurouracil) and topical immunostimulants (eg imiquimod)	Conditional	Very low	429
		Mavorixafor (for WHIM)	Strong	Moderate	632

Abbreviations: CGD, chronic granulomatous disease; CID, combined immunodeficiency disorder; CVID, common variable immunodeficiency; HIES, hyper IgE syndrome; IEI, inborn error(s) of immunity; TNF, tumor necrosis factor; WAS, Wiskott-Aldrich syndrome; WHIM, warts, hypogammaglobulinemia, infections, and myelokathexis.

management should focus on improvement of skin barrier with emollient therapy and control of inflammation with topical corticosteroids.[629] For some patients, particularly those who have had recurrent bacterial skin infections, dilute bleach baths or swimming in chlorinated pools 2 to 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.[630] 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.[631]

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 (Section 13).[632] 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 (Section 11).

Neurodevelopmental Disorders

Speech, gross, and fine motor delays are associated with many IEI; therefore, early intervention with physical, occupational, and speech therapy is essential.[633–635]

Rheumatologic and Musculoskeletal Disease

Bone health optimization should be considered with vitamin D replacement, if needed, and adequate calcium intake.[488] Treatment with bisphosphonates may not reduce fracture risk but is considered when there are recurrent fractures and osteoporosis. Patients with STAT3-HIES frequently have retained primary teeth, and consultation with a dentist regarding the timing of extraction of retained incisors and molars is recommended (Table 10D).[636]

Autoimmune manifestations occur in various IEI characterized primarily by immune deficiency. Inflammatory myopathy, connective tissue disease, and noninfectious arthritis occur in patients with antibody deficiencies and WAS. Physical activity has been found to reduce symptoms, such as fatigue and pain, and improve function and mental health.[637] Patients are more likely to adopt better health practices when recommended by their physician,[638] 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.[447,639–641]

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 patients with STAT3-

Table 10D
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	488
Retained primary teeth	STAT3-HIES	Consultation with dentist for extraction of retained incisors and molars	Strong	Moderate	636
SLE and SLE-like symptoms	Antibody deficiencies, CGD, CGD carriers	Standard treatment of SLE	Conditional	Moderate	642 315
Small-medium vessel vasculitis	Complement deficiency, WAS	NSAIDs, corticosteroids, methotrexate, cyclophosphamide, azathioprine, rituximab	Strong	Low	447
		High-dose IVIG	Conditional	Low	645,646
Inflammatory myopathy. Persistent noninfectious oligo- or poly-articular arthritis	Antibody deficiencies, WAS	NSAIDs, corticosteroids, and steroid-sparing agents, such as methotrexate, sulfasalazine, cyclosporine, or biological agents	Strong	Moderate	639 640 641
		Physical therapy and exercise therapy	Strong	Moderate	637

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, nonsteroidal anti-inflammatory drug; PAD, primary antibody deficiency; TNF, tumor necrosis factor; WAS, Wiskott-Aldrich syndrome.

Table 10E
Management of Hematologic/Oncologic Disease

Manifestation	Associated IEI	Intervention/management	Strength of recommendation	Certainty of evidence	References
Severe anemia or thrombocytopenia	SCID, CID	Only irradiated, leukocyte-depleted cellular blood products	Strong	Moderate	650
Autoimmune anemia or thrombocytopenia	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	Strong	Low	436, 654
		High-dose IVIG			652
		Do not use splenectomy, unless splenic sequestration or severe, refractory cytopenias	Conditional	Moderate	655
Autoimmune neutropenia	Antibody deficiencies, immunodysregulatory disorders	Granulocyte-colony stimulating factor (G-CSF) to achieve an ANC of 1000-1500 cells/μl for patients with recurrent and severe infections	Conditional	Low	656, 657
		Do not treat autoimmune neutropenia without infections	Strong	Moderate	658
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 QoL	Conditional	Very low	660
Malignancies	All IEI	Radiation sensitivity testing before cancer therapy in patients with IEI without molecular diagnosis	Conditional	Low	281
		Standard treatment regimens of shorter duration	Conditional	Low	492
HLH/MAS	All IEI	Coordinated treatment by a multidisciplinary team with expertise in hyperinflammation.	Strong	Low	661, 660
		Defer HLH treatment in stable patients until associated malignancy and infection have been ruled out			

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.

HIES.[315,641–643] These symptoms should be treated like SLE even in the absence of classic serologic findings because serology is not confirmatory in many patients and carriers.[315,642]

Patients with WAS have a high incidence of small vessel vasculitis which affects the skin, gastrointestinal system, and kidney.[447] Aortic aneurysms were reported in 5 cases.[644] Treatment of vasculitis includes standard therapies such as corticosteroids, methotrexate, cyclophosphamide, azathioprine, rituximab, and high-dose IVIG.[645,646]

Recommendation 10.2: We recommend 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 (Tables 7.2 and 7.3).[647] 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.[648] The development of manifestations such as cytopenias and malignancies warrants prompt treatment in patients with IEI (Table 10E).

Cytopenias

Autoimmune cytopenias occur often 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.[649] Interventions to increase the safety of blood product transfusions in patients with IEI include the use of leukocyte-depletion and irradiation (Recommendation 9.2). The use of irradiation is reserved for HSCT, in which the recipient is at risk for transfusion-associated graft-vs-host disease (TA-GvHD), a complication resulting from allogeneic attack from passenger donor T cells.[650] TA-GvHD risk is increased when the recipient has compromised T-cell function and when the donor has shared HLA-haplotypes with the recipient. Irradiation is not required for cryoprecipitate, frozen plasma, or fractionated plasma products.[650]

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 and monoclonal antibodies targeting B cells. B-cell depletion has demonstrated good initial response rates but high rates of relapse.[651,652] Use of serotherapy against B cells may result in prolonged B-cell aplasia or hypofunction,[653,654] 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 now rarely used.[655]

Most patients with autoimmune neutropenia are asymptomatic despite having very low levels of circulating neutrophils. A few patients with autoimmune neutropenia will develop recurrent or severe infections or stomatitis from impaired mucosal surveillance. In these clinical scenarios, G-CSF administration has demonstrated clinical benefit in retrospective registry analyses and is well tolerated.[656] As myelopoiesis is partially or fully intact in autoimmune neutropenia, clinical benefit can be achieved by small doses of 0.5 to 3 μg/kg/d of G-CSF given every 1 to 3 days to increase the ANC to a target maintenance of 1000 to 1500 cells/μL.[657] Immune suppression to treat primary autoimmune neutropenia has very limited success and is not recommended due to risk of infection.[658]

Management of Malignancy

Current recommendations for patients with IEI consider standard treatment regimens of shorter duration to avoid extensive periods of high infectious risk.[500] 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 development of therapy-related malignancy.[659] For patients with IEI but no genetic diagnosis, we recommend performing a radiation sensitivity assay before initiating treatment of malignancy.[281]

Outcomes for malignancy in IEI 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.[648] 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 cancer 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, and primary or reactivation of herpetic viral infections. Initial evaluation should include a complete blood cell count, complete metabolic panel, coagulation studies (PT/PTT/fibrinogen), ferritin, sIL2R, CXCL9, IL-18, bone marrow biopsy, flow cytometry for perforin, CD107a mobilization, SAP and XIAP, quantitative immunoglobulins, T/B/NK cell subsets, brain magnetic resonance imaging, a comprehensive genetic panel for IEI, and consideration 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 comorbidities such as infections or underlying organ dysfunction. A multidisciplinary care team can lead to improved patient care.[660,661] 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, whereas use of immune suppression in the setting of severe infection may lead to overwhelming illness.

Section 11. Immunizations in the Management of Inborn Errors of Immunity

Recommendation 11.1: We recommend the use of vaccine recommendations from public agencies (eg, WHO and CDC) and professional medical organizations (eg, AAAAI, ACAAI, and CIS) for patients with IEI.

Strength of recommendation: **Strong**

Certainty of evidence: **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, affecting individuals with IEI and their household contacts. These include vaccines for the prevention of COVID-19, respiratory syncytial virus, herpes zoster virus, human papillomavirus, *N meningitidis, S pneumoniae*, and mpox virus. Providers may refer to guidelines from public agencies (eg, World Health Organization, CDC) and professional medical organizations (eg, AAAAI, ACAAI, and CIS) as their recommendations may supersede the practice parameter guidelines. The CDC works with the Advisory Committee on Immunization Practices (ACIP) recommendations, which historically includes specific guidance for individuals with IEI.

IEI Patients With Severe Immune Defects (Cellular, Phagocytic, and/or Humoral) Should Not Receive Live, Replicating Vaccines

Live vaccines should be avoided in all infants with SCID or complete athymia.[87] Unfortunately, vaccine-strain infections after administration of live attenuated rotavirus to newborns with SCID have been reported, occurring before the implementation of routine NBS.[87, 88] BCG vaccination, which is still recommended in countries with high-prevalence of tuberculosis, has caused disseminated or localized granulomatous disease in infants with SCID, IFN-γ pathway defects, or chronic granulomatous disease.[662] Vaccine strain rubella virus has been detected in skin granulomas in patients with IEI, including AT, CID, and even patients with humoral immunity defects (Table 11).[627]

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 1 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 have a blistering rash after VZV vaccination or shingles outbreak.

Individuals With Isolated T-Cell Lymphopenia and Preserved Cellular and Humoral Functions May Receive Live Viral Vaccines

This includes infants with abnormal NBS results indicating T-cell lymphopenia (but not SCID) and pediatric patients with idiopathic T-cell lymphopenia, DGS, or CHARGE syndrome.

Infants with abnormal NBS results for SCID who do not meet the criteria for SCID diagnosis are at risk for preventable infectious disease before 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,[663] and VZV vaccination can prevent 97% of infections in children annually in the United States.[664] Rotavirus infection after 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.[665]

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 provide an explanation for T-cell lymphopenia.[666] Recent guidelines for children with T-cell lymphopenia recommend administering live viral vaccines if CD4 T cells are more than 400 cell/μL, CD8 T cells are more than 200 cells/μL, naive CD4 T cells are more than 20% of CD4 T cells, and they have protective antibody titers in response to tetanus vaccination.[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

During the COVID-19 pandemic, patients with IEI on IgRT were given COVID-19 vaccines (before the emergence of serologic immunity in the IgRT products) and demonstrated surprisingly robust T-cell responses and serologic responses.[667] As such, patients with IEI are strongly recommended to receive COVID-19 vaccine and consider ongoing boosters. Pemgarda (Pemibart) is a monoclonal antibody indicated for pre-exposure COVID-19 prophylaxis (passive immunization) in immunocompromised patients, aged 12 years and older, every 3 months, under emergency use authorization.

A live, nonreplicating, 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 contraindication for immunocompromised individuals. There have not been reports of use of this vaccine in patients with IEI.

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. Approximately 80% of sexually active individuals will acquire genital HPV infection in their lifetime.[668] Protection before 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.[669] 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

Table 11
Vaccination Considerations in IEI

Vaccination approaches	Associated IEI	Vaccines of relevance	Strength of recommendation	Certainty of evidence	References
Contraindicated	Severe IEI—including SCID, athymia, 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. (Note: CGD may receive viral vaccines, if not immunosuppressed) All live bacterial (BCG, typhoid)	Strong	Low	87 662 384
Active vaccination while receiving IgRT: target vaccine preventable- diseases	Patients with IEI with adequate T-cell function AND receiving IgRT	mRNA vaccines, eg, COVID-19 emerging strains	Conditional	Low	667
		HPV vaccines	Conditional	Very low	669
		Seasonal inactivated vaccines, eg, influenza	Conditional	Low	678
		Recombinant zoster vaccine for shingles	Conditional	Very low	674 675
Vaccination and boosters with conjugated vaccines for patients at risk for severe bacterial infections	Complement deficiencies Asplenia/hyposplenia TLR defects	Early administration of MenACWY (<5 y); 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	674 675
Vaccination of household contacts of patients with IEI	Household contacts of any patient with IEI	Scheduled routine vaccinations are encouraged, including routine live viral vaccines, except oral polio vaccine and ACAM2000 mpox vaccine	Strong	Low	85 87 284

Abbreviations: BCG, bacillus Calmette-Guerin; CID, combined immunodeficiency; HPV, human papilloma virus; IEI, inborn error(s) of immunity; NK, natural killer; SCID, severe combined immunodeficiency; TLR, toll-like receptor.

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[670] in addition to vaccination.

In 2023, routine vaccination for RSV has been recommended for "at risk" adults 60 to 74 years, all individuals older than 75 years old,[671] and pregnant women to prevent infection in infants.[672] In the same year, RSV monoclonal antibody infusions for toddlers were approved up to 24 months of age.[673] The approach to vaccinate pregnant women or administer monoclonal antibody infusions in nonprotected infants also applies for families affected by IEI.

For patients with IEI who 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 (eg, PCV20 or PPSV23) and meningococcal (A, C, Y, W135, and B) infections. Administration of meningitis vaccines is 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 health care needs, the CDC has developed algorithmic tools to assist providers with decision making around pneumococcal vaccines (Recommendation 4.6).

We recommend that patients with IEI who no longer require IgRT (ie, THI) receive live viral vaccines according to catchup schedule, at least six to eight months 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, RZV was approved for administration to immunocompromised adults 18 years 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.[674,675] 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 currently approved for the prevention of primary varicella infection in patients who have been exposed to live VZV 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 through varicella zoster immune globulin (VZIG).[676] Patients receiving IgRT are likely protected if IVIG is given within 3 weeks of exposure.[677]

Section 12. Immune Reconstitution Therapy for Inborn Errors of Immunity

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%,[679] but this estimate varies depending on the underlying IEI, donor-patient 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.[82] In contrast, patients with diseases of immune dysregulation, such as *LRBA* deficiency or *CTLA-4* haploinsufficiency, are typically only considered for allogeneic HSCT once the disease expression in patients has proven to be severe.[680] HSCT for IEI associated with radiation sensitivity and chemosensitivity necessitates 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.[681]

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 to 2 years of age.[56] HSCT outcomes are optimal for patients diagnosed by NBS with greater than 90% 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.[59,82,682]

For patients with SCID, the decision to proceed to allogeneic HSCT is straightforward (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 CTTI (Recommendation 12.3).[83]

For patients with SCID undergoing allogeneic HSCT, the use of pretransplant myeloablative conditioning regimen is associated with improved B-cell reconstitution,[682] 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, patients with SCID who have genetic variants associated with radiation and chemotherapy sensitivity should receive treatment with reduced doses of alkylator-based conditioning agents, 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 patients with SCID 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 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.[683] Self-inactivating (SIN) gammaretroviral and lentiviral vectors were later developed, with modification of viral promoters and enhancers to reduce the risk of malignancy.[684] 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 using 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 is similar, both greater than 90%.[81]

Recommendation 12.3: We recommend that patients with congenital athymia disorders be treated with CTTI.

Strength of recommendation: **Strong**

Certainty of evidence: **Moderate**

The treatment of patients with congenital athymia with CTTI at the time of writing is clinically available at Duke Health Center (North Carolina) and Great Ormond Street Hospital (London, United Kingdom). T-cell reconstitution, sufficient to prevent overwhelming infections, typically develops 6 to 12 months after CTTI. The 2-year survival among 95 patients with congenital athymia treated with CTTI was reported at 76%.[83,685] CTTI should be pursued, when possible, in all patients with severe congenital athymia disorders (eg, 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.[686–688]

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.[689,690] A major consideration is whether CID disease manifestations can be corrected by replacement of hematopoietic stem cells and derived lymphocyte populations.[691] 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 for 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* spp. infection. Survival for patients older than 10 years of age or with these comorbidities ranged from approximately 40% to 60%.[692] 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 toward better survival for patients who received HSCT before 8 years of age, 96% vs 78% in older patients.[693] More than 100 patients with MHC class II deficiency have been treated with allogeneic HSCT with OS ranging between 66% and 100% in more recent years, and outcomes appear better in patients transplanted before the age of 2 years.[694]

Allogeneic HSCT can be curative for patients with WAS, and HSCT is recommended to prevent the severe disease complications of WAS. Survival outcomes after allogeneic HSCT are highest for patients transplanted at less than 2 to 5 years of age. The 5-year OS in patients transplanted younger than 5 years of age is reported to be greater than 90%.[695] 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 more than 50% as lower levels are associated with increased risk of thrombocytopenia and the development of autoimmunity after HSCT.[695]

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).[696,697] 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 after allogeneic HSCT in patients with CHH from several case series range from 63% to 100%.[697]

Recommendation 12.5: We recommend 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.[698] 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.[699] Decision for HSCT in patients with Chediak-Higashi syndrome should take genetic testing and cytotoxicity assay results into account along with the clinical phenotype.[700] The risk of HLH is low in patients with Hermansky-Pudlak syndrome type 2, and HSCT is typically not justified.[701]

Patients with SH2D1A deficiency, or XLP1, are offered allogeneic HSCT due to the high risk of fatal HLH associated with EBV infection along with the risks of lymphoma, humoral deficiency, vasculitis, and other rare complications.[702] Patients with XIAP deficiency (XLP2) 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.[703] Of note, deficiency of XIAP confers a high risk of severe GVHD, and aggressive measures should be taken to prevent GVHD.[704]

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 considered in patients with isolated central nervous system HLH.[705,706] Asymptomatic siblings identified due to family history should be offered HSCT, as outcomes are superior before onset of HLH symptoms.[707,708] 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.[709] 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.[710] A European study reported 100% OS at a median follow-up of 36 months for patients treated with busulfan and fludarabine.[711]

Recommendation 12.6: We suggest 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 pretreatment complications, the potential need to control the underlying immune dysregulation before 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 vs conventional treatments.

Despite the limited number of patients reported, patients with IL-10R and IL-10 deficiencies appear to do well after 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.[712,713] 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 patients with IPEX 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).[714] However, new autoimmune problems continued to develop in 51% of patients treated with immune suppression compared with 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%[680] and among 23 patients with STAT3 GOF was 62%.[445] Although 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.[715]

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%.[716] Notably, allogeneic HSCT prevented new vascular complications.

Recommendation 12.7: We recommend allogeneic HSCT for patients with defects in neutrophil number and function associated with severe clinical phenotypes.

Strength of recommendation: **Strong**

Certainty of evidence: **High**

Most patients with LAD types I and III and with CGD are considered for allogeneic HSCT due to the severity of disease complications and longstanding HSCT experience. The largest multicenter retrospective cohort analysis of outcomes in LAD types I (N = 69) and III (N = 11) reported 83% 3-year OS.[717] Survival was greater than 90% for patients with a fully matched related or unrelated donor and for patients transplanted in infancy.[717] 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%.[718] Survival was greater for patients transplanted before the age of 18 years and for patients with HLA-matched donors.[718] 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.[719]

HSCT for severe congenital neutropenia is discussed in Recommendation 12.8 Data on definitive treatment of patients with other congenital defects of phagocyte number or function is limited.

Recommendation 12.8: We suggest 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 MSMD, 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 IFN-γ which contribute to graft rejection.[720] A review of 12 cases of IFN-γR1 deficiency noted only 4 successful transplantations,[721] and a single-center series of 7 patients with IFN-γR2 deficiency reported 71% event-free survival.[722] 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.[723] Strategies to mitigate the effects of IFN-γ may improve transplant outcomes in these patients.[724]

Patients with congenital neutropenia or Schwachman-Diamond syndrome who develop MDS, leukemia, or other bone marrow diseases can be treated with allogeneic HSCT. Furthermore, 5% to 10% of patients with MDS will develop aplastic anemia, 20% to 33% will develop cytogenetic abnormalities or MDS, and 12% to 25% will transform into leukemia and require allogeneic HSCT.[725,726] Several studies have reported superior survival for patients with marrow failure (70%-80%) vs those with MDS/AML (15%-40%).[727,728] 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.[729] 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%,[730] and a series of 65 patients with MDS reported 5-year OS of 75%.[731]

Recommendation 12.9: We recommend that any patient with IEI who receives definitive treatment with allogeneic HSCT, CTTI, or gene therapy receive lifelong 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 after definitive treatment. Evaluation of immune reconstitution during the first 2 years after treatment is critical. Even patients without IEI who receive allogeneic HSCT may have impaired immune function after HSCT.[732] Evaluation of immune reconstitution facilitates decisions regarding ending isolation practices, withdrawing prophylactic antimicrobial medications, and beginning routine post-HSCT vaccinations. Complete immune reconstitution after allogeneic HSCT is estimated to occur within 1 to 2 years, or sooner, in the absence of GVHD. Recommendations exist regarding vaccination strategies for patients with HSCT in general and for patients with specific IEI, such as SCID. Initiation of vaccine schedules is guided by time post-HSCT or, preferably, immunology evaluation.[733–735] 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 after CTTI, and guidance regarding vaccination of patients who received CTTI is available.[83,736]

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.[737–739]

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 to as precision medicine (Table 13A). Several of these medications are currently approved by the FDA (Table 13B).

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 1 of 4 JAK proteins, which phosphorylate and recruit 1 of 7 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 GvHD. Mechanistic studies and cohort case reports have revealed partial or complete response to treatment in JAK/STAT GOF disorders, specifically STAT1 GOF and STAT3 GOF.[445,585,740–749] JAK inhibitors have also demonstrated clinical efficacy in cohort studies and case reports in treating interferonopathies (Table 13A).[750–755]

JAK inhibitors are administered starting with the recommended dose for FDA-approved indications and titrated every 4 to 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. Furthermore, 50 mg/m^2/dose has been tolerated in children, but the long-term data on high dose are not adequate to recommend this dose longitudinally.[756] Baricitinib may be used 2 mg daily and increased to 4 mg daily within 4 to 6 weeks, again according to clinical response and tolerance. In children under 9 years of age, use 2 mg/d.[757] Dose escalation of 25% weekly until goal dose is achieved is suggested.[587] Given the increased risk for herpes virus infections, prophylaxis with acyclovir is suggested.[587] Clinical assessments should be taken every 4 to 6 months for opportunistic infections,[445,587] cardiovascular disease, thromboembolic disease, malignancy, or severe liver disease.[445]

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 less than 0.02 mmol/L within 3 to 6 months.[758–760] 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/wk intramuscularly in infants with ADA-SCID, which is divided into 2 doses per week. Longitudinal monitoring of plasma ADA levels, erythrocyte deoxyAXP levels, and blood counts and lymphocyte subsets should be performed at least every 6 months to ensure adequate response. Updosing by 0.033 mg/kg/wk is recommended if trough plasma ADA level remains less than 30 mmol/h/L or if trough dAXP level exceeds 0.02 mmol/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/wk is recommended to maintain trough plasma ADA levels more than 30 mmol/h/L, which may be given in a single dose weekly. Known medication interactions include vidarabine, which is a substrate for

Table 13A
Key Examples of Precision Medicine in IEI

Associated IEI	Therapeutic agent	Biomarkers[a]	Strength of recommendation	Certainty of evidence	Reference
JAK/STAT gain-of-function disorders					
STAT1 gain of function	Ruxolitinib Baricitinib	CXCL9 T_H17	Conditional	Moderate	741 587 740 743 742
STAT3 gain of function	Ruxolitinib Tofacitinib	Double-negative T cells	Strong	Moderate	445 746 653
STAT4 gain of function	Ruxolitinib	IL-6	Conditional	Very low	749
STAT5b gain of function	Ruxolitinib	Eosinophilia	Conditional	Low	748
SOCS1 deficiency	Baricitinib Tofacitinib	CXCL9	Strong	Low	747
Interferonopathies					
USP18 deficiency, SAVI, Aicardi-Goutières syndrome, CANDLE	Ruxolitinib Baricitinib Tofacitinib	Interferon activity	Strong	Low	750 754 753 751 752
SCID due to ADA deficiency					
ADA deficiency	Elepegademase	Plasma ADA activity, ddNDP	Strong	High	758 759
CVID with complications					
CTLA-4 haploinsufficiency LRBA deficiency	Abatacept or Belatacept (CTLA-4-Ig)	cT_{FH}, soluble CD25	Strong	Moderate	761 762
Inflammasome-related disorders					
CAPS (FCAS1, MWS, NOMID/CINCA; NLRP3)	Anakinra Rilonacept Canakinumab	WBC (ANC), CRP, SAA, proteinuria	Strong	High	766
TRAPS (TNFRSF1A) FMF (MEFV) MKD (MVK)	Canakinumab	WBC (ANC), CRP, SAA, proteinuria	Strong	High	767
DIRA (IL1RN)	Anakinra Rilonacept	CRP, SAA CRP, SAA	Strong	Moderate	783
PAPA syndrome (PSTPIP1) FCAS2 (NLRP12) Majeed syndrome (LPIN2)	Anakinra Canakinumab	CRP, SAA CRP, SAA	Conditional	Low	773 776 775 777
NOCARH (CDC42) FCAS4 (NLRC4)	Anakinra Canakinumab	CRP, SAA, ferritin CRP, SAA, ferritin	Conditional Conditional	Low Low	782 781
Non-syndromic SCN					
SCN type 1 SCN type 2 SCN type 3 SCN type 4 XL congenital neutropenia, CXCR2 deficiency	G-CSF	ANC	Strong	High	784 785
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	786 794 725 791 792 788 789 575
IEI with SCN and hypopigmentation					
Chediak-Higashi syndrome Hermansky-Pudlak syndrome type 2 Griscelli syndrome type 2	G-CSF	ANC	Strong	High	725 791

(*continued*)

Table 13A (*Continued*)

Associated IEI	Therapeutic agent	Biomarkers[a]	Strength of recommendation	Certainty of evidence	Reference
WHIM syndrome					
WHIM syndrome	Plerixafor Mavorixafor	CBC	Strong	Moderate	792 793 794
Disorders of vitamin B12 and folate metabolism					
TCN2 deficiency	Cyanocobalamin Hydroxycobalamin	Vitamin B12 Folate	Strong	Low	795
SLC46A1 deficiency	High-dose intravenous folinic acid				796 797
MTHFD1 deficiency, CblF LBMRD1	Hydroxycobalamin Folinic acid				798
Innate immune disorders of IFN-γ signaling					
IL-12 IL-23RB1 IL-12p40 deficiency IL-12RB2 deficiency AD partial IFN-gR1 or R2 deficiency STAT1 LOF IRF8 deficiency	IFN-γ		Strong	Very low	801 802
IFN-γ deficiency	IFN-γ		Strong	Very low	803
Leukocyte adhesion disorder					
LAD-II	Fucose	CBC with differential	Strong	Low	804 805
Activate PI3K delta syndrome					
APDS1 APDS2	Leniolisib	IgM; transitional B cells $CD8+_{TEMRA}$ $CD4+_{TEMRA}$ cells	Strong	High	807

Abbreviations: ADA, adenosine deaminase; CBC, complete blood cell count; IEI, inborn error(s) of immunity; SCID, severe combined immunodeficiency; SCN, severe congenital neutropenia.
[a]Biomarkers are recommended but are not included in the strength of recommendation and are only provided as a guide to therapeutic efficacy.

Table 13B
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 with diff, liver panel, chem 10, viral PCR	Lifelong or until transplant	587
Elapegademase	ADA deficiency SCID[a]	Medication interactions	Whole blood ADA level, CBC, lymphocyte subsets	Until transplant	760
Anakinra	NOMID[a], DIRA[a]	Injection site reactions, infection	CRP, ESR, SAA	Lifelong	764
Canakinumab	FCAS[a], MWS,[a] NOMID[a], FMF, TRAPS, HIDS/MKD	Injection site reactions, infection	CRP, ESR, SAA	Lifelong	764
Rilonacept	FCAS[a]/MWS[a]	Injection site reactions, infection	CRP, ESR, SAA	Lifelong	783
Abatacept	CTLA-4 haploinsufficiency LRBA deficiency	Live vaccines should not be given concurrently or within 3 mo of discontinuation Do not give with TNF inhibitors	None	Lifelong	762
Plerixafor	WHIM syndrome	Teratogenic	CBC	Lifelong	793
Mavorixafor	WHIM syndrome[a]		CBC	Lifelong	632
Cyanocobalamin Hydroxycobalamin	TCN2 deficiency	None	CBC, vitamin B12 Folate	Lifelong	795
Folinic acid	SLC46A1 deficiency MTHFD1 deficiency	None	CBC, vitamin B12 Folate	Lifelong	796 798
IFN-γ 1-b	CGD[a] and immune disorders of interferon signaling	Liver enzyme elevations Renal toxicity, fever	Liver enzymes Chem 10 CBC with diff	Lifelong or until transplant	809
Leniolisib	APDS[a]	Possible fetal harm Medication interactions	CBC Immunoglobulin	Lifelong	808

Abbreviations: ADA, adenosine deaminase; APDS, activated phosphoinositide 3-kinase delta syndrome; CBC, complete blood cell count; CGD, chronic granulomatous disease; FDA, Food and Drug Administration; GOF, gain of function; IEI, inborn error(s) of immunity; PCR, polymerase chain reaction.
[a]FDA-approved indication.

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, 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 before curative treatments, such as allogeneic HSCT.

CTLA-4 Immunoglobulin for Patients With CTLA-4 Haploinsufficiency and LRBA Deficiency

CTLA-4 is an inhibitor checkpoint protein that works in competition with the co-stimulatory molecule CD28 for the ligands CD80 and CD86. LRBA is essential for intracellular recycling of proteins, including CTLA-4. 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.[761] Abatacept has been found to induce improvement in symptoms in patients with CTLA-4 haploinsufficiency.[680,762] A case series of subjects with LRBA deficiency revealed 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.[761] Long-term follow-up of patients with LRBA deficiency on abatacept revealed 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.[762]

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 found 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, regulatory approvals, cost, and availability. These drugs have different half-lives that may affect clinical and patient preference: anakinra has a terminal half-life of 4 to 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.[763] 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 are limited. To avoid increasing morbidity associated with delays associated with achieving a molecular diagnosis, a trial of IL-1 blockade with anakinra, rilonacept, or canakinumab may aid in the diagnosis of IL-1–mediated disorders.[764]

IL-1 inhibitors are used for treatment of patients with periodic fever syndromes with increased inflammation due to cryopyrin-associated periodic syndrome, Hyper IgD syndrome, or FMF unresponsive to colchicine, or 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.[765,766] Long-term studies of each of the therapies independently demonstrate a favorable safety profile, reduction in symptoms, and improved QoL in children and adults.[765–770]

Randomized controlled trials of canakinumab in FMF revealed resolution of baseline flares in greater than 80% of patients, with approximately 60% having 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.[766] Notably, anti–IL-1 blockade is efficacious in reducing proteinuria.[766] Long-term efficacy of both anakinra and canakinumab has been reported for patients with colchicine-resistant FMF.[769,770] A randomized controlled trial of canakinumab in mevalonate kinase deficiency revealed resolution of baseline flares in 60% of patients, with 35% having complete resolution. Increased dosing led to resolution in 57% of participants.[766] 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%.[771] A randomized controlled trial of canakinumab in TRAPS revealed resolution of baseline flares in more than 60% of patients, with 45% having complete resolution. Increased dosing led to clinical responses in greater than 73% of participants.[765] Long-term studies of canakinumab demonstrate a favorable safety profile, reduction in symptoms, and improved QoL in children and adults.[766–772]

Anakinra and canakinumab have been effective in patients with certain variants in *PSTPIP1*, causing PAPA syndrome.[773,774] 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 found to reduce systemic inflammatory markers and sterile osteomyelitis in affected individuals.[775–777] IL-1 treatment for patients with missense mutations in *NLRP12* has led to improvement in febrile episodes, though some patients experienced relapse of symptoms.[778,779] IL-1 blockade with canakinumab or anakinra has been effective in patients with FCAS4 or mild NLRC4-AID with symptoms to cold stimuli.[780,781] Treatment with anakinra reduces inflammatory episodes associated with Neonatal-Onset Cytopenia, Autoinflammation, Rash and Hemophagocytic lymphohistiocytosis (NOCARH).[782] Patients demonstrated 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.[782] Use of rilonacept produces similar anti-inflammatory efficacy in patients with cryopyrin-associated syndromes.[783]

G-CSF in Neutropenia

The administration of G-CSF to patients with neutropenia is summarized in Table 13A.[783–790] Recombinant granulocyte-colony stimulating factor (rG-CSF) stimulates neutrophil mobilization and delays neutrophil apoptosis.[789] A randomized, controlled, phase 3 trial of 173 patients with severe chronic neutropenia (ANC < 500 cells/μL) revealed an increase in ANC (median 1500 cells/μL), increased proportion of maturing neutrophils within the bone marrow, and significant reduction in infection-related events.[790]

Plerixafor and Mavorixafor for Patients With WHIM Syndrome as Initial Therapy

Plerixafor is a small molecule antagonist of CXCR4 and has demonstrated efficacy in treating patients with WHIM syndrome. In clinical trials, plerixafor has been found to reverse panleukopenia within 1 to 2 weeks of initiation and reduce the burden of infections including skin and anogenital warts due to HPV.[791,792] In a phase 3 randomized crossover study, plerixafor was nonsuperior to G-CSF for reduction of infection severity scores but superior for resolution of leukopenia.[793,794] 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 to 0.04 mg/kg/dose. Longitudinal monitoring of blood counts should be performed regularly to ensure adequate response. Updosing of 0.01 mg/kg/dose may be undertaken if, within 2 to 3 weeks of starting therapy, inadequate responses are found. 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 found 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.[791] Dosing is based on weight; more than 50 kg is 400 mg daily and less than 50 kg 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 after mitogen stimulation, hypogammaglobulinemia, and impaired antibody responses. These abnormalities return to normal with folate therapy.[795–798] 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, and giardiasis who had resolution of infections after treatment with cobalamin therapy.[798]

IFN-γ in the Treatment of Mycobacterial Infections in Patients With IL-12p40 Deficiency, IL-12RB2 Deficiency, and IL-23R Deficiency, AD Partial IFN-γR1 or R2, TYK2 Deficiency, IRF8 Deficiency, and ISG15 Deficiency

In vitro data reveal 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.[345,799] Patients with disseminated mycobacterial infections demonstrated improvement after treatment with IFN-γ[800]; several of these patients were identified as having NEMO deficiency. Treatment with IFN-γ at 50 mcg/m^2 in addition to anti-mycobacterial therapy has led to improvement of disseminated BCG and other mycobacterial infections in patients with IL-12RB2 deficiency and IFN-γR1 deficiencies.[801–803]

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, 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.[804] Discontinuation has led to loss of selectin ligands and leukocytosis.[805,806]

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 to 75 years of age with APDS in an international phase 3, triple-blinded, placebo-controlled clinical trial with 2:1 randomization.[807] 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 nonswitched 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.[807,808] Results of this trial led to FDA approval of leniolisib for the treatment of patients 12 years of age and older.

Section 14. Quality of Life in Inborn Errors of Immunity

Recommendation 14.1*:* We recommend performing QoL measurements in patients with IEI, inclusive of PRO measurements 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 QoL (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 1 or more *concepts* (ie, 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 found 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, for example, 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), whereas others are disease-specific HR-QoL instruments, such as the validated Primary Antibody Deficiency-QoL (PAD-QoL)[810] and the Common Variable Immunodeficiency QoL (CVID-QoL)[811] 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.[811]

Many patient-reported surveys have been published evaluating treatment satisfaction and the comparison between IVIG and SCIG replacement therapy in patients with IEI. Most surveys have used a generic HR-QoL instrument, for example, the Medical Outcomes Study 36-item Short Form Health Survey (SF-36) and a Life Quality Index and Treatment Satisfaction Question Survey (Table 14). Several studies have revealed more favorable patient QoL among patients receiving immunoglobulin therapy at home compared with hospital or infusion center-based IgRT particularly if the IgRT is given subcutaneously.[812–814] Patients reported greater convenience, comfort, and treatment schedule flexibility. Using the SF-36 general health questionnaire and the Toronto Alexithymia Scale questionnaire, it was found 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. Limitation in daily activities due to lower physical health was a major problem faced by patients.[814] Using the SF-36 and the LQI instruments, patients demonstrated significant improvement regardless of the form of administration of IgRT and preference for home SCIG infusions.[815] Before IgRT, patients with CVID experienced diminished HR-QoL vs the general population and a chronic disease control group.[816] The SF-36 and the General Health Questionnaire (GHQ-12) were used to reveal that almost one-third of patients with CVID were at risk for anxiety and depression at all time points and affected two-thirds of females.[510] More than 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 patients with CGD receiving conservative management, whereas transplanted patients had QoL comparable to healthy children on PedsQL survey instrument.[817]

Recommendation 14.2: We suggest that PROs should be measured using a disease-specific QoL instrument and at important management changes in the patient's clinical journey.

Strength of recommendation: **Conditional**

Table 14
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.	510
Child Health Questionnaire Parent Form 50 (CHQ-PF50)	Generic measure of health-related QoL with 15 domains. Specifically designed for children 5-13 y of age.	815
Pediatric QoL Inventory (PedsQL 4.0)	23-Item instrument for children ages 2-18 y. Scales are multidimensional for child self-report and parent proxy-report scales for healthy and acute and chronic health conditions.	817
Life Quality Index (LQI)	Measure of treatment preferences relative to enhancement of life with 4 domains. Used in patients with IEI receiving IgG.	815
General Health Questionnaire (GHQ-12)	12-Item questionnaire designed to measure psychological stress and to detect depression and anxiety.	510
Treatment Satisfaction Questionnaire for Medication (TSQM)	Generic measure of treatment satisfaction with 4 domains	835
PROMIS-29	Generic measure of QoL and was used to assess fatigue in patients with CVID	835
CVID-QoL	32-Item validated HR-QOL instrument for adult patients with CVID	811
PADQOL-16	16-Item validated HR-QOL instrument for adult patients with primary antibody deficiency	810

Abbreviations: CVID, common variable immune deficiency; IEI, inborn error(s) of immunity; QoL, quality of life.

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,[818] ataxia-telangiectasia,[819] X-linked agammaglobulinemia,[820] and antibody deficiencies, in general,[821] 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.[822,823] In some cases, HSCT has been reported to improve HR-QoL[822,824]; 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.[825] 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.[510] Co-occurrence of autoinflammatory 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.[826]

Recommendation 14.3: We suggest that patients with IEI 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.[827] Typically, PH is measured on a 5-point scale as assessed by a single question ranging from poor to excellent (ie, “Would you rate your health today as poor, fair, good, very good, or 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.[828] Within the realm of IEI, determinants of PH have been studied and include sleep quality,[829] route of immunoglobulin replacement,[830] hematopoietic stem cell transplant status,[831] and cognitive status.[511]

Recommendation 14.4: We suggest that patients with IEI be assessed for fatigue at each clinical encounter.

Strength of recommendation: **Conditional**

Certainty of evidence: **Low**

Patients with a primary antibody deficiency[515] and those with CVID[516] often report fatigue as a subjective concern. In addition, pediatric patients with IEI have fatigue at rates ranging from approximately 19% to 65%,[832] which appears to be unrelated to disease activity. Clear drivers of fatigue are not evident; however, the symptom is widely found among studies evaluating IEI QoL,[832,833] 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,[834] optimization of IgRT,[835] and therapeutic options for subtypes and complications of IEI[836] offer opportunities for improving IEI-associated fatigue.

Recommendation 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.

Strength of recommendation: **Conditional**

Certainty of evidence: **Low**

The benefits of shared decision making for patients with IEI are best illustrated in IgRT. Different routes of IgRT affect HR-QoL and patient-reported outcomes. Many of the HR-QoL studies comparing IVIG with SCIG suggested that the latter was more acceptable to patients and improved certain aspects of HR-QoL parameters. Pulvirenti et al[837] 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 patients with CVID 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.

Disclosures

Dr Abraham reports receiving grant support from Amgen; receiving honoraria from ClinGen, National Institutes of Health (NIH), and ClearView; serving as a Deputy Editor of *Journal of Immunology*; and serving as a Clinical Immunology Society committee member. Dr Ballow reports serving as a consultant for Pharming, Green Cross, Immune Deficiency Foundation, and CSL Behring; receiving honorarium from UpToDate; serving on the Syneos Health Data Safety Monitoring Board for GlaxoSmithKline; and serving as a speaker for CSL Behring and ADMA. Dr Barmettler reports serving as a consultant for CSL Behring; serving on the advisory board for CSL Behring and OctaPharma; serving as a speaker for OctaPharma; and receiving grant support from Bristol Myers Squibb. Dr Broderick reports receiving clinical trial support from Novartis and serving as a speaker for SOBI. Dr Butte reports serving on the advisory board for ADMA; receiving grant support from X4 and Pharming; serving as a consultant for Pharming; and serving as a speaker for Grifols. Dr Chan reports serving on the advisory board for SOBI and receiving grant support from NIH and Jeffrey Modell Foundation. Dr Chandrakasan reports serving on the advisory board and receiving honoraria from SOBI, Pharming,

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Supplementary Data

GLOSSARY

Antibody deficiency, A condition characterized by impaired production or function of 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 variations (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 a 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 amino acid 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.

Uniparental disomy, A genetic condition in which a person receives two copies of a chromosome, or of a chromosomal segment, from one parent and none from the other.

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.