Introduction to Inborn Errors of Immunity

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ABSTRACT Inborn errors of immunity (IEI), formerly referred to as primary immunodeficiencies, are a growing spectrum of over 550 genetically defined disorders of the immune system. As our understanding of the mechanisms of these disorders grows, immune dysregulation syndromes, autoimmunity, malignancy, bone marrow failure with immunodeficiency, and phenocopies are recognized as part of the clinical spectrum of IEI. Early recognition and accurate classification are critical as many IEI conditions have specific therapeutic implications, including targeted immune modulation, immunoglobulin replacement therapy, hematopoietic stem cell transplantation, and gene therapy. In this review, we present recent changes in classification, updated laboratory workup strategies, and therapeutic advances.

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KEY WORDS: immune dysregulation, inborn errors of immunity (IEI), primary immunodeficiency, recurrent infections

Inborn errors of immunity (IEI), formerly referred to as primary immunodeficiencies (PID), are a growing spectrum of over 550 genetically defined disorders of the immune system [1]. IEI represent a dynamic and expanding field that lies at the intersection of immunology, hematology, and genetics with a diverse clinical spectrum. Once regarded exclusively as pediatric disorders involving recurrent infections, IEI are now recognized as a diverse spectrum of diseases spanning all ages and presenting with a broad array of clinical manifestations, including autoimmunity, autoinflammation, allergy, lymphoproliferation, and malignancy, as well as infection susceptibility [2,3].

The first described case of immunodeficiency was reported in 1952, when Ogden Bruton described the first case of congenital agammaglobulinemia in a boy with recurrent bacterial infections who was subsequently treated with immunoglobulin replacement. This discovery marked the beginning of a rapidly expanding field. The International Union of Immunological Societies (IUIS) Expert Committee has periodically released updated classifications since 1999 with the number of recognized IEI expanding from fewer than 50 disorders to over 180 by 2012 and now exceeding 550 in 2024. As articulated by Notarangelo et al. [4], this evolution reflects parallel advances in clinical recognition of non-infectious phenotypes, mechanistic immunology and pathway-based classification, genomic diagnostics, and therapeutic innovation, including targeted immunomodulation, cell therapy, and gene therapy [4,5]. The term IEI has therefore substituted the term PID to reflect the comprehensive clinical presentations, acknowledging that immune dysfunction may manifest with variable penetrance and expressivity, lending itself to heterogenous phenotypes, even among individuals with identical genetic variants.

Recent epidemiological data suggest that IEI are not as rare as previously believed, with a prevalence approaching 1:1000 to 1:5000 in some populations and an estimated 6 per 10,000 in the United States [6]. While these estimates highlight that IEI are more common than historically perceived, population-based prevalence data remain highly dependent on case ascertainment, diagnostic access, and registry coverage. In Israel, comprehensive national prevalence estimates across all IEI categories are still evolving. Notably, the high rate of consanguinity in certain populations contributes to increased prevalence of autosomal recessive IEI. In addition, large real-world registry data demonstrate that although the majority of IEI diagnoses occur in childhood, a substantial number of new diagnoses continue into adulthood [7,8].

In this review, we summarize the current principles in evaluating suspected IEI, integrating the updated 2024 IUIS classification [9,10], highlighting the transition from phenotype-based diagnosis to mechanism-based precision medicine. Accordingly, contemporary IEI practice increasingly integrates phenotype, immune function, and genotype to define the underlying mechanism, thereby aligning diagnosis with pathway-directed management rather than syndromic labels alone.

IEI CLINICAL SPECTRUM AND WARNING SIGNS

The hallmark of IEI is the presence of recurrent, severe, or unusual infections [Table 1 A-C]. However, clinicians must recognize that infections represent only one part of the clinical spectrum. Reliance solely on infection-based warning signs may miss up to 25% of IEI cases [11]. In addition to the traditional 10 warning signs, several other red flag features are now recognized as key indicators of possible IEI. These include autoimmune manifestations, hematologic or oncologic disorders, chronic dermatitis or eczema refractory to standard therapy, chronic diarrhea or enteropathy, and lymphadenopathy or splenomegaly [Table 1 B,D] [12]. Laboratory findings such as persistent lymphopenia or hypogammaglobulinemia, as well as syndromic features (i.e., dysmorphism or congenital heart defect) should raise further suspicion [13].

When IEI are suspected, secondary causes of immunodeficiency must be excluded, and the patient should be referred for targeted immunologic evaluation. IEI affects patients across their lifespan. Large real-world registry data from European Society for Immunodeficiencies (ESID), analyzing 16,486 patients, demonstrate that while two-thirds of patients with IEI present before age 6 years, approximately one-quarter of patients develop initial symptoms only as adults. Infection was the most frequent initial presenting manifestation of IEI. Different initial

Table 1. Inborn errors of immunity warning signs

A	Warning signs: pediatric
1	Four or more new ear infections within 1 year
2	Two or more serious sinus infections within 1 year
3	Two or more months on antibiotics with little effect
4	Two or more pneumonias within 1 year
5	Failure of an infant to gain weight or grow normally
6	Recurrent, deep skin or organ abscesses
7	Persistent thrush in mouth or fungal infection on skin
8	Need for intravenous antibiotics to clear infections
9	Two or more deep-seated infections including septicemia
10	A family history of IEI

B	Additional pediatric warning signs
1	Autoimmunity (i.e., autoimmune cytopenias, endocrinopathies, enteropathies)
2	Hematologic or oncologic disorders (i.e., lymphoproliferation, lymphoma, leukemia, persistent unexplained cytopenias)
3	Severe or refractory eczema
4	Severe or multiple allergies
5	Chronic diarrhea or gastrointestinal symptoms
6	Laboratory abnormalities (i.e., persistent lymphopenia, hypogammaglobulinemia)
7	Syndromic features (i.e., dysmorphic features, congenital heart disease)

C	Warning signs: adult
1	Two or more new ear infections within 1 year
2	Two or more new sinus infections within 1 year, in the absence of allergy
3	One pneumonia per year for more than 1 year
4	Chronic diarrhea with weight loss
5	Recurrent viral infections (colds, herpes, warts, condyloma)
6	Recurrent need for intravenous antibiotics to clear infections
7	Recurrent, deep abscesses of the skin or internal organs
8	Persistent thrush or fungal infection on skin or elsewhere
9	Infection with normally harmless tuberculosis-like bacteria
10	A family history of IEI

D	Additional adult warning signs
1	Unexplained cytopenias (autoimmune hemolysis, ITP, neutropenia)
2	Refractory eczema/dermatitis (adult-onset or severe)
3	Chronic diarrhea/enteropathy with weight loss
4	Lymphadenopathy/splenomegaly or unexplained lymphoproliferation
5	Recurrent or severe viral infections (warts, herpes), or opportunistic infections
6	Family history suggestive of IEI, late diagnoses, or consanguinity

IEI = inborn errors of immunity, ITP = immune thrombocytopenia

manifestations were observed in specific age groups: 10% presented with syndromic features as the sole manifestation in the first 6 years of life. Between 6 and 25 years of age, approximately 25% of patients initially presented with immune dysregulation (with or without infection). IEI patients older than 30 years 80% presented with infection without immune dysregulation. There is also a sex-based shift, with male predominance until age 10 years, transition to female predominance after age 40 years [7].

Adult-onset IEI may result from several mechanisms: hypomorphic variants with residual protein function, variable penetrance influenced by environmental or epigenetic factors, or somatic mosaicism. Common adult-onset phenotypes include antibody deficiency with recurrent sinopulmonary infections, immune dysregulation with autoimmune cytopenia or lymphoproliferation and chronic inflammatory or enteropathy phenotypes. Clinicians should recognize that warning signs in adults differ from those in children [Table 1].

The traditional Jeffrey Modell foundation warning signs were developed primarily for pediatric populations and have reduced sensitivity in adults (fewer than 45% of adults with IEI present with more than 2 warning signs, compared to 64% sensitivity in children) [11,12]. While pediatric patients more commonly present with failure to thrive, recurrent pneumonia and serious bacterial infections, adults more frequently present with recurrent sinusitis, chronic diarrhea with weight loss, and recurrent viral infections. Additional adult-specific red flags include unexplained cytopenia, refractory eczema or dermatitis, bronchiectasis, and persistent lymphadenopathy [13]. Importantly, the absence of a positive family history should not exclude consideration of IEI. Although the severity of a genetic defect determines molecular dysfunction, incomplete penetrance is common in many disorders, particularly those affecting innate immunity, immune dysregulation and autoinflammation IEI. Family members carrying identical pathogenic variants may exhibit discordant clinical phenotypes due to environmental factors, pathogen exposure and modifier genes [14].

INBORN ERRORS OF IMMUNITY REPRESENT A HETEROGENEOUS GROUP OF MORE THAN 550 GENETIC DISORDERS, ENCOMPASSING BOTH INFECTIOUS AND NON-INFECTIOUS MANIFESTATIONS ACROSS ALL AGE GROUPS. APPROXIMATELY 25% OF PATIENTS PRESENT WITHOUT INFECTION-RELATED SYMPTOMS.

UPDATED IEI CLASSIFICATION

The 2024 IUIS classification recognizes ten main categories of IEI [9,10], organized according to underlying immune mechanism and clinical phenotype. For non-immunologists, the updated IUIS groups IEI by which part of the immune system is predominantly dysfunctional. Each category has characteristic clinical presentations and first-line diagnostic tests [Table 2]:

- Combined T-cell and B-cell defects (i.e., severe combined immunodeficiency/ combined immunodeficiency [SCID/CID]). Patients present with severe infections in early infancy, failure to thrive, chronic diarrhea, and opportunistic infections such as *Pneumocystis jirovecii* pneumonia or disseminated BCG. The first-line diagnostic test is lymphocyte subsets showing absent or profoundly reduced T cells.
- Syndromic immunodeficiencies (i.e., DiGeorge syndrome, ataxia-telangiectasia, Wiskott-Aldrich syndrome). Immunodeficiency occurs alongside characteristic non-immune features. DiGeorge syndrome presents with hypocalcemia, cardiac defects, and characteristic facies. Ataxia telangiectasia presents with cerebellar ataxia with oculocutaneous telangiectasia. Wiskott-Aldrich syndrome presents with thrombocytopenia, eczema, and recurrent infections. The first-line diagnostic testing varies by syndrome, for example, platelet count and size for WAS and array comparative genomic hybridization (CGH) for DiGeorge syndrome.
- Predominant antibody deficiencies (i.e., common variable immunodeficiency [CVID] and X-linked agammaglobulinemia [XLA]). Characterized by recurrent sinopulmonary infections, chronic lung disease and gastrointestinal infections. First-line testing is quantitative immunoglobulins (IgG, IgA, IgM).
- Immune dysregulation disorders (i.e., CTLA4 haploinsufficiency or LRBA deficiency, ALPS, IPEX). Autoimmunity and lymphoproliferation are the dominant features, including autoimmune cytopenias, enteropathy, endocrinopathy and lymphadenopathy/splenomegaly.
- Phagocyte defects (i.e., chronic granulomatous disease). Characterized by deep-seated bacterial and fungal infections, granuloma formation, and infection with catalase-positive organisms. The first-line test is the dihydrorhodamine flow cytometry for detection of the oxidative burst.
- Intrinsic/innate immune defects (i.e., Mendelian susceptibility to mycobacterial disease [MSMD], TLR signaling defects). These diseases present with selec-

tive susceptibility to specific pathogens. Specifically, MSMD present with severe mycobacterial infections including BCG-osis. The first-line diagnostic test is the IFN-γ/IL-12 pathway analysis.

- Autoinflammatory diseases (i.e., inflammasome- or interferon-driven syndromes such as familial Mediterranean fever and interferonopathies). These patients present with episodic or chronic sterile inflammation with fever, dermatitis, arthropathy and serositis without high-titer autoantibodies. The first-line diagnostic tests are inflammatory markers (CRP and SAA) and genetic testing.
- Complement deficiencies (i.e., C3 deficiency, terminal complement defects, hereditary angioedema). Presentation includes invasive bacterial *Neisseria* infections with late completement defects, autoimmunity with early complement defects and recurrent angioedema with C1-INH defects.
- Bone marrow failure syndromes with immunodeficiency (i.e., GATA2 deficiency, telomere biology disorders). This category of patients will present with cytopenias, myelodysplasia, and immunodeficiency. GATA2 deficiency may present with monocytopenia, mycobacterial/fungal infections, or MDS/AML. The first-line diagnostic test is a CBC and bone marrow evaluation.
- Phenocopies of IEI (i.e., anti- IFN- γ autoantibodies, anti-GM-CSF autoantibodies) These conditions are acquired and mimic genetic IEI. Anti-IFN-γ autoantibodies cause disseminated mycobacterial infections in previously healthy adults. The first-line diagnostic test are autoantibodies.

The 2024 update reflects important conceptual shifts. First, there is increasing recognition that immune dysregulation, not just infection susceptibility, is a cardinal feature in many IEI. Disorders affecting regulatory T cell function (CTLA-4, LRBA), interferon signaling pathways, and defects in intracellular signaling now constitute a substantial proportion of newly described IEI. Second, traditional boundaries separating immunodefi-

Table 2. Inborn errors of immunity classification

(1) Immunodeficiencies affecting cellular and humoral immunity
T-B+ SCID, T-B- SCID, CID, generally less profound than SCID
(2) Combined immunodeficiencies with syndromic features
Immunodeficiency with congenital thrombocytopenia, DNA repair defects, thymic defects with additional congenital anomalies, immunoosseous dysplasias, syndromes associated with elevated IgE and/or atopic disease, defects of vitamin B12 and folate metabolism, anhidrotic ectodermodysplasia with immunodeficiency, calcium channel defects, other defects
(3) Predominantly antibody deficiencies
(4) Diseases of immune dysregulation
FHL syndromes, HLH syndromes associated with hypopigmentation, regulatory T-cell defects, disorders of autoimmunity with or without lymphoproliferation, immune dysregulation with colitis, autoimmune lymphoproliferative syndromes, and disorders associated with susceptibility to EBV and lymphoproliferative disease
(5) Congenital defects of phagocytes
Congenital neutropenia, defects of motility, defects of respiratory burst, other nonlymphoid defects
(6) Defects in intrinsic and innate immunity
MSMD, epidermodysplasia verruciformis (HPV), predisposition to severe viral infection, HSE, predisposition to invasive fungal diseases, predisposition to mucocutaneous candidiasis, TLR signaling pathway deficiency, other IEI related to nonhematopoietic tissues, other IEI related to leukocytes
(7) Autoinflammatory diseases
Type 1 interferonopathies, defects affecting the inflammasome, non-inflammasome–related conditions
(8) Complement deficiencies
(9) Bone marrow failure syndromes
(10) Phenocopies and autoantibody-mediated IEI mimics
Associated with somatic mutations, associated with autoantibodies

CID = combined immunodeficiency, EBV = Epstein-Barr virus, FHL = familial hemophagocytic lymphohistiocytosis, HPV = human papillomavirus, HSE = Herpes simplex encephalitis, IEI = inborn errors of immunity, MSMD + Mendelian susceptibility to mycobacterial disease, SCID = severe combined immunodeficiency, TLR = toll-like receptors

ciency, autoinflammation, and syndromic disease have been blurred, as many genes with biological functions beyond classical immune lineages can cause immune dysfunction. A critical implication is that genotypes do not reliably predict phenotypes. Individuals carrying pathogenic variants in the same IEI gene may present with markedly different clinical manifestations. For example, CTLA-4 haploinsufficiency, classified under disorders of immune dysregulation, may present primarily with features of combined immunodeficiency (T-cell dysfunction and hypogammaglobulinemia requiring immunoglobulin replacement therapy), predominant autoimmunity (autoimmune cytopenia, enteropathy or endocrinopathy), lymphoproliferative disease (lymphadenopathy, splenomegaly, or lymphocytic organ infiltration), or severe neuroinflammation (demyelinating lesions mimicking multiple sclerosis).

Similarly, GATA2 deficiency demonstrates marked phenotypic diversity. GATA2 patients may present with recurrent disseminated mycobacterial infection, severe human papillomavirus infections with malignant transformation, bone marrow failure with myelodysplastic syndrome, primary lymphedema, pulmonary alveolar proteinosis, or even inflammatory bowel disease enteropathy [15,16]. This phenotypic heterogeneity reflects the influence of variant type, inheritance pattern, incomplete penetrance (only 67% of CTLA-4 mutation carriers develop clinical disease; some GATA2 mutation carriers remain asymptomatic despite harboring pathogenic variants), variable expressivity and likely additional genetic or environmental modifiers [Table 3]. The age of onset is similarly unpredictable, ranging from early childhood to the sixth decade of life for CTLA-4 deficiency, and from ages 3 to 80 years for GATA2 deficiency, with most GATA2 presentation occurring between adolescence and early adulthood [17].

This classification underscores the complexity of IEI and the importance for mechanism-based rather than purely phenotype-based diagnosis and management. Recognizing the underlying immune pathway defects, rather than simply cataloging clinical features, enables targeted therapies and prognosis assessment and genetic counseling.

EARLY IDENTIFICATION OF THE UNDERLYING DEFECT ENABLES PRECISION-BASED THERAPIES SUCH AS TARGETED BIOLOGICS, JAK INHIBITORS, HEMATOPOIETIC STEM CELL TRANSPLANTATION, AND GENE THERAPY, WHICH CAN SIGNIFICANTLY IMPROVE PATIENT OUTCOMES.

IEI DIAGNOSIS

The diagnosis of IEI has evolved over the past two decades, from descriptive phenotyping to mechanistic precision medicine, fundamentally changing how clinicians approach these disorders. Rather than relying solely on clinical presentation to guide empiric therapy, contemporary practice integrates molecular diagnosis with functional immune pathway analysis to select targeted interventions that address the specific defect. This mechanism-driven framework has transformed IUIS classification, which now prioritizes immune pathway dysfunction over phenotype alone, directly linking diagnosis to pathway-directed treatment.

The evaluation of a patient with suspected IEI begins with a comprehensive clinical assessment. Key historical features include recurrent or unusually severe infections, infections requiring prolonged or repeated antibiotic courses, poor response to standard antimicrobial therapy, and infections caused by opportunistic or atypical

Table 3. Mechanisms of disease in inborn errors of immunity

Example	Mechanism	Genetic mechanism
ADA (SCID), BTK (XLA)	Protein loss of function	Loss of function
STAT1-GOF, STAT3-GOF	Protein gain of function	Gain of function
CARD11 DN, PIK3CD DN	The mutant protein decreases the activity of the normal protein	Dominant-negative
CTLA4, GATA2	One copy of the gene is not sufficient, for normal activity of the protein, biallelic expression is needed	Haploinsufficiency
VEXAS (UBA1), NLRC4	Somatic mutation, not heritable	Somatic mutation

ADA = adenosine deaminase deficiency, BTK = Bruton's tyrosine kinase, CARD11 = caspase recruitment domain family member 11, CTLA4 = cytotoxic T-lymphocyte-associated protein 4, GATA2= GATA-binding factor 2, GOF = gain of function, SCID = severe combined immunodeficiency, XLA = X-linked agammaglobulinemia

pathogens. Additional red flags include failure to thrive, chronic diarrhea, persistent lymphadenopathy or hepatosplenomegaly, recurrent or early-onset autoimmunity, severe atopy, and a positive family history of immunodeficiency, early infant deaths, or consanguinity. On physical examination, findings such as growth delay, absent or hypoplastic tonsils and lymph nodes, chronic skin or mucosal infections, severe eczema, oral candidiasis beyond infancy, dysmorphic features, or clubbing may suggest involvement of specific immune pathways [Table 4]. Recognition of these features is essential, as they often precede abnormal laboratory findings and should prompt targeted immunological evaluation [17,18].

An exclusive focus on infection-centered warning signs would miss approximately 25% of patients with IEI who initially present with other manifestations [7]. Initial laboratory screening remains the cornerstone of investigation. A complete blood count with differential, quantitative immunoglobulins (IgG, IgA, IgM), and lymphocyte subset analysis (CD3, CD4, CD8, CD19, CD16/56) together provides a broad overview of immune system integrity. Complement activity (CH50 for classical pathway, AH50 for alternative pathway) can reveal complement defects.

These first-line studies are essential both to identify classical immune deficiencies and to determine whether more advanced testing is indicated. When the clinical picture or initial results suggest an immune defect, functional assays are used to evaluate the quality of immune responses. These assessments may include vaccine-specific antibody production (i.e., responses to pneumococcal polysaccharide, tetanus, diphtheria), lymphocyte proliferation or activation, neutrophil oxidative burst by dihydrorhodamine testing, NK cell cytotoxicity, and analysis of thymic output using T-cell receptor excision circle (TREC) copies. In selected cases, T-cell receptor repertoire studies can reveal restricted diversity or clonal expansion. Advanced functional assays are increasingly applied to define the molecular mechanism underlying disease. Phospho-flow cytometry allows direct evaluation of signal transduction through pathways such as JAK–STAT, NF-κB, and PI3K. Other mechanistic studies assess apoptosis, activation-induced cell death, or intracellular protein expression, for example, loss of CTLA-4, LRBA, DOCK8, or WASP expression.

These pathway-level analyses bridge the gap between genotype and cellular function, often confirming the relevance of candidate variants detected by genetic sequencing. Newborn screening (NBS) has become a transformative tool for the early identification of selected life-threatening IEI, most notably SCID through TREC quantification. In Israel, national implementation of NBS was initiated in 2015, enabling presymptomatic identification of affected infants. Over the first 5 years of Israel's national newborn screening program for SCID, 937,953 newborn samples were screened and 32 infants with SCID were identified, corresponding to an incidence of approximately 1 in 29,000 births. This incidence is higher than that reported in many Western populations and may be attributable, at least in part, to the higher prevalence of consanguineous marriages and founder variants in specific Israeli populations [19].

Notably, no SCID cases were missed during this period. Among the 32 infants diagnosed with SCID, 22 underwent HSCT, achieving a 91% survival rate. These outcomes underscore that early detection through NBS facilitates timely referral, implementation of protective measures, and definitive therapy, thereby markedly improving survival and prognosis for SCID patients [19]. Genetic evaluation, including targeted gene panels, whole-exome sequencing, or whole-genome sequencing, has become integral to the modern diagnostic process.

Table 4. Age of onset and typical clinical manifestations of inborn errors of immunity

Age	IEI syndromes	Typical clinical manifestations
Infancy	SCID, HLH	Severe infections, failure to thrive
Early childhood	IPEX, *CTLA4*	Diabetes, rash, chronic diarrhea
School age	ALPS	Recurrent infections, anemia, lymphoproliferation, diarrhea
Adolescence	STAT3-GOF	Autoimmunity, psoriasis, pancytopenia
Adult onset	CVID	Recurrent sinopulmonary infections, recurrent infections, lymphoproliferation

ALPS = autoimmune lymphoproliferative syndrome, *CTLA4* = cytotoxic T-lymphocyte-associated protein 4, CVID = common variable immunodeficiency, HLH = hemophagocytic lymphohistiocytosis, IEI = inborn errors of immunity, IPEX = immune dysregulation, polyendocrinopathy, enteropathy X-linked, SCID = severe combined immunodeficiency, STAT3-GOF = STAT3 gain-of-function, TLR = toll-like receptors

Given the wide variability in clinical presentation and substantial phenotypic overlap among syndromes, genetic testing is increasingly pursued early when suspicion of IEI is high, rather than being reserved as a final confirmatory step. The diagnostic yield depends on the sequencing strategy and the population studied. Targeted next-generation sequencing panels yield a diagnosis in approximately 24–56% of pediatric patients and 9–32% of unselected cohorts, whereas WES has an average yield of approximately 38% and may also identify novel disease-causing genes. The yield of WES is generally higher in pediatric cohorts and in selected IEI categories, particularly immune dysregulation and phagocyte disorders [20,21].

DIAGNOSIS OF INBORN ERRORS OF IMMUNITY REQUIRES AN INTEGRATED, MECHANISM-BASED APPROACH THAT INCLUDES CLINICAL EVALUATION, TARGETED IMMUNOLOGIC TESTING, AND MOLECULAR GENETIC ANALYSIS. FUNCTIONAL ASSAYS BRIDGE GENOTYPE AND PHENOTYPE, CONFIRMING PATHOGENICITY AND GUIDING THERAPY SELECTION.

Immune dysfunction may also arise in the context of chromosomal abnormalities and copy number variations. Chromosomal disorders with immune involvement are increasingly recognized as syndromic immune dysregulation states rather than classical primary immunodeficiencies. In these conditions, immune abnormalities may include combined defects of innate and adaptive immunity, immune dysregulation, and increased susceptibility to infections and autoimmunity, partially overlapping with mechanisms observed in monogenic IEI. In this context, chromosomal microarray analysis plays an important diagnostic role, enabling the detection of pathogenic copy number variants underlying syndromic immune phenotypes, developmental delay, dysmorphism, or congenital anomalies, and should be considered an integral component of the genetic evaluation in selected patients with suspected IEI.

However, genetic and molecular findings must always be interpreted in the context of the clinical and immunologic phenotypes. Modern diagnostic strategies increasingly combine genomic analysis with functional immune assays to define the underlying mechanism which then directly informs therapy selection. Functional validation remains essential for variants of uncertain significance, hypomorphic mutations, or conditions with variable expressivity. Well established functional studies that demonstrate a deleterious effect of a variant provide strong evidence for pathogenicity, whereas absence of such an effect argues that the variant is benign. In many cases, definitive variant analysis requires detailed mechanistic studies available only in research laboratories, including flow cytometry for protein expression and phosphorylation, immunoblotting or transgenic mouse models. Identification of the precise molecular defect can directly guide targeted therapy. Recognition of STAT1 or STAT3 gain-of-function mutations has enabled the use of JAK inhibitors such as ruxolitinib or baricitinib to restore cytokine signaling balance, with overall improvement of clinical symptoms in 87% of STAT1 gain-of-function and 90% of STAT3 gain-of-function patients [21].

Patients diagnosed with CTLA-4 or LRBA deficiency benefit from Abatacept (CTLA4-Ig) to replace the missing regulatory pathway, while those with PI3Kδ-activating mutations (APDS) may respond to selective PI3Kδ inhibition with drugs such as leniolisib. Similarly, the discovery of IL-1 or interferon-pathway dysregulation in autoinflammatory and type-I interferonopathies has led to successful use of IL-1 blockade or JAK inhibition, respectively.

These examples illustrate how defining the molecular mechanism transforms IEI management from empiric immunosuppression to mechanism-based precision therapy. The diagnostic process in IEI is inherently dynamic. By integrating phenotype, immune function, and genotype, clinicians move beyond syndromic labels toward mechanism-based classification. This approach not only improves diagnostic precision but also aligns treatment with the disrupted pathway, whether through targeted cytokine inhibition, immune reconstitution, or hematopoietic stem cell transplantation [22].

SUMMARY AND SYSTEMIC RECOMMENDATIONS

The field of IEI has transformed over the past decade from a collection of rare pediatric syndromes into a dynamic and clinically relevant discipline central to modern medicine. Today, pediatricians, immunologists, hematologists, geneticists, and primary care physicians collaborate in the recognition, diagnosis, and management of these disorders. Advances in molecular diagnostics and personalized medicine have enabled precise, mechanism-based treatments that improve outcomes and long-term quality of life. Therapeutic breakthroughs, including hematopoietic stem cell transplantation, targeted biologics, gene therapy [23], and engineered T-cell approaches have fundamentally altered prognosis for many patients. IEI now stands at the intersection of immunology, genetics, and translational medicine, exemplifying how scientific discovery can be directly translated into individualized patient care.

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Capsule

Extended dual antiplatelet therapy for multivessel coronary artery disease

In this multicenter randomized trial, **Tian** et al. studied whether extending dual antiplatelet therapy (DAPT) beyond the conventional treatment period provides additional protection in patients with multivessel coronary artery disease following coronary revascularization. Patients were assigned either to prolonged DAPT or to standard-duration therapy. The primary endpoint was the occurrence of major adverse cardiovascular events. Extended DAPT significantly reduced the incidence of cardiovascular death, myocardial infarction, and ischemic stroke compared with standard-duration treatment. The benefit was particularly evident among patients with diffuse coronary disease and high ischemic risk. Although prolonged therapy increased the frequency of clinically relevant bleeding events, severe or fatal bleeding remained uncommon, resulting in a favorable overall balance between ischemic protection and bleeding risk in appropriately selected patients.

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