The Ever-evolving Landscape of Inborn Errors of Immunity

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Inborn errors of immunity (IEI) result from pathogenic germline variants. These disorders are clinically characterized by increased susceptibility to infections and immune dysregulation, often leading to reduced survival [1]. By linking specific monogenic defects to immune phenotypes, IEI serve as experiments of nature that provide powerful models for dissecting human immunology [2]. The International Union of Immunological Societies (IUIS) currently classifies IEI into 10 major categories with overlapping phenotypes [3]: combined T- and B-cell immunodeficiencies, combined immunodeficiencies with syndromic features, predominantly antibody deficiencies, diseases of immune dysregulation, congenital defects of phagocytes, defects in intrinsic and innate immunity, autoinflammatory diseases, complement deficiencies, bone marrow failure, and phenocopies of IEIs. The recent 2024 IUIS update was designed to serve clinicians and researchers and to inform the design of targeted sequencing panels that facilitate the genetic diagnosis of IEI. It lists 508 genes underlying 559 conditions [3]. Of note, molecular, cellular, and clinical investigations of IEI have transformed our understanding of disease pathogenesis and enabled effective targeted therapies.

In this issue of the *Israel Medical Association Journal* (*IMAJ*), which is dedicated to IEI, we have assembled a collection of articles that reflects the breadth of the field, spanning genetics, immunology, diagnostics, and clinical care. We present a comprehensive overview of the IEI field, including original research and case reports, representing the different IEI categories as well as reviews on important themes, to make this broad domain accessible to all physicians, as clinicians across different specialties may encounter patients with manifestations of IEIs.

The original research study by Mandola et al. [4] on tricho-hepato-enteric syndrome represents a typical example of a syndromic IEI category. Different types of syndromes are associated with IEI, including syndromes with congenital thrombocytopenia, DNA repair defects, thymic defects with additional congenital anomalies, immuno-osseous dysplasias, syndromes associated with elevated IgE and/or atopic disease, defects of vitamin B12 and folate metabolism, anhidrotic ectodermodysplasia with immunodeficiency, calcium channel defects, and other non-specified defects. By reporting on two patients with tricho-hepato-enteric syndrome, each carrying different genetic defects, Mandola and colleagues highlighted the disease as a prototypic RNA-metabolism-related disorder linking epithelial dysfunction, inflammation, and immune dysregulation. They ended by suggesting that clinicians should consider a syndromic IEI when features of immune deficiency, such as recurrent infections, chronic inflammation, or autoimmunity, coexist with extra-immune manifestations including gastrointestinal disease, liver dysfunction, hair or skin abnormalities, dysmorphic features, or growth failure.

Somech and Grunebaum [5] present a perspective on how recent scientific advances and emerging technologies are reshaping the diagnosis and management of IEI. The authors argued that these developments require corresponding changes in medical education and professional training to prepare future clinicians for the increasing complexity of IEI care. They emphasized that the next generation of immunologists should be equipped with both strong immunological expertise and translational

medicine skills to optimize the diagnosis and management of patients with IEI.

Bone marrow failure syndromes comprise a diverse group of inherited disorders characterized by defective hematopoiesis. Among these conditions, dyskeratosis congenita (DC) is a severe multisystem disorder caused by defects in telomere maintenance. In a study by Somekh et al. [6], the authors reported the genetic and immunological characterization of a 2-year-old patient with DC who presented with failure to thrive and pancytopenia. Whole-exome sequencing identified a homozygous pathogenic variant in *TERT*. The study further included a functional assessment of telomere biology using a flow-FISH assay, which demonstrated marked telomere shortening in the patient cells compared with healthy controls.

Another noteworthy original study by Benor and colleagues [7] presents a single-center retrospective analysis of patients with granulomatous lymphocytic interstitial lung disease (GLILD) associated with common variable immunodeficiency (CVID). CVID is characterized by hypogammaglobulinemia, recurrent infections, and varying degrees of immune dysregulation. In addition to autoimmune manifestations, GLILD is a well-recognized noninfectious pulmonary manifestation that can lead to progressive lung dysfunction, highlighting the importance of early recognition and diagnosis. The authors described the clinical features of five patients with GLILD-CVID and provided detailed immunological profiling for four of them. Although multi-organ involvement was observed, no patients had significant gastrointestinal manifestations. Immunophenotyping demonstrated expanded $CD21^{low}$ B-cell populations in three patients, whereas all four evaluated individuals exhibited reduced numbers of naïve $CD4^+$ and $CD8^+$ T cells. These findings suggest that such immunological markers may serve as useful tools for the early identification and risk stratification.

This issue if *IMAJ* also presents several interesting case reports. Autoinflammatory disorders are subclassified into interferonopathies, inflammasome-related disorders, and non-inflammasome-related conditions. From this category, Lassman and co-authors [8] presented a case of familial STING disorder. The STING (stimulator of interferon genes) autoinflammatory disorder is medically known as SAVI (STING-associated vasculopathy with onset in infancy). It can be inherited in either an autosomal dominant or an autosomal recessive mode. The responsible gene for this disorder, *TMEM173*, is known to activate both the NF-kB and IRF3 transcription pathways to induce the expression of an interferon genetic signature. Clinical manifestations suggestive or autoinflammation include recurrent fevers, early-onset rash and skin vasculopathy, inflammatory lung disease, polyarthritis, presence of autoantibodies, increased inflammatory markers, intracranial calcification, and familial chilblain lupus.

The most severe type of inborn error of immunity is severe combined immunodeficiency (SCID), which comprises a genetically heterogeneous group of disorders characterized by profound impairment of thymopoiesis and T-cell development, which is frequently accompanied by defective B-cell and/or NK-cell ontogeny and results in near-complete loss of adaptive immune competence. Timely diagnosis and definitive immune reconstitution are important as SCID without a diagnosis is associated with overwhelming susceptibility to opportunistic infections and high mortality during early infancy. Yet, diagnosis is sometimes a challenge, especially in patients with leaky mutation, which is defined as hypomorphic genetic variant. In an interesting case report, Lapidus and colleagues [9] presented an infant with compound heterozygous mutations in *DCLRE1C* caused leaky SCID phenotype yet fortunately was still detected by newborn screening.

Primary complement component deficiencies can underlie systemic hematologic disorders and should be considered when there is a high suspicion of an IEI. Illustrating this association, Kristal and co-authors [10] described a 6-month-old infant who was born to consanguineous parents and presented with atypical hemolytic uremic syndrome. Exome sequencing, followed by multiplex ligation-dependent probe amplification (MLPA), identified a pathogenic variant in *CFH* causing complement factor H (CFH) deficiency. Notably, serum CFH levels were within the normal range, suggesting a functional defect rather than a quantitative deficiency. The patient was ultimately treated with eculizumab, resulting in improved hemoglobin levels and discontinuation of antihypertensive therapy.

In addition, this special issue of *IMAJ* features an intriguing case report of an 8-month-old girl presenting with recurrent sinopulmonary infections, bronchiectasis, agammaglobulinemia, and hearing loss. Keren David and colleagues [11] described the comprehensive investigation of the underlying cause of the patient's disease. Given the absence of a pathogenic variant in the *BTK* gene, the authors discussed both autosomal recessive and autosomal dominant forms of agammaglobulinemia, highlighting the expanding spectrum of genetic etiologies. Notably, the patient exhibited markedly reduced numbers

of class-switched memory B cells. Although a definitive genetic diagnosis has not yet been established, this report illustrates the complexity of diagnosing patients with atypical presentations of agammaglobulinemia.

Last, several informative review articles are included in this issue of *IMAJ*. An important review by Toker et al. [12] provides a comprehensive introduction to IEI from an immunologist's perspective. Beyond defining IEI, the authors described the key clinical red flags that should prompt suspicion of these disorders, placing particular emphasis on noninfectious manifestations that are often overlooked in routine clinical practice. They also presented a detailed overview of the updated IUIS classification and summarized the immunological investigations currently available for diagnostic evaluation. The review equips clinicians with practical tools for recognizing IEI and facilitates timely diagnosis and appropriate patient management.

Matza-Porges and co-authors [13] reviewed IEI from the perspective of clinical genetics. They outlined the diverse genetic mechanisms underlying IEI and discussed the molecular diagnostic approaches currently used in routine clinical practice. The authors covered techniques ranging from Sanger sequencing to whole-genome sequencing and examined the strengths and limitations of each method. They also presented a practical diagnostic algorithm to guide clinicians, immunologists, and other healthcare professionals in selecting the most appropriate genetic testing strategy for patients with suspected IEI.

Finally, expanding the overview of immune system disorders, Frizinsky et al. [14] presented a comprehensive review of inborn disorders of neutrophil function. Using the case of a patient with chronic granulomatous disease, the authors broaden the discussion to encompass both inherited and acquired neutrophil disorders. They classify these conditions according to the underlying mechanism of neutrophil dysfunction, including defects in migration, impaired respiratory burst activity, and abnormal neutrophil extracellular trap formation. The review provides a thorough overview of the clinical manifestations associated with neutrophil dysfunction, together with current diagnostic approaches and available treatment strategies.

CONCLUSIONS

The diagnosis and management of patients with IEI extend well beyond the fields of immunology and genetics. We hope this special issue will enhance the awareness of clinicians of IEI, broaden their understanding of these complex disorders, and facilitate the application of the diagnostic and clinical principles presented herein to everyday practice.

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References

1. Kindle G, Alligon M, Albert MH, et al. Inborn errors of immunity: manifestation, treatment, and outcome-an ESID registry 1994-2024 report on 30,628 patients. *J Hum Immun* 2025; 1 (3): e20250007.
2. Notarangelo LD, Bacchetta R, Casanova JL, Su HC. Human inborn errors of immunity: an expanding universe. *Sci Immunol* 2020; 5 (49): eabb1662.3.
3. Poli MC, Aksentijevich I, Bousfiha AA, et al. Human inborn errors of immunity: 2024 update on the classification from the International Union of Immunological Societies Expert Committee. *J Hum Immun* 2025; 1 (1): e20250003.
4. Mandola AB, Frizinsky S, Somech I, Naor S, Somech R. Tricho-hepatoenteric syndromic immunodeficiency: clinical spectrum, pathobiology, and emerging therapies. *IMAJ* 2026; 28 (8): 487-93.
5. Somech R, Grunebaum E, Redefining expertise: preparing the next generation of physicians caring for patients with inborn errors of immunity. IMAJ 2026; 28 (8): 484-6.
6. Somekh I, Mandola AB, Frizinsky S, et al. Bone marrow failure syndromes: *TERT*-associated dyskeratosis congenita. *IMAJ* 2026; 28 (8): 494-9.
7. Benor S, Hentschel F, Freund T, Hagin D. Granulomatous lymphocytic interstitial lung disease in common variable immunodeficiency. *IMAJ* 2026; 28 (8): 500-7.
8. Lassman S, Reiter J, Matza-Porges S, Berkun Y. A familial STING: a father and daughter journey to SAVI diagnosis. *IMAJ* 2026; 28 (8): 508-10.
9. Lapidus T, Lev A, Barel O, Somech R. Compound Heterozygous mutations in *DCLRE1C* caused leaky SCID phenotype. *IMAJ* 2026; 28 (8): 511-13.
10. Kristal E, Arotzker S, Geylis M, Elamour S, Ling G, Schreiber R. Alternative pathway complement dysregulation in atypical HUS: a case communication. *IMAJ* 2026; 28 (8): 514-16.
11. Keren David L, Dalal I, Ovadia A. Unusual case of agammaglobulinemia. *IMAJ* 2026; 28 (8): 517-19.
12. Toker O, Eisenberg R, Introduction to inborn errors of immunity. *IMAJ* 2026; 28 (8): 520-27.
13. Matza-Porges S, Shamriz O, The genetic basis of inborn errors of immunity: a clinical guide. *IMAJ* 2026; 28 (8): 528-34.
14. Frizinsky S, Mandola AB, Rechavi E, Somekh I, Somech R. Inborn neutrophil disorders: a unique case of chronic granulomatous disease and a review of the literature. *IMAJ* 2026; 28 (8): 535-42.