Redefining Expertise: Preparing the Next Generation of Physicians Caring for Patients with Inborn Errors of Immunity

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ABSTRACT The field of inborn errors of immunity (IEI), previously known as primary immune deficiencies, includes susceptibility to infections, autoimmunity, uncontrolled inflammation and malignancy is rapidly expanding. Novel scientific discoveries together with artificial intelligence and machine learning are transformed into advances in the diagnosis and treatment of affected patients. These changes require adjustments in the knowledge, skills and attitudes of health care providers, and particularly expert clinicians managing patients with IEI. In this perspective, we highlighted some of the educational needs that should be adapted to ensure that the next generation of physicians provide best care for those affected by IEI.

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In 1958, Hitzig and colleagues [1] described an infant with recurrent infections, absent immunoglobulins, and lymphopenia, characterized largely through clinical observation and limited laboratory testing. Initially considered a severe variant of Bruton's agammaglobulinemia [2], subsequent identification of similar cases over the following decades led to clearer delineation of the disorder and its recognition as severe combined immunodeficiency (SCID). Advances in molecular biology and human genetics subsequently transformed the field, enabling mechanistic understanding of agammaglobulinemia, SCID, and other primary immunodeficiency diseases, which are now known as inborn errors of immunodeficiency (IEI). This finding led to earlier diagnosis and the development of effective therapies including immunoglobulin replacement, hematopoietic stem cell transplantation (HSCT), and genetically based treatments [3-5]. Together, these innovations have fundamentally altered the management of patients with IEI and reshaped the knowledge, skills, and attitudes required of those who provide care for IEI. As medicine enters an era defined by genomic medicine and increasing system complexity, it is essential to reconsider how the next generation of physicians is prepared to care for individuals affected by IEI.

IEI was coined as *experiments of nature* by Dr. Robert Good, a pioneer in the field [6] and has served as an excellent window to explore fundamental immunologic mechanisms. The 2024 International Union of Immunological Societies identified 559 IEI caused by mutations in 508 genes, which were classified into 10 phenotypic and mechanistic groups associated with infection susceptibility, autoimmunity, immune dysregulation, inflammation, syndromic features, and bone marrow failure [7]. As this field is consistently growing, it is clear today that IEI is not only immunodeficiency and susceptibility to acquire infections but rather a much broader field including hyper inflammatory responses, autoimmunity, and more. Moreover, IEI pathologies are not restricted to hematopoietic cell-autonomous defects but may reflect defects in immune extra-hematopoietic organs. Thus, the new generation of physicians will have to deal with all aspects of immunity errors. Advances in high-throughput sequencing, functional immune phenotyping, and improved understanding of disease mechanisms continue to dramatically reshape the diagnosis and management of these conditions. As a result, clinicians must recognize increasingly complex clinical presentations, interpret large-scale genomic and functional data, and integrate these findings to guide personalized therapeutic decisions.

These developments challenge traditional models of medical training that had prioritized knowledge acquisition, physical examination, and individual expertise. Instead, clinicians caring for patients with IEI will need to integrate clinical judgment with data science, understand the capabilities and limitations of emerging genomics and technologies, collaborate across interdisciplinary teams, and navigate ethical decision-making in uncertain and rapidly evolving environments. As diagnostic tools improve, those affected by IEI will be identified prior to symptom onset, while broader access to genomic testing will continue to reveal new diseases and phenotypes.

Therapeutic options for IEI are also rapidly evolving to include novel indications for allogeneic and ex-vivo gene-corrected HSCT [8], sophisticated in-vivo gene editing [9], targeted small molecules [10], biologics [11], and cellular therapies [12]. The use of these approaches necessitate familiarity with advanced laboratory technologies, critical evaluation of emerging evidence, and collaboration among the clinical and research teams to guide diagnosis, monitoring, and treatment selection.

A particularly important consideration for future physicians involved in IEI is the rapid integration of artificial intelligence (AI) and machine learning (ML) into the management of these conditions [13]. Emerging studies already demonstrate the potential of AI-driven tools to improve diagnosis, risk stratification, and outcomes in IEI, including the use of predictive algorithms and automated analysis of genomic and electronic health record data [14]. These technologies shorten the diagnostic odyssey and support more precise, timely clinical decision-making. Clinicians must understand the strengths and limitations of AI systems, advocate for equitable access to high-quality and diverse datasets, and ensure that appropriate ethical, regulatory, and governance frameworks are in place. As AI becomes embedded in diagnostic and health system infrastructures, physicians play a critical role in guiding responsible implementation while maintaining clinical oversight and patient trust.

Additional developments will further shape the care for IEI over the coming decade. Prenatal testing and expansion of newborn screening beyond SCID [15] enables diagnosis and intervention before symptoms onset. In parallel, safer and efficacious HSCT with continued progress in gene addition and editing provide definitive treatment options for an increasing number of single-gene IEI. Improved survival of children with severe IEI, together with the growing recognition of IEI in adolescence, necessitate structured transition programs that bridge pediatric care to adult services [16].

Beyond IEI, clinicians with expertise in immune compromise are increasingly engaged in the expanding field of secondary immunodeficiencies [17]. Collectively, these trends further underscore the need for healthcare providers who can adapt to evolving diagnostic pathways, long-term disease management, and complex systems.

To meet the rapidly evolving challenges in IEI, clinicians will need to be proficient in immunology, genomics, and biomarker interpretation, including the ability to assess genetic variants using advanced computational tools. Fluency in emerging technologies, including AI/ML-supported diagnostics, are essential for early disease detection and precision care.

Beyond technical expertise, IEI experts need strong cognitive and translational skills, including critical thinking, data interpretation, and the ability to apply complex experimental and clinical evidence to patient care. These skills require sustained engagement with innovative research, continuous professional development, and close collaboration with medical specialties, laboratory scientists, and research teams. Equally important are the human and ethical dimensions of care. Managing chronic and complex immune disorders demands empathy, effective communication, and shared decision-making with patients and families. Given the rarity of many IEIs, participation in international networks and global data-sharing initiatives are critical to enhance knowledge, ensure equity, and improve outcomes.

Preparing the next generation of immunologists for the evolving landscape of IEI requires comprehensive educational programs that reflect the advances in diagnostics, therapies, and AI/ML integration. Training must emphasize multidisciplinary collaboration, translational research, ethical decision-making, and patient-centered care, ensuring that clinicians are equipped to deliver personalized, evidence-based management for complex immune disorders. Proficiency in laboratory techniques, genomics, and emerging functional methodologies are essential, as is the ability to critically evaluate new data and incorporate the knowledge into clinical practice.

By promoting these skills, medical education must train clinicians who are capable of leading, innovating, and adapting to a rapidly changing IEI field, ultimately improving outcomes for patients worldwide.

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I do not want art for a few, any more than education for a few, or freedom for a few.

William Morris (1834–1896), English textile designer, poet, artist, writer, and socialist activist associated with the British Arts and Crafts movement

Capsule

Genome-wide sweeps create ecological units in the human gut microbiome

The human gut microbiome contains thousands of bacterial strains that continuously evolve. In this study, **Yu** et al. analyzed large-scale global metagenomic datasets to investigate how bacterial populations change over time. The researchers found that genome-wide selective sweeps, events in which a highly fit bacterial clone rapidly replaces other members of the same species, occur much more frequently than previously recognized. These sweeps can spread internationally within only a few decades, producing epidemic-like population structures in common gut bacteria. The findings challenge the traditional view that gut bacterial evolution occurs mainly through gradual accumulation of mutations. Instead, entire bacterial genomes with advantageous traits can rapidly dominate populations across different geographic regions. The study also demonstrated that these sweeps create distinct ecological units, groups of bacteria that behave as coherent evolutionary populations despite belonging to the same species. Factors such as antibiotic exposure, dietary adaptation, bacteriophage interactions, and microbial competition likely drive these global replacement events.

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