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REVIEW ARTICLE

Human inborn errors of immunity: a quarter-century of paradigm shifts in classification, clinical phenotyping, and molecular diagnosis

Errores innatos de la inmunidad humana: veinticinco años de cambios de paradigma en clasificación, fenotipificación clínica y diagnóstico molecular

Erros inatos de imunidade em humanos: um quarto de século de mudanças de paradigma na classificação, fenotipagem clínica e diagnóstico molecular

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ABSTRACT

Introduction: inborn errors of immunity (IEI) are predominantly monogenic disorders presenting with infections, autoimmunity, autoinflammation, allergy, and malignancy. Over the last 25 years, the International Union of Immunological Societies (IUIS) Expert Committee has published 14 classification reports, tracking the field's evolution. **Objective:** to synthesize the conceptual and quantitative evolution of IEI as documented in IUIS classification reports from 1999 to 2024. **Method:** scoping review following Arksey & O'Malley's framework. We systematically searched PubMed for IUIS reports (1999–2024). Data extracted included number of recognized disorders, genetic defects, classification structure, and clinical manifestations. Clinical phenotypes were categorized as infectious, autoimmune, autoinflammatory, allergic, malignant, or non-immunological. **Results:** recognized IEI increased eightfold from 59 disorders in 1999 to 559 in 2024, arising from 508 genes plus 17 phenocopies. Three growth phases were identified: linear (1999–2005), accelerated (2005–2015), and exponential with structural consolidation (2015–2024). Major paradigm shifts included: creation of immune dysregulation and autoinflammatory tables (2005), nomenclature change to "inborn errors of immunity" (2017), and introduction of somatic mutation phenocopies (2014). In 2024, 43% of newly described IEI fall into autoinflammatory or immune dysregulation categories. Non-immunological manifestations are present in 100% of syndromic IEI and bone marrow failure syndromes. **Conclusions:** the evolution of IEI classification reflects a fundamental reconceptualization of immune dysfunction, from infection-focused deficiencies to multi-system dysregulation disorders. This framework supports pathway-based diagnosis and precision therapy, with implications for rheumatology, hematology, allergy, and neurology.

Keywords: inborn errors of immunity; primary immunodeficiency diseases; immune system diseases; immunologic deficiency syndromes; inborn genetic diseases; autoimmune diseases

RESUMEN

Introducción: los errores innatos de la inmunidad (IEI) son trastornos predominantemente monogénicos que cursan con un espectro clínico que incluye infecciones, autoinmunidad, autoinflamación, alergia y neoplasias. En 25 años, la IUIS ha publicado 14 informes de clasificación que han guiado el campo. **Objetivo:** sintetizar la evolución conceptual y cuantitativa de los IEI documentada en los informes de la IUIS desde 1999 hasta 2024. **Método:** revisión de alcance (Arksey & O'Malley) con búsqueda sistemática en PubMed de los informes oficiales (1999-2024). Se extrajeron el número de trastornos, defectos genéticos, clasificación y fenotipos clínicos, categorizados en infecciosos, autoinmunes, autoinflamatorios, alérgicos, malignos o no inmunológicos. **Resultados:** los IEI reconocidos aumentaron en ocho veces, pasando de 59 en 1999 a 559 en 2024, derivados de 508 genes y 17 fenocopias somáticas. Se identificaron tres fases de crecimiento: lineal (1999-2005), acelerada (2005-2015) y exponencial con consolidación estructural (2015-2024). Los principales cambios de paradigma incluyeron tablas específicas de desregulación y autoinflamación (2005), el cambio de nomenclatura a "errores innatos de la inmunidad" (2017) y la introducción de fenocopias (2014). En 2024, el 43 % de los nuevos IEI son de autoinflamación o desregulación. Las manifestaciones no inmunológicas afectan al 100 % de los IEI sindrómicos y a síndromes de insuficiencia medular. **Conclusiones:** la evolución de la clasificación refleja una reconceptualización fundamental, de deficiencias infecciosas a trastornos multisistémicos por desregulación. Este marco respalda el diagnóstico por vías moleculares y la terapia de precisión, con implicaciones en reumatología, hematología, alergología y neurología.

Palabras clave: errores innatos de la inmunidad; inmunodeficiencias primarias; enfermedades del sistema inmune; trastornos de la inmunidad; enfermedades genéticas innatas; autoinmunidad

RESUMO

Introdução: os erros inatos da imunidade (EII) são trastornos predominantemente monogênicos que cursam com um espectro clínico que inclui infecções, autoimunidade, autoinflamação, alergia e neoplasias. Ao longo de 25 anos, a União Internacional de Sociedades de Imunologia (IUIS) publicou 14 relatórios de classificação que orientaram o campo. **Objetivo:** sintetizar de forma abrangente a evolução conceitual e quantitativa dos EII documentada nos relatórios publicados pela IUIS desde 1999 até 2024. **Método:** revisão de escopo da literatura (Arksey & O'Malley) com uma busca sistemática na base de dados PubMed dos relatórios oficiais (1999-2024). Foram extraídos os dados referentes ao número de transtornos, defeitos genéticos, classificação e fenótipos clínicos, categorizados em infecciosos, autoimunes, autoinflamatórios, alérgicos, malignos ou não imunológicos. **Resultados:** os EII reconhecidos aumentaram em oito vezes, passando de 59 em 1999 para 559 em 2024, derivados de 508 genes e 17 fenocópias somáticas. Identificaram-se três fases de crescimento: linear (1999-2005), acelerada (2005-2015) e exponencial com consolidação estrutural (2015-2024). As principais mudanças de paradigma incluíram tabelas específicas de desregulação e autoinflamação (2005), a mudança de nomenclatura para "erros inatos da imunidade" (2017) e a introdução de fenocópias (2014). Em 2024, 43% dos novos EII são de autoinflamação ou desregulação. As manifestações não imunológicas afetam 100% dos EII sindrômicos e das síndromes de insuficiência da medula óssea. **Conclusões:** a evolução da classificação reflete uma reconceituação fundamental, de deficiências infecciosas para transtornos multissistêmicos por desregulação. Este arcabouço apoia o diagnóstico por vias moleculares e a terapia de precisão, com implicações na reumatologia, hematologia, alergologia e neurologia.

Palavras-chave: erros inatos da imunidade; doenças da imunodeficiência primária; doenças do sistema imunológico; transtornos da imunidade; doenças genéticas inatas; doenças autoimunes

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INTRODUCTION

In 1952, Colonel Ogden Bruton described an eight-year-old boy with recurrent pneumococcal infections and absent serum gamma globulins, marking the first recognized case of what would later be termed primary immunodeficiency.[1] This seminal observation initiated a field that, over the subsequent seven decades, has transformed our understanding of human immunity, from a descriptive discipline into a molecular science, capable of explaining the fundamental mechanisms of host defense, immune regulation, and the intricate interplay between genetics and clinical phenotype.

The systematic classification of these disorders began in 1970, when a committee convened by the World Health Organization established the first unified nomenclature for primary immunodeficiencies.[2,3] Later on, the International Union of Immunological Societies (IUIS) Expert Committee has published regular updates[2,4,5,6,7,8,9] on the classification of these conditions, providing a continuously evolving framework that reflects the exponential growth of knowledge in the field. These biennial reports, spanning from the turn of the millennium to the present, serve as historical documents that chart the course of our understanding of human immune system dysfunction.[4]

Over this 25-year period, the conceptual landscape has undergone profound transformations. What were once considered rare disorders defined predominantly by susceptibility to infections have been re-conceptualized as a diverse spectrum of monogenic conditions that can present virtually any manifestation of immune dysregulation: infections, autoimmunity, autoinflammation, allergy, bone marrow failure, and malignancy.[1,4,10,11,12] This shift culminated in the official change of nomenclature from "Primary Immunodeficiency Diseases" to "Inborn Errors of Immunity" (IEI) in 2017,[13] reflecting the recognition that these disorders represent fundamental errors in the genetic programming of the immune system, manifesting not only as deficiency but as dysregulation in its broadest sense.

The IUIS classification reports represent a unique longitudinal dataset, compiled by the same expert committee, using consistent methodologies across three decades. These documents offer an unparalleled opportunity to examine not only the quantitative growth of the field, but also the qualitative evolution of scientific thinking regarding immune system function, disease mechanisms, and diagnostic approaches.[4,14]

It is important to note that IUIS reports, while the most authoritative source, reflect expert consensus and may be influenced by geographical biases and the availability of diagnostic technologies. Furthermore, the criteria for including new entities have evolved, which could influence the observed growth rates.

However, the comprehensive narrative contained within these sequential reports has never been systematically synthesized. Individual analyses of each update exist, yet the field lacks an integrated overview that traces the conceptual threads connecting the foundational 1999 report to the current 2024 classification. Such a synthesis is essential for several reasons: documenting the shifting conceptual paradigms that have fundamentally altered how clinicians and researchers conceptualize immune-mediated diseases; tracing the technological drivers of discovery; understanding the evolving classification frameworks that have sought to organize increasingly complex knowledge into clinically

useful structures; and appreciating the expanding clinical spectrum of IEI, which now encompasses conditions managed by rheumatologists, hematologists, allergists, dermatologists, and neurologists, not solely immunologists.

This scoping review aims to synthesize the evolution of inborn errors of immunity as documented in the International Union of Immunological Societies Expert Committee classification reports from 1999 to 2024.

By doing so, this review aims to provide clinicians, researchers, and educators with a comprehensive understanding of how our knowledge of human inborn errors of immunity has evolved, the forces that have driven this evolution, and the current framework that underpins diagnosis and management of these complex conditions. This historical and conceptual synthesis serves not only as documentation of the field's remarkable progress but also as a foundation for anticipating future directions in the molecular diagnosis and precision therapy of immune-mediated diseases.

METHOD

This scoping review was conducted adhered to the methodological framework proposed by Arksey and O'Malley[15] in 2005 for scoping reviews, as subsequently refined by Levac, et al.[16] in 2010, which is appropriate for synthesizing a heterogeneous body of literature and identifying key concepts, gaps, and patterns across a defined topic area. Given the objective of tracing conceptual and quantitative evolution over time rather than assessing intervention efficacy, a scoping review methodology was selected over a systematic review of clinical outcomes.

The primary data sources for this review were the official classification reports published by the IUIS Expert Committee on Inborn Errors of Immunity (formerly Primary Immunodeficiency Diseases). Reports were identified through systematic search of PubMed/MEDLINE (January 1999 through December 2024) using the following search strategy:

("International Union of Immunological Societies" OR "IUIS") AND ("primary immunodeficiency" OR "inborn errors of immunity") AND ("classification" OR "update" OR "report")

No language restrictions were applied, although all of these reports are published in English.

Reports were included if they met the following criteria:

- Published as official expert classification documents.
- Reported between January 1999 and December 2024.
- Provided comprehensive enumeration of recognized IDP/IEI with associated clinical and genetic features.
- Represented the definitive version of classification for the specified year.

Excluded were preliminary reports, conference abstracts, and publications focused exclusively on phenotypic classification without listing specific genetic defects.

A data extraction form was developed to capture information systematically from each classification report. The form included the following domains:

Report characteristics:

- Publication year and citation.
- Report type (full report *versus* interim update).
- Number of recognized disorders/conditions.
- Number of identified genetic defects.
- Number of newly added genes since previous report.

Classification structure:

- Number and organization of tables.
- Subtable categories and their content.
- Nomenclature changes and their rationale.

Quantitative data:

- Total IEI counts per report.
- Distribution across tables for the most recent reports.
- Frequency of novel gene inclusions per category.

Phenotypic data (2024 Report):

- For each condition: associated features as described in the "Associated features" column.
- Categorization of manifestations as infectious, autoimmune, autoinflammatory, allergic, malignant/tumor, or non-immunological.
- Presence of multiple manifestation types per condition recorded separately.

Data extraction was performed by two reviewers, with verification through independent review of extracted data by a third reviewer to ensure accuracy and consistency. Discrepancies were resolved through discussion and consensus.

Manifestations were coded as present if explicitly described in the "Associated features" column of the published tables. For conditions where the associated features column was incomplete or referenced a previously described phenotype, the primary literature cited in the report was consulted to confirm manifestation presence.

Classification of clinical manifestations

To enable systematic analysis of phenotypic evolution, clinical manifestations were categorized using a predefined framework that reflects the expanding conceptualization of IEI:

1. Infectious manifestations: any documented increased susceptibility to bacterial, viral, fungal, or parasitic infections, including recurrent infections, infections with opportunistic pathogens, severe atypical infections, or disseminated infections. This category was coded as present when the associated features column explicitly described infection susceptibility.

2. Autoimmune/immune dysregulation manifestations: features indicative of loss of self-tolerance, including cytopenias (immune thrombocytopenia, autoimmune hemolytic anemia, neutropenia), autoimmune endocrinopathies (diabetes mellitus, thyroiditis, hypoparathyroidism), inflammatory bowel disease, autoimmune hepatitis, systemic lupus erythematosus, vasculitis, arthritis, Sjögren's syndrome, alopecia, vitiligo, and lymphoproliferation with autoantibody production.

3. Autoinflammatory manifestations: features indicative of sterile inflammation, including recurrent fevers, serositis, rash (urticarial, pustular, erythematous), arthritis (non-autoimmune), mucosal ulcers, periodic fever syndromes, macrophage activation syndrome, hemophagocytic lymphohistiocytosis, elevated acute phase reactants without identifiable infection, and interferon signature-associated conditions.

4. Allergic manifestations: features including eczema/atopic dermatitis, elevated IgE, eosinophilia, food allergies, allergic rhinitis, asthma, anaphylaxis, and other atopic conditions.

5. Malignant/tumor manifestations: documented increased risk of malignancy, including lymphoma (Hodgkin and non-Hodgkin), leukemia, solid tumors (carcinomas, sarcomas), and other neoplastic conditions.

6. Non-immunological manifestations: features involving organ systems beyond the immune system, including:

    a) Skeletal: short stature, dysplasias, fractures, scoliosis, metaphyseal abnormalities.
    b) Neurological: developmental delay, intellectual disability, ataxia, microcephaly, encephalopathy, stroke.
    c) Cardiovascular: congenital heart defects, vasculopathy, aneurysm.
    d) Dermatological: ectodermal dysplasia, albinism, hyperpigmentation, ichthyosis, alopecia.
    e) Endocrine: growth hormone deficiency, adrenal insufficiency, hypoparathyroidism.
    f) Gastrointestinal: malabsorption, hepatic veno-occlusive disease, enteropathy.
    g) Renal: nephropathy, glomerulonephritis.
    h) Ocular: cataracts, retinal dystrophy.
    i) Auditory: sensorineural hearing loss

Any other clinical sign, symptom or manifestation listed as an associated feature of IEI not encompassed by the previous categories should also be added on this one. This categorization framework was applied consistently across all conditions, with each condition coded for the presence or absence of each manifestation category based on explicit documentation in the classification tables.

Although the IUIS reports were not subjected to a formal quality assessment, since they represent expert consensus documents, it is recognized that these reports may be subject to selection bias and reflect committee priorities. To mitigate this, all published reports were included without exclusions based on quality criteria, which is consistent with the scoping review methodology.

This scoping review synthesizes published classification reports and does not involve human subjects, primary data collection, or analysis of individual patient data. Ethical approval was not required. The review adheres to principles of scientific integrity, including accurate representation of the original reports, transparent reporting of methods, and appropriate citation of sources.

RESULTS

Between 1999 and 2024, the International Union of Immunological Societies (IUIS) Expert Committee on Inborn Errors of Immunity (formerly Primary Immunodeficiencies) published 14 major classification reports, including comprehensive full reports and interim updates. These documents collectively chronicle the evolution of the field from a catalog of approximately 60 primary immunodeficiency diseases to a sophisticated classification of 559 distinct inborn errors of immunity (IEI) arising from mutations in 508 genes, complemented by 17 phenocopies due to somatic mutations or neutralizing autoantibodies (Table 1).

Table 1. Chronological Summary of IUIS Classification Reports (1999–2024)

Year	Reference	Report Type	Total Conditions	New Defects	Key Conceptual/Structural Changes
1999	Rosen et al.[17]	Full report	59	-	Classification by immune component (T cells, B cells, phagocytes, complement)
2003	Chapel et al.[18]	Update	74	15	Added conditions to tables 1, 2, 3 and 5. Recognition of CVID heterogeneity
2005	Notarangelo et al.[2]	Full report	118	44	Creation of tables for immune dysregulation (4) and autoinflammatory disorders (7).
2007	Geha et al.[5]	Full report	139	21	Expansion of innate immunity table
2009	Notarangelo et al.[3]	Full report	154	15	Introduction of frequency column; early susceptibility genes
2011	Al-Herz et al.[19]	Full report	180	71	Reordering of tables; addition of OMIM numbers
2014	Al-Herz et al.[6,20]	Full report	251	49	Introduction of "Phenocopies of PID" table
2015	Picard et al.[7]	Full report	300	54	Decision to list each defect in one table only; expansion of 9 tables
2017	Picard et al.[13]	Full report	354	34	Nomenclature change to "Inborn Errors of Immunity"; digitalization of list; expansion to 10 tables

Year	Reference	Report Type	Total Conditions	New Defects	Key Conceptual/Structural Changes
Continuation of the above table					
2019	Tangye et al.[8]	Full report	430	76	Creation of Bone Marrow Failure table; 10-table structure consolidated
2022	Tangye et al.[9]	Full report	485	55	COVID-19 discoveries; expansion of somatic mutation phenocopies
2024	Poli et al.[4]	Full report	559	67	Recognition of "multimorphic" mutations; > 40 genes with multiple entries

Quantitative growth of recognized IEI (1999–2024)

The number of recognized IEI has increased eightfold over the 25-year period examined. The growth trajectory reveals three distinct phases (Figure 1).

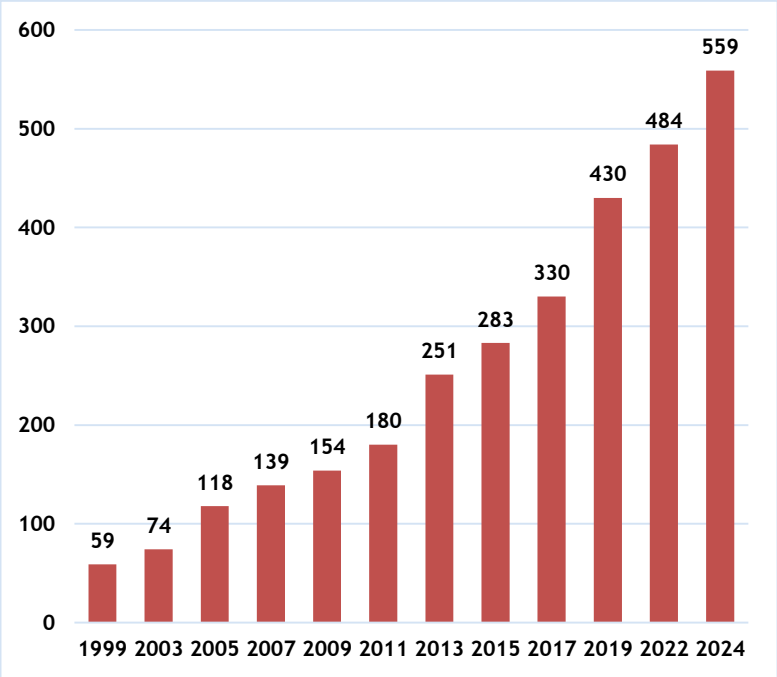

Fig 1. Cumulative growth of recognized IEI (1999 - 2024).

From 1999 to 2005: linear growth with a mean of about 20 new entities identified per biennial report. Discovery was driven by candidate gene sequencing and linkage analysis. Classification remained stable, organized by affected immune component (T cells, B cells, phagocytes, complement).

From 2005 to 2015: the growth accelerated. Discovery rate increased to approximately 30–40 new entities per report. The introduction of next-generation sequencing (NGS) technologies in 2010 marked an inflection point; nearly half of all currently known IEI-related genes were discovered after 2010. During this phase entirely new classification categories were created (immune dysregulation, autoinflammatory disorders, innate immunity disorders) to accommodate expanding phenotypic spectra.

From 2015 to 2024: exponential growth with structural consolidation. The 2017 nomenclature change to "Inborn Errors of Immunity" heralded a period of rapid gene discovery coupled with stabilization of the classification framework. The 10-table structure established in 2017 has proven sufficiently robust to absorb new discoveries without major reorganization.

Evolution of classification structure

Component-based classification. The 1999 report followed an established classification organized by the primary immune component affected:

- Combined immunodeficiencies (T and B cell defects).
- Predominantly antibody deficiencies.
- Other well-defined immunodeficiency syndromes.
- Complement deficiencies.
- Congenital defects of phagocyte number and/or function.

This structure, while foundational, proved increasingly inadequate, as discoveries revealed that single gene defects could affect multiple immune components and present with non-infectious phenotypes.

The creation of new categories

A major conceptual breakthrough occurred with the introduction of tables IV, VI and VII:

- Diseases of Immune Dysregulation: recognizing that autoimmunity, lymphoproliferation, and hemophagocytic syndromes could be primary manifestations of IEI, not merely complications.
- Defects in Innate Immunity: initially focusing on NF-κB pathway defects, this table expanded to encompass Mendelian susceptibility to mycobacterial disease (MSMD), viral susceptibility, and fungal susceptibility.
- Autoinflammatory Disorders: formal recognition that sterile inflammation without autoantibodies could result from monogenic defects, establishing a new clinical discipline at the interface of immunology and rheumatology.

Pragmatic reorganization and consolidation

By 2015, the proliferation of disorders and the recognition that many conditions could fit into multiple categories prompted a critical decision: each disorder would be listed in only one table, based on its most fundamental and pronounced defect. This pragmatic approach prioritized clinical usability over biological exhaustiveness.[7]

The 2017 report introduced the transformative nomenclature change to "Inborn Errors of Immunity" (IEI), reflecting recognition that "deficiency" inadequately described gain-of-function and dysregulatory disorders; the expansion of the field beyond infection-predominant phenotypes; and the need for a unifying term encompassing all monogenic immune disorders.[13]

The 10-table structure established in 2017 has been maintained, with each table now subdivided into clinically coherent subtables (Table 2). The 2019 addition of table 9 (Bone Marrow Failure) consolidated previously dispersed disorders (Fanconi anemia, dyskeratosis congenita, MECOM deficiency) into a unified framework.[8]

Table 2. Current IUIS IEI classification structure (2024)

Table	Category	Number of Subtables	Total Conditions (genes)
1	Immunodeficiencies affecting cellular and humoral immunity	3	62 (73 genes)
2	Combined immunodeficiencies with associated or syndromic features	9	72 (79 genes)
3	Predominantly antibody deficiencies	4	55 (49 genes)
4	Diseases of immune dysregulation	7	77 (75 genes)
5	Congenital defects of phagocyte number or function	4	37 (45 genes)
6	Defects in intrinsic and innate immunity	9	39 (90 genes)
7	Autoinflammatory disorders	3	59 (75 genes)
8	Complement deficiencies	–	29 (37 genes)
9	Bone marrow failure	–	12 (56 genes)
10	Phenocopies of IEI	2	17 conditions

From infection to multi-system immune dysregulation

The 1999 report conceptualized IEI almost exclusively through the lens of infection susceptibility. Non-infectious manifestations were cataloged as "associated features" or complications. The immunologist's diagnostic approach centered on identifying the "defective" component of the immune system responsible for specific infection patterns (e.g., pyogenic bacteria suggesting antibody deficiency; opportunistic infections suggesting T cell deficiency).

The creation of dedicated tables for immune dysregulation (now table 4) and autoinflammatory disorders (now table 7) in 2005 formalized the recognition that IEI could present with autoimmunity, lymphoproliferation, or sterile inflammation as primary manifestations, often in the absence of significant infections (see Figure 2). Key milestones on this matter would be the inclusion of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) and immune dysregulation-polyendocrinopathy-enteropathy-X-linked (IPEX) in the immune dysregulation table; the expansion of autoinflammatory disorders to include NLRP12 deficiency and DIRA (deficiency of the IL-1 receptor antagonist) and the creation of the "Phenocopies" table, distinguishing that identical phenotypes could arise from somatic mutations or autoantibodies.

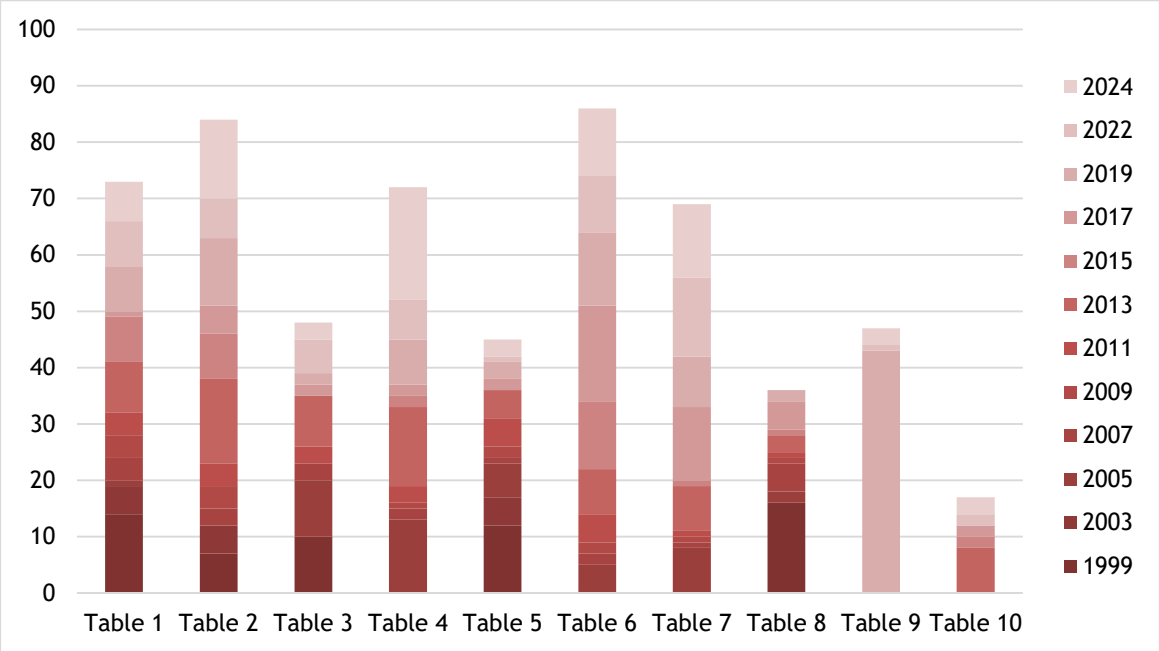

Fig. 2. Yearly growth of recognized IEI by tables/groups (1999 - 2024).

The most recent reports demonstrate complete integration of infectious and non-infectious phenotypes. In the 2024 update, 43% (29/67) of newly described IEI are classified in the autoinflammatory or immune dysregulation tables, reflecting that these categories now drive discovery as much as classic immunodeficiency.[4]

Technological drivers of discovery

Early discoveries relied on functional candidate gene approaches, linkage analysis in large families, and homozygosity mapping in consanguineous kindreds. The 1999 report identified genes such as BTK (XLA), CD40LG (hyper-IgM syndrome), and JAK3 (autosomal recessive SCID). Discovery rates were modest but produced foundational insights into immune pathways.

The introduction of whole-exome and whole-genome sequencing transformed the field. This technology enabled the discovery of ultra-rare disorders; many new IEI are initially described in a single patient or family, with inclusion criteria shifting from case numbers to mechanistic evidence; identification of non-canonical inheritance: recognition that genes previously associated only with autosomal recessive disease could cause autosomal dominant disease through different mechanisms (e.g., TCF3, IKZF1, PIK3CD); detection of somatic mutations: increased read depth enabled identification of mosaic mutations causing adult-onset autoinflammatory syndromes (e.g., UBA1 in VEXAS syndrome, TLR8 in cytopenias); and discovery of gain-of-function mutations: activating mutations in genes such as STAT1, STAT3, PIK3CD, and TLR7 cause distinct disease phenotypes, expanding the mechanistic framework beyond loss of function.

Conceptual advances in understanding disease mechanisms

Early reports assumed a linear relationship between genotype and phenotype. The 1999 classification described each disorder as a distinct entity with a predictable clinical presentation. Subsequent updates revealed that hypomorphic mutations in SCID-associated genes (RAG1/2, IL7R, Artemis) can cause Omenn syndrome, leaky SCID, or combined immunodeficiency with autoimmunity; allelic series in genes such as WAS produce distinct phenotypes ranging from classic Wiskott-Aldrich syndrome to isolated thrombocytopenia; and different variants in the same gene can cause loss-of-function, gain-of-function, or dominant-negative disease (e.g., STAT1, STAT3, CARD11, RAC2).

The 2007 report first highlighted STAT1 gain-of-function as a cause of chronic mucocutaneous candidiasis. By 2024, over 40 genes have multiple entries reflecting distinct mechanisms (loss-of-function, gain-of-function, dominant-negative, haploinsufficiency). The 2024 update introduced the concept of "multimorphic" mutations (IRF4), where a single mutation confers a novel function (neomorphism) distinct from both loss and gain of function.[4]

Recent reports[3,4,7,13] acknowledge that many IEI exhibit incomplete penetrance, with healthy family members carrying pathogenic variants. The 2024 update highlights monoallelic expression as a newly recognized contributor to variable penetrance, explaining why some individuals with identical mutations develop disease while others remain asymptomatic.

The 2014 introduction of the "Phenocopies" table formally recognized that somatic mutations can produce phenotypes indistinguishable from germline IEI. Autoantibodies against cytokines may also phenocopy IEI. Even when not considered actual IEI, phenocopies must be considered when clinically evaluating the patient, understanding probable causes for signs and symptoms unrelated with hereditary conditions.[4,21,22]

Current state of IEI classification (2024)

The 2024 IUIS classification encompasses 559 conditions, distributed across 10 tables (Table 2). Analysis of the phenotypic distribution reveals the centrality of multi-system manifestations (Table 3).

Table 3. Phenotypic manifestations across IEI tables (2024)

Table	N	Infections (%)	Autoimmunity (%)	Autoinflammation (%)	Malignancy (%)	Non-Immunological (%)
1	74	100	27	–	20	20
2	87	80	35	–	23	100
3	48	100	42	–	10	31
4	72	49	100	–	35	28
5	45	100	–	11	–	67
6	87	100	6	9	–	29
7	69	14	36	100	7	51
8	36	61	44	11	–	33
9	47	100	11	–	100	100
10	17	41	59	29	12	35

Note: Percentages indicate proportion of conditions within each table that manifest the specified phenotype. Many conditions exhibit multiple manifestations; percentages reflect presence of any feature within that category.

Infections remain universal in tables 1, 3, 5, and 9, but are less frequent in autoinflammatory disorders (table 7; 14%) and phenocopies (table 10; 41%).

Autoimmunity is most prevalent in table 4 (100%), table 8 (44%), and table 3 (42%), reflecting the loss of self-tolerance as main characteristic of immune dysregulation disorders, complement deficiencies (especially on initial cascade and regulating molecules) and some antibody deficiencies. Though it may not be a main clinical trait, it's the cause of nine phenocopies. Autoinflammation is concentrated in table 7 (100%) but autoinflammatory manifestations also appear in table 5 (CGD-related inflammatory bowel disease), 6 (ZNFX1 deficiency), and 8 (complement-mediated inflammation).

Malignancy risk is highest in bone marrow failure syndromes (100%), immune dysregulation disorders (35%), and syndromic immunodeficiencies (23%), particularly those with DNA repair defects or EBV susceptibility.

Non-immunological manifestations are universal in syndromic IEI (100%) and bone marrow failure (100%), and very common in phagocyte defects (67%) and autoinflammatory disorders (table 7, 51%), emphasizing the multi-system disorder model that IEI often represent.

DISCUSION

The evolution of inborn errors of immunity (IEI) classification from 1999 to 2024 represents one of the most remarkable trajectories in modern medical science. Over this quarter-century, the field has transformed from a discipline focused on rare pediatric conditions defined by infection susceptibility into a sophisticated molecular specialty that illuminates fundamental principles of human immunology while providing diagnostic and therapeutic insights for a broad spectrum of immune-mediated diseases. This discussion interprets the findings of our scoping review within the context of the theoretical frameworks that have shaped the field, assesses the implications for clinical practice and research, and acknowledges the limitations inherent in this synthesis.

From a descriptive catalog to an integrative framework

The quantitative growth documented in this review, from approximately 60 recognized disorders in 1999 to 559 in 2024, reflects not merely the accumulation of new knowledge, but a fundamental transformation in how we conceptualize immune system dysfunction. This trajectory can be understood through the lens of Thomas Kuhn's framework of scientific paradigm shifts; wherein anomalous observations accumulate until a new conceptual framework emerges that can accommodate them.

The 1999 classification embodied the foundational paradigm established by the World Health Organization in 1970: that primary immunodeficiencies could be understood as defects in discrete components of the immune system, T cells, B cells, phagocytes, or complement, manifesting as predictable patterns of infection susceptibility.[1] This framework, derived from the clinical

observations of Bruton (1952), Good (1962), and others, represented a remarkable achievement in its time. It provided a structured approach to diagnosis, enabled the development of registries, and established a common language for clinicians and researchers worldwide.

However, this component-based classification implicitly assumed that immune function could be understood as the sum of independent parts. It treated the immune system as a collection of separable modules rather than an integrated network; furthermore, treated the immune as a "separated system" from the body. This assumption, while practically useful, proved increasingly inadequate as molecular discoveries revealed the interconnectedness of immune pathways and the pleiotropic effects of single gene defects.

The emergence of dedicated tables for immune dysregulation and autoinflammatory disorders signaled a shift toward a network-based conceptualization of the immune system. This new framework recognized that immune function emerges from complex interactions between cells, cytokines, and regulatory pathways. A single genetic defect could disrupt these networks in multiple directions, producing not only increased susceptibility to infection but also autoimmunity, autoinflammation, lymphoproliferation, or allergy, sometimes simultaneously within the same patient.

This paradigm shift was informed by advances in systems biology and network theory, which emphasize that complex biological systems exhibit emergent properties not predictable from analysis of individual components. The immune system, with its multiple feedback loops, redundant pathways, and checkpoints, exemplifies such a system. Within this framework, IEI are understood as perturbations that alter network dynamics, with clinical manifestations determined by the specific node affected, the nature of the perturbation, and the presence of modifying genetic and environmental factors.[3]

The 2017 nomenclature change to "Inborn Errors of Immunity" reflected a third conceptual shift: the recognition that these disorders are not merely medical curiosities but constitute a systematic dissection of human immune function. As Casanova*, et al.*[7,23,24] have eloquently argued, IEI represent "experiments of nature" that reveal non-redundant functions of genes in human immunity.

This has profound implications. It positions IEI research not as a narrow subspecialty focused on rare diseases but as a fundamental approach to understanding human biology. Each newly discovered IEI provides insight into a gene's essential function in host defense, immune regulation, or both. The observation that approximately 20% of known immune-related genes (1800 - 2000 genes) have been implicated in IEI suggests that a substantial portion of the immune system operates with minimal functional redundancy.[25] These finding challenges assumptions derived from mouse models, where redundancy often masks essential functions.[24]

Technological determinism and discovery

The accelerated growth of recognized IEI following the introduction of next-generation sequencing (NGS) in 2010 exemplifies the profound impact of technological innovation on biomedical discovery. Prior to NGS, gene identification relied on candidate gene approaches, linkage analysis in large families,

and homozygosity mapping in consanguineous populations. These methods, while successful for many early discoveries, were inherently biased toward conditions with high penetrance and sufficient familial cases for genetic analysis.[26,27]

NGS removed these constraints. The ability to sequence exomes or genomes of individual patients enabled the discovery of ultra-rare conditions, many initially described in single kindred or even a single patient. This capability necessitated revision of the evidentiary standards for IEI inclusion. The 2014 guidelines[23] established that a novel variant could be considered disease-causing if accompanied by compelling mechanistic data, even in the absence of multiple families.

This shift recognized that the rarity of a condition does not invalidate its biological significance.

NGS also enabled detection of somatic mutations, revealing that disorders previously considered exclusively germline could arise from post-zygotic mutations. The 2024 update includes eight conditions caused by somatic mutations, including VEXAS syndrome, which exemplifies the importance of considering somatic variants in adult-onset inflammatory diseases.[28] Similarly, the identification of autoantibodies against cytokines as phenocopies of IEI, notably anti-type I IFN antibodies in severe COVID-19,[29,30] demonstrates that acquired mechanisms can produce phenotypes indistinguishable from monogenic disorders.[24]

Clinical implications

The conceptual and technological evolution documented in this review has profound implications for clinical practice. Perhaps the most significant is the recognition that IEI are not confined to pediatric infectious disease clinics. The 2024 report[4] explicitly notes that patients with IEI may present to rheumatologists, hematologists, allergists, dermatologists, neurologists, gastroenterologists, and pulmonologists, depending upon their spectrum of presenting clinical features.

This expansion of scope requires that clinicians across disciplines consider IEI in their differential diagnoses. The identification of monogenic lupus due to TLR7 or UNC93B1 gain-of-function mutations places IEI within the purview of rheumatology.[31] The discovery of LACC1 deficiency as a cause of juvenile arthritis indistinguishable from polygenic forms further erodes traditional boundaries between "primary immunodeficiency" and "autoimmune disease." The recognition that severe allergic disease can result from STAT6 gain-of-function mutations similarly integrates IEI into allergy practice.[32,33]

From a diagnostic perspective, these findings argue for broader consideration of genetic testing in patients with immune-mediated diseases. The cost-effectiveness of whole-exome sequencing compared to targeted testing, combined with the decreasing cost of genomic analysis, makes broad genetic screening increasingly feasible. However, the interpretation of variants requires specialized expertise, as the same gene can produce distinct phenotypes depending on the specific mutation, and variants may exhibit incomplete penetrance or monoallelic expression.[24,34,35]

Therapeutic implications

The detailed mechanistic understanding derived from IEI research has direct therapeutic implications. Mechanistic insights can translate across apparently distinct genetic disorders. The concept of pathway-based therapy, targeting the molecular pathway rather than the specific gene, is likely to become increasingly important as the number of IEI grows. The 2024 update[4] highlights emerging therapeutic approaches. As the mechanisms of IEI become increasingly well-characterized, the prospect of mechanism-based therapy, treating the underlying pathway rather than the symptoms, becomes increasingly realistic.

Limitations

Several limitations of this scoping review must be acknowledged, and their potential impact on this paper findings and conclusions warrants careful consideration.

First and foremost, the current analysis is inherently dependent on the content of the IUIS classification reports. While these represent the authoritative synthesis of the field, they are, by design, consensus documents. The IUIS Expert Committee requires robust mechanistic and genetic evidence for inclusion, and the criteria for accepting new entities have evolved over time. This reliance, while necessary, may have led to an underestimation of the true number of recognized IEI, particularly in the early years of the period studied. The committee's conservative approach and the limited availability of diagnostic tools in the 1990s and early 2000s likely meant that many conditions now recognizable were not yet cataloged. This potential undercount could affect the absolute growth estimates, especially the slope of the curve in the first phase of this analysis (1999-2005). However, the impact on our core conclusions is minimal. The criteria have become more inclusive and standardized over time, but the overall trajectory, from component-based deficiency to pathway-based dysregulation, is a robust observation that transcends the exact number of entities. The qualitative paradigm shifts described here are well-documented in the committee's own narrative, and the trends are consistent across multiple independent studies and registries.

Second, this review does not systematically assess the quality of evidence supporting individual gene inclusions. The rapid pace of discovery, driven by next-generation sequencing, inevitably means that some included conditions have limited supporting literature, often based on a single patient or a single family. This could introduce variability in the robustness of the clinical manifestations we extracted. For instance, the presence or absence of a particular non-immunological manifestation in a newly described disease might be based on incomplete phenotypic data, potentially affecting the precision of our phenotypic distribution analysis. However, the IUIS committee's rigorous criteria ensure a high threshold for acceptance. Furthermore, our analysis focuses on broad phenotypic categories (e.g., autoinflammation, non-immunological manifestations) across large groups of disorders. While individual data points may be preliminary, the aggregate pattern across hundreds of conditions is consistent and aligns with the field's conceptual evolution. The shift toward multi-system involvement is so pronounced that it is unlikely to be an artifact of incomplete reporting.

Third, the classification structure itself introduces a potential bias. Since 2015, each disorder has been placed in only one table based on its "most fundamental" defect. This pragmatic decision, while enhancing clinical utility, may artificially compartmentalize conditions that have multi-faceted pathophysiologies. For example, a disorder placed in the "immune dysregulation" table might also have significant autoinflammatory features, which are not captured in its primary classification. This could affect our interpretation of how phenotypes cluster.

Fourth, this review does not address geographic disparities in IEI diagnosis and care. The discovery of IEI genes has been concentrated in centers with advanced genomic capabilities, and the availability of genetic testing and specialized care remains highly variable globally. The phenotypic spectrum described in the IUIS reports may be heavily weighted toward the clinical presentations seen in high-income countries, potentially missing distinct manifestations in populations with limited diagnostic access. While this limitation is significant, the biological principles we describe, the conceptual shift from infection to dysregulation and the molecular understanding of pathways, are universal. The framework is valid even if the data informing it are geographically skewed. Our conclusions regarding paradigm shifts are based on the conceptual and technological evolution of the field, which is well-documented and internationally recognized, even if the application of these concepts is not globally uniform.[36]

Finally, this scoping review, by design, synthesizes broad trends and patterns rather than performing a meta-analysis of clinical outcomes or a systematic evaluation of specific therapeutic interventions. The focus on conceptual and quantitative evolution is well-suited to our objective, but it limits the direct clinical applicability of our results for bedside decision-making. However, it does not undermine our core conclusion, which is that the reconceptualization of IEI has established a new framework that underpins pathway-based diagnosis and precision therapy. The clinical implications we discuss are derived from this framework and are supported by the wealth of mechanistic data in the literature, even if not quantitatively synthesized in our review. Our findings thus serve as a conceptual roadmap, not a clinical guideline, and this distinction is important for the reader to keep in mind.

Future directions

The trajectory documented in this review suggests several strategic directions for future development. Below, we outline these recommendations, explicitly linking each to our findings and prioritizing them according to their potential clinical and research impact.

To prioritize therapeutic development targeting immune dysregulation and autoinflammatory pathways: Our finding that 43 % of newly described IEI fall into autoinflammatory or immune dysregulation categories represents one of the most compelling signals from the 2024 update. This is not merely a statistical observation but a reflection of where the field's most significant unmet clinical needs now lie. Unlike classic immunodeficiencies, where immunoglobulin replacement and antimicrobial prophylaxis have established efficacy, many dysregulatory and autoinflammatory disorders lack standardized, targeted therapies.

To establish multidisciplinary care teams as a mandatory standard for syndromic IEI: Our phenotypic analysis revealed that non-immunological manifestations are present in 100% of syndromic IEI and bone marrow failure syndromes. This finding underscores that IEI are not immune system diseases but multisystem disorders with immune involvement. Patients with conditions such as DNA repair defects, cartilage-hair hypoplasia, dyskeratosis congenita, or STAT3 loss-of-function (hyper-IgE syndrome) present with skeletal, neurological, endocrine, dermatological, and hematological features that demand comprehensive, coordinated management.

Multidisciplinary care is not optional but essential from the time of diagnosis: Should include, at minimum, clinical immunology, rheumatology, hematology-oncology, dermatology, gastroenterology, pulmonology, neurology, and genetics. Transition programs from pediatric to adult care must be established, as many syndromic IEI now have improved survival into adulthood due to advances in supportive care and hematopoietic stem cell transplantation. The urgency of this recommendation is high because delayed recognition of non-immunological complications (e.g., pulmonary fibrosis, hepatic veno-occlusive disease, endocrine insufficiency) contributes significantly to morbidity and mortality. Furthermore, the integration of specialists ensures that complications are anticipated and managed proactively rather than reactively, improving quality of life and long-term outcomes.

Efforts to improve access to genetic diagnosis must be prioritized: Concurrently, the interpretation of novel genetic variants requires standardized approaches and access to specialized databases. Several platforms and resources are now essential for the classification of genetic variants identified in patients with suspected IEI.

To integrate IEI research with other medical specialties to identify monogenic subsets of common diseases: Our analysis of the expanding clinical spectrum of IEI, which now includes monogenic forms of lupus (TLR7, UNC93B1), juvenile arthritis (LACC1), severe allergy (STAT6 gain-of-function), and inflammatory bowel disease (IL10RA/B, XIAP), suggests that the distinction between IEI and other categories of human disease is becoming increasingly blurred. This has profound implications for specialties beyond immunology.

To address global disparities in IEI diagnosis and care: International collaborations, such as those supported by the IUIS, the Jeffrey Modell Foundation, and the Latin American Society for Immunodeficiencies (LASID), should be strengthened to support diagnostic capacity building, training, and registry development in underserved regions. The development of low-cost, point-of-care screening tests (e.g., dried blood spot analysis for T-cell receptor excision circles and kappa-deleting recombination excision circles) and tiered diagnostic algorithms can improve access to initial evaluation, with referral to regional centers for genetic confirmation. This carries high urgency from an equity perspective and is essential for accurate global prevalence estimates, which in turn inform healthcare policy and resource allocation. The continued growth of the IUIS classification will be most impactful when it reflects a truly global perspective, incorporating clinical phenotypes and genetic variants from diverse populations.

CONCLUSIONS

The evolution of inborn errors of immunity classification from 1999 to 2024 documents a remarkable journey. Over 25 years, the field has grown eightfold, undergone major paradigm shifts, and transformed from a descriptive discipline into a molecular science with direct translational impact. The IUIS classification reports provide a unique longitudinal record of this evolution, capturing not only the accumulation of knowledge but the conceptual advances that have reshaped our understanding of immune system function and dysfunction.

The current framework represents the maturity of the field. It accommodates the complexity of IEI while maintaining clinical utility, and it provides a foundation for the next generation of discovery. Looking forward, the continued integration of IEI research with genomics, systems biology, and precision medicine promises to further illuminate the fundamental principles of human immunity, while improving diagnosis and treatment for patients with these challenging conditions.

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