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RESEARCH

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International multidisciplinary consensus on the definition and clinical approach for monogenic inflammatory immune dysregulation disorders

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Abstract

Objective To achieve consensus on the definition and clinical approach of Monogenic Inflammatory Immune Dysregulation Disorders (MIIDDs), a collective term for rare conditions marked by inflammation, immune dysregulation, and infection susceptibility. These consensus guidelines specifically apply to pathogenic (or likely pathogenic) gene mutations affecting both innate and adaptive immunity, excluding variants of unknown significance (VUS).

Methods A multi-step, evidence-based, multidisciplinary consensus process was employed, consisting of: (1) a systematic literature review across four electronic databases (Cochrane Library, Web of Science, Scopus, and MEDLINE via PubMed), updated through December 31, 2024; (2) a pre-Delphi electronic survey completed by 95 international adult and pediatric immunologists and rheumatologists; and (3) a modified online Delphi process with an international multidisciplinary expert panel, where statements were iteratively analyzed and refined until achieving consensus (≥ 80% agreement among panelists).

Results Fifteen experts from 12 countries participated in two rounds of the Delphi process, resulting in the development of eight overarching principles and 10 consensus statements. These were categorized into five domains: (1) definitions and conceptual framework, (2) diagnostic and monitoring considerations, (3) treatment and therapeutic strategies, (4) multidisciplinary and collaborative care, and (5) patient education and support.

Conclusion This consensus defines MIIDDs and provides a structured clinical framework to streamline research efforts and improve patient outcomes.

Keywords Inborn errors of immunity, Genetic, Inflammatory, Autoimmune, Autoinflammatory, Immune dysregulation, Consensus

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Introduction

Primary immunodeficiencies (PIDs) traditionally describe inherited immune system disorders that impair the human defense against infections. In the 1970s, the World Health Organization formed a committee to classify PIDs [1], a responsibility later assumed by the International Union of Immunological Societies (IUIS) in the 1990s [2]. Over time, it became evident that PIDs are associated with a spectrum of autoinflammatory, autoimmune, atopic manifestations, and susceptibility to malignancy. Notably, noninfectious manifestations are often the primary or initial clinical features of many of these disorders [3]. The growing understanding of their genetic basis, supported by advancements in molecular genetic testing, has led to the adoption of the term inborn errors of immunity (IEIs) due to the identification of mutations without immune deficiency (loss-function) but rather immune over-activation (gain-of-function) [4].

In the most recent IUIS classification update, 555 distinct IEIs are categorized into 10 groups based on immunologic and genetic defects [5]. However, certain disorders from different groups exhibit overlapping features, such as pronounced inflammation alongside immune dysregulation, highlighting the need for unifying term.

The term 'Monogenic Inflammatory Immune Dysregulation Disorders' (MIIDDs) has been introduced as an umbrella concept for a heterogeneous group of conditions. It describes patients with pathogenic gene mutations affecting both innate and adaptive immunity, clinical features of inflammation, and evolving features of immune dysregulation. This unifying term may facilitate the grouping of related disorders within a single conceptual framework, supporting research integration on overlapping disorders regardless of their underlying pathophysiology, as seen in monogenic lupus.

Establishing this framework is important for advancing research and improving patient outcomes. To address this, we conducted a systematic literature review and a modified online Delphi study, engaging an international panel of experts. This process aimed to achieve consensus on the definition and clinical management for patients with MIIDDs.

Materials and methods

Study design and overview

Given the limited empirical evidence on disorders categorized under MIIDDs, a modified Delphi method was utilized. This systematic, iterative approach was selected for its ability to gather consensus among geographically dispersed experts while maintaining participant anonymity, minimizing dominance effects, and ensuring balanced input. The development of the consensus involved a multi-step process (see Supplement, Figure I).

Step one: establishment of the core group

The project was initiated by SMA, who formed a core group comprising three additional members (LOM, IAA, and HMA). The team included two pediatric rheumatologists, one adult rheumatologist, and one clinical allergist/immunologist. The core group was tasked with overseeing the study's design and implementation, focusing on patients with combined clinical features of non-infectious sterile inflammation (autoimmune or autoinflammatory disorders), immune dysregulation, and confirmed genetic mutations.

Step two: statement development via systematic literature review

Two authors (SMA and HMA) conducted a systematic literature review (SLR) across four electronic databases: the Cochrane Library, Web of Science, Scopus, and MEDLINE (via PubMed). The search included peer-reviewed publications available through October 31, 2023, and was updated through December 31, 2024, with only studies published in English being considered. Reference lists of identified records were also screened for relevant studies. Keywords, Topics, and Medical Subject headings (MeSH) terms were used to broaden the search scope. Disagreements during the review were resolved by reconciliation or consultation with a third reviewer (IAA).

Studies related to polygenic disorders, genetic mutations with unclear pathogenic significance, case reports, case series, reviews, editorials, opinions, abstracts-only studies, basic science research, and non-English publications were excluded. Titles and abstracts were initially screened, followed by a full-text review for eligibility (see Supplement for the search strategy and the PRISMA flow diagram).

Step three: pre-Delphi process

An online survey derived from the SLR findings was developed to explore current practices and future care needs. The survey was disseminated via SurveyMonkey® to an international cohort of adult and pediatric immunologists and rheumatologists identified through scientific societies and special interest groups. A snowball sampling method was employed to gather more responses. Survey responses were collected between November 30, 2023, and January 4, 2024, with 95 participants completing the survey (see Supplement documents, Table-S1 for participant demographics). The results of this exercise yielded valuable insight that was incorporated into the main Delphi process.

Step four: Delphi panel selection and process

The core group identified potential panelists from different disciplines (allergy/immunology, immunogenetics, rheumatology, and infectious diseases) based on

expertise and interest as identified through special interest groups and previous publications. A total of 15 panelists from 12 countries (spanning Africa, Asia, Europe, and South America) participated in two rounds of an online Delphi exercise conducted via SurveyMonkey®.

The modified Delphi process comprised 20 statements organized under five domains (Table 1). The first round included both open- and closed-ended questions, while the second round refined statements for agreement scoring on a 5-point Likert scale.

After each round, results were summarized and tabulated. The percentage agreement and descriptive statistics were calculated. Statements not reaching consensus were modified by the core group and then re-sent to panelists in an iterative process until consensus (≥ 80% agreement) was achieved.

Informed consent and ethical approval

All participants received an introductory statement at the start of each survey outlining the study's purpose, the voluntary nature of participation, and assurances of confidentiality and anonymity. The participants' decision to proceed with the survey implied consent. The Research Advisory Council (RAC) at King Faisal Specialist Hospital and Research Center (RAC2231314) granted ethical approval for the study.

Results

All 15 panelists successfully completed the two rounds of the modified Delphi process. After the first round, eight statements were rephrased to improve clarity, while two statements were omitted (see Supplement, Table S2 for results from the First Round of Voting and Table S3 for modifications after the first round). Ultimately, eight overarching principles and ten consensus recommendation statements were finalized and organized into five core domains (see Table 1). The eight overarching principles provide a contemporary perspective on defining and managing MIIDDs, establishing a framework for the subsequent recommendations (see Table 2).

Domain A: definitions and conceptual framework

The term MIIDDs is proposed as a unifying umbrella term for a heterogeneous group of conditions characterized by pathogenic (or likely pathogenic) gene mutations affecting both innate and adaptive immunity, excluding variants of unknown significance (VUS). These mutations lead to autoimmune or autoinflammatory manifestations, or other features of immune system dysregulation, with evolving clinical features. Notably, pathogenic/likely pathogenic classifications are based on functional validation studies, the American College of Medical Genetics and Genomics (ACMG) classification, or both.

Table 1 Core Domains Addressed in the Consensus

Domain A	Definitions and Conceptual Framework
Domain B	Diagnostic and Monitoring Considerations
Domain C	Treatment and Therapeutic Options
Domain D	Multidisciplinary and Collaborative Care
Domain E	Patient Education and Support

Domain B: diagnostic and monitoring considerations

The availability, accessibility, and accurate interpretation of genetic testing are crucial for identifying MIIDDs patients and optimizing their care outcomes. Molecular genetic testing has revolutionized the diagnosis of immune-mediated inflammatory conditions and enhanced our understanding of the link between IEIs and inflammatory conditions [6]. However, delayed diagnosis remains a challenge for patients with monogenic IEIs, highlighting the need to expand access to genetic testing and functional assessment of VUS [7]. In addition to genetic evaluation, panelists emphasized the importance of systemic clinical monitoring, documenting laboratory improvements as indicators of treatment responses, and screening for non-inflammatory autoimmune conditions such as autoimmune thyroiditis, celiac disease, and vitiligo. These conditions are integral to diagnosis, requiring appropriate treatment and long-term monitoring, often managed by rheumatologists or immunologists. Furthermore, future research should prioritize the identification of tailored biomarkers, the establishment of standardized definitions for disease remission, and the development of validated indices for disease activity and damage.

Domain C. treatment and therapeutic options

Achieving clinical improvement is a feasible goal for MIIDDs patients. Depending on the clinical presentation and immunologic profile, different treatment modalities may be employed. These include corticosteroids, conventional disease-modifying antirheumatic drugs, intravenous immunoglobulin, and antibiotic prophylaxis [8]. The identification of pathogenic mutations and deciphering disease mechanisms has facilitated the development of precision medicine, offering tailored treatments such as hematopoietic stem cell transplant, gene therapy, and the use of targeted biologics or small molecules [9].

Domain D: multidisciplinary and collaborative care

Depending on the dominant clinical presentation, the primary healthcare provider may be either a rheumatologist or an immunologist. However, panelists unanimously agreed that joint rheumatology/immunology care or clinics are advocated for optimizing care for MIIDDs patients [10]. Given the diverse spectrum of MIIDDs, a multidisciplinary approach is essential. Collaboration with genetic counselors and family planning specialists is occasionally necessary, as certain monogenic

Table 2 Overarching Principles and Final Recommendations for Patients with Monogenic Inflammatory Immune-Dysregulation Disorders (MIIDDs)

		Agreement	Descriptive Statistics		
		Percentage (%)	Mean	Standard deviation	Interquartile range
Overarching Principles					
A.1	Monogenic Inflammatory Immune-Dysregulation Disorders (MIIDDs) is an umbrella term for a heterogeneous group of disorders.	100	4.93	0.24	0.0
A.2	A patient with Monogenic Inflammatory Immune-Dysregulation Disorder (MIIDD) is defined as having a pathogenic gene mutation, immune system dysregulation, and inflammatory manifestations with clinical features that can evolve over time.	100	4.66	0.47	1.0
B.3	The availability, accessibility, and accurate interpretation of genetic testing will enhance patient identification and improve overall care outcomes.	93.33	4.73	0.99	0.0
B.4	There is a need for the development of a definition of disease remission in patients with MIIDDs.	100	4.6	0.48	1.0
B.5	There is a need for the development and validation of disease activity and damage indices for patients with MIIDDs.	100	4.4	0.48	1.0
C.6	Clinical improvement while on treatment is a feasible goal in the management of patients with MIIDDs.	93.33	4.26	0.57	1.0
C.7	More effective therapeutic options for the management of patients with MIIDDs should be explored and tested.	100	4.8	0.4	0.0
C.8	There is a need for the development of therapeutic guidelines for the management of patients with MIIDDs.	100	4.8	0.4	0.0
Recommendations					
B.1	Clinical and laboratory improvement should be used to assess the response to treatment.	100	4.6	0.48	1.0
B.2	Patients with MIIDDs should be screened for other non-inflammatory autoimmune conditions, such as autoimmune thyroiditis.	86.67	4.26	0.67	1.0
C.2	Corticosteroids may serve as a therapeutic option for some patients with MIIDDs, depending on the clinical context and individual patient needs.	93.33	4.13	0.71	0.5
C.3	Both conventional and/or biologic disease-modifying antirheumatic drugs may serve as therapeutic options for some patients with MIIDDs, depending on the clinical context and individual patient needs.	100	4.4	0.48	1.0
C.4	Intravenous immunoglobulin (IVIG) may serve as a therapeutic option for some patients with MIIDDs, depending on the clinical context and individual patient needs.	100	4.33	0.47	1.0
C.5	Antibiotic prophylaxis may be required for some patients with MIIDDs, depending on the clinical context and individual patient needs.	86.67	3.93	0.44	0.0
C.6	A hematopoietic stem cell transplant may be needed for some patients with MIIDDs, depending on the clinical context and individual patient needs.	86.67	3.93	0.44	0.0
D.7	Based on the predominant clinic picture in patients with MIIDDs, the primary healthcare provider can be a rheumatologist or an immunologist. However, joint rheumatology/immunology care or clinics are advocated to provide optimum care for patients with MIIDDs.	100	4.73	0.44	0.5
D.8	Collaboration with other subspecialties as needed is advocated in the care of patients with MIIDDs.	100	4.8	0.4	0.0
E.10	Patients with MIIDDs should be educated regarding their disease and provided with ongoing support.	100	4.8	0.4	0.0

disorders may manifest even in the carrier state. Patients should also be screened for additional non-inflammatory autoimmune conditions or malignancies. Furthermore, non-inflammatory complications, including growth impairment secondary to chronic disorder (potentially requiring endocrine consultation), ophthalmologic evaluation for disorder-associated or drug-induced toxicity, and structured transitional care from pediatric to adult services, should be systematically integrated into comprehensive patient management.

Domain E: patient education and support

Patient education and ongoing support are strongly advocated, given the limited availability of publicly accessible information on rare disorders.

Discussion

This study introduces the concept of MIIDDs as a unifying framework for a heterogeneous subgroup of IEIs characterized by pathogenic and likely pathogenic genetic mutations, immune dysregulation, and prominent inflammatory features. Through an SLR and a modified Delphi process, we sought to address the current

gaps in defining and approaching these rare disorders. The MIIDDs framework recognizes the overlap between immunodeficiencies, autoimmunity, and autoinflammation in IEIs, integrating clinical and genetic features under a single umbrella [11–15]. This approach promotes a deeper understanding of shared pathophysiological mechanisms, streamlining research efforts, and fostering cohesive clinical guidelines.

Our findings highlight the critical role of genetic testing in identifying MIIDDs. Expanding access to genetic testing and training clinicians in interpreting molecular genetic data are essential for early diagnosis and effective management [16–20]. The consensus underscores the need for validated tools, such as standardized definitions of disease remission and activity indices, to monitor disease progression and treatment outcomes [21–23].

Treatment strategies for MIIDDs are diverse and evolving [8]. While conventional approaches, such as corticosteroids and immunosuppressants, remain pivotal, advances in precision medicine, including biologics, small molecules, and gene therapies, offer promising, targeted, and more effective interventions [24–27]. Individualized treatment plans based on specific pathogenic mutations could significantly improve patient outcomes [28, 29].

Given the diverse clinical manifestations of MIIDDs, joint immunology-rheumatology clinics, and multidisciplinary care teams are essential for optimizing patient management. The consensus strongly advocates for integrating subspecialists, including infectious disease experts, geneticists, genetic counselors and family planning specialists, as certain monogenic disorders may manifest even in the carrier state, along with other relevant disciplines, into the care model. This collaborative approach addresses the broad spectrum of features and comorbidities observed in MIIDDs. Additionally, patient education and psychosocial support are integral, given the emotional and logistical challenges faced by patients and families [23, 30].

In conclusion, this consensus-driven framework established foundational principles for defining and approaching MIIDDs, improving the current classification for IEIs with inflammatory features. Future efforts should focus on validating this framework through clinical and genetic studies, developing disease-specific indices, and fostering international collaboration to advance research and improve outcomes for these complex disorders.

Abbreviations

PIDs	Primary immunodeficiencies
IUIS	International union of immunological societies
IEIs	Inborn errors of immunity
MIIDDs	Monogenic inflammatory immune dysregulation disorders
SLR	Systematic literature review
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
RAC	Research advisory council

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12969-025-01109-z.

Supplementary Material 1

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None.

Author contributions
Conception and design of study: SMA, HMA. Data analysis and/ or interpretation of data: HMA, SMA, LOM, IAA, All authors made substantial contributions to the interpretation of data for the work. SE, HA, SJ, HM, MO, AA, TA, WC, GE, MF, AG, DH, NM, HW contributed to data interpretation, manuscript drafting, or critical revision for intellectual content. All authors reviewed and approved the final manuscript. All authors are accountable for all aspects of the work.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The research protocol was approved by the Research Advisory Council (RAC) at King Faisal Specialist Hospital and Research Center (RAC2231314). The study was carried out in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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