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Pathways to progress: navigating the evolving field of PIDs and associated conditions — proceedings from the IPOPI Global Multi-Stakeholders' Summit (July 2025)

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Introduction: In July 2025, the International Patient Organisation for Primary Immunodeficiencies (IPOPI) held its fourth consecutive Global Multi-Stakeholders' Summit, bringing together key stakeholders and experts in primary immunodeficiencies (PIDs) and related fields to discuss current challenges and opportunities for improving patient care.
Methods: This edition focused on current and projected trends to 2035 in artificial intelligence and quantum computing, the gap between primary and secondary immunodeficiencies, and the role of preventive medicine in patients' quality of life.
Results: Stakeholders from all around the world gathered to examine current knowledge gaps, needs and avenues to improve the care of patients with immunodeficiency in the next ten years.
Discussion: Recommendations on how digital technologies can contribute to equitable access to innovative therapies are proposed. Mechanisms by which multidisciplinary teams can work together to improve the care of patients with immunodeficiencies are outlined, including how innovative screening and care plans can reduce the risk of multiorgan involvement and complications in these patients. Within the next decade, digital tools in conjunction with improved multistakeholder collaborations is most likely to contribute to the collection of standardised data, inclusive studies, and personalised treatments that will prolong, with quality, the lives of patients with immunodeficiencies.

KEYWORDS

artificial intelligence, digital health technologies (DHTs), global equity, immunoglobulin replacement therapy (IGRT), innovative therapies, primary immunodeficencies (PID), quantum computing, secondary immunodeficiencies (SIDs)

Introduction

Multi-stakeholder engagement and collaboration are the foundation for significant change and innovation that impacts patients' lives (1) globally. To foster partnership across borders and specialties, the International Patient Organisation for Primary Immunodeficiencies (IPOPI) hosts an annual meeting — the Global Multi-Stakeholders' Summit — in which stakeholders and experts from different fields are challenged to identify current needs and align on recommendations to improve future outcomes and quality of life for patients with primary immunodeficiencies (PIDs, also referred to as Inborn Errors of Immunity, IEIs) and associated conditions worldwide (1–3).

PIDs/IEIs or Primary Immune Disorders, are a group of rare heterogeneous conditions affecting primarily the immune system with multi-organ ramifications that may include allergic phenotypes, autoimmunity, autoinflammation and an increased risk of malignancies. Key priorities and opportunities identified during these discussions are essential towards shaping the future of patients with PIDs and associated conditions and have been published in previous years (1–5).

The fourth edition of the Global Multi-Stakeholders' Summit took place in July 2025 with challenging prospective topics on the evolving field of PIDs and associated conditions: i) achieving global equity in access to innovative therapies through artificial intelligence (AI), quantum computing and digital health technologies, ii) bridging the gap between primary and secondary immunodeficiencies (SIDs), and iii) preventive medicine in PIDs and associated conditions. Needs, opportunities and recommendations were proposed to achieve an ideal situation by 2035 and are expanded upon in the next sections.

PART 1: AI, quantum computing and digital health – will we achieve global equity in access to innovative therapies for immune deficiencies with these technologies by 2035?

Harnessing next-generation computing to close gaps in diagnosis, research and access in PIDs

The convergence of AI, machine learning (ML), deep learning (DL), large language models (LLM) and quantum computing (QC) is reshaping the technological landscape of biomedical innovation. For PIDs/IEIs and other rare immune disorders, where data scarcity, diagnostic heterogeneity, and limited specialist availability remain pervasive challenges, these technologies offer complementary and potentially transformative capabilities (6–10). Yet, their effective deployment also requires a critical understanding of their limitations, legal and ethical implications, and infrastructural demands (11). Achieving global equity in access to diagnosis and treatment by 2035 will depend not only on technological progress, but mostly on the integration of high-quality data, harmonised classifications, and ethically grounded implementation frameworks (4).

From a computational perspective, QC introduces capacities beyond classical systems by improving diagnostic precision and probability calculations, exploiting superposition, entanglement, and quantum interference. Unlike traditional processors, many Quantum Processing Units operate at temperatures near absolute zero and rely on qubits (quantum bits: the basic unit of quantum information, analogous to a classical bit but able to exist in a combination of 0 and 1 states until measured. Some qubits do not require cryorefrigerators, such as photonic qubits and NV diamond centres) whose lifetime, error rates, and interconnectivity are critical determinants of performance. As emphasised, progress in QC is not simply a matter of increasing qubit count; it requires improvements in qubit stability, gate fidelity, and quantum error correction, as well as interdisciplinary collaboration to translate mathematical capabilities into biomedical applications. Whilst the technology remains in a formative stage, QC-as-a-service models allow early experimentation in areas such as molecular simulation, protein folding, genomic and epigenetic alterations and drug–target interaction prediction, domains in which classical computing faces exponential scaling limits (12). Although quantum communication networks remain nascent, their promise for secure medical data exchange may become increasingly relevant for rare disease registries and multinational collaborations.

Case studies, such as the large-scale calculated globulin-based screening initiative in Brazil, illustrate how real-world evidence and risk stratification can uncover thousands of patients potentially affected by PIDs despite longstanding challenges in specialist access and diagnostic pathways (13). Similar approaches may be expanded to settings where 80–90% of patients remain undiagnosed, enabling earlier referral and more efficient use of specialist resources. AI approaches, including ML and DL (including neural networks and LLMs) in PID care span early diagnosis, phenotype extraction, population screening, and clinical decision support.

However, the reliability and applicability of AI systems depend fundamentally on the quality and structure of the underlying data. Rare disease datasets often suffer from heterogeneity, small sample sizes, and biases introduced by literature-derived knowledge. The work of Robinson et al. explores the power and limitations of knowledge-driven classification systems such as the Human Phenotype Ontology (14). By embedding ontologies within knowledge graphs, they were able to cluster rare diseases into coherent biological groups, yet these clusters inevitably inherit the biases of published case descriptions. Conversely, data-driven extraction of phenotypes from Electronic Health Records (EHRs) using natural language processing (NLP), ontology expansion, and embedding methods could expand the phenotypic rare diseases landscape (15–17). Associations between clinical signs and the pathogenic mechanism must be carefully controlled in advance in the generation of ontologies to ensure high-quality annotation and interpretation of data, including a necessary specialist control provided later in the output phase of data extraction. Hybrid models combining ontologies, large language models (LLMs), and multimodal embeddings may therefore represent the next major shift in rare disease representation, enabling both greater flexibility and improved interpretability (18).

AI is also beginning to support phenotyping beyond textual data. Dysmorphology tools such as in the AIDY project leverage image-based embeddings derived from facial features to identify rare disease patients with similar syndromes, propose new hypotheses, and support diagnosis in highly heterogeneous conditions (19). Nevertheless, these systems rely heavily on curated ontologies and high-quality annotations to ensure interpretability, interoperability, and fairness.

Despite these advances, significant epistemological, ethical, regulatory and legal challenges remain. AI systems are powerful correlational machines but struggle to distinguish causation from spurious associations. Small datasets, partial registries, and inconsistent documentation introduce biases that may amplify inequities or produce misleading outputs. As highlighted by Corteel, the illusion of deterministic "Laplace's demon" (the idea of perfect predictive intelligence) in translational biomedicine must be rejected; uncertainty is intrinsic to both biological systems and data-driven models. The development of "moral AI" remains controversial, and current systems lack robust ethical reasoning, explainability, and mechanisms to respect patient autonomy. Rigorous evaluation involving randomised trials, transparent validation, and regulatory oversight will be crucial to ensuring responsible deployment (20, 21).

Industry perspectives echo these themes, emphasizing the potential of AI to accelerate diagnostics, drug discovery, and decision support, whilst acknowledging the slow translation of research innovations into clinical practice. AI-powered decision support tools are increasingly being introduced in hospitals and primary care settings, yet challenges persist regarding benchmarking, generalizability, and data completeness. QC holds promise for improving the efficiency of compound screening, simulating complex biochemical reactions, and optimizing multi-step drug development processes, but remains limited by technological maturity and long deployment timelines.

Ultimately, achieving equitable access to these innovations requires much more than technical capability. It demands scalable implementation strategies, interoperable data infrastructures, international regulatory harmonization, and investment in AI/digital and ethical literacy amongst clinicians, patients, and policymakers. Next-generation computing will only reduce diagnostic delays and treatment inequalities if health systems worldwide can adopt, trust (including reducing potential biases and adhering to the highest

Abbreviations: AI, Artificial Intelligence; B-CLPD, B-cell Lymphoproliferative Disease; CLL, Chronic Lymphocytic Leukaemia; CVID, Common Variable Immune Deficiency; DL, Deep Learning; EHRs, Electronic Health Records; HCPs, Healthcare Professionals; HPO, Human Phenotype Ontology; HSCT, Hematopoietic Stem Cell Transplantation; IEIs, Inborn Errors of Immunity; Igs, Immunoglobulins; IgRT, Immunoglobulin Replacement Therapy; IPOPI, International Patient Organisation for Primary Immunodeficiencies; LLMs, Large Language Models; ML, Machine Leaning; MDTs, Multidisciplinary Teams; MM, Multiple Myeloma; NDDs, Neurodevelopmental Deficits; NLP, Natural Language Processing; PANS, Pediatric Acute-onset Neuropsychiatric Syndrome; PANDAS, Pediatric Acute-onset Neuropsychiatric Disorder Associated with Streptococcal Infections; PIDs, Primary Immunodeficiencies; QC, Quantum Computing; RD, Rare Diseases; SCID, Severe Combined Immunodeficiency; SIDs, Secondary Immunodeficiencies; sIgAD, selective IgA deficiency.

ethics standards), fund and operationalise these tools within their existing care pathways.

See Table 1 for the summary on the prospective (Where do we want to be? and How are we going to get there?).

PART 2: Bridging the gap between primary and secondary immunodeficiencies – from common ground to better patient care

PIDs and SIDs are inherently distinct immunodeficiency conditions: whilst PIDs are generally accepted to stem from genetic mutations, whether they've been identified and described, SIDs are acquired (22, 23). Common causes of SIDs include underlying conditions, such as B-cell lymphoproliferative disease (B-CLPD) and other haematological malignancies, *e.g.*, chronic lymphocytic leukaemia (CLL), and multiple myeloma (MM), use of immunosuppressants, biologics, and chemotherapy, amongst other drugs, solid organ transplantation or hematopoietic stem cell transplantation (HSCT), protein loss, infection with human immunodeficiency virus and malnutrition amongst others (24). These factors can directly increase severe infection risks by causing hypogammaglobulinemia, altering cellular immunity, causing neutropenia and impairing complement function. When the underlying disorder is treated or removed, patients may experience immune recovery, unlike patients with PIDs. However, due to their nature, PIDs and SIDs patients share symptomatology, diagnostic tools, therapies, potential complications, healthcare professional specialists, and advocacy needs. This common ground supports strengthening cross-disciplinary collaboration to improve patient care in the near future.

TABLE 1 AI, quantum computing and digital health – will we achieve global equity in access to innovative therapies for immune deficiencies with these technologies by 2035?

Where do want to be?	What are the barriers?	How are we going to get there?
High-quality data, improve the predictive performances of algorithms used. Advance personalised medicine approaches.	Overcome the limited accessibility and technical constraints of quantum computing, including its infrastructure demands and the need for ultra-fast execution due to qubit instability.	Private-Public partnerships to scale infrastructures to help leveraging quantum technology/computing (QC) can help in many areas of health especially in the field of rare diseases (RD). QC can optimise and accelerate the use cases of AI, can help to reduce data problems in PIDs as well as improve security.
Enhance existing ontologies and classifications to better capture the complexity and variability of rare diseases.	Current ontologies and classifications are often incomplete, fragmented, or not regularly updated, limiting their ability to represent the full clinical spectrum of RD and PIDs and support accurate diagnosis or AI applications.	Knowledge driven vs. data driven research and applications: foster strategic alignment and advocacy to enable integration of knowledge-driven and data-driven approaches such as combining AI/LLMs and QC in RD and PIDs research.
Consider biases and heterogeneity, especially in data derived from small populations/RD. Full transparency, patient autonomy, providing guidance, improvement in phenotype discovery, inc. endotypes and deep phenotyping.	Persistent biases and heterogeneity in RD datasets, limited phenotypic resolution and underdeveloped quantum applications challenge fairness, interpretability, and decision-making. Ethical gaps, low AI literacy, and weak interdisciplinary collaboration risk misuse of technologies and limit patient-centred, transparent adoption.	QC could help in identifying biased datasets and results. AI incorporated ethical frameworks to support medical decision-making. Develop/Cultivate AI literacy + ethical awareness and critical AI culture amongst HCPs and patients (societal dimension) + Foster interdisciplinarity.
Drug discovery and repurposing (higher speed and processing power) + improved RCTs.	High computational demands, limited access to advanced technologies and integration challenges slow the acceleration of drug discovery or timely diagnostics.	Advances in computing can bridge to better and timely diagnosis and to therapeutics Integrate AI and QC to improve processing power, accelerate drug discovery, optimise RCTs, and identify therapeutic candidates faster.
Equitable/Unbiased/Universal access to discoveries/knowledge (need for societally oriented choices)	Societal, economic, and infrastructural disparities hinder equitable access to innovations and fair management of patients with primary immunodeficiencies.	Find vectors for a meaningful and equitable change in management of patients with PIDs
Equity in accessibility. Ensure timely and fair access to AI-driven diagnostics, digital tools, and innovative therapies for PIDs and RD.	Healthcare disparities and limited scalability in expertise hinder equitable access and effective implementation of AI-driven innovations globally.	Scalability and implementation science to adapt technologies to diverse healthcare systems or to international standards
Harmonised legal and regulatory frameworks to support cross-border data sharing and AI deployment in healthcare.	Disjointed legal and regulatory frameworks complicate cross-border data sharing, AI governance, and the adoption of interoperable healthcare standards.	Encourage regulatory harmonization for data sharing, AI governance, and digital therapeutics across borders. Promote the use of common data models (e.g., openEHR) to improve data quality, structure, and interoperability across systems.
Provide a digitally literate and ethically aware healthcare ecosystem in which clinicians, patients, and policymakers understand, trust, and actively participate in the development and responsible use of AI and digital tools.	Insufficient AI literacy and ethical guidance amongst stakeholders hinder trust, engagement, and responsible adoption of digital health technologies.	Foster AI literacy and ethical awareness amongst clinicians, patients and policymakers through education, engagement, and co-design of tools. Promoting ethical guidelines in the use of AI or other computational tools.

Underdiagnosis and misdiagnosis

PIDs and SIDs should not be regarded as silos, as their shared biological and clinical foundations may extend deeper than previously thought. Both patients with PIDs and SIDs may present recurrent, prolonged, severe, or unusual infections, sometimes coupled with inflammatory or autoimmune complications, leading to fatal outcomes. Indeed, mortality in conditions like CLL or MM is associated with infections (25-45%), with SIDs affecting over 85% of patients (25–27). The prevalence of hypogammaglobulinemia is high in patients with B-cell lymphoid malignancies and is magnified by current and upcoming treatment options, such as CAR-T and bispecific monoclonal antibodies. Despite this knowledge, SID diagnosis is often delayed, similar to the long diagnostic timelines seen in PIDs. Moreover, specialists and patients often don't consider SIDs as a disease, but as a side effect of treatment, meaning there's a lack of understanding of SIDs potentially being an intrinsic aspect of the condition the patients are receiving treatment for.

Another bridge between these immunodeficiencies is the interplay between PID and cancer. PID have been correlated with up to a 5-fold increased risk of cancer, with a study revealing 62% of PID diagnoses in children with lymphoproliferative diseases. Cancer is a leading cause of mortality in PID patients, which is in line with recent data indicating that up to 20% of global human cancers are estimated to be related to infections, which are more frequent in immunodeficient patients. PID genetic variants may also become increasingly important when describing malignancy, as recent genetic screening studies have identified PID variants in patients with B-CLPD and have linked them to altered immunosurveillance, defects in DNA repair, and impaired B-cell biology (28). Such studies indicate that SIDs in these patients may be a consequence of undiagnosed underlying PID. However, many clinical manifestations are common between PIDs and SIDs, making differentiation challenging for physicians. Recent literature highlights the need to obtain individual and family medical histories, evaluate immunological parameters, and eventually conduct genetic studies when conditions such as B-CLPD are diagnosed, to help distinguish the two immunodeficiencies and optimise patient treatment (22). To accomplish this, risk stratification should be improved by incorporating predictors of infection risk, developing and employing treatments that mitigate the risk of SID, integrating faster treatment escalation plans, and conducting appropriate clinical trials of innovative therapies. Meanwhile, diagnostic approaches to immunodeficiency should evolve from reactive (*i.e.*, tests only when a severe infection occurs) to proactive (*i.e.*, preventing infections) by in-depth immune phenotyping and antibody testing before immune therapies are used and by considering evidence of immune dysregulation, syndromic features, malignancy, and family history (genetic sequencing) for appropriate and swift diagnosis.

Multidisciplinary team: two-way street

The increased risk of infections for patients with cancer and haematological malignancies highlights the necessity of multiple specialties in their care. The increased rates of pneumonia, upper respiratory tract infections, urinary infections, and skin and gastrointestinal infections justify the early onboarding of pulmonologists, urologists, dermatologists, gastroenterologists, amongst other specialties (29, 30). Moreover, given the nature of these infections, the inclusion of an immunologist on multidisciplinary teams (MDTs) is essential. Not only do infection prevention and management strategies often rely on PIDs expertise, but immunological and genetic testing may also bridge the current evidence gap, enabling stronger recommendations. Multidisciplinary on-line consultation platforms may help to face the issue of undiagnosed cases with complex and poorly defined phenotype, including patients with genetic disorders with some described immunodeficiency (such as in some metabolic diseases or in complex genetic diseases) (31). Personalised patient care approaches rely on partnerships between healthcare professionals (HCPs) and patients, ensuring that patients understand their diagnoses and treatments and take an active role in their health. Specialised nursing is essential in this context to ensure accessibility, support, ongoing follow-up and therapeutic education. Other specialties may be required depending on the clinical manifestations, with psychologist, psychiatrist or neurologist often needed in the case of neurodevelopmental deficits. The creation of highly specialised MDTs depends on establishing and strengthening collaborations across specialties and training HCPs. In particular, clinical immunologists and onco-haematologists or hematologist-oncologists should collaborate closely during the management of patients for whom SID is a likely outcome of first-line therapy (e.g. B-cell depletion). Furthermore, increased awareness of the shared territory amongst cancer, infections, and immune dysregulation would improve early diagnostic rates of immunodeficiency across specialties and facilitate monitoring and treatment optimisation. These steps would be advantageous for the long-term care of patients in onco-haematology departments, whether they develop SIDs or have underlying PIDs.

The central role of immunoglobulins

SID preventive strategies overlap with those used for patients with PIDs, namely antimicrobial prophylaxis, immunoglobulin replacement therapy (IgRT), and vaccination strategies, where appropriate. Current literature points to a relation between prophylactic IgRT and a reduced risk of clinically documented infection by 28% in patients with haematological malignancies, though more studies are needed to ascertain a correlation (32). The European Medicines Agency's current recommendations on IgRT in SIDs patients rely on a history of severe or recurrent infections or ineffective antimicrobial treatment, and/or proven specific antibody failure to pneumococcal polysaccharide and polypeptide antigen vaccines, or a serum IgG level of <4 g/L (considered hypogammaglobulinemia) (33). Recent advances in cancer immunotherapies, such as bispecific antibodies and CAR T-cell therapies, have increased their appeal due to their personalised, durable, and targeted effects, despite their potential for long-term immune system impact. In patients with MM receiving anti-BCMA bispecific antibodies and presenting with low IgG levels, IgRT has been associated with a marked reduction in severe infections, supporting its role as a primary prophylactic strategy even before

infections occur (34). This underscores the urgent need for recommendations specifically tailored to emerging cancer immunotherapies, which may require prophylactic or concomitant use of IgRT.

Although immunoglobulins (Igs) are the principal treatment for most patients with PIDs, their use is not exclusive to immunodeficiency patients. It is currently estimated that a third of the immunoglobulin supply worldwide is used to treat immunodeficiencies; whilst the rest is used in other Neurology and Haematology indications or might be used off-label (35). However, with the development of alternative treatments for certain neuropathologies, a reduction in IgRT use amongst these patients is expected, potentially facilitating an increase of supply towards PIDs and SIDs patients. This is the case for myasthenia gravis and chronic inflammatory demyelinating polyneuropathy, amongst others, for which therapies like anti-FcRn antibodies, complement inhibitors, CAR-T cells, and hypersialylated intravenous Igs are either approved or under evaluation in clinical trials. The adoption of these treatments as first line could reduce 12-25% of total Igs use for these conditions, increasing to 40% the use of Igs by patients with PIDs and SIDs by 2035. Moreover, the development of innovative HSCT procedures, including with haploidentical donors, and the emergence of gene therapies may reduce the number of patients with PIDs who require IgRT. Simultaneously, recombinant and engineered immunoglobulin approaches are being explored and may become available within the next few decades. With increasing rates of diagnosis of both PIDs and SIDs and increased use of innovative immunotherapy malignancy treatments, the number of patients requiring IgRT will grow. This projected demand growth of 5-6%/year in the next decade demands robust policies to ensure availability, accessibility, and affordability for patients globally. This will require increased plasma collection and yield, as well as resilient regional models that can withstand market and geopolitical challenges.

Redesigning the system

Optimisation of care for patients with PID and SID depends on the unification of efforts and proactive approaches across specialties that manage both groups. As the knowledge and understanding regarding the overlap of these conditions grows, multiple stakeholders need to adjust and redesign systems in most parts of the world to incorporate measures that leverage this knowledge and stand to significantly improve patient outcomes and quality of life.

Increased awareness and education amongst physicians about immunodeficiency amongst patients with haematological malignancies or autoimmune disorders is a crucial first step, followed by the adoption of MDTs as the standard of care. MDTs can help establish international guidelines for malignancy screening in immunodeficiency patients and for differential diagnosis to ensure early diagnosis of underlying PIDs in malignancy and SIDs cases, and to support adequate treatment and monitoring approaches. Exploration of the genomic landscapes of lymphoproliferative diseases, as is the case with B-CLPD, underscores the importance of interdisciplinary collaboration and integrated approaches to patient care, and the need for more data on this intersection with PIDs. Designing clinical trials aiming at elucidating the impact of immunotherapies could be a starting point to in these populations and to guide recommendations before treatment adoption and potential complications. Likewise, population-wide initiatives to identify opportunities for early intervention, thereby mitigating healthcare costs and patient burden, would be most beneficial in the long run. Novel multistakeholder collaboration models are at the centre of these paradigm improvements. Joint interdisciplinary scientific meetings, inclusion of patient organisations, and public-private partnerships are important mechanisms to strengthen collaboration amongst stakeholders and academic societies that currently operate in silos. Finally, pathways to improve patients' journeys when being diagnosed with PIDs or SIDs after a haematological diagnosis would also contribute significantly to their autonomy and quality of life. Proactive screening and early diagnosis of SID, personalised therapeutic approaches, specialised nurse care, and improved individual data collection are critical paths to enhance patient care and outcomes by 2035.

See Table 2 for the summary on the prospective (Where do we want to be? and How are we going to get there?).

PART 3: Preventive medicine in 2035: How will it apply to PIDs and associated conditions?

The field of PIDs and associated conditions is inherently complex and heterogeneous. The rule 'no size fits all' applies to PIDs, with or without an identified genetic cause, due to the diverse immune system components that may be affected, levels of penetrance, variables of unknown significance, and phenotypic variation. This results in varying clinical trajectories that may complicate diagnosis, treatment, monitoring, and care for these patients. However, new approaches to improve the quality of life for patients with PIDs are emerging, such as preventive medicine and mechanistic approaches, which could address complications before they develop. Exploring new microbiota therapeutic methods, elucidating the mechanisms underlying neurological symptoms in PIDs, and defining strategies to limit age-associated morbidity represent opportunities to improve outcomes in this population.

Microbiota's potential role in PIDs

Systemic IgG rarely reaches mucosal sites, except in cases of gut leakage, which may be induced by gut inflammation (36). Mucosal protection rather relies on locally produced antibodies, notably secretory IgA, which regulate the microbiota and present antigens to the immune system. This process is essential not only for managing densely populated ecosystems such as in the gut, where the microbiota can reach richness of as many as 10^{14} bacteria, but also for protecting against potential infections. Studies focusing on the link between gut colonisation and pathology are emerging, some suggesting a possible correlation, such as in the case of allergy, colorectal cancer, diabetes, and neurodevelopmental disease (37–40). Given the extensive relationship between the gut microbiota and the immune system, the phenotypes and severity of PIDs and

TABLE 2 Bridging the gap between primary and secondary immunodeficiencies – from common ground to better patient care.

Where do we want to be?	How are we going to get there?
1. Diagnosis of underlying PIDs in patients with SIDs as a standard procedure/part of the diagnostic guidelines. 2. Strengthen collaboration between immunologists and onco-haematologists for early diagnosis of PIDs and SIDs and appropriate treatment. 3. SIDs patients are followed by a specialised multidisciplinary team. 4. Reduction to zero delays in SIDs screening, monitoring and treatment strategies. 5. Immunoglobulins/IgRT are available to address growing demand and are accessible globally. 6. Have population-wide initiatives to identify opportunities for early intervention, mitigating burden and costs. 7. Have international guidelines and clinical trial designs to optimise the development of diagnosis, treatment and monitoring approaches for immunodeficiency patients.	1. Change diagnosis approach from classical/reactive to proactive, including using AI-assisted tools to identify underlying PIDs in patients with SIDs. 2. Generate more data on the intersection between PIDs and haematological conditions to develop guidelines and to implement multidisciplinary teams to care for patients. 3. Develop training and collaborations to train highly specialised multidisciplinary teams. 4. Improve risk stratification for better and faster treatment decisions by identifying predictors of infection risk in SIDs patients, developing engineered therapies that mitigate the risk of SIDs, designing new clinical trials that address SIDs and treatment efficacy in SIDs, and increasing efforts in raising awareness and education for immunodeficiency (SIDs/PIDs) amongst physicians. 5. Optimisation of plasma-derived immunoglobulin yield, distribution, affordability, and accessibility that is resilient to threats and changes in the geopolitical and economic climate. 6. Identify and integrate novel multistakeholder collaboration models and develop pathways to improve the patient's journey. 7. Strengthen collaboration between academic societies, including joint interdisciplinary scientific meetings, and patient organisations and public-private partnerships.

associated conditions may be linked to how dysregulation affects these interactions.

In this context, selective IgA deficiency (sIgAD) may be considered (41). Whilst sIgAD is the most common PID, it is believed to be underdiagnosed as it does not always lead to clinical disease (42). Despite associations with sinopulmonary infections, atopy, autoimmunity, and gastrointestinal infections, sIgAD is not correlated with severe immunodeficiency phenotypes. A study by Fadlallah et al. revealed that patients with sIgAD have bacterial diversity comparable to that of healthy individuals, differing mainly in the abundance of certain genera characterised by being bound to secretory IgA in healthy individuals. Interestingly, many bacterial genera bound to secretory IgA in healthy individuals did not have altered abundance in sIgAD patients, which was attributed partial IgM rescue, which, although not binding to all beneficial symbionts, partially compensated for the absence of IgA in these patients. Because of this incomplete compensation, microbiota disorganisation persisted, consistent with the patients' reports of respiratory and gastrointestinal infections. SIgAd patients have a private systemic IgG response to their own gut microbiota associated with less inflammation, which may be of interest to use for IgRT in PID patients with IgG deficiency rather than IgG from healthy donors (43). This may also justify why patients with Common Variable Immunodeficiency (CVID), the most common symptomatic/diagnosed PID, who receive IgRT, report ongoing gut inflammation.

Substitutive or targeted treatments for patients whose microbiota is affected, leading to recurrent infections, gastrointestinal inflammation, and other complications, remain lacking. Furthermore, preventive therapies to preserve microbiota diversity and regulate inflammation could also benefit quality of life and reduce the risk of complications in patients with PIDs. Supplementation with microbes at mucosal sites could be valuable if established as soon as possible in paediatric patients and preserved in adults, albeit bearing in mind that organisms considered commensal under normal circumstances can cause invasive or disseminated infections in patients with PID. Microbiome-based interventions in IEI remain investigational and may need to be tailored according to the underlying immune defect, weighing the potential benefits as well as the safety concerns. A potential treatment could be to produce patient-derived monoclonal IgG that retains the individual's unique capacity to interact with the patient's microbiota. Whilst personalised and potentially costly, it could be an efficient treatment for these patients when the technology permits it. Similarly, supplementing IgRT with IgG from sIgAD patient pools may provide additional protection for patients with CVID and dysbiotic gut microbiota, although challenges and manufacturing costs would need to be considered (43). Use of IgRT products that contain IgM and IgA, and mucosal antibody supplementation could also show advantages in these patients. However, further studies are needed to evaluate the efficacy, feasibility, and safety of these approaches, as the understanding of microbiota biology across multiple mucosal sites and its effects on health and disease remains insufficient, particularly in the field of PIDs.

Brightening the future of the mental health of patients with PIDs

Rare chronic diseases such as PIDs are associated with heavy mental burdens for patients, caregivers, and entourage. Be it because of long diagnostic odysseys with health deterioration and no answers, searching or struggling for access to the right treatment, or uncertainty regarding the future, living with immunodeficiencies may be psychologically distressing and emotionally overwhelming (44, 45). A broad range of psychological symptoms is reported by patients with PIDs, including fear of infections, social isolation, and lack of support, culminating in anxiety disorders and depression (44). Interventions should go beyond symptom management to achieve complete disease control that also include normalisation of health related quality of life. Beyond this psychosocial dimension, PIDs are also related to mental disorders and neuropsychiatric

comorbidities (46). In addition to patient self-reported data and questionnaires, genetic studies have now established a clearer link between PIDs and neurodevelopmental deficits (NDDs), autism spectrum disorder, and intellectual disability. Notably, a recent study by Serra et al. found that one-third of PIDs-causing genes are associated with NDDs, highlighting immune-NDD interactions mainly related to DNA repair pathways (47). NDDs aggravate the risk for mental health disorders, making it clear that with diagnosis of PIDs with genes related to NDDs should come a dimension of psychological support, though this is generally not the case. Moreover, besides genetic causes, infections can also cause neurological disorders. X-linked agammaglobulinemia is linked to central nervous system infections and the onset of neuropsychological deterioration, including dementia in young adults, despite IgRT and often without a known cause (46, 48). Aberrant (auto)immune responses to infections may also be associated with the emergence of NDDs, as suggested in Pediatric Acute-onset Neuropsychiatric Syndrome (PANS), Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal Infections (PANDAS), Sydenham's chorea (with psychiatric symptoms), and Post-Acute Infection Syndrome (PAIS).

Studies to explore whether genetic overlap between PIDs and NDDs may be wider than reported so far are warranted, along with evaluations on the contribution of nutrition, delay of PIDs diagnosis and treatment, autoantibody-mediated neuropsychiatric syndromes (e.g., anti-NMDA receptor antibodies in autoimmune disease), and post-infectious neuropsychiatric syndromes on the development of NDD by these patients. More data is also needed on gene-environment interactions, which may affect both the neurological and immunological compartments, and their intersection. Hence, collaboration between neuroscience and immunology ("neuro-immunology") is of utmost importance for the care and prevention of neurocognitive comorbidities in patients with PIDs. Additionally, standardised screening tools to facilitate early detection of NDDs in patients with PIDs and, conversely, of immune changes in patients with NDDs, could reduce diagnostic delays and make treatment and prevention strategies available sooner for these patients. To accomplish this, protocols for systematic assessment of mental health during and beyond clinic visits should be implemented. Tools such as wearables and mobile apps that detect subtle neurodevelopmental and sensorimotor deficits (e.g., eye tracking, hand-eye coordination, pulse-prepulse inhibition) and yield measurable, standardised data could also potentially aid physicians in understanding responses to treatment and disease progression [see: https://www.blinklab.org/] (49). Matching this information with genomic stratification and immune phenotyping would be ideal, fostering preventive and proactive approaches. Moreover, accounting for NDDs or learning delays in these patients early on can aid them and their caregivers in accessing care improving their QoL. Early behavioural interventions, social support, and follow-up by MDTs will contribute to preventing the development of anxiety disorders, depression, and other complications in these patients. Finally, reducing the stigma associated with PIDs and NDDs, and ensuring equitable access to psychological support for patients and caregivers are the first steps to improving their mental health. To achieve this, awareness, educational programmes on the importance of mental health, along with an introduction of NDDs screening tools and providing psychological and neurological support in PIDs centres, could significantly shift the paradigm and improve the well-being of patients.

Aging, immunity and immunodeficiency

Aging is a complex biological phenomenon that directly and indirectly affects the immune system (50). Age-related immune dysfunction leads to impaired specialised responses to self and foreign antigens with a decline in function, number and efficiency of components of the immune system (51). Also termed immunosenescence, this dysfunction is often associated with a low-grade chronic inflammation (called "inflammaging"), in which senescent immune cells release pro-inflammatory molecules leading to a senescence-associated secretory phenotype. As a result, aging individuals experience more infections and a higher prevalence of cardiovascular and neurological disease, malignancies, and autoimmune disease, with greater mortality and morbidity than other age groups (51). Whilst PIDs can often present in childhood, most patients are adults and age similarly to the general population, particularly given advances in clinical immunology (52). This warrants adapting the transition from adult to geriatric care in the field of PIDs.

The increase in infections and chronic inflammation with age is detrimental, accelerating immunosenescence and morbidity in patients with PIDs. Most PIDs prognoses are rarely described in elderly patients, leading to evidence gaps. A retrospective analysis of adults with CVID found that autoimmunity incidence was higher in patients older than 65 years and that neoplasia was the most prevalent complication in this age group when compared to younger patients (53). Other PIDs populations may benefit from similar studies to elucidate which complications may develop. A lower immunisation response in older patients also leaves them more vulnerable to infections. In parallel, patients with PIDs develop multimorbidity (*e.g.*, diabetes, hypertension, dementia), similarly to other elderly, necessitating specialists from those areas to monitor these conditions to preserve their quality of life.

Research indicates that the age-related onset of multimorbidity occurs earlier in socioeconomically deprived areas, with a concurrent increase in mental health disorders and the number of physical morbidities (54). Although data are limited in the PIDs population, it is reasonable to expect that the availability, accessibility, and affordability of care can adversely affect comorbidity indices in these patients. Thus, it is essential to ensure robust mechanisms of access to care and to complement them with cardiovascular screenings and other preventive strategies to mitigate the risk of morbidity (55). Additionally, a better understanding of the impact of treatments, such as HSCT and targeted therapies, on ageing and immunosenescence may help prevent morbidity and alleviate the infection burden. Research and registries can also substantially inform clinical recommendations for this population by collecting data on non-PIDs comorbidities (52). The development of longitudinal studies using appropriate metrics of ageing in patients with immunodeficiencies is crucial for evaluating the risk of cancer and morbidities and for guiding the development of preventive

approaches and innovative therapies to address immune exhaustion. By incorporating patients' perspectives on aging with PIDs and promoting shared decision-making, it is possible to develop personalised plans for aging with quality and to prepare end-of-life care. As life expectancy increases and understanding of PIDs and aging deepens, multidisciplinary collaboration, guidelines, standardised screening, psychological support, access to treatment, and inclusive preclinical and clinical trials will be the foundation to limiting senescence and slowing aging.

See Table 3 for the summary on the prospective (Where do we want to be? And how are we going to get there?).

Conclusions and recommendations

The fourth IPOPI Global Multi-Stakeholders' Summit identified key priorities and opportunities to improve the care of patients with PIDs and associated conditions by 2035. Recent technological and clinical developments represent opportunities to shape the next decade in the field of PIDs and associated conditions. Global equity in access to innovative therapies that can prolong longevity and quality of life for immunodeficient patients is increasingly attainable. Quantum communication networks and AI-derived risk stratification and screening tools can reach populations of patients that remain underdiagnosed and have the potential to reduce diagnostic delays and treatment inequalities in the future, provided their limitations and infrastructural demands are addressed and incorporated into ethically grounded frameworks. Investment in digital literacy, collection of high-quality, unbiased data, and inclusive clinical studies are essential to realise these technologies efficiently and fairly.

PIDs and SIDs share common ground, including symptomatology, diagnostic tools, therapies, and specialists, and should not be managed in silos. Both patients with PIDs and SIDs can benefit from streamlined diagnostic approaches and screenings that shift from reactive to proactive, including evaluation of immune status, as well as mental health and microbiota status. Drug discovery, even in fields parallel to immunodeficiencies, can directly and indirectly benefit patients by increasing the global availability of IgRT and by optimising personalised treatments.

Data collection from standardised tests and screenings will increase the size and quality of datasets, enhancing data registries and aiding AI systems in distinguishing causation from spurious associations. Curation of this data by MDTs can help distinguish trends and lead to robust guidelines for patient treatment and for the prevention and management of comorbidities, thereby reducing health-related burden and costs and improving care at the end of life. The psychological impact of PIDs and SIDs on patients remains largely overlooked, and the strong association between PID-causing genes and NDDs warrants guidelines and closer collaboration between neuroscience and immunology fields. Understanding the multiple facets of the immune system, such as the impact of the gut microbiota in immune regulation, offers options to personalise therapies and supplementation, which are promising venues for managing lifelong conditions like PIDs. Thus, preventive medicine offers substantial opportunities to improve quality of life and limit multiorgan complications in patients with PIDs and SIDs.

To achieve these improvements by 2035, two core principles should be instituted globally: strengthen multistakeholder

TABLE 3 Preventive medicine in 2035: how will it apply to PIDs and associated conditions?

Where do we want to be?	How are we going to get there?
1. Leverage understanding of microbiota biology (in different systems such as the gut, the respiratory tract and the skin) and its effect on health and disease to improve immunodeficiency therapies and prevent complications. 2. Use personalised approaches, including dietary measures and supplementation, based on scientific studies. 3. Neurology guidelines to explore the possibility of an NDD when a particular subset of symptoms arises. 4. Routinely implement established screening protocols for mental health and related issues during and outside clinical visits for PID patients at risk and support them as needed. 5. Establish a neuroscience and immunology ("neuro-immunology") field to optimise diagnosis, treatment and monitoring of patients at risk of mental health issues. 6. Use real-time patient data with wearables, software and patient-reported data to establish baselines, evaluate diagnosis outcomes, monitor treatment effects, start early interventions, and implement targeted therapies. 7. Equitable patient-centred care with multidisciplinary teams of clinical psychologists, neurologists, immunologists, gastroenterologists, and other specialties focused on monitoring, aging, and prevention of comorbidities. 8. Eliminate the stigma associated with PIDs and mental health and Neurodevelopmental Disorders/Disabilities. 9. Tackle the increase in the ageing-related comorbidity index as well as the burden of infections, multiorgan involvement, and complications in patients with PIDs. 10. Expand the metrics related to ageing in human health/biology and in patients with immunodeficiency, focusing on the life course of patients, including different transitions and events. 11. Incorporate patient perspective around ageing with PIDs and shared decision-making around end-of-life care.	1. Develop studies and generate data on microbiota physiology and dysbiosis in immunodeficiencies (and vice versa), including in inflammation, liver diseases, and respiratory diseases, to develop standardised tests and guidelines. 2. Carry out epidemiological studies on existing cohorts of patients to generate recommendations on dietary and supplementation measures. 3. Develop standardised tests and measurement tools to evaluate neurological/psychological disorders in PIDs patients. 4. Gather data and develop screening protocols focusing on the intersection between PIDs and Neurodevelopmental Disorders/Disabilities and establish support tools and systems for patients at risk. 5. Foster basic and translational research as well as clinical care bridging neuroscience and immunology. 6. Develop standardised wearable, software, and patient-reported data mechanisms to create tools that can be used by health care professionals and patients. 7. Train specialisation of multiple healthcare professionals to include aging and prevention of comorbidities in the patient-centred care focus. 8. Develop awareness and educational programmes on the importance of mental health and care in patients with PIDs. 9. Increase the understanding of inflammageing and immuno-senescence in PIDs and of the impact of treatments (e.g. targeted therapies, HSCT) on the ageing PIDs population through longitudinal studies and computational science approaches and develop innovative therapies to address immune exhaustion/boost the immune system. 10. Improve understanding of factors contributing towards immunodeficiency patients' ageing with complications, namely roles of germline mutations and epigenetic changes, disease-associated chronic inflammation as well as factors influencing these changes, such as microbiome, environmental factors (incl. endocrine dysregulations, climate change, medications, etc.). 11. Develop guidelines and screening tests to help patients and healthcare professionals plan for aging with quality.

collaboration and place the patient at the centre of development processes from inception. Education and awareness amongst HCPs of immunodeficiencies and the interconnections amongst specialties are imperative for the development of holistic, personalised care strategies that improve both quality of life and longevity in patients. In parallel, patient experience can raise awareness amongst all stakeholders, including the general population, whilst contributing first-hand knowledge to the development of databases, studies, and recommendations that will benefit the whole community.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

LM: Writing – original draft, Writing – review & editing. RS: Writing – original draft, Writing – review & editing. JP: Writing – review & editing. SF: Writing – review & editing. NG: Writing – review & editing. MC: Writing – review & editing. MH: Writing – review & editing. SS-R: Writing – review & editing. EC: Writing – review & editing. ML: Writing – review & editing. AB: Writing – review & editing. RC: Writing – review & editing. AA: Writing – review & editing. IB: Writing – review & editing. TA: Writing – review & editing. NR: Writing – review & editing. DL: Writing – review & editing. SB: Writing – review & editing. MvH: Writing – review & editing. RA: Writing – review & editing. MP: Writing – review & editing. JR: Writing – review & editing. NM: Writing – original draft, Writing – review & editing.

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Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

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