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Review

Immunomodulation in Congenital Immunodeficiencies: Targeting Innate and Adaptive Pathways

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Abstract

Primary immunodeficiency diseases (PIDs) or congenital immunodeficiencies are a heterogenous group of more than 450 genetically inherited diseases that involve defects in development, regulation or functioning of the immune system. Such conditions impair both innate and adaptive immunity, exposing patients to frequent infections, autoimmunity and inflammatory complications, as well as malignancy. Traditionally, supportive strategies including immunoglobulin replacement and prophylaxis with antimicrobial agents have been of significant use to management of the conditions. Nevertheless, current developments in immunological and molecular medicine are changing the horizon towards mechanism-directed immunomodulatory regimens targeting pathogenic cellular and molecular lesions. Unlike other recent reviews that would generally list novel agents by category, or focus on just a few key mechanisms to understand gene therapy/Hematopoietic Stem Cell Transplantation (HSCT), this review offers a synthesis of immunomodulatory strategies, centred around pathways, of both innate (e.g., Toll-like receptor stimulation, interferon signalling, and natural killer (NK) cell enhancement) and adaptive (e.g., T-cell reinstatement, B-cell regulation, and cytokine inhibition) immune axes. It explicitly reports the association between each strategy and its underlying immunology. We considered the newer modalities, such as cytokine mimics, immune checkpoint inhibition, gene therapy and gene editing, and small-molecule inhibitors (e.g., Janus kinase [JAK] and mechanistic target of rapamycin [mTOR] inhibitors), in the context of clinical rationale, molecular specificity, response durability, and long-term safety. One of our key contributions is our precision-focused immunology through omics, which describes how a multi-omics profile can be applied to classify PID endotypes, predict therapeutic responsiveness, and select interventions tailored to the individual. We also discuss useful and ethical obstacles to action, such as access inequities, doubts about the long-term immune effects, and ethical issues relating to pediatric gene editing. All these developments highlight the potential of the new era of precision immunomodulation to improve outcomes in congenital immunodeficiency disorders.

Keywords

Immunodeficiency diseases, Immunomodulation, Innate immunity, Adaptive immunity, Gene therapy, Biologics, Precision medicine

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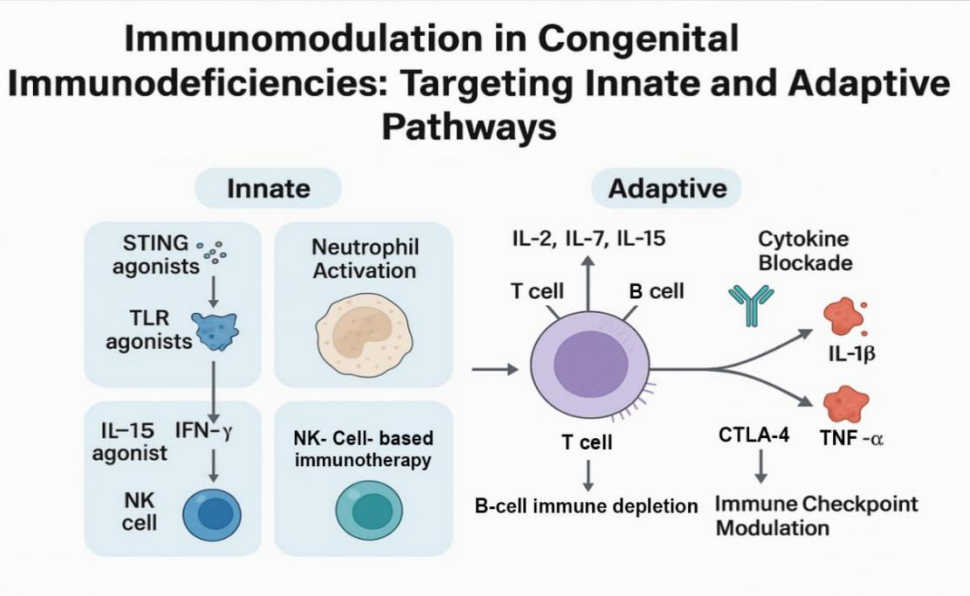
Graphical Abstract



This graphical abstract illustrates immunomodulatory strategies in congenital immunodeficiencies by targeting both innate and adaptive immune pathways. It highlights interventions such as stimulator of interferon genes (STING)/TLR agonists, NK cell-based therapies, and neutrophil activation on the innate side, alongside cytokine modulation, immune checkpoint regulation, and T- and B- cell–directed therapies within the adaptive immune system.

1. Introduction

Among congenital immunodeficiencies are primary immunodeficiency diseases (PIDs), characterised by a variety of disease genes that weaken the immune system [1,2]. Due to advances in genomics and immunology, these disorders are now being recognized more often, as they affect only a small number of births worldwide. When crucial genes involved in immune regulation, signalling, or cell growth are mutated, this can result in PIDs that may affect innate immunity, adaptive immunity, or both [3,4]. Some individuals with common variable immunodeficiency (CVID) experience frequent or harsh infections, long-lasting inflammation, various autoimmune markers, increased white blood cells and an increased risk of cancer [5]. In the past, patient care for severe combined immunodeficiency (SCID) focused on administering antibiotics to prevent infections, immunoglobulin therapy, and Hematopoietic Stem Cell Transplantation (HSCT) when needed [6]. Whilst they help many recover, they fail to restore the immune system and can result in unwanted complications, such as graft-versus-host disease (GvHD) or insufficient immune function. Thanks to new insights into immune function, scientists have developed drugs that target molecular pathways in the immune system [7,8]. The goal of our review is to examine foremost congenital immunodeficiencies in terms of innate and adaptive immunity, noting that affected immune signals can now be corrected using new biologics, mouse-like cytokines, gene therapy, and small-molecule inhibitors. Next, we consider the range of current and emerging treatments, the adoption of omics technologies for tailored care, the challenges of reaching patients, ensuring safety over time, and supporting young people. Targeting both the innate and adaptive immune systems, immunomodulatory treatments may help manage and cure diseases caused by defective immunity.

2. Characteristics of the Human Immune System and Patterns of Immunodeficiency Caused by Genetic Factors

2.1 Organization and Structural Functions of the Human Immune System

Even though it consists of cells, molecules, and tissues, human immunity maintains self-tolerance. They are divided into inborn immunity and acquired immunity, which act together [9]. The innate immune system quickly responds to any pathogen without any special targeting. The body's defences include its acidic interior, the skin and the mucous membranes. [10,11] Meanwhile, the adaptive immune system can recognize specific targets and remember them in the future. Within the system are B-cells that make antibodies, along with T lymphocytes, certain of which are helper or cytotoxic cells [12,13]. The large number of antigen receptors in this system arises from antigen presentation and genetic recombination [12]. The adaptive immune response takes time to mount, yet it is far more effective at handling pathogens if they recur [14].

2.2 Immunogenetic Background and Main Classes of Congenital Immunodeficiency Disorders

Disorders in important immune system genes are the reason inborn errors of immunity are now referred to as primary immunodeficiencies [2]. A person with these disorders may develop symptoms such as an increased risk of infection,

autoimmune diseases, inflammatory conditions, and certain cancers [15,16]. Mutations found in X-linked severe combined immunodeficiency (X-SCID) are located in Interleukin-2 Receptor Gamma chain (IL2RG), which constrains the γ-chain found in the receptors for interleukins 2,4,7,15 and 21 (IL-2, IL-4, IL-7, IL-15 and IL-21), causing both low T and NK cell numbers, along with inactive B-cells [17,18]. A decrease in V(D)J recombination is seen when recombination activating gene 1 or 2 (RAG1 or RAG2) is mutated, and this is what results in a lack of different antigen receptors and the typical Absence of T-cells and B-cells with preserved Natural Killer (NK) cells ($T^{-}B^{-}NK^{+}$) SCID [19]. Furthermore, chronic granulomatous disease (CGD) occurs when mutations in the Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase, particularly the Cytochrome b-245 Beta Chain (CYBB), prevent phagocytes from responding effectively to infections by bacteria and fungi [20].

2.3 Immune Dysregulation Beyond Infection Susceptibility

Although infections are a key feature of congenital immunodeficiencies, it has recently emerged that patients with PIDs may also exhibit immune dysregulation, among other problems. It is clear from this information that both an underactive and an overactive immune system can happen at the same time. If Cytotoxic T-Lymphocyte–Associated Protein 4 (CTLA-4) is homozygously deleted, it can lead to immune system dysfunction and cause autoimmune cytopenias and organ swelling [21]. Signal transducer and activator of transcription 1 or 3 (STAT1 or STAT3) mutations that allow STAT1 or STAT3 to acquire new immune functions can lead to issues such as candidiasis, cytopenias, and problems with the autoimmune endocrine system [22]. At present, increased inflammasome activity, metabolic control problems, and abnormal immune cell migration are associated with the development of many PIDs [23]. The overactivation of the NOD-Like Receptor Family, Pyrin Domain-Containing 3 (NLRP3) inflammasome explains how inflammation in the body can cause cryopyrin-associated periodic syndromes (CAPS), which are part of autoinflammatory disorders [24].

2.4 Evolving Classification and Therapeutic Implications

Prior to now, categorizing congenital immunodeficiencies was based mainly on the effects of the disease and the types of immune cells affected [25]. As our understanding of these areas improves, we classify these disorders primarily based on changes in their molecular pathways [25,26]. Using functional classification, assessing disease has become more reliable, and careful changes in the immune system can be identified. Those with a gain-of-function mutation in Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Delta (PIK3CD) can be treated with PI3Kδ inhibitors, whereas patients missing CTLA-4 benefit from abatacept, which helps restore proper immune function [27]. At the moment, these treatments are tailored to each individual's condition, using interferon gamma (IFN-γ) as an example for CGD. It is vital to fully understand how the two parts of the immune system function together and the exact causes of these diseases to design customized treatments for each pathway. Following precise medicine approaches is changing the trajectory and future of severe conditions that could not be treated before. Table 1 gives an overview of this.

Table 1. Immune components, genetic defects, clinical features, and targeted immunomodulation.

Immune Component	Associated Defect	Clinical Manifestations	Immunomodulatory Strategies	Ref.
Innate barriers (skin, mucous membranes, acidic milieu)	Not specified (functional barrier failure)	Increased susceptibility to diverse pathogens	Non specified	[9-12]
Adaptive immunity (T & B lymphocytes)	IL2RG mutation (X-SCID; common γ-chain for IL-2/4/7/15/21 receptors)	Low T and NK cells; inactive B-cells; severe/recurrent infections	Non specified	[14-18]
Adaptive immunity (antigen receptor generation)	RAG1/RAG2 mutations (↓V(D)J recombination)	$T^{-}B^{-}NK^{+}$ SCID; absent/limited antigen receptor diversity	Non specified	[17-20]
Neutrophils & phagocytes (oxidative burst)	NADPH oxidase deficiency CGD, often CYBB mutation	Recurrent bacterial/fungal infections; impaired phagocyte killing	IFN-γ therapy	[28,29]
Immune checkpoint regulation	CTLA-4 deletion/deficiency	Autoimmune cytopenias; organ swelling (immune dysregulation)	Abatacept	[21,22]
JAK–STAT signaling (immune regulation)	STAT1 or STAT3 gain-of-function mutations	Candidiasis; cytopenias; autoimmune endocrine disease	Non specified	[22]
Inflammasome signaling	NLRP3 inflammasome over-activation	CAPS; autoinflammation	Non specified	[24]
PI3K pathway signaling	PIK3CD gain-of-function mutation	Not specified	PI3Kδ inhibitors	[26]

Table 1 summarizes major immune components alongside representative genetic defects, their key clinical manifestations, and corresponding targeted immunomodulatory strategies. Overall, it highlights how specific pathway

disruptions (e.g., IL2RG, RAG1/2, CYBB, CTLA-4, STAT1/3, NLRP3, PIK3CD) map to characteristic infection susceptibility and immune dysregulation phenotypes, with select precision therapies available (e.g., IFN-γ, abatacept, PI3Kδ inhibitors).

3. Modifying the Innate Immune Pathway for Immunotherapy

When a pathogen enters the body, the innate immune system is the first to notice and react. It has cell components: neutrophils, monocytes, macrophages, dendritic cells and NK cells, as well as sensors on cells called Toll-like receptors (TLRs), NOD-like receptors (NLRs) and other pattern recognition receptors (PRRs) [28]. When working together, these parts detect pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), initiate inflammation, and direct the adaptive immune system. In primary immunodeficiencies, when both the adaptive and innate immune systems are defective, individuals tend to develop more infections from bacteria, viruses, and fungi, as well as problems with inflammation and autoimmunity [29]. Immunotherapy that works with the body's innate immune system is increasingly used, alongside or instead of HSCT and gene therapy.

3.1 Toll-like Receptors (TLRs) and Pattern Recognition Receptors (PRRs)

TLRs are essential components of innate immunity that help detect lipopolysaccharides (LPS), viruses, and unmethylated DNA motifs called Cytosine-Phosphate-Guanine (CpG) DNA [30,31]. Scientists found that defects in the signalling pathways of Myeloid Differentiation Primary Response 88 (MyD88) and Interleukin-1 Receptor–Associated Kinase 4 (IRAK4), which are linked to TLRs, can cause rare forms of immunodeficiency in children, often leading to severe and frequent bacterial infections [32]. Therefore, substances such as CpG Oligodeoxynucleotides (CpG ODNs) are being developed as synthetic versions of bacterial DNA to help stimulate dendritic cell maturation and cytokine release [33,34]. By taking agonists, immunodeficient people may see a stronger response to vaccines. Moreover, while investigating their effects, STING agonists have been found to enhance type I interferon activity [35]. They seem to offer great potential for immune-related conditions in which interferons are not correctly produced.

3.2 When Neutrophils and Phagocytes are Activated, They Attack Bacterial Cells

These two cells are important for their bactericidal action, as they both perform phagocytosis and release reactive oxygen species (ROS) through NADPH oxidase [36]. The CYBB gene mutation in CGD causes low ROS levels, leading the body to fail to clear infections, leaving it in a constant state of inflammation and resulting in granulomas [37]. In CGD, interferon gamma significantly enhances macrophage activity and reduces the risk of infection. Still, the use of IL-1 receptor antagonists, such as anakinra, helps manage symptoms of CGD-associated autoinflammation by reducing excessive inflammasome activity [38,39]. In addition, new strategies targeting oxidative bursts and phagocyte function are being studied to control the body's immune response without causing excessive tissue damage.

3.3 NK Cell Treatments

NK cells are naturally occurring lymphocytes that help eliminate virus-infected and cancerous cells. When NK cells do not function properly, the resulting condition or combination of symptoms is evident in guanine-adenine-thymine-adenine (GATA) Binding Protein 2 (GATA2) deficiency, disorders linked to the Minichromosome Maintenance Complex Component 4 (MCM4) gene, and some instances of combined immunodeficiency [40,41]. NK cell immunotherapy uses IL-15 superagonists to boost NK cell numbers and enhance NK cell killing of cancer cells [42]. Also, Bispecific Killer Cell Engagers and Trispecific Killer Cell Engagers (BiKEs and TriKEs) have been developed to direct NK cells toward targets to help manage PIDs and virus-related cancers [43]. These techniques are currently being investigated in both early laboratory and clinical experiments.

3.4 Balancing Efficacy and Safety

Although stimulating the innate immune system provides a quick systemic immune boost, the main challenge is avoiding immune overactivation and cytokine release. To prevent or reduce these risks, medicines should be given with precision, patients should be selected based on biomarkers, and the best doses should be chosen. Despite this, managing congenital immune diseases with innate immunomodulation shows great potential in cases where HSCT cannot be used, or the patient has only partial immune weakness.

4. Modulation of Adaptive Immune Pathways

The body's precise and lasting immune responses are organized by the adaptive immune system which consists of T and B lymphocytes. The process includes clonal selection, the ability to remember past infections and identifying specific antigens, safeguarding people from illness and helping them tolerate their own body [44,45]. Several congenital problems in immunity disrupt the growth, functioning and organization of T-and B- cells, leading to repeated infections, immune disorders and cancer [46]. Adjusting the immune system in specific ways could improve its function and control any problems Table 2.

Table 2. Mechanism and therapies by the immune pathway (Adaptive immune modulation).

Immune pathway	Key node(s)	Defect/mechanism	Representative disorder/phenotype	Targeted therapy	Effect	Ref.
T-cell development/ reconstitution	IL2RG, JAK3; RAG1/2; ADA; HSC	T-cell aplasia; lymphopenia; V(D)J failure; toxic metabolites	SCID (X-linked; ADA-SCID)	Gene addn (HSC); HSCT	Immune reconstitution; infection control	[47-50]
T-cell homeostasis (lymphopenia)	IL-7; IL-15	Low thymopoiesis; low peripheral T-cells	Post-HSCT delay; chronic viral lymphopenia	Cytokine support: rIL-7, rIL-15	↑thymic output; ↑T-cell expansion	[51,52]
Treg tolerance	FOXP3; Treg	Treg deficiency/dysfxn; loss of tolerance	IPEX	Low-dose IL-2 (Treg expand)	↑Treg; ↓autoimmunity/inflammation	[53]
Treg–effector balance/ lymphoproliferation	mTOR axis	Effector skew; lymphoproliferation	ALPS	Sirolimus (mTOR mod)	↓lymphoproliferation; immune balance	[54]
B-cell antibody production	B-cell maturation; Ig	Hypogammaglobulinemia; poor vaccine response	XLA; Hyper-IgM; CVID	Ig replacement (IVIG/SCIG)	Passive protection; ↓infections	[55]
B-cell clonal expansion/ auto-cytopenias	$CD20^{+}$ B-cells	Autoreactive/ expanded clones	$CVID^{+}$ auto-cytopenias; B-cell hyperplasia	Rituximab (anti-CD20)	↓abnormal clones; ↓cytopenias	[56]
PI3Kδ hyper-signaling (B/T)	PI3Kδ pathway	Gain-of-signal; immune dysregulation	APDS (lymphadenopathy; infections; autoimmunity)	Rapamycin; Leniolisib	Signal normalization; clinical improvement	[57-60]
Th1/IFN-γ axis	IL-12Rβ1; IFN-γ	↓Th1; ↓IFN-γ; weak macrophage activation	Mycobacterial susceptibility (e.g., TB risk)	rIFN-γ (bypass)	↑macrophage activation; improved control	[61,62]
Th17 overactivity/ cytokine excess	STAT3; IL-6; IL-17	Th17↑; inflammation↑	CMC; autoimmunity; lymphoproliferation	Tocilizumab (IL-6R); Secukinumab (IL-17A)	↓IL-6/IL-17 inflammation; targeted control	[63,64]
Precision repair (future)	CRISPR/ Cas9; multi-omics biomarkers	Mechanism-matched correction	Personalized immune deficiency/dysregulation care	Gene editing; biologics; biomarker-guided tx	Precision immune restoration; ↓complications	[65-68]

Table 2 summarizes the major adaptive immune pathways (T-cell, B-cell, Th1/Th17, and Treg axes), highlighting key molecular nodes, associated immunodeficiency/dysregulation phenotypes, and the dominant therapeutic targets. It provides a concise mapping from pathogenic mechanism → targeted intervention (gene therapy/HSCT, cytokines, biologics, pathway inhibitors) to the expected immunologic or clinical benefit, with supporting references.

4.1 T-Cell Pathways: Development, Regulation, and Reconstitution

T lymphocytes are involved in cellular immunity, acting in cytotoxic defense, providing help and managing immune responses. Because IL2RG (γ-chain), RAG1, RAG2, Adenosine deaminase (ADA) and JAK3 genes are mutated, SCID leads to failure of T-cells and absence of most lymphocytes [47]. Scientists have managed to correct these mutations in patients by adding appropriate genes to the hematopoietic stem cells with lentiviral or retroviral vectors [48,49]. In X-linked SCID and ADA-deficient SCID patients, corrective stem cell transplantation has helped restore their immune function [50]. Cytokine-based immunotherapies are investigated to support and increase the number of T-cells. Recombinant IL-7 and IL-15 have beneficial effects on thymus function and on T-cell growth in the peripheral blood during times of lower immunity. IL-7 has proved effective in helping T-cells recover after a transplant and in cases of long-term viral infections [51,52]. In the immune disorder known as Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-linked syndrome (IPEX) syndrome, a Forkhead Box P3 (FOXP3) mutation sometimes causes an excessive immune response throughout the body by affecting Tregs [53]. Therapeutic methods use low-dose IL-2 to increase the number of Tregs, consequently recovering the immune system's tolerance. In autoimmune lymphoproliferative syndrome (ALPS), sirolimus and similar drugs are prescribed to balance Tregs and effector T-cells and, thereby, control lymphoproliferation and prevent further harm to the body caused by the immune system [54].

4.2 B-Cell Pathways: Antibody Production and Signal Modulation

Humoral immunity depends on B-cells and their ability to produce antibodies. X-linked agammaglobulinemia, hyper

IgM syndrome and CVID are included in primary B-cell immunodeficiencies. They are marked by frequent infections of the nose and lungs, along with poor reactions to vaccines [55]. Among treatment options, management includes giving immunoglobulins regularly by injection which gives the patient short-term protection. Generally, monoclonal antibodies play a role in changing immune function in diseases triggered by B-cells. In CVID patients experiencing autoimmune problems with blood cells or an abnormal growth of B-cells, rituximab works to lower abnormal B-cell clones [56]. Activated Phosphoinositide 3-Kinase (PI3K) Delta Syndrome is an example of a disease due to excess activity in B-cell and T-cell signals. In some cases, it causes an enlargement of the lymph nodes, many infections and autoimmune diseases. Medications like rapamycin and leniolisib decrease abnormal signals and bring the immune system back to normal, improving the outcomes for patients [57].

4.3 Alterations in T Helper Cell Differentiation and Regulation of Related Cytokine Pathways

The immune system's response is guided mainly by t-helper (Th) cells which work through the subsets included Th1, Th2 and Th17 cells [58]. Subsets of T-cells do specific functions for host defense: Th1 mediates immunity for cells inside the body by making IFN-γ, Th2 supports the body's humoral immune response against parasitic worms by releasing IL-4, IL-5 and IL-13 and Th17 is necessary for fighting fungi and extracellular bacteria since it makes IL-17 and IL-22 [59,60]. Selective infections and problems with the immune system may be the result of abnormalities that interfere with cytokine signals. In particular, changes in IL-12Rβ1, the receptor for IL-12 and IL-23, allow Th1 cells to develop poorly and produce less IFN-γ [61]. As a result, patients are more at risk from diseases like tuberculosis which are spread directly into their cells. Here, the use of recombinant IFN-γ therapy is helpful since it restores macrophages' activation, working around the initial issue [62]. However, too much activity in the Th17 signaling pathways characterizes immune dysfunction states resulting from overactivity in the STAT3 protein. Usually, these conditions include chronic mucocutaneous candidiasis, autoimmunity and lymphoproliferation [63]. Because IL-6 and IL-17 are involved in inappropriate inflammation, new treatments are being made that target these proteins such as tocilizumab and secukinumab. What we have learned at the clinic points to the significance of careful control of Th cells. Now, instead of always weakening the immune system, immunotherapies are working to correct the problems with Th cells using special cytokine modulators [64]. Approaches aimed at addressing certain defects in the immune system may improve care for patients with inherited immunity problems and help stop both infections and autoimmune complications.

4.4 Outlook for Adaptive Immune Modulation

There is a current shift from treating patients with immunosuppressive drugs to tailor-made therapies that manage their specific needs. In addition to the usual immunoglobulin and prophylactic antibiotics, there are now steps being taken to handle the molecular reasons behind unique immune deficiencies. Thanks to advances in Clustered Regularly Interspaced Short Palindromic Repeats / CRISPR-associated protein 9 (CRISPR/Cas9) and related gene editing tools, it will soon become possible to correct issues caused by a single gene mutation which could change how the immune system is repaired [65]. Furthermore, handling immune deficiency and dysregulation has benefited from IFN-γ and IL-7 injections and monoclonal antibodies. By adjusting important T-cell and cytokine responses, biologics allow doctors to adjust the immune system without suppressing it completely [66,67]. Use of multi-omics tools such as genomics, transcriptomics and proteomics now improves the accuracy of medical decisions in clinical settings. Using biomarkers in the right way during therapy improves the success rate of personalized immunotherapy for clinicians [68]. They bring together a new way of handling adaptive immunity which could provide patients with better correction of their immune system, improved living conditions and help prevent serious future complications.

5. Immunomodulatory Therapies and Biologics

The availability of biologics and small-molecule drugs has improved how various PIDs with immune dysregulation or similar symptoms are managed [69]. They influence certain molecules and cells that activate the immune system, providing a targeted way to tackle diseases, cause fewer serious systemic problems and may keep the immune system adjusted over the long run.

5.1 Cytokine Blockade in Inflammatory PIDs

These days, doctors are turning to biologic therapies that target inflammatory cytokines to treat PIDs with high autoinflammatory rates [70]. They are better than traditional immunosuppressive therapies as they focus on controlling harmful cytokines and leave the immune system largely unaffected. Disorders caused by the inflammasome have been successfully addressed using IL-1 blockade. Using anakinra and canakinumab or other IL-1 receptor antagonists or IL-1β-blocking antibodies, has helped in treating colitis linked to CGD and joint problems in systemic juvenile idiopathic arthritis, as well as many other monogenic autoinflammatory syndromes [71]. The therapies work by interrupting the cascade caused by IL-1 which becomes too active due to errors in the genes regulating the inflammation system. IL-1 inhibitors have greatly helped patients by reducing fever, abdominal symptoms and signs of inflammation and also avoid the widespread immunosuppression corticosteroids can cause. Likewise, disease-modifying drugs called TNF-α inhibitors which include infliximab and etanercept, are provided to people with PIDs and granulomas such as

CVID [72]. Such agents are able to ease the symptoms of lymphoid hyperplasia, difficulties with the lungs and ongoing diseases of the digestive system. Still, using TNF-α blockers can increase the chance of reactivating tuberculosis, histoplasmosis and other infections in people who have had them in the past [73]. For this reason, it is important to screen the patient before treatment and to carefully keep an eye on them during the entire process. There are unique cases where anti-TNF therapy is favored, since standard immunosuppressants are either unable to work or thought to be unsafe.

5.2 Checkpoint Inhibitors and mTOR Inhibitors

Many primary immunodeficiency syndromes are characterized by immune dysregulation that leads to autoimmune disease, more lymphatic cells and ongoing inflammation. For this reason, using drugs that affect immunity and cell communication is becoming a common and rational approach. Sometimes, patients are treated with abatacept which copies CTLA-4 and acts as an immune checkpoint receptor that suppresses the activity of T-cells [74]. Since patients with CTLA-4 haploinsufficiency or lipopolysaccharide-responsive beige-like anchor protein (LRBA) deficiency have Treg impairment and uncontrolled effector T-cells, abatacept works by controlling T-cell activation. In patients, the drug has been seen to help manage autoimmune cytopenias, bowel problems and overactive lymph cells by correcting issues with T-cell tolerance [75]. Simultaneously, controlling the mTOR pathway has been helpful for patients with ALPS and activated PI3K delta syndrome. By using sirolimus, the mTOR inhibitor, lymphoproliferation and autoimmune symptoms are controlled because it increases the number and stability of regulatory T-cells which decreases the activity and amount of cytokines from overactive T-cells [76]. The use of immunotherapy has helped many patients whose disease does not respond to other treatments to go into remission. In general, using immunomodulatory drugs to target certain immune pathways illustrates how precision medicine is becoming common in PIDs.

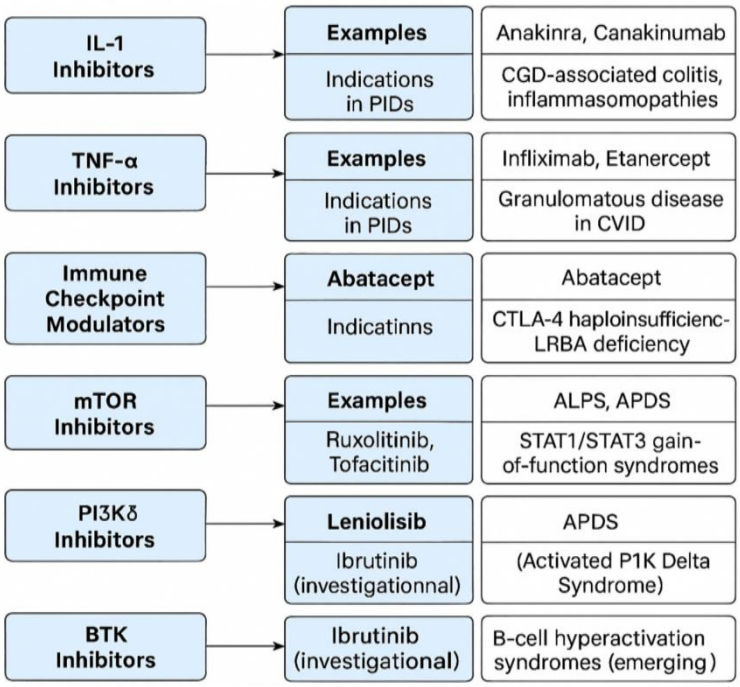


Figure 1. Selected biologics and targeted therapies in PIDs.

Figure 1 summarizes targeted immunomodulatory therapies used in primary immunodeficiencies (PIDs), grouped by pathway: IL-1 inhibitors, TNF-α inhibitors, immune checkpoint modulators, mTOR/JAK-targeting agents, PI3Kδ inhibitors, and BTK inhibitors. For each class, the figure lists representative drugs and highlights selected PID-related indications, illustrating how pathway-directed therapy can be matched to specific inflammatory or immune dysregulation phenotypes.

5.3 Targeting Intracellular Signalling Cascades

In many cases in which the immune system is constantly hyperactive and leads to autoimmunity, a disrupted JAK-STAT intracellular signalling pathway is responsible [77]. Alterations involving the STAT1 and STAT3 genes, known as gain of function (GOF), are reported in a high percentage of studies on SCID [78]. They increase gene activity involved in inflammation, leading to problems in T-cell development, persistent inflammation of the skin and mouth, autoimmunity, and too many white blood cells. Treatment with ruxolitinib and tofacitinib has become a useful means to control the overactivation of JAK kinases. When these agents block JAK-related phosphorylation of signal transducer and activator of transcriptions (STATs), cytokine responses become normal, and tolerance is restored in the

body. Treatment with JAK inhibitors [79] has shown positive results for autoimmune cytopenias, intestinal inflammation, and other inflammatory conditions in patients harbouring active STAT1 or STAT3 mutations, when combined with effective follow-up. In cases like APDS, which result from PIK3CD or PIK3R1 alterations in B-cells, excessive activity in the PI3K-AKT-mTOR pathway is responsible for lymphadenopathy, frequent infections, and disturbances in the immune system. In patients with APDS, leniolisib appears to reduce lymphoma growth and restore immune cell levels to normal [80]. Furthermore, BTK inhibitors, which were initially created for B-cell cancer, are being considered for use in patients with hyperactive immune systems [81]. Because these interventions are precise, they help manage altered intracellular signalling cascades and have made a major impact on treating immunodeficiencies defined by the genes involved. As agents gain experience, they are expected to play a key role in therapy for some PIDs.

5.4 Precision Use of Biologics

Advances in technology are changing how primary immunodeficiencies are managed. Now, biologics and small-molecule therapies can be selected based on patients' genetics and immunology, not just their symptoms. Therefore, precise immunotherapy is increasingly important in PID care, as it is guided by disease progression. Newer biologic medicines are prescribed more often to target specific abnormal molecules, such as IL-1, IL-6, IL-17, CD20, or CTLA-4 [71,82]. Cancer treatments also benefit from using smaller molecules, called inhibitors, to redirect signalling messengers called JAK, PI3K and mTOR [83]. As a result, the treatment becomes more effective, and the risks of having strong immunity, other infections and side effects are reduced. In fact, the accurate use of biologics helps patients with PIDs get treated sooner, alters the disease process, and helps maintain their organs over the long term. Further progress in biologic therapies will benefit patients as new monitoring and adjusting management methods are introduced. The use of a more precise strategy is shifting the field of inborn errors of immunity care toward a focus on specific causes.

6. Application of Gene and Cellular Therapy in Congenital Immunodeficiencies

Gene and cellular therapies have led to significant improvements in the management of PIDs. Older immunology treatments manage reactions, but newer ones address the underlying issue in the immune system and can restore immunity indefinitely. Thanks to our improved knowledge of immunity and genes, cell and gene therapy is now being studied for some serious illnesses in children.

6.1 Hematopoietic Stem Cell Transplantation

For severe PIDs with extreme T-cell insufficiency, such as SCID, Wiskott-Aldrich syndrome, and some combined disorders, HSCT is considered the primary treatment that can cure the condition [84]. A healthy stem cell from a suitable donor is infused into the patient's blood through a needle while they receive medicine to keep the donated stem cells alive. Due to improvements in donor selection, the use of mild chemotherapy, and better GVHD prevention methods, outcomes of HSCT have improved in the last few years. People with matched HLA donors have better chances of surviving, especially when they receive an organ transplant during childhood before any serious infections start [85]. Most infants with SCID who undergo rapid HSCT show significant improvement in their immune system and tend to live much longer [86]. Still, HSCT carries some risks. Conditioning can lead to toxic side effects and serious or lasting GVHD, as well as slow recovery of B-cells, which may be managed through long-term immunoglobulin replacement and other steps [87]. It is important to select patients wisely, diagnose them quickly, and apply different protocols to minimise long-term problems after transplants.

6.2 Autologous Gene Therapy: Correction at the Source

Using a patient's own genes (autologous) is now considered a better alternative to using hematopoietic stem cells from other donors (allogeneic) for the initial treatment of PIDs. Unlike HSCT, the patient's hematopoietic stem cells are not infected with the disease, and there is no risk of GVHD because their own stem cells are used. In this method, stem cells are removed from the patient's body, modified in a laboratory using viral vectors, and returned to the patient after conditioning with conditioning drugs. Several well-documented immunodeficiency syndromes have responded well to this type of therapy. Examples of these diseases are SCID due to IL2RG mutations (X-SCID), the lack of the enzyme ADA-SCID, Wiskott-Aldrich syndrome (WAS) and CGD caused by mutations in the CYBB gene [84]. Enzyme expression and the number of T-cells remain high in patients with ADA-SCID treated with lentiviral gene therapy, and these outcomes are comparable to those observed in children treated with HSCT [88]. While gene therapy in X-SCID assists T-cells, B-cells and NK-cells do not develop fully. The latest developments in vector design, safety, and clinical trial organisation have enabled gene therapy to target more types of PIDs. When gene therapy becomes accessible worldwide, it may help treat more patients with immunogenetic diseases.

6.3 Gene Editing and CRISPR-Cas9 Technologies

With CRISPR-Cas9, gene-editing technologies are enabling more effective treatment of PIDs. Unlike the traditional viral vector approach, CRISPR-Cas9 can repair faulty genes and genetic mutations at their genomic locations [89]. It

allows cells to use their own networks instead of synthesising new ones, which means more genes are changed if the virus accidentally inserts itself somewhere in the genome. When used with CRISPR-Cas9, a custom-designed RNA directs double-stranded breaks at a specific site in DNA. Usually, the process involving Homology-Directed Repair or Non-Homologous End Joining (HDR or NHEJ) in cells is used to correct the break and repair the mutation [90]. Studies outside of clinical trials have successfully repaired RAG1 and RAG2 mutations and corrected IL7R and STAT3 gain-of-function mutations using CRISPR in mouse cells [91]. There are still barriers to this technology being used by medical professionals. Examples of these challenges include editing the DNA at the wrong place, getting editing molecules into the required cells, and ensuring the corrected cells remain functional in the body. Some platforms, such as prime editing and base editing, are now being invented that avoid cutting both DNA strands [92,93]. They may thus provide safer and more precise methods for clinical use in the future.

6.4 T-Cell and CAR-T-Based Therapies

People with PIDs who continuously suffer from viral infections or have disturbances in their immune system are now sometimes treated with adoptive T-cell therapy. People facing this condition benefit from using virus-specific cytotoxic T lymphocytes and, in particular, Epstein-Barr Virus-specific cytotoxic T Lymphocytes (EBV-specific CTLs). These days, Chimeric Antigen Receptor T-cell (CAR-T) therapy, originally developed for blood cancers, is being considered for individuals with weakened immune systems [94]. The purpose of CAR-T therapies is to destroy troublesome cells, leaving the typical immune system capable of action. They may use T-cells collected from a patient or provided by donors, and they can be tailored to each patient's needs. In cases involving PIDs, CAR-T therapy shows potential for treating refractory infections, lymphoproliferative disorders, and malignancies associated with immune disorders [95]. While still under investigation, these technologies can help control diseases more effectively and provide additional treatment options for people with weak immune systems in difficult cases.

6.5 Challenges and Future Directions

Even so, it is very costly to develop and maintain these therapies, and follow-up with patients afterwards takes time. All possible efforts should be directed toward preventing problems such as insertional oncogenesis, unintended editing errors, and harmful effects on the immune system. In some regions, there are not enough funds and equipment to use these types of medical treatments. Still, having additional trials, sharing efforts across borders, and using updated strategies increase the likelihood that these therapies will be made safe. It is expected that, in a few years, gene and cellular therapies will become the primary means by which healthcare providers treat many PIDs [96,97]. Gene and cellular therapies target the main genetic and cellular problems in patients with PIDs. Even though many rely on HSCT for a cure, alternatives for patients include autologous gene therapy and gene editing. Recent techniques for managing persistent infections and cancers that involve the immune system are virus-specific CTLs and CAR-T-cells [98]. The main strategies are outlined in Table 1, and their use in the treatment of congenital immunodeficiencies is also explained there.

7. Precision Immunology and Biomarker-Driven Approaches

The application of precision immunology to health care will change treatment of congenital PIDs. In addition to relying on the easy indicators and making random prescriptions, the accuracy immunology depends on official information provided by the DNA, proteins, RNA, biochemicals and bacteria of a person to promote individualized medical services [99]. In such a way, the physicians can be confident about the diagnosis, be able to plan the future, prioritize the disease, and cure each case to achieve the best results. Table 3 gave an overview of therapeutic strategies for PID.

Table 3. Overview of gene and cellular therapies for PIDs.

Therapy Type	Target Conditions	Advantages	Challenges	Ref.
Allogeneic HSCT	SCID, Wiskott-Aldrich Syndrome, CGD	Established curative approach; broad immune reconstitution	GVHD, donor matching, conditioning toxicity	[84-87]
Autologous Gene Therapy	X-SCID, ADA-SCID, Wiskott-Aldrich Syndrome, CGD	Patient-derived cells; no GVHD risk; sustained gene correction	Vector integration risks, limited access, high cost	[84,88]
CRISPR-Cas9 Gene Editing	RAG1/2 Deficiency, IL7R Deficiency, STAT3 GOF (preclinical)	Precise gene correction; endogenous regulation preserved	Off-target editing, delivery barriers, early clinical stage	[89-93]
Virus-Specific CTLs	EBV-Associated Lymphoproliferative Disease (post-HSCT)	Targeted viral control; minimal off-target effects	Short-term persistence, donor cell preparation	[96]
CAR-T Therapy	Immunodeficiencies with refractory autoimmunity or malignancies	Specific immune targeting; potential for immune sparing	Cytokine release syndrome, manufacturing complexity	[94-96]

Table 3 provides an overview of gene and cellular therapies for PIDs, detailing their target conditions, benefits, and limitations. It includes established treatments like allogeneic HSCT and emerging approaches such as CRISPR-Cas9 gene editing and CAR-T therapy. While these strategies offer the potential for lasting correction or targeted immune modulation, they are often limited by risks like GVHD, off-target effects, and high technical demands.

7.1 The Use of Genomic Sequencing in Both the Diagnostic and Prognostic Approached

Whole-genome sequencing has greatly enhanced the ability to identify genes responsible for PIDs. Currently, whole-exome sequencing (WES), whole-genome sequencing (WGS), and targeted gene panels are standard approaches for identifying immunodeficiency-associated genes [100]. These techniques enable comprehensive analysis of the entire DNA sequence, including regions that may be missed by conventional diagnostic tests. Through scientific research, clinicians have been able to correlate variants in immune-related genes-such as IL2RG, ADA, RAG1/2, CTLA-4, LRBA, and members of the STAT gene family-with disease phenotype, age of onset, potential complications, and optimal treatment strategies [101-103]. X-SCID is confirmed by the presence of IL2RG mutations in infants presenting with profound lymphopenia and typically necessitates HSCT or gene therapy [104]. Similarly, when WES identifies pathogenic ADA mutations in patients exhibiting poor or delayed weight gain, gene therapy can be initiated promptly [105]. Genetic analysis is therefore valuable not only for predicting disease prognosis but also for guiding therapeutic decision-making. In cases involving CTLA-4 or LRBA mutations, the clinical presentation is usually immune dysregulation syndrome, for which biologic agents such as abatacept or sirolimus are commonly administered [75]. Furthermore, the detection of pathogenic RAG1 variants can explain impaired immune function and support the use of immunoglobulin replacement therapy and antimicrobial prophylaxis [103,106]. Importantly, genomic sequencing also facilitates family screening and genetic counseling [107]. Early identification of affected siblings or carriers allows healthcare professionals to monitor at-risk individuals and implement timely interventions to prevent disease manifestation [108]. As sequencing technologies become increasingly cost-effective and efficient, their integration into routine clinical testing will reduce prolonged diagnostic delays and enable earlier, more precise treatment, ultimately improving outcomes and quality of life for patients with PIDs.

7.2 Immune Profiling and Dynamic Biomarkers

The basic concept is provided by genomic sequencing which looks into the mistakes in PIDs and the immune profiling indicates the working of the immune system nowadays. These methods are quite applicable in studying the activities, variations and abnormality of immune cells in the body under short time [109]. Regulatory T-cells can be carefully analyzed by use of flow cytometry; other forms of B and NK cells can be analyzed too [110]. With these profiles, CVID or ALPS can be diagnosed and choices on useful preemptive treatment made. In addition, HLA-DR, CD38, PD-1 and CTLA-4 will come in handy to ascertain the state of immune cells in the condition of continuous inflammation or infection [111]. It provides a closer information on the immune state of the body by distinguishing between immune system components that have been put into action and those that have not. When a patient with a fever demonstrates the presence of high levels of IL-1b, IL-6 or IFN-gamma, it could be considered an autoinflammatory syndrome, however, high levels of IL-10 or TNF-alpha may be observed in hyperinflammatory conditions - such as hemophagocytic lymphohistiocytosis (HLH) [112,113]. Biomarkers can be used to monitor the response of the patient to these immunosuppressant or cytokine medications and customize treatment. It is now becoming appreciated that immune repertoire sequencing of B and T-cells is available. An unbalanced proportion of antibodies can indicate that the immune system is not functioning well and there is a probability of lymphoma just as it happens in common variable immune deficiency and other forms of immunodeficiencies [113]. Integrating the dynamic biomarkers and clinical parameters can enhance the diagnosis of an illness and assist in tracking and categorizing the illness as time goes by [114]. Overall, the immune system analysis can be useful in the context of genomic information, enabling physicians to choose appropriate treatment options, monitor the effects of the treatment and anticipate potential autoimmune, infectious or cancerous problems in the patients with PIDs.

7.3 Multi-Omics and Microbiome Insights

Multi-omics technologies have aided to fortify on the comprehension of the immune system in the patients with PIDs. Whereas genomic sequencing merely identifies the changes in DNA, the omics technologies track the changing activities of genes or proteins, metabolism and controls of diseases, treatment or environmental changes [115]. They also provide us with a chance to identify new disease biomarkers to early detect diseases, to warn about upcoming flares, to measure therapy response and to know why certain treatments do not work. With the help of proteomics, one is able to reveal proteins which are either more prevalent in activated or suppressed immune systems. In addition, an increase of acute-phase proteins or S100A8/A9 indicates that the inflammation or an autoimmune process continues to occur [115,116]. The examination of transcriptomes in peripheral blood allows establishing whether a child with an IEI has a fever with an infectious or an autoimmune cause [117]. These non-invasive tests prevent cases where many unnecessary biopsies are conducted and antibiotics used without knowing the type of microbe that is the cause of the infection. The scientists have discovered that the amino acids, lipids and microbial metabolites have specific alterations due to the occurrence of the disease. The breakdown of tryptophan and increased production of kynurenine can be altered to cause repeated inflammations and the down-regulation of the immune system in CVID patients [118]. The observation of the

trends exhibited by genes and proteins is useful in enabling clinicians to identify the degree of risk of a patient, employ immunotherapy where necessary and predict autoimmunity and cancers. In the meantime, the investigation of the gut microbiome (microbiomics) is gaining importance, primarily connected with the HSCT and the restoration of the immune system. In the present day, researchers view the gut microbiome as an important element in the development of the immune system of a person, tolerance and balance [119]. It is demonstrated that the lower the levels of microbes before or after a transplant, the higher the risk of GVHD, infections and mortality after transplantation [120]. Administering antibiotics that are specific, altering the diet of a patient or administering probiotics can allow the microbiome to be helpful and successful in the transplant. It has also been indicated that, by influencing the host immune cells, the short-chain fatty acids released by microbes can change the functionality of the gut barrier and the differentiation of T-cells in all immune response domains [121,122]. In combination with multi-omics and medical data, the microbiome information will assist the doctors to treat immune dysfunction in PIDs.

7.4 Pharmacogenomics and Targeted Therapy Design

The ability of genes to influence the response of a person to drugs is being utilized in designing immunotherapies that target individuals with PIDs and immune dysregulation disorders [70]. The list of immune diseases is becoming longer; therefore, an additional knowledge in terms of how genes and some drugs interact is needed to achieve better results and address any adverse outcomes. Individuals that have STAT1 or STAT3 GOF mutations might respond variably to JAK2 or JAK3 inhibitors like ruxolitinib or ofacitinib. Therefore, the location of the mutation in a gene can have an impact on immune response and even efficacy of different treatments. Through study of patient genetics, physicians can prescribe therapy to the patient only when there is likelihood that it would help them. Just like other illnesses, patients with APDS, brought about by mutations in PIK3CD or PIK3R1 are assisted by leniolisib that specifically inhibits PI3Kd [123]. They offer an alternative to general immunosuppression, whereby an easy suppression to only the damaged tissue may be done and infection risks, as well as the potential of harmful chemicals reaching the entire body, are reduced. It is crucial to check the outcome of molecular tests to select a drug and define the dose and resistances in the future. Pharmacogenomics are used in the design of BTK, NF-kB and IL-1-targeted therapies. Use of proof that inflammasome is overactive in the autoinflammatory disease determines the correct IL-1 blockade drug to be used in NLRP3-associated autoinflammatory diseases [124]. In addition, drugs with a high level of specificity such as abatacept, emapalumab or dupilumab are under investigation in rare diseases in which the etiology is established. Pharmacogenomics may assist in the predicting of the adverse effect of medications. The immunosuppressants may be metabolised differently due to any variation in enzymes or transporters that metabolise drugs (e.g. of the CYP450 family), hence additional monitoring or alteration in drug use is required [125]. It is particularly important to use pharmacogenomics in immunology in the context of immunosuppression used after organ transplant. Due to this, the work with patients may be better and the drug testing process can be facilitated. It provides the possibility of applying existing drugs to certain categories of individuals that does not only contribute to their well-being but also their budget. In case of the development of gene-drug interaction databases and bioinformatics, pharmacogenomics will be a requisite in the treatment of individuals who are born with immune disorders.

7.5 Challenges and Future Prospects

Using precision immunology to detect and treat PID patients is still associated with many issues. Table 4 shows available precision tools and their clinical applications. Expenses are ranked among the primary factors that led to the failure to apply genomic, proteomic and metabolomic technologies on a large scale [126]. Due to their high cost and inability to be repaired easily, quality assurance in large amounts and qualified professionals are frequently lacking, which leads to a slow or even absent diagnosis of health care in LMICs. People are further impeded by a lack of qualified professionals to take advantage of the exact diagnostics since there are not enough available [127]. Most ordinary clinics are unable to process complex genomic and multi-omic data as they do not have experts in the area. In addition, the exchange of such data in electronic health systems and the medical decision-makers process does not occur on large scale as yet [128,129]. Issues of ethical and regulatory issues are also problematic. These concerns relate to the issues in the data privacy, unexpected discoveries and the role of the frame-of-reference in creating new ethical concerns in genetics [130]. Cases with pediatrics are contrasting, since the long-term consequences of genetic information can cause problems with insurance coverage, adverse social responses and alterations in the psychological state of the patient. As immune diseases may develop or evolve over a period of time, one point of analysis may not help to explain them well. The symptoms in a person can vary over time or with other circumstances hence the need to review the situation with time. Genomic data also has many variant of uncertain significance (VUS) and it is incredibly hard to describe what they signify and make actionable solutions less likely [131]. Nevertheless, the future of the field is bright. Machine learning and artificial intelligence are enhancing the precision of the prediction of the genomic and proteomic data. The more data is accessed due to patient registries and global data sharing, the more we get to know about genotype-phenotype interactions, which can be useful in early and correct diagnosis and in the promotion of novel therapies. On-site, bioinformatics, internet-based, immune analyzers, handheld sequencers are being created so that every individual can easily conduct precision immunology with ease [132]. It may not take long before technology will be able to identify early diseases, swiftly intervene and constantly measure the impact of the medication in the areas that are only partially supplied. Overall, as long as research, training and collaborative efforts with other nations are maintained, precision immunology will enhance the manner in which care is being offered to the immunologically

crippled individuals. Precision immunology is the integration of the genomic, proteomic, transcriptomic and microbiomic data to assist in the diagnosing and treatment of individuals with PIDs[133]. Consequently, earlier and more accurate identification of the condition, the ability of doctors to make accurate assumptions about the success of treatment, the selection of more efficient medications and the adjustment of the immune system. Owing to the current possibility to provide more patients with WES, flow cytometry and cytokine profiling, patient outcomes are currently being improved: patients are being addressed individually.

Table 4. Precision tools and their clinical applications in PIDs.

Precision Tool	Clinical Application	Ref.
WES/WGS	Identifying pathogenic variants, establishing genotype-phenotype correlations	[98-101]
Targeted Gene Panels	Focused PID diagnosis based on known genes	[75,103]
Flow Cytometry	Quantification of immune subsets and activation markers	[101,104,105]
Cytokine Profiling	Monitoring inflammation, distinguishing between infection and autoimmunity	[106-111]
Transcriptomics	Non-invasive diagnosis of flares vs infection; disease activity monitoring	[112-117]
Proteomics	Biomarker discovery for diagnosis and prognosis	[112-117]
Microbiomics	Predicting HSCT outcomes, managing GVHD risk	[112-117]
Pharmacogenomics	Tailoring response to biologics and small molecule inhibitors	[70,120,121]

Table 4 summarizes precision diagnostic and monitoring tools used in the clinical management of PIDs. These tools, including WES/WGS, flow cytometry, and pharmacogenomics, enable accurate diagnosis, disease monitoring, and personalized treatment strategies.

8. Prospects and Direction for Future Research

Although numerous novel immunomodulatory treatment options of congenital immunodeficiencies have been introduced, further problems should be addressed. To ensure that the treatment outcomes of everyone will improve over time and care is provided equally to all, issues need to be addressed in science, hospitals, delivery of treatment and ethics. Low- and middle-income countries can hardly give their patients advanced therapies and biologics since they are not always available. In case health care is very costly, most people are compelled to make decisions that are not necessarily the best in the situation. There is a lack of knowledge on the potential impacts of immunomodulatory agents following an extended duration. By using cytokine inhibitors, mTOR and JAK inhibitors (as explained earlier in section 5.1) and immune checkpoint modulators over a long duration, the children will have increased risks to be infected, get new cancers and weaker immune system. I would also continue to track the use and utilize drug data to identify any new problems with drugs and alter my perception of the dangers and benefits of every drug. Without a proper understanding of how the immune system is involved, therapy could sometimes lead to the overworking of the immune system and the fact that the immune system is activated in an unintentional manner. This is why more work needs to be conducted with the help of not only systems but also single-cell analysis. Ethics should be taken into consideration in editing the genes in children. Everything related to the issues of informed consent, distribution of DNA alterations in reproduction, and the investigation of the findings over a considerable period must be taken under control. In the near future, with the use of artificial intelligence, medicine will be in a position to diagnose issues and offer the appropriate type of treatment to a patient with a high rate. To achieve success in immunomodulation to congenital immunodeficiencies, it is necessary to put an emphasis on networks, provide an equal access and increased funding to translational immunology.

9. Conclusion

The emerging immunological therapies have enabled physicians to identify and correct various defects in the immunology of children with congenital immunodeficiencies. Due to the great findings of the molecular immunology, nowadays one can target drugs at certain locations within the immune system. They enable the sick people to recover quickly and reduce the chances of them getting the same disorders and conditions in future. In essence, genomic and biomarker diagnostics enable physicians to have an individual treatment of a patient based on my genes. Still, the issues of reduced length of therapy sessions, child protection and ethical cases should be discussed. Provided that translational research is funded, countries will collaborate, and these cures will be spread equally, they will change the way congenital immunodeficiencies are addressed and may help the patients.

Consent to Publish

All authors consented to the publication of this article.

Data Availabilty Statement

Data sharing is not applicable as no datasets were generated being a review article.

Conflict of Interest

Authors declare no competing interests to the best of their knowledge.

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The authors declare that no Gen AI was used in the creation of this manuscript.

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