Asia Pacific Academy of Science Pte. Ltd.

Journal of Biological Regulators and Homeostatic Agents 2026, 40(1), 3683.
https://doi.org/10.54517/jbrha3683

Review

Primary minor immunodeficiencies as a cause of immunodependent pathology in humans: Etiology, epidemiology, classification, diagnosis, and treatment (Systematic review)

Dmytro Maltsev

Experimental and Clinical Medicine Institute, O'Bogomolets National Medical University,13, Shevchenka Ave 01054, Kyiv, Ukraine; dmaltsev@ukr.net

CITATION

Maltsev D. Primary minor immunodeficiencies as a cause of immunodependent pathology in humans: Etiology, epidemiology, classification, diagnosis, and treatment (Systematic review). Journal of Biological Regulators and Homeostatic Agents. 2026; 40(1): 3683. https://doi.org/10.54517/jbrha3683

ARTICLE INFO

Received: 5 May 2025
Revised: 11 July 2025
Accepted: 29 August 2025
Available online: 14 January 2026

Abstract: Deficiencies in immune protection (both congenital and acquired through life) significantly influence a human's life quality. Primary minor immunodeficiencies (PMDs) are more common in the population than classical immunodeficiencies and place a high burden on society. However, the evidence on PMDs is not systematized. The aim of the current research became the analysis and synthesis of the evidence on etiology, epidemiology, diversity, clinical manifestations, diagnosis, and treatment of PMD in humans to synthesize a scientific concept. In this way, the systematic review of publications from PubMed and SCOPUS databases has been conducted by the keywords. The time of analysis was the period from 1960 to 2025. Out of 2937 primary publications, 424 that met the selection criteria were included in the final list. As a result, terminology, genetic heterogeneity, epidemiology, spectrum of manifestation, structuring of clinical syndromes, and classification of PMD were clarified due to the current research. A distinction is made between PMD and classical immunodeficiencies. The algorithms of diagnostics and immunotherapeutic interventions were considered. The scientific concept of PMD diagnosis and treatment was proposed, which presents PMDs as a universal natural model of the development of different human immune-dependent pathologies on a population scale. PMDs, by their prevalence in the population, diversity, and degree of clinical manifestation, can explain the development of the entire described spectrum of immunodependent diseases in humans. The proposed PMD concept can allow optimizing the clinical management of patients with associated immunodependent pathology using an integrative personalized multidisciplinary approach with the availability of etiology estimation and etiotropic treatment providing.

Keywords: eosinophilic peroxidase; immunodiagnostics; immunomodulation; immunotherapy; mannose binding lectin; myeloperoxidase; natural killer cells; natural killer T-lymphocytes; phagocytosis

1. Introduction

Over 450 human primary immunodeficiencies are described [1]. They differ in inheritance, population prevalence, immune system's affected branches, flowing severity, prognosis, and available treatment approaches [2]. Primary immunodeficiencies are rather heterogeneous diseases that can differ significantly in laboratory and clinical phenotypes [3,4]. We can distinguish between classical (major) immunodeficiencies, which, traditionally, are associated with the phenomenon of primary immunodeficiency in humans, and minor immunodeficiencies [5]. Primary minor (mild) immunodeficiency (PMD) was described a little later and does not correspond

to or, sometimes, even contradict, classical immunodeficiencies in terms of the main associated clinical and laboratory phenomena [6]. PMDs destroy the established stereotype of primary immunodeficiencies as rare diseases with early mortality and dramatically severe morbidity. They are quite common in the population, become a part of routine practice, can clinically debut at any age, and are accompanied by moderate or even mild clinical symptoms [7]. At the same time, the terms minor and mild are used by various research groups as synonyms, denoting the same immunological phenomenon.

Thus, PMDs are common diseases of the immune system in the population with a variable course and heterogeneous clinical picture that do not correspond to the established ideas about primary immunodeficiencies as a phenomenon.

Authors who have published reports on PMD sometimes used such epithets as forgotten [8], ignored [9], or underestimated [10] immune system disease. However, research results show that PMDs contribute significantly to the morbidity of modern humans and form a great burden on the state and society, causing numerous immunodependent clinical manifestations and associated financial costs.

The first PMDs were described much later than a number of classical genetically determined immune diseases. In 1969, Cain et al. described selective IgE deficiency in patients with chronic sinopulmonary infections [7]. While selective natural killer (NK) deficiency was reported by Portaro et al. [11]. Litzman et al. in 1995 first used the term "minor immunodeficiency" to refer to deficiencies of certain subpopulations of T-lymphocytes, IgA, IgM, and components of the complement system (C3 and C4) in patients who often suffered from infectious episodes [6]. However, the term "minor anomaly of the immune system" was used by Vel'tishchev [12]. Instead, the term "mild immunodeficiency" was initially used by Van Kessel et al. in 1999 to refer to cases of selective IgG1 subclass deficiency [13]. Today, these terms are still occasionally relevant: in 2018, Janssen et al. used "mild hypogammaglobulinemia" to describe that even a small decrease in serum immunoglobulin concentrations can have severe consequences to a patient's health [14]. In 2023, Catli et al. used "mild immunodeficiency" to describe clinical consequences of a new homozygous STAT5B mutation [15].

Currently, diagnostic and therapeutic approaches must be developed to improve the detection and clinical consequences of PMD, which would affect the frequency and severity of associated immunodependent human diseases. Therefore, there is a need to systematize data on human PMD by forming a generalized scientific concept that would regulate the classification of these diseases, describe the range of associated manifestations, and provide algorithms for their diagnostics and treatment.

The aim of the current study was to collect, analyze, and summarize the accumulated evidence on the etiology, epidemiology, diversity, clinical manifestations, diagnosis, and treatment of PMD in humans to synthesize a scientific concept for theoretical and practical medicine on the diagnosis and treatment of associated immunodependent syndromes.

2. Materials and methods

Selection process. A systematic review of scientific publications from peer-reviewed medical journals indexed in the electronic scientometric bibliographic refer-

ence databases such as PubMed (MEDLINE) and SCOPUS for the period from 1960 to 2025 was conducted as a two-stage process. At the first stage of systematic search, the keywords "minor" or "mild immunodeficiency" were used, which were combined in any order with additional keywords such as "etiology", "pathogenesis", "epidemiology", "clinical picture", "diagnosis", and "treatment."

Firstly, 2937 research papers that met the above selection criteria were selected. Then, constructing the final reference list for this systematic review, most of the initially selected publications were removed in the course of further research.

Based on the data from the first stage of the search, it was possible to formulate a working definition of PMD, criteria for separating PMD from classical immunodeficiencies used by research groups, and to define a list of nosological forms that can be defined as PMD.

Thus, the following criteria for identifying primary immunodeficiency as a minor disease of the immune system were applied (based on results of scientific publications from the last 65 years—inclusion criteria):

1) High frequency in the population, which contradicts the established notion of primary immunodeficiencies as rare diseases;
2) Damage to only one immune factor;
3) The possibility of debuting at any age, not only in childhood;
4) The possibility of an asymptomatic course throughout ontogenesis in at least 20% of patients;
5) Variable clinical course with periods of asymptotic nature of varying duration with sudden clinical manifestation, heterogeneous in nature, severity, and duration;
6) Heterogeneous clinical picture, which differs in both the closest relatives from the same family with the same immunodeficiency, and in the patient himself at different periods of his ontogenesis;
7) Mild clinical manifestation, indistinguishable from clinical immune-dependent lesions in immunocompetent individuals in routine clinical practice;
8) Presence of reports of spontaneous resolution of clinical symptoms;
9) Presence of reports of unpredictable prognosis or favorable prognosis;
10) Presence of reports of unexpected complications;
11) Presence of reports of sudden unexpected death;
12) Presence of some signs of selective advantage in individuals with immunodeficiency;
13) Presence of a historical period of ignoring the immunodeficiency as an "insignificant" disease.

Immunodeficiency was considered minor in published papers if at least 9 of the 13 proposed criteria were met (all nosological units from panel 1 correspond to at least 9 of 13 criteria).

At the second stage of systemic scientific search such obtained at the first stage key words as "transient hypogammaglobulinemia of infancy", "unclassified hypogammaglobulinemia", "selective immunoglobulin's (Ig) deficiencies (IgM, IgA, IgG, IgE, IgD)", "myeloperoxidase deficiency (MPOD)", "eosinophilic peroxidase deficiency (EPOD)", "mannose binding lectin deficiency", "deficiency of serine proteases associated with mannose binding lectin", "NK-cell deficiency", "NKT-

cell deficiency", "CD16 molecule deficiency", "CD8 molecule deficiency (CD8D)", "CD64 molecule deficiency (CD64D)", "idiopathic CD4+ T-cell lymphopenia", "chronic idiopathic neutropenia", "familial benign neutropenia (FBN)", and "cyclic neutropenia (CyN)" were used. These words were combined in any order with key words such as "etiology", "pathogenesis", "epidemiology", "clinical picture", "diagnosis", and "treatment."

The second stage of the search allowed us to study the main clinical attributes of various nosological forms of PMD, previously identified at the first stage of the search, such as etiology, epidemiology, clinical picture, diagnosis, and treatment, which became separate chapters of this systematic review, demonstrating the diversity of the phenomenon of PMD in humans.

Exclusion criteria were: less than 9 of the 13 proposed criteria were met, no asymptomatic course of disease, high rate of death in the childhood period without substitutional treatment or bone marrow transplantation, and no publication about immunodeficiency in the past 2000 years.

Risk of bias assessment was associated with the absence of placebo-controlled randomized trials, meta-analysis, and systematic reviews dedicated to some PMDs, a low number of publications about some form of PMDs, no consensus diagnostic criteria for some PMDs, and controversial data about some PMDs.

Data extraction. Descriptions of single clinical cases, if they were not of historical or situational value, were removed from the final reference list due to the low level of evidence presented. Letters to the editor, articles commenting on other publications and responses to these comments, publications not in English, papers without access to the full text, studies with duplicate results, and papers which used outdated diagnostic methods (such as the rosette method for the diagnosis of cellular immune deficiencies) that cast doubt on the accuracy of immune diagnosis and the authors' conclusions were removed. Preference was given to articles published within the last decade, which reflect the latest and most relevant data in the field of immunodiagnostics. However, given the absence of previous systematic analyses on the problem of primary minor immunodeficiencies in humans, we still tried to reflect a holistic picture of the accumulated evidence and experience in diagnosis and treatment over the entire available search period. Since publications on some diseases of the immune system are extremely unevenly represented in different decades. So artificially limiting the search to a relatively short period of time would inevitably lead to a distortion of information, representing a reductionist approach. The quality of the publication was of fundamental importance in selecting the article for the final list of references, in particular, the research design, methods of statistical analysis, informative and relevant laboratory diagnostic methods, and the availability of adequate illustrative material to demonstrate the primary material. All the figures in this review are not borrowed, but obtained from the author's own archives, reflecting his personal clinical experience in the diagnosis of primary minor immunodeficiencies in humans.

Only 424 references (meta-analyses and systematic reviews, population-based studies, controlled clinical trials, retrospective case series, and in-depth literature reviews based on relevant clinical trials and reports) became the base of the current research.

3. Results

3.1. Differences between major and minor immunodeficiencies

There are more similarities than differences between major and minor immunodeficiencies. The similarity of PMD and classical immunodeficiency is the affection of the immune system, genetic origin, pentad of main immunodependent syndromes (infectious, allergic, autoimmune, immunoinflammatory, oncological) as clinical manifestation, approaches to laboratory evaluation, the immunological phenotype, and susceptibility to immunotherapy and bone marrow transplantation as treatment strategies in general.

So, knowledge of fundamental differences between them is essential in correctly interpreting clinical and laboratory data in patients with immunodependent pathology (**Table 1**), which became a way to determine a patient's management strategy.

3.2. PMD etiology

PMDs are genetically caused and are quite heterogeneous. They can be caused by chromosomal aberrations [9], mendelian mutations in structural genes [25], regulatory gene mutations [26], and pathogenic polymorphic single-nucleotide substitutions [27]. Some immunodeficiencies (like EPOD) are caused by a single mutation in the EPO gene [25]. Others are a collective group of genetically different immune system

Table 1. Comparative characteristics of major and minor immunodeficiencies.

Feature	Major immunodeficiency	Minor immunodeficiency
Known pathologies	Over 400	About 30
Affected immune factors	Involved a lot of factors such as all classes of Ig in X-linked agammaglobulinemia [16].	Usually, a single factor is affected. For example, there is deficiency of only IgA or IgM molecules. It is selective [17] or isolated [18] immunodeficiency.
Symptoms severity	A severe, life-threatening clinical phenotype, usually, signs' complex consists of heterogeneous overlapping immunodependent syndromes with a predominance of invasive infections.	Variable phenotype with a wide range of manifestations: from asymptomatic and mild (such as EPOD) [19] to severe (such as idiopathic CD4+ T-cell lymphocytopenia) [20]. However, mostly single syndromes of immunodependent manifestations (autoimmunity, allergy, etc.) prevail over the infectious syndrome.
Clinical course	Continuous, progressive with frequent relapses, tendency to form severe chronic inflammatory and oncological lesions, and early mortality.	Variable, with alternating periods of exacerbations and remissions, varying in nature, severity and duration, often with the usual endurance of patients
Frequency in population	Less than a 1 percent	About 20% (see **Table 3**)
Asymptomatic course possibility	Rare. Atypical mild forms of X-linked agammaglobulinemia [16]; atypical Chédiak–Higashi syndrome (10% of all cases in childhood but lead to delayed neurodegeneration) [21].	At least 20% cases according to results of clinical trial dedicated to the structure of clinical manifestation—for selective IgA deficiency [22], selective IgM deficiency [17], and idiopathic CD4+ T-cell lymphocytopenia [20].
Debut of symptoms	In early childhood. For example, combined and cellular immune deficiencies debut immediately after birth; X-linked agammaglobulinemia—in 6 months after birth after maternal trans-placental antibodies catabolism [4].	From early childhood to old age. For example, Endoh et al. reported that selective IgM deficiency (17 mg/dl) signs debut at the age of 85 years [23] – so called the "*late onset mild immunodeficiency in the elderly*" [24].
Typical clinical symptoms	Basically, a typical phenotype is observed. But not always. For example, the triad of ataxia, telangiectasia, and immunodeficiency in Louis–Barr syndrome [5].	Heterogeneous and variable nonspecific clinical courses differ even in close relatives. Common immunodependent syndromes from routine practice which have no specific signs for a particular immunodeficiency.
Outcome	Unfavorable without specific treatment.	Often favorable but can be unpredictable— "*unpredictable outcome*" [17].

diseases with a common laboratory phenotype. For example, selective IgA deficiency can be caused by multiple mutations in different genes [28], while CyN can be caused by multiple mutations in a single gene—ELANE [29–31]— "*multigenerational patterns of inheritance consistent with single gene*" [32]. The same immunodeficiencies can be caused by different mutations, while the same mutation can cause different immunophenotypes in different patients. So, mutations in the TACI gene can manifest as selective IgA deficiency and combine IgA and IgG deficiency, common variable immunodeficiency, and a syndrome resembling common variable immunodeficiency (so-called unclassified hypogammaglobulinemia) [33]. The phenotype of primary immunodeficiency can change even in the same individual at different periods of ontogenesis: the progression of selective IgA deficiency to common variable immune deficiency is well known [34]. So, Sgrulletti et al. talked about different evolutionary scenarios of immunodeficiency development throughout human ontogenesis [35].

Among PMD, autosomal dominant (AD) [36] and autosomal recessive (AR) inheritance [25] as well as X-linked transmission to offspring [16], and even cases of codominant inheritance [37] were described. A part of PMD patients are compound heterozygotes [38,39]. It has been described in functional hemizygosity [40] and haploinsufficiency [41] cases. Certain PMDs have a non-Mendelian type of inheritance: primary mannose-binding lectin deficiency (MBLD) requires a combination of a single nucleotide polymorphism (SNP) in the promoter region with several pathogenic polymorphic single nucleotide substitutions in MBL2 structural genes [42]. Epigenetic regulation processes, including the methylation mechanisms disorders, can affect the penetrance of a pathological gene in some PMDs like selective IgA deficiency [43], NK deficiency [44], or primary neutropenias [45] (**Table 2**).

Table 2. Genetic nature of some primary minor immunodeficiencies.

Immunodeficiency	Type of immunity	Branch of immune system	Characterized genetic nature	Inheritance type
Neutrophil MPOD	Innate	Phagocytosis	Significant heterogeneity. Classical missense mutation R569W [36], mutations Y173C, M251T, and 14-base deletion in exon 9 [39]; SNP (single nucleotide polymorphism) –453G/A in the MPO gene [27] in Europe; nonsynonymous mutation R499C of the MPO gene in Japan [46]; bigenic model of inheritance [37].	AD; AR; codominant
EPOD	Innate	Phagocytosis	Transition 2060G > A in the EPO gene [25].	AR
FBN (constitutional [FCN] and ethnic [FEN])	Innate	Phagocytosis	SNP –67T > C in the DARC gene (duffy antigen receptor for chemokines) [47,48].	AD
CyN	Innate	Phagocytosis	Multigenerational patterns of inheritance are consistent with a single ELANE (elastase neutrophil expressed) or ELA2 (elastase 2) gene. However, ELANE deletion (c.224 + (4_19)del16) is characterized better [49].	AD, AR, X-linked
CD64D	Innate	Phagocytosis	C > T substitution in exon 1, codon 92 of the hFc gamma RIA (human Fcγ receptor I) gene [50].	Not specified
NK cell deficiency (NKD)	Innate	Cellular	Significant heterogeneity. Mutations in receptors—FCG3RA3 (Fcγ receptor type III), in transcription proteins—GATA2 (GATA binding protein 2), IRF8 (interferon regulatory factor 8), in the cell cycle—RTEL1 (regulator of telomere elongation helicase 1), GINS1 (GINS Complex Subunit 1), MCM4 (mini-chromosome maintenance complex component 4) [51], in signale protein PLCG2 (phospholipase C gamma 2) [41], NK cells' actin cytoskeleton [52], and epigenetic regulation disorders [53].	AD (GATA2); AR (FCG3RA3, IRF8, RTEL1, GINS1, MCM4) with variable penetrance due to epigenetic factors influence

Table 2. (*Continued*).

Immunodeficiency	Type of immunity	Branch of immune system	Characterized genetic nature	Inheritance type
NKT cell deficiency (NKTD)	Innate	Cellular	Mutations in the Nkt1 locus on chromosome 1 are associated with partial deficiency of NKT cells in SLE, Nkt2 on chromosome 2—in type 1 diabetes mellitus (T1DM), and on chromosome 18—with total deficiency of NKT cells [54] and with epigenetic regulation disorders [53].	AD, AR with variable penetrance due to epigenetic factors
Deficiency of the CD16 molecule (CD16D)	Innate	Cellular	T to A substitution at position 230 in fcγ receptor of the IIIa gene (Fcγ RIIIA-48H/H) [55], L66H substitution in the FcγRIIIA gene [56], c.526G>T (p.V176F) polymorphisms in exon 4 and c.197T>A (p.L66H) polymorphisms in exon 3 [57].	AR
THI	Acquired	Humoral	Significant heterogeneity. From SIgAD to common variable immunodeficiency. In many cases, the genetic basis is not characterized (UH).	Not specified
UH	Acquired	Humoral	Genetic basis not characterized	Not installed
Selective IgM deficiency (SIgMD)	Acquired	Humoral	Chromosomal deletion 2q11.2 [9].	Congenital disease
Selective IgA deficiency (SIgAD)	Acquired	Humoral	Significant heterogeneity. Trisomy X chromosome [58], deletions and SNPs of the constant region of IgA heavy chain (immunoglobulin heavy chain constant region alpha, IGαHC) [59]; some chromosomal abnormalities (abnormalities of the 18th chromosome, trisomy of the 10th chromosome, translocation of 10q to 4p, etc.) [60]; mutations/polymorphisms of TNFRSF13B (tumor necrosis factor receptor superfamily, member 13B) or TACI gene (transmembrane activator and calcium-modulating cyclophilin ligand interaction), gene regulation disorders in C4A-21-OHA deletion [61], methylation effect on expression [43].	Mostly AD with variable penetrance due to the influence of epigenetic factors
Selective IgA1 subclass deficiency (SIgA1D)	Acquired	Humoral	Heavy-chain deletions of α-1 gene (delIGα_1 HC) [62].	Mostly AD with variable penetration
Selective IgA2 subclass deficiency (SIgA2D)	Acquired	Humoral	Heavy-chain deletions of α-2 gene (delIGα_2 HC) [62].	Mostly AD with variable penetration
Selective secretory IgA deficiency (SsIgAD)	Acquired	Humoral	Mutations of the polymorphic epithelial cell immunoglobulin receptor (pIgR), including the A580V missense mutation [63].	Mostly AD with variable penetration
Selective IgG subclass deficiency (SIgGSD: SIgG1D, SIgG2D, SIgG3D, SIgG4D)	Acquired	Humoral	Deletions of the constant region of the IgG1-4 heavy chain genes (delIGγHC) [59] and SNPs in IGγHC in combination with HLA-D in IgG4 deficiency [64].	Mostly AD with variable penetration
Selective IgE deficiency (SIgED)	Acquired	Humoral	SNPs of the regulatory gene AICDA (activation-induced cytidine deaminase) 5923A/G and 7888C/T [26].	AD
Deficiency of specific (antipolysaccharide) antibodies (SAD, SPAD)	Acquired	Humoral	Mainly, it was not identified. Hypomorphic mutations c.125 A > G in RAG1 gene (recombination activating gene 1) and c1342-3delCT, pSer381Terfs*1; c683G > A, pGly95Arg in the RAG2 gene [65].	Not specified
Combined deficiencies of immunoglobulin classes/subclasses	Acquired	Humoral	A combination of deletions IGγ_2HC, IGγ_4HC, IGα_1HC, IGεHC [66], IG$\gamma_{1,}$HC, IGγ_3HC, IGεHC [67], and others.	Not specified
Idiopathic CD4+ T-cell lymphocytopenia (ICD4+TL)	Acquired	Cellular	Nonsense mutation c.C49T:p.Q17X in the ITK gene (IL2 inducible T Cell kinase) [68]; dominant-negative missense mutation V22G in Unc119 gene (lipid binding chaperone) [69].	AR; AD
CD8D	Acquired	Cellular	Misense gly90>ser mutation in the CD8alpha gene [70] and p.Gly111Ser mutation in CD8α gene [71].	AR
MBLD	Innate	Complement system	Combination of promoter SNPs –550 (H/L) or –221 (XY) and SNPs in structural genes R52C, G54D and G57E of the MBL2 gene [42].	AD

Table 2. (*Continued*).

Immunodeficiency	Type of immunity	Branch of immune system	Characterized genetic nature	Inheritance type
MBL-associated serine protease 2 deficiency (MASP2D)	Innate	Complement system	SNP D120G of the MASP2 gene [72].	AR
C6 deficiency (C6D)	Innate	Complement system	Deletions 1195delC, 1936delG of the C6 gene (in African Americans) and deletion 878delA of the C6 gene (in African Americans and Europeans) [73].	AR
C7 deficiency (C7D)	Innate	Complement system	Premature codon termination mutations K416 X 419 and S620 X 630 of C7, missense mutation G357R [74], missense mutation G379R and deletion of 3'UTR (c.*99_*101delTCT) of C7 gene [40].	AR
C8 deficiency (C8D)	Innate	Complement system	C8A-type I (3' Splice Site C8A) [74] and C8B-type II (p.Arg428* C8B) [75].	AR
C9 deficiency (C9D)	Innate	Complement system	Arg95Stop mutation of the C9 gene [76].	AR

3.3. PMDs epidemiology

PMDs collectively affect at least 20% of the modern world's human population (**Table 3**). Its high prevalence is facilitated by the predominant AD mode of transmission to offspring and the possibility of an asymptomatic or mildly symptomatic course for long periods. Paradoxically, advances in drug therapy are also likely to have an impact on the increasing prevalence of PMD, for example, by ensuring patient survival in severe cases of infectious lesions, as demonstrated by the case of recovery from acute Candida meningitis in MPOD [77].

PMDs frequency varies widely from one case per a million inhabitants in CyN (low) [78], through one case per 14 thousand people in EPOD (medium) [19], to one case per every third person in central Africa in MBLD (high frequency) [79,80] (**Table 3**).

Table 3. Prevalence and typical manifestations of PMD among modern people.

PMD	Frequency	Specific gravity	Prevalence estimate	Manifestations
THI	1:164 confirmed THI + 1:103 possible THI [93].	0.6% confirmed THI +0.9% possible THI [93].	Frequent	Broad clinical phenotype
UH	4/5 patients with a primary diagnosis of THI [94].	80% of patients with a primary diagnosis of THI [94].	Frequent	Broad clinical phenotype
SIgMD	1:265 for Iran [95], 1:385 for Europe [96], 1:2216 for China [97].	0.37% for Iran [95], 0.26% for Europe [96], 0.045% for China [97].	Frequent	Broad clinical phenotype
SIgG1D	1:26 in Europe [98].	3.8% in Europe [98].	Frequent	Pyogenic respiratory infections
SIgG2D	1:28 cases among children with recurrent respiratory infections [99].	3.5% of cases among children with recurrent respiratory infections [99].	Frequent	Pyogenic respiratory infections
SIgG3D	1:25 cases among children with recurrent respiratory infections [99].	4% of cases among children with recurrent respiratory infections [99].	Frequent	Viral respiratory infections
SIgG4D	1:400 in Europe [64].	0.25% in Europe [64].	Frequent	Pyogenic respiratory infections or asymptomatic
SIgAD	1:160–1:500 in Europe and the USA [100], 1:2000–1:4000 in China [88].	0.06–0.2% in Europe and the USA [100], 0.05–0.025% in China [88].	Frequent	Broad clinical phenotype
SIgED	1:30 in Europe and the USA [101,102,103].	3% in Europe and the USA [101,102,103].	Extremely frequent	Broad clinical phenotype

Table 3. (*Continued*).

PMD	Frequency	Specific gravity	Prevalence estimate	Manifestations
SIgDD	1:12–1:14 in Europe [104].	8–9% in Europe [104].	Extremely frequent	Mainly, asymptomatic
MBLD	1:10–1:20 in Europe [86], 1:3 in central Africa [79,80].	5–10% in Europe [86], 35% in central Africa [79,80].	Extremely frequent	Broad clinical phenotype
SPAD	1:9–1:1.6 in groups of patients with recurrent pneumococcal infections [65].	11–60% in groups of patients with recurrent pneumococcal infections [65].	Frequent	Recurrent pneumococcal infections
MASP2D	1:25 among the population of Europe, up to 1:6 in some regions of Africa [105].	4% among the population of Europe, up to 18% in some regions of Africa [105].	Extremely frequent	Bacterial infections (pneumococcal pneumonia, pulmonary tuberculosis, skin abscesses, sepsis), systemic lupus erythematosus, interstitial lung disease
FBN	1:2–1:4 in Africans, 1:22 in African Americans, 1:9 in Arabs, 1:8 in Yemeni Jews, 1:6 in black Ethiopian Jews, less than 1:100 in general US population [89].	25–50% in Africans, 4.5% in African Americans, 10.7% in Arabs, 11.8% in Yemeni Jews, 15.4% in black Ethiopian Jews, <1% in the general US population [89].	Frequent	Persistent periodontitis, recurrent oral candidiasis, recurrent neutropenic ulceration of the oral mucosa, agranulocytosis to certain medications
CIN	1–2:1 000000 [106]	0.0001–0.0002% [106]	Rare	Recurrent bacterial respiratory, urinary, and gastrointestinal infections; agranulocytosis to certain medicines
CyN	1:1 000000 [78]	0.0001% [78]	Rare	Periodical hyperthermia with bacterial urinary, gastrointestinal, and respiratory infections with 21-day cycle
EPOD	1:14,000 in Europe [19]	0.007% in Europe [19].	Medium	Mostly asymptomatic
C6D	C6Q0 is 1:1600 among African Americans and 1:40,000 among Europeans [73].	C6Q0—0.06% among African Americans and 0.0025% among Europeans [73].	Medium	Invasive Neisseria infections
C7D	1:24273 in Japan [40,107]	0.0041% in Japan [40, 107]	Medium	Invasive Neisseria infections
C8D	For C8A 1:36410 in Japan [75].	For C8A 0.0027% in Japan [75].	Medium	Invasive Neisseria infections
C9D	1:1000 (homozygous) [21] and 1:15 (heterozygous mutation) [76] in Japan.	0.1% (homozygous) [21] and 6.7% (heterozygous mutation) [76] in Japan.	Frequent	Invasive Neisseria infections
MPOD	1:2000–1:4000 in Europe and the USA [36], 1:10,000 in Japan [83].	0.05–0.025% in Europe and the USA [36] and 0.01% in Japan [83].	Medium	Invasive Candidiasis
ICD4+TL	1:400 in Europe [108].	0.25% in Europe [108].	Frequent	Herpesvirus infections, toxoplasmosis, atypical mycobacteriosis, JCV, histoplasmosis, and pneumocystis
CD8D	1:250 among Gypsies [71]	0.4% among Gypsies [71]	Frequent	Recurrent respiratory infections with the formation of pneumosclerosis

The heterogeneity in the PMD spread in different world regions is due to the founder and selective advantage effects [81]. The founder effect indicates an increased incidence of immunodeficiencies in the region of mutation origin, especially in the practice of consanguineous marriages, and an abnormally low incidence in other populations, especially if they are close to interbreeding with representatives of other regions. The founder effect is well observed in MPOD, which occurs with an abnormally high frequency in the Brescia [82] and Friuli–Venezia Giulia [82] Italy regions (one case per 500 inhabitants), and is rare in Japan (1:10,000) [83]. The effect of selective advantage indicates that the abnormal accumulation of a particular PMD in a region may contribute to some minority positive health effects that can paradoxically be provided by immunodeficiencies. This effect is clear in MBLD. It is actual for 30% central Africans [79,80] and reduces the severity of pulmonary tuberculosis [84], meningitis [79], and schistosomiasis [85]. For the world population, it is in the range of 5–10% [86].

PMD prevalence is dependent on geographical, ethnic, racial, age, and gender factors. Japan, as a geographically isolated area, has a significantly different prevalence of immunodeficiencies [83,87]. Chinese people have a lower frequency of SIgAD compared to Europeans [88]. It was found that the differences in FBN frequency for different ethnic groups [89]. C6D frequency is 1:1600 among African Americans and 1:40,000 for Europeans [73]. SIgG2D is more common among children, and SIgG3D in adults [90]. NKD can be more severe in women due to estrogen influence [91]. The women demonstrate an increasing serum IgD level compared to men [92].

3.4. PMD classification

PMDs can be independent and isolated genetic diseases [109,110]. They can also be a component of other genetic diseases with a broader phenotype. PMD, as an isolated disease, is the recent report by Hua et al. of a case of SIgAD in a 48-year-old patient with multiple autoimmune disorders—hemolytic anemia, systemic lupus erythematosus, and Hashimoto's thyroiditis [111]. PMD, as a component of a broader genetic disease, was reported by Chaushu et al.: SIgAD in patients with Down syndrome, which results in recurrent upper respiratory and gastrointestinal infections [112]. Abnormally reduced IgA levels in parotid gland secretions were observed in at least 83% of patients with Down syndrome ($p < 0.001$) [112]. Jeraiby et al. showed that in Down syndrome, 69.57% IgG4 deficiency exists [113]. An additional deletion of IGHG4 is noted, which causes this immunodeficiency [113]. PMDs can affect systemic (most diseases) or local (SsIgAD) immunities [113]. There are quantitative (FBN) [114] and qualitative, or functional immunodeficiencies (MPOD) [115]. The same cellular immunodeficiency can be quantitative and qualitative depending on the causative mutation: "*classical*" NKD (cNKD) (GATA2 mutation) and "*functional*" NKD (fNKD) (FCG3RA3 mutation) [51]. PMD can be divided according to the affected immune system branch: phagocytosis [83], natural killer cells (cellular component of innate immunity) [51], T-lymphocytes (cellular component of adaptive immunity) [20], complement system [116], and immunoglobulins [117] (Panel 1). PMDs can be compensated (asymptomatic) [12], subcompensated (low-symptomatic "*mild symptoms*"[20]), and decompensated (clinically manifest; most described

cases). Partial and total PMDs can be distinguished by the depth of the decrease in the number of immune factors affected. Jamee et al. substantiated the distinction between total (serum IgA <7 mg/dL—"*selective IgA deficiency*" [SIgAD]) and partial IgA deficiency (PIgAD—serum IgA concentration is less than the lower limit but above 7 mg/dL) show that both forms of immunodeficiency are due to an abnormally increased number of autoimmune polyendocrinopathies [118]. Sometimes, complete immunodeficiency forms were distinguished if the amount of the investigated immune factor was non [119]. Among partial immunodeficiencies, some authors distinguished subtotal ("*subtotal C6 and C7 deficiencies*" by Orren—C6SD and C7SD) as opposed to total C6 and C7 deficiencies (C6Q0, C7Q0) [120] and subnormal ("*subnormal IgG2 deficiency*") [121,122] forms (**Figure 1**). It is also advisable to distinguish between temporary, or transient [123] (such as transient hypogammaglobulinemia of infancy) [117] and permanent, or persistent [123] PMDs (most diseases). It can be fixed by a combination of several PMDs in one person (*combined immunodeficiencies* [66] such as "*combined C6D/C7D*" [120]). There are combinations of primary classical immunodeficiency and PMD (for example, DiGeorge syndrome and MPOD [124], Leukocyte adhesion molecules deficiency type III and NKD [125], or C2 deficiency and C8BD [126]), but no specific term for these cases has been proposed yet, except the term "complex immunodeficiency" by Wawrzycka-Adamczyk K. et al. [127]. Sometimes PMD mimics secondary immunodeficiencies [128]. According to symptom dynamics, it is possible to distinguish between cyclic immune deficiencies (CyN with 21-day cycles of manifestation) [49] and immune deficiencies with irregular manifestations (most diseases). No term has been proposed for PMDs that a patient has acquired after allogeneic bone marrow transplantation, as these are both genetic diseases that meet the criteria for primary immunodeficiency and acquired diseases that meet the criteria for secondary immunodeficiency [129] (**Table 4**).

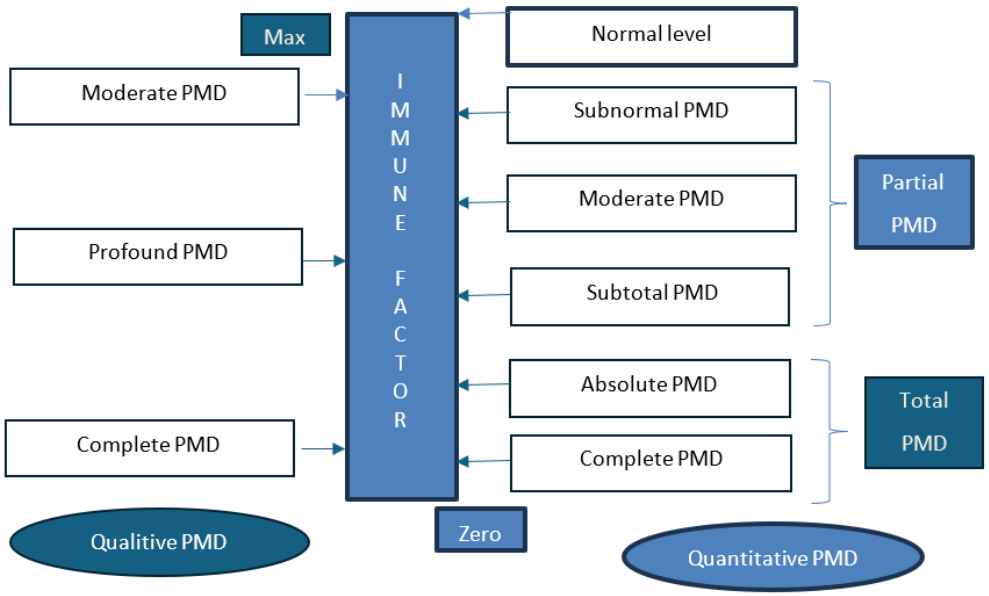

Figure 1. Correlation of different forms of quantitative and qualitative PMD by the depth of deficiency of the affected immune factor.

Table 4. Synopsys of proposed PMD classifications rubrics demonstrating diseases—clinical and laboratory variety.

№	Classification rubric	Variety
1	By origin of the disease	– Hereditary, inborn (congenital), acquired
2	By the affected form of immunity	– Diseases of inborn and adaptive (acquired) immunity
3	By affected branch of immunity	– Cellular, humoral
4	By affected immune factor/factors	More than 30 immunodeficiencies with titles according to name of affected immune factor (see panel 1)
5	By family history	familial, sporadic
6	By time of debut	Intrauterine, at the day of birth, early onset (pediatric-onset), late onset (adult-onset), elderly onset
7	By frequency in population	Rare, medium, frequent
8	By genetic nature	According to mendelian laws of inheritance: – Mendelian and non-mendelian – According to type of inheritance: – AD, AR, X-linked, codominant – According to number of affected genes: – Monogenic, bigenic, polygenic – According to type of genetic anomaly: – Chromosome aberrations, structure genes mutations, SNPs, mutations in immunoregulatory genes, epigenetic disorders – According to pattern of genotype-phenotype relationships: – Monogenerational patterns of inheritance consistent with single gene, multigenerational patterns of inheritance consistent with single gene, multigenerational patterns of inheritance consistent with different genes
9	By clinical picture	According to character of clinical manifestation: – Asymptomatic and symptomatic (minor infections, allergic, autoimmune, oncological and severe phenotypes) – According to number of clinical syndromes: – Clinically isolated (monosyndromic) or combined (olygo-, polysyndromic; mono-, polymodal) – According to predominant affected compartment: – Cutaneous, oral, gastroenterological, respiratory etc. – According to predominant of associated nosological unit: – PMDs in systemic lupus erythematosus, bronchial asthma, leukemias, sarcoidosis, COVID-19 etc.
10	By depth of the immune factor damage	– Quantitative (numerical) and qualitive (functional) – Total and partial (for quantitative), total: complete and absolute; partial: subtotal, moderate and subnormal – complete, profound, moderate (for qualitive)
11	By severity of the patient's condition	– Mild, moderate and severe (don't correspond to depth of the immune factor damage)
12	By duration of immunological phenotype existence	– Persistent and transitory
13	By evolutionary scenario of development	– Newly diagnosed, progressive, chronic, oscillating, normalizing, reversible (reversal)
14	By regularity of the disease manifestation	Irregular, regular (cyclic)
15	By spread of immune system damage	– Systemic and local (skin and mucosal)
16	By combination with other diseases	– Isolated (selective), combined (complex)
17	By curability	Treatable, non-treatable
18	By specific rubrics	Different in each disease

Panel 1: Classification of PMD in humans, taking into account both the affected branch of the immune system and affected immune factor

I. Disorders of the cellular branch of innate immunity

A) Quantitative:
   (a) Neutrophil disorders:
      – Familial benign [47,89,114,130,131] (constitutional, ethnic) [132–134] neutropenia (FBN, FCN, FEN), or "*Duffy null neutrophil count*" [78,135–137] or "*Duffy null phenotype*" [138];
      – Chronic idiopathic neutropenia (CIN) [139–141], or chronic primary neutropenia [142–144];
      – CyN [49,145–147], or ELANE-related neutropenia [148,149].
   (b) Disorders of monocytes:
      – Primary monocytopenia (PM) [150].
   (c) Disorders of eosinophils:
      – Chronic idiopathic eosinopenia (CIE) [151–153].
   (d) Disorders of lymphocytes:
      – Natural killer cell deficiency (NKD) [51,154–156];
      – Natural killer T-cell deficiency (NKTD) [157–159];
      – CD16 molecule deficiency (CD16D) [55,119].

B) Qualitative:
      – Neutrophil MPOD [115];
      – EPOD [19];
      – CD64D [50];
      – Primary perforin deficiency (PPD) [160].

II. Disorders of the humoral branch of innate immunity

      – Deficiency of proteins of the complement system [161,162], primarily the terminal components of the cascade that form the membrane-attacking complex [163]—C6D [116], C7D [40,164], C8D [165], C9D [87];
      – Mannose binding protein (lectin) deficiency (MBLD) [86,166,167,168];
      – Mannose binding lectin associated serine protease 2 deficiency (MASP2D) [169];

III. Disorders of the cellular branch of adaptive immunity

      – Idiopathic CD4+ T-cell lymphocytopenia (ICD4+TL) [15,108, 170,–172], or so-called "AIDS without HIV" [173,174,175];
      – CD8D [70].

IV. Disorders of the humoral branch of adaptive immunity

A) Hypogammaglobulinemias:
      – Transient hypogammaglobulinemia of infancy (THI) [117,176–179];
      – Unclassified hypogammaglobulinemia (UH) [14,176,180];

B) Dysimmunoglobulinemias:
   (a) Selective isotype deficiencies [181]:
      – Selective (isolated) IgM deficiency (SIgMD) [182–184];
      – Selective (isolated) IgG deficiency (SIgGD) [185];
      – Selective (isolated) IgA deficiency (SIgAD) [186–188];
      – Selective (isolated) secretory IgA deficiency (SsIgAD) [189];

- Selective (isolated) IgE deficiency (SIgED) [190–193], or "very low IgE producer" [194], or"undetectable serum IgE" [195], "ultra-low IgE" [196], "very low IgE" [197], or "low IgE" [198].
- Selective (isolated) IgD deficiency (SIgDD) [104];

(b) Selective subclass deficiencies [181]:
- Selective (isolated) IgG subclass deficiencies (SIgGSD) [99,199–201]: SIgG1D [13], SIgG2D [121,202], SIgG3D [203], SIgG4D [64,204];
- Selective (isolated) IgA subclasses deficiencies (SIgASD) [205]: SIgA1D [206], SIgA2D [207];

(c) Qualitive immunoglobulin deficiency [208]:
- Selective specific antibodies deficiency (SSAD) [209,210], including anti-polysaccharide antibodies (selective anti-polysaccharide antibodies deficiency, SPAD) [211,212];
- Impaired glycosylation of IgA1 [147], or galactosa-deficient IgA1 [213].

(d) Other dysimmunoglobulinemias:
- Combined deficiencies of immunoglobulins of different classes and/or subclasses, such as combined IgA1, IgG2, IgG4, and IgE deficiencies in two siblings caused by deletions of the constant regions of heavy chains [66].

3.5. PMD clinical manifestations

PMDs are characterized by heterogeneous clinical pictures (so-called "different faces" [214]) and variable clinical course [115,215]. Asymptomatic PMD periods are associated with compensation mechanisms inside the immune system. In SIgAD, sometimes natural IgM molecules can be compensatory increased [216]. IgG and IgM cooperate in coating of intestinal bacteria in SIgAD [217]. NKT can compensate ICD4+TL in some cases [218]. The thesis of lifelong asymptomatic clinical course as a representative sign of PMD was refuted by Koskinen et al., who found that severe immune-dependent lesions develop during long-term follow-up in at least of 80% cases in initially asymptomatic blood donors with SIgAD [22].

Six key principles are applied to PMD: universality, heterogeneity, variability, non-linearity, non-specificity, and ambivalence (**Figure 2**).

The clinical picture of PMD is compound and includes at least four different levels, which are integrated as a whole clinical presentation in each case.

Level I (pentad of five main immunodependent syndromes)

PMDs are characterized by five main and five immunodependent syndromes: infectious [219–221], autoimmune [222–224], allergic [225,226], immunoinflammatory (for example, persistent immunoinflammatory enteropathy) [193], and oncological [227,228].

PMD clinical spectrum is well demonstrated by Picado et al. [193] on SIgED example: recurrent respiratory infections occurred in 34.6%, pneumonia in 30.7%, bronchiectasis in 30.7%, bronchial asthma in 19.2%, autoimmune syndromes in 34.6% (autoimmune Hashimoto's thyroiditis of 19%, rheumatoid arthritis of 10%, and autoimmune thrombocytopenia and/or neutropenia of 5.7%), eczematous derma-

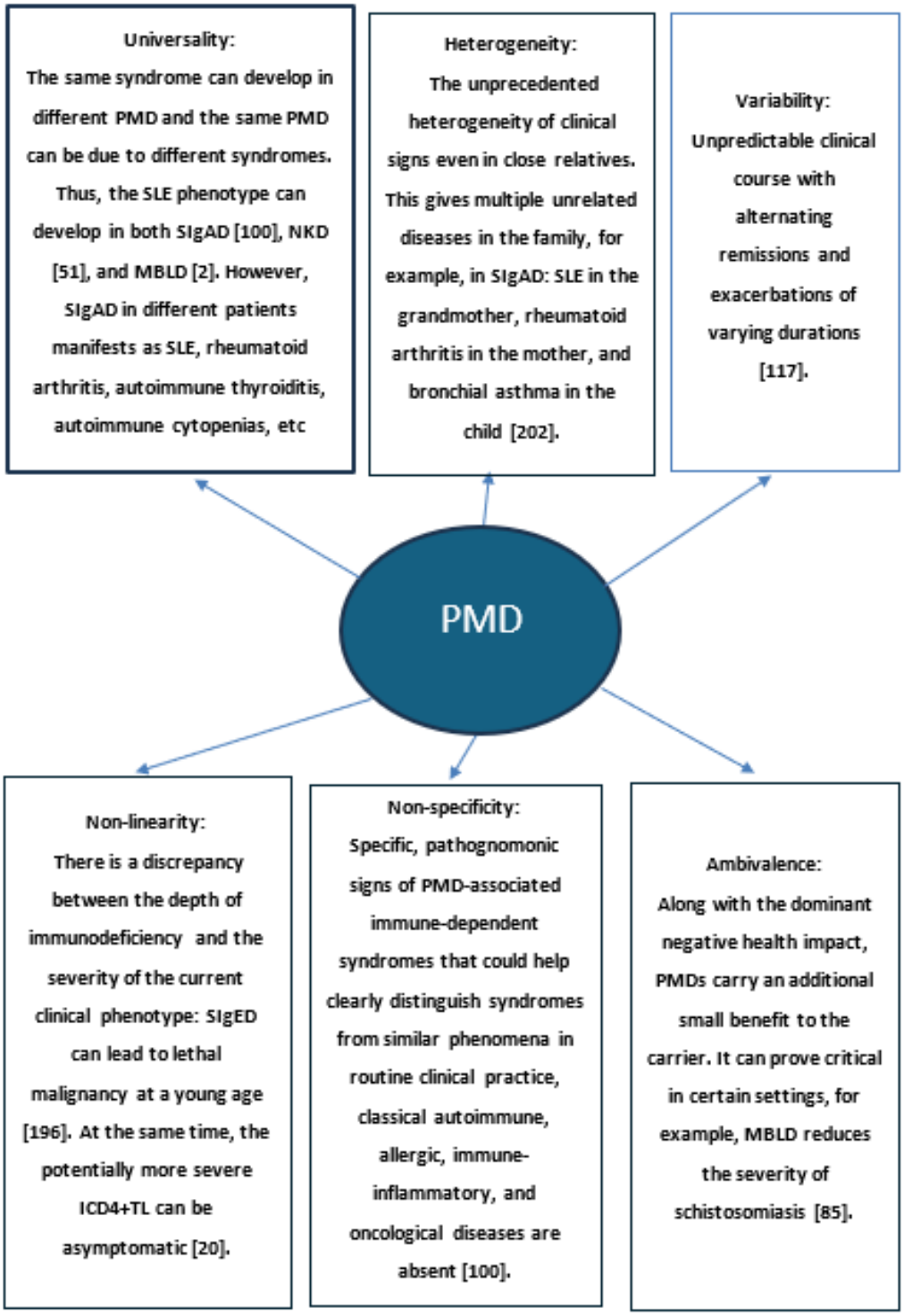

Figure 2. The main principles of PMD that will determine their peculiarity.

titis of 15.3%, chronic spontaneous urticaria of 17.3%, persistent immunoinflammatory enteropathy of 21%, and malignant neoplasms with predominance of non-Hodgkin's lymphoma of 13.4% of cases [193].

The results of a systematic review and meta-analysis of randomized controlled clinical trials prepared by Vosughimotlagh A. et al. show that in SIgAD, infectious manifestations occur in 64.8%, allergic lesions in 26.16%, and autoimmune syndromes in 22.0% of cases [188].

According to Caka et al., 24% SIgMD cases were asymptomatic, 45% had respiratory and skin infectious manifestations; in 18% autoimmune and immunoinflammatory syndromes (Behcet's syndrome, immune cytopenias, Crohn's disease, Guillain-Barré syndrome, and type 1 diabetes mellitus) were noted, allergies fixed in 15% patients, and in 9% malignant tumors diagnosed [17].

Régent et al. indicated that in patients with ICD4 + TL, opportunistic infections occur in 65% (in 50% of cases—invasive papillomavirus episodes), in 35%—autoimmune syndromes, in 12.5%—malignant tumors, and mild symptoms or asymptomatic status noted in 20% cases [20].

In the epidemiological study of 18,487 people, a close association of SIgED was fixed with bronchial tree hyper-reactivity, otitis media, and bronchial asthma in children and chronic sinusitis, autoimmune syndromes, and neoplasia in both children and adults [191].

Epidemiological study of 34,809 patients (21,875 children and 12,934 adults) demonstrated the association of SIgED and malignancies (26%) and autoimmune diseases (15.4% of cases) [197].

The development mechanisms of immunopathology in PMD are diverse. One reason for the development of allergic, autoimmune, and immunoinflammatory pathologies is the suppression of γ-IFN-mediated Th1 activity [229]. Secondary dysfunction of regulatory T-cells is also possible [229].

In PMDs, the infectious syndrome is an important, but often not such dramatic clinical phenomenon as in classical immune system diseases [230,231]. Infectious episodes may be atypical [232–236]. Some PMDs have a rather narrow spectrum of infectious manifestations, such as deficiencies of complement terminal proteins, which selectively increased the risk of meningococcal meningitis by 1000–10000 times [165], or SPAD, which developed almost exclusively pneumococcal lesions of the respiratory system [76].

Most known PMDs have a wide range of infectious manifestations. For example, MBLD develops bacterial [237], viral [238], fungal [239], and protozoal [240] lesions. Different PMDs are characterized by certain close associations with certain infectious agents such as MPOD selectively promotes the development of severe Candida lesions [36], NKD promotes predominantly herpes and papillomavirus infections [51], and ICD4+TL to intracellular opportunistic agents [107,108,241], such as cytomegaly, toxoplasmosis, aspergillosis, histoplasmosis, atypical mycobacteriosis, JCV and pneumocystis lesions [242–246] (**Table 5**).

Figure 3 shows the most indicative results of paraclinical studies of various organs and systems in patients with PMD from the author's own clinical practice to demonstrate the diversity, multitropy, and severity of organ and system lesions in these diseases of the immune system, as well as the absence of paraclinical pathognomonic signs.

In a population-based cohort study involving 2100 patients with SIgAD and 18,653 control persons, a significantly higher incidence of type 1 diabetes mellitus (5.9% vs. 0.57%), Crohn's disease (2.4% vs. 0.42%), ulcerative colitis (1.7% vs. 0.46%), rheumatoid arthritis (2.2% vs. 0.5%), juvenile idiopathic arthritis (0.76% vs. 0.09%), systemic lupus erythematosus (0.57% vs. 0.06%), and autoimmune thyroid

Table 5. Differences in the main microbial factors depending on the affected immune factor in PMD.

PMD	Affected immune factor	Type of immunity	Branch of immune system	Microbes
FBN, CIN, CyN	Neutrophils	Innate	Phagocytosis	*Staphylococcus, Streptococcus, Candida* spp.
MPOD	Neutrophils, monocytes	Innate	Phagocytosis	*Candida* spp.
EPOD	Eosinophils	Innate	Phagocytosis	No
NKD, NKTD, CD16D	NK, NKT-cells	Innate	Cellular	Herpesviruses, papillomaviruses
THI, UH, class and subclass deficiencies	Immunoglobulins	Acquied	Humoral	Pyogenic Gram-positive cocci
SPAD	Immunoglobulins	Acquied	Humoral	Pneumococcal infections
ICD4 + TL	T-helpers	Acquied	Cellular	Herpesviruses, *toxoplasmosis*, atypical mycobacteriosis, JCV, *histoplasmosis*, *pneumocystis*
CD8D	Cytotoxic T-cell	Acquied	Cellular	Herpesviruses, respiratory viruses, *Staphylococcus aureus*
MBLD	Mannose binding lectin	Innate	Complement	*Staphylococcus aureus, Streptococcus pyogenes, Haemophilus influenzae, Pseudomonas aeruginosa, Escherichia coli*
MASPD	Serin protease type 2 associated with mannose binding lectin	Innate	Complement	*Staphylococcus* spp., *Streptococcus* spp., *Mycobacterium tuberculosis*
C6D, C7D, C8D, C9D	Proteins 6, 7, 8, 9 of complement system	Innate	Complement	*Neisseria* spp.

disease (2.46% vs. 0.59%) [100]. The results of meta-analyses of randomized controlled clinical trials indicate an association of MBLD with rheumatoid arthritis [247] and systemic lupus erythematosus [2].

The results of a meta-analysis of randomized controlled clinical trials by Gao et al. indicated that MBLD doubled the risk of sepsis in children (SMD = 1.00, 95%CI = 0.35 ~ 1.65, $P = 0.003$) as an example of immunoinflammatory syndrome [248].

Speaking about the allergic syndrome in PMD, the systematic review of randomized controlled clinical trials by Borta et al. indicated the development of atopic bronchial asthma in patients with MBLD [249].

Controlled studies indicated an association of SIgED with malignancy [190,196]. Therefore, the European Academy of Allergy and Clinical Immunology recommended that ultra-low serum IgE concentration had to be considered as a predictor of tumor growth syndrome [196]. The large population-based cohort study (2,320 patients with SIgAD and 23130 controls) demonstrated the association of SIgAD and cancer (especially gastrointestinal) HR = 1.64; CI = 1.07–2.50 [250] (**Figure 4**).

Level II (compound secondary syndromes)

PMDs lead to the development of a number of additional integral syndromes with complex pathogenesis, which are the result of the combined effect of the pentad immunodependen syndromes in ontogenesis such as sudden unexpected death [251], inborn anatomy anomalies [180], poor nutrition status [252], decrease of life quality

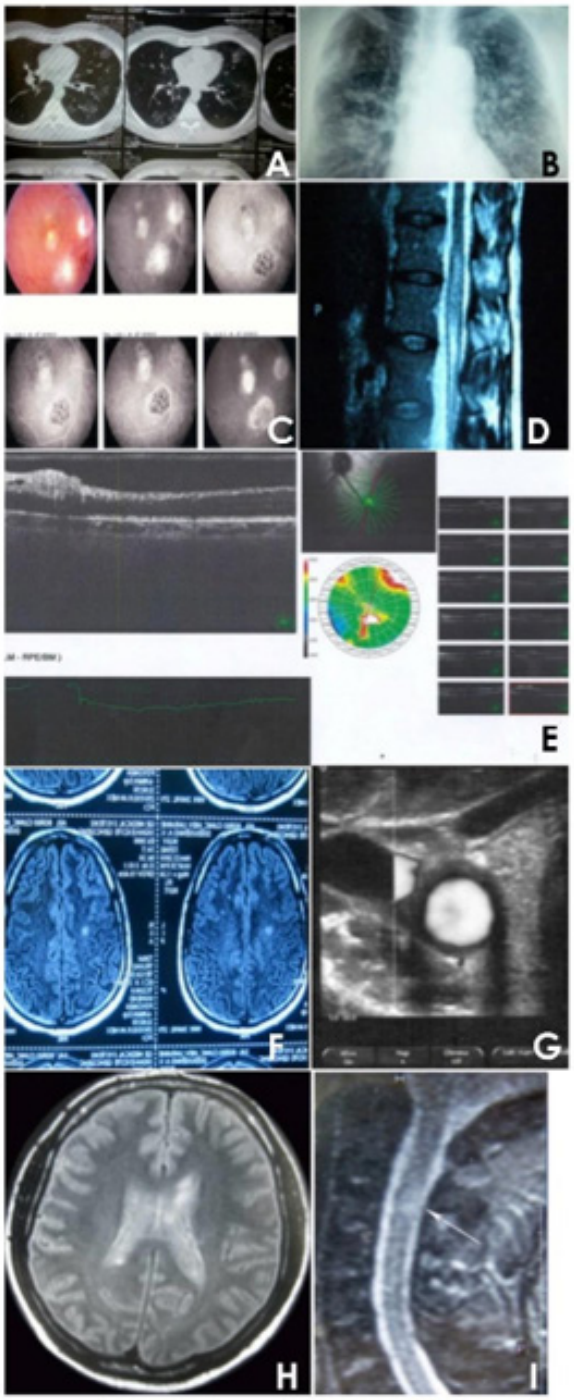

Figure 3. Semiotics of primary minor immunodeficiency manifestations according to paraclinical examinations (own observations):
Horizontal chest CT scan: bilateral interstitial pneumonitis in a patient with SIgMD; B. Anterior chest X-ray: pulmonary sarcoidosis in NKTD; C. Ophthalmoscopic picture of toxoplasma chorioretinitis in MPOD; D. MRI of the lumbosacral spine in sagittal projection in T2-weighted mode: lumbar myelitis of HSV-2 etiology in NKD; E. Optical coherence tomography data: local disorganization of neuroretinal layers in HHV-7-induced ANA-positive uveitis in MBLD; F. MRI of the brain in horizontal projection in FLAIR mode showing diffuse VZV-induced vasculopathy of small cerebral arteries in NKD; G. MRI of the brain in horizontal projection in T2-weighted mode, demonstrating the pattern of HHV-8-induced ventriculitis in ICD4+TL; H. Ultrasonographic data visualizing the phenomenon of pathological thickening of the carotid artery intima-media complex as a manifestation of VZV-induced vasculopathy in NKD; I. MRI of the cervical spine in sagittal projection in T2-weighted mode with a pattern of HHV-8-induced myelitis in ICD4+TL (own observations).

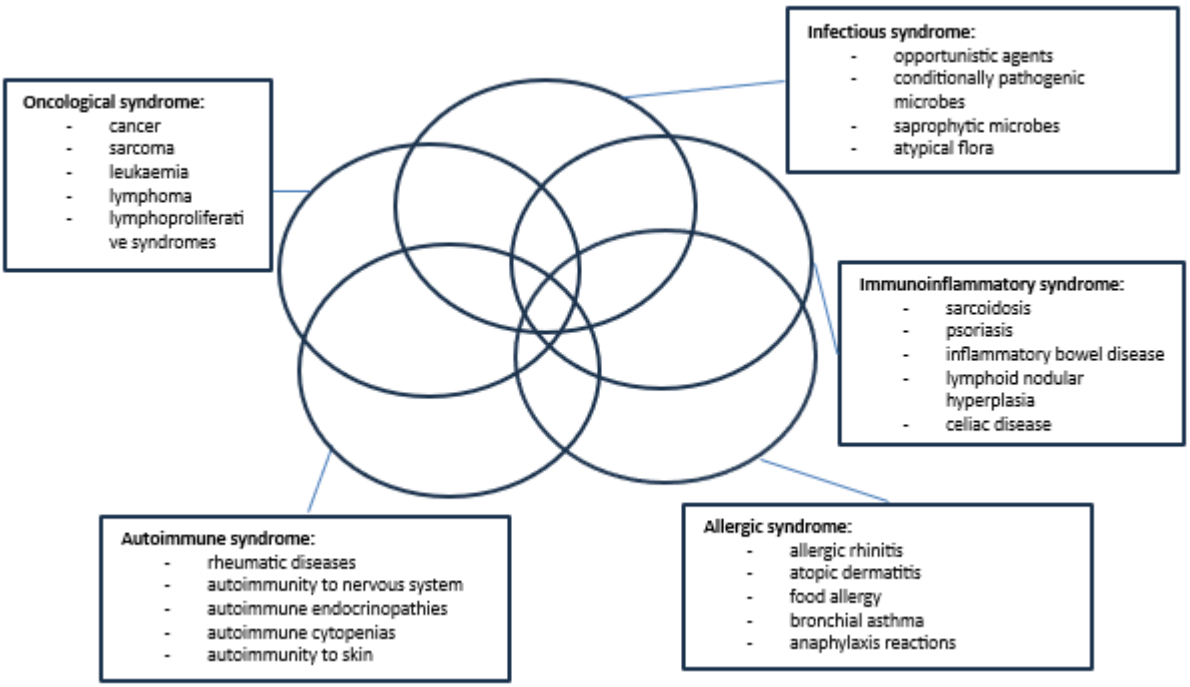

Figure 4. Principal scheme of core PMDs clinical picture—so-called main pentad of immunodependent syndromes.

[253], accumulation of pathological structural changes in organs [189], fertility disorders [254], hemocoagulatory disturbances [255], endocrine disorders [118], intestinal dysfunction [256], premature aging [257], increased mortality [258], the nervous [42] and psychical [259,260] disorders.

A large, controlled study showed a decrease in health-related quality of life in patients with SIgAD. The most significant risk factors for poor quality of life were the number of antibiotic courses per year ($p < 0.001$), the number of medications taken daily ($p < 0.01$), allergic rhinoconjunctivitis ($p < 0.05$), chronic musculoskeletal symptoms ($p < 0.05$), and anxiety and/or insomnia ($p < 0.005$) [253].

Patients with PMD can accumulate pathological structural changes in organs at a young age, such as bronchiectasis in SIgGSD [189] or bronchial tree remodeling due to bronchiolar damage in SsIgAD [189].

A population-based cohort study (613 women with SIgAD and 5,758 pregnant women without immunodeficiency) showed a high rate of low birthweight, prematurity, and caesarean section in women with SIgAD [254].

A population-based study of 57,133 people showed that MBLD doubled the risk of myocardial infarction in persons aged 29–62 (OR = 2.04, 95%CI = 1.29 – 3.24) as an example of premature aging [255].

The development of autoimmune polyendocrinopathies in SIgAD (9.4% of all cases of multiple endocrine gland involvement) leads to secondary disruption of endocrine homeostasis regulations [118]. The cross-sectional clinical study showed that anterior pituitary insufficiency and executive endocrine disorders were typical for humoral immunodeficiencies, including SIgGSD and SPAD [261].

PMDs can induce persistent intestinal dysbiosis [256] and bacterial overgrowth syndrome [262], chronic inflammatory enterocolitis with atypical histological changes [67], and intestinal lymphoid nodular hyperplasia [263], persistent malabsorption syndrome [264] and pathological permeability of the intestinal wall

(leaky gut syndrome) [262] as well as celiac [265] and Moyamoya [266] diseases, which can exist outside of a direct relationship with existing infectious, allergic, and autoimmune syndromes.

Patients with SIgED more often affected by hypertension [34 (37.7%) vs. 187 (18.2%), $p < 0.001$], carotid stenosis [5 (4.9%) vs. 7 (0.7%), $p = 0.003$], coronary heart disease [26 (25.2%) vs. 87 (8.4%), $p < 0.001$], cerebrovascular [3 (2.9%) vs. 5 (0.5%), $p = 0.029$], and peripheral vascular disease [4 (3.9%) vs. 9 (0.9%), $p = 0.024$] [257].

According to the results of a population study, death risk in the first years after SIgAD diagnosis increased by 10 to 15 times [258].

PMD can affect both the central and peripheral nervous systems. Rudolph et al. showed that MPOD leads to autonomic dysfunction with impaired regulation of vascular tone, as the affected enzyme is involved in the regulation of the nitric oxide system [267]. Gibson et al. demonstrated that MBLD was an independent predictor for cerebral palsy development [42].

There is an association of SIgAD with obsessive-compulsive syndrome [260] and autism spectrum disorders [268]. MBLD can be associated with panic attacks and bipolar disorders [269]. A population-based study of 14 million respondents showed that primary humoral immunodeficiencies (including SIgGSD and SPAD) are associated with various physical disorders and suicidal behavior in adulthood development [270]. Data from a cohort study (1973–2013) of 4,294,169 participants indicated primary humoral immunodeficiency in mothers, including selective SIgGSD and SPAD, led to an increased incidence of physical illness and suicidal behavior in children [271].

Level III (modification of another disease)

PMD, manifested by a pentad of major syndromes and secondary to inducing a number of additional phenomena with complex pathogenesis, can affect other genetic [165] and nongenetic [166] human diseases with modifying diseases' manifestations and course, and causing the nosological interaction phenomenon.

PMD can modify [263] and critically complicate, including: by infectious syndrome [272], another genetic disease as Down syndrome and cystic fibrosis. PMDs can facilitate the transmission of highly virulent infectious pathogens (such as HIV) [273], modulate negative classical infections clinical course with complications: viral (including COVID-19 [274] and RSV [275]), bacterial (including brucellosis) [276], or protozoan (including leishmaniasis) [277], and even due to death [278,279]. PMD can aggravate somatic diseases (liver cirrhosis [280], gastritis or peptic ulcer [43], or pneumonia [281,282]). Garcia-Laorden et al. in a clinical trial (of 848 persons with community-acquired pneumonia and 1,447 controls) showed that people with primary MBLD had more severe sepsis ($P = .007$), more frequent acute respiratory failure ($P = .009$), multiorgan dysfunction ($P = 036$), intensive care unit admissions ($P = .020$), and higher mortality ($P = .003$) [283]. However, the severity of some diseases can be paradoxically reduced, for example, mild schistosomiasis in patients with MBLD [85] or protection from COVID-19 complications in SIgAD [284].

Level IV (modification of paraclinical data and interventions)

PMDs can affect the information content of diagnostic tests [285] and instrumental examinations [286], the efficiencies of therapeutic [287,288] and preventive actions [289], surgical interventions [290], and contraception [91]. MPOD can cause pseudoneutropenia in automated blood formula calculation [285], EPOD prevents the formation of eosinophilia in rheumatoid arthritis exacerbations [291], SIgED complicates the serological diagnosis of atopic allergy [292], SIgAD—celiac disease [293], and SIgMD leads to errors in blood group determination by the ABO system [294]. MPOD causes pseudo-genitive dihydrorhodamine test results in diagnostics of the chronic granulomatous disease [77]. ICD4 + TL due to a false positive diagnosis of AIDS [295].

NKD makes an impact on CT findings in pulmonary alveolar proteinosis [296] and MBLD on radiocontrast-induced renal damage [286].

Patients with PMD have a higher need for drugs [253], impaired drug biotransformation [106], reduced effectiveness of therapy [288] because of lower intestinal drug absorption [264], impaired tolerance to drugs [297, 298] with induction of side effects [299,300–302].

PMDs can reduce the immunization effect of vaccines [289,303,304]. PMDs increase the need for vaccination [212] and frequency of vaccine-associated side effects [305,306].

Koturoglu et al. [287] noted, MBLD is a significant reason for adenoidectomies and tonsillectomies in children due to recurrent bacterial infections of the upper respiratory tract lymphatic organs. SIgMD [307] due to early postoperative infections and CyN [308] changes the perioperative curative strategy in surgery. FBN and CyN can complicate dental interventions [309]. PMDs influence on the choice of anesthesia [310].

NKD is a contraindication to oral contraceptives [91].

PMDs can induce complications in medical procedures such as allogeneic hematopoietic stem cell transplantation [311], bone marrow transplantation [129], and solid organ transplantation [312] (**Figure 5**).

3.6. PMD diagnosis

There are several fundamental stages in PMD diagnosis:

1) Physical examination for assessing the current state of the patient's health.
2) Anamnesis examination considering the frequency and severity of infectious, allergic, immunoinflammatory, autoimmune, and neoplastic episodes that may be associated with immunodeficiencies, as well as the atypical course of other diseases that may have been affected by immunodeficiency [115,313–315].
3) Performing general clinical laboratory tests, including searching for screening signs of PMD (decreased serum gamma-fraction of proteins in hypogammaglobulinemia [316], decreased number of large granular lymphocytes in NKD, NKTD [51], etc.).
4) Study of the laboratory phenotype of immunodeficiency underlying immunodeficiency diseases and related manifestations, considering the peculiarities of laboratory diagnostics in such patients [317–320].

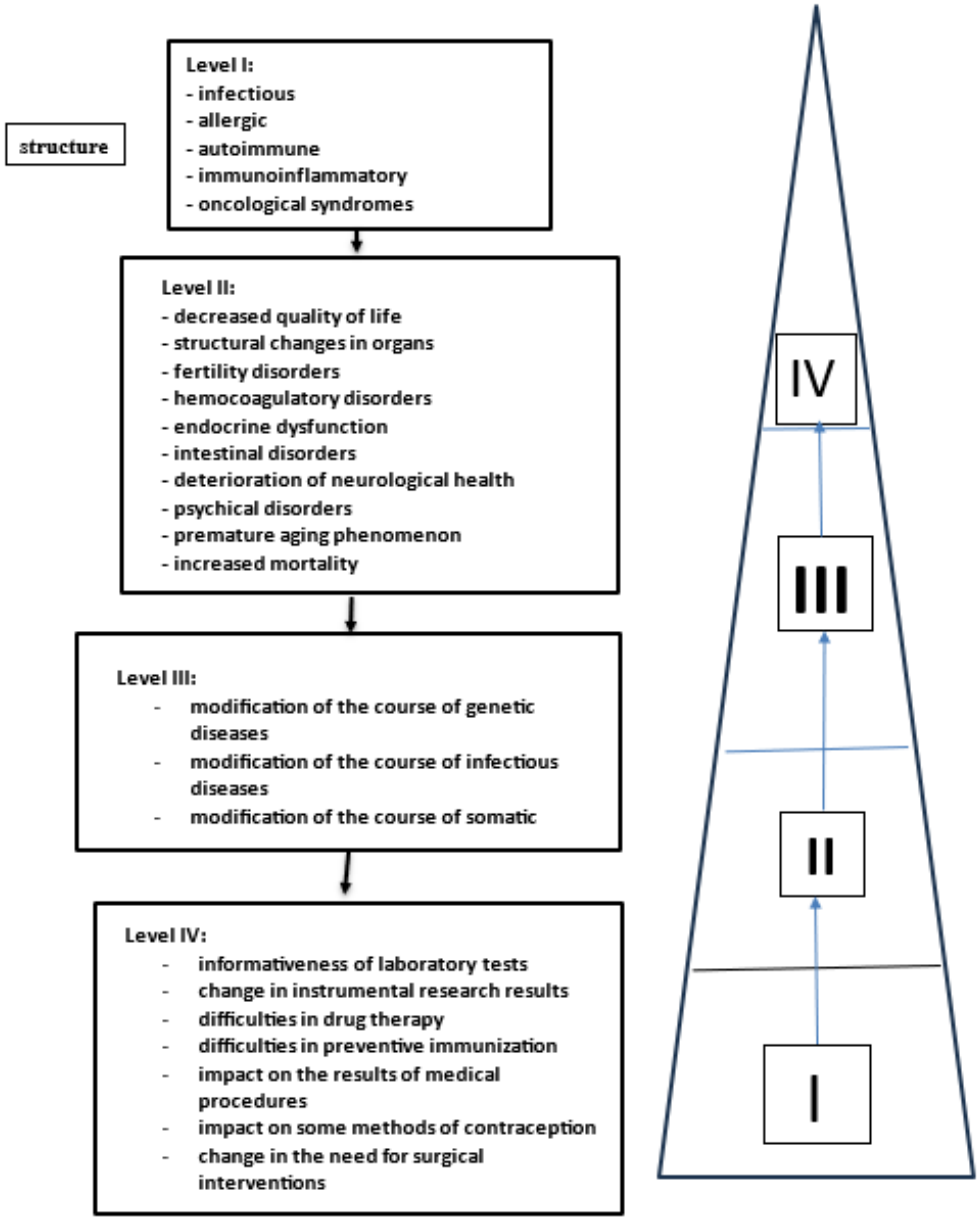

Figure 5. Compound clinical picture of PMD with multilevel structure.

5) Integral health assessment to determine the presence and severity of additional phenomena associated with immunodeficiencies, such as fertility disorders, manifestations of premature aging, etc. [321,322].
6) Conducting differential diagnosis and formulating a primary clinical diagnosis.
7) Performing karyotyping, chromosomal microarray, and/or molecular genetic testing to identify chromosomal aberrations, mutations, or SNPs of genes associated with immunodeficiency [323,324].

It is important to have a proper immunological observation with including the determination of all laboratory parameters related to the identification of common immune system diseases. Currently, there are a few laboratory centers where immunological tests meet the current requirements for PMD diagnosis. Below is a list of tests that should be included in the so-called "*ideal*" immunological observation for the diagnosis of PMD:

- A common analysis of blood with a leukocyte formula.
- Serum immunoglobulin class concentrations (IgM, IgG, IgA, IgE, IgD).
- Serum IgG subclasses concentrations (IgG1, IgG2, IgG3, IgG4).
- Serum IgA subclasses concentrations (IgA1, IgA2).
- Concentration of secretory IgA in saliva, urine, and/or feces.
- Serum titer/concentration measurement for specific antibodies to infectious agents, e.g., anti-pneumococcal antibodies, including before and after anti-pneumococcal vaccine introduction.
- The number of CD3 + CD4 + T-lymphocytes in the blood.
- The number of CD3 + CD8 + T-lymphocytes in the blood.
- The number of CD3 + CD16 +CD56+ lymphocytes in the blood.
- The number of CD3–CD16 +CD56+ lymphocytes in the blood.
- The number of CD3–CD19 + B lymphocytes in the blood.
- The number of CD64+ cells in the blood.
- The concentration of complement system proteins in blood serum (C6–C9).
- The concentration of mannose-binding lectin in the blood serum.
- Serum concentration of serine proteases 1 and 2 associated with mannose-binding lectin.
- Neutrophil MPOD activity in the blood.
- Eosinophilic peroxidase activity in the blood (**Table 6**).

3.7. PMD treatment

Lifestyle modifications and symptomatic treatment of comorbidities (anxiety, depression, or insomnia) can significantly improve the life quality of PMD patients [253]. Prophylactic or occasional antibiotic therapy can be used to prevent or treat bacterial infections in immunocompromised patients. In case of viral and fungal diseases, antiviral and antimycotic drugs can be prescribed. It seems obvious that the strategy of antimicrobial chemotherapy does not adequately affect the risk of allergic, autoimmune, and neoplastic PMD complications. Repeated vaccination with a 23-valent conjugate antipneumococcal vaccine and a nonconjugate *Hemophilus influenzae* vaccine can be used in SPAD [212]. The drug OM-85 BV (broncho-vaxom) has undergone several controlled trials to reduce the frequency of infections in patients with SIgAD and SIgGSD [338].

For patients with severe PMD who fail to reduce the frequency of infectious episodes with an antimicrobial treatment strategy, basic immunotherapy is recommended according to the results of controlled trials and clinical reports (level of evidence C, except for intravenous immunoglobulin for humoral immunodeficiencies—B) (panel 2). The advantage of basic immunotherapy is not only the systemic effect on the infectious process but can help with allergic, autoimmune, and neoplastic complications of PMD.

In humoral PMD, 5–10% normal human IgG-containing intravenous immunoglobulin is used as a basic substitutional (replacement or reconstitution [339]) immunotherapy [340,341] with low incidence of side effects [342,343]. During the saturation phase, immunoglobulin is introduced dosage of 600–800 mg/kg/month, and during the maintenance phase, 200–400 mg/kg/month under the control of the results of immuno-

Table 6. Methods of measurement, reference values of laboratory parameters, and criteria for immunodeficiency in the diagnosis of PMD.

Indicator	Method	Reference values	Immunodeficiency criteria	Units	Availability
FBN, CIN, CyN	CBA	2.0–4.5 [47]	<2.0 [47]	x10^9/L	Available
THI, UH		Total serum concentration of all Ig classes from 7.0 to 18.0	<7.0 [14] or less than 2 SD from the lower limit of normal range for each class of immunoglobulin [94]	g/L	Available
SIgMD	ELISA, nephelometry, Mancini immune-diffusion, radioimmunoassay	0.8–1.6	0.8–0.4—"*unclassified primary antibody deficiency*" (unPAD) [325], "*possible sIgMdef*" (PIgMD) [18]—below 2 SD from the lower limit of normal range [10]; <0.4—total immunodeficiency, SIgMD [95], or "*truly sIgMdef*" [184]	g/L	Available
SIgGD		6–15	<6 [185]	g/L	Available
SIgAD		0.6–2.5	0.6–0.07—partial, <0.07—total immunodeficiency [118]	g/L	Available
SIgED	ELISA	30–100	10–5—partial, 5–0—total immunodeficiency (classic ELISA) [326]; lower 2.0 (modern high-sensitive ELISA) [195, 193]	IU/mL, or kU/L	Available
SIgDD	ELISA	14–85 [92]	<14 [92]	mg/L	Rare
SIgG1D	ELISA, IBA	60–70	<60, <3.6 g/L [90], or less than 2SD of the age median [122]; or IgG1:IgG2:IgG3:IgG4 is equivalent 22:8:2:1 (better demonstrates subclass deficiency than absolute and relative values) [327]	%	Rare
SIgG2D	ELISA, IBA	20–30	<20 or <1.2 g/L [90]; or less than 2SD of the age median [122]; or <IgG1:IgG2:IgG3:IgG4 is equivalent 22:8:2:1[327]	%	Rare
SIgG3D	ELISA, IBA	5–8	<5 or <0.3 g/L [90] or less than 2SD of the age median [122] or <IgG1:IgG2:IgG3:IgG4 is equivalent 22:8:2:1 [327]	%	Rare
SIgG4D	ELISA, IBA	1–3%	<1 or <0.06 g/L [90] or IgG1:IgG2:IgG3:IgG4 =22:8:2:1 [327]	%	Rare
SIgA1D	ELISA	IgA1: IgA2 is equivalent 9:1 [328]	<9:1 [328]	–	Rare
SIgA2D	ELISA	IgA2:IgA1=1:9 [328]	<1:9 [328]	–	Rare
SsIgAD	Micro-ELISA, immune-turbidometry	4–30 [329]	<4 [329]	mg/dL	Available
SPAD	ELISA	IgM = 37–75; IgG = 26–79; IgA = 13–44 [330]	Absent or reduced serum concentration of specific antibodies to the causative agent of recurrent infections, especially antipolysaccharide antibodies in pneumococcal lesions, absence or reduced response to the multivalent antipneumococcal vaccine [331] (<0.035 μg/mL) [90]	U/mL	Rare
CD4 + TL	FC	500–1,500 [108]	<500 [108]	Cells/μL	Available
NKD	FC	5–15 [51]	<5 (75 × 10^9/L) [51]	%	Available
NKTD	FC	3–8 [53]	<3 (45 × 10^9 /L) [53]	%	Available
CD8D	FC	21–35	<21 (315 × 10^9/L) [70]	%	Available

Table 6. (*Continued*).

Indicator	Method	Reference values	Immunodeficiency criteria	Units	Availability
C6D	Hemolytic assay (CHA50, AHA50, LHA50), SDS-PAGE, IBA, ELISA	45 (±16) or 20–80 [120]	<0.03 for the total form and range from 0 to 37 and even from 0 to 79 for the subtotal form [120]	mcg/mL	Rare
C7D		90 (±36) or 30–180 [332]	<0.03 for the total form [332], 0–27 and even 0–69 for the subtotal form [120]	µg/mL	Rare
C8D		72.5 (±3.54) [75]	<0.03 for the total form, 13.0 (±0.64), 12.0 (±0.86) and 15.0 (±1.17) as examples of subtotal deficit [75]	µg/mL	Rare
C9D		28.5–99 [76]	<0.03 for the total form [76]	µg/mL	Rare
MBLD	ELISA	1000–4500 [333]	1,000–500—partial, <500—total, <50—complete immunodeficiency [335]; or very low (<100), low (200–999) [334]	ng/mL	Rare
MASP2D	ELISA	100–1200 [335]	<100 [105]	ng/mL	Rare
MPOD	ELISA, FC, western blot, guaiacol peroxidation, alanine decarboxylation test	18–23 [336]	<18 [336]	conventional units	Rare
EPOD	Immunohistochemistry	1.25–80 [25,337]	<1.25 [25,337]	ng/mL	Rare

CBA—Common blood analysis
ELISA—Enzyme-linked immunosorbent assay
IBA—Immunoblotting analysis
FC—Fluid cytometry
SDS-PAGE—Sodium dodecyl sulphate poly acrylamide gel electrophoresis

globulin concentration measuring [344,345]. In intravenous immunoglobulin intolerance, 10% normal human IgG-containing immunoglobulin for the intramuscular route at a dosage of 25–50 mg/kg/week can be used as an exception to the rule [346]. Normal human IgG-containing immunoglobulin enriched with IgA and IgM can be used for the treatment of isolated deficiencies in these immunoglobulin classes, but the evidence base for the effectiveness of this drug is limited to case reports and the results of small, controlled trials [347]. Immunoglobulin therapy is more than just a replacement treatment. The immunoglobulin drugs can modulate antibody production by affecting B-lymphocytes' Fc-receptors, suppress allergic [348–351], autoimmune, and some neoplastic [352] complications associated with PMD.

Figure 6 shows data from the author's clinical practice, which demonstrates a dramatic positive dynamic of paraclinical signs of severe lesions of organs and systems after the addition of targeted immunotherapy, taking into account not the form of associated immune-dependent lesions, but the form of causal immunodeficiency. The data in this figure clearly demonstrate the enormous potential of stratifying immune-dependent diseases by causal PMDs to ensure targeted immunotherapy of PMDs as an etiological factor of immune-dependent syndromes.

In MBLD, as well as in deficiencies of complement proteins C6–C9, fresh frozen or cryopreserved human blood plasma from a compatible donor is used in an intravenous drip (dosage of 10–15 mL/kg once every 2 weeks) due to enough content of necessary immune factors in healthy human blood serum [353]. Natural [354] and recombinant [355] human mannose-binding protein successfully passed several controlled trials in MBLD. It has advantages over plasma due to greater selectivity and better tolerability [355].

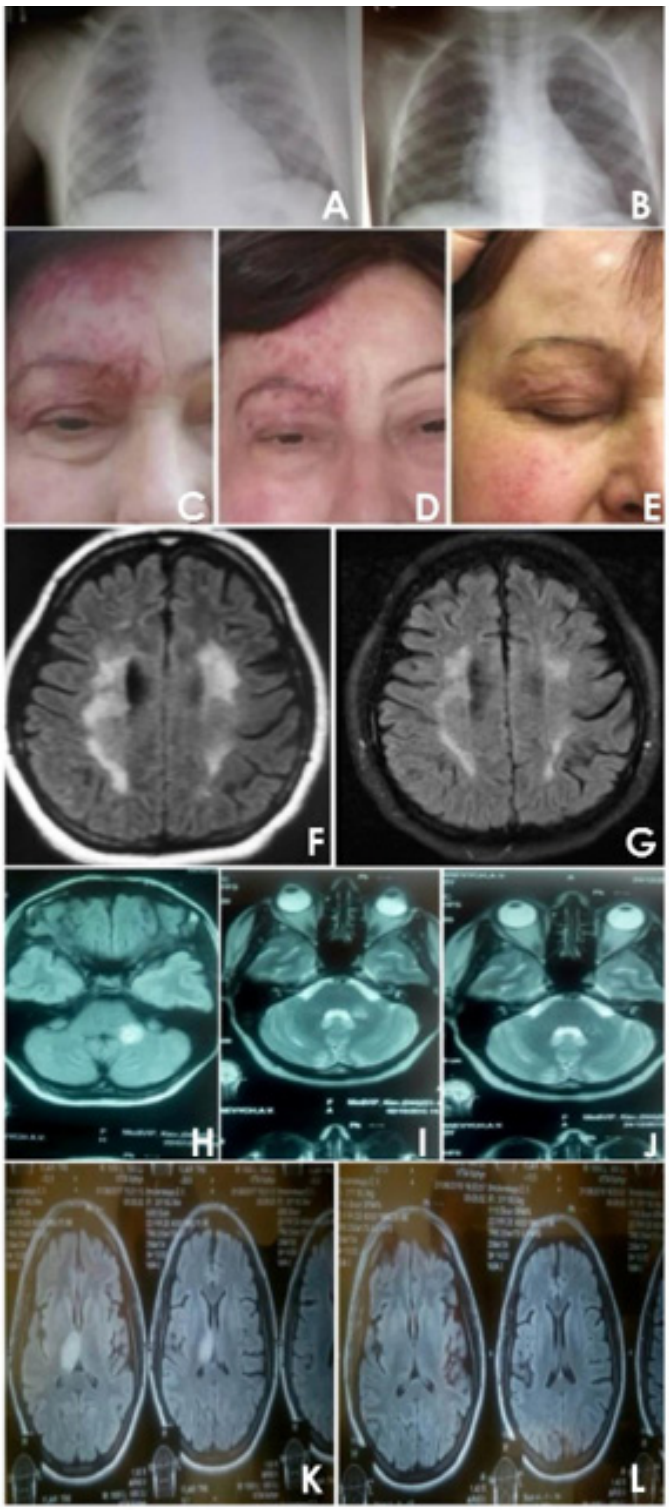

Figure 6. Results of immunotherapy of immunodependent manifestations in primary minor immunodeficiencies (own observations):
Elimination of EBV-induced bilateral interstitial pneumonitis in a child with SIgED with intravenous immunoglobulin therapy (A—before treatment, B—after treatment). Achievement of remission of refractory recurrent herpes zoster in a patient with MBLD on the background of cryopreserved blood plasma (C, D—before treatment, E—after immunotherapy). Positive dynamics of HHV-6-associated multifocal leukoencephalitis during the use of rhIFNγ in MPOD (F, G). Regression of EBV-induced cerebellitis on the background of rhIFN-α2b immunotherapy for NKD (H—before treatment, I—1 month, J—2 months after the immunotherapy started). Elimination of CMV-induced thalamic encephalitis on the background of rhIFN-α2b immunotherapy for NKD (K—before immunotherapy, L—after immunotherapy).

In case of cellular immunodeficiencies, cytokine therapy—natural, lymphoblastoid, recombinant α–, β–- and γ-interferons (rhIFN–α, –β, –γ), recombinant human interleukin-2 and -7 (rhIL2, rhIL-7)—is used as basic immunotherapy [306,356–358]. The peptide-based immunotherapeutic agent thymosin-α1 (Thα1) was successfully tested in clinical trials for ICD4 + TL [359] and NKTD [360] in humans. The controlled trial demonstrated a clear benefit of the long-term continuous immunomodulatory effect of rhIFN-γ in MPOD [336].

In case of primary neutropenia, natural and recombinant human granulocyte and granulocyte-macrophage colony-stimulating factors (rhG-CSF, rhGM-CSF) are prescribed as basic immunotherapeutic agents (dosage of 5–10 μg/kg by subcutaneous, intramuscular injections, or intravenous infusions) from 3 times a week to twice a month depending of the neutropenia severity, under the blood neutrophil granulocytes count control [361,362]. In contrast to Costman's disease, such therapy does not increase the risk of myelocytic leukaemia development in PMD [78].

Several successful attempts have been made to transplant allogeneic bone marrow into patients with severe ICD4+TL, NKD, SIgAD, and SIgGSD, which ensured complete restoration of the immunological phenotype. Suga et al. reported a successful bone marrow transplantation in an 8-year-old boy with severe SIgG1D from an HLA-identical MLC-negative sister, as neither prophylactic antibiotic therapy nor intravenous immunoglobulin reduced the frequency of infectious episodes. After transplantation, there was a recovery of serum IgG1 concentration and full compensation of the clinical status [363]. However, there were cases of PMDs' unexpected transmission from the donor to the recipient, such as SIgG2D, which indicates the need for a thorough immunological examination of the donors before transplantations [129]. Rarely, allogeneic hematopoietic stem cells have also been successfully transplanted in the case of NKD caused by a GATA2 mutation [364]. However, in PMDs, in case mutant genes were expressed outside the immune system (for example, in hepatocytes in MBLD), bone marrow transplantation can be ineffective.

Panel 2: Immunotherapeutic agents as basic therapy for PMD in humans

Cellular immunodeficiencies:

- Preparations of natural (leukocyte), lymphoblastoid, and recombinant (α2a–, α2b–) human IFN-alpha (nhIFN–α, lhIFN–α, rhIFN–α2a, rhIFN–α2b) in a dose of 1–3 million IU, intramuscular or subcutaneous once every 48 h [358,365–368];
- Recombinant human IFN–beta1a (rhIFNβ1a), dosage 22–44 μg (6–12 million IU), three times a week by intramuscular or subcutaneous injections [369];
- Recombinant human IFN–γ (rhIFNγ), dosage of 500,000–2 million IU, intramuscular or subcutaneous use, once every 48 h [306,370,371];
- Recombinant human IL–2 (rhIL–2), dosage of 1.5 million MO per day; four subcutaneous injections with an interval of 3 weeks for a course [357,372,373];
- Recombinant human IL–7 (rhIL–7), dosage of 10 μg/kg [61,356,374];
- Thymosin-alpha1 (Thα1), dosage of 1.6 μg twice a week by intramuscular or subcutaneous [359,360,375];

- Preparations of natural α/β-defensins combined by alarmines/adrenomedullin [53,376] or isolated [377–380], dosage of 2 mL of standardized solution by intramuscular route, once every 24 or 48 h;
- Human dialyzable leukocyte extract (hDLE) for intramuscular administration of 4 mL once a week [3381] and oral of 1 fl of standardized solution once a week [382,383];
- polyinosinic-polycytidylic acid (poly I:C, Poly(I)-Poly(C)), dosage of 10 mg/mL, intranasal [384];
- Reduced L-glutathione (rL-GTH), dosage of 1,000–2,000 mg per day per os [364,385–387];
- Glycyrrhizic acid (GA) at a dose of 400–1600 mg per day per os [24];
- Adoptive T-cell transfer [389];
- Transplantation of allogeneic human hematopoietic cells [364, 390, 391];
- Cord blood transplantation [392];
- Allogenic bone-marrow transplantation [363].

Humoral immunodeficiencies (antibody deficiencies):

- Immunoglobulin replacement therapy (5–10% IgG-containing normal human immunoglobulin for intravenous infusions at a dose of 200–800 mg/kg per month [344,349,393,394] and for intramuscular use at a dose of 25–50 mg/kg per week [346], (or even subcutaneously [395,396]);
- Normal IgG-containing human immunoglobulin enriched with IgA and IgM molecules, dosage of 100–400 mg/kg per month by intravenous infusions [347,397–399];
- Fresh frozen and cryopreserved human blood plasma, dosage of 10–15 mL/kg by intravenous infusions once every two weeks, considering the blood group type [400];
- Transfer factor based on bovine colostrum standardized immune extract, dosage from 1 to 60 g per day per os [401–403];
- Microbial lysate medicines, including OM-85 BV at a dose of 3.5–7 μg per day per os, a course of 10 days with 20-day intervals [338] and natural beta-glucan at a dose of 900–1800 mg per day per os [404–406];
- Vaccination with 23-valent conjugate antipneumococcal vaccine [212].

Phagocytic immunodeficiencies:

- Recombinant human IFN-gamma (rhIFNγ), dosage of 500,000 IU by intramuscular or subcutaneous injections once every 48 h [336,407];
- Muramyldil(tri)peptide (MDP, MTP) at a dose of 2 mg by intramuscular injections once every 5 days [408,409].

Deficiencies of complement proteins:

- Fresh frozen and cryopreserved human blood plasma, dosage of 10–15 mL/kg by intravenous infusions once every 2 weeks, considering the blood group type [353,354,410];
- natural and recombinant human mannose-binding protein (nhMBL, rhMBL) (in progress) [354,355];
- vaccination with MenB-4C antimeningococcal vaccine [165].

Neutropenia

– Natural and recombinant human granulocyte colony-stimulating factor (rhG-CSF, or filgastim, lenograstim) by intramuscular or subcutaneous injections in a dose of 10-15 μg/kg 2-3 times a week [313,362,411–413];
– Recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF or sargramostim), dosage of 2-3 μg/kg by intramuscular or subcutaneous injections [361];
– Human leukocyte mass [414].

4. Discussion

4.1. Conception of PMDs in humans

This systematic review summarizes the deep and diverse scientific knowledge on PMD in humans, having analyzed all the main clinical attributes of this pathology, from etiology to treatment. The accumulated data allow us to form a theory about PMD. The basis of this theory may be the idea of the heterogeneity and complexity of the phenomenon of immunocompromise in humans. Along with the classic primary immunodeficiencies, rare extreme experiments of nature, there are a large number of minor diseases of the immune system, which are widely represented in the population and form a different pattern of immunocompromise among carriers. These PMDs, by their combined frequency among people and diversity, can explain the origin and heterogeneity of immune-dependent pathology in humans, the association of this pathology with microbial triggers, as well as the tendency to increase its frequency in the population. It can be said that PMD is a universal model of the etiological factor of immune-dependent pathology on a population scale. Recognizing the concept of PMD, we transfer immune-dependent syndromes from the category of idiopathic to the category of symptomatic. This fundamentally changes both theoretical ideas about immune-dependent syndromes and has important practical consequences.

The essence of the concept lies in the fact that PMD, due to the loss of one or more immune factors, forms a state of immune imbalance, which in the long term can lead to the formation of two interrelated phenomena. The first of them is a decrease in immune resistance due to the loss of the function of the affected immune factor. This reduced immune resistance in the clinic is realized in the form of infectious and oncological syndromes. The second phenomenon is called immune dysregulation. This condition is formed due to the loss of reciprocal relationships between immune factors that balance the system, with the loss of one of them. Immune dysregulation, in turn, manifests itself clinically in the form of immunoinflammatory, allergic, and autoimmune syndromes. This is how the main immune-dependent syndromes in PMD are formed.

The relationship between the phenomena of reduced immune resistance and immune dysregulation is obvious. For example, infectious agents that can accumulate in the body of people with PMD as a result of decreased immune resistance can act as triggers of autoimmunity in conditions of immune dysregulation, and the autoimmune reaction itself, mediated by immune dysregulation, can exacerbate the phenomenon of reduced immune resistance due to additional consumption of the affected immune factor when it is involved in the implementation of immune reactions of autoaggression

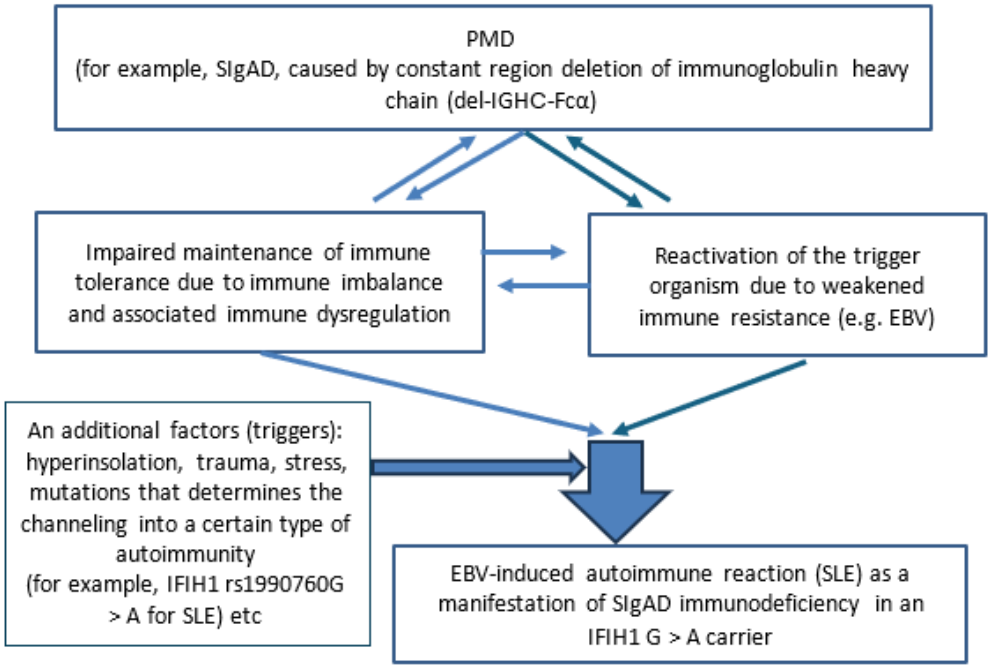

Figure 7. Elementary schematic diagram of the mechanism of induction of autoimmunity in immunocompromised individuals with PMD (for example, system SIgAD-EBV-SLE in IFH1 carrier).

(synergistic effect). However, antagonistic forms of interaction are also possible, when the loss of an immune factor that causes reduced immune resistance can weaken the effector mechanisms of immune-dependent syndromes, if the key component of these mechanisms is the lost immune factor. It can be said that the complex interaction between the phenomena of reduced immunoresistance and immune dysregulation as a manifestation of the dialectical law of struggle and unity of opposites is a kind of internal engine that determines the dynamics of the development of the clinical phenotype of PMD during the interaction of a person with environmental factors during ontogenesis (**Figure 7**).

4.2. Scientific advancement

No systematic review has been published on the problem of PMD to date. Therefore, this is the first generalization of scientific data in more than 60 years of scientific research. The need for such a generalization has long been overdue. The data obtained allows us to create a foundation for the study of PMD in humans by summarizing and systematizing the scientific data accumulated to date, showing where we are currently on the path of continuous scientific discoveries, to understand the accumulated evidence, identify its advantages, disadvantages, and gaps, and choose the optimal paths for further clinical research. The presented systematic review allows us to take a deeper look at the causes of the development of immune-dependent pathology in humans, the trend of increasing the frequency of such lesions in modern humans, and to improve our knowledge of the mechanisms of development of associated with PMDs infectious pathology, malignant neoplasms, ways of disruption of immune tolerance with the development of autoimmune and allergic pathology, as well as to find ways and means of better management of the pathological pro-

cess. Therefore, these data enrich the arsenal of knowledge of many disciplines—clinical immunology, infectious diseases, oncology, rheumatology, allergology, and many others. At the same time, this will allow us to revise the existing concepts of infectious, oncological, allergic, and autoimmune pathology in humans, making significant adjustments to the ideas about the origin of this pathology, factors of predisposition and prevention, identification of individual risk of formation, diversity of pathogenesis pathways, as well as diagnostic and treatment algorithms. The data presented in this systematic review allows us to initiate additional clinical studies not only in clinical immunology regarding the diagnosis of PMD, the study of their heterogeneity, improvement of approaches to diagnosis and treatment, but also in related disciplines—oncology, infectious diseases, allergology, rheumatology to assess the heterogeneity and multivariate nature of these phenomena, differences in pathogenesis, clinical picture, informativeness of diagnostic tests and effectiveness of therapeutic interventions. It is possible to study the heterogeneity of immune-dependent syndromes depending on different causal PMDs, which affects both the mechanism of development of immune-dependent pathology, prevalence in the population, gender- and age-dependent differences, possibility of approbation of new diagnostic, treatment and prophylactic approaches, and other important clinical attributes.

4.3. Clinical implications

It should be recognized that at present, most PMDs are ignored in clinical practice. There are no requirements for identifying the causes of immune-dependent diseases, which are still considered idiopathic phenomena. This narrows the possibilities of using a multidisciplinary approach and the possibilities of personalized medicine, and deprives access to etiological treatment. The introduction of the concept and classification of PMD into clinical practice can revolutionize the clinical management of patients with immune-dependent pathology. First, the conceptual approach changes. It is currently postulated that primary immunodeficiencies are rare phenomena. The concept of PMD indicates the opposite, that primary immunodeficiency is a component of the routine practice of a doctor. This increases the requirements for the level of knowledge of general practitioners, as well as specialists in immune-dependent pathology, in clinical immunology. This requires improving access to immunological services, increasing the number of laboratories, expanding the range of available immunological tests, and wider coverage of patients with immunodependent pathologies under the supervision of general practitioners with immunological examinations. This also necessitates significant changes in the interpretation of immunological examination results—it is necessary not to ignore the detected PMDs, but to recognize their clinical significance in accordance with the evidence accumulated so far, to carry out genetic verification of the diagnosis, to include the detected PMDs in the structure of clinical diagnoses as an ethological factor of associated immunodependent pathology, to stratify immune-mediated syndromes by forms of causal PMDs and, conversely, different forms of PMD by types of associated immunodependent pathology, to more widely involve multidisciplinary groups including clinical immunologists, to add etiotropic immunotherapy to the conventional pathogenetic and symptomatic therapy of immunodependent syndromes, which is the basic therapy of causal immunodeficiency, opening the way to

complex personalized treatment. Corresponding changes should be made to statistical documentation and electronic databases of medical histories, as well as to clinical guidelines and recommendations.

4.4. Limitations

It is necessary to admit that PMDs are studied heterogeneously, along with deeply studied immunodeficiencies, such as SIgAD, MBLD. There are nosologies that have been reported quite a bit, for example, EPOD, SIgDD. For some forms of PMD, there are still no thorough reviews, systematic reviews, and meta-analyses. During the long period covered by this systematic review, different laboratory measurement methods, units, and different diagnostic criteria for some PMDs were used, which makes it difficult to compare and generalize the results. Some immunotherapy methods that have been tested for certain PMDs have not yet undergone randomized controlled clinical trials. All these features create certain limitations in the systematization of knowledge about PMDs, and the correction of these shortcomings should be the subject of further clinical research.

4.5. Directions for further research

Analysis of the accumulated scientific data in the field of PMD studies allows us to identify gaps and contradictions that should be the subject of further scientific research. Efforts should be directed to identify new forms of PMD in order to form a holistic picture of the spectrum of these diseases, expand the list of genetic abnormalities underlying these or other PMDs, conduct an in-depth study of the pathogenetic mechanisms of the development of immune-dependent pathology in PMD, clarify data on the correlation between laboratory and clinical phenotype, validate clinical and laboratory criteria for the diagnosis of PMD, improve laboratory tests for the identification of certain forms of PMD, and also develop additional methods of immunotherapy. The goal of such research should be the development of means of primary and secondary prevention of PMD on a population scale to achieve control over the associated immune-dependent pathology.

5. Conclusion

The presented systematic review summarizes the accumulated data on PMD in humans over the past 65 years. This is the first attempt to systematize knowledge on this problem throughout the entire period of its study. Due to the work carried out, it was possible to propose a definition of the term PMD, outline the main differences from classical immunodeficiencies, propose diagnostic criteria for PMD, outline their genetic heterogeneity, differences in prevalence in the population, present the classification of these diseases, demonstrate the structure of the clinical picture, and approaches to diagnosis and treatment. Thus, all clinical attributes of PMD as human diseases were worked out. This allowed us to form a scientific concept of PMD, which can form the basis of both the modern doctrine of PMD in humans and ideas about the state of immunocompromise and immunodependent pathology. The obtained data have significant scientific and practical significance and determine the optimal directions of further scientific research in this area.

Al et al. [197] in their population-based study ask an important question: "*Is There a Clinical Significance of Very Low Serum Immunoglobulin E Level*?" ultimately demonstrating a sharp increase in the frequency of allergic, autoimmune, and oncological syndromes in individuals with this PMD. Thus, physicians should be well informed about the problem of PMD, and this pathology should be widely diagnosed in clinical practice in diverse immune-dependent pathologies. Currently, it is believed that PMDs are common genetic immune diseases that lead to form infectious, allergic, autoimmune, immunoinflammatory, and oncological syndromes, some integral phenomena with a complex pathogenesis (premature aging, fertility disorders, endocrine dysregulation, etc.), modify the course of genetic, infectious and somatic diseases, and create difficulties in diagnostic, therapeutic, and preventive interventions. Due to their high frequency in the population (and for some nosological forms, extremely high) and a sufficient degree of manifestation, PMDs form a great burden on the medical care system, society, and the state, including financial costs, being mostly a hidden phenomenon that is often ignored in clinical practice. The concept of PMD provides information on the etiology of various immunodependent syndromes in humans, which are currently considered mostly idiopathic, and, at the same time, allows for not only pathogenetic and symptomatic but also etiotropic treatment in such cases. Such an approach's introduction into clinical practice could revolutionize the diagnosis and treatment of PMD-associated immunodependent diseases. This will allow uniting seemingly heterogeneous immunodependent syndromes by a single etiological factor, implementing an integrative approach to patients' health assessment and clinical management. Therefore, the expected benefit from the proper implementation of PMD diagnostics among patients with immune-dependent diseases and, accordingly, the coverage of these individuals with targeted immunotherapy may be an important step towards improving the health of modern humans. Scientific efforts in this direction are difficult to overestimate.

However, the doctrine of PMD was formed spontaneously, so there are certain difficulties in systematizing knowledge on this problem. Taietti et al., on the example of SIgMD, demonstrate the achievements, controversies, and gaps in the modern scientific view on PMD [399]. Therefore, scientific research into PMDi in humans should be intensified.

Despite certain difficulties, the existing evidence base allows for an appropriate diagnostic and treatment process for PMDs. Vo Ngoc et al. referred to the "*long and winding road*" of scientific research and clinical understanding of PMDs on the SIgAD example [415], emphasizing the unprecedented philosophical and organizational challenges faced by scientists and clinicians in dealing with these diseases [416,417]. We have effective and safe immunotherapeutic approaches to PMDs now [418,419]. "*Forgotten"*, "*ignored"*, and "*underestimated*" PMD should become a more frequent object of clinical research and an important component of the routine clinical practice of medical specialists of various profiles, which can bring medical care for immuno-compromised patients to a qualitatively new level [420–424]. It is necessary to intensify further research into the key clinical attributes of PMD, which will allow the application of etiotropic personalized strategies for the management of patients with immune-dependent pathology, achieving eradication or, at least, deeper

control over the pathological process, and allowing for more effective primary and secondary prevention of immune-mediated pathology at the population scale through the integration of related medical disciplines.

Funding: None.

Ethical approval: Not applicable.

Informed consent statement: Not applicable.

Conflict of interest: The author declares no conflict of interest.

References

1. Bilyk L, Korylchuk N, Maltsev D, et al. Transformation of Ukrainian healthcare to the new conditions of development: Risks, solutions, modernisation options. Georgian Medical News. 2023; (344): 47–52.
2. Yuan ZC, Xu WD, Lan YY, et al. Association of MBL2 gene polymorphisms and systemic lupus erythematosus susceptibility: A meta-analysis. International Journal of Rheumatic Diseases. 2021; 24(2): 147–158. doi: 10.1111/1756-185x.14017
3. Garritano CRO, Nubila FD, Couto RM, et al. Use of transfer factor in immunosuppressed surgical patients. Revista do Colégio Brasileiro de Cirurgiões. 2017; 44(5): 452–456. doi: 10.1590/0100-69912017005005
4. Giardino G, Di Matteo G, Giliani S, et al. Consensus of the Italian primary immunodeficiency network on the use and interpretation of genetic testing for diagnosing inborn errors of immunity. Journal of Allergy and Clinical Immunology. 2025; 155(4): 1149–1160. doi: 10.1016/j.jaci.2024.11.030
5. Amirifar P, Ranjouri MR, Lavin M, et al. Ataxia-telangiectasia: Epidemiology, pathogenesis, clinical phenotype, diagnosis, prognosis and management. Expert Review of Clinical Immunology. 2020; 16(9): 859–871. doi: 10.1080/1744666x.2020.1810570
6. Litzman J, Bartonkova D, Lokaj J. The efficacy of levamisole treatment in patients with clinical signs of minor immunodeficiency. Scripta Medica. 1995; 68(3–4): 103–112.
7. Cain WA, Ammann AJ, Hong R, et al. IgE deficiency associated with chronic sinopulmonary infection. The Journal of Clinical Investigation. 1969; 48: 12a. doi: 10.1056/nejm196908282810904
8. García Pavón Osorio S, López Tiro JJ, Gómez Vera J. Deficiencia de IgE: Un padecimiento olvidado? Revista Alergia México. 2009; 56(6): 192–197.
9. Louis AG, Gupta S. Primary selective IgM deficiency: An ignored immunodeficiency. Clinical Reviews in Allergy & Immunology. 2014; 46(2): 104–111. doi: 10.1007/s12016-013-8375-x
10. Gupta S, Gupta A. Selective IgM deficiency— An underestimated primary immunodeficiency. Frontiers in Immunology. 2017; 8: 1056. doi: 10.3389/fimmu.2017.01056
11. Portaro JK, Zighelboim J, Fahey JL. Hereditary deficiency of K cells in a normal subject. Clinical Immunology and Immunopathology. 1978; 11(4): 458–469. doi: 10.1016/0090-1229(78)90173-3
12. Vel'tishchev IuE. Compensated or minor anomalies of the immune system. Sovetskaya Meditsina. 1988; (7): 46–50.
13. Van Kessel DA, Horikx PE, Van Houte AJ, et al. Clinical and immunological evaluation of patients with mild IgG1 deficiency. Clinical and Experimental Immunology. 1999; 118(1): 102–107. doi: 10.1046/j.1365-2249.1999.01023.x
14. Janssen LMA, Bassett P, Macken T, et al. Mild hypogammaglobulinemia can be a serious condition. Frontiers in Immunology. 2018; 9: 2384. doi: 10.3389/fimmu.2018.02384
15. Catli G, Gao W, Foley C, et al. Atypical STAT5B deficiency, severe short stature and mild immunodeficiency associated with a novel homozygous STAT5B Variant. Molecular and Cellular Endocrinology. 2023; 559: 111799. doi: 10.1016/j.mce.2022.111799
16. Hashimoto S, Miyawaki T, Futatani T, et al. Atypical X-linked agammaglobulinemia diagnosed in three adults. Internal Medicine. 1999; 38(9): 722–725. doi: 10.2169/internalmedicine.38.722
17. Caka C, Cimen O, Kahyaoğlu P, et al. Selective IgM deficiency: Follow-up and outcome. Pediatric Allergy and Immunology. 2021; 32(6): 1327–1334. doi: 10.1111/pai.13497

18. Janssen LMA, van Hout RWNM, de Vries E, et al. Challenges in investigating patients with isolated decreased serum IgM: The SIMcal study. Scandinavian Journal of Immunology. 2019; 89(6): e12763. doi: 10.1111/sji.12763
19. Cappelletti P, Doretto P, Signori D, et al. Eosinophilic peroxidase deficiency. Cytochemical and ultrastructural characterisation of 21 new cases. American Journal of Clinical Pathology. 1992; 98(6): 615–622. doi: 10.1093/ajcp/98.6.615
20. Régent A, Autran B, Carcelain G, et al. Idiopathic CD4 lymphocytopenia: Clinical and immunological characteristics and follow-up of 40 patients. Medicine. 2014; 93(2): 61–72. doi: 10.1097/md.0000000000000017
21. Introne WJ, Westbroek W, Cullinane AR, et al. Neurological involvement in patients with atypical Chediak-Higashi disease. Neurology. 2016; 86(14): 1320–1328. doi: 10.1212/wnl.0000000000002551
22. Koskinen S. Long-term follow-up of health in blood donors with primary selective IgA deficiency. Journal of Clinical Immunology. 1996; 16(3): 165–170. doi: 10.1007/bf01540915
23. Endoh M, Kaneshige H, Tomino Y, et al. Selective IgM deficiency: A case study. Tokai Journal of Experimental and Clinical Medicine. 1981; 6(3): 327–331.
24. van de Vosse E, van Ostaijen-Ten Dam MM, Vermaire R, et al. Recurrent respiratory tract infections (RRTI) in the elderly: A late onset mild immunodeficiency? Clinical Immunology. 2017; 180: 111–119. doi: 10.1016/j.clim.2017.05.008
25. Nakagawa T, Ikemoto T, Takeuchi T, et al. Eosinophilic peroxidase deficiency: Identification of a point mutation (D648N) and prediction of structural changes. Human Mutation. 2001; 17(3): 235–236. doi: 10.1002/humu.10
26. Roa S, Isidoro-Garcia M, Davila I, et al. Molecular analysis of activation-induced cytidine deaminase gene in immunoglobulin-E deficient patients. Clinical and Developmental Immunology. 2008; 2008: 146715. doi: 10.1155/2008/146715
27. Castillo-Tong DC, Pils D, Heinze G, et al. Association of myeloperoxidase with ovarian cancer. Tumour Biology. 2014; 35(1): 141–148. doi: 10.1007/s13277-013-1017-3
28. Zhang J, van Oostrom D, Li J, et al. Innate mechanisms in selective IgA deficiency. Frontiers in Immunology. 2021; 12: 649112. doi: 10.3389/fimmu.2021.649112
29. Komvilaisak P, Yudhasompop N, Kanchanakamhaeng K, et al. Screening for ELANE, HAX1 and GFI1 gene mutations in children with neutropenia and clinical characterization of two novel mutations in ELANE gene. BMC Pediatrics. 2023; 23(1): 592. doi: 10.1186/s12887-023-04428-w
30. Wen LY, Ma X, Peng HF, et al. Neutrophil elastase gene mutation-induced cyclic neutropenia: A case report. Zhonghua Nei Ke Za Zhi. 2023; 62(2): 193–196. doi: 10.3760/cma.j.cn112138-20220618-00460
31. Zeidler A, Borbaran-Bravo N, Dannenmann B, et al. Differential transcriptional control of hematopoiesis in congenital and cyclic neutropenia patients harboring ELANE mutations. Haematologica. 2024; 109(5): 1393–1402. doi: 10.3324/haematol.2023.284033
32. Horwitz MS, Corey SJ, Grimes HL, et al. ELANE mutations in cyclic and severe congenital neutropenia: Genetics and pathophysiology. Hematology/Oncology Clinics of North America. 2013; 27(1): 19–41. doi: 10.1016/j.hoc.2012.10.004
33. Kakkas I, Tsinti G, Kalala F, et al. TACI Mutations in primary antibody deficiencies: A nationwide study in Greece. Medicina. 2021; 57(8): 827. doi: 10.3390/medicina57080827
34. Aghamohammadi A, Mohammadi J, Parvaneh N, et al. Progression of selective IgA deficiency to common variable immunodeficiency. International Archives of Allergy and Immunology. 2008; 147(2): 87–92. doi: 10.1159/000135694
35. Sgrulletti M, Costagliola G, Giardino G, et al. The evolutionary scenario of pediatric unclassified primary antibody deficiency to adulthood. Journal of Clinical Medicine. 2023; 12(13): 4206. doi: 10.3390/jcm12134206
36. Nauseef WM, Brigham S, Cogley M. Hereditary myeloperoxidase deficiency due to a missense mutation of arginine 569 to tryptophan. Journal of Biological Chemistry. 1994; 269(2): 1212–1216.
37. Kutter D. Prevalence of myeloperoxidase deficiency: Population studies using Bayer-Technicon automated hematology. Journal of Molecular Medicine (Berlin). 1998; 76(10): 669–675. doi: 10.1007/s001090050266
38. Petrides PE. Molecular genetics of peroxidase deficiency. Journal of Molecular Medicine (Berlin). 1998; 76(10): 688–698. doi: 10.1007/s001090050269
39. Romano M, Patriarca P, Melo C, et al. Hereditary eosinophil peroxidase deficiency: Immunochemical and spectroscopic studies and evidence for a compound heterozygosity of the defect. Proceedings of the National Academy of Sciences of the United States of America. 1994; 91(26): 12496–12500. doi: 10.1073/pnas.91.26.12496
40. Balduit A, Bianco AM, Mangogna A, et al. Genetic bases of C7 deficiency: Systematic review and report of a novel deletion determining functional hemizygosity. Frontier in Immunology. 2023; 14: 1192690. doi: 10.3389/fimmu.2023.1192690

41. Alinger JB, Mace EM, Porter JR, et al. Human PLCG2 haploinsufficiency results in a novel natural killer cell immunodeficiency. Journal of Allergy and Clinical Immunology. 2024; 153(1): 216–229. doi: 10.1016/j.jaci.2023.09.002
42. Gibson CS, MacLennan AH, Goldwater PN, et al. Mannose-binding lectin haplotypes may be associated with cerebral palsy only after perinatal viral exposure. American Journal of Obstetrics and Gynecology. 2008; 198(5): 509.e1–8. doi: 10.1016/j.ajog.2008.02.027
43. Magen E, Schlesinger M, Ben-Zion I, et al. Helicobacter pylori infection in patients with selective immunoglobulin E deficiency. World Journal of Gastroenterology. 2015; 21(1): 240–245. doi: 10.3748/wjg.v21.i1.240
44. Marin-Bejar O, Romero-Moya D, Rodriguez-Ubreva J, et al. Epigenome profiling reveals aberrant DNA methylation signature in GATA2 deficiency. Haematologica. 2023; 108(9): 2551–2557. doi: 10.3324/haematol.2022.282305
45. Mosley JD, Shelley JP, Dickson AL, et al. Clinical associations with a polygenic predisposition to benign lower white blood cell counts. Nature Communications. 2024; 15(1): 3384. doi: 10.1038/s41467-024-47804-5
46. Persad AS, Kameoka Y, Kanda S, et al. Arginine to cysteine mutation (R499C) found in a Japanese patient with complete myeloperoxidase deficiency. Gene Expression. 2006; 13(2): 67–71. doi: 10.3727/000000006783991863
47. Barreto MESF, Lipay ME, Santos LD, et al. Duffy phenotyping and FY*B-67T/C genotyping as a screening test for benign constitutional neutropenia. Hematology, Transfusion and Cell Therapy. 2021; 43(4): 489–493. doi: 10.1016/j.htct.2020.08.015
48. Charles BA, Hsieh MM, Adeyemo A, et al. Analyses of genome-wide association data, cytokines, and gene expression in African-Americans with benign ethnic neutropenia. PLoS One. 2018; 13(3): e0194400. doi: 10.1371/journal.pone.0194400
49. Little KM, Conant JL, Devitt KA, et al. Novel ELANE mutation associated with a clinical presentation of cyclic neutropenia. Journal of the Association of Genetic Technologists. 2023; 49(4): 167–170.
50. van de Winkel JG, de Wit TP, Ernst LK, et al. Molecular basis for a familial defect in phagocyte expression of IgG receptor I (CD64). Journal of Immunology. 1995; 154(6): 2896–2903.
51. Orange JS. How I manage natural killer cell deficiency. Journal of Clinical Immunology. 2020; 40(1): 13–23. doi: 10.1007/s10875-019-00711-7
52. Reed AE, Peraza J, van den Haak F, et al. β-Actin G342D as a cause of NK cell deficiency impairing lytic synapse termination. Journal of Immunology. 2024; 212(6): 962–973. doi: 10.4049/jimmunol.2300671
53. Maltsev D, Stefanyshyn V. The efficacy of combined immunotherapy with propes and inflamafertin in adult patients with genetic deficiency of the folate cycle and selective deficiency of NK and NKT cells. Immunology. 2022; 167(3): 443–450. doi: 10.1111/imm.13548
54. Jordan MA, Fletcher J, Baxter AG. Genetic control of NKT cell numbers. Immunology and Cell Biology. 2004; 82(3): 276–284. doi: 10.1111/j.0818-9641.2004.01264.x
55. de Vries E, Koene HR, Vossen JM, et al. Identification of an unusual Fc gamma receptor IIIa (CD16) on natural killer cells in a patient with recurrent infections. Blood. 1996; 88(8): 3022–3027.
56. Grier JT, Forbes LR, Monaco-Shawver L, et al. A human immunodeficiency-causing mutation implicates CD16 in spontaneous NK cell cytotoxicity. Journal of Clinical Investigation. 2012; 122(10): 3769–3780. doi: 10.1172/jci64837
57. Karaselek MA, Kurar E, Keleş S, et al. Association of NK cell subsets and cytotoxicity with FCGR3A gene polymorphism in functional NK cell deficiency. Revista da Associação Médica Brasileira. 2024; 70(2): e20230872. doi: 10.1590/1806-9282.20230872
58. Leone F, Gori A, Cinicola BL, et al. Extra X, extra questions: Trisomy X syndrome and IgA deficiency—A case report. Frontiers in Immunology. 2024; 15: 1518076. doi: 10.3389/fimmu.2024.1518076
59. Terada T, Kaneko H, Li AL, et al. Analysis of Ig subclass deficiency: First reported case of IgG2, IgG4, and IgA deficiency caused by deletion of C alpha 1, psi C gamma, C gamma 2, C gamma 4, and C epsilon in a Mongoloid patient. Journal of Allergy and Clinical Immunology. 2001; 108(4): 602–606.
60. Saiga T, Hashimoto K, Kimura N, et al. Trisomy 10p and translocation of 10q to 4p are associated with selective dysgenesis of IgA-producing cells in lymphoid tissue. Pathology International. 2007; 57(1): 37–42. doi: 10.1111/j.1440-1827.2007.02054.x
61. Sheikh V, Porter BO, DerSimonian R, et al. Administration of interleukin-7 increases CD4 T cells in idiopathic CD4 lymphocytopenia. Blood. 2016; 127(8): 977–988. doi: 10.1182/blood-2015-05-645077
62. Cunningham-Rundles C. Genetic aspects of immunoglobulin A deficiency. Advances in Human Genetics. 1990; 19: 235–266. doi: 10.1007/978-1-4757-9065-8_4

63. Su T, Chapin SJ, Bryant DM, et al. Reduced immunoglobulin A transcytosis associated with immunoglobulin A nephropathy and nasopharyngeal carcinoma. Journal of Biological Chemistry. 2011; 286(52): 44921–44925. doi: 10.1074/jbc.m111.296731
64. Gallina R, Bottaro A, Boccazzi C, et al. The genetics of IgG4 deficiency: Role of the immunoglobulin heavy chain constant region and HLA loci. European Journal of Immunology. 1992; 22(1): 227–233. doi: 10.1002/eji.1830220133
65. Geier CB, Piller A, Linder A, et al. Leaky RAG Deficiency in adult patients with impaired antibody production against bacterial polysaccharide antigens. PLoS One. 2015; 10(7): e0133220. doi: 10.1371/journal.pone.0133220
66. Plebani A, Carbonara AO, Bottaro A, et al. Two siblings with deficiency of IgA1, IgG2, IgG4 and IgE due to deletion of immunoglobulin heavy chain constant region genes. Yearbook of Immunology. 1993; 7: 231–235.
67. Drygiannakis I, Theodoraki E, Tsafaridou M, et al. Crohn's disease—Like features in a patient with IgE and selective IgG1 and IgG3 deficiency. Cureus. 2023; 15(2): e34655. doi: 10.7759/cureus.34655
68. Serwas NK, Cagdas D, Ban SA, et al. Identification of ITK deficiency as a novel genetic cause of idiopathic CD4+ T-cell lymphopenia. Blood. 2014; 124(4): 655–657. doi: 10.1182/blood-2014-03-564930
69. Gorska MM, Alam R. A mutation in the human uncoordinated 119 gene impairs TCR signalling and is associated with CD4 lymphopenia. Blood. 2012; 119(6): 1399-13406. doi: 10.1182/blood-2011-04-350686
70. De la Calle-Martin O, Hernandez M, Ordi J, et al. Familial CD8 deficiency due to a mutation in the CD8 alpha gene. Journal of Clinical Investigation. 2001; 108(1): 117–123. doi: 10.1172/jci10993
71. Mancebo E, Moreno-Pelayo MA, Mencía A, et al. Gly111Ser mutation in the CD8A gene causing CD8 immunodeficiency is found in Spanish gypsies. Molecular Immunology. 2008; 45(2): 479–484. doi: 10.1016/j.molimm.2007.05.022
72. Ytting H, Christensen IJ, Steffensen R, et al. Mannan-binding lectin (MBL) and MBL-associated serine protease 2 (MASP-2) genotypes in colorectal cancer. Scandinavian Journal of Immunology. 2011; 73(2): 122–127. doi: 10.1111/j.1365-3083.2010.02480.x
73. Zhu Z, Atkinson TP, Hovanky KT, et al. High prevalence of complement component C6 deficiency among African-Americans in the southeastern USA. Clinical and Experimental Immunology. 2000; 119(2): 305–310. doi: 10.1046/j.1365-2249.2000.01113.x
74. Densen P, Ackermann L, Saucedo L, et al. A point mutation creating a 3' splice site in C8A is a predominant cause of C8α-γ deficiency in African Americans. Journal of Immunology. 2020; 205(6): 1535–1539. doi: 10.4049/jimmunol.2000272
75. Dellepiane RM, Dell'Era L, Pavesi P, et al. Invasive meningococcal disease in three siblings with hereditary deficiency of the 8(th) component of complement: Evidence for the importance of an early diagnosis. Orphanet Journal of Rare Diseases. 2016; 11(1): 64–70. doi: 10.1186/s13023-016-0448-5
76. Kira R, Ihara K, Watanabe K, et al. Molecular epidemiology of C9 deficiency heterozygotes with an Arg95Stop mutation of the C9 gene in Japan. Journal of Human Genetics. 1999; 44(2): 109–111. doi: 10.1007/s100380050119
77. Milligan KL, Mann D, Rump A, et al. Complete myeloperoxidase deficiency: Beware the "false-positive" dihydrorhodamine oxidation. Journal of Pediatrics. 2016; 176: 204–206. doi: 10.1016/j.jpeds.2016.05.047
78. Merz LE, Story CM, Osei MA, et al. Absolute neutrophil count by Duffy status among healthy Black and African American adults. Blood Advances. 2023; 7(3): 317–320. doi: 10.1182/bloodadvances.2022007679
79. Dossou-Yovo OP, Lapoumeroulie C, Hauchecorne M, et al. Variants of the mannose-binding lectin gene in the Benin population: Heterozygosity for the p.G57E allele may confer a selective advantage. Human Biology. 2007; 79(6): 687–97. doi: 10.3378/027.081.0630
80. Lipscombe RJ, Sumiya M, Hill AV, et al. High frequencies in African and non-African populations of independent mutations in the mannose binding protein gene. Human Molecular Genetics. 1992; 1(9): 709–715. doi: 10.1093/hmg%2F2.3.342
81. Alcaïs A, Abel L, Casanova JL. Human genetics of infectious diseases: Between proof of principle and paradigm. Journal of Clinical Investigation. 2009; 119(9): 2506–2514. doi: 10.1172/jci38111
82. Airo' R, Milanesi B, Ferrari CM, et al. Deficit di mieloperossidasi: Prevalenza nella provincia di brescia e studio dell'attivita' microbicida dei granulociti Myeloperoxidase deficiency: prevalence in the Brescia Province and a study of microbicidal activity in granulocytes. Haematologica. 1985; 70(1): 12–18.
83. Nunoi H, Kohi F, Kajiwara H, et al. Prevalence of inherited myeloperoxidase deficiency in Japan. Microbiology and Immunology. 2003; 47(7): 527–531. doi: 10.1111/j.1348-0421.2003.tb03414.x

84. Garcia-Laorden MI, Pena MJ, Caminero JA, et al. Influence of mannose-binding lectin on HIV infection and tuberculosis in a Western-European population. Molecular Immunology. 2006; 43(14): 2143–2150. doi: 10.1016/j.molimm.2006.01.008
85. Antony JS, Ojurongbe O, van Tong H, et al. Mannose-binding lectin and susceptibility to schistosomiasis. Journal of Infectious Diseases. 2013; 207(11): 1675–1683. doi: 10.1093/infdis/jit081
86. Garred P, Madsen HO, Hofmann B, et al. Increased frequency of homozygosity of abnormal mannan-binding-protein alleles in patients with suspected immunodeficiency. Lancet. 1995; 346(8980): 941–943. doi: 10.1016/s0140-6736(95)91559-1
87. Hayama K, Sugai N, Tanaka S, et al. High-incidence of C9 deficiency throughout Japan: There are no significant differences in incidence among eight areas of Japan. International Archives of Allergy and Applied Immunology. 1989; 90(4): 400–404. doi: 10.1159/000235061
88. Feng L. Epidemiological study of selective IgA deficiency among 6 nationalities in China. Zhonghua Yi Xue Za Zhi. 1992; 72(2): 88–90.
89. Atallah-Yunes SA, Ready A, Newburger PE. Benign ethnic neutropenia. Blood Reviews. 2019; 37: 100586. doi: 10.1016/j.blre.2019.06.003
90. Stanford E, Ladhani S, Borrow R, et al. Immunoglobulin G deficiency in United Kingdom children with invasive pneumococcal disease. Pediatric Infectious Disease Journal. 2011; 30(6): 462–465. doi: 10.1097/inf.0b013e3182191dfa
91. Baker DA, Salvatore W, Milch PO. Effect of low-dose oral contraceptives on natural killer cell activity. Contraception. 1989; 39(1): 119–124. doi: 10.1016/0010-7824(89)90020-6
92. Vladutiu AO. Immunoglobulin D: Properties, measurement, and clinical relevance. Clinical and Diagnostic Laboratory Immunology. 2000; 7(2): 131–140. doi: 10.1128/cdli.7.2.131-140.2000
93. Walker AM, Kemp AS, Hill DJ, et al. Features of transient hypogammaglobulinemia in infants screened for immunological abnormalities. Archives of Disease in Childhood. 1994; 70(3): 183–186. doi: 10.1136/adc.70.3.183
94. Keles S, Artac H, Kara R, et al. Transient hypogammaglobulinemia and unclassified hypogammaglobulinemia: Similarities and differences. Pediatric Allergy and Immunology. 2010; 21(5): 843–851. doi: 10.1111/j.1399-3038.2010.01010.x
95. Entezari N, Adab Z, Zeydi M, et al. The prevalence of selective immunoglobulin M deficiency (SIgMD) in Iranian volunteer blood donors. Human Immunology. 2016; 77(1): 7–11. doi: 10.1016/j.humimm.2015.09.051
96. Hobbs JR. IgM deficiency. Birth Defects. 1975; 11(1): 112–116.
97. Ni J, Zhang J, Chen Q, et al. The epidemiology and clinical features of selective immunoglobulin M deficiency: A single-centre study in China. Journal of Clinical Laboratory Analysis. 2020; 34(7): e23289. doi: 10.1002/jcla.23289
98. Lacombe C, Aucouturier P, Preud homme JL. Selective IgG1 deficiency. Clinical Immunology and Immunopathology. 1997; 84(2): 194–201. doi: 10.1006/clin.1997.4386
99. Özcan C, Metin A, Erkoçoğlu M, et al. Bronchial hyperreactivity in children with antibody deficiencies. Allergologia et Immunopathologia. 2015; 43(1): 57–61. doi: 10.1016/j.aller.2013.09.014
100. Ludvigsson JF, Neovius M, Hammarström L. Association between IgA deficiency and other autoimmune conditions: A population-based matched cohort study. Journal of Clinical Immunology. 2014; 34(4): 444–451. doi: 10.1007/s10875-014-0009-4
101. Levin TA, Ownby DR, Smith PH, et al. Relationship between extremely low total serum IgE levels and rhinosinusitis. Annals of Allergy, Asthma & Immunology. 2006; 97(5): 650–652. doi: 10.1016/S1081-1206%2810%2961095-2
102. Makin T, Borish L, Nylund CM, et al. IgE deficiency is not associated with hypogammaglobulinemia in a large cohort of military recruits. Annals of Allergy, Asthma & Immunology. 2024; (24): S1081–1206. doi: 10.1016/j.anai.2024.04.025
103. Unsworth DJ, Virgo PF, Lock RJ. Immunoglobulin E deficiency: A forgotten clue pointing to possible immunodeficiency? Annals of Clinical Biochemistry. 2011; 48(Pt 5): 459–461. doi: 10.1258/acb.2011.011052
104. Fraser PA, Schur PH. Hypoimmunoglobulinemia D: Frequency, family studies, and association with HLA. Clinical Immunology and Immunopathology. 1981; 19(1): 67–74. doi: 10.1016/0090-1229(81)90048-9
105. García-Laorden MI, Hernández-Brito E, Muñoz-Almagro C, et al. Should MASP-2 deficiency be considered a primary immunodeficiency? Relevance of the lectin pathway. Journal of Clinical Immunology. 2020; 40: 203–210. doi: 10.1007/s10875-019-00714-4
106. Kim J, Hwang S, Hwang N, et al. Severe congenital neutropenia mimicking chronic idiopathic neutropenia: A case report. Journal of Yeungnam Medical Science. 2023; 40(3): 283–288. doi: 10.12701/jyms.2022.00353

107. Kavirayani V, Negi A, Prabhu MM. Acute cryptococcal meningitis in a patient with idiopathic CD4 lymphocytopenia: A rare clinical entity. Cureus. 2023; 15(8): e43417. doi: 10.7759/cureus.43417
108. Busch MP, Valinsky JE, Paglieroni T, et al. Screening of blood donors for idiopathic CD4+ T-lymphocytopenia. Transfusion. 1994; 34(3): 192–197. doi: 10.1046/j.1537–2995.1994.34394196614.x
109. Gunn E, Powers JM, Rahman AF, et al. Diagnosis and management of isolated neutropenia: A survey of pediatric hematologist oncologists. Pediatric Blood & Cancer. 2023; 70(2): e29946. doi: 10.1002/pbc.29946
110. Njue L, Porret N, Schnegg-Kaufmann AS, et al. Isolated severe neutropenia in adults, evaluation of underlying causes and outcomes, real-world data collected over a 5-year period in a tertiary referral hospital. Medicina (Kaunas). 2024; 60(10): 1576. doi: 10.3390/medicina60101576
111. Hua L, Guo D, Liu X, et al. Selective IgA deficiency with multiple autoimmune comorbidities: A case report and literature review. Iranian Journal of Immunology. 2023; 20(2): 232–239. doi: 10.22034/iji.2023.97452.2513
112. Chaushu S, Yefenof E, Becker A, et al. Severe impairment of secretory Ig production in parotid saliva of Down syndrome individuals. Journal of Dental Research. 2002; 81(5): 308–312. doi: 10.1177/154405910208100504
113. Jeraiby MA. Molecular basis of immunoglobulin heavy constant G4 gene (IGHG4)-related low serum IgG4 subclasses in down syndrome. Saudi Medical Journal. 2021; 42(9): 975–980.
114. Andreou A, Jayaram J, Walker A, et al. Re-examining the utility and validity of benign ethnic neutropenia: A narrative literature review. Schizophrenia Research. 2023; 253: 48–53. doi: 10.1016/j.schres.2022.02.009
115. Nasser NMF, Pastorino AC, de Moura TCL, et al. Understanding the natural history of selective IgA deficiency. Journal of Pediatrics (Rio de Janeiro). 2025; S0021-7557(25)00065-8. doi: 10.1016/j.jped.2025.03.002
116. Li PH, Wong WW, Leung EN, et al. Novel pathogenic mutations identified in the first Chinese pedigree of complete C6 deficiency. Clinical & Translational Immunology. 2020; 9(7): e1148. doi: 10.1002/cti2.1148
117. Cipe FE, Doğu F, Güloğlu D, et al. B-cell subsets in patients with transient hypogammaglobulinemia of infancy, partial IgA deficiency, and selective IgM deficiency. Journal of Investigational Allergology and Clinical Immunology. 2013; 23(2): 94–100.
118. Jamee M, Alaei MR, Mesdaghi M, et al. The prevalence of selective and partial immunoglobulin A deficiency in patients with autoimmune polyendocrinopathy. Immunological Investigations. 2022; 51(4): 778–786. doi: 10.1080/08820139.2021.1872615
119. Pérez-Portilla A, Moraru M, Blázquez-Moreno A, et al. Identification of the first cases of complete CD16A deficiency: Association with persistent EBV infection. Journal of Allergy and Clinical Immunology. 2020; 145(4): 1288–1292. doi: 10.1016/j.jaci.2019.11.049
120. Orren A, Würzner R, Potter PC, et al. Properties of a low molecular weight complement component C6 found in human subjects with subtotal C6 deficiency. Immunology. 1992; 75(1): 10–16.
121. Barton JC, Barton JC, Bertoli LF, et al. Characterisation of adult patients with IgG subclass deficiency and subnormal IgG2. PLoS One. 2020; 15(10): e0240522. doi: 10.1371/journal.pone.0240522
122. Shackelford PG, Granoff DM, Polmar SH, et al. Subnormal serum concentrations of IgG2 in children with frequent infections associated with varied patterns of immunological dysfunction. Journal of Pediatrics. 1990; 116(4): 529–538. doi: 10.1016/S0022-3476(05)81598-7
123. Jongco AM 3rd, Sporter R, Hon E, et al. Characterization of infants with idiopathic transient and persistent T cell lymphopenia identified by newborn screening—A single-center experience in New York State. Journal of Clinical Immunology. 2021; 41(3): 610–620. doi: 10.1007/s10875-020-00957-6
124. Abraitytė S, Kotsi E, Devlin LA, et al. Unexpected combination: DiGeorge syndrome and myeloperoxidase deficiency. BMJ Case Reports. 2020; 13(2): e232741. doi: 10.1136/bcr-2019-232741
125. Chavoshzadeh Z, Sharafian S, Alavi S, et al. Leukocyte adhesion deficiency type III in an infant presenting with intestinal perforation and low percentage of natural killer cells: First case report from Iran. BMC Pediatrics. 2025; 25(1): 315. doi: 10.1186/s12887-025-05674-w
126. Mannes M, Halbgebauer R, Wohlgemuth L, et al. Combined heterozygous genetic variations in complement C2 and C8B: An explanation for multidimensional immune imbalance? Journal of Innate Immunity. 2023; 15(1): 412–427. doi: 10.1159/000528607

127. Wawrzycka-Adamczyk K, Matyja-Bednarczyk A, Giza A, et al. Coexistence of ataxia telangiectasia syndrome and idiopathic CD4 lymphopenia: Diagnostic difficulties in a complex immunodeficiency case report. Polish Archives of Internal Medicine. 2022; 132(5): 16202. doi: 10.20452/pamw.16202
128. Huynh I, Woody DM, Ahmed-Khan MA, et al. Lost and found: Misdiagnosis of AIDS-related bone marrow suppression as neutropenic fever and benign ethnic neutropenia in a patient with congenital HIV. Cureus. 2024; 16(9): e68632. doi: 10.7759/cureus.68632
129. Hammarström L, Smith CI. Development of IgG2 deficiency in a bone-marrow-transplanted patient. Implication for generation of the anticarbohydrate antibody repertoire in subclass-deficient individuals. Transplant. 1987; 43(6): 917–919.
130. AlShomar A. Isolated benign neutropenia in healthy individuals from Saudi Arabia's central region: A comprehensive study. International Journal of Health Sciences (Qassim). 2023; 17(6): 23–27.
131. Borinstein SC, Agamasu D, Schildcrout JS, et al. Frequency of benign neutropenia among black versus white individuals undergoing a bone marrow assessment. Journal of Cellular and Molecular Medicine. 2022; 26(13): 3628–3635. doi: 10.1111/jcmm.17346
132. Centor RM, Chung CP, Mosley JD. Web Exclusive. Annals on call-Understanding benign neutropenia. Annals of Internal Medicine. 2022; 175(11). doi: 10.7326/a21-0022
133. Chok R, Price V, Steele M, et al. Pediatric benign neutropenia: Assessing practice preferences in Canada. Journal of Pediatric Hematology/Oncology. 2022; 44(6): 318–322. doi: 10.1097/mph.0000000000002427
134. Ponder R. A protected class, an unprotected condition, and a biomarker - A method/formula for increased diversity in clinical trials for the African American subject with benign ethnic neutropenia (BEN) - CORRIGENDUM. American Journal of Law & Medicine. 2023; 49(4): 525. doi: 10.1017/amj.2023.24
135. Elhadad D, Simon AJ, Bronstein Y, et al. Presence of "ACKR1/DARC null" polymorphism in Arabs from Jisr az-Zarqa with benign ethnic neutropenia. Pediatric Research. 2022; 91(5): 1012–1014. doi: 10.1038/s41390-021-01623-2
136. Gay K, Dulay K, Ravindranath Y, et al. Duffy-null phenotype-associated neutropenia is the most common etiology for leukopenia/neutropenia referrals to a tertiary children's hospital. Journal of Pediatrics. 2023; 262: 113608. doi: 10.1016/j.jpeds.2023.113608
137. Hysong MR, Shuey MM, Huffman JE, et al. Characterization of the phenotypic consequences of the Duffy-null genotype. Blood Advances. 2025; 9(6): 1452–1462. doi: 10.1182/bloodadvances.2024014399
138. Zammar G, Fong E, Creeper KJ. Clinical parameters of patients with Duffy null phenotype: A single centre, retrospective review. Pathology. 2025; 57(4): 484–488. doi: 10.1016/j.pathol.2024.11.010.
139. Bizymi N, Damianaki A, Aresti N, et al. Characterization of myeloid-derived suppressor cells in the peripheral blood and bone marrow of patients with chronic idiopathic neutropenia. Hemasphere. 2024; 8(9): e70005. doi: 10.1002/hem3.70005
140. Chennapragada SS, Sharma S, Dadi N, et al. Real-world data of leukopenia evaluation as seen in a community academic center. Journal of Community Hospital Internal Medicine Perspectives. 2023; 13(6): 126–128. doi: 10.55729/2000-9666.1273
141. Donadieu J, Frenz S, Merz L, et al. Chronic neutropenia: How best to assess severity and approach management? Expert Review of Hematology. 2021; 14(10): 945–960. doi: 10.1080/17474086.2021.1976634
142. Fattizzo B, Bosi A, Sorrenti M, et al. Natural history of chronic idiopathic neutropenia of the adult. Scientific Reports. 2024; 14(1): 21891. doi: 10.1038/s41598-024-71719-2
143. Gkoufa A, Sklapani P, Trakas N, et al. A challenging cutaneous lesion in a patient with chronic idiopathic neutropenia. Cureus. 2022; 14(1): e21225. doi: 10.7759/cureus.21225
144. Ogbue OD, Kewan T, Bahaj WS, et al. New approaches to idiopathic neutropenia in the era of clonal hematopoiesis. Experimental Hematology & Oncology. 2023; 12(1): 42. doi: 10.1186/s40164-023-00403-4
145. Anzinger H, Cadili L, Li A, et al. A distinct case of an 8-year-old female with cyclic neutropenia presenting with C. Septicum abdominal sepsis and myonecrosis requiring a bowel resection and leg fasciotomy. Journal of Surgical Case Reports. 2023; 2023(9): 1–3. doi: 10.1093/jscr/rjad512
146. Guarino AD, Luglio G, Imperatore N, et al. Cyclic neutropenia mimicking Crohn's disease: Two case reports and a narrative review. Journal of Clinical Medicine. 2023; 12(19): 6323. doi: 10.3390/jcm12196323
147. Kapogiannis C, Zaggogianni T, Stergiou N, et al. Cyclic neutropenia and concomitant IgA nephropathy: A case report. BMC Nephrology. 2023; 24(1): 124. doi: 10.1186/s12882-023-03179-1

148. Li JL, Zhao JJ, Li RJ, et al. Cyclic neutropenia: A case report and literature review. American Journal of Translational Research. 2025; 17(2): 1153–1161. doi: 10.62347/olfs3168
149. Tayal A, Meena JP, Kaur R, et al. A novel homozygous HAX1 mutation in a child with cyclic neutropenia: A case report and review. Journal of Pediatric Hematology/Oncology. 2022; 44(2): e420-e423. doi: 10.1097/mph.0000000000002110
150. Benavides-Nieto M, Adam F, Martin E, et al. Somatic RAP1B gain-of-function variant underlies isolated thrombocytopenia and immunodeficiency. Journal of Clinical Investigation. 2024; 134(17): e169994. doi: 10.1172/jci169994
151. Magen E, Geishin A, Weizman A, et al. High rates of mood disorders in patients with chronic idiopathic eosinopenia. Brain, Behavior, and Immunity – Health. 2024; 40: 100847. doi: 10.1016/j.bbih.2024.100847
152. Magen E, Merzon E, Green I, et al. Chronic idiopathic eosinopenia and chronic spontaneous urticaria. Journal of Allergy and Clinical Immunology: In Practice. 2023; 11(8): 2583–2586. doi: 10.1016/j.jaip.2023.03.057
153. Magen E, Vinker-Shuster M, Merzon E, et al. Chronic idiopathic eosinopenia, allergic, and autoimmune disorders. Journal of Allergy and Clinical Immunology: In Practice. 2024; 12(7): 1933–1936.e1. doi: 10.1016/j.jaip.2024.03.048
154. Abdalgani M, Hernandez ER, Pedroza LA, et al. Clinical, immunologic, and genetic characteristics of 148 patients with natural killer cell deficiency. Journal of Allergy and Clinical Immunology. 2025; 155(5): 1623–1634. doi: 10.1016/j.jaci.2025.01.030
155. Conte MI, Poli MC, Taglialatela A, et al. Partial loss-of-function mutations in GINS4 lead to NK cell deficiency with neutropenia. JCI Insight. 2022; 7(21): e154948. doi: 10.1172/jci.insight.154948
156. Martinot M, Li SS, Farnarier C, et al. Persistent NK cell deficiency associated with pulmonary cryptococcosis. Annals of Clinical Microbiology and Antimicrobials. 2025; 24(1): 6. doi: 10.1186/s12941-024-00771-7
157. Cho YN, Kee SJ, Lee SJ, et al. Numerical and functional deficiencies of natural killer T cells in systemic lupus erythematosus: Their deficiency related to disease activity. Rheumatology. 2011; 50(6): 1054–1063. doi: 10.1093/rheumatology%2Fkeq457
158. Ho LP, Urban BC, Thickett DR, et al. Deficiency of a subset of T-cells with immunoregulatory properties in sarcoidosis. Lancet. 2005; 365(9464): 1062–1072. doi: 10.1016/s0140-6736(05)71143-0
159. Lee SJ, Cho YN, Kim TJ, et al. Natural killer T cell deficiency in active adult-onset Still's disease: Correlation of natural killer T cell deficiency with natural killer cell dysfunction. Arthritis and Rheumatism. 2012; 64(9): 2868–2877. doi: 10.1002/art.34514
160. Merselis LC, Jiang SY, Nelson SF, et al. MPEG1/Perforin-2 haploinsufficiency associated polymicrobial skin infections and considerations for interferon-γ therapy. Frontiers in Immunology. 2020; 11: 601584. doi: 10.3389/fimmu.2020.601584
161. McMurray JC, Schornack BJ, Weskamp AL, et al. Immunodeficiency: Complement disorders. Allergy and Asthma Proceedings. 2024; 45(5): 305–309. doi: 10.2500/aap.2024.45.240050
162. Szilágyi Á, Csuka D, Geier CB, et al. Complement genetics for the practicing allergist immunologist: focus on complement deficiencies. Journal of Allergy and Clinical Immunology: In Practice. 2022; 10(7): 1703–1711. doi: 10.1016/j.jaip.2022.02.036
163. Staels F, Meersseman W, Stordeur P, et al. Terminal complement pathway deficiency in an adult patient with meningococcal sepsis. Case Reports in Immunology. 2022; 2022: 9057000. doi: 10.1155/2022/9057000
164. Khalil SM, Aqel S, Mudawi DS, et al. The first case report of complement component 7 deficiency in Qatar and a 10-year follow-up. Frontiers in Immunology. 2023; 14: 1253301. doi: 10.3389/fimmu.2023.1253301
165. van den Broek B, Coolen JPM, de Jonge MI, et al. Neisseria meningitidis serogroup Z meningitis in a child with complement C8 deficiency and potential cross protection of the MenB-4C vaccine. Pediatric Infectious Disease Journal. 2021; 40(11): 1019–1022. doi: 10.1097/inf.0000000000003259
166. Daungsupawong H, Wiwanitkit V. Humoral and cellular response to the third COVID-19 vaccination in patients with inborn errors of immunity or mannose-binding lectin deficiency: Correspondence. Wiener klinische Wochenschrift. 2025; 137(1–2): 58–59. doi: 10.1007/s00508-024-02481-8
167. Ramphul M, Poghosyan A, Afzal J, et al. Respiratory outcomes at 5-year follow-up in children with mannose-binding lectin deficiency: A retrospective cohort study. Thoracic Research and Practice. 2023; 24(2): 85–90. doi: 10.5152/ThoracResPract.2023.22121
168. Ruffles T, Basu K, Inglis SK, et al. Mannose-binding lectin genotype is associated with respiratory disease in young children: A multicenter cohort study. Pediatric Pulmonology. 2022; 57(11): 2824–2833. doi: 10.1002/ppul.26109

169. Stengaard-Pedersen K, Thiel S, Gadjeva M, et al. Inherited deficiency of mannan-binding lectin-associated protein protease 2. New England Journal of Medicine. 2003; 349(6): 554–560. doi: 10.1056/nejmoa022836
170. Agyemang EA, Makanga DM, Abdallah M, et al. Idiopathic CD4 lymphocytopenia: A case report and literature review. Cureus. 2024; 16(3): e56968. doi: 10.7759/cureus.56968
171. Baomo L, Guofen Z, Jie D, et al. Disseminated cryptococcosis in a patient with idiopathic CD4+ T lymphocytopenia presenting as prostate and adrenal nodules: Diagnosis from pathology and mNGS, a case report. BMC Infectious Diseases. 2024; 24(1): 26. doi: 10.1186/s12879-023-08926-1
172. Bukhamseen F, Al-Shamrani A. An under-recognized disease: A rare case of idiopathic CD4 lymphopenia mislabeled as primary ciliary dyskinesia. Children (Basel). 2022; 9(10): 1534. doi: 10.3390/children9101534
173. Cudrici CD, Boulougoura A, Sheikh V, et al. Characterization of autoantibodies, immunophenotype and autoimmune disease in a prospective cohort of patients with idiopathic CD4 lymphocytopenia. Clinical Immunology. 2021; 224: 108664. doi: 10.1016/j.clim.2021.108664
174. Kumar G, Schmid-Antomarchi H, Schmid-Alliana A, et al. Idiopathic CD4 T cell lymphocytopenia: A case of overexpression of PD-1/PDL-1 and CTLA-4. Infectious Disease Reports. 2021; 13(1): 72–81. doi: 10.3390/idr13010009
175. Li B, Li T, Lu Q, et al. Severe disseminated Talaromyces marneffei infection in idiopathic CD4 lymphopenia. IDCases. 2025; 39: e02148. doi: 10.1016/j.idcr.2025.e02148
176. Darmawan D, Raychaudhuri S, Lakshminrusimha S, et al. Hypogammaglobulinemia in neonates: Illustrative cases and review of the literature. Journal of Perinatology. 2024; 44(7): 929–934. doi: 10.1038/s41372-023-01766-6
177. Emsen A, Uçaryılmaz H, Güler T, et al. Regulatory T and B cells in transient hypogammaglobulinemia of infancy. Turkish Journal of Pediatrics. 2022; 64(2): 228–238. doi: 10.24953/turkjped.2021.83
178. Ito T, Iwamoto S, Hirayama M, et al. Transient hypogammaglobulinemia of infancy may be associated with reduced switched memory B cells and del (16) (p11.2p12). Clinical Case Reports. 2021; 9(6): e3837. doi: 10.1002/ccr3.3837
179. Justiz-Vaillant AA, Hoyte T, Davis N, et al. A systematic review of the clinical diagnosis of transient hypogammaglobulinemia of infancy. Children (Basel). 2023; 10(8): 1358. doi: 10.3390/children10081358
180. Ulman H, Aygün A, Çağlar D, et al. Transient hypogammaglobulinemia of infancy and unclassified syndromic immunodeficiencies are highly common in oesophageal atresia patients. Scandinavian Journal of Immunology. 2024; 99(2): e13338. doi: 10.1111/sji.13338
181. Imam K, Huang J, White AA. Isotype deficiencies (IgG subclass and selective IgA, IgM, IgE deficiencies). Allergy and Asthma Proceedings. 2024; 45(5): 317–320. doi: 10.2500/aap.2024.45.240055
182. Batista CHR, Smanio MCM, Poltronieri PB, et al. Selective IgM deficiency: Evaluation of 75 patients according to different diagnostic criteria. Immunologic Research. 2024; 73(1): 15. doi: 10.1007/s12026-024-09568-4
183. Crescenzo F, Turazzini M, Rossi F. Selective IgM hypogammaglobulinemia and multiple sclerosis treated with natalizumab and ofatumumab: A case report. Journal of Personalized Medicine. 2025; 15(4): 155. doi: 10.3390/jpm15040155
184. Janssen LMA, Macken T, Creemers MCW, et al. Truly selective primary IgM deficiency is probably very rare. Clinical and Experimental Immunology. 2018; 191(2): 203–211. doi: 10.1111/cei.13065
185. Filion CA, Taylor-Black S, Maglione PJ, et al. Differentiation of common variable immunodeficiency from IgG deficiency. Journal of Allergy and Clinical Immunology: In Practice. 2019; 7(4): 1277–1284. doi: 10.1016/j.jaip.2018.12.004
186. Altiner S, Ekinci A. Adult-onset periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis syndrome on the basis of selective IgA deficiency. Case Reports in Dermatological Medicine. 2024; 2024: 9845501. doi: 10.1155/2024/9845501
187. Amiel A, Van Gucht T, Bolliet M, et al. Selective IgA deficiency and aseptic liver abscess as initial indicators of Crohn's disease in a young woman: A case study. American Journal of Case Reports. 2024; 25: e944829. doi: 10.12659/ajcr.944829
188. Vosughimotlagh A, Rasouli SE, Rafiemanesh H, et al. Clinical manifestation for immunoglobulin A deficiency: A systematic review and meta-analysis. Allergy, Asthma & Clinical Immunology. 2023; 19(1): 75. doi: 10.1186/s13223-023-00826-y
189. Polosukhin VV, Richmond BW, Du RH, et al. Secretory IgA deficiency in individual small airways is associated with persistent inflammation and remodelling. American Journal of Respiratory and Critical Care Medicine. 2017; 195(8): 1010–1021. doi: 10.1164/rccm.201604-0759oc
190. Agress A, Oprea Y, Roy S, et al. The association between malignancy, immunodeficiency, and atopy in IgE-deficient patients. Journal of Allergy and Clinical Immunology: In Practice. 2024; 12(1): 185–194. doi: 10.1016/j.jaip.2023.10.026
191. Magen E, Schlesinger M, David M. Selective IgE deficiency, immune dysregulation, and autoimmunity. Allergy and Asthma Proceedings. 2014; 35(2): e27–33. doi: 10.2500/aap.2014.35.3734

192. Nemet S, Elbirt D, Cohen R, et al. IgE deficiency (<2.5 IU/mL) in children: Clinical insights from a population-based study of 123,393 subjects. Pediatric Allergy and Immunology. 2025; 36(4): e70092. doi: 10.1111/pai.70092
193. Picado C, de Landazuri IO, Vlagea A, et al. Spectrum of disease manifestations in patients with selective immunoglobulin E deficiency. Journal of Clinical Medicine. 2021; 10(18): 4160. doi: 10.3390/jcm10184160
194. Matricardi PM. The very low IgE producer: Allergology, genetics, immunodeficiencies, and oncology. Biomedicines. 2023; 11(5): 1378. doi: 10.3390/biomedicines11051378
195. Famuyiwa F, Rubinstein I. Chronic sinopulmonary inflammatory diseases in adults with undetectable serum IgE in inner-city Chicago: A preliminary observation. Lung. 2012; 190(3): 291–294. doi: 10.1007/s00408-012-9375-y
196. Ferastraoaru D, Bax HJ, Bergmann C, et al. AllergoOncology: Ultra-low IgE, a potential novel biomarker in cancer—A position paper of the European academy of allergy and clinical immunology (EAACI). Clinical and Translational Allergy. 2020; 10(1): 32. doi: 10.1186/s13601-020-00335-w
197. Al S, Asilsoy S, Uzuner N, et al. Is there a clinical significance of very low serum immunoglobulin E level? Journal of Clinical Immunology. 2021; 41(8): 1893–1901. doi: 10.1007/s10875-021-01127-y
198. Ünsal H, Ekinci A, Aliyeva G, et al. Characteristics of patients with low serum IgE levels and selective IgE deficiency: Data from an immunodeficiency referral center. Clinical Immunology. 2025; 270: 110403. doi: 10.1016/j.clim.2024.110403
199. Barton JC, Barton JC, Bertoli LF, et al. HLA-A and -B type and haplotype frequencies in IgG subclass deficiency subgroups. Archivum Immunologiae et Therapiae Experimentalis. 2020; 68(3): 14–21.
200. Dogru D, Dogru Y, Atschekzei F, et al. Reappraisal of IgG subclass deficiencies: A retrospective comparative cohort study. Frontiers in Immunology. 2025; 16: 1552513. doi: 10.3389/fimmu.2025.1552513
201. Ozkan H, Atlihan F, Genel F, et al. IgA and/or IgG subclass deficiency in children with recurrent respiratory infections and its relationship with chronic pulmonary damage. Journal of Investigational Allergology and Clinical Immunology. 2005; 15(1): 69–74.
202. Zhang Y, Clarke A, Regan KH, et al. Isolated IgG2 deficiency is an independent risk factor for exacerbations in bronchiectasis. QJM: An International Journal of Medicine. 2022; 115(5): 292–297. doi: 10.1093/qjmed/hcab129
203. Noori SA, Gungor S. Spinal epidural abscess associated with an epidural catheter in a woman with complex regional pain syndrome and selective IgG3 deficiency: A case report. Medicine. 2018; 97(50): e13272. doi: 10.1097/md.0000000000013272
204. Keyeux G, Lefranc MP, Chevailler A, et al. Molecular analysis of the IGHA and MHC class III region genes in one family with IgA and C4 deficiencies. Experimental and Clinical Immunogenetics. 1990; 7(3): 170–180.
205. Sugai S. Selective deficiency of IgA subclass. Ryoikibetsu Shokogun Shirizu. 2000; (32): 78–80.
206. Kaneko H, Suzuki H, Kondo N. IgA subclass and IgA deficiency. Nihon Rinsho Meneki Gakkai Kaishi. 2009; 32(3): 142–148. doi: 10.2177/jsci.32.142
207. Canales-Herrerias P, Garcia-Carmona Y, Shang J, et al. Selective IgA2 deficiency in a patient with small intestinal Crohn's disease. Journal of Clinical Investigation. 2023; 133(12): e167742. doi: 10.1172/jci167742
208. Chen R, Mu H, Chen X, et al. Qualitative immunoglobulin deficiency causes bacterial infections in patients with STAT1 gain-of-function mutations. Journal of Clinical Immunology. 2024; 44(5): 124. doi: 10.1007/s10875-024-01720-x
209. Castaño-Jaramillo LM, Munevar A, Marín AC, et al. Clinical and immunological features of specific antibody deficiency in a pediatric hospital in Colombia. Biomedica. 2024; 44(Sp. 2): 72–79. doi: 10.7705/biomedica.7562
210. Hatcher VR, Alix VC, Hellu TS, et al. Primary immunodeficiency: Specific antibody deficiency with normal IgG. Allergy and Asthma Proceedings. 2024; 45(5): 321–325. doi: 10.2500/aap.2024.45.240057
211. Perrard N, Stabler S, Sanges S, et al. Diagnosis, characteristics, and outcome of selective anti-polysaccharide antibody deficiencies in a retrospective cohort of 55 adult patients. Journal of Clinical Immunology. 2025; 45(1): 82. doi: 10.1007/s10875-025-01874-2
212. Misbah SA, Griffiths H, Mitchell T, et al. Antipolysaccharide antibodies in 450 children with otitis media. Clinical and Experimental Immunology. 1997; 109(1): 67–72. doi: 10.1046/j.1365-2249.1997.4291322.x
213. Vaz de Castro PAS, Amaral AA, Almeida MG, et al. Examining the association between serum galactose-deficient IgA1 and primary IgA nephropathy: A systematic review and meta-analysis. Journal of Nephrology. 2024; 37(8): 2099–2112. doi: 10.1007/s40620-023-01874-8
214. Vinci L, Strahm B, Speckmann C, et al. The different faces of GATA2 deficiency: Implications for therapy and surveillance. Frontiers in Oncology. 2024; 14: 1423856. doi: 10.3389/fonc.2024.1423856

215. Cagdas D, Halacli SO, Tan C, et al. Diversity in serine/threonine protein kinase-4 deficiency and review of the literature. Journal of Allergy and Clinical Immunology: In Practice. 2021; 9(10): 3752–3766.e4. doi: 10.1016/j.jaip.2021.05.032
216. Mella MA, Lavrinienko A, Akhi R, et al. Compensatory IgM to the rescue: Patients with selective IgA deficiency have increased natural IgM antibodies to MAA-LDL and no changes in oral microbiota. Immunohorizons. 2021; 5(4): 170–181. doi: 10.4049/immunohorizons.2100014
217. Eriksen C, Moll JM, Myers PN, et al. IgG and IgM cooperate in coating of intestinal bacteria in IgA deficiency. Nature Communications. 2023; 14(1): 8124. doi: 10.1038/s41467-023-44007-2
218. Sortino O, Dias J, Anderson M, et al. Preserved mucosal-associated invariant T-cell numbers and function in idiopathic CD4 lymphocytopenia. Journal of Infectious Diseases. 2021; 224(4): 715–725. doi: 10.1093/infdis/jiaa782
219. Seto N, Suzuki T, Fukuchi T, et al. Disseminated nocardiosis in idiopathic CD4 lymphocytopenia: A rare case and literature review. Internal Medicine. 2025; 64(18): 2797–2803. doi: 10.2169/internalmedicine.4984-24
220. Varmpompiti K, Westwood AJ, Ben-Joseph A, et al. Progressive multifocal leukoencephalopathy secondary to idiopathic CD4 lymphocytopenia treated with pembrolizumab. Journal of Neuroimmunology. 2023; 385: 578248. doi: 10.1016/j.jneuroim.2023.578248
221. Yadav P, Kumar D, Bohra GK, et al. Progressive disseminated histoplasmosis in idiopathic CD4 lymphocytopenia an underdiagnosed combination - A case report. Medicine and Pharmacy Reports. 2022; 95(2): 209–213. doi: 10.15386/mpr-1908
222. Sener S, Basaran O, Batu ED, et al. Childhood-onset Takayasu arteritis and immunodeficiency: Case-based review. Clinical Rheumatology. 2022; 41(9): 2883–2892. doi: 10.1007/s10067-022-06295-9
223. Sharma S, Nadig PL, Pilania RK, et al. Kawasaki disease and inborn errors of immunity: Exploring the link and implications. Diagnostics (Basel). 2023; 13(13): 2151. doi: 10.3390/diagnostics13132151
224. Zhang D, Su G, Hao S, et al. Paediatric autoimmune diseases with ELANE mutations associated with neutropenia. Pediatric Rheumatology Online Journal. 2023; 21(1): 41. doi: 10.1186/s12969-023-00824-9
225. Belfrage E, Jinnestål CL, Jönsen A, et al. Role of Mannose-binding lectin and association with microbial sensitization in a cohort of patients with atopic dermatitis. Acta Dermato-Venereologica. 2023; 103: adv2405. doi: 10.2340/actadv.v103.2405
226. Yan C, Qiu J, Pan X, et al. Mixed pulmonary infection, asthma, and nephrotic syndrome in a patient diagnosed with selective IgA deficiency: A case report. Journal of Inflammation Research. 2025; 18: 127–132. doi: 10.2147/jir.s492482
227. Shavit R, Maoz-Segal R, Frizinsky S, et al. Combined immunodeficiency (CVID and CD4 lymphopenia) is associated with a high risk of malignancy among adults with primary immune deficiency. Clinical and Experimental Immunology. 2021; 204(2): 251–257. doi: 10.1111/cei.13579
228. Yu L, Li Y, Li W, et al. Case report: A cyclic neutropenia patient with ELANE mutation accompanied by hemophagocytic lymphohistiocytosis. Frontiers in Immunology. 2024; 15: 1474429. doi: 10.3389/fimmu.2024.1474429
229. Rutkowska-Zapała M, Grabowska A, Lenart M, et al. Transcriptome profiling of regulatory T cells from children with transient hypogammaglobulinemia of infancy. Clinical and Experimental Immunology. 2023; 214(3): 275–288. doi: 10.1093/cei/uxad116
230. Maltsev D. Clinic-radiological classification of herpesviral encephalitis in humans (systematic review). Journal of NeuroVirology. 2025; 31(3): 219–241. doi: 10.1007/s13365-025-01250-1
231. Otaki Y, Ogawa E, Higuchi T, et al. Invasive haemophilus influenzae type b infection in a patient with transient hypogammaglobulinemia of infancy. Journal of Infection and Chemotherapy. 2021; 27(12): 1756–1759. doi: 10.1016/j.jiac.2021.07.023
232. Pienthong T, Apisarnthanarak A, Khawcharoenporn T, et al. Intestinal basidiobolomycosis in a patient with idiopathic CD4 lymphocytopenia. Journal de Mycologie Médicale (Journal of Medical Mycology). 2022; 32(3): 101260. doi: 10.1016/j.mycmed.2022.101260
233. Samji NS, Verma R, Mohammed SY, et al. Disseminated histoplasmosis involving soft palate, duodenum, sigmoid colon and bone marrow in a patient with isolated CD4+ T-lymphocytopenia. Cureus. 2021; 13(11): e19748. doi: 10.7759/cureus.19748
234. Shah PM, Hingolikar AP, Tandan S, et al. Idiopathic CD4 lymphocytopenia presenting as cryptococcal meningitis. Journal of Global Infectious Diseases. 2021; 13(1): 56–58. doi: 10.4103/jgid.jgid_182_20
235. Somboonviboon D, Thongtaeparak W, Suntavaruk P, et al. Disseminated coinfection with mycobacterium avium complex and mycobacterium kansasii in a patient with idiopathic CD4+ lymphocytopenia: A case report. Journal of Infection and Chemotherapy. 2023; 29(12): 1167–1171. doi: 10.1016/j.jiac.2023.08.006

236. Wu X, Zhai M, Xu A, et al. Disseminated Mycobacterium abscessus infection with idiopathic CD4+ T-lymphocytopenia: A case report and review of the literature. Journal of Medical Case Reports. 2024; 18(1): 645. doi: 10.1186/s13256-024-05009-w
237. Chen N, Zhang X, Zheng K, et al. Increased risk of group B streptococcus causing meningitis in infants with mannose-binding lectin deficiency. Clinical Microbiology and Infection. 2019; 25(3): 384.e1–384.e3.
238. Manuel O, Pascual M, Trendelenburg M, et al. Association between mannose-binding lectin deficiency and cytomegalovirus infection after renal transplantation. Transplantation. 2007; 83(3): 359–362.
239. Damiens S, Poissy J, François N, et al. Mannose-binding lectin levels and variation during invasive candidiasis. Journal of Clinical Immunology. 2012; 32(6): 1317–1323. doi: 10.1007/s10875-012-9748-2
240. Carmolli M, Duggal P, Haque R, et al. Deficient serum mannose-binding lectin levels and MBL2 polymorphisms increase the risk of single and recurrent cryptosporidium infections in young children. Journal of Infectious Diseases. 2009; 200(10): 1540–1547. doi: 10.1086/606013
241. DeRenzi A, Penico J. Lymphoproliferative disease in a non-transplant patient and spironolactone's activity against epstein barr virus. HCA Healthcare Journal of Medicine. 2021; 2(4): 263–266. doi: 10.36518/2689-0216.1241
242. Dewangan A, Singh J, Kumar D, et al. Disseminated cryptococcosis in idiopathic CD4+ lymphocytopenia. Infectious Disorders – Drug Targets. 2023; 23(1): e210622206242. doi: 10.2174/1871526522666220621110723
243. Fang L, Zhang J, Lv F. Disseminated cryptococcosis with varicella-zoster virus coinfection of idiopathic CD4+T lymphocytopenia: A case report and literature review. Virology Journal. 2022; 19(1): 38. doi: 10.1186/s12985-022-01765-7
244. Fukumoto T, Sakashita Y, Katada F, et al. "Burnt-out" progressive multifocal leukoencephalopathy in idiopathic CD4+ lymphocytopenia. Neuropathology. 2021; 41(6): 484–488. doi: 10.1111/neup.12773
245. Goto R, Shiota S, Kaimori R, et al. Disseminated nontuberculous mycobacterial infection in a patient with idiopathic CD4 lymphocytopenia and IFN-γ neutralizing antibodies: A case report. BMC Infectious Disease. 2023; 23(1): 58. doi: 10.1186/s12879-023-08020-6.
246. Kanagiri T, Meena DS, Kumar D, et al. Recurrent pulmonary nocardiosis due to nocardia otitidiscaviarum in a patient with isolated CD4 lymphocytopenia: A case report. BMC Infectious Diseases. 2024; 24(1): 1033. doi: 10.1186/s12879-024-09981-y
247. Xu J, Chen G, Yan Z, et al. Effect of mannose-binding lectin gene polymorphisms on the risk of rheumatoid arthritis: Evidence from a meta-analysis. International Journal of Rheumatic Diseases. 2021; 24(3): 300–313. doi: 10.1111/1756-185X.14060
248. Gao DN, Zhang Y, Ren YB, et al. Relationship of serum mannose-binding lectin levels with the development of sepsis: A meta-analysis. Inflammation. 2015; 38(1): 338–347. doi: 10.1007/s10753-014-0037-5
249. Borta S, Popetiu R, Donath-Miklos I, et al. Genetic polymorphism of MBL 2 in patients with allergic bronchial asthma. Maedica. 2019; 14(3): 208–212. doi: 10.26574/maedica.2019.14.3.208
250. Ludvigsson JF, Neovius M, Ye W, et al. IgA deficiency and risk of cancer: A population-based matched cohort study. Journal of Clinical Immunology. 2015; 35(2): 182–188. doi: 10.1007/s10875-014-0124-2
251. Heathfield LJ, Martin LJ, van der Heyde Y, et al. Clinical exome sequencing elucidates underlying cause of death in sudden unexpected death of infants: Two case reports. International Journal of Legal Medicine. 2024; 138(2): 693–700. doi: 10.1007/s00414-023-03065-3
252. Castaño-Jaramillo LM, Rodríguez O, Vélez-Tirado N. Nutritional status in pediatric patients with predominant antibody deficiency. Biomedica. 2024; 44(Sp. 2): 51–62. doi: 10.7705/biomedica.7398
253. Jörgensen GH, Gardulf A, Sigurdsson MI, et al. Health-related quality of life (HRQL) in immunodeficient adults with selective IgA deficiency compared with age- and gender-matched controls and identification of risk factors for poor HRQL. Quality of Life Research. 2014; 23(2): 645–658. doi: 10.1007/s11136-013-0491-9
254. Ludvigsson JF, Neovius M, Stephansson O, et al. IgA deficiency, autoimmunity & pregnancy: A population-based matched cohort study. Journal of Clinical Immunology. 2014; 34(7): 853–863. doi: 10.1007/s10875-014-0069-5
255. Vengen IT, Madsen HO, Garred P, et al. Mannose-binding lectin deficiency is associated with myocardial infarction: The HUNT2 study in Norway. PLoS One. 2012; 7(7): e42113. doi: 10.1371/journal.pone.0042113
256. Sharma M, Dhaliwal M, Tyagi R, et al. Microbiome and its dysbiosis in inborn errors of immunity. Pathogens. 2023; 12(4): 518. doi: 10.3390/pathogens12040518

257. Magen E, Mishal J, Vardy D. Selective IgE deficiency and cardiovascular disease. Allergy and Asthma Proceedings. 2015; 36(3): 225–229. doi: 10.2500/aap.2015.36.3825
258. Ludvigsson JF, Neovius M, Hammarström L. IgA deficiency and mortality: A population-based cohort study. Journal of Clinical Immunology. 2013; 33(8): 1317–1324. doi: 10.1007/s10875-013-9948-4
259. Merzon E, Farag R, Ashkenazi S, et al. Increased prevalence of attention deficit hyperactivity disorder in individuals with selective immunoglobulin A deficiency: A nationwide case-control study. Journal of Clinical Medicine. 2024; 13(20): 6075. doi: 10.3390/jcm13206075
260. Williams K, Shorser-Gentile L, Sarvode Mothi S, et al. Immunoglobulin A dysgammaglobulinemia is associated with pediatric-onset obsessive-compulsive disorder. Journal of Child and Adolescent Psychopharmacology. 2019; 29(4): 268–275. doi: 10.1089/cap.2018.0043
261. Coopmans EC, Chunharojrith P, Neggers SJCMM, et al. Endocrine disorders are prominent clinical features in patients with primary antibody deficiencies. Frontiers in Immunology. 2019; 10: 2079. doi: 10.3389/fimmu.2019.02079
262. Pignata C, Budillon G, Monaco G, et al. Jejunal bacterial overgrowth and intestinal permeability in children with immunodeficiency syndromes. Gut. 1990; 31(8): 879–882. doi: 10.1136/gut.31.8.879
263. Ida H, Maruyama D, Maeshima AM, et al. Duodenal nodular lymphoid hyperplasia in a patient with IgA deficiency. Clinical Case Reports. 2020; 8(12): 3594–3595. doi: 10.1002/ccr3.3298
264. Agarwal S, Mayer L. Diagnosis and treatment of gastrointestinal disorders in patients with primary immunodeficiency. Clinical Gastroenterology and Hepatology. 2013; 11(9): 1050–1063. doi: 10.1016/j.cgh.2013.02.024
265. Demirtaş Güner D, Baskın K. Allergic and immunologic evaluation of children with celiac disease. Frontiers in Pediatrics. 2025; 13: 1568174. doi: 10.3389/fped.2025.1568174
266. Kato M, Kudo Y, Hatase M, et al. Moyamoya disease associated with a deficiency of complement component 6. Journal of Stroke and Cerebrovascular Diseases. 2022; 31(8): 106601. doi: 10.1016/j.jstrokecerebrovasdis.2022.106601
267. Rudolph TK, Wipper S, Reiter B, et al. Myeloperoxidase deficiency preserves vasomotor function in humans. European Heart Journal. 2012; 33(13): 1625–1634. doi: 10.1093/eurheartj/ehr193
268. Magen E, Geishin A, Merzon E, et al. Prevalence of neurological diseases among patients with selective IgA deficiency. Allergy and Asthma Proceedings. 2023; 44(5): e17–e21. doi: 10.2500/aap.2023.44.230036
269. Foldager L, Köhler O, Steffensen R, et al. Bipolar and panic disorders may be associated with hereditary defects in the innate immune system. Journal of Affective Disorders. 2014; 164: 148–154. doi: 10.1016/j.jad.2014.04.017
270. Isung J, Williams K, Isomura K, et al. Association of primary humoral immunodeficiencies with psychiatric disorders and suicidal behaviour and the role of autoimmune diseases. JAMA Psychiatry. 2020; 77(11): 1147–1154. doi: 10.1001/jamapsychiatry.2020.1260
271. Isung J, Isomura K, Williams K, et al. Association of primary immunodeficiencies in parents with psychiatric disorders and suicidal behaviour in their offspring. JAMA Psychiatry. 2023; 80(4): 323–330. 10.1001/jamapsychiatry.2022.4786
272. Carlsson M, Sjöholm AG, Eriksson L, et al. Deficiency of the mannan-binding lectin pathway of complement and poor outcome in cystic fibrosis: Bacterial colonisation may be decisive for a relationship. Clinical and Experimental Immunology. 2005; 139(2): 306–313. doi: 10.1111/j.1365-2249.2004.02690.x
273. Ji X,Gewurz H, Spear GT. Mannose binding lectin (MBL) and HIV. Molecular Immunology. 2005; 42(2): 145–152. doi: 10.1016/j.molimm.2004.06.015
274. van Leeuwen LPM, Van Coillie S, Prévot J, et al. Long term effects of COVID-19 in primary immunodeficiency patients: An IPOPI worldwide survey. Journal of Allergy and Clinical Immunology. 2025: S0091-6749(25)00497-X.
275. Ameratunga R, Leung E, Woon ST, et al. Selective IgA deficiency may be an underrecognized risk factor for severe COVID-19. Journal of Allergy and Clinical Immunology: In Practice. 2023; 11(1): 181–186. doi: 10.1016/j.jaip.2022.10.002 Tokutake H, Chiba S. A case report of respiratory syncytial virus-infected 8p inverted duplication deletion syndrome with low natural killer cell activity. Tohoku Journal of Experimental Medicine. 2022; 257(4): 347–352. doi: 10.1620/tjem.2022.j052
276. Bayram N, Ozkinay F, Onay H, et al Mannose-binding lectin gene codon 54 polymorphism susceptible to brucellosis in Turkish children. Turkish Journal of Pediatrics. 2012; 54(3): 234–238.
277. Thizy G, Caumes E, Molher J, et al. Disseminated mucocutaneous leishmaniasis in a traveller with idiopathic CD4 lymphocytopenia. Journal of Travel Medicine. 2023; 30(8): taad063. doi: 10.1093/jtm/taad063

278. Leister J, McCarthy L. Pediatric coronavirus (COVID-19) death in a child with cyclic neutropenia. Pediatric Blood & Cancer. 2021; 68(10): e29171. doi: 10.1002/pbc.29171
279. Schearer J, Merrick C. Idiopathic CD4 lymphocytopenia: An uncommon but fatal cause of pneumocystis pneumonia. Respiratory Medicine Case Reports. 2025; 54: 102177. doi: 10.1016/j.rmcr.2025.102177
280. Altorjay I, Vitalis Z, Tornai I, et al. Mannose-binding lectin deficiency confers risk for bacterial infections in a large Hungarian cohort of patients with liver cirrhosis. Journal of Hepatology. 2010; 53(3): 484–491. doi: 10.1016/j.jhep.2010.03.028
281. Núnez-Núñez ME, Monraz-Monteón D, Lona-Reyes JC, et al. Neumonía necrosante en un paciente con deficiencia selectiva de IgA Necrotizing pneumonia in a patient with selective IgA deficiency. Revista Alergia México. 2024; 71(3): 205–211. doi: 10.29262/ram.v71i3.1344
282. Sarma A. Idiopathic CD4 lymphocytopenia manifesting as chronic non-resolving pneumonia. Lung India. 2023; 40(6): 557–559. doi: 10.4103/lungindia.lungindia_256_23
283. Garcia-Laorden MI, Sole-Violan J, Rodriguez de Castro F, et al. Mannose-binding lectin and mannose-binding lectin-associated serine protease 2 in susceptibility, severity, and outcome of pneumonia in adults. Journal of Allergy and Clinical Immunology. 2008; 122(2): 368–374. doi: 10.1016/j.jaci.2008.05.037
284. AlShanableh Z, Haidous M, Wong KM, et al. Immunodeficiency: A protective factor for COVID-19? Cureus. 2022; 14(3): e23094. doi: 10.7759/cureus.23094
285. Roh S, Ham JY, Song KE, et al. Myeloperoxidase deficiency manifesting as pseudoneutropenia with low mean peroxidase index and high monocyte count in 4 adult patients. Laboratory Medicine. 2020; 51(2): e16–e19. doi: 10.1093/labmed/lmz060
286. Osthoff M, Trendelenburg M. Impact of mannose-binding lectin deficiency on radiocontrast-induced renal dysfunction. BioMed Research International. 2013; 2013: 962695. doi: 10.1155/2013/962695
287. Koturoglu G, Onay H, Midilli R, et al. Evidence of an association between mannose binding lectin codon 54 polymorphism and adenoidectomy and/or tonsillectomy in children. International Journal of Pediatric Otorhinolaryngology. 2007; 71(8): 1157–1161. doi: 10.1016/j.ijporl.2007.05.004
288. Picado C, Mascaró JJ, Vlagea A, et al. Selective IgE deficiency predicts poor or no response of chronic spontaneous urticaria to omalizumab. Journal of Investigational Allergology and Clinical Immunology. 2022; 32(6): 504–506. 10.18176/jiaci.0796
289. Noonan E, Straesser MD, Makin T, et al. Impaired response to polysaccharide vaccine in selective IgE deficiency. Journal of Clinical Immunology. 2023; 43(6): 1448–1454. doi: 10.1007/s10875-023-01501-y
290. Osthoff M, Rovó A, Stern M, et al. Mannose-binding lectin levels and major infections in a cohort of very long-term survivors after allogeneic stem cell transplantation. Haematologica. 2010; 95(8): 1389–1396. doi: 10.3324/haematol.2009.017863
291. Cuesta Andres M, Hidalgo C, et al. Eosinophilia in rheumatoid arthritis masked by eosinophil peroxidase deficiency. Clinical and Laboratory Haematology. 1993; 15(1): 67. doi: 10.1111/j.1365-2257.1993.tb00124.x
292. Cohen B, Oprea Y, Rosenstreich D, et al. Skin testing is useful in assessing aeroallergen sensitisation in IgE deficient patients with environmental allergy-like symptoms. American Journal of Rhinology & Allergy. 2022; 36(4): 451–458. doi: 10.1177/19458924211073850
293. Lock RJ, Unsworth DJ. Identifying immunoglobulin-A-deficient children and adults does not necessarily help the serological diagnosis of coeliac disease. Journal of Pediatric Gastroenterology and Nutrition. 1999; 28(1): 81–83. doi: 10.1097/00005176-199901000-00018
294. Jung CL, Cha MK, Jun BH, et al. A case of IgM deficiency with B cell deficiency detected by ABO discrepancy in a patient with acute osteomyelitis. Annals of Laboratory Medicine. 2013; 33(3): 208–211. doi: 10.3343/alm.2013.33.3.208
295. Mohamed H, Hedriana HD, Holbrook EA, et al. HIV false-positive test in the setting of CD4 lymphocytopenia. Cureus. 2024; 16(1): e51515. doi: 10.7759/cureus.51515
296. Dournes G, Bégueret H, Demant X, et al. CT features of genetic mutation-related pulmonary alveolar proteinosis (CCR2 and GATA2 deficiency. Diagnostic and Interventional Imaging. 2025: 106(9):327–329. doi: 10.1016/j.diii.2025.04.007
297. Anani W, Triulzi D, Yazer MH, et al. Relative IgA-deficient recipients have an increased risk of severe allergic transfusion reactions. Vox Sanguinis. 2014; 107(4): 389–392. doi: 10.1111/vox.12192
298. Aziri H, Vallianatou K, Balgobin B, et al. Genetic identification of undiagnosed benign ethnic neutropenia in patients receiving clozapine treatment. British Journal of Psychiatry. 2024: 1–5. doi: 10.1192/bjp.2024.236
299. Mimura K, Shimomura A, Watanabe K, et al. Severe cytopenia during adjuvant chemotherapy for early breast cancer in a patient with idiopathic CD4+ lymphocytopenia. Oncology Letters. 2023; 26(2): 357. doi: 10.3892/ol.2023.13943

300. Schreier A, Munoz-Arcos L, Alvarez A, et al. Racial disparities in neutrophil counts among patients with metastatic breast cancer during treatment with CDK4/6 inhibitors. Breast Cancer Research and Treatment. 2022; 194(2): 337–351. doi: 10.1007/s10549-022-06574-8
301. Taylor D, Vallianatou K, Gandhi S, et al. Severe neutropenia unrelated to clozapine in patients receiving clozapine. Journal of Psychopharmacology. 2024; 38(7): 624–635. doi: 10.1177/02698811241262767
302. Youniss L, Thomas M, Davis EAK. Probable haloperidol decanoate-induced fever in an African American with benign ethnic neutropenia: A case report. Mental Health Clinician. 2021; 11(5): 301–304. doi: 10.9740/mhc.2021.09.301
303. Rocco JM, Boswell KL, Laidlaw E, et al. Immune responses to SARS-CoV-2 mRNA vaccination in people with idiopathic CD4 lymphopenia. Journal of Allergy and Clinical Immunology. 2024; 153(2): 503–512.
304. Vossen MG, Kartnig F, Mrak D, et al. Humoral and cellular response to the third COVID-19 vaccination in patients with inborn errors of immunity or mannose-binding lectin deficiency: A prospective controlled open-label trial. Wiener klinische Wochenschrift. 2024; 136(21–22): 598–607. doi: 10.1007/s00508-024-02459-6
305. Mpofu R, Otwombe K, Mlisana K, et al. Benign ethnic neutropenia in a South African population, and its association with HIV acquisition and adverse event reporting in an HIV vaccine clinical trial. PLoS One. 2021; 16(1): e0241708. doi: 10.1371/journal.pone.0241708
306. Samileh N, Ahmad S, Farzaneh A, et al. Immunity status in children with bacille Calmette-Guerin adenitis. A prospective study in Tehran, Iran. Saudi Medical Journal. 2006; 27(11): 1719–1724.
307. Chan K, Loh CYY. Early postoperative infection in patient with IgM deficiency. International Wound Journal. 2024; 21(7): e70003. doi: 10.1111/iwj.70003
308. Nishikawa S, Hamaoka M, Nakahara H, et al. Management of acute cholecystitis in patient with cyclic neutropenia: A case report. Surgical Case Reports. 2021; 7(1): 29. doi: 10.1186/s40792-021-01117-7
309. Cahuana-Bartra P, Brunet-Llobet L, Rabassa-Blanco J, et al. Spontaneous osteonecrosis of the jaw in the presence of periodontal disease in an adolescent with cyclic neutropenia. Journal of Dentistry for Children (Chicago). 2025; 92(1): 44–47.
310. Sakuma Y, Ogawa M, Nakagawa C, et al. Dental treatment under general anesthesia with nasal intubation in a patient with selective immunoglobulin A deficiency. Anesthesia Progress. 2023; 70(3): 140–141. doi: 10.2344/anpr-70-02-13
311. Parta M, Shah NN, Baird K, et al. Allogeneic hematopoietic stem cell transplantation for GATA2 deficiency using a busulfan-based regimen. Biology of Blood and Marrow Transplantation. 2018; 24(6): 1250–1259. doi: 10.1016/j.bbmt.2018.01.030
312. Worthley DL, Johnson DF, Eisen DP, et al. Donor mannose-binding lectin deficiency increases the likelihood of clinically significant infection after liver transplantation. Clinical Infectious Diseases. 2009; 48(4): 410–417. doi: 10.1086/596313
313. Shete M, Thompson JW, Naidu SI, et al. Olaryngological manifestations in children with chronic neutropenia. International Journal of Pediatric Otorhinolaryngology. 2012; 76(3): 392–395. doi: 10.1016/j.ijporl.2011.12.018
314. Sumida H, Sato S. Refractory and recurrent skin manifestations in an adult with selective immunoglobulin M deficiency. Cureus. 2024; 16(4): e59015. doi: 10.7759/cureus.59015
315. Tadjali A, Pan S, Perli E, et al. Clinical presentation of idiopathic CD4 lymphocytopenia. BMJ Case Reports. 2023; 16(7): e254746. doi: 10.1136/bcr-2023-254746
316. Frias Sartorelli de Toledo Piza C, Aranda CS, Solé D, et al. Calculated globulin can be used as a screening test for antibody deficiency in children and adolescents. Frontiers in Immunology. 2024; 15: 1495564. doi: 10.3389/fimmu.2024.1495564
317. Nepesov S, Yaman Y, Elli M, et al. Chronic neutropenia in childhood: Laboratory and clinical features. Indian Journal of Pediatrics. 2022; 89(9): 894–898. doi: 10.1007/s12098-022-04104-4
318. Oloyede E, Dzahini O, Barnes N, et al. Benign ethnic neutropenia: An analysis of prevalence, timing and identification accuracy in two large inner-city NHS hospitals. BMC Psychiatry. 2021; 21(1): 502. doi: 10.1186/s12888-021-03514-6
319. Oz-Alcalay L, Steinberg-Shemer O, Elron E, et al. Clinical and laboratory characteristics of pediatric patients with ACKR1/DARC-associated neutropenia. Pediatric Blood & Cancer. 2025; 72(1): e3143. doi: 10.1002/pbc.31430
320. Tsaknakis G, Gallì A, Papadakis S, et al. Incidence and prognosis of clonal hematopoiesis in patients with chronic idiopathic neutropenia. Blood. 2021; 138(14): 1249–1257. doi: 10.1182/blood.2021010815
321. Wågström P, Hjorth M, Appelgren D, et al. Immunological characterization of IgG subclass deficiency reveals decreased tregs and increased circulating costimulatory and regulatory immune checkpoints. Frontiers in Immunology. 2024; 15: 1442749. doi: 10.3389/fimmu.2024.1442749

322. Wang B, Singh H, Ellis M, et al. Hidden in the absence: Clinicopathologic insights on kidney diseases associated with selective IgA deficiency. Laboratory Investigation. 2025; 105(7): 104163. doi: 10.1016/j.labinv.2025.104163
323. Murdaca G, Paladin F, Gangemi S. Potential genetic approach to specific primary immunodeficiencies: Which perspectives? Frontiers in Bioscience (Landmark Edition). 2025; 30(3): 36795. doi: 10.31083/fbl36795
324. Soomann M, Bily V, Elgizouli M, et al. Variants in IGLL1 cause a broad phenotype from agammaglobulinemia to transient hypogammaglobulinemia. Journal of Allergy and Clinical Immunology. 2024; 154(5): 1313–1324.e7. doi: 10.1016/j.jaci.2024.08.002
325. Sgrulletti M, Baselli LA, Castagnoli R, et al. IPINeT Ped-unPAD study: Goals, design, and preliminary results. Journal of Clinical Medicine. 2024; 13(15): 4321. doi: 10.3390/jcm13154321
326. Schoettler JJ, Schleissner LA, Heiner DC. Familial IgE deficiency associated with sinopulmonary disease. Chest. 1989; 96(3): 516–21. doi: 10.1378/chest.96.3.516
327. Park JK, Kim D, Lee JM, et al. Clinical utility of personalised serum IgG subclass ratios for the differentiation of IgG4-related sclerosing cholangitis (IgG4-SC) from primary sclerosing cholangitis (PSC) and cholangiocarcinoma (CCA). Journal of Personalized Medicine. 2022; 12(6): 855.
328. Steffen U, Koeleman CA, Sokolova MV, et al. IgA subclasses have different effector functions associated with distinct glycosylation profiles. Nature Communications. 2020; 11(1): 120. doi: 10.1038/s41467-019-13992-8
329. Chawda JG, Chaduvula N, Patel HR, et al. Salivary SIgA and dental caries activity. Indian Pediatrics. 2011; 48(9): 719–21. doi: 10.1007/s13312-011-0113-y
330. Parker AR, Allen S, Harding S. Concentration of anti-pneumococcal capsular polysaccharide IgM, IgG and IgA specific antibodies in adult blood donors. Practical Laboratory Medicine. 2016; 5: 1–5. doi: 10.1016/j.plabm.2016.02.004
331. Janssen WJ, Bloem AC, Vellekoop P, et al. Measurement of pneumococcal polysaccharide vaccine responses for immunodeficiency diagnostics: Combined IgG responses compared to serotype-specific IgG responses. Journal of Clinical Immunology. 2014; 34(1): 3–6. doi: 10.1007/s10875-013-9925-y
332. Barroso S, Sánchez B, Alvarez AJ, et al. Complement component C7 deficiency in two Spanish families. Immunology. 2004; 113(4): 518–523. doi: 10.1111/j.1365-2567.2004.01997.x
333. Ammann RA, Bodmer N, Simon A, et al. Serum concentrations of Mannan-binding lectin (MBL) and MBL-associated serine protease-2 and the risk of adverse events in pediatric patients with cancer and fever in neutropenia. Journal of the Pediatric Infectious Diseases Society. 2013; 2(2): 155–161. doi: 10.1093/jpids/pit005
334. Fidler KJ, Wilson P, Davies JC, et al. Increased incidence and severity of the systemic inflammatory response syndrome in patients deficient in mannose-binding lectin. Intensive Care Medicine. 2004; 30(7): 1438–1445. http://dx.doi.org/10.1007/s00134-004-2302-9
335. Møller-Kristensen M, Jensenius JC, Jensen L, et al. Levels of mannan-binding lectin-associated serine protease-2 in healthy individuals. Journal of Immunological Methods. 2003; 282: 159–167. doi: 10.1016/j.jim.2003.08.012
336. Maltsev DV. Effectimness of long-term continuous immunomodulatory therapy with gamma-recombinant interferon in patients with clinically manifest forms of neutrophil myeloperoxidase deficiency. Archivos Venezolanos de Farmacología y Terapéutica. 2020; 39(5): 672–679. doi: 10.5281/zenodo.4256793
337. Ochkur SI, Kim JD, Protheroe CA, et al. A sensitive high throughput ELISA for human eosinophil peroxidase: A specific assay to quantify eosinophil degranulation from patient-derived sources. Journal of Immunological Methods. 2012; 384(1–2): 10–20. doi: 10.1016/j.jim.2012.06.011
338. Genel F, Kutukculer N. Prospective, randomised comparison of OM-85 BV and a prophylactic antibiotic in children with recurrent infections and immunoglobulin A and/or G subclass deficiency. Current Therapeutic Research, Clinical and Experimental. 2003; 64(8): 600–615. doi: 10.1016/j.curtheres.2003.09.008
339. Mousallem T, Hall G, Pan A, et al. Updates in the understanding of immunoglobulin replacement therapy in primary immune deficiency disorders: Function, composition, and role in reconstitution and immunomodulation. Immunology and Allergy Clinics of North America. 2025; 45(2): 251–265. doi: 10.1016/j.iac.2025.01.007
340. Melo KM, Alves LM, Valente CFC, et al. One-year intravenous immunoglobulin replacement therapy: Efficacy in reducing hospital admissions in pediatric patients with inborn errors of immunity . Journal of Pediatrics (Rio de Janeiro). 2022; 98(2): 190–195. doi: 10.1016/j.jped.2021.05.011

341. Szaflarska A, Lenart M, Rutkowska-Zapała M, et al. Clinical and experimental treatment of primary humoral immunodeficiencies. Clinical and Experimental Immunology. 2024; 216(2): 120–131. doi: 10.1093/cei/uxae008
342. Özer M, Tekeli S, Doğan S, et al. Adverse events associated with intravenous immunoglobulin infusions in pediatric patients with primary immunodeficiency: A 10-year single-center study. Archives of Pediatrics. 2025; 32(4): 231–237. doi: 10.1016/j.arcped.2025.01.008
343. Mokhtari S, Asquith JM, Kareem SS, et al. Intravenous immunoglobulin (IVIG) for patients with severe neurotoxicity associated with chimeric antigen receptor T-cell (CAR-T) therapy. International Journal of Molecular Sciences. 2025; 26(8): 3904. doi: 10.3390/ijms26083904
344. Olinder-Nielsen AM, Granert C, Forsberg P, et al. Immunoglobulin prophylaxis in 350 adults with IgG subclass deficiency and recurrent respiratory tract infections: A long-term follow-up. Scandinavian Journal of Infectious Diseases. 2007; 39(1): 44–50. doi: 10.1080/00365540600951192
345. Vivarelli E, Matucci A, Bormioli S, et al. Effectiveness of low-dose intravenous immunoglobulin therapy in minor primary antibody deficiencies: A 2-year real-life experience. Clinical and Experimental Immunology. 2021; 205(3): 346–353. doi: 10.1080/00365540600951192
346. Lieberman P, Berger M. Intramuscular versus intravenous immunoglobulin replacement therapy and measurement of immunoglobulin levels during immunoglobulin replacement therapy. Journal of Allergy and Clinical Immunology: In Practice. 2013; 1(6): 705–706. doi: 10.1016/j.jaip.2013.08.007
347. Dinleyici EC, Frey G, Kola E, et al. Clinical efficacy of IgM-enriched immunoglobulin as adjunctive therapy in neonatal and paediatric sepsis: A systematic review and meta-analysis. Frontiers in Pediatrics. 2023; 11: 1239014. doi: 10.3389/fped.2023.1239014
348. Burnim M, Putcha N, LaFon D, et al. Serum immunoglobulin G levels are associated with risk for exacerbations: An analysis of SPIROMICS. American Journal of Respiratory and Critical Care Medicine. 2025; 211(2): 215–221. 10.1164/rccm.202311-2184OC
349. Page R, Friday G, Stillwagon P, et al. Asthma and selective immunoglobulin subclass deficiency: Improvement of asthma after immunoglobulin replacement therapy. Journal of Pediatrics. 1988; 112(1): 127–131. doi: 10.1016/S0022-3476(88)80137-9
350. Vivarelli E, Matucci A, Parronchi P, et al. Primary antibody deficiencies represent an underestimated comorbidity in asthma patients: Efficacy of immunoglobulin replacement therapy in asthma control. Journal of Asthma. 2023; 60(6): 1227–1236. doi: 10.1080/02770903.2022.2140435
351. Vivarelli E, Perlato M, Accinno M, et al. Asthma phenotype can be influenced by recurrent respiratory infections in patients with primary antibody deficiency: The impact of Ig therapy. Respiration. 2025; 104(7): 1–9. doi: 10.1159/000543792
352. Fishman P, Bar-Yehuda S, Shoenfeld Y. IVIg to prevent tumour metastases. International Journal of Oncology. 2002; 21(4): 875–880.
353. Natrus LV, Maltsev DV, Klys YG, et al. The effectiveness of therapy w cryopreserved human plasma in patients with deficiency of mannose binding lectin suffering from herpes virus infection. Wiadomości Lekarskie. 2021; 74(8): 1824–1828.
354. Frakking FN, Brouwer N, van de Wetering MD, et al. Safety and pharmacokinetics of plasma-derived mannose-binding lectin (MBL) substitution in children with chemotherapy-induced neutropenia. European Journal of Cancer. 2009; 45(4): 505–5012. doi: 10.1016/j.ejca.2008.11.036
355. Petersen KA, Matthiesen F, Agger T, et al. Phase I safety, tolerability, and pharmacokinetic study of recombinant human mannan-binding lectin. Journal of Clinical Immunology. 2006; 26(5): 465–475. doi: 10.1007/s10875-006-9037-z
356. Alstadhaug KB, Croughs T, Henriksen S, et al. Treatment of progressive multifocal leukoencephalopathy with interleukin 7. Journal of the American Medical Association Neurology. 2014; 71(8): 1030–1035. doi: 10.1001/jamaneurol.2014.825
357. Baume DM, Robertson MJ, Levine H, et al. Differential responses to interleukin 2 define functionally distinct subsets of human natural killer cells. European Journal of Immunology. 1992; 22(1): 1–6. doi: 10.1002/eji.1830220102
358. See DM, Tilles JG. alpha-Interferon treatment of patients with chronic fatigue syndrome. Immunological Investigations. 1996; 25(1–2): 153–164. doi: 10.3109/08820139609059298
359. King R, Tuthill C. Immune modulation with thymosin alpha 1 treatment. Vitamins and Hormones. 2016; 102: 151–178. doi: 10.1016/bs.vh.2016.04.003
360. Sugahara S, Ichida T, Yamagiwa S, et al. Thymosin-alpha1 increases intrahepatic NKT cells and CTLs in patients with chronic hepatitis B. Hepatology Research. 2002; 24(4): 346–354. doi: 10.1016/s1386-6346(02)00145-6

361. Chen TK, Batra JS, Michalik DE, et al. Recombinant human granulocyte-macrophage colony-stimulating factor (rhu GM-CSF) as adjuvant therapy for invasive fungal diseases. Open Forum Infectious Diseases. 2022; 9(11): ofac535. doi: 10.1093/ofid/ofac535
362. Dale DC, Cottle TE, Fier CJ, et al. Severe chronic neutropenia: Treatment and follow-up of patients in the severe chronic neutropenia international registry. American Journal of Hematology. 2003; 72(2): 82–93. doi: 10.1002/ajh.10255
363. Suga S, Tanaka R, Tabata N, et al Successful bone marrow transplantation in a child with combined IgG subclass deficiency and neutropenia. Bone Marrow Transplantation. 1995; 16(6): 847–848.
364. Simonis A, Fux M, Nair G, et al. Allogeneic hematopoietic cell transplantation in patients with GATA2 deficiency-A case report and comprehensive review of the literature. Annals of Hematology. 2018; 97(10): 1961–1973. doi: 10.1007/s00277-018-3388-4
365. Appasamy R, Bryant J, Hassanein T, et al. Effects of therapy with interferon-alpha on peripheral blood lymphocyte subsets and NK activity in patients with chronic hepatitis C. Clinical Immunology and Immunopathology. 1994; 73(3): 350–357. doi: 10.1006/clin.1994.1209
366. Bolay H, Karabudak R, Aybay C, et al. Alpha interferon treatment in myasthenia gravis: effects on natural killer cell activity. Journal of Neuroimmunology. 1998; 82(2): 109–115. doi: 10.1016/s0165-5728(97)00146-x
367. Okumura A, Ishikawa T, Maeno T, et al. Changes in natural killer T cell subsets during therapy in type C hepatitis and hepatocellular carcinoma. Hepatology Research. 2005; 32(4): 213–217. doi: 10.1016/J.HEPRES.2005.02.008
368. Yamagiwa S, Matsuda Y, Ichida T, et al. Sustained response to interferon-alpha plus ribavirin therapy for chronic hepatitis C is closely associated with increased dynamism of intrahepatic natural killer and natural killer T cells. Hepatology Research. 2008; 38(7): 664–672. doi: 10.1111/j.1872-034x.2008.00317.x
369. Gigli G, Caielli S, Cutuli D, et al. Innate immunity modulates autoimmunity: Type 1 interferon-beta treatment in multiple sclerosis promotes growth and function of regulatory invariant natural killer T cells through dendritic cell maturation. Immunology. 2007; 122(3): 409–417. doi: 10.1111/j.1365-2567.2007.02655.x
370. Holland SM, Eisenstein EM, Kuhns DB, et al. Treatment of refractory disseminated nontuberculous mycobacterial infection with interferon gamma. A preliminary report. New England Journal of Medicine. 1994; 330(19): 1348–1355. doi: 10.1056/nejm199405123301904
371. Netea MG, Brouwer AE, Hoogendoorn EH, et al. Two patients with cryptococcal meningitis and idiopathic CD4 lymphopenia: Defective cytokine production and reversal by recombinant interferon-gamma therapy. Clinical Infectious Diseases. 2004; 39(9): e83–e87.
372. Caligiuri MA, Murray C, Robertson MJ, et al. Selective modulation of human natural killer cells in vivo after prolonged infusion of low dose recombinant interleukin 2. Journal of Clinical Investigation. 1993; 91(1): 123–132. doi: 10.1172/jci116161
373. Cunningham-Rundles C, Murray HW, Smith JP. Treatment of idiopathic CD4 T lymphocytopenia with IL-2. Clinical and Experimental Immunology. 1999; 116(2): 322–325. doi: 10.1046/j.1365-2249.1999.00886.x
374. Francois B, Jeannet R, Daix T, et al. Interleukin-7 restores lymphocytes in septic shock: The IRIS-7 randomised clinical trial. JCI Insight. 2018; 3(5): e98960. doi: 10.1172/jci.insight.98960
375. Chen J. Effects of thymosin-alpha1 on cell immunity function in patients with septic shock. Zhongguo Wei Zhong Bing Ji Jiu Yi Xue. 2007; 19(3): 153–155.
376. Maltsev D, Stefanyshyn V. Efficacy of combined immunotherapy with propes and inflamafertin in selective deficiency of NK and NKT cells in children with autism spectrum disorders associated with genetic deficiency of the folate cycle. Romanian Journal of Neurology. 2021; 25(4): 536–540.
377. Hirna H, Maltsev D. Alpha/beta-defensins influence on the humoral immunity and complications in cancer of the oral cavity and oropharynx. Immunotherapy. 2024; 16(13): 869–878. doi: 10.1080/1750743X.2024.2376517
378. Hirna HA, Maltsev DV, Kostyshyn ID, et al. Results of the study of factors predicting the risk of the development of grade III radiation-induced mucositis during radiation or chemoradiation therapy in patients with oral cavity and oropharynx cancer. Klinická Onkologie. 2024; 37(3): 189–201. doi: 10.48095/ccko2024189
379. Hirna HA, Maltsev DV, Natrus LV, et al. Study of the immunomodulating influence of preparation alpha/beta-defensins on chemo/radiotherapy of patients with oral and oropharyngeal cancer. Physiology Journal. 2021; 67(4): 86–96. doi: 10.15407/fz67.04.086

380. Hirna HA, Maltsev DV, Rozhko MM, et al. Results of the study of mucosal immunity indices in patients with cancer of the oral cavity and oropharynx during radiotherapy or chemoradiotherapy therapy and immunotherapy with alpha/beta-defensins. Klinická Onkologie. 2023; 36(2): 112–123. doi: 10.48095/ccko2023112
381. Wang JF, Park AJ, Rendini T, et al. Lawrence transfer factor: Transfer of specific immune memory by dialyzable leukocyte extract from a CD8+ T cell line. Journal of Drugs in Dermatology. 2017; 16(12): 1198–1206.
382. Castrejón Vázquez MI, Reséndiz-Albor AA, Ynga-Durand MA, et al. Dialysable leukocyte extract (Transferon™) administration in sepsis: Experience from a single referral pediatric intensive care unit. BioMed Research International. 2019; 2019: 8980506. doi: 10.1155/2019/8980506
383. Homberg TA, Lara I, Andaluz C, et al. Quality of life in adult patients using dialyzable leukocyte extract for allergic rhinitis. Medicine (Baltimore). 2023; 102(27): e34186. doi: 10.1097/md.0000000000034186
384. Guo C, Ye JZ, Song M, et al. Poly I: C promotes malate to enhance innate immune response against bacterial infection. Fish and Shellfish Immunology. 2022; 131: 172–180. doi: 10.1016/j.fsi.2022.09.064
385. Morris D, Guerra C, Khurasany M, et al. Glutathione supplementation improves macrophage functions in HIV. Journal of Interferon and Cytokine Research. 2013; 33(5): 270–279. doi: 10.1089/jir.2012.0103
386. Richie JP Jr, Nichenametla S, Neidig W, et al. Randomised controlled trial of oral glutathione supplementation on body stores of glutathione. European Journal of Nutrition. 2015; 54(2): 251–263. doi: 10.1007/s00394-014-0706-z
387. Sinha R, Sinha I, Calcagnotto A, et al. Oral supplementation with liposomal glutathione increases body stores of glutathione and markers of immune function. European Journal of Clinical Nutrition. 2018; 72(1): 105–111. doi: 10.1038/ejcn.2017.132
388. Richard SA. Exploring the pivotal immunomodulatory and anti-inflammatory potentials of glycyrrhizic and glycyrrhetinic acids. Mediators of Inflammation. 2021; 2021: 6699560. doi: 10.1155/2021/6699560
389. Naik S, Nicholas SK, Martinez CA, et al. Adoptive immunotherapy for primary immunodeficiency disorders with virus-specific T lymphocytes. Journal of Allergy and Clinical Immunology. 2016; 137(5): 1498–1505. doi: 10.1016/j.jaci.2015.12.1311
390. Cuellar-Rodriguez J, Gea-Banacloche J, Freeman AF, et al. Successful allogeneic hematopoietic stem cell transplantation for GATA2 deficiency. Blood. 2011; 118(13): 3715–3720. doi: 10.1182/blood-2011-06-365049
391. Sicre de Fontbrune F, Chevillon F, Fahd M, et al. Long-term outcome after allogeneic stem cell transplantation for GATA2 deficiency: An analysis of 67 adults and children from France and Belgium. British Journal of Haematology. 2024; doi: 10.1111/bjh.19691
392. Yamamoto K, Najima Y, Iizuka H, et al. Successful cord blood transplantation for idiopathic CD4+ lymphocytopenia. Acta Haematologica. 2021; 144(6): 698–705. doi: 10.1159/000516347
393. Karaman S, Erdem SB, Gülez N, et al. The significance of B-cell subsets in patients with unclassified hypogammaglobulinemia and association with intravenous immunoglobulin replacement requirement. Iranian Journal of Immunology. 2018; 15(1): 1–13. doi: ijiv15i1a1
394. Söderström T, Söderström R, Enskog A. Immunoglobulin subclasses and prophylactic use of immunoglobulin in immunoglobulin G subclass deficiency. Cancer. 1991; 68(6): 1426–1429. doi: 10.1002/1097-0142(19910915)68:6+%3C1426::aid-cncr2820681404%3E3.0.co;2-r
395. Ghia D, Thota P, Ritchie T, et al. Feasibility and resource utilization of nurse-administered subcutaneous immunoglobulin therapy in antibody deficiency: A cross-sectional study. PLoS One. 2025; 20(1): e0316797. doi: 10.1371/journal.pone.0316797
396. Moral Moral P, Cabanero-Navalon MD, López-León PT, et al. Infectious outcomes of a standardized subcutaneous immunoglobulin dose reduction strategy in primary immune deficiencies amid global shortage. Frontiers in Immunology. 2025; 15: 1527514.
397. Fregonese B, Canepa C, Pasino M, et al. Selective IgA deficiency. Substitute treatment with human IgA-enriched immunoglobulins. Minerva Pediatrica. 1986; 38(17–18): 751–758.
398. Langereis JD, van der Flier M, de Jonge MI. Limited innovations after more than 65 years of immunoglobulin replacement therapy: Potential of IgA- and IgM-enriched formulations to prevent bacterial respiratory tract infections. Frontiers in Immunology. 2018; 9: 1925. doi: 10.3389/fimmu.2018.01925
399. Taietti I, Votto M, De Filippo M, et al. Selective IgM deficiency: Evidence, controversies, and gaps. Diagnostics. 2023; 13(17): 2861. doi: 10.3390/diagnostics13172861

400. Langereis JD, Jacobs JFM, de Jonge MI, et al. Plasma therapy leads to an increase in functional IgA and IgM concentration in the blood and saliva of a patient with X-linked agammaglobulinemia. Journal of Translational Medicine. 2019; 17(1): 174. doi: 10.1186/s12967-019-1928-x
401. Crooks CV, Wall CR, Cross ML, et al. The effect of bovine colostrum supplementation on salivary IgA in distance runners. International Journal of Sport Nutrition and Exercise Metabolism. 2006; 16(1): 47–64. doi: 10.1123/ijsnem.16.1.47
402. Mero A, Miikkulainen H, Riski J, et al. Effects of bovine colostrum supplementation on serum IGF-I, IgG, hormone, and salivary IgA during training. Journal of Applied Physiology. 1997; 83(4): 1144–1151. doi: 10.1152/jappl.1997.83.4.1144
403. Patıroğlu T, Kondolot M. The effect of bovine colostrum on viral upper respiratory tract infections in children with immunoglobulin A deficiency. Clinical Respiratory Journal. 2013; 7(1): 21–26. doi: 10.1111/j.1752-699x.2011.00268.x
404. Jesenak M, Majtan J, Rennerova Z, et al. Immunomodulatory effect of pleuran (β-glucan from pleurotus ostreatus) in children with recurrent respiratory tract infections. International Immunopharmacology. 2013; 15(2): 395–399. doi: 10.1016/j.intimp.2012.11.020
405. McFarlin BK, Carpenter KC, Davidson T, et al. Baker's yeast beta glucan supplementation increases salivary IgA and decreases cold/flu symptomatic days after intense exercise. Journal of Dietary Supplements. 2013; 10(3): 171–183. doi: 10.3109/19390211.2013.820248
406. Park SY, Kim KJ, Jo SM, et al. Euglena gracilis (euglena) powder supplementation enhanced immune function through natural killer cell activity in apparently healthy participants: A randomised, double-blind, placebo-controlled trial. Nutrition Research. 2023; 119: 90–97. doi: 10.1016/j.nutres.2023.09.004
407. Maltsev DV, Hurzhii OO. Toxoplasma chorioretinitis in primary myeloperoxidase deficiency. Journal of Ophthalmology. 2019; 4: 75–81. doi: 10.31288/oftalmolzh201947581
408. Jakopin Ž. Murabutide revisited: A review of its pleiotropic biological effects. Current Medicinal Chemistry. 2013; 20(16): 2068–2079. doi: 10.2174/0929867311320160002
409. Vidal V, Dewulf J, Bahr GM. Enhanced maturation and functional capacity of monocyte-derived immature dendritic cells by the synthetic immunomodulatormurabutide . Immunology. 2001; 103(4): 479–487. doi: 10.1046/j.1365-2567.2001.01269.x
410. Keizer MP, Wouters D, Schlapbach LJ, et al. Restoration of MBL-deficiency: Redefining the safety, efficacy and viability of MBL-substitution therapy. Molecular Immunology. 2014; 61(2): 174–184. doi: 10.1016/j.molimm.2014.06.005
411. Fioredda F, Skokowa J, Tamary H, et al. The European guidelines on diagnosis and management of neutropenia in adults and children: A consensus between the European hematology association and the EuNet-INNOCHRON COST Action. Hemasphere. 2023; 7(4): e872. doi: 10.1097/hs9.0000000000000872
412. Lubitz PA, Dower N, Krol AL. Cyclic neutropenia: An unusual disorder of granulopoiesis effectively treated with recombinant granulocyte colony-stimulating factor. Pediatric Dermatology. 2001; 18(5): 426–432. doi: 10.1046/j.1525-1470.2001.01974.x
413. Oshio M, Yamauchi T. Successful treatment of chronic idiopathic neutropenia in an elderly with ciclosporin. Rinsho Ketsueki. 2022; 63(7): 753–758. doi: 10.11406/rinketsu.63.753.
414. Kobayashi M, Ueda K, Kojima S, et al. Serum granulocyte colony-stimulating factor levels in patients with chronic neutropenia of childhood: Modulation of G-CSF levels by myeloid precursor cell mass. British Journal of Haematology. 1999; 105(2): 486–490.
415. Vo Ngoc DT, Krist L, van Overveld FJ, et al. The long and winding road to IgA deficiency: Causes and consequences. Expert Review of Clinical Immunology. 2017; 13(4): 371–382. doi: 10.1080/1744666x.2017.1248410
416. Magen E, Blum I, Waitman DA, et al. Autoimmune inner ear disease among patients with selective IgA deficiency. Audiology and Neurotology. 2021; 26(2): 127–134. doi: 10.1159/000509577
417. Magen E, Merzon E, Green I, et al. Selective IgA deficiency and COVID-19. Journal of Allergy and Clinical Immunology: In Practice. 2023; 11(6): 1936–1938. doi: 10.1016/j.jaip.2023.02.016
418. Patel NC, Walter JE, Wasserman RL, et al. Efficacy, safety, tolerability, and serum IgG trough levels of hyaluronidase-facilitated subcutaneous immunoglobulin 10% in US pediatric patients with primary immunodeficiency diseases. Journal of Clinical Immunology. 2025; 45(1): 81. doi: 10.1007/s10875-025-01862-6
419. Ramírez-Ramírez D, Vadillo E, Arriaga-Pizano LA, et al. Early differentiation of human CD11c+NK Cells with γδ T cell activation properties is promoted by dialyzable leukocyte extracts. Journal of Immunological Research. 2016; 2016: 4097642.

420. Bourseau-Quetier C, Doutre MS. Diffuse molluscum contagiosum associated with GATA2 deficiency. Annales de Dermatologie et de Vénéréologie. 2025; 152(2): 103378. doi: 10.1016/j.annder.2025.103378
421. Feng Y, Wu Q, Zhang T, et al. Natural killer cell deficiency experiences higher risk of sepsis after critical intracerebral hemorrhage. International Journal of Immunopathology and Pharmacology. 2021; 35: 20587384211056495. doi: 10.1177/20587384211056495
422. Ilonze C, Galipp KM, Scordino T, et al. A case of cyclic neutropenia and associated amyloidosis. Journal of Pediatric Hematology/Oncology. 2021; 43(8): e1115–e1117. doi: 10.1097/mph.0000000000002217
423. Lao Z, Fu J, Wu Z, et al. Case report: Five-year periodontal management of a patient with two novel mutation sites in ELANE-induced cyclic neutropenia. Frontiers in Genetics. 2022; 13: 972598. doi: 10.3389/fgene.2022.972598
424. Lisco A, Ortega-Villa AM, Mystakelis H, et al. Reappraisal of idiopathic CD4 lymphocytopenia at 30 years. New England Journal of Medicine. 2023; 388(18): 1680–1691. doi: 10.1056/nejmoa2202348