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Clinic-Laboratory Classification of Primary Minor Immunodeficiencies in Humans

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Abstract: Only some primary immunodeficiencies are often found in the population, characterized by a mild clinical phenotype and creating a significant burden on society, so-called primary minor immunodeficiencies (PMD). The study aims to create a clinical and laboratory classification of PMD in humans for basic science and practical medicine. A systematic review of scientific publications in PubMed (MEDLINE) from 1980 to 2025 was conducted using keywords through a sequential two-stage search. The terminology has been clarified and an original clinical and laboratory classification of PMD in humans has been developed according to the following rubrics: origin, affected immune factor, immune system branch and form of immunity, family history, time of debut, frequency in the population, genetic nature, clinical picture, depth of immune factor damage, severity of the patient's condition, duration of the immunological phenotype, evolutionary development scenario, regularity of manifestations, involvement of local and systemic immunity, combinations with each other and with other diseases, curability and some special headings. The significance of the developed classification for fundamental science and clinical practice has been clarified, and promising directions for further research to improve the proposed classification have been indicated. The introduction of a classification will demonstrate the diversity of PMD in humans, enabling both improved clinical diagnosis in individuals with associated immune-dependent pathology and a contribution to the intensification and optimization of clinical research.

Keywords: Immunocompromise State; Immune-Dependent Pathology; Immunodiagnosis; Immunotherapy; Immunoprophylaxis; Diversity

1. Introduction

More than 400 primary immunodeficiencies have been described in humans, demonstrating the unprecedented heterogeneity of the phenomenon of genetically determined immune system disease in the human population [1]. The data obtained allows us to understand that primary immunodeficiencies are a much broader and heterogeneous concept than previously thought. According to classical views, it was postulated that primary immunodeficiency should have the following characteristics: a positive family history, rarity of distribution in the population, early debut in the first weeks/months/years of life, severe clinical picture, unfavorable course, and high mortality [2]. These are the so-called classical [3], or major [4] primary immunodeficiencies. However, several primary immunodeficiencies have now been described and well characterized, which do not meet the classical postulates and often even directly contradict their basic requirements, since they may have no family history, are common in the population, demonstrate delayed onset and significant asymptomatic periods, are characterized by a usual

picture of morbidity from the routine practice of the clinician, show a variable course and do not always lead to an obvious increase in mortality in childhood. These are the so-called mild [5,6] or minor [7] primary immunodeficiencies (PMD).

Thus, primary minor immunodeficiencies 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.

Classical immunodeficiencies and PMD differ significantly phenomenologically, which is important not only for understanding different states of immunocompromise in humans in theoretical medicine, but also for clinical practice, since PMD may require different approaches to screening, assessing the severity of the patient's condition, using verification diagnostic laboratory tests, prognosis, prevention of complications, and therapeutic interventions.

However, despite the large number of scientific publications in this area, clinical and laboratory classification of PMD has not yet been developed, which complicates both the formation of a holistic scientific concept and the synthesis of practical recommendations for clinical medicine. The development of such a classification would allow us to deepen and structure our knowledge of the variety of disorders of the immune system in humans and provide practical medicine with effective screening and diagnostic algorithms for the timely and effective treatment of immunocompromised patients with various immunodependent lesions.

The study aims to analyze publications from peer-reviewed medical periodicals to search for data on the diversity of primary minor immunodeficiencies in humans. The study will then construct a clinical and laboratory classification of these diseases to organize and systematize the accumulated evidence for theoretical and practical medicine.

2. Research Objectives

1. To study the data of published articles on primary minor immunodeficiencies to determine the diversity of these diseases in the human population.

2. To clarify the terminology for the designation of primary minor immunodeficiencies in humans.

3. To establish distinctive clinical and laboratory rubrics to systematize the identified diversity of primary minor immunodeficiencies in the form of a classification structure.

4. To develop a clinical and laboratory classification of primary minor immunodeficiencies according to the identified diversity and the selected distinctive rubrics.

5. To analyze the advantages and disadvantages of the developed classification of primary minor immunodeficiencies in humans, ways of its improvement, and prospects for application in clinical practice.

3. Materials and Methods

To achieve the aim and fulfill the developed tasks, a systematic review of the results of scientific publications on the outlined topic was conducted from the abstract electronic scientometric bibliographic database of publications from peer-reviewed medical periodicals PubMed (MEDLINE) for the period from 1980 to 2025 by keywords through a sequential two-stage search.

At the first screening stage of the search, the following keywords were used: “primary immunodeficiency”, “genetic immunodeficiency”, “inherited immunodeficiency”, “primary immune defects”, “primary immunosuppression”, “primary immunodepression”, “inborn errors in immunity”, which were combined arbitrarily with other keywords that characterized the specifics of minor immunodeficiencies, namely: “unsignificant disease”, “high frequency”, “late debut”, “asymptomatic course”, “clinical variability”, “mild symptoms”, “clinical heterogeneity”, “unpredictable outcome”, “spontaneous resolution”, “favorable prognosis”, “unexplained complication”, “rapid death”, “selective advantage”. As a result of the search at the first stage, a list of previously described PMDs was found, which characterized the diversity of these diseases in the human population (1243 publications). The results of this stage allowed us to divide the identified PMDs into three main classification categories: form of immunity (innate/acquired), affected immune factor(s), and branch of immunity (phagocytosis, complement system, cellular and humoral adaptive immunity) (71 articles).

Thus, the following criteria for identifying primary immunodeficiency as a minor disease of the immune system

were applied:

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 debut 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 historical period of ignoring the immunodeficiency as an "unsignificant" disease.

Immunodeficiency was considered minor if at least 9 of the 13 proposed criteria were met (all nosological units from **Table 1** correspond to at least 9 of the 13 criterions).

Table 1. Synopsis 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
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, very frequent, and extreme frequent
8	by genetic nature	According to mendelian laws of inheritance: - mendelian and non-mendelian According to type of inheritance: - autosomal dominant, autosomal recessive, X-linked, codominant According to number of affected genes: - monogenic, bigenic, polygenic According to type of genetic anomaly: - chromosome aberrations, structure genes mutations, single nucleotide polymorphisms, 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

Table 1. *Cont.*

№	Classification Rubric	Variety
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, and respiratory. According to predominant of associated nosological unit: - PMDs in systemic lupus erythematosus, bronchial asthma, leukemias, sarcoidosis, and COVID-19.
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, concurrent, multidimensional; monomodal, bimodal homogeneous, bimodal heterogeneous, polymodal homogeneous polymodal heterogeneous; true and pseudo combinations)
17	by curability	treatable, non-treatable
18	by specific rubrics	different in each disease

In the second, refining, stage of the scientific search, keywords were used that denoted the names of PMDs identified in the first search stage, such as "transitory hypogammaglobulinemia of infancy", "unclassified hypogammaglobulinemia", "selective IgM deficiency", "selective IgA deficiency", "selective IgG subclasses deficiency", "selective IgE deficiency", "selective IgD deficiency", "selective myeloperoxidase deficiency", "selective eosinophilic peroxidase deficiency", "selective mannose binding lectin deficiency", "deficiency of serine proteases, associated with mannose binding lectin", "NK-cell deficiency", "NKT-cell deficiency", "CD16 molecule deficiency", "perforin deficiency", "CD8 molecule deficiency", "CD64 molecule deficiency", "idiopathic CD4+ T-cell lymphopenia", "chronic idiopathic neutropenia", "chronic benign neutropenia", "cyclic neutropenia", "chronic idiopathic eosinopenia", "chronic idiopathic monocytonenia", which were combined in random order with other keywords describing the main attributes of PMD as clinical phenomena, namely - "etiology". "pathogenesis", "epidemiology", "clinical picture", "diagnosis", "differential diagnostic", "complications", "prognosis", "treatment", "prophylactic". At this stage of the scientific search (1127), through a thorough analysis of the clinical attributes of known PMD, it was possible to identify additional classification rubrics, including origin, genetic nature, frequency in the population, depth of immunodeficiency,

clinical picture, course of the disease, and combinations with other pathologies (137 publications).

When forming the list of references, preference was given to meta-analyses and systematic reviews, population studies, randomized controlled clinical trials, retrospective analyses of clinical cases, and thorough reviews of the literature based on relevant clinical trials and reports. Descriptions of single clinical cases, if they did not represent a certain value from the historical or situational (contextual) side, were removed from the final list of references due to the low level of evidence of the data presented. Letters to the editor, articles-comments to other publications and responses to these comments, abstracts, positional author publications, reports from scientific conferences, chapters of monographs and textbooks, publications not in English, articles without access to an informative abstract and/or full text, as well as works using outdated diagnostic methods that question the correctness of immunodiagnostics and the authors' conclusions were also subject to removal. 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 lack of previous systematic analyses on the problem, an attempt was made to reflect a holistic picture of the accumulated evidence base, facts, and experience of diagnosis and treatment for the entire available search period. Since publications on some diseases of the immune system are extremely unevenly represented in different decades, artificially limiting the search to a relatively short period would inevitably lead to a distortion of information, presenting an inappropriate reductionist approach. Preference was also given to publications in which the proposed term or classification rubric was substantiated in detail and included in the title of the article. The quality of the publication was of fundamental importance when selecting an article for the final list of literature, in particular, the design of the studies, methods of statistical analysis, informativeness and relevance of laboratory diagnostic methods, the presence of appropriate illustrative material demonstrating the primary material, and the weightiness of the authors' conclusions (**Figure 1**).

4. Results and Discussion

4.1. Part I

4.1.1. General Data

As a result of the present research, scientific publications from periodical sources for the specified search period were selected and analyzed, and based on the data obtained, important terminological clarifications were made both to designate the phenomenon of PMD in general and for individual nosological units. It has been established that the term “primary minor immunodeficiency” is the most acceptable, since it has been proposed and well-founded by many independent groups of authors, most accurately describes the phenomenology of the studied immunodeficiencies, and is not used to denote other phenomena in clinical immunology, which would avoid terminological confusion.

A list of known and well-characterized PMDs in humans was outlined, and their heterogeneity and diversity were studied both among themselves and within individual nosological units. These data allowed us to identify key classification rubrics for dividing PMDs into certain subgroups, which would be helpful to both for systematizing and stratifying modern scientific knowledge about diseases of the immune system, which contributes to both a better understanding of the phenomenology of PMDs in humans and a wider detection of these diseases in routine clinical practice and rationalization of further clinical research in the specified direction. Such classificational rubrics were defined as origin, affected form of immunity, affected branch of immune system, affected immune factor/factors, family history, time of debut, frequency in population, genetic nature, clinical picture, depth of immune factor damage, severity of the patient's condition, duration of existence of immunological phenotype, evolutionary scenario of development, regularity of the disease, spread of the damage across the immune system, combination with other diseases, curability and special rubrics. The division into subgroups within each of the above 17 classification categories (except special rubrics, which were reported in passing) is presented in detail in separate subsections of the results of this study.

As a result of studying the diversity of PMD and identifying key classification categories regarding PMD heterogeneity, it became possible to develop a complete, modern, original clinical and laboratory classification of PMD in humans. The developed classification can be conditionally presented as a large (academic) one, which includes all subgroups of each of the 17 classification headings, comprehensively representing the current state of affairs in the study of the heterogeneity of PMD in humans (**Table 1**), and a small, or utilitarian one, which has a purely practical

significance and covers only subgroups of the three main applied headings (affected form of immunity, affected branch of the immune system and affected immune factor/factors). So, PMD large classification includes small, or core classification (utilitarian one for practical medicine with 3 main rubrics) and supplementary classification (all other rubrics that clarify and supplement the core headings).

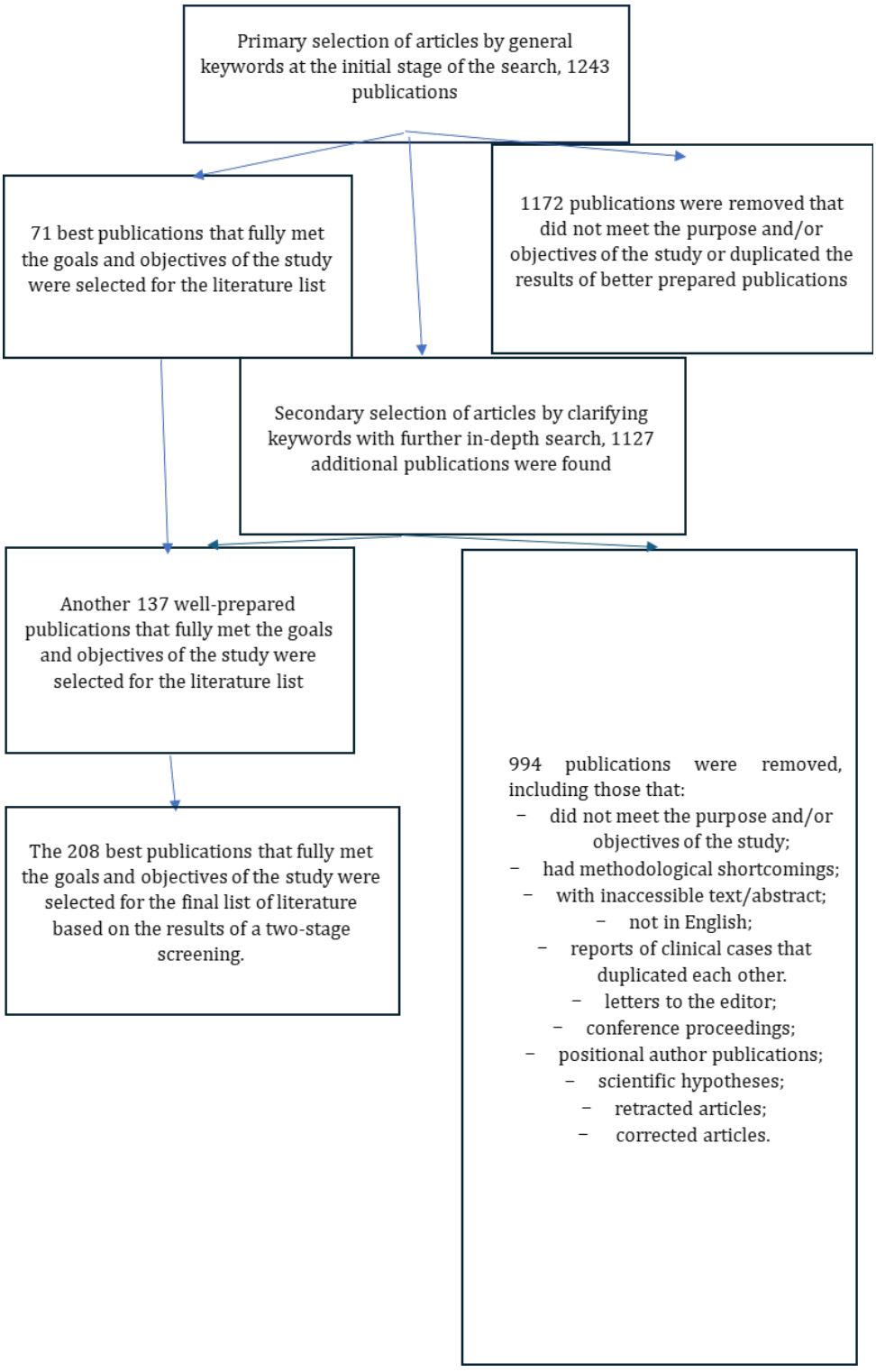

Figure 1. Structure of the study.

The large and small classifications can be called primary. On this basis, secondary classifications can be further developed according to special headings within nosological units, which, in particular, are described by the small classification. The development of a secondary classification is not the subject of this study, since this is an unattainable goal without prior coordination of the primary classifications. To explain the relationship between the large, small, and secondary classifications, the principle of matryoshka can be applied: the large classification completely includes the small one, and the small one completely covers the secondary ones.

4.1.2. Terminology Clarifications

One of the key tasks of this study is to clarify and unify terminology, since for several decades different groups of authors have proposed different terms to denote the same phenomenon and, conversely, fundamentally different phenomena have been accidentally designated by the same term. Therefore, in the study of PMD, there is undoubtedly a certain terminological confusion. So far, no detailed review has been published devoted to attempts to untie the Gordian knot of terminological uncertainty about PMD. Without eliminating terminological confusion, it is impossible to form a unified classification; therefore, the consideration of the results of this study begins with attempts to solve this problem. The solution to this problem is carried out in a historical, comparative, and critical manner.

The term primary minor immunodeficiency (PMD) was first proposed by Litzman et al. in 1995 to denote deficiencies of certain subpopulations of T lymphocytes, IgA, and IgM molecules, and complement system proteins C3 and C4 in patients who often suffered from infectious episodes [8]. Later, Qjuawo et al. used the term PMD to describe deficiencies of IgA, IgG2, and IgG4 molecules [9], and Latcham et al., in addition, deficiencies of CD8+ cytotoxic T lymphocytes and natural killers [10]. This term is sometimes used in modern studies. In particular, Vivarelli et al. in 2021 used the term PMD to describe IgG subclass deficiencies and unclassified antibody deficiencies (unPAD) in patients with frequent episodes of upper and lower respiratory tract infections receiving immunoglobulin replacement therapy [11].

Different terms are used to designate diseases that meet the proposed PMD criteria. For example, sometimes mild/minor immunodeficiencies are designated as incomplete [12], since some of them, but not all, do indeed form incomplete phenotypes of classical immunodeficiencies, for example, selective IgA deficiency [13] can be represented as an incomplete immunological phenotype of hypogammaglobulinemia in common variable immunodeficiency [14]. Based on similar considerations, Bossuyt et al. propose to designate PMD as partial immunodeficiencies [15]. The term atypical [16] immunodeficiencies is also sometimes used to emphasize the significant difference between PMD in terms of clinical and laboratory phenotype from classical primary immunodeficiencies.

Although the literature still uses two different terms in parallel – both "mild" [17, 18] and "minor" [11] immunodeficiency, we consider the term "minor immunodeficiency" to be more useful in order to avoid confusion with the frequently used term "mild" to denote not the form of immunodeficiency itself, but only cases of a slight decrease in the amount [5] or function [19] of a certain immune factor, as well as mild clinical phenotype [20–22] or immunological phenotype [23], associated infectious lesions (mild infections) [24] or the course of the immune system disease (mild course) [25], both in PMD [16] and classical primary immunodeficiencies [26, 27], and even in secondary immunosuppression [28, 29].

To designate primary immunodeficiencies, including PMD, the term "inborn errors in immunity" is often used [30], which, in addition to its purely pathogenetic, rather than clinical, focus, has an additional drawback, since it does not fully cover the spectrum of primary immunodeficiencies, since genetic diseases of the immune system acquired postnatally cannot be included here [31].

PMDs are sometimes referred to as "immune defects" [32], "immune abnormalities" [33], or even "immune phenotypes" [34], although these terms are mostly pathogenetic rather than clinical. PMDs are also sometimes incorrectly referred to in scientific publications by the alternative terms "immune dysfunction" [35], "defective immune response" [36], or "impaired immune response" [37], which seem more like a functional characteristic of the immune system at a certain point in time than a holistic disease that exists throughout the patient's life. Thus, the publication by Fernando et al. is devoted to the study of immune dysregulation in common variable immunodeficiency [38], that is, the name of the disease is common variable immunodeficiency, and immune dysregulation is only an attribute of this disease, a functional characteristic of the immune system at a certain point in time. This same principle should be extended to PMD and not replace the name of the disease with an indication of the functional state of the affected system, which is variable. It should be emphasized that in the asymptomatic course of

PMD, there will be no impairment of the immune system function; therefore, PMD is a more capacious term than immune dysfunction.

Sometimes even in the latest publications, clearly erroneous terms are used, such as "selective IgM hypogammaglobulinemia" [39], although with an isolated deficiency of the IgM molecule, due to the small specific gravity of this class of immunoglobulins among the total antibody pool, the phenomenon of gamma-globulin deficiency in the blood serum is usually not formed.

One can agree with the position of Nunes-Santos et al. to use the term "primary immunodeficiency disease" [40], rather than primary immunodeficiency, since the first term covers all clinical aspects, and does not only denote the immunological laboratory phenotype of the disease. However, this practice has not yet become widely used in scientific publications.

4.2. Part II

4.2.1. Classicational Rubrics

By Origin of the Disease

Although all PMDs are genetically determined diseases, they still differ significantly in the origin of the causative genetic disorders that underlie the disease of the immune system. By origin, PMDs can be hereditary [41] (genetic abnormality in the germ cells of the parents), inborn [42] or congenital [43] (somatic genetic abnormality that arose during the period of intrauterine development without/with the involvement of germ cells), and acquired (somatic genetic abnormality acquired postnatally [31] or epigenetic disorders [44]). An example of a hereditary PMD is primary myeloperoxidase deficiency in a family with the R569W mutation of the MPO gene [41]. An example of a congenital PMD, or inborn error of immunity [45], is selective IgM deficiency as a consequence of a chromosomal deletion of 2q11.2 [46]. An example of an acquired PMD is selective IgA deficiency transferred from a donor to a recipient during allogeneic bone marrow transplantation in the postnatal period of ontogenesis [31]. Congenital and acquired PMD should be distinguished from secondary immunodeficiencies, which are phenocopies of PMD. Confusion may arise because secondary immunodeficiencies can manifest from birth, as can congenital PMD (for example, in the case of congenital HIV infection) [47], and PMD itself, if it develops during postnatal ontogenesis, can also be called acquired [48], as acquired secondary immunodeficiencies [49]. In addition, pre-existing PMDs may induce secondary immunodeficiency, for example, through the production of autoantibodies to immune factors [50,51], sometimes leading to the dissolution of the narrow immunological phenotype of PMD into the broader immunological phenotype of associated secondary immunosuppression [52]. The clinical outcome may be the result of interaction, rather than a simple summation, of different PMDs among themselves and with other immunodeficiencies. Therefore, the development of additional clarifying terminological nomenclature is needed to distinguish different forms of immunodeficiencies by origin, considering the full range of complexity.

By the Affected Immune Factor, the Branch of the Immune System and the Form of Immunity

In humans, there are innate and acquired (adaptive) forms of immunity. As is known, such links of the immune system as phagocytosis and the complement system are distinguished—cellular and humoral adaptive immunity. Currently, more than 300 different structural and functional purpose immune factors (proteins and cells) have been described, which form the basis of the human immune system. Currently known PMDs can relate to the defeat of various forms of immunity, branches of the immune system, and many immune factors identified so far. Li et al. substantiate the concept of "type" of immunodeficiency, which is understood as the affected immune system, branch of the immune system, and immune factor/factors [53]. Accordingly, **Table 2** shows the classification of known PMDs by the affected form of immunity, branch of the immune system, and, in fact, the immune factor/factors. However, even such a detailed classification does not reflect the full diversity of PMD in humans, which requires consideration of several additional classification rubrics, which are sequentially listed below.

By Family History

The study of family history allows us to identify cases of identical immunological phenotypes and/or associated clinical immune-dependent syndromes in the proband's close and distant relatives. Freiberger et al., using the example of SIgAD, suggest distinguishing between sporadic and familial forms of PMD in humans [116]. The term "sporadic primary immunodeficiency" was supported by Sogkas et al. in 2022 in a publication on genetic testing in diseases of the immune system [117], and Hay et al., the term "familial immunodeficiency" [118]. Familial forms can

include hereditary cases of PMD with a positive family history, and sporadic forms include congenital to acquired PMD, as well as some cases of hereditary PMD when family history is unavailable. Results of a cross-sectional clinical study by Soler-Palacín et al. indicate approximately the same clinical severity of sporadic and familial forms of PMD, as well as the feasibility of family screening for PMD, since the proband's closest relatives have a suspended morbidity associated with immune-dependent pathology [119]. In particular, according to the longitudinal study by Lougaris et al., a positive family history is noted in 16.0% of cases with total SIgAD [120].

Table 2. Classification of known PMDs in humans by affected immune factors, immune system branch, and form of immunity.

I. Disorders of the Cellular Component of Innate Immunity: 1. Numerical cellular innate immunodeficiencies [54]: A. Quantitative phagocytic cell defects [55]: a. neutrophil disorders (chronic isolated neutropenias) [56]: - familial benign (ethnic) neutropenia (FB(E)N) [57], or Duffy-null phenotype (genotype) [58]; - chronic idiopathic neutropenia (CIN) [59]; - cyclic neutropenia (CyN) [60]. b. eosinophil disorders: - chronic idiopathic eosinopenia (CIE) [61]. c. monocyte disorders: - selective monocytopenia (SM) [62]. B. Numerical lymphocyte subset deficiencies [63]: - natural killer cell deficiency (NKD) [64]; - natural killer T-cell deficiency (NKTD) [65]; - CD16 molecule deficiency (CD16D) [66]. 2. Functional cellular innate immunodeficiencies [54]: A. Qualitative phagocytic cells defects [55]: a. peroxidase deficiencies [67]: - neutrophil myeloperoxidase deficiency (MPOD) [41]; - eosinophilic peroxidase deficiency (EPOD) [68]. b. deficiencies of Fc-gamma receptors [69]: - CD64 molecule deficiency (FcγRI) [70]. B. Functional lymphocyte subset deficiencies [63]: a. functional disorders of cytotoxic cells [71]:* - primary perforin deficiency (PPD), [72] including PRF1 SNVs [73].** -	**III. Deficiency of the Humoral Component of Adaptive Immunity:** IIIa. Primary antibody deficiencies (PAD) [83]: 1. Quantitive immunoglobulin deficiencies [83]: A. Hypogammaglobulinemias [84]: a. Transitory hypogammaglobulinemia of infancy (THI) [85]; b. Unclassified hypogammaglobulinemia (UH) [86]; B. Dysgammaglobulinemias [87]: a. Primary isotype (class) deficiencies [88]: - selective (isolated) IgM deficiency (SIgMD) [89]; - selective (isolated) IgG deficiency (SIgGD) [90,91]; - selective (isolated) IgA deficiency (SIgAD) [92]; - selective (isolated) secretory IgA deficiency (SsIgAD) [93]; - selective (isolated) IgE deficiency (SIgED) [94]; - selective (isolated) IgD deficiency (SIgDD) [95]; b. Immunoglobulin subclass deficiencies [96]: - selective (isolated) IgG subclass deficiencies (SIgGSD) [97]: SIgG1D [5], SIgG2D [98], SIgG3D [99], SIgG4D [100]; - selective (isolated) IgA subclass deficiencies (SIgASD) [101]: SIgA1D [102], SIgA2D [103]; e. Other dysimmunoglobulinemias (combined deficiencies of immunoglobulins of different classes and/or subclasses), such as combined deficiency of IgA1, IgG2, IgG4, and IgE [104], or deficiency of IgG1, IgG3, and IgE [105], or deficiency of IgG2, IgG4, IgA1 [106]. 2. Qualitative immunoglobulin deficiencies [107]: a. Selective specific antibodies deficiency (SAD) [108], including selective antipolysaccharide antibodies deficiency (SPAD) [109], or "monogenic inborn errors of immunity with impaired IgG response to polysaccharide antigens, but normal IgG levels and normal IgG response to protein antigens" [110]; b. galactose deficient IgA1 [111].
II. Humoral Innate Immunodeficiencies: 1. Complement deficiencies [74,75]: A. Lectin pathway disorders [76]: a. mannose binding protein (lectin) deficiency (MBLD) [77]; b. mannose binding protein (lectin) associated serine protease 2 deficiency (MASP2D) [76]; B. deficiency of terminal components of the cascade that form the membrane-attack complex (terminal complement pathway deficiency) [78], - C6D [79], C7D [80], C8D [81], C9D [82].	**IV. Deficiency of the Cellular Component of Adaptive Immunity:** 1. Primary T-cell immunodeficiencies [112]: - idiopathic CD4+ T-cell lymphocytopenia (ICD4+TL) [113]; - CD8 molecule deficiency (CD8D) [114], or selective deficiency of CD8+ cytotoxic T-lymphocytes (SCD8+CTLD) [115]

Note: *the disorder concerns not only NK and NKT, but also cytotoxic CD8+ T lymphocytes, which are related to adaptive immunity. **excluding hemophagocytic lymphohistiocytosis.

By Time of Debut

The fact that clinical debut occurs in early childhood is not a mandatory feature of PMD. PMD can be divided into early-onset (according to Zhou et al. [121]) and late-onset [17], or late diagnosis [122] forms. There is also talk of a pediatric-onset and adult-onset form in primary immunodeficiencies in humans [14]. PMD can make its clinical debut, as well as be first diagnosed, at any age, and not only in children or young adults. The record holder in terms of the delay in manifestations and clinical diagnosis is still the report by Endoh et al. on the initial detection of SIgMD in an 85-year-old patient [123].

By Frequency in Population

Although PMD is generally a common phenomenon in the human population, there is considerable heterogene-

ity in frequency within this group. Due to the possibility of long asymptomatic periods, PMD may evade natural selection. Therefore, PMD with an autosomal dominant mode of inheritance is generally more common in humans than with an autosomal recessive mode. Geographic, regional, racial, ethnic, gender, and age factors are also important. The ultimate frequency of a particular PMD in the human population is determined by the combined action of the founder effect and selective advantage [124]. An example of a founder effect is the different frequencies of MPOD in Europe and Japan [41], and of a selective advantage is the reduced risk of blood-brain barrier damage in PRF1 SNVs [73]. PMD can be classified as rare (e.g., CyN – from 0.5 to 1 case per 1 million inhabitants worldwide [125]); medium (1 case per 3,400 [126] to 14,000 people [127] worldwide in EPOD, and 1:2,000–4,000 inhabitants of Western Europe and the USA in MPOD [41]); frequent (SIgAD – from 1:163 [128] to 1:600 people [129] in Europe); very frequent (SIgED – 1:30 people (3.4%) in Europe and the USA [130]); and extreme frequent (MBLD – from 5–10% of the general population [131] to 1 case per every third person in central Africa [124].

By Genetic Nature

PMDs are quite heterogeneous in their genetic nature. Mendelian [132] and non-Mendelian [133] forms of PMD can be distinguished. These diseases can be caused by chromosomal aberrations [134], Mendelian mutations in structural genes [41], pathological polymorphic nucleotide substitutions [77], and gene regulatory disorders [44].

PMDs can be inherited in various ways, although autosomal dominant inheritance predominates [4], cases of autosomal recessive [126], and X-linked inheritance are also known [135]. In some cases of PMD, a bigenic model of inheritance has been discussed [126].

PMDs can be monogenic [110] and polygenic [133] in nature. For example, a combination of three mutations in PIK3CD, PIK3R1, and NFKB1 has been described, which formed a complex immunodeficiency phenotype in one family [133].

Some immunodeficiencies, such as EPOD, are caused by a single mutation in a single gene (2060G>A EPO) [127]. In contrast, others are a collective group of genetically distinct immune system diseases with a common laboratory immunological phenotype. Horwitz et al. [60] note that three variants of PMD are possible according to the heterogeneity of the genetic nature: monogenerational patterns of inheritance consistent with single gene (only one mutation in only one gene; example, EPOD) [126,127], multigenerational patterns of inheritance consistent with single gene (different mutations in only one gene; example, mutations in the ELANE gene in CyN) [135], and multigenerational patterns of inheritance consistent with different genes (different genetic abnormalities in different genes; example, SIgAD) [136]. Mutations in the same gene can lead to different immunological phenotypes, for example, IGLL1 (Immunoglobulin lambda like polypeptide 1) variants are widely manifested from the agammaglobulinemia phenotype to manifestations of THI [137]. Heterogeneous genetic abnormalities can cause the same immunological phenotypes, for example, SIgAD can be caused by both trisomy of the X chromosome [138] and deletion of the constant region of the alpha gene of the IgA molecule [106].

According to the Clinical Picture

As noted by Fekrvand et al., PMDs are multi-complex diseases with compound pathogenesis and associated clinical phenotype [139]. From a clinical point of view, PMD is a multifaceted phenomenon ("different faces" according to Vinci et al. [140]) and has a highly personalized course ("individual natural history" according to Fattizzo et al. [141]). It is possible to distinguish asymptomatic [142] and symptomatic [143] forms of PMD in humans. The phenomenon of asymptomatic should be considered exclusively as a dynamic, not a static phenomenon (sudden clinical manifestation of previously asymptomatic PMD is possible at any time [142]). Asymptomatic should not be confused with compensation of the pathological process in PMD (for example, a multivariate profile of autoantibody production [143] or the formation of intestinal dysbiosis [144] is possible even in the asymptomatic phase of PMD).

Yazdani et al., considering the phenomenon of heterogeneity of the clinical picture, propose a classification of PMD according to the current clinical phenotype using SIgAD as an example, distinguishing asymptomatic, minor infections, allergic, autoimmune, and severe phenotypes of the immune system disease [145]. Régent et al., using ICD4+TL as an example, distinguish such clinical forms as opportunistic infections, autoimmune syndromes, malignancies, and mild or no symptoms [146]. Picado et al., using SIgED as an example, described infectious, autoimmune, allergic, and oncological forms of the disease according to clinical manifestations [147]. In addition, the authors have distinguished the concepts of clinically isolated forms, when only one clinical syndrome manifests,

and combined forms, when several syndromes develop [147]. In combined forms of PMD, the combination of syndromes can be monomodal, when the combined syndromes have the same nature (modality), for example, two different autoimmune syndromes [148], and polymodal, when syndromes of different natures are combined [13]. As Picado et al. found, isolated monomodal autoimmune syndromes in SIgED occur in 19%, and combined monomodal autoimmune syndromes in 15% of cases [147].

Picado et al. also introduced the concept of a spectrum of disease manifestations in PMD [147]. Some PMDs have a narrow spectrum of manifestations, manifesting almost exclusively as a monosyndromic phenomenon. An example is MPOD, in which only candidiasis manifestations often develop [149]. Other PMDs are characterized by an oligosyndromic spectrum of manifestations, which includes a clearly defined list of several syndromes, such as FBN, when ulcerative stomatitis, oral candidiasis, and periodontitis develop [150]. Most PMDs are polysyndromic phenomena with the principle of universality of clinical manifestations. Some PMDs, such as EPOD [127], are still considered asymptomatic phenomena, while many PMDs, such as SIgED, which were previously mistakenly considered asymptomatic, are now positioned as clinically manifest diseases in which severe clinical manifestations can develop, including oncological lesions [94].

Since partial clinical phenotypes are common in PMD, attempts have been made to subdivide these immune diseases by the affected compartments of the human body, for example, cutaneous or oral forms of SIgAD, in which lesions of the skin or oral cavity are almost exclusively noted [151], by the associated immune-dependent pathology, for example, primary immunodeficiencies in systemic lupus erythematosus [152], or even by a specific microbial factor, for example, SIgAD in the form of COVID-19-associated clinical consequences [153].

According to the Depth of the Immune Factor Damage

According to the depth of the immune factor damage, quantitative and qualitative forms of PMD can be distinguished. Some of the PMDs are monomodal phenomena under this heading, for example, MPOD is exclusively a qualitative PMD [149], and FBN [150] is only a quantitative disorder of neutrophils. However, many PMDs can be quantitative, qualitative, and combined (both quantitative and qualitative disorders). Orange proposed dividing NKD into quantitative, or classic (classic, cNKD) and qualitative, or functional (functional, fNKD) forms [64]. Abdalgani et al., having analyzed the data of 148 patients with NKD, showed that fNKD occurred in all examined individuals, and in 44% of cases a combined form was noted, since there were also signs of cNKD [154].

Quantitative PMD can be divided into partial [155] and total [74] forms according to the depth of the deficiency of the affected immune factor. Occasionally, total forms of PMD are designated as absolute [156] or severe [157]. In turn, partial PMD can also be divided into subnormal [158,159], moderate [160], and subtotal [74], and a subgroup PMD with zero value of affected immune factor is described as a complete [161] form of the disease. Dato et al. propose to designate subnormal PMD as borderline [162]. Qualitative PMDs are divided into moderate [163], profound [164], and complete [149] according to the depth of the decrease in the function of the affected immune factor (**Figure 2**).

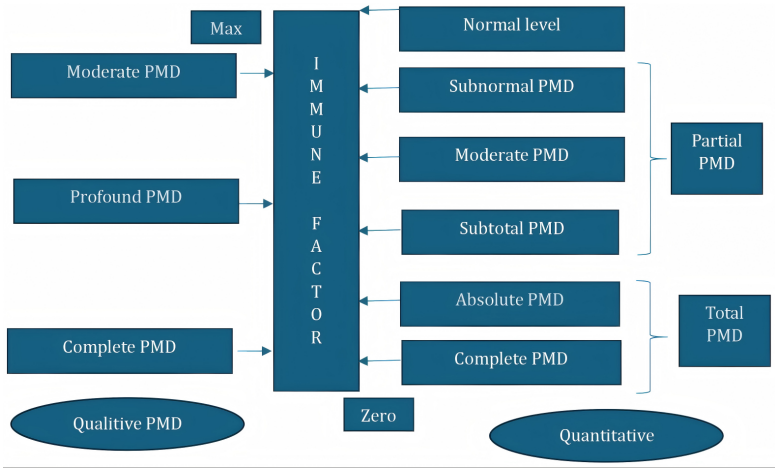

Figure 2. Correlation of different forms of quantitative and qualitative PMD by the depth of deficiency of the affected immune factor.

For each nosological unit, its criteria for the distribution of immunodeficiency according to the depth of damage to the immune factor have been proposed. However, not all of the proposed classification boundaries are generally accepted. For example, in SIgAD, the partial form is diagnosed when the serum IgA concentration is below 0.6 g/l (PIgAD), and the total form is below 0.07 g/l (SIgAD), and both forms are clinically manifest [155]. It is important to note that all forms of PMD can be clinically significant—from subnormal to complete [158,159], therefore, due attention should be paid to even small deviations in immunological indicators in patients with PMD [26]. The use of reductionist approaches, where only one form of PMD is recognized, mostly only complete, leads to the diagnosis of many clinically manifest unclassified forms of PMD, as seen in the example of SIgMD [165], falsely presenting a phenomenon common in the population as a rare pathology [166]. However, the principle of nonlinearity may be valid, where subnormal PMD leads to severe clinical manifestations [158,159], while complete PMD remains an asymptomatic phenomenon [127], justifying a personalized approach to the clinical management of patients with PMD.

According to the Severity of the Patient's Condition

The allocation of this category separately from the clinical picture and the depth of the immune factor damage is justified by the fact that the clinical picture does not directly correlate with the depth of the immune factor lesion, and the severity of the patient's condition—with the severity of the clinical picture caused by PMD, since the overall severity of the patient's condition is also influenced by other factors, such as comorbid pathology, age, gender, race, ethnic characteristics, timeliness of diagnosis, and availability of therapeutic interventions.

Li et al. substantiate the concept of severity of immunodeficiency [53]. According to the severity of the patient's condition, mild [20], moderate [167], and severe [167] forms of PMD can be distinguished. However, a mechanistic approach to assessing the severity of PMD should be avoided due to the variability of the clinical course of these diseases. Thus, the combination of ICD4+TCL and SIgAD can have a long asymptomatic course [168], while the deficiency of only one minority subclass of IgG4 is associated with persistently recurrent respiratory infections [169]. The severity of PMD is determined not only by the functional purpose of the lost immune factor, but also by the characteristics of the host organism and the influence of the external environment, which leads to the phenomenon of discrepancy between clinical and immunological phenotypes in PMD [170]. Therefore, it is more correct to speak of a severe patient with PMD rather than to speak of severe PMD per se [167].

By Duration of Existence of Immunological Phenotype

The vast majority of PMDs are permanent phenomena, since the representative immunological phenotype, undergoing some changes, persists throughout the life of the host (persistent forms) [171]. However, in some PMDs, the temporality of the existence of the representative immunological phenotype (transitory forms) is noted [171]. In turn, transient forms of PMD can be obligate, when the disappearance or transformation of the representative immunological phenotype over a certain time is an obligatory feature, as, for example, in THI, when hypogammaglobulinemia must be compensated by the age of three years of the child [84], and facultative, in which the disappearance or transformation of the representative immunological phenotype of PMD is possible, but not obligatory. Facultative transient forms have been described in many PMDs, and both a reduction (positive scenario) and an increase (negative scenario) in the severity of the representative immunological phenotype as it transforms over time can be observed. For example, SIgAD can sometimes dramatically evolve to common variable immunodeficiency with a hypogammaglobulinemic picture [172], and, conversely, a pre-existing common variable immunodeficiency phenotype can spontaneously or be induced to reduce to a limited SIgAD phenotype with normalization of previously reduced serum concentrations of immunoglobulins of other classes [173].

According to the Evolutionary Scenario of Development

The allocation of this heading separately from the time of existence of the immunological phenotype is dictated by the need to emphasize the fact that not only transient, but also persistent forms of PMV are not static, but a completely dynamic phenomenon that is constantly changing over time. A favorable course of the disease by the time of contacting a doctor does not mean a guarantee of a further favorable prognosis of the disease. Often, in the clinic, such patients are marked as healthy based on a favorable previous course of PMD, which leads to their exclusion from follow-up observation, making it impossible to respond promptly when the scenario of events changes.

It is a mistake to consider PMD as a static immunological phenomenon. Sgrulletti et al. introduce the concept of an evolutionary scenario of PMD development during human ontogenesis, which may have an impact on the risk and manner of clinical manifestation of the disease [174]. Instead, Kazi et al. propose an alternative term

to denote a similar phenomenon—temporal patterns of PMD [175]. These evolutionary scenarios/temporal patterns are quite diverse and are determined not so much by the nosological form of PMD as by the host organism, i.e., they are individual. Persistent and transient forms of PMD were discussed above. In the case of a transient immunological phenotype, intra- and inter-nosological drift of the immunological phenotype of PMD is possible. With intra-nosological drift, only the form, but not the nosological unit of PMD, can change. An example is the transformation of total SIgAD into partial SIgAD in childhood, which is a measure of the maturation of the immune system [176]. In inter-nosological drift, changes in the immunological phenotype during PMD transformation are so profound that, as a result of their implementation, a picture of another immunodeficiency is formed. An example is the evolution of the SIgAD phenotype to common variable immunodeficiency with a decrease in serum concentrations of all classes of immunoglobulins, not just IgA [172]. Suppose during the evolutionary scenario there is a complete normalization of the immunological phenotype, then we speak of reversal forms [176], while with a deepening deficiency of the affected immune system factor, we speak of progressive forms of PMD [177]. However, normalization of the content of the affected immune factor in PMD does not necessarily mean clinical recovery of the patient, since the causative pathological gene can manifest itself differently both within the immune system and outside it. Therefore, the closest relatives of patients with verified PMD, as shown by the results of some studies, also have an abnormally increased frequency of associated immune-dependent syndromes, even if they do not form the immunological phenotype of PMD [122,163].

Kazi et al. using the example of SIgED proposed a classification of PMD according to the evolutionary scenario of events, distinguishing chronic, when the depth of the immune factor deficiency is almost the same in different periods of ontogenesis, oscillating, when this depth changes significantly throughout life in different directions, newly diagnosed with a still unknown further development scenario, and normalized forms of the disease with a gradual approach of the affected immune indicator to the normal level during a certain period of ontogenesis [175]. Nunes-Santos et al. introduce the term "newly described primary immunodeficiency" [40], emphasizing uncertainty about the evolutionary scenarios of the development of such forms of disease due to the lack of a sufficient number of clinical reports (**Figure 3**).

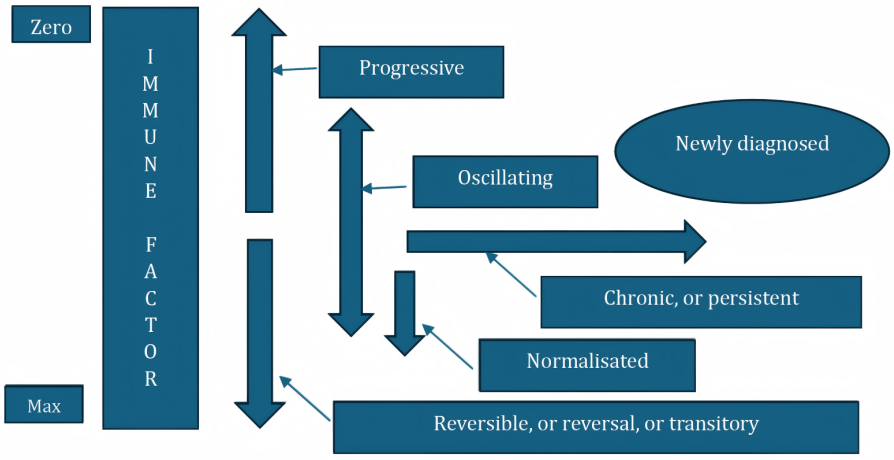

Figure 3. Variety of evolutionary scenarios for PMD development by the number of affected immune factors.

Lougaris et al., having analyzed the clinical data of 184 patients with SIgAD, demonstrated different trajectories of the evolutionary scenario of the development of newly diagnosed total SIgAD during long-term follow-up. In 85% of cases, chronic immunodeficiency was noted with the preservation of the immunophenotype of total SIgAD, in 9% of cases, normalizing SIgAD with the transformation of total into partial SIgAD (incomplete variant of normalizing PMD) took place, in 4% of cases, the serum IgA concentration eventually reached the lower limit of the age norm (complete variant of normalizing PMD). In 2% of cases, progressive SIgAD was noted with the gradual formation of the phenotype of common variable immunodeficiency [120].

By Regularity of the Disease

Although most PMDs have a persistent immunological phenotype, clinical manifestations are mostly formed

only from time to time, at irregular intervals—the so-called "light periods" (irregular forms). However, in some PMDs, the regular periodicity of laboratory and/or clinical manifestations can be a key feature of the disease (cyclic forms). An example is CyN, in which so-called neutropenic crises with signs of inflammation and bacterial infections are formed almost at regular 21-day intervals [178].

By Spread of the Damage Across the Immune System

Although most PMDs concern primarily the damage to systemic immunity, and local immunity is involved secondarily due to the weakened supply of immune factors from the systemic circulation, there are such forms of PMD when only systemic or local immunity is affected. SsIgAD is an example of an isolated lesion of local mucosal immunity, since in such patients the synthesis of the secretory component by epithelial cells of the mucous membranes is impaired, and not the IgA molecule itself by plasma cells of the lymphoid organs [93]. Salomon et al., studying data on 1300 infants with recurrent respiratory infections, found IgA deficiency in serum and secretions in 11, only in serum = in 9, and only in secretions in 6 children [179].

By Combination With Other Diseases

PMDs are most often isolated [98] or selective [147] phenomena. Although the term "selective" is more often used than "isolated", in our opinion it is more appropriate to use the term "isolated" to avoid confusion with the so-called selective primary immunodeficiencies with a predisposition to only one microbe, for example, primary deficiency of the TLR3 molecule with a picture of temporal necrotizing hemorrhagic encephalitis caused by herpes simplex virus type 1 [180].

There are also reports of combined [81,181] forms of PMD, when two or more diseases of the immune system are simultaneously noted in one patient. Since the final phenotype of combined forms may not be a simple sum of the phenotypes of each of the PMDs due to the phenomenon of interaction [77]. Therefore, Hogendorf et al. propose to call such cases not combined, but complex (several PMDs aggravate and or negatively transform clinical status by interplaying with each other) [182], Erkoçoğlu et al.—concurrent (several PMDs weaken each other by concurrent relationships) [183], and Mannes et al.—multidimensional (several PMDs form separate clinical phenotypes that coexist in one person as present or hidden manifestations) [81] immunodeficiencies. Abraitytė et al. call such forms of immunodeficiencies "unexpected combinations", since the detection of only one immunodeficiency from the combination often leads to premature termination of the diagnostic search due to the formation of the illusion of definitive clarification of the cause of the immune-dependent pathology [184].

Currently, 4 forms of disease combinations involving PMD are known: (1) with other genetic diseases associated with immunosuppression, such as SIgAD with idiopathic pulmonary hemosiderosis [183], (2) with classic PID, such as chronic granulomatous disease and SIgAD [185], (3) with other PMD, such as the combination of SIgMD and SIgG4SD [186], and (4) with secondary immunodeficiencies, such as the combination of AIDS and SMBLD [187], which affects the risk, nature, and severity of associated immune-dependent syndromes and sensitivity to treatment.

When it comes to the combination of different PMDs in one patient, one should distinguish between combinations of different PMDs with damage to one branch of immune system, for example, phagocytosis in the combination of MPOD and CyN [178] (monomodal), and different branches of immune systems, for example, the complement system as a part of innate immunity and the humoral part of adaptive immunity in the combination of SMBLD and SIgGSD [188] (bimodal heterogeneous combinations) or the cellular and humoral part of adaptive immunity in the combination of ICD4+TCL and SIgAD (bimodal homogeneous combinations) [168]. It is possible to combine not only two, but many different PMDs in one patient in an arbitrary manner (polymodal homo- and heterogeneous combinations). For example, Bijker et al. reported the simultaneous presence of SIgMD, NKD, and SPAD in the same patient with invasive pneumococcal infection [189]. A distinction should be made between cases of a single immunodeficiency with the phenotype of several PMDs (pseudocombinations), for example, the combination of SIgAD and SIgED with a hypomorphic mutation in the DCLRE1C gene (DNA Cross-Link Repair 1C) [190], and combinations of several independent genetically heterogeneous PMDs, such as the combination of C6D and C7D caused by two independent mutations in the C6 and C7 genes in one patient [191] (true combinations). The distinction between true and pseudo combinations may have not only academic but also purely practical significance, for example, when considering gene therapy, in which, in the case of pseudo combinations, only one corrected gene can be introduced into the genome, regardless of the associated number of affected immune factors, while in the case of a true combination, replacing only one of the affected genes will not provide the full clinical effect.

When talking about the combination of PMD and secondary immunodeficiency, one should distinguish between the combination of unrelated diseases, as discussed above regarding the combination of AIDS and SMBLD [187], and the related PMD and secondary immunodeficiency, which is essentially a consequence of PMD. Thus, it has been shown that SsIgG2D can lead to the production of autoantibodies to IgA molecules with the formation of secondary IgA deficiency [50], and ICD4+TCL—to the production of autoantibodies to gamma interferon [51], which expands the immunological phenotype of cellular PMD.

Wang et al describe the phenomenon of "hidden in the absence" [52], and Huynh et al. – "lost and found" [57], when the causal PMD dissolves in the broader immunological phenotype of induced secondary immunodeficiency, which developed both because of PMD-associated immune-dependent pathology [52], and in an independent manner [57].

By Curability

For the vast majority of PMD, basic immunotherapy has been developed that can compensate for the disease. In such cases, one speaks of "druggable" [192] or "treatable" [193] forms of PMD; for example, immunoglobulin therapy may be useful in humoral immunodeficiencies [194]. Only a minority of PMD can currently be considered an incurable pathology.

By Special Rubrics

So far, universal classification rubrics have been discussed, but for some PMDs, special criteria for sub-grouping have been proposed based on specific disease attributes. For example, in CBN, it is proposed to distinguish normoplastic and hypoplastic forms of immunodeficiency based on the state of the red bone marrow [195]. In SIgAD, it is recommended to distinguish between types I and II of the disease based on the number of memory B cells [196].

This classification focuses on the general attributes that are common to all, or at least most, PMD, and indicates the presence of special rubrics in general, without delving into each nosological unit. The above are only examples of the presence of special rubrics within individual nosological units that cannot be transferred to others. The examples given are demonstrated only for illustrative purposes and do not claim to be an exhaustive analysis of the diversity of PMD by specific attributes. It is necessary to develop secondary special classifications, based on the currently presented primary general classification, which would apply separately to each nosological unit and in which special rubrics for each disease of the immune system would be considered in detail, taking into account its specificity, which distinguishes it from other nosologies. The development of secondary classifications is possible after the publication, discussion, refinement, scientific acceptance, and clinical implementation of the currently proposed primary classification, and is not the aim of this study.

4.2.2. Critical Analysis of Classification

The presented classification is developed as an exhaustive analysis of potential nomenclature headings related to PMD in humans proposed from 1980 to 2025 (**Table 2**). The work focuses on the novelty and exhaustiveness of the analysis of the accumulated ideas about the diversity and heterogeneity of PMD according to laboratory and clinical attributes. The classification does not contain new terms specially developed by the authors of this article, but only systematizes the terminology that has already been proposed and substantiated by other author groups over 45 years of clinical research and observations. So far, no attempt has been made to systematize the accumulated knowledge, and no classification of PMD has been developed. It is also important to analyze all the data to draw a common conclusion from our long-term scientific research, demonstrating our current position in studying the phenomenology of PMD. That is why the format of systematic analysis was chosen, which ensures the completeness of the presentation of substantiated data for a certain period without artificial limitations. These complete data are useful for theoretical medicine and further planning of clinical research, since scientific research is always aimed at a comprehensive study of the problem, no matter how complex and unusual it may be. We understand that due to the completeness of the analysis of the material over a very long period, the classification turned out to be cumbersome and difficult for clinical medicine, which may complicate its implementation in the therapeutic and diagnostic process. In contrast to theoretical medicine, a utilitarian approach is very flawed in clinical practice, ensuring the use of the most clinically relevant rubrics that have the greatest impact on the assessment of the patient's condition and clinical decision-making. Further broad discussions are needed on which of the proposed rubrics are more useful and informative for clinical practice, and which do not carry a special practical burden. Such decisions can be made in the future on a collegial basis by professional communities of specialists in clinical immunology after

an appropriate period of scientific discussion and debate. However, in order to draw attractive clinical conclusions, one should be based on the primary comprehensive material, which is what this systematic review provides.

4.2.3. Validation of Classification

The proposed rubrics and subgroups within the selected rubrics have been published and properly substantiated by various research groups in peer-reviewed medical journals, and therefore can be considered scientific. However, the question of validation of each of the selected subgroups and determination of relevance remains open. The development of a comprehensive classification not only enriches us with theoretical knowledge about the diversity of PMD but also paves the way for a rational organization of the validation process as criteria for diagnosing PMD, as well as the proposed classification rubrics and subgroups within them. Extensive studies applying its retrospective design to large PMD cohorts, using modern design and methods of statistical analysis, artificial intelligence technology are needed to validate key aspects of the heterogeneity of the PMD phenomenon, which are reflected in the presented work. In the future, it is necessary to create prospective registries, with which experts could find consensus decisions based on the accumulated evidence. Without an initial delineation of the phenomenon of PMD and the development of an initial classification format, a consistent and exhaustive process of validation of the proposed criteria and classification rubrics is not possible. Therefore, the presented work can be a foundation for initiating further studies on the validation of the obtained data.

4.2.4. Ways of Classification Implementation

Although the proposed rubrics require further validation, the evidence base accumulated to date over 45 years of scientific research allows for the clinical application of the presented classification, which would allow determining the etiology of immune-dependent syndromes and integrating into common phenotypes heterogeneous immune-mediated lesions, previously considered as independent diseases. This would provide a multidisciplinary personalized approach to patient management with better clinical outcomes. Special educational programs realisation, changes in current diagnostic and treatment algorithms, including new data to electronic health record templates and statistical records forms, could facilitate using this classification in clinical practice. They would improve the quality of medical care for a wide range of patients with PMD-associated immune-dependent lesions.

5. The Significance of the Developed Classification in Clinical Practice, Advantages and Disadvantages, Directions of Further Research

This work aimed to systematize knowledge about PMD in humans. This may be useful for basic science and practicing physicians involved in immune-dependent pathology. It has now been established that PMD is a fairly common and heterogeneous phenomenon in clinical practice, which, however, is still rarely 6diagnosed [197]. Louis et al. rightly refer to PMD as an ignored disease of the immune system [198]. The introduction of a substantiated classification may contribute to both a better understanding of the phenomenology of PMD in humans and a more frequent diagnosis of these immunodeficiencies by clinicians. This would allow determining the etiology of various associated immune-dependent syndromes, which would affect the effectiveness of therapeutic and preventive interventions. The introduction of new standardized diagnostic tests demonstrates a trend towards an increase in the frequency of diagnosing PMD in patients with immune-dependent pathology [199,200]. Boz et al. indicate many hidden monogenic diseases of the immune system among the common immune-dependent syndromes that are treated by medical specialists of various profiles [192]. Chennapragada et al. indicate the need to establish real-world data on the prevalence of several PMDs, which remain unspecified [201]. Taietti et al. indicate that despite the accumulated large evidence base, the doctrine of PMD is not without gaps and controversies [89]. The classification proposed in this article can help to better understand the current state of the evidence base by structuring a large layer of information under representative classification headings, identify both the most significant achievements and gaps in knowledge and fundamental contradictions, identify the most promising areas of further research, and be a convenient tool for planning, conducting, and evaluating the results of clinical trials in the field of PMD in humans. This will help not only to prescribe basic immunotherapy to patients with a verified diagnosis of PMD, but also to implement personalized treatment strategies for associated immune-dependent pathology according to the causative PMD, such as intravenous immunoglobulin therapy for the treatment of refractory bronchial

asthma in patients with SIgGSD [83] or recombinant human gamma-interferon for inflammatory skin lesions in a patient with MPEG1/Perforin-2 Haploinsufficiency [72].

Despite the obvious differences in the main clinical features, it is often difficult to distinguish between classical primary immunodeficiencies and PMD, since sometimes atypically forms of classical primary immunodeficiencies occur with unexpectedly mild clinical and laboratory phenotypes, as, in the case of a new mutation of the BTK gene (Bruton tyrosine kinase), when instead of typical agammaglobulinemia, the SIgMD phenotype is formed [202]. PMD, on the contrary, can acquire abnormally severe forms, imitating the clinical picture and immunological laboratory profile of classical immunodeficiency, as, a case of staphylococcal infection of the deep tissues of the neck and associated sepsis in a child with THI, which resembled Bruton's disease [203].

Further clinical research on PMD is needed to clarify the diversity of these diseases and their main clinical attributes, to improve laboratory approaches to diagnosis, tools for prognosis and prevention, and to deepen understanding of the differences with classical immunodeficiencies to improve classification rubrics. However, it is already possible to present a useful classification of PMD in humans for clinical practice, which may improve the diagnosis of common immune system diseases in the population [204].

6. Conclusion

This article substantiates the phenomenon of PMD and presents a modern, comprehensive classification of the currently known PMDs in humans. In this classification, PMDs are presented as various multicomplex diseases of the immune system with multidimensional clinical manifestations and an individualized natural course, common in populations. These data are important for theoretical medicine, as they deepen modern ideas about the heterogeneity of the phenomenon of immunocompromise and open the way for expanding the search field for conducting clinical studies in the field of immunodependent pathology [205,206]. For practical medicine, the importance of such a classification is difficult to overestimate, since the introduction of the concept of PMD revolutionizes the approaches to the detection and management of diseases of the immune system in humans, transferring the phenomenon of primary immunodeficiency from the zone of rare clinical outbreaks to routine clinical practice [207,208]. The use of the classification will allow identifying the cause of the development of many immunodependent syndromes, which have so far been considered idiopathic. This means that such patients can be offered not only pathogenetic and symptomatic, but also etiotropic treatment. The classification will allow us to rationalize both the diagnostic and therapeutic process, integrating into a single phenotype diverse immune-dependent syndromes, which until now were considered separately from each other. This is the way to the effective functioning of multidisciplinary medical teams and the implementation of integrative and individualized medicine approaches, which take into account the characteristics of each specific patient, ensuring a higher level of medical care. However, despite significant progress, it is necessary to conduct additional clinical studies to identify new forms of PMD, check the complexity of current PMD diversity, and validate and assess the relevance of the already proposed diagnostic criteria, classification rubrics, and subgroups within them.

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Conflicts of Interest

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