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Global overview of primary immunodeficiencies: a report from Jeffrey Modell Centers worldwide focused on diagnosis, treatment, and discovery

Vicki Modell · Megan Knaus · Fred Modell · Chaim Roifman · Jordan Orange · Luigi D. Notarangelo

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Abstract Primary immunodeficiencies (PI) are defects of the immune system that cause severe infections if not diagnosed and treated appropriately. Many patients with PI are undiagnosed, under-diagnosed, or misdiagnosed. Over the last decade, the Jeffrey Modell Foundation has implemented a Physician Education and Public Awareness Campaign (PEPAC) to raise awareness, assure early diagnosis, appropriate treatment, and management, with the overall goal to reduce morbidities and mortalities related to PI. In order to evaluate the PEPAC program, data are requested annually from physician experts within the Jeffrey Modell Centers Network (JMCN). The JMCN, consisting of 556 expert physicians, at 234 academic institutions, in 196 cities, and 78 countries spanning six continents, provides the infrastructure for referral, diagnosis, and appropriate treatment for patients with PI. In addition, the JMCN has made a significant contribution to the field of immunology with the discovery of new genes at the centers. These advancements have led to an overall better understanding of the immune system and will continue to improve quality of life of those with PI.

Keywords Primary immunodeficiencies (PI) · Jeffrey Modell Foundation (JMF) · Jeffrey Modell Centers Network (JMCN) · Awareness · Education · Diagnosis · Treatment · Gene discovery

Abbreviations

PI	Primary immunodeficiencies
JMF	The Jeffrey Modell Foundation
PEPAC	Physician Education and Public Awareness Campaign
JMCN	Jeffrey Modell Centers Network
SCID	Severe combined immunodeficiency
IUIS	International Union of Immunological Societies
HSCT	Hematopoietic stem cell transplantation
CVID	Common variable immunodeficiency
IG	Immunoglobulin therapy
IVIG	Intravenous immunoglobulin therapy
SCIG	Subcutaneous immunoglobulin therapy
WAS	Wiskott–Aldrich syndrome
MUD	Matched unrelated donors

Introduction

Primary immunodeficiencies (PI) [1, 2] are genetic defects of the immune system that result in chronic, serious, and often life-threatening infections, if not diagnosed and treated [3, 4]. Recent studies have shown that PI may be more common than previously estimated [5], and that 1–2 % of the population may be affected with a PI when all types and varieties are considered [6]. Over the last decade,

V. Modell · M. Knaus · F. Modell (✉)
Jeffrey Modell Foundation, 780 Third Avenue, 47th Floor, New York City, NY 10017, USA
e-mail: fmodell@jmfworld.org

C. Roifman
Hospital for Sick Children, University of Toronto, Toronto, ON, Canada

J. Orange
Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA

L. D. Notarangelo
Division of Immunology, Boston Children's Hospital, Boston, MA, USA

improvements in molecular diagnosis, genetic sequencing, and cutting edge treatments have led to a better understanding of the immune system, as well as improved quality of life for those living with PI. However, awareness of PI among physicians and the general public remains challenging and there continues to be a need for appropriate and timely management of these conditions [7, 8].

In order to raise awareness of PI with the overall goal to reduce associated morbidity and mortality, the Jeffrey Modell Foundation (JMF) established the Physician Education and Public Awareness Campaign (PEPAC) in 2003 [7, 8]. The PEPAC program has been expanded globally throughout the last decade. The main objectives of the program are to (1) identify patients with PI as early as possible, (2) refer "at-risk" patients to specialized healthcare institutions in the Jeffrey Modell Centers Network (JMCN) worldwide, (3) diagnose patients precisely in order to identify specific defects, and (4) treat the defects effectively [7, 8].

The program's target audience includes primary care physicians, family practitioners, pediatricians, subspecialists, emergency room physicians, school nurses, registered nurses, third-party payers, patients, government, and the public [7, 8]. Educational materials such as the 10 Warning Signs of PI, the physician algorithm for PI, and graphic posters of the immune system were developed and disseminated by JMF. Symposia and continuing medical education activities, informational websites, KIDS days, World Immunology Network (WIN) grant support for patients and clinical professionals, and public service advertising are all components of the PEPAC program that assist in achieving the intended goals and objectives [7, 8].

The JMCN provides the infrastructure appropriate for referral, diagnosis, and treatments. Currently, JMCN consists of 556 expert physicians at 234 institutions, in 196 cities, and 78 countries spanning six continents. In order to provide data to measure effectiveness of the PEPAC program, JMF developed a survey for physician experts within the JMCN to report on the number of patients identified with PI, and the treatment modalities. In 2009 and 2011, JMF reported results of the data provided by the physician experts within the Network. A similar survey was developed and data collection was conducted in 2012 and 2013 to update the impact of the PEPAC program and the growing number of patients identified with PI worldwide [7, 8].

The JMF is committed to early diagnosis, meaningful treatments and, ultimately, cures through basic and clinical research, physician education, public awareness, advocacy, patient support, and newborn screening. The JMCN has collectively contributed many new gene discoveries underlying PI that have impacted an understanding of the mechanisms of disease and provided new hopes for accelerated diagnosis and rational therapies. Increasing knowledge of the function of the immune system has significant potential to impact not only the field of PI and immunology, but other related fields in which diseases result from the immunological inadequacies such as allergy, rheumatology, oncology, and infectious disease [9].

Methods

Center surveys

The JMF survey on PI was developed using the categories and gene defects identified by the International Union of Immunological Societies (IUIS) Expert Committee Classification of PI [10]. Survey data were requested in 2012. An updated survey was sent to the JMCN in 2013, requesting current data. The revisions incorporated five new gene defects known to cause PI and an optional demographics section. Each JMCN Center Director was asked to provide information on the number of patients followed with a primary immunodeficiency, the number of patients identified with specific defects, and the number of patients referred to each institution. Specific PI diagnoses were grouped by the IUIS classifications and analyzed. Physicians were given the opportunity to list "unspecified" or "other deficiencies" for any additional gene mutations not listed in the survey. Reports of specific defects were analyzed regionally, and by frequency of defects. Data collected within the period of 2012–2013 were compared to data obtained from previous surveys received in 2011, 2009, and 2004 [7, 8].

The JMF survey also included questions assessing immunoglobulin therapies. Specifically, the survey included data fields to determine the number of patients receiving immunoglobulin therapy intravenously (in the clinic or at home), by subcutaneous administration, or other methods of administration. Information was also requested on the number of patients treated by hematopoietic stem cell transplantation (HCST) or thymus transplantation, including donor type and stem cell source, as well as patients experimentally treated with gene therapy.

An optional demographics portion was included in the 2013 JMF survey. Physicians had the opportunity to provide data on gender and age of patients treated at each center.

Results

Center surveys

Surveys were sent to physicians at the 234 centers within the JMCN. A total of 225 surveys were completed and

analyzed from 78 countries spanning six continents. Physicians reported a total of 138,847 patients followed. A total of 77,193 of these patients were identified as having a specific named PI disease, and 64,822 patients were referred to a JMCN institution (Fig. 1). There has been continuous growth of patients followed, identified, and referred since the inception of the program. The distribution of patients with PI varies by geographical region. Figure 2 illustrates the distribution of patients categorized into the eight major subgroups of PI as classified by the IUIS [10]. Globally, the subgroup "predominantly antibody deficiencies" was the most common, with a total of 48.6 % of patients identified, followed by "well-defined immunodeficiency syndromes," with 14.2 % of patients identified. Internationally, reporting of "autoinflammatory disorders" (9.8 %),"complement deficiencies" (7.4 %), "combined T and B cell immunodeficiencies" (6.7 %), and "congenital defects of phagocyte numbers and function" (6.5 %) was more common than in the USA, whereas "other unspecified deficiencies" (8.4 %) and "diseases of immune dysregulation" (5.4 %) were more commonly identified in the USA than internationally. A thorough report of the total number of each defect identified at JMCN centers is reported in "Appendix 1." A regional breakdown is provided in "Appendix 2." The prevalence of 90 specific defects listed from highest frequency to lowest frequency is illustrated in "Appendix 3."

Demographic data reported by select physicians presented differences in gender and age. Fifty-seven percent of patients reported were male, and a total of 62 % of patients identified were in the pediatric age range of less than 1–19 years old (see Fig. 3).

The 15 most commonly identified specific defects comprise 68.1 % of all defects reported (Table 1). There was substantial variation in the prevalence of the 15 most common PI observed across geographical regions. In the USA, Canada, and Africa, common variable immunodeficiency (CVID) was the most frequently reported (3,151, 579, and 146 patients, respectively). In Latin America and Western Europe, IgA deficiency was most frequently reported (1,050 and 3,605 patients, respectively). In Eastern Europe, the Middle East, and Asia, hypogammaglobulinemia of infancy (1,895 patients), Familial Mediterranean fever (1,601 patients), and Agammagloblulnemia of X-linked pattern inheritance (230 patients) were the most frequently reported, respectively.

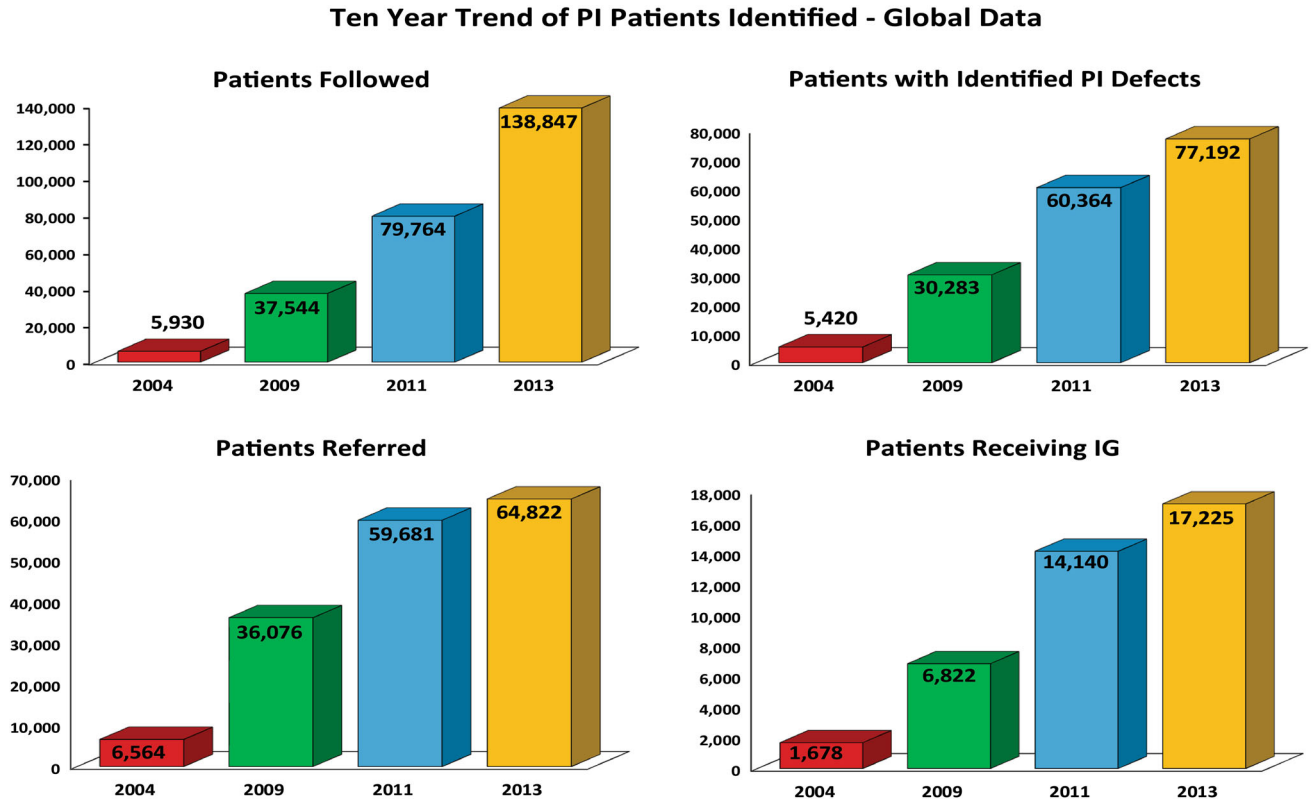

Fig. 1 Ten-year trend of patients followed, identified, referred, and treated. This figure shows a 10-year trend of the number of patients followed with a suspected primary immunodeficiency, identified with specific primary immunodeficiency defects, referred to institutions within the Jeffrey Modell Centers Network, and received immunoglobulin therapy in 2004, 2009, 2011, and 2013

Categories	Global		US		International	
Combined T and B cell Immunodeficiencies	4,876	6.3%	1,251	5.5%	3,625	6.7%
Other Well Defined Immunodeficiency Syndromes	10,984	14.2%	4,755	20.9%	6,229	11.4%
Predominantly Antibody Deficiencies	37,532	48.6%	10,783	47.3%	26,749	49.2%
Diseases of Immune Dysregulaton	2,833	3.7%	1,228	5.4%	1,605	2.9%
Congenital defects of Phagocyte Numbers and Function	4,649	6.0%	1,129	5.0%	3,520	6.5%
Defects in Innate Immunity	924	1.2%	266	1.2%	658	1.2%
Autoinflammatory Disorders	6,001	7.8%	642	2.8%	5,359	9.8%
Complement Deficiencies	4,810	6.2%	807	3.5%	4,003	7.4%
Other Unspecified Deficiencies	4,584	5.9%	1,920	8.4%	2,664	4.9%
Total	**77,193**		**22,781**		**54,412**	

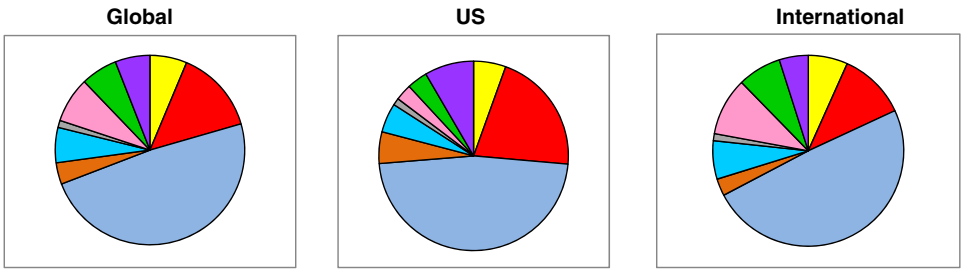

Fig. 2 Major categories of PI. This figure represents the distribution and percentages of patients diagnosed with primary immunodeficiency, using the categories identified by the International Union of Immunological Societies Expert Committee classification of primary immunodeficiencies [10]. Graphical representations are presented to show distribution globally, in the USA, and internationally

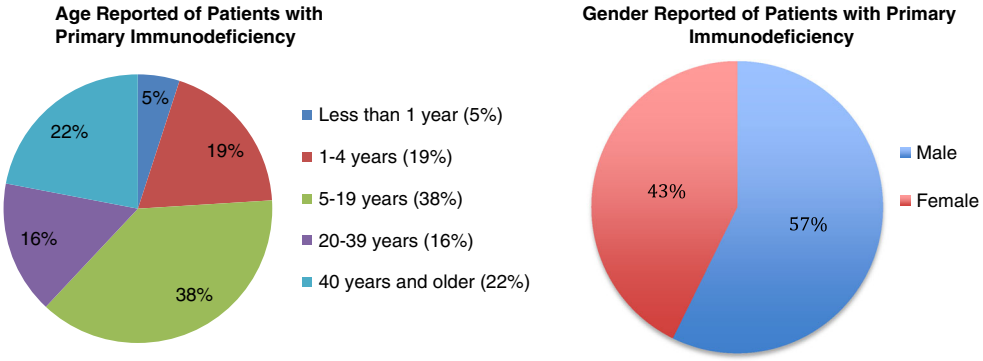

Fig. 3 Demographics reported of patients with primary immunodeficiency. This figure shows the distribution of age and gender of patients diagnosed with primary immunodeficiency as reported by physicians within the Jeffrey Modell Centers Network. Patients aged 5–19 years old (38 %), and males (57 %) were most commonly reported as diagnosed with a primary immunodeficiency

In order to measure the growth of the PEPAC program, data collected in 2013 on the number of patients followed, the number of patients identified with a specific defect, and the number of patients referred were compared to previous data reported in 2011. Table 2 reports that the number of patients followed increased by 74 %, the number of patients identified with a specific defect increased by 27.9 %, and the number of patients referred increased by 8.6 %.

Treatment route and modalities in patients with PI

Antibody deficiencies are the most commonly diagnosed category of primary immunodeficiencies (48.6 %). Treatment with immunoglobulin replacement therapy (IG) has been highly successful in preventing and managing patients' susceptibility to infections [11–15]. Immunoglobulin therapy is most commonly administered through the intravenous route (IVIG). Subcutaneous immunoglobulin therapy

Table 1 Fifteen PI defects identified globally by region

	US	Canada	Latin America	Western Europe	Eastern Europe	Middle East	Asia	Australia	Africa	Total
1 Common variable immunodeficiency (CVID)	3,151	579	465	2,983	842	277	134	5	146	8,582
2 IgA deficiency, selective	1,547	157	1,050	3,605	1,887	87	28	0	76	8,437
3 DiGeorge anomaly (Chrom 22qll.2 deletion syndrome)	2,905	274	253	1,175	497	72	89	8	39	5,312
4 IgG subclass deficiency, isolated	743	35	48	3,044	333	30	17	0	15	4,265
5 Hypogammaglobulinemia unspecified	1,786	86	329	780	698	32	10	13	37	3,771
6 Hypogammaglobulinemia of infancy (transient)	594	228	351	539	1,895	47	8	3	29	3,694
7 Specific antibody deficiency (normal Ig and B cells)	1,569	67	272	684	58	10	13	1	7	2,681
8 Familial Mediterranean fever	125	24	17	500	334	1,601	25	10	16	2,652
9 C1 inhibitor deficiency	292	52	41	1,533	512	23	23	0	52	2,528
10 Ataxia telangiectasia (A-T)	1,120	43	218	362	362	170	18	2	144	2,439
11 PFAPA syndrome	283	28	78	998	369	630	11	9	0	2,406
12 Agammaglobulinemia, (XLA)—BTK deficiency	449	57	270	606	307	106	230	3	36	2,064
13 Other combined immunodeficiencies	231	51	136	400	211	175	84	1	81	1,370
14 Other complement deficiencies	58	2	7	1,121	9	3	10	0	2	1,212
15 Chronic granulomatous disease, X-linked	196	31	125	366	97	181	126	4	3	1,129

The distribution of the 15 most commonly identified PI in the USA, Canada, Latin American countries, Western European countries, Eastern European countries, Middle Eastern countries, Asia, Australia, and Africa

Table 2 2013 data compared to 2011 data previously published [7]

	2011	2013	Increase (%)
Number of patients followed	79,764	138,847	74.1
Number of patients with an identified PI defect	60,364	77,193	27.9
Number of patients referred	59,681	64,822	8.6
Number of patients receiving IG	14,140	17,225	21.8

The reported total number of patients followed with a suspected primary immunodeficiency, identified with a specific primary immunodeficiency defect, referred to institutions within the JMCN, and receiving immunoglobulin therapy in 2011 and 2013. Percent increases are shown for data comparison

Table 3 Number of patients receiving IG—2013 data

IVIG-clinic	8,857	51 %
IVIG-home	4,298	25 %
SCIG	2,841	17 %
Other	1,229	7 %
Total	17,225	100 %

The total number of patients receiving immunoglobulin therapy (IG) in the clinic intravenously, at home intravenously, subcutaneously, and by other reported treatment route or modality

Table 4 Patients treated with IG in 2004, 2009, 2011, and 2013

No. of patients in 2004	No. of patients in 2009	No. of patients in 2011	No. of patients in 2013
1,678	6,822	14,140	17,225

The number of patients treated with immunoglobulin therapy in 2004, 2009, 2011, and 2013, as reported by physicians within the JMCN

(SCIG) offers a safe and efficacious alternative that is typically administered at home [16]. Patient preference, physical and financial access, cultural, and societal influences can impact the decision to receive care in the clinic or in the home [7]. The JMF survey requested data from physicians to provide patient information on route of transmission (IVIG, SCIG, other) and modalities (home, clinic). A total of 17,225 patients were reported as receiving immunoglobulin therapy, an increase by 22 % since 2011 data were provided. The majority of patients received immunoglobulin therapy through the intravenous route (76 %), while 17 % of patients received IG via the subcutaneous route (Table 3). Fifty-one percent of patients received IVIG in the clinic. A comparison of the total number of patients receiving IG therapy in 2004, 2009, 2011, and 2013 is shown in Table 4 [7, 8].

Patients identified with severe forms of PI, such as SCID, require more aggressive cellular therapies, such as

HSCT and gene therapy [17, 18]. Promising results have been obtained with gene therapy in some forms of SCID and in patients with Wiskott–Aldrich syndrome (WAS) [19, 20]. Physicians were asked to provide information regarding the type of cellular therapies their patients were receiving. A total of 2,049 patients received HSCT or thymus transplantation [21], representing a 98 % increase in patients transplanted. A total of 488 patients were treated with gene therapy, representing nearly a tenfold increase over the 1-year period since the prior survey (Table 5). Physicians provided data on donor type for 1,835 patients and stem cell source for 1,682 of the patients receiving transplantation (see Tables 6, 7). The majority of patients received transplantation from matched unrelated donors (MUD) (37.9 %) [22–24]. Bone marrow was the most common source of stem cells (61.1 %), although over 10 % of transplants for PI used cord blood-derived hematopoietic stem cells.

Table 5 Treatment by transplantation and gene therapy in 2011 and 2013

	2011	2013
Patients treated by transplant	1,036	2,049
Patients receiving gene therapy	53	488

The total number of patients with severe forms of primary immunodeficiency, such as severe combined immunodeficiency, that have received a hematopoietic stem cell or thymus transplant or have received gene therapy, as reported in 2011 and 2013

Table 6 Stem cell donor type data reported in 2013

	No. of patients
Matched related donor (MRD)	548
Matched unrelated donor (MUD)	695
Parental donor (Haplo)	429
Mismatched unrelated donor (mMUD)	163
Total	1,835

The distribution of the number of patients who received bone marrow transplants from matched related donors, matched unrelated donors, parental donors, and mismatched unrelated donors, as reported by physicians within the JMCN

Table 7 Stem cell source data reported in 2013

	No. of patients
Bone marrow (BM)	1,028
Cord blood (cord)	191
Peripheral stem cell (PBSC)	454
Other	9
Total	1,682

The number of patients who received transplantation through the source of bone marrow, cord blood, peripheral stem cells, or other stem cell source

Gene discovery

Over the past decade, improvements in diagnostics and implementation of newborn screening programs for severe combined immunodeficiency have led to a greater understanding of PI and allowed for clearer assessments of prevalence. Simultaneously, advancement in genomic technologies has led to a better understanding of the underlying mechanisms that lead to monogenic defects of the immune system [9]. These advancements and new discoveries will continue to impact the field of immunology, as well as contribute to related fields such as genomics, infectious disease, and oncology [9].

There are many PI that remain undiscovered. As genomic sequencing technologies advance, additional PI will be identified, contributing to an understanding of the mechanisms of diseases of the immune system, as well as basic cellular pathology [9]. It is important that as genetic technologies advance, access to these technologies also increases to reduce inequalities in diagnostics worldwide.

Currently, there are over 200 primary immunodeficiency defects identified [25]. In 2011, the IUIS Expert Committee for Primary Immunodeficiency updated classifications, adding novel disease entities and restructuring categories. The JMF conducted a literature review in 2010 and identified 44 genes that had been discovered by expert physicians within the JMCN. A review of the most recent IUIS publication, and other literature, found that 16 new genes (see Table 8) had been identified by the JMCN, totaling 60 gene discoveries at Jeffrey Modell Centers. The JMF survey report and resulting database includes substantive numbers of various genotypes and aims to continue to provide a strong platform for collaboration, contributing to international coordination of studies to promote further gene discovery.

Conclusion

Ten years after the initiation of the PEPAC program and the inception of the Jeffrey Modell Centers Network, there has been a continued increase in the number of patients with PI identified, diagnosed, and treated. A total of 77,193 patients have been identified with a PI within the JMCN. By increasing awareness and education, suspected patients are being identified and referred so that they can receive early and appropriate diagnosis.

Table 8 Gene discovery within the Jeffrey Modell Centers Network

Defect identified	OMIM number	Authors	Journal and publication date
Table I. Combined immunodeficiencies			
1 CD 27 deficiency	615122	J. M. van Montfrans I. Hoepelman, J. S. Orange et al.	Journal of Allergy and Clinical Immunology, 2012
			Journal of Allergy and Clinical Immunology, 2012
2 MST1/STK4	614868	C. Klein, N. Rezaei, B. Grimbacher, et al.; Nehme N. T., Pachlopnik S. J., Debeurme F., et al.	Blood; 2012
Table III. Predominantly antibody deficiencies			
3 CD20 deficiency	112210	T. W. Kuijpers, T. Tedder, et al.	Journal of Clinical Investigations; 2010
Table IV. Diseases of immune dysregulation			
4 FHL5, STXBP2/Munc 18-2	613101	U. zur Stadt, S. Ehl, et al. M. Cote, F. Le Deist, A. Fischer, et al.	American Journal of Human Genetics; 2009
5 FADD deficiency	613759	A. Bolze, A. Cant, J. L. Casanova, et al.	Journal of Clinical Investigations; 2009
6 ITCH deficiency	613385	N. Lohr, K. Strauss, N. Rider, D. H. Morton, et al.	American Journal of Human Genetics; 2010
Table V. Congenital defects of phagocyte number, function, or both			
7 CGD, p40	601488	J. D. Matute, D. Lewis, et al. Blood; 2009	American Journal of Human Genetics; 2010
8 MSMD, gp91 phox	306400	C. Picard, L. Abel, J. L. Casanova, et al.	Annals of the New York Academy of Sciences; 2011
9 GATA 2 deficiency	137295	A. P. Hsu, J. S. Orange, et al.	Blood; 2011
Table VI. Defects in innate immunity			
10 HSE TRAF3 AD	N/A	R. Perez de Diego, C. Picard, L. Abel, J. L. Casanova, et al.	Immunity; 2010
11 CMC, AD IL-17RA	605461	A. Puel, M. Galicchio, L. Abel, C. Picard, J. L. Casanova, et al.	Science; 2011
12 CMC, AD IL-17F	606496	A. Puel, M. Galicchio, L. Abel, C. Picard, J. L. Casanova, et al.	Science; 2011
13 CMC, STAT1	614162	A. Liu, J. L. Casanova, et al.	Journal of Experimental Medicine; 2011
14 CD16 deficiency	N/A	J. Grier, J. S. Orange, et al.	Journal of Clinical Investigation; 2012
15 MCM4 deficiency	602638	L. Gineau, L. Abel, C. Picard, J. L. Casanova, et al.	Journal of Clinical Investigation; 2012
Table VII. Autoinflammatory disorders			
16 Early-onset inflammatory bowel disease	146933	B. Begue, A. Fischer C. Klein, et al.	American Journal of Gastroenterology; 2011

Sixteen novel gene defects discovered by researchers within the JMCN. The Online Mendelian Inheritance in Man (OMIM) number, the researchers and authors who contributed to discovery of the novel defects, and the journal and publication date of which novel gene defects were published are also included

Additionally, the findings show that there are regional differences throughout the Network, which reflect greater prevalence of specific gene defects based on occurrences such as founder effect and consanguinity [7]. Because of this, awareness campaigns must be targeted to meet the unique needs in each of these diverse geographical regions. Furthermore, it is important to expand on epidemiological and demographic assessments of specific genes, which may lead to more targeted efforts, and lead to tailoring of continuing medical education, with more precise risk categories identified.

In efforts to increase education and awareness, JMF developed the "10 Warning Signs of Primary Immunodeficiency" in 1993, which has been revised, most recently in 2013. Two versions, for adults and children, have been generated, and over forty countries have developed the Warning Signs in culturally appropriate and language-specific designs. The reach of these educational materials

continues to expand and influences the number of patients identified with primary immunodeficiency all over the world.

Early recognition of PI is essential to avoid associated morbidities and mortality. In an effort to promote awareness and facilitate early identification and diagnosis, JMF created the SPIRIT® Analyzer software, which matches the 10 Warning Signs and ICD-9 codes to identify at-risk patients [7]. Previous analysis showed that with this software, 1,581 out of 846,721 patients in the USA were identified, resulting in an incidence of 1:535 [7]. The SPIRIT® Analyzer software continues to be distributed to medical providers and healthcare insurance companies. As software advances and the use of electronic medical records increases, the time is opportune to utilize the SPIRIT® software and integrate point-of-care screening tools to assist with the identification of patients with PI and referrals to appropriate care and treatment.

It is the mission of the JMF to continue to expand the JMCN, so that all patients living with PI will be identified, diagnosed, and appropriately treated. The JMCN continues to tremendously impact the field of immunology, as 60 new gene discoveries have been identified at these centers within the last decade. Additionally, the JMCN continues to serve as a unique resource, promoting awareness of PIs, disseminating of patient education, and facilitating access to diagnosis and treatment for patients worldwide. The advancement of genetic technologies and expansion of newborn screening programs will continue to support identification of patients with PI, so they can receive the earliest possible treatment necessary to live a healthier life.

Appendix 1

See Table 9.

Table 9 Patients with identified PI defects—global data

Table I. Combined immunodeficiencies			
ADA deficiency	310	ITK deficiency	10
Artemis deficiency (DCLRE1C)	134	JAK3 deficiency	162
Cartilage hair hypoplasia	102	MAGT1 deficiency	8
CD3δ/CD3ε/CD3ζ deficiency	39	MHC class II deficiency	309
CD27 deficiency	9	MST1/STK4 deficiency	17
CD40 deficiency	41	Omenn Syndrome	319
CD40 ligand deficiency	285	ORAI-I deficiency	5
CD45 deficiency	0	PNP deficiency	40
Cernunnos/NHEJl deficiency	16	RAG 1/2 deficiency	352
Complete DiGeorge syndrome	344	Reticular dysgenesis (AK2 deficiency)	33
Coronin-1A deficiency	6	STAT5b deficiency	9
DNA ligase IV deficiency	25	STIM-1 deficiency	1
DNA PKcs deficiency	2	TAP1/TAP2/Tapasin deficiency	4
DOCK8 deficiency	111	TCR α subunit constant gene (TRAC) mutation	0
γc deficiency	607	Winged helix deficiency (nude)	1
IKAROS deficiency	1	ZAP-70 deficiency	74
IL-7Rα deficiency	130	Other combined immunodeficiencies	1,370
		Total	4,876
Table II. Well-defined syndromes with immunodeficiency			
AD-HIES (hyper IgE syndrome)-Job syndrome	820	Hepatic veno-occlusive disease with immunodeficiency (VODI)	14
AR-HIES (hyper IgE syndrome)-DOCK8, TYK2 deficiency	192	ICF-ID centromeric instability and facial anomalies	30
Ataxia telangiectasia (A-T)	2,439	Nijmegen breakage syndrome	284
Ataxia telangiectasia like disease (ATLD)	68	Riddle syndrome	1
Bloom syndrome	52	Roifman syndrome	9
Cartilage hair hypoplasia	152	Schimke syndrome	42
Comel-Netherton syndrome	78	WIPF1 deficiency	3
DiGeorge anomaly (Chrom 22qll.2 deletion syndrome)	5,312	Wiskott–Aldrich syndrome (WAS)	964
Dyskeratosis congenita (DKC)	110	Other well-defined immunodeficiencies	414
		Total	10,984

Table 9 continued

Table III. Predominantly antibody deficiencies			
Agammaglobulinemia (XLA)—BTK deficiency	2,064	Igα deficiency	9
Agammaglobulinemia (unknown molecular basis)	580	IgA deficiency, selective	8,437
AID deficiency	81	IgA with IgG subclass deficiency	1,109
BAFF receptor deficiency	60	IgG subclass deficiency, isolated	4,265
BLNK deficiency	2	Igβ deficiency	2
CD19 deficiency	13	μ Heavy chain deficiency	22
CD20 deficiency	8	Myelodysplasia with hypogammaglobulinemia	17
CD21 deficiency	1	PMS2 deficiency	5
CD40 deficiency	92	Specific antibody deficiency (normal Ig and B cells)	2,681
CD40L deficiency	372	TACI deficiency (mutation TNFRSF1JB)	160
CD81 deficiency	4	Thymoma with immunodeficiency	123
Common variable immunodeficiency (CVID)	8,582	UNG deficiency	4
Hyper IgM syndrome (unspecified)	326	κ chain deficiency	0
Hypogammaglobulinemia of infancy (transient)	3,694	λ5 deficiency	1
Hypogammaglobulinemia unspecified	3,771	Other predominantly antibody deficiencies	994
ICOS deficiency	46		
		Total	37,532
Table IV. Diseases of immune dysregulation			
Activating K-Ras defect	2	FHLJ, MunclJ-4 deficiency	141
Activating N-Ras defect	8	FHL4, STX11 deficiency	22
ALPS-CASP10	21	FHL5, MunclS-2 deficiency	54
ALPS-FAS	343	Griscelli syndrome type 2	139
ALPS-FASLG	50	Hermansky–Pudlak syndrome (type 2; AP3 deficiency)	314
APECED (APS-1)	182	IPEX(X-linked)	101
CASPASE 8 defect	0	IPEX-like syndrome	99
CD2S deficiency	15	ITCH deficiency	0
Chediak–Higashi syndrome	211	PLCG2 deficiency (cold urticaria, immunodeficiency)	5
FADD deficiency	4	XLP1, SH2D1A deficiency	231
FHL1 syndrome	39	XLP2, XIAP deficiency	74
FHL2, perforin deficiency	196	Other diseases of immune dysregulation	582
		Total	2,833
Table V. Congenital defects of phagocyte #, function, or both			
β-Actin deficiency	0	MSMD (IL12RB)	51
Barth syndrome	21	MSMD (STAT1 deficiency)	62
CGD, p22 deficiency	133	Neutropenia, benign congenital	327
CGD, p40 deficiency	106	P14 deficiency	2
CGD, p47 deficiency	202	Papillon–Lefèvre syndrome	29
CGD, p67 deficiency	100	Poikiloderma with neutropenia	1
CGD, XL	1,129	Rac 2 deficiency	10
Cohen syndrome	39	SCN1 (ELANE deficiency)	152
Cyclic neutropenia	636	SCN2 (GFI1 deficiency)	16
Glycogen storage disease type lb	44	SCN J (HAX1 deficiency)	29
Leukocyte adhesion deficiency type 1 (LAD1)	190	SCN4, all others	83
Leukocyte adhesion deficiency type 2 (LAD2)	11	Severe congenital neutropenia, basis unknown	393
Leukocyte adhesion deficiency type 3 (LAD3)	17	Shwachman–diamond syndrome	111
Localized juvenile periodontitis	0	Specific granule deficiency	3
MSMD (IFN-γRl/2)	56	X-linked neutropenia/myelodysplasia	14
MSMD (IL-12p40)	33	Other congenital defects of phagocytes	649
		Total	4,649

Table 9 continued

Table VI. Defects in innate immunity			
CD16 deficiency	2	Herpes simplex encephalitis HSE (TRAF3)	3
CMC-IL-17F deficiency	92	Herpes simplex encephalitis HSE (TRIF)	3
CMC-IL-17RA deficiency	23	Herpes simplex encephalitis HSE (Unc93B)	8
CMC-STAT1 gain-of-function	140	IRAK4 (IL-1 receptor-associated kinase 4)	38
EDA-ID, AD (NFKBIA mutation)	19	IRF-8 mutation	1
EDA-ID, XL (NEMO deficiency)	101	MCM4 deficiency	0
Epidermodysplasia verruciformis (EVER mutation)	11	MyD88 deficiency	17
GATA-2 mutation	31	NK cell deficiency	145
Herpes simplex encephalitis HSE (IKBKG)	1	WHIM syndrome	54
Herpes simplex encephalitis HSE (TLR3)	7	Other defects in innate immunity	230
		Total	924
Table VII. Auto inflammatory disorders			
Blau syndrome (NOD2 or CARD15)	40	Muckle–Wells syndrome	47
DIRA (ILIRN)	10	NOMID or CINCA	56
Early-onset inflammatory bowel disease	91	PAPA syndrome	5
Familial cold autoinflammatory syndrome	65	PFAPA syndrome	2,406
Familial Mediterranean fever	2,652	TNF receptor-associated periodic fever-TRAPS	146
Hyper IgD syndrome	162	Other autoinflammatory disorders	298
Majeed syndrome (mutation of LPIN2)	23		
		Total	6,001
Table VIII. Complement deficiencies			
3MC syndrome COLEC11 deficiency	0	CD46 deficiency	1
C1 inhibitor deficiency	2,528	CD59 deficiency	1
Clq deficiency	20	CR3-complement receptor 3 deficiency	1
Clr deficiency	4	Factor D deficiency	1
Cls deficiency	9	Factor H deficiency	25
C2 deficiency	258	Factor 1 deficiency	34
C3 deficiency	63	Ficolin 3 deficiency	5
C4 deficiency	95	MBL deficiency	378
C5 deficiency	21	MASP1 deficiency	10
C6 deficiency	33	MASP2 deficiency	2
C7 deficiency	23	Paroxysmal nocturnal hemoglobinuria(PIGA)	18
C8 deficiency (a & b)	29	Properdin deficiency	34
C9 deficiency	5	Other complement deficiencies	1,212
		Total	4,810
Other Primary Immunodeficiency diseases unspecified and unclassified			4,583

Appendix 2

See Table 10.

Table 10 Patients identified with PI defects by region

Region	Patients identified with PI defects	% of total
Western Europe	25,518	33.06 %
United States	22,781	29.51 %
Eastern Europe	11,886	15.40 %
Latin America	5,361	6.94 %
Middle East	4,370	5.66 %
Canada	3,880	5.03 %
Asia	1,843	2.39 %
Africa	1,463	1.90 %
Australia	91	0.12 %
Total	77,193	100.00 %

Appendix 3

See Table 11.

Table 11 PI defects listed by prevalence (90 out of 200 defects listed)

	Total PI	Global	US	International
1	Common variable immunodeficiency (CVID)	8,582	5,431	3,151
2	IgA deficiency, selective	8,437	6,890	1,547
3	DiGeorge anomaly (Chrom 22q11.2 deletion syndrome)	5,312	2,407	2,905
4	Other unclassified PID	4,583	2,665	1,918
5	IgG subclass deficiency, isolated	4,265	3,522	743
6	Hypogammaglobulinemia unspecified	3,771	1,985	1,786
7	Hypogammaglobulinemia of infancy (transient)	3,694	3,100	594
8	Specific antibody deficiency (normal Ig and B cells)	2,681	1,112	1,569
9	Familial Mediterranean fever	2,652	2,527	125
10	C1 inhibitor deficiency	2,528	2,236	292
11	Ataxia telangiectasia (A-T)	2,439	1,319	1,120
12	PFAPA syndrome	2,406	2,527	125
13	Agammaglobulinemia, (XLA)—BTK deficiency	2,064	1,615	449
14	Other combined immunodeficiencies	1,370	1,139	231
15	Other complement deficiencies	1,212	1,154	58
16	CGD, XL	1,129	933	196
17	IgA with IgG subclass deficiency	1,109	890	219
18	Other predominantly antibody deficiencies:	994	896	98
19	Wiskott–Aldrich syndrome (WAS)	964	701	263
20	AD-HIES (hyper IgE syndrome)-Job syndrome	820	650	170
21	Other congenital defects of phagocyte	649	604	45
22	Cyclic neutropenia	636	239	397
23	γc deficiency	607	405	202
24	Other diseases of immune dysregulation	582	245	337
25	Agammaglobulinemia (unknown molecular basis)	580	434	146
26	Other well-defined syndromes immunodeficiency	414	332	82
27	Severe congenital neutropenia, basis unknown	393	324	69
28	CD40L deficiency	372	272	100
29	RAG 1/2 deficiency	352	277	75
30	Complete DiGeorge syndrome	344	139	205
31	ALPS-FAS	343	231	112
32	Neutropenia, benign congenital	327	184	143
33	Omenn syndrome	319	225	94
34	Hermansky–Pudlak syndrome (type 2; AP3 deficiency)	314	16	298
35	ADA deficiency	310	197	113
36	MHC class II deficiency	309	286	23
37	Other autoinflammatory disorders	298	255	43
38	CD40 ligand deficiency	285	215	70
39	Nijmegen breakage syndrome	284	266	18
40	C2 deficiency	258	178	80
41	XLP1, SH2D1A deficiency	231	154	77
42	Other defects in innate immunity:	230	193	37
43	Chediak–Higashi syndrome	211	181	30
44	CGD, p47 deficiency	202	165	37
45	FHL2, perforin deficiency	196	86	110
46	AR-HIES (hyper IgE syndrome)-DOCK8, TYK2 deficiency	192	159	33
47	Leukocyte adhesion deficiency type 1 (LAD1)	190	168	22
48	APECED (APS-1)	182	149	33
49	Hyper IgD syndrome	162	126	36
50	JAK3 deficiency	162	116	46
51	TACI deficiency (mutation TNFRSF13B)	160	117	43
52	SCN1 (ELANE deficiency)	152	120	32
53	Cartilage hair hypoplasia	152	87	65
54	TNF receptor-associated periodic fever-TRAPS	146	118	28
55	NK cell deficiency	145	46	99
56	FHL3, Munc13-4 deficiency	141	95	46
57	CMC-STAT 1 gain-of-function	140	126	14
58	Griscelli syndrome type 2	139	125	14
59	Artemis deficiency (DCLRE1C)	134	100	34
60	CGD, p22 deficiency	133	106	27
61	IL-7Rα deficiency	130	89	41
62	Thymoma with immunodeficiency	123	104	19
63	DOCK8 deficiency	111	98	13
64	Shwachman–Diamond syndrome	111	93	18
65	Dyskeratosis congenita (DKC)	110	55	55
66	CGD, p40 deficiency	106		
67	EDA-ID, XL (NEMO deficiency)	101	44	57
68	IPEX (X-linked)	101	58	43

Table 11 continued

	Total PI	Global	US	International
69	CGD, p67 deficiency	100	61	39
70	IPEX-like syndrome	99	49	50
71	C4 deficiency	95	63	32
72	CD40 deficiency	92	71	21
73	CMC-IL-17F deficiency	92	77	15
74	Early-onset inflammatory bowel disease	91	42	49
75	SCN4, all others	83	73	10
76	AID deficiency	81	71	10
77	Comel-Netherton syndrome	78	59	19
78	ZAP-70 deficiency	74	42	32
79	XLP2, XIAP deficiency	74	17	57
80	Ataxia telangiectasia like disease (ATLD)	68	64	4
81	Familial cold autoinflammatory syndrome	65	26	39
82	C3 deficiency	63	45	18
83	MSMD STAT1 deficiency	62	5	57
84	BAFF receptor deficiency	60	59	1
85	MSMD (IFN-γR1/2)	56	52	4
86	NOMID or CINCA	56	46	10
87	WHIM syndrome	54	44	10
88	FHL5, Munc 18-2 deficiency	54	21	33
89	Bloom syndrome	52	5	47
90	MSMD (IL12RB)	51	49	2

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