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Global study of primary immunodeficiency diseases (PI)—diagnosis, treatment, and economic impact: an updated report from the Jeffrey Modell Foundation

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Abstract A large population of patients with recurring infections are undiagnosed or under diagnosed and Primary Immunodeficiency (PI) is more common than had been previously estimated. The results strongly indicate the measurable impact of Physician Education and Public Awareness in identifying patients with an underlying PI. The Jeffrey Modell Centers Network (JMCN) provides the infrastructure for referral, diagnosis and appropriate treatment. All disease classifications and identified defects increased significantly over the study period. Quality of Life for referred and diagnosed patients dramatically improved compared to undiagnosed patients. There is a substantial cost savings for diagnosed patients compared to undiagnosed, even if regular IgG is required. The SPIRIT® Software successfully identified patients with PI in a large database and at three pilot sites. The Software was successfully tested for specificity and sensitivity.

Keywords Primary immunodeficiencies (PI) · Jeffrey Modell Foundation (JMF) · Jeffrey Modell Centers Network (JMCN) · Immunoglobulin replacement therapy · Awareness · Economic impact · Diagnosis · Treatment

Abbreviations

PI	Primary immunodeficiency
JMF	The Jeffrey Modell Foundation
JMCN	Jeffrey Modell Centers Network
PEPAC	Physician Education and Public Awareness Campaign
SPIRIT®	Software for primary immunodeficiency recognition, intervention, and tracking
IgG	Immunoglobulin replacement therapy
HSCT	Hematopoietic stem cell transplantation
ESID	European society for immunodeficiencies

Jeffrey Modell Foundation: Vicki and Fred Modell established the Jeffrey Modell Foundation (JMF) in 1987, in memory of their son Jeffrey, who died at the age of fifteen from complications of Primary Immunodeficiency (PI)—a genetic condition that is chronic, serious, and often fatal. JMF is a global nonprofit organization dedicated to early diagnosis, meaningful treatments, and cures through research, physician education, public awareness, advocacy, patient support, and newborn screening. There are more than 100 Jeffrey Modell Diagnostic and Research Centers and 230 Referral Centers worldwide. The Foundation has established a Network of 490 expert immunologists in 64 countries spanning six continents. More information about PI can be found at http://www.info4pi.org, by contacting JMF at (212) 819-0200 or info@jmfworld.org.

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Introduction

Primary immunodeficiencies (PIs) [1, 2] are devastating disorders primarily resulting from monogenic defects of the human immune system [3] and occur in as many as 500,000 persons in the United States alone [4]. Left undiagnosed and untreated PIs are often associated with severe morbidity and increased mortality [5]. Many PIs can be easily diagnosed, and effective treatment options are available [6]. However, awareness of PIs and appropriate and timely management of these conditions are low among both physicians and the general public, and many patients are left undiagnosed.

Considering the high morbidity and mortality associated with PI, the Jeffrey Modell Foundation (JMF) established a Physician Education and Public Awareness Campaign (PEPAC) in 2003, and data collection began the following year. The goals of the Program are to (1) identify patients with PIs as early as possible; (2) refer ''at-risk'' patients to specialized Centers in the Jeffrey Modell Centers Network (JMCN) worldwide; (3) diagnose patients precisely in order to identify the specific defect; and (4) treat the defect effectively.

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. Components utilized in the program include 10 warning signs posters, physician algorithm, CME symposia, Web sites for physicians and patients, graphic posters of the immune system, kids days, WIN program support, and public service advertising.

In 2009, the Jeffrey Modell Foundation (JMF) reported the results of a survey that was conducted by contacting physicians from the Jeffrey Modell Centers Network (JMCN) of Diagnostic, Research and Referral Centers worldwide [7]. A similar survey was conducted in 2011 to update the impact of PEPAC on diagnosis of PIs worldwide and on treatment modalities for patients receiving immunoglobulin replacement therapy or treated by cellular therapy.

In 2009, JMF reported results of the quality of life and economic data survey, sent to JMCN Center Directors, in which they were asked to examine records of PI patients 1 year before diagnosis and for the year subsequent to diagnosis. Eighty-five centers in the JMCN responded. Table 13 represents the results of the survey and is updated to reflect 2011 costs for undiagnosed versus diagnosed patients.

In a separate study, the JMF reached out to payers and providers to test and pilot JMF's newly developed software, SPIRIT® Analyzer (Software for Primary Immunodeficiency Recognition, Intervention and Tracking). The software matches the ICD-9 codes in an existing database to JMF's 10 warning signs of PI with the purpose to identify ("flag") patients at "high risk" of having a PI. Using the SPIRIT® Analyzer Software, studies were carried out on risk assessment and on costs of treating "at-risk" patients flagged by the SPIRIT® Analyzer Software.

Methods

PI survey

A newly developed questionnaire form was sent to Physician Experts at 254 centers in the JMCN. Survey data were requested during the fourth quarter of 2010 and the first quarter of 2011. Each Center Director was asked to provide the number of patients with a specific PI diagnosis. Reports of specific defects were analyzed by region and type of treatment intervention. Data collected in 2010–2011 were compared with data obtained through previous surveys conducted in 2009 [7] and in 2004. PI diagnoses were grouped into eight categories according to the classification of PIs of the International Union of Immunological Societies (IUIS). [8] In addition, patients with other PIs that are not included in the IUIS Classification were assigned to the "Other immunodeficiencies" subgroup.

The questionnaire included data fields to determine the number of patients on immunoglobulin replacement therapy receiving intravenous immunoglobulin in the clinic or at home or treated with subcutaneous administration of immunoglobulins. For patients treated with cellular therapy, information was retrieved on the number of patients treated by HSCT or gene therapy, donor type, and stem cell source. All surveys were collected, collated, and secured by JMF.

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Quality of life and updated economic data

The updated economic data were generated as follows: hospital charges and length of stay data were obtained from the Hospital Cost and Utilization Project (HCUP), Nationwide Inpatient Sample, under the auspices of the Agency for Healthcare Research and Quality (AHRQ) [9]. Data were collected by individual states and provided to AHRQ. Principal diagnosis was based on clinical classification software; charges were based on hospital accounting reports from the Centers for Medicare and Medicaid Services. Charges represent hospital billings, not hospital costs or percentage of costs actually collected by hospitals; a unit of analysis for HCUP data is a hospital stay, based on discharge data per patient. A patient admitted to the hospital multiple times in 1 year was counted each time as a separate discharge. The study assumes minimum frequency of adverse events re: infections and hospitalizations. Costs related to severe combined immune deficiency (SCID) are not included in the study. Experts report significant costs of repeated/prolonged ICU admissions in connection with SCID. "Inpatient" information was obtained from the HCUP Web site [9]; "outpatient" information was obtained from the Aetna Web site [10]. Charges are based on "In network" coverage, with "Out of network" costs 2–4 times greater [10]. Healthcare costs data for privately insured patients were included [11, 12]; healthcare costs data from the Centers for Medicare and Medicaid statistics were included [13, 14]; economic factors underlying growth in Medicare spending were determined by CBO, Congressional Budget Office data [15]; employer-sponsored coverage data were provided by the Employee Benefit Research Institute Issue: Washington, DC [16, 17].

Risk assessment using SPIRIT® Analyzer software

In a separate study, JMF reached out to payers and providers to beta-test and pilot JMF's newly developed software, SPIRIT® Analyzer (Software for Primary Immunodeficiency Recognition, Intervention and Tracking). The software matches more than 350 weighted ICD-9 codes in an existing database to 9 of the JMF's 10 warning signs of PI and calculates risk points to establish low-, medium-, and high-risk categories. Each of the 350 ICD-9 codes is identified as a chronic or acute condition. The Analyzer identifies specific exclusion criteria. The 10th JMF warning sign, a family history of PI, is not applicable as this information cannot be obtained via claims data. Rather, this is to be assessed by a clinician during an office visit. The SPIRIT® Analyzer generates HIPPA-Compliant, de-identified reports, that describe the patient population via the following metrics related to PI: (a) population overview (gender and age); (b) distribution by PI warning sign; (c) distribution by risk category and by number of warning signs; (d) use of antibiotics; (e) average healthcare costs by all patients screened by the SPIRIT® Analyzer and by risk category and number of warning signs; (f) average healthcare costs by total costs broken out as medical costs and pharmacy costs; (g) provider measure of patients in each risk category (High, Medium, and Low); (h) patient measure: risk category and number of warning signs.

Patients identified as being at "high risk" of PI were flagged by the SPIRIT® Analyzer, which can sort more than 1 million patient records in less than 30 min. Specificity and sensitivity tests were conducted, and risk assessment and economic consequences were quantified.

Statistical analysis

Statistical analysis was conducted using two-way Anova and Student's t-test for paired data. P values less than 0.05 were considered significant.

Results and discussion

Characteristics of PI patients followed at JMCN centers

Questionnaires were sent to physicians at 254 centers of the JMCN. Four hundred and ninety physicians from 192 centers (75.6%) representing 64 countries across six continents responded with information on a total of 79,764 patients with suspected or well-defined PI followed at these centers. Of these, 60,364 patients have received a specific diagnosis, and 59,681 were referred to a JMCN center (Fig. 1). As compared to data from 2004 and 2009, there is a continuous growth in the number of PI patients followed at JMCN centers (Fig. 1). The distribution of questionnaires returned, and of patients with well-defined forms of PI followed at JMCN centers in various geographic areas, is reported in Supplementary Table 1. Figure 2 illustrates the distribution of patients with defined forms of PIs into the 8 major subgroups of the IUIS classification. As expected, the most numerous subgroup was represented by "Predominantly antibody deficiencies" (51.6% of all patients), followed by "Other well-defined immunodeficiency syndromes" (15.6%) and "Other immunodeficiencies" (7.1%). A similar pattern of distribution of patients into the 8 major subgroups was identified globally versus patients followed at JMCN centers in the United States. Reporting of autoinflammatory disorders and of "Other well-defined immunodeficiency syndromes" was less and more common, respectively, in the United States than in other geographic areas. Furthermore, as shown in Table 1, a similar distribution of PIs into nine subgroups was

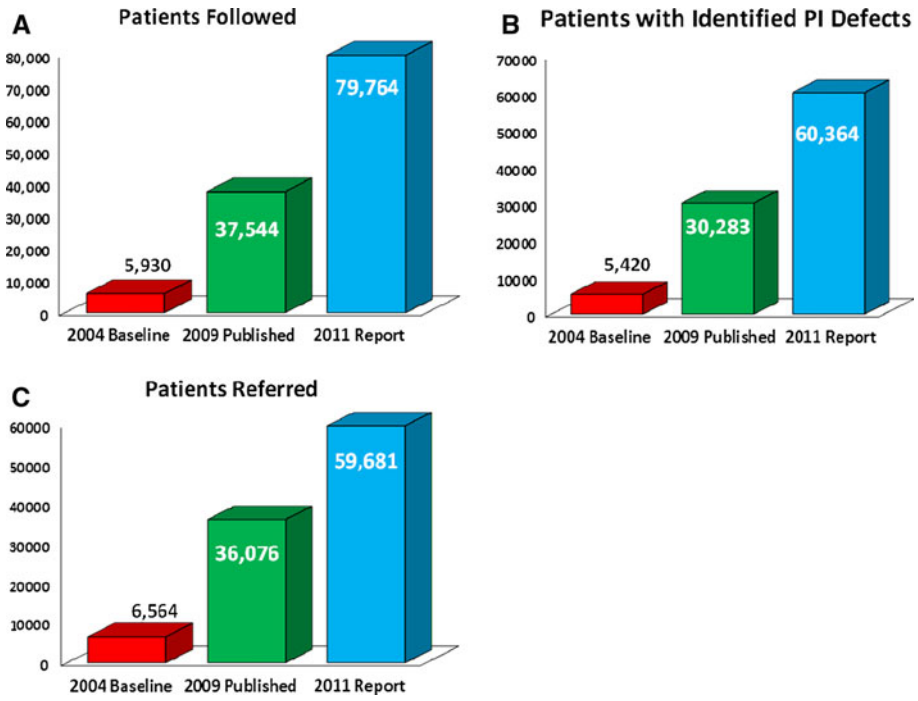

Fig. 1 Patients followed, identified, and referred with specific PI defects

observed at JMCN centers and in the European Society for Immune Deficiencies (ESID) Registry [18] (P = NS).

The number of patients with specific forms of PIs within each of the eight major subgroups at JMCN centers is reported in Supplementary Table 2 (worldwide analysis), Supplementary Table 3 (United States), and Supplementary Table 4 (non-United States centers). The prevalence of 83 PIs at all centers (global), in the United States and in other non-US centers (International), is shown in Supplementary Table 5.

Significant variability in the prevalence of the 15 most common PIs was observed in various geographic areas (Table 2). For example, DiGeorge syndrome was the most common PI reported in Canada and the second most common in the United States but was only ninth in the Middle East and seventh in Australia. Unspecified hypogammaglobulinemia represented the third most common diagnosis in the United States but was very rarely reported in the Middle East and Asia, and no patients were given such diagnosis in Australia.

To measure the efficacy of PEPAC in improving diagnosis of PIs and facilitating patient referral to experienced centers, we compared results of the 2011 survey with those of the survey performed in 2009 [7]. As shown in Table 3, the number of centers contacted increased by 33.6%, as a result of the increase in the number of JMCN centers in the last 2 years. Between 2009 and 2011, there was a marked increase (+112.4%) in the number of patients followed at JMCN centers. The number of patients referred to JMCN centers increased by 65.4%. Detailed description of the number of patients with defined PIs followed at JMCN centers in 2004, 2009, and 2011 is provided in Supplementary Table 6.

Treatment modalities in patients with PIs

Antibody deficiencies represent the most common form of PI. Treatment for these disorders is primarily based on immunoglobulin replacement therapy and prompt diagnosis and treatment for infections [19, 20]. The intravenous (IV) route represents the most common route utilized to administer immunoglobulins (IVIG) and has generally been highly successful in protecting patients with antibody deficiencies from severe infections [21]. The subcutaneous (SC) route for administering immunoglobulins (SCIG) was initially used in Northern Europe [22] and gradually introduced to North America and other areas of the world. Although IVIG can be administered either in the hospital or at home, SCIG is typically given at home. Access to home versus hospital-based treatment with immunoglobulin varies in different countries. Furthermore, cultural and social issues also impact on the decision to treat patients at home or in clinic. Through the survey, we collected information on the route and modality (home vs. clinic) of administration of immunoglobulins in 14,140 patients (Tables 4, 5). The vast majority (74.4%) of the patients received IVIG; of these, 78.6% were treated in clinics. A comparison of the number of patients receiving Ig replacement therapy at JMCN centers in 2004, 2009, and 2011 is shown in Table 5.

Fig. 2 Major categories of PI

Major Categories of PI

Categories	Global		U.S.A.		International	
Combined T and B–cell Immunodeficiencies	3,163	5.24%	608	3.90%	2,555	5.71%
Other Well Defined Immunodeficiency Syndromes	9,427	15.62%	3,413	21.88%	6,014	13.44%
Diseases of Immune Dysregulaton	1,553	2.57%	282	1.81%	1,271	2.84%
Congenital Defects of Phagocyte Numbers and Function	3,189	5.28%	461	2.95%	2,728	6.09%
Predominantly Antibody Deficiencies	31,162	51.62%	8,388	53.76%	22,774	50.88%
Defects in Innate Immunity	328	0.54%	118	0.76%	210	0.47%
Autoinflammatory Disorders	3,600	5.96%	352	2.26%	3,248	7.26%
Complement Deficiencies	3,652	6.05%	564	3.61%	3,088	6.90%
Other Immunodeficiencies	4,290	7.11%	1,416	9.08%	2,874	6.42%
Total	**60,364**		**15,602**		**44,762**	

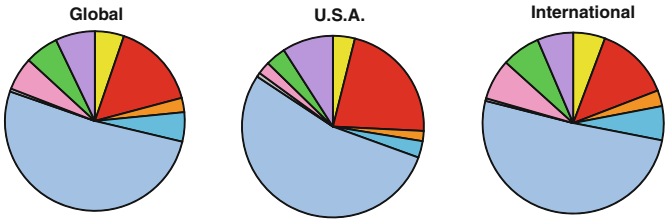

Table 1 Comparison between JMCN global survey reports and ESID registry data [18]

Major primary immunodeficiencies categories	JMCN		ESID	
Combined T- and B-cell immunodeficiencies	3,163	5.24%	1,014	7.66%
Other well-defined immunodeficiency syndromes	9,427	15.62%	2,232	16.87%
Diseases of immune dysregulation	1,553	2.57%	183	1.38%
Congenital defects of phagocyte numbers and function	3,189	5.28%	1,345	10.16%
Predominantly antibody deficiencies	31,162	51.62%	7,342	55.49%
Defects in innate immunity	328	0.54%	N/A	N/A
Autoinflammatory disorders	3,600	5.96%	256	1.93%
Complement deficiencies	3,652	6.05%	624	4.72%
Other immunodeficiencies	4,290	7.11%	236	1.78%
Total	60,364	100%	13,232	100%
Number of respondents	192		77	

Cellular therapy represents the mainstay of treatment for severe forms of PI that involve cell-mediated immunity [23]. Hematopoietic stem cell transplantation (HSCT) is the most common for cellular treatment for PIs [24]. However, patients with complete DiGeorge syndrome or with FOXN1 deficiency benefit from thymus transplantation [25]. Finally, promising results have been obtained with gene therapy in some forms of severe combined immune deficiency (SCID) and in patients with the Wiskott–Aldrich syndrome (WAS) [26]. We have reviewed the number of patients followed at JMCN centers treated by cellular therapy. A total of 1,036 patients have received HSCT or thymus transplantation, and 53 patients have been treated with gene therapy (Table 6). Data on donor type (Table 7) and source of stem cells (Table 8) were available for 893 and 877 transplantations, respectively. Transplantation from matched unrelated donors (MUD) was used more often (39.7% of transplants), and bone marrow was the most common source of stem cells (59.2% of transplants).

PI risk assessment using SPIRIT® Analyzer software

Prompt recognition of PIs is essential to avoid severe, often irreversible, and potentially fatal complications of these disorders. In an attempt to promote awareness and facilitate

Table 2 15 PI defects identified by worldwide by region

		USA	Canada	Latin America	Western Europe	Eastern Europe	Middle East	Asia	Australia	Africa	Total
1	Common variable immunodeficiency (CVID)	2,501	452	484	2,460	498	248	380	464	126	7,613
2	IgA deficiency, selective	1,209	155	834	3,339	1,148	73	139	94	70	7,061
3	DiGeorge syndrome (DGS)	1,858	575	255	1,002	386	62	107	21	44	4,310
4	IgG subclass deficiency, isolated	533	24	38	2,884	76	18	55	234	16	3,878
5	Combined T- and B-cell immunodeficiencies	608	129	160	1,336	172	255	241	61	201	3,163
6	Hypogammaglobulinemia unspecified	1,445	247	157	1,122	140	7	5	0	25	3,148
7	Hypogammaglobulinemia of infancy (transient)	551	245	254	1,015	514	35	65	8	26	2,713
8	Ataxia-telangiectasia (A-T)	1,005	38	223	288	227	168	109	0	132	2,190
9	Specific antibody deficiency (normal Ig and B-cells)	1,278	59	162	523	40	7	29	36	4	2,138
10	Agammaglobulinemia (XLA)	425	77	246	571	231	96	358	80	48	2,132
11	C1 inhibitor deficiency	226	35	90	1,350	279	22	10	0	33	2,045
12	Familial mediterranean fever	100	32	14	421	25	1,102	3	0	18	1,715
13	PFAPA syndrome	171	43	36	652	62	550	3	0	1	1,518
14	IgA with IgG subclass deficiency	172	27	15	441	375	4	10	0	11	1,055
15	CGD, XL	198	38	161	278	70	180	91	0	13	1,029

early recognition of PIs, the JMF developed "The 10 warning signs" of PI in 1993, which has been revised twice, most recently in 2010 [27]. Two versions, for adults and children, have been generated. The 10 warning signs have been used in more than 35 countries around the world as a primary screening tool for PI. In spite of this, underdiagnosis or delayed diagnosis of PIs remains a challenge. To help address this issue, JMF created a software, SPIRIT® Analyzer, which matches more than 350 weighted ICD-9 Codes to the 10 warning signs and calculates risk points to establish low-, medium- and high-risk categories for subjects potentially affected with PI. Functionality and efficacy of this software were initially beta-tested first using the IMS Health LifeLink Health Plan Claims Database.

The IMS Database comprises fully adjudicated medical and pharmaceutical claims for over 60 million unique patients from 90 health plans across the United States and includes both inpatient and outpatient diagnoses in ICD-9-CM format and procedures in CPT-4 and HCPCS formats. Retail and mail order prescription records including the NDC code and quantity dispensed for each drug prescribed are provided in the database. Furthermore, the database provides information on demographic variables by age, gender, and geographic region. Lastly, payer type such as HMO, PPO, commercial or self-pay, using start and stop dates for plan enrollment, is included in the database.

Table 3 2011 Data compared to 2009 previously published results [2]

	2011	2009	Increase (%)
Number of patients followed	79,764	37,544	112.45
Number of patients with identified PI defects	60,364	30,283	99.33
Number of patients referred	59,681	36,076	65.43
Number of patients receiving IgG	14,140	6,822	107.27
Number of surveys requested	254	190	33.68
Number of surveys received	192	138	39.13
Compliance rate (%)	75.59	72.63	2.96

Table 4 Number of patients receiving IgG

IVIG-clinic	8,269
SCIG	3,330
IVIG-home	2,255
Other	286
Total	14,140

Table 5 Patients treated with IgG 2004 baseline versus 2009 published versus 2011 report

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

Table 6 Treatment by transplantation and gene therapy

Patients treated by transplant	
International	749
USA	287
Global	1,036
Patients receiving gene therapy	
International	18
USA	15
Global	53

Table 7 Stem cell donor type

Matched unrelated donor (MUD)	355
Matched related donor (MRD)	295
Parental Haplo (Haplo)	180
Mis-matched unrelated donor (mMUD)	63
Total	893

Table 8 Stem cell source

Bone marrow (BM)	519
Cord blood (Cord)	210
Peripheral blood stem cell (PBSC)	138
Other	10
Total	877

A sampling of 2,056,857 patients in the IMS database was screened using the SPIRIT® Analyzer. Among these, 712,144 patients had at least one medical and/or pharmacy claim of interest. In particular, 1,489 patients screened had two or more warning signs of PI. This translates to an incidence of 1:478 of those patients in the database with at least one medical and/or pharmacy claim of interest.

Patients with scores of over 10 points were considered high risk. There were 1,221 high-risk patients identified by the Analyzer, for an incidence of 1:583. Patients with scores of 8–10 points were considered moderate risk. There were 3,024 moderate-risk patients identified by the Analyzer, for an incidence of 1:235. Altogether, high- and moderate-risk patients totaled 4,245, for an overall incidence of 1:167.

Patients with a previously diagnosed underlying PI ("279" ICD-9 Codes) were excluded from the above data. Subsequently, after adding back-excluded patients with at least one medical or pharmacy claim of interest, we identified 1,581 patients out of 846,721 with a PI. This translates to an incidence of 1:535.

Subsequent to this beta-testing using the data from the IMS LifeLink Health Plan Claims Database, three health plans pilot tested the SPIRIT® Analyzer utilizing their plans' records and provided JMF with top-level, de-identified, blinded data. As shown in Table 9, there was excellent concordance between the results obtained during beta-testing of the software and the results obtained at each of the three health plans. The only exception was a low

Table 9 Reports on SPIRIT® Analyzer software

	Benchmark data		Pilot site 1		Pilot site 2		Pilot site 3		Average percent
	Patients	Percent	Patients	Percent	Patients	Percent	Patients	Percent	
Claim type (all patients of interest)									
PI warning sign diagnosis only	153,861	22	1,572	1	27,370	15	14,533	16	17.78
Antibiotic only	264,379	37	70,643	58	64,031	35	26,162	29	38.31
PI warning sign diagnosis + antibiotic	293,904	41	49,870	41	92,487	50	51,109	56	43.91
Gender (all patients of interest)									
Female	408,997	57	71,985	59	102,927	56	54,805	59.70	57.55
Male	303,147	43	50,100	41	80,946	44	36,982	40.30	42.45
Age group (years) (all patients of interest)									
<5	78,384	11	9,373	8	33,203	18	33,738	36.80	13.94
5–10	84,154	12	9,915	8	20,846	11	16,588	18.10	11.85
11–17	80,001	11	11,792	10	18,449	10	12,508	13.60	11.06
18–25	82,121	12	12,085	10	19,706	11	8,388	9.10	11.02
26–35	97,697	14	12,412	10	27,159	15	6,905	7.50	12.99
36–60	289,787	41	58,100	48	51,589	28	7,400	8.10	36.66
Total patient population	2,056,857		525,000		700,000		200,000		3,481,857
Total patients of interest	712,144 (34%)		122,085 (23%)		183,888 (26%)		91,787 (46%)		1,109,904 (32%)

Table 10 Reports on SPIRIT® Analyzer software

	Benchmark data		Pilot site 1		Pilot site 2		Pilot site 3	
	Patients	Percent	Patients	Percent	Patients	Percent	Patients	Percent
Number of PI warning signs								
2 warning signs	1,403	0.20	257	0.21	307	0.17	346	0.38
3+ warning signs	86	0.01	32	0.03	33	0.02	33	0.04
Risk category								
High (>10 risk points)	1,221	0.17	281	0.23	228	0.12	560	0.61
Moderate (8–10 risk points)	1,793	0.25	288	0.24	413	0.22	433	0.47
Low (1–7 risk points)	307,730	43.21	4,009	3.28	6,698	3.64	4,607	5.02
Patients with 0 risk points	401,400	56.37	117,507	96.25	176,549	96.02	86,187	93.90

Table 11 Reports on SPIRIT® Analyzer software

Prevalence	Benchmark data	Pilot site 1	Pilot site 2	Pilot site 3	Average
2 or more of the 10 WS	1:478	1:423	1:598	1:243	1:444
High-risk category	1:583	1:430	1:806	1:165	1:485
Moderate-risk category	1:235	1:428	1:445	1:212	1:379
High + moderate categories combined	1:167	1:214	1:287	1:92	1:213

Table 12 SPIRIT® Analyzer tests of specificity and sensitivity

Classification	Number of patient records examined	Number of patients with 1 or more of the 10 warning signs	Specificity/sensitivity (%)
Not of interest	878,073	0	100[a]
Diagnostic code 279, indicative of a PI diagnosis	800	504[a]	63[a]

[a] 100% of these patients had ICD-9 Codes reflective of related medical conditions such as autoimmune disease, anemia, chronic inflammatory disease, cancer, and disorders not specifically included in the 350 ICD-9 Codes screened by the Analyzer

yield of flagging achieved at Pilot site 1 when using the 10 warning signs only. Furthermore, a similar distribution of "at-risk" subjects according to their age was observed at each site.

The proportion of patients flagged as being at high or moderate risk of PI, according to the SPIRIT® Analyzer software, is reported in Tables 10 and 11. In this case, excellent concordance was observed across two of the pilot sites and benchmark data, whereas a higher proportion of patients at high or moderate risk of PI were identified at the third pilot site.

In an effort to confirm that patients' records that were "not of interest" were appropriately excluded from the data set being analyzed, we reviewed 878,073 "not of interest" patients' records. None of them had clinical history compatible with 1 or more of the 10 warning signs (Table 12). To confirm that patients' records already identified with a PI were appropriately excluded from the data set being analyzed, we reviewed 800 patients' records with ICD-9 diagnostic code 279. Of these, 504 had a clinical history compatible with one or more of the warning signs (Table 12), and all of them had ICD-9 codes reflective of medical conditions such as autoimmune disease, anemia, chronic inflammatory disease, cancer, and disorders not specifically included in the 350 ICD-9 codes screened by the Analyzer. Overall, these data indicate that the SPIRIT® Analyzer is an effective tool to screen patients' medical records and flag subjects at higher risk of PI. However, it should be emphasized that it is not a diagnostic tool, and appropriate clinical and laboratory assessment is required to confirm or rule out the suspicion of PI.

Lastly, we have attempted to quantify the costs of Ig replacement therapy for patients that would be flagged by the SPIRIT® Analyzer as being "at high risk" of PI. For this purpose, we assumed that patients referred to the JMCN are also considered at "high risk" of PI and receive extensive immunological work-up to confirm the diagnosis. According to the 2011 survey, 60,364 patients with a defined PI are followed at JMCN centers (Fig. 1). Of these, 23.42% (14,140 subjects) required Ig replacement therapy

Table 13 Costs of the most frequent conditions affecting patients with PI—comparing the year before and the year after diagnosis (Us only)

Condition	Average # of episodes before diagnosis	Average # of episodes postdiagnosis	Cost per patient per episode/day ($)	Annual cost per patient before diagnosis ($)	Annual cost per patient postdiagnosis ($)	Annual savings per patient ($)
# of acute infections	6.38	1.78	3,953	25,299	7,115	18,184
# of severe infections	4.32	0.59	7,649	34,229	4,588	29,641
# of bacterial pneumonias	2.84	0.62	10,089	28,249	6,053	22,196
Days with chronic infections	44.66	12.63	48	2,175	612	1,562
# of physician/hospital/ER visits	70.88	11.79	168	11,875	1,977	9,899
Days hospitalizations	19.18	5.08	1,552	29,792	7,913	21,880
Days on antibiotics	166.22	72.87	6	946	414	532
School/work days missed	33.9	8.9	182	6,195	1,625	4,569
Totals per patient				138,760	30,297	108,462

A *T* test was performed comparing the diagnosed and undiagnosed groups, and the significance was established with a *P* value of 0.001 in all cases

Table 14 Costs of treating "at-risk" patients flagged by SPIRIT® Analyzer

Number of patients followed	79,764
Number of patients with identified PI defects	60,364
Number of patients receiving IgG therapy	14,140
Percentage of patients with identified PI defects on IgG therapy	23.42%
Annual cost per patient pre-Dx	$138,760
Annual cost per patient post-Dx (excluding costs for IgG therapy)	$30,297
Annual savings per patient (excluding costs for IgG therapy)	$108,463
Annual % cost of diagnosed versus undiagnosed (excluding costs for IgG therapy)	21.80%
Annual cost per patient for IgG therapy (average)	$30,000
Annual cost per patient post-Dx (including costs for IgG therapy)	$60,297
Annual savings per patient that requires IgG therapy	$78,166
Annual % cost of diagnosed versus undiagnosed (including costs for IgG therapy)	43.40%

(Table 4). We estimated the costs of medical care per patient in the year before and in the year after diagnosis was made (Table 13). As shown in Table 14, the prediagnosis annual costs per patient in the United States would be $138,760. The annual costs after diagnosis and initiation of Ig replacement therapy (including the cost of such treatment) are estimated to be $60,297, with annual savings per patient of $78,166. As reported by the JMCN, Table 5 demonstrates a difference of 7,318 additional patients as treated with Ig replacement therapy from 2009 to 2011. The cost of this treatment is estimated at an average of $30,000 per patient per year (Table 14). These 7,318 patients who required Ig replacement therapy have an annual cost of $219,540,000. However, if these patients were left undiagnosed and untreated, the annual cost would be increased nearly 5-fold to $1,015,445,680 (Tables 5, 13, 14).

In conclusion, 8 years after initiation of PEPAC, and following the creation of a Network of experienced centers in the diagnosis and treatment for PIs worldwide, a continuous increase in the number of patients referred to and followed by JMCN centers is seen. Although the overall distribution of PIs among JMCN centers is similar to what is reported by other international organizations, regional differences exist, which reflect a higher prevalence of specific gene defects due to founder effect and/or higher degree of parental consanguinity. Because of this, awareness campaigns must also be targeted to meet the unique needs that each geographic area may present. There is further need to promote awareness of PIs and facilitate access to diagnosis and treatment for these patients worldwide. While the "10 warning signs" of PI and the JMCN itself may represent a unique resource in this sense, additional tools must be developed to facilitate identification of patients at higher risk of PIs. We have presented here one such screening tool, the SPIRIT® Analyzer. Both beta-testing and pilot-testing have demonstrated the power of this software in identifying subjects with possible PI. If this quality is confirmed on a larger scale, screening of subjects at risk of PI and timely confirmation of diagnosis will help improve the quality of life for these individuals and may allow the reduction of healthcare-related costs significantly, an important objective at a time of global economic crisis.

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