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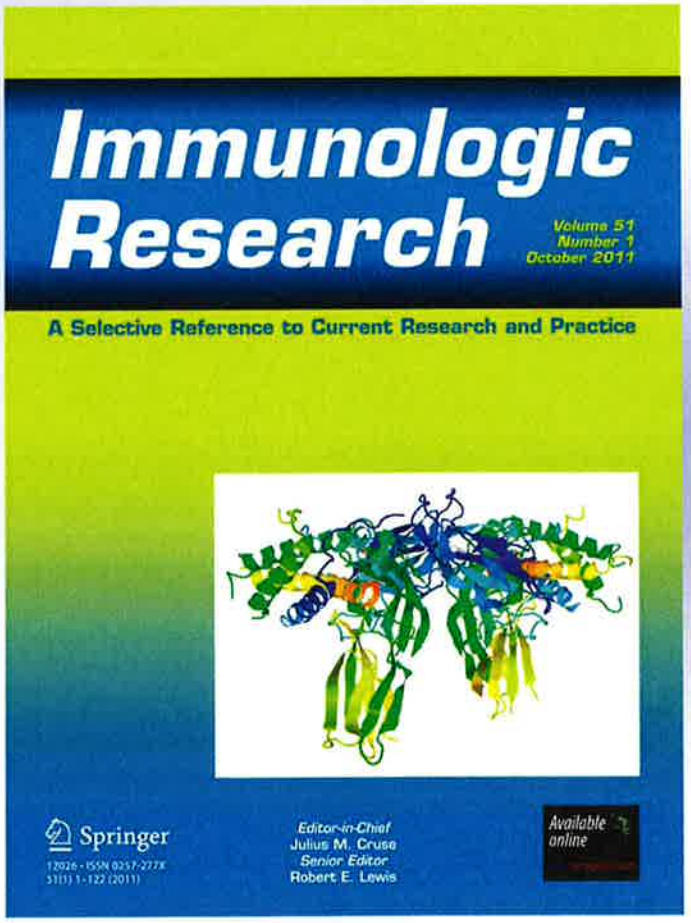

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Global study of primary immunodeficiency diseases (PI)—diagnosis, treatment, and economic impact: an updated report from the Jeffrey Modell Foundation

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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

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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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

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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

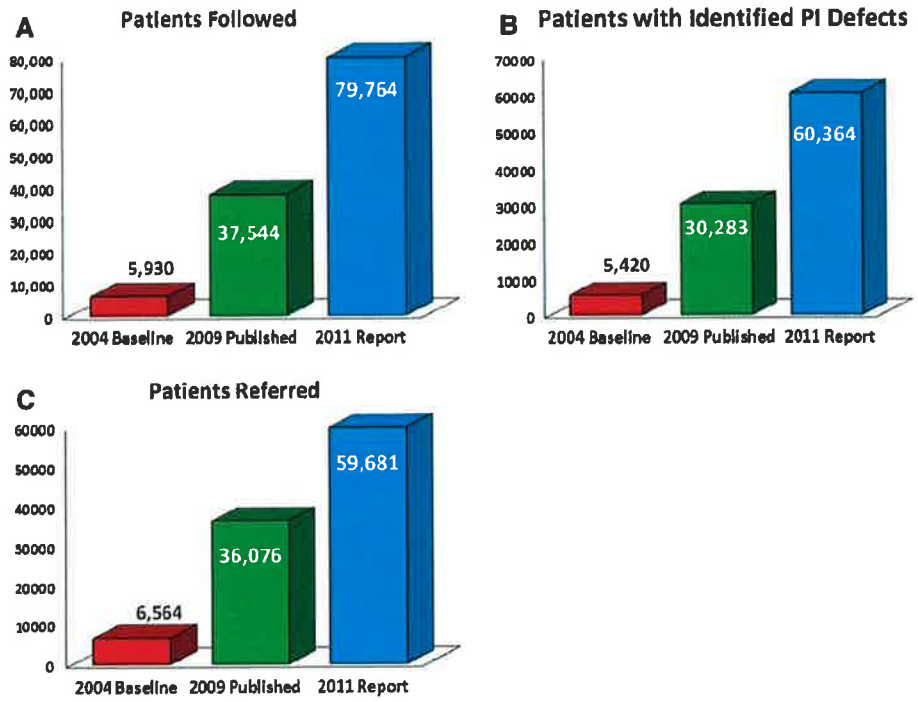

Fig. 1 Patients followed, identified, and referred with specific PI defects

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

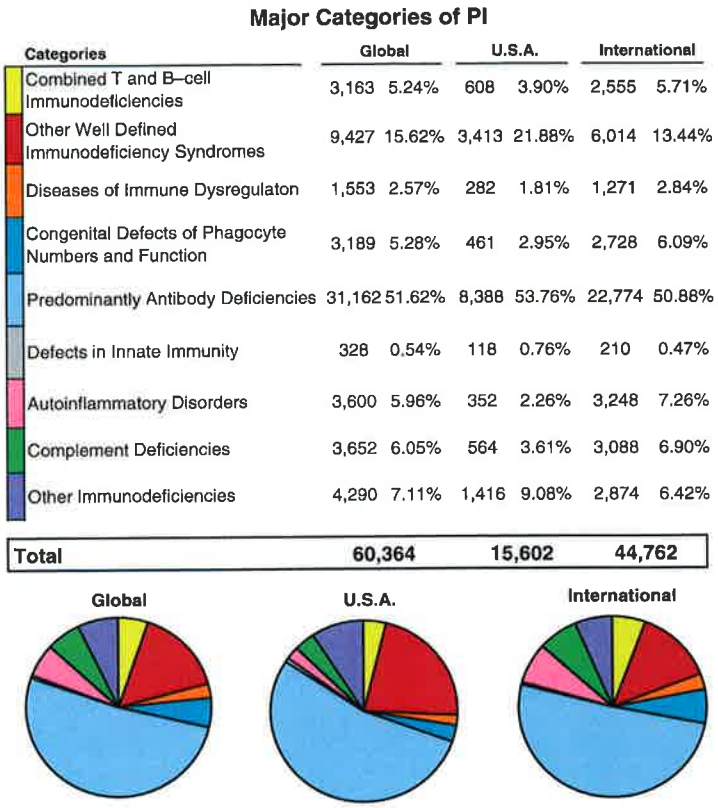

Table 1 Comparison between JMCN global survey reports and ESID registry data [18]

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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Supplementary Table 1.

Patients with Identified PI Defects by Region

Region	Number of Surveys Received	Compliance Rate	Patients with Identifed PI Defects	% of Total
Western Europe	52	82.26%	22,701	37.61%
United States	56	67.06%	15,602	25.85%
Eastern Europe	26	85.19%	5,367	8.89%
Latin America	17	80.95%	4,275	7.08%
Middle East	6	54.55%	3,432	5.69%
Canada	8	88.89%	3,423	5.67%
Asia	17	68.97%	3,127	5.18%
Africa	7	87.50%	1,228	2.03%
Australia	3	100.00%	1,209	2.00%
Total	**192**	**75.59%**	**60,364**	**100.00%**

Supplementary Table 2.

Patients with Identified PI Defects – Global

TABLE I. Combined T and B–cell immunodeficiencies	
ADA Deficiency	298
Artemis Deficiency (DCLREIC)	101
CD3 δ / CD3 ε / CD3 ζ Deficiency	25
Cernunnos Deficiency	10
DNA Ligase IV Deficiency	14
γc Deficiency	454
IL-2Ralpha Deficiency (CD25 Deficiency)	34
IL-7R α Deficiency	98
JAK3 Deficiency	116
MHC Class I or II Deficiency	226
Omenn Syndrome	237
PNP Deficiency	38
RAG 1/2 Deficiency	312
Reticular Dysgenesis (AK2 Deficiency)	15
ZAP-70 Deficiency	51
Other SCID:	1,134
Total	3,163

TABLE II. Other well defined immunodeficiency syndromes	
Ataxia-Telangiectasia (A-T)	2,190
Ataxia-Telangiectasia like Disease (ATLD)	22
Bloom Syndrome	26
Cartilage Hair Hypoplasia	135
Chronic Mucocutaneous Candidiasis	456
Comel-Netherton Syndrome	59
DiGeorge Syndrome (DGS)	4,310
Dyskeratosis Congenita	37
Hyper IgE, AD (STAT3, Job Syndrome)	760
Hyper-IgE, AR (DOCK8, TYK2 Deficiency)	156
ICF-ID Centromeric Instability and Facial Anomalies	15
Nijmegen Breakage Syndrome	227
PMS2 Deficiency	4
Schimke Syndrome	30
Wiskott Aldrich Syndrome (WAS)	1,000
Total	9,427

TABLE III. Diseases of immune dysregulaton	
ALPS Type 1a, CD95 (fas) Defects	242
ALPS, other types	210
APECED	165
Chediak-Higashi Syndrome	174
Griscelli Syndrome Type 2	96
Hermansky Pudlak Syndrome (Type 2; AP3 deficiency)	11
HLH (other types, Munc13-4, Munc 18-2, STX11)	183
HLH Perforin Deficiency	101
IPEX (X-Linked)	80
IPEX-Like Syndrome	77
XLP1, SH2D1A Deficiency	189
XLP2, XIAP Deficiency	25
Total	1,553

TABLE IV. Congenital defects of phagocyte #s and function	
CGD, AR	964
CGD, XL	1,029
Glycogen Storage Disease Type 1b	31
Leukocyte Adhesion Deficiency I	168
Leukocyte Adhesion Deficiency II, III, and others	26
MSMD (IL-12p40, IL12RB, IFN-γR1/2, STAT1 Deficiency)	150
Neutropenia w/ Cardiac + Urogenital Malformations	12
Neutropenia, Cyclical	269
Neutropenia, Severe Congenital (ELA2, HAX1)	505
Neutropenia, XL (WASP mutation)	21
Papillon-Lefèvre Syndrome	14
Total	3,189

TABLE V. Predominantly antibody deficiencies	
Agammaglobulinemia, (XLA)	2,132
Agammaglobulinemia, AR	413
Common Variable Immunodeficiency (CVID)	7,613
Hyper IgM (X Linked, TNFSF5)	465
Hyper IgM, AR (AICDA, UNG, CD40)	304
Hypogammaglobulinemia of Infancy (Transient)	2,713
Hypogammaglobulinemia unspecified	3,148
Ig Heavy Chain Mutations and Deletions	10
IgA Deficiency, Selective	7,061
IgA with IgG Subclass Deficiency	1,055
IgG Subclass Deficiency, Isolated	3,878
Specific Antibody Deficiency (normal Ig and B cells)	2,138
TACI mutation (TNFRSF13B)	159
Thymoma with Immunodeficiency (Good Syndrome)	73
Total	31,162

TABLE VI. Defects in innate immunity	
EDA-ID, AD (NFKBIA mutation)	25
Epidermodysplasia verruciformis (EVER mutation)"	11
Herpes simplex encephalitis HSE (Unc93B, TLR3, others	36
IRAK4 (IL-1 Receptor Associated Kinase 4)	36
MyD88 Deficiency	12
NEMO Deficiency	96
NK cell Deficiency	69
WHIM Syndrome	43
Total	328

TABLE VII. Autoinflammatory disorders	
Blau Syndrome (NOD2 or CARD15)	28
DIRA (IL1RN)	4
Familial Cold Autoinflammatory Syndrome	27
Familial Mediterranean Fever	1,715
Hyper IgD Syndrome	96
Majeed Syndrome (Mutation of LPIN2)	21
Muckle-Wells syndrome	32
NOMID or CINCA	45
PFAPA Syndrome	1,518
TRAPS-TNF Receptor-Associated Periodic Fever	114
Total	3,600

TABLE VIII. Complement deficiencies	
C1 Inhibitor Deficiency	2,045
C1q Deficiency	29
C1r Deficiency	6
C2-C9 Deficiency	580
CD46 Deficiency	10
CR3-Complement Receptor 3 Deficiency	3
Factor D Deficiency	1
Factor H Deficiency	22
Factor I Deficiency	33
MBP/MBL or MASP Deficiency	881
Paroxysmal Nocturnal Hemoglobinuria(PIGA)	22
Properdin Deficiency	20
Total	3,652

"Unspecified" Tables I through VIII:	4,290

Total: 60,364

Supplementary Table 3.

Patients with Identified PI Defects – United States

TABLE I. Combined T and B–cell immunodeficiencies	
ADA Deficiency	99
Artemis Deficiency (DCLREIC)	15
CD3 δ / CD3 ε / CD3 ζ Deficiency	2
Cernunnos Deficiency	1
DNA Ligase IV Deficiency	5
γc Deficiency	135
IL-2Ralpha Deficiency (CD25 Deficiency)	5
IL-7R α Deficiency	34
JAK3 Deficiency	30
MHC Class I or II Deficiency	15
Omenn Syndrome	62
PNP Deficiency	4
RAG 1/2 Deficiency	42
Reticular Dysgenesis (AK2 Deficiency)	6
ZAP-70 Deficiency	18
Other SCID:	135
Total	608

TABLE II. Other well defined immunodeficiency syndromes	
Ataxia-Telangiectasia (A-T)	1,005
Ataxia-Telangiectasia like Disease (ATLD)	11
Bloom Syndrome	1
Cartilage Hair Hypoplasia	57
Chronic Mucocutaneous Candidiasis	90
Comel-Netherton Syndrome	13
DiGeorge Syndrome (DGS)	1,858
Dyskeratosis Congenita	11
Hyper IgE, AD (STAT3, Job Syndrome)	144
Hyper-IgE, AR (DOCK8, TYK2 Deficiency)	19
ICF-ID Centromeric Instability and Facial Anomalies	2
Nijmegen Breakage Syndrome	17
PMS2 Deficiency	0
Schimke Syndrome	4
Wiskott Aldrich Syndrome (WAS)	181
Total	3,413

TABLE III. Diseases of immune dysregulaton	
ALPS Type 1a, CD95 (fas) Defects	43
ALPS, other types	33
APECED	28
Chediak-Higashi Syndrome	19
Griscelli Syndrome Type 2	4
Hermansky Pudlak Syndrome (Type 2; AP3 deficiency)	1
HLH (other types, Munc13-4, Munc 18-2, STX11)	38
HLH Perforin Deficiency	19
IPEX (X-Linked)	28
IPEX-Like Syndrome	26
XLP1, SH2D1A Deficiency	34
XLP2, XIAP Deficiency	9
Total	282

TABLE IV. Congenital defects of phagocyte #s and function	
CGD, AR	105
CGD, XL	198
Glycogen Storage Disease Type 1b	4
Leukocyte Adhesion Deficiency I	20
Leukocyte Adhesion Deficiency II, III, and others	4
MSMD (IL-12p40, IL12RB, IFN-γR1/2, STAT1 Deficiency)	5
Neutropenia w/ Cardiac + Urogenital Malformations	0
Neutropenia, Cyclical	39
Neutropenia, Severe Congenital (ELA2, HAX1)	78
Neutropenia, XL (WASP mutation)	8
Papillon-Lefèvre Syndrome	0
Total	461

TABLE V. Predominantly antibody deficiencies	
Agammaglobulinemia, (XLA)	425
Agammaglobulinemia, AR	66
Common Variable Immunodeficiency (CVID)	2,501
Hyper IgM (X Linked, TNFSF5)	93
Hyper IgM, AR (AICDA, UNG, CD40)	62
Hypogammaglobulinemia of Infancy (Transient)	551
Hypogammaglobulinemia unspecified	1,445
Ig Heavy Chain Mutations and Deletions	6
IgA Deficiency, Selective	1,209
IgA with IgG Subclass Deficiency	172
IgG Subclass Deficiency, Isolated	533
Specific Antibody Deficiency (normal Ig and B cells)	1,278
TACI mutation (TNFRSF13B)	33
Thymoma with Immunodeficiency (Good Syndrome)	14
Total	8,388

TABLE VI. Defects in innate immunity	
EDA-ID, AD (NFKBIA mutation)	5
Epidermodysplasia verruciformis (EVER mutation)"	1
Herpes simplex encephalitis HSE (Unc93B, TLR3, others	3
IRAK4 (IL-1 Receptor Associated Kinase 4)	4
MyD88 Deficiency	6
NEMO Deficiency	49
NK cell Deficiency	44
WHIM Syndrome	6
Total	118

TABLE VII. Autoinflammatory disorders	
Blau Syndrome (NOD2 or CARD15)	7
DIRA (IL1RN)	0
Familial Cold Autoinflammatory Syndrome	16
Familial Mediterranean Fever	100
Hyper IgD Syndrome	22
Majeed Syndrome (Mutation of LPIN2)	1
Muckle-Wells syndrome	5
NOMID or CINCA	3
PFAPA Syndrome	171
TRAPS-TNF Receptor-Associated Periodic Fever	27
Total	352

TABLE VIII. Complement deficiencies	
C1 Inhibitor Deficiency	226
C1q Deficiency	2
C1r Deficiency	3
C2-C9 Deficiency	129
CD46 Deficiency	9
CR3-Complement Receptor 3 Deficiency	0
Factor D Deficiency	1
Factor H Deficiency	3
Factor I Deficiency	3
MBP/MBL or MASP Deficiency	162
Paroxysmal Nocturnal Hemoglobinuria(PIGA)	7
Properdin Deficiency	19
Total	564

"Unspecified" Tables I through VIII:	1,416

Total: 15,602

Supplementary Table 4.

Patients with Identified PI Defects – International

TABLE I. Combined T and B–cell immunodeficiencies	
ADA Deficiency	199
Artemis Deficiency (DCLREIC)	86
CD3 δ / CD3 ε / CD3 ζ Deficiency	23
Cernunnos Deficiency	9
DNA Ligase IV Deficiency	9
γc Deficiency	319
IL-2Ralpha Deficiency (CD25 Deficiency)	29
IL-7R α Deficiency	64
JAK3 Deficiency	86
MHC Class I or II Deficiency	211
Omenn Syndrome	175
PNP Deficiency	34
RAG 1/2 Deficiency	270
Reticular Dysgenesis (AK2 Deficiency)	9
ZAP-70 Deficiency	33
Other SCID:	999
Total	2,555

TABLE II. Other well defined immunodeficiency syndromes	
Ataxia-Telangiectasia (A-T)	1,185
Ataxia-Telangiectasia like Disease (ATLD)	11
Bloom Syndrome	25
Cartilage Hair Hypoplasia	78
Chronic Mucocutaneous Candidiasis	366
Comel-Netherton Syndrome	46
DiGeorge Syndrome (DGS)	2,452
Dyskeratosis Congenita	26
Hyper IgE, AD (STAT3, Job Syndrome)	616
Hyper-IgE, AR (DOCK8, TYK2 Deficiency)	137
ICF-ID Centromeric Instability and Facial Anomalies	13
Nijmegen Breakage Syndrome	210
PMS2 Deficiency	4
Schimke Syndrome	26
Wiskott Aldrich Syndrome (WAS)	819
Total	6,014

TABLE III. Diseases of immune dysregulaton	
ALPS Type 1a, CD95 (fas) Defects	199
ALPS, other types	177
APECED	137
Chediak-Higashi Syndrome	155
Griscelli Syndrome Type 2	92
Hermansky Pudlak Syndrome (Type 2; AP3 deficiency)	10
HLH (other types, Munc13-4, Munc 18-2, STX11)	145
HLH Perforin Deficiency	82
IPEX (X-Linked)	52
IPEX-Like Syndrome	51
XLP1, SH2D1A Deficiency	155
XLP2, XIAP Deficiency	16
Total	1,271

TABLE IV. Congenital defects of phagocyte #s and function	
CGD, AR	859
CGD, XL	831
Glycogen Storage Disease Type 1b	27
Leukocyte Adhesion Deficiency I	148
Leukocyte Adhesion Deficiency II, III, and others	22
MSMD (IL-12p40, IL12RB, IFN-γR1/2, STAT1 Deficiency)	145
Neutropenia w/ Cardiac + Urogenital Malformations	12
Neutropenia, Cyclical	230
Neutropenia, Severe Congenital (ELA2, HAX1)	427
Neutropenia, XL (WASP mutation)	13
Papillon-Lefèvre Syndrome	14
Total	2,728

TABLE V. Predominantly antibody deficiencies	
Agammaglobulinemia, (XLA)	1,707
Agammaglobulinemia, AR	347
Common Variable Immunodeficiency (CVID)	5,112
Hyper IgM (X Linked, TNFSF5)	372
Hyper IgM, AR (AICDA, UNG, CD40)	242
Hypogammaglobulinemia of Infancy (Transient)	2,162
Hypogammaglobulinemia unspecified	1,703
Ig Heavy Chain Mutations and Deletions	4
IgA Deficiency, Selective	5,852
IgA with IgG Subclass Deficiency	883
IgG Subclass Deficiency, Isolated	3,345
Specific Antibody Deficiency (normal Ig and B cells)	860
TACI mutation (TNFRSF13B)	126
Thymoma with Immunodeficiency (Good Syndrome)	59
Total	22,774

TABLE VI. Defects in innate immunity	
EDA-ID, AD (NFKBIA mutation)	20
Epidermodysplasia verruciformis (EVER mutation)"	10
Herpes simplex encephalitis HSE (Unc93B, TLR3, others	33
IRAK4 (IL-1 Receptor Associated Kinase 4)	32
MyD88 Deficiency	6
NEMO Deficiency	47
NK cell Deficiency	25
WHIM Syndrome	37
Total	210

TABLE VII. Autoinflammatory disorders	
Blau Syndrome (NOD2 or CARD15)	21
DIRA (IL1RN)	4
Familial Cold Autoinflammatory Syndrome	11
Familial Mediterranean Fever	1,615
Hyper IgD Syndrome	74
Majeed Syndrome (Mutation of LPIN2)	20
Muckle-Wells syndrome	27
NOMID or CINCA	42
PFAPA Syndrome	1,347
TRAPS-TNF Receptor-Associated Periodic Fever	87
Total	3,248

TABLE VIII. Complement deficiencies	
C1 Inhibitor Deficiency	1,819
C1q Deficiency	27
C1r Deficiency	3
C2-C9 Deficiency	451
CD46 Deficiency	1
CR3-Complement Receptor 3 Deficiency	3
Factor D Deficiency	0
Factor H Deficiency	19
Factor I Deficiency	30
MBP/MBL or MASP Deficiency	719
Paroxysmal Nocturnal Hemoglobinuria(PIGA)	15
Properdin Deficiency	1
Total	3,088

"Unspecified" Tables I through VIII:	2,874

Total: 44,762

Supplementary Table 5.

PI Defects Listed by Prevalence

1	Common Variable Immunodeficiency (CVID)	7,613	2,501	5,112
2	IgA Deficiency, Selective	7,061	1,209	5,852
3	DiGeorge Syndrome (DGS)	4,310	1,858	2,452
4	IgG Subclass Deficiency, Isolated	3,878	533	3,345
5	Combined T and B–cell immunodeficiencies	3,163	66	2,555
6	Hypogammaglobulinemia unspecified	3,148	1,445	1,703
7	Hypogammaglobulinemia of Infancy (Transient)	2,713	551	2,162
8	Ataxia-Telangiectasia (A-T)	2,190	1,005	1,185
9	Specific Antibody Deficiency (normal Ig and B cells)	2,138	1,278	860
10	Agammaglobulinemia, (XLA)	2,132	425	1,707
11	C1 Inhibitor Deficiency	2,045	226	1,819
12	Familial Mediterranean Fever	1,715	100	1,615
13	PFAPA Syndrome	1,518	171	1,347
14	IgA with IgG Subclass Deficiency	1,055	172	883
15	CGD, XL	1,029	198	831
16	Wiskott Aldrich Syndrome (WAS)	1,000	181	819
17	CGD, AR	964	105	859
18	MBP/MBL or MASP Deficiency	881	162	719
19	Hyper IgE, AD (STAT3, Job Syndrome)	760	144	616
20	C2-C9 Deficiency	580	129	451
21	Neutropenia, Severe Congenital (ELA2, HAX1)	505	78	427
22	Hyper IgM (X Linked, TNFSF5)	465	93	372
23	Chronic Mucocutaneous Candidiasis	456	90	366
24	Agammaglobulinemia, AR	413	66	347
25	Hyper IgM, AR (AICDA, UNG, CD40)	304	62	242
26	Neutropenia, Cyclical	269	39	230
27	ALPS Type 1a, CD95 (fas) Defects	242	43	199
28	Nijmegen Breakage Syndrome	227	17	210
29	ALPS, other types	210	33	177
30	XLP1, SH2D1A Deficiency	189	34	155
31	HLH (other types, Munc13-4, Munc 18-2, STX11)	183	38	145
32	Chediak-Higashi Syndrome	174	19	155
33	Leukocyte Adhesion Deficiency I	168	20	148
34	APECED	165	28	137
35	TACI mutation (TNFRSF13B)	159	33	126
36	Hyper-IgE, AR (DOCK8, TYK2 Deficiency)	156	19	137
37	MSMD (IL-12p40, IL12RB, IFN-γR1/2, STAT1 Deficiency)	150	5	145
38	Cartilage Hair Hypoplasia	135	57	78
39	TRAPS-TNF Receptor-Associated Periodic Fever	114	27	87
40	HLH Perforin Deficiency	101	19	82
41	Griscelli Syndrome Type 2	96	4	92
42	NEMO Deficiency	96	49	47
43	Hyper IgD Syndrome	96	22	74
44	IPEX (X-Linked)	80	28	52
45	IPEX-Like Syndrome	77	26	51
46	Thymoma with Immunodeficiency (Good Syndrome)	73	14	59
47	NK cell Deficiency	69	44	25
48	Comel-Netherton Syndrome	59	13	46
49	NOMID or CINCA	45	3	42
50	WHIM Syndrome	43	6	37
51	Dyskeratosis Congenita	37	11	26
52	Herpes simplex encephalitis HSE (Unc93B, TLR3, others)	36	3	33
53	IRAK4 (IL-1 Receptor Associated Kinase 4)	36	4	32
54	Factor I Deficiency	33	3	30
55	Muckle-Wells syndrome	32	5	27
56	Glycogen Storage Disease Type 1b	31	4	27
57	Schimke Syndrome	30	4	26
58	C1q Deficiency	29	2	27
59	Blau Syndrome (NOD2 or CARD15)	28	7	21
60	Familial Cold Autoinflammatory Syndrome	27	16	11
61	Bloom Syndrome	26	1	25
62	Leukocyte Adhesion Deficiency II, III, and others	26	4	22
63	EDA-ID, AD (NFKBIA mutation)	25	5	20
64	XLP2, XIAP Deficiency	25	9	16
65	Ataxia-Telangiectasia like Disease (ATLD)	22	11	11
66	Factor H Deficiency	22	3	19
67	Paroxysmal Nocturnal Hemoglobinuria(PIGA)	22	7	15
68	Majeed Syndrome (Mutation of LPIN2)	21	1	20
69	Neutropenia, XL (WASP mutation)	21	8	13
70	Properdin Deficiency	20	19	1
71	ICF-ID Centromeric Instability and Facial Anomalies	15	2	13
72	Papillon-Lefèvre Syndrome	14	0	14
73	MyD88 Deficiency	12	6	6
74	Neutropenia w/ Cardiac + Urogenital Malformations	12	0	12
75	Epidermodysplasia verruciformis (EVER mutation)"	11	1	10
76	Hermansky Pudlak Syndrome (Type 2; AP3 deficiency)	11	1	10
77	CD46 Deficiency	10	9	1
78	Ig Heavy Chain Mutations and Deletions	10	6	4
79	C1r Deficiency	6	3	3
80	DIRA (IL1RN)	4	0	4
81	PMS2 Deficiency	4	0	4
82	CR3-Complement Receptor 3 Deficiency	3	0	3
83	Factor D Deficiency	1	1	0

Supplementary Table 6.

Patients with Identified PI Defects – Global

2004 Baseline vs. 2009 Published vs. 2011 Report

TABLE I. Combined T and B–cell immunodeficiencies	2004	2009	2011
ADA Deficiency	60	166	298
Artemis Deficiency (DCLRE1C)	N/A	90	101
CD3δ / CD3ε / CD3ζ Deficiency	N/A	8	25
Cernunnos Deficiency	N/A	N/A	10
DNA Ligase IV Deficiency	N/A	N/A	14
γc Deficiency	83	312	454
IL-2Ralpha Deficiency (CD25 Deficiency)	N/A	N/A	34
IL-7Rα Deficiency	N/A	74	98
JAK3 Deficiency	N/A	54	116
MHC Class I or II Deficiency	10	110	226
Omenn Syndrome	6	110	237
PNP Deficiency	N/A	14	38
RAG 1/2 Deficiency	N/A	118	312
Reticular Dysgenesis (AK2 Deficiency)	N/A	N/A	15
ZAP-70 Deficiency	N/A	27	51
Other SCID:	287	847	1,134
Total	446	1,930	3,163

TABLE II. Other well defined immunodeficiency syndromes	2004	2009	2011
Ataxia-Telangiectasia (A-T)	324	1,487	2,190
Ataxia-Telangiectasia like Disease (ATLD)			22
Bloom Syndrome	N/A	N/A	26
Cartilage Hair Hypoplasia	N/A	62	135
Chronic Mucocutaneous Candidiasis	N/A	253	456
Cornel-Netherton Syndrome	N/A	N/A	59
DiGeorge Syndrome (DGS)	864	2,665	4,310
Dyskeratosis Congenita	N/A	N/A	37
Hyper IgE, AD (STAT3, Job Syndrome)	N/A	528	760
Hyper-IgE, AR (DOCK8, TYK2 Deficiency)	N/A		156
ICF-ID Centromeric Instability and Facial Anomalies	N/A	N/A	15
Nijmegen Breakage Syndrome	6	145	227
PMS2 Deficiency	N/A	N/A	4
Schimke Syndrome	N/A	N/A	30
Wiskott Aldrich Syndrome (WAS)	151	706	1,000
Total	1,345	5,846	9,427

TABLE III. Diseases of immune dysregulaton	2004	2009	2011
ALPS Type 1a, CD95 (fas) Defects	97	333	242
ALPS, other types			210
APECED	N/A	127	165
Chediak-Higashi Syndrome	12	113	174
Griscelli Syndrome Type 2	3	46	96
Hermansky Pudlak Syndrome (Type 2; AP3 deficiency)	N/A	N/A	11
HLH (other types, Munc13-4, Munc 18-2, STX11)	N/A	N/A	183
HLH Perforin Deficiency	N/A	N/A	101
IPEX (X-Linked)	15	62	80
IPEX-Like Syndrome			77
XLP1, SH2D1A Deficiency	40	140	189
XLP2, XIAP Deficiency			25
Total	167	821	1,553

TABLE IV. Congenital defects of phagocyte #s and function	2004	2009	2011
CGD, AR	186	1,399	964
CGD, XL			1,029
Glycogen Storage Disease Type 1b	N/A	N/A	31
Leukocyte Adhesion Deficiency I	33	127	168
Leukocyte Adhesion Deficiency II, III, and others			26
MSMD (IL-12p40, IL12RB, IFN-γR1/2, STAT1 Deficiency)	N/A	N/A	150
Neutropenia w/ Cardiac + Urogenital Malformations	82	553	12
Neutropenia, Cyclical			269
Neutropenia, Severe Congenital (ELA2, HAX1)			505
Neutropenia, XL (WASP mutation)			21
Papillon-Lefèvre Syndrome	N/A	N/A	14
Total	301	2,079	3,189

TABLE V. Predominantly antibody deficiencies	2004	2009	2011
Agammaglobulinemia, (XLA)	369	1,347	2,132
Agammaglobulinemia, AR	N/A	247	413
Common Variable Immunodeficiency (CVID)	745	4,292	7,613
Hyper IgM (X Linked, TNFSF5)	83	327	465
Hyper IgM, AR (AICDA, UNG, CD40)	88	285	304
Hypogammaglobulinemia of Infancy (Transient)	127	1,771	2,713
Hypogammaglobulinemia unspecified	N/A	N/A	3,148
Ig Heavy Chain Mutations and Deletions	N/A	N/A	10
IgA Deficiency, Selective	867	3,072	7,061
IgA with IgG Subclass Deficiency	N/A	N/A	1,055
IgG Subclass Deficiency, Isolated	326	3,239	3,878
Specific Antibody Deficiency (normal Ig and B cells)	144	2,261	2,138
TACI mutation (TNFRSF13B)	N/A	N/A	159
Thymoma with Immunodeficiency (Good Syndrome)	N/A	N/A	73
Total	2,749	16,841	31,162

TABLE VI. Defects in innate immunity	2004	2009	2011
EDA-ID, AD (NFKBIA mutation)	N/A	N/A	25
Epidermodysplasia verruciformis (EVER mutation)*	N/A	N/A	11
Herpes simplex encephalitis HSE (Unc93B, TLR3, other	N/A	N/A	36
IRAK4 (IL-1 Receptor Associated Kinase 4)	N/A	N/A	36
MyD88 Deficiency	N/A	N/A	12
NEMO Deficiency	3	72	96
NK cell Deficiency	N/A	N/A	69
WHIM Syndrome	N/A	26	43
Total	3	98	328

TABLE VII. Autoinflammatory disorders	2004	2009	2011
Blau Syndrome (NOD2 or CARD15)	N/A	N/A	28
DIRA (IL1RN)	N/A	N/A	4
Familial Cold Autoinflammatory Syndrome	N/A	N/A	27
Familial Mediterranean Fever	N/A	N/A	1,715
Hyper IgD Syndrome	N/A	N/A	96
Majeed Syndrome (Mutation of LPIN2)	N/A	N/A	21
Muckle-Wells syndrome	N/A	N/A	32
NOMID or CINCA	N/A	N/A	45
PFAPA Syndrome	N/A	N/A	1,518
TRAPS-TNF Receptor-Associated Periodic Fever	N/A	N/A	114
Total	0	0	3,600

TABLE VIII. Complement deficiencies	2004	2009	2011
C1 Inhibitor Deficiency	7	602	2,045
C1q Deficiency			29
C1r Deficiency			6
C2-C9 Deficiency			580
CD46 Deficiency			10
CR3-Complement Receptor 3 Deficiency			3
Factor D Deficiency			1
Factor H Deficiency			22
Factor I Deficiency			33
MBP/MBL or MASP Deficiency			881
Paroxysmal Nocturnal Hemoglobinuria(PIGA)			22
Properdin Deficiency			20
Total	7	602	3,652

*"Unspecified" Tables I through VIII:	402	2,066	4,290
Total:	**5,420**	**30,283**	**60,364**