From genotype to phenotype. Further studies measuring the impact of a Physician Education and Public Awareness Campaign on early diagnosis and management of Primary Immunodeficiencies

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Abstract *Rationale* The objective of these studies was to assess the impact of the Jeffrey Modell Foundation's Physician Education and Public Awareness Campaign (PEPAC) on early diagnosis and management of Primary Immunodeficiencies (PI), and to make available an overview of the data provided by physician experts from the Jeffrey Modell Centers Network (JMCN) of Diagnostic, Research, and Referral Centers worldwide. The Network includes over 304 expert physicians at 138 academic teaching hospitals and medical schools in 39 countries and 120 cities, spanning 6 continents. *Methods* A survey was sent to the director of each center to ask how many patients were referred, diagnosed, followed, and treated at the centers. Each center was also asked to provide a list of the specific PI defects seen among their patients. *Results* (i) The PEPAC generated substantial increases in diagnosis, referrals, and treatment of patients with PI disease. (ii) The number of diagnostic tests performed by participating physicians at Jeffrey Modell Centers increased annually by nearly 5 times over a 4 year period. (iii) The number of patients reported with a suspected PI disease totaled 37,544 and 30,283 of these patients were identified with specific PI defects. (iv) The data was sorted and reported in the order of the 43 major PI diseases, and classified by the 8 major PI groups. The data was further organized by the 9 major geographic regions participating and the 15 leading defects by region. (v) The JMCN reports were compared to the European Society for Immunodeficiencies (ESID) registry and there was little difference in the respective percentages for the major immunodeficiency groups. *Conclusions* These studies provide insight on the number of patients followed, diagnosed, and treated at Jeffrey Modell Centers around the world, the specific PI defect of 30,283 patients, where they were diagnosed and treated, who diagnosed and treated them, and what type of treatment that they are receiving.

Keyword Primary 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 US 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 their management is low amongst both physicians and the general public and many patients are left undiagnosed.

Considering the high morbidity and mortality associated with PIs, 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 PEPAC are to: (1) identify patients with PI as early as possible, (2) refer ''At Risk'' patients to specialized JMF Centers, (3) diagnose patients precisely to identify the specific defect, and (4) treat the defect effectively.

The campaign's target audiences include primary care physicians, family practitioners, pediatricians, sub specialists, emergency rooms, school nurses, registered nurses, third party payers, patients, and the public. Components utilized in the PEPAC program include: 10 Warning Signs poster, Physician Algorithm, CME symposia, websites for physicians and patients, graphic posters of the immune system, Kids Days, WIN program support, and public service advertising.

To assess the impact of the PEPAC, in terms of referral and diagnosis rates and to measure the clinical and economic impact of PI diagnosis, 6 separate studies were conducted. The data was compiled from reports provided by physician experts from the Jeffrey Modell Centers Network (JMCN) of Diagnostic, Research, and Referral Centers worldwide.

The quality of the physician network is reflected, in part, by the significant presence of Jeffrey Modell Diagnostic, Research, and Referral Centers among the 30 best pediatric hospitals in the United States. Nine of the top 10 and 24 of the top 30 pediatric hospitals are Jeffrey Modell Diagnostic, Research, and Referral Centers [7].

The following studies are included in this publication:

Study I: The impact of the PEPAC on Referrals, Diagnoses, and Treatment at Jeffrey Modell Centers worldwide.
Study II: Identifying the specific PI defects of 30,283 out of a total of 37,544 patients with a suspected PI disease at Jeffrey Modell Centers worldwide, with a breakdown by US and International.
Study III: Identifying the 43 major PI diseases in 9 geographic regions reported by JMCN worldwide.
Study IV: Evaluating the quality and consistency of the data by comparing survey reports from the JMCN and the ESID Registry.
Study V: Measuring clinical outcomes and quality of life data before and after diagnosis for patients with PI disease.
Study VI: Comparing the economic impact of undiagnosed and diagnosed patients with PI (in the US only).

Study I: The impact of the PEPAC on referrals, diagnoses, and treatment at Jeffrey Modell Centers worldwide

To assess the impact of the PEPAC, in terms of referral and diagnosis rates, data was collected from 304 physicians at 138 academic teaching hospitals and medical schools in 39 countries and 120 cities, spanning 6 continents. All participating physicians follow a large number of patients with PI disease.

The data was generated as follows:

- Three hundred and four physicians from 138 Jeffrey Modell Diagnostic, Research, and Referral Centers participated by responding to the survey questions provided by JMF.
- Responses came from Centers in the United States, Canada, Western and Eastern Europe, the Middle East, Latin America, Asia, Australia, and Africa.
- JMF received survey responses from physicians in 39 countries and 120 cities, spanning 6 continents.
- The submitted data was collected in 2007 and early 2008. The data was measured against baseline surveys previously submitted in 2002, 2003, and 2004.
- All percentages reflect average annual increases.

Results

The following Figs. (1, 2, 3, 4, 5, 6) represent the results of the number of patients being followed, number of patients identified with PI defects, number of patients referred, number of patients receiving treatment, number of patients receiving IVIG, and number of diagnostic tests performed.

The results show a significant impact on referrals, diagnosis and treatment of patients with PI as a result of the PEPAC.

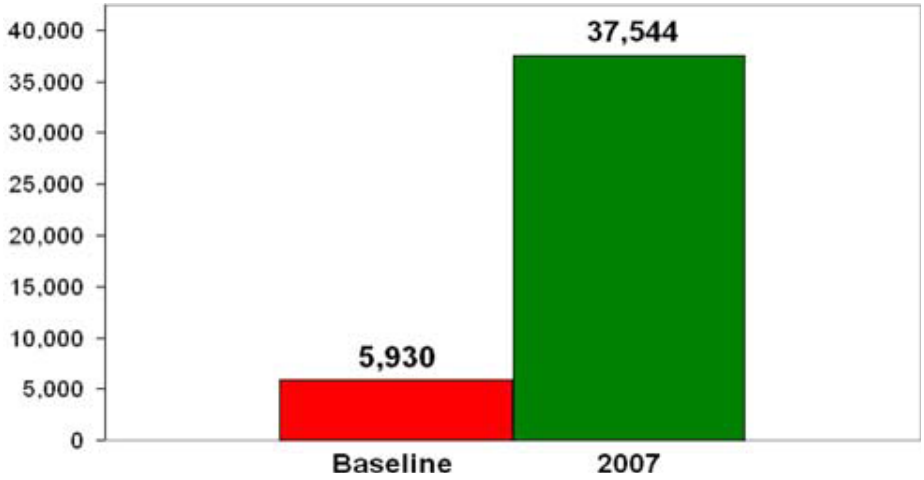


Fig. 1 Number of patients being followed. Average annual increase of 133%. 2007 data measured against baseline (2002–2004). *Source:* Survey of Jeffrey Modell Centers

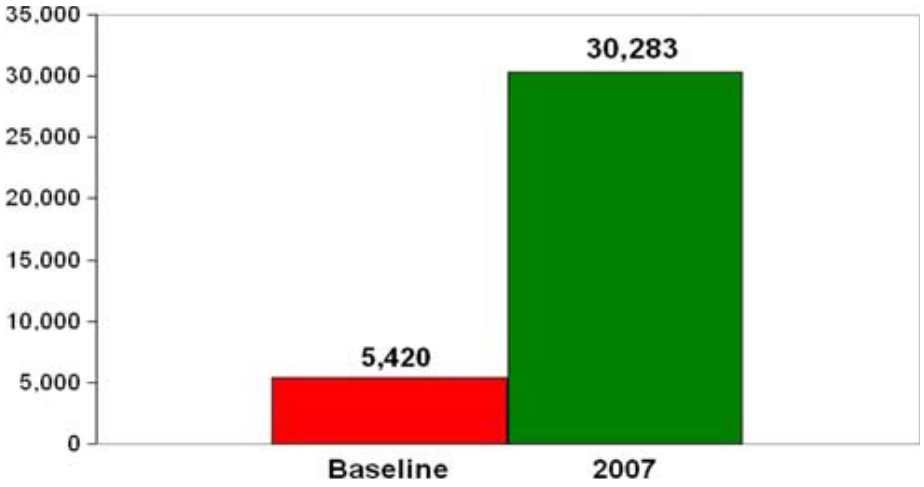


Fig. 2 Number of patients with identified PI defects. Average annual increase of 115%. 2007 data measured against baseline (2002–2004). *Source:* Survey of Jeffrey Modell Centers

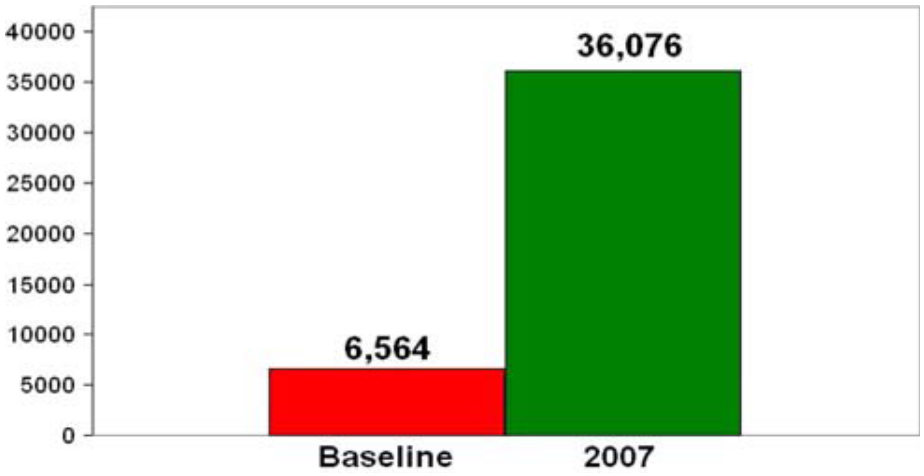


Fig. 3 Number of patients referred. Average annual increase of 112%. 2007 data measured against baseline (2002–2004). *Source:* Survey of Jeffrey Modell Centers

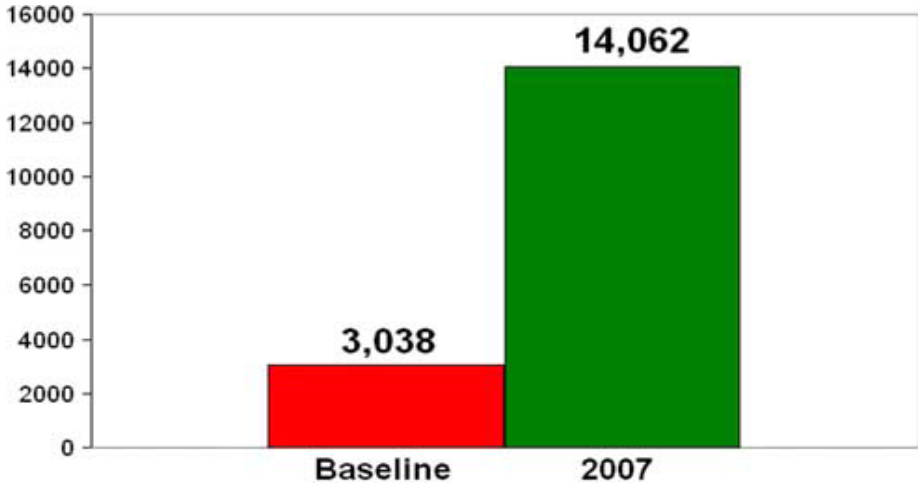


Fig. 4 Number of patients receiving treatment. Average annual increase of 91%. 2007 data measured against baseline (2002–2004). *Source:* Survey of Jeffrey Modell Centers

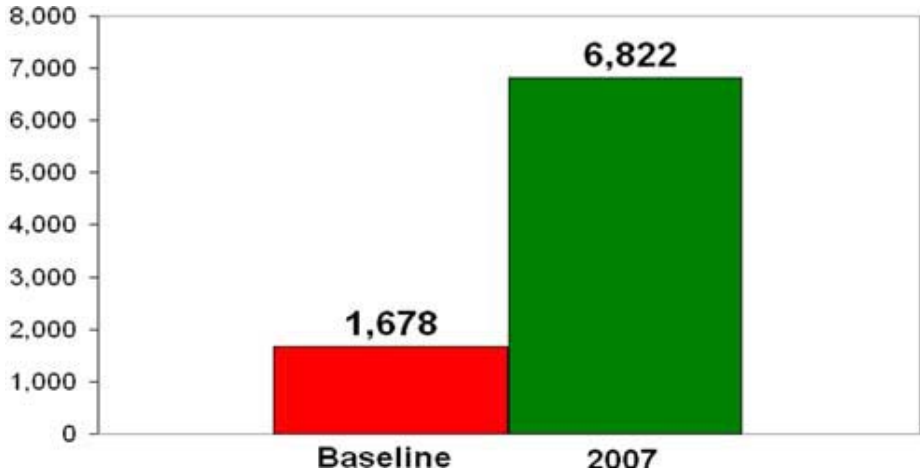


Fig. 5 Number of patients receiving IVIG. Average annual increase of 77%. 2007 data measured against baseline (2002–2004). *Source:* Survey of Jeffrey Modell Centers

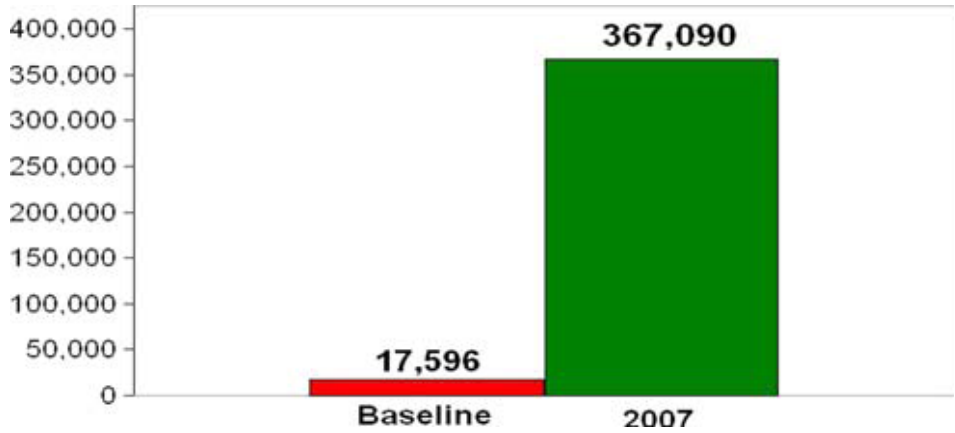


Fig. 6 Number of diagnostic tests performed. Average annual increase of 497%. 2007 data measured against baseline (2002–2004). *Source:* Survey of Jeffrey Modell Centers

Study II: Identifying the specific PI defects of 30,283 out of a total of 37,544 patients with a suspected PI disease at Jeffrey Modell Centers worldwide, with a breakdown by US and International

The data was generated as follows:

- Surveys were distributed to physician experts at the Jeffrey Modell Diagnostic, Research, and Referral Centers worldwide. The surveys were completed and returned to JMF by 304 physicians at 138 academic hospitals and medical schools, in 39 countries and 120 cities, spanning 6 continents.
- Survey participants provided information on the total number of patients they followed, as well as the number of patients with specific PI defects.
- Overall, 37,544 patients were reported as being followed with a suspected PI disorder and 30,283 patients were identified with specific PI defects.
- The diseases reported were broken down by Global, United States, and International and classified by the 8 major PI groups.

Results

The total number of patients with specific PI defects globally, broken down within the major immunodeficiency groups, is represented in Table 1.

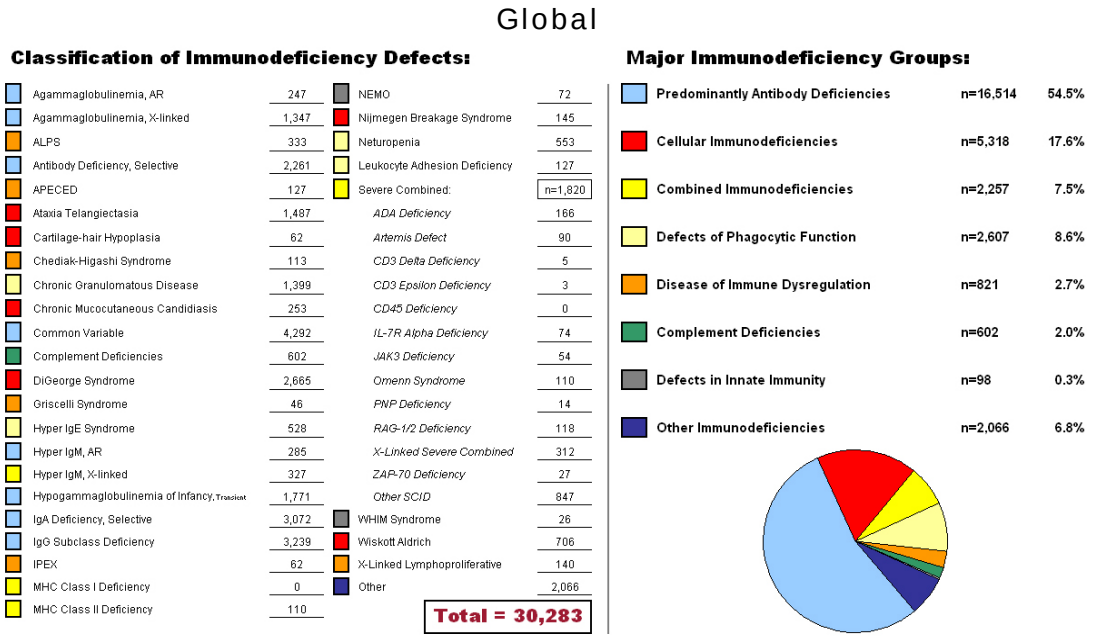
The total number of patients with specific PI defects in the United States, broken down within the major immunodeficiency groups, is represented in Table 2.

The total number of patients with specific PI defects internationally (outside the United States), broken down within the major immunodeficiency groups, is represented in Table 3.

The incidence and prevalence of PI diseases classified within the 8 major PI groups is represented in Table 4.

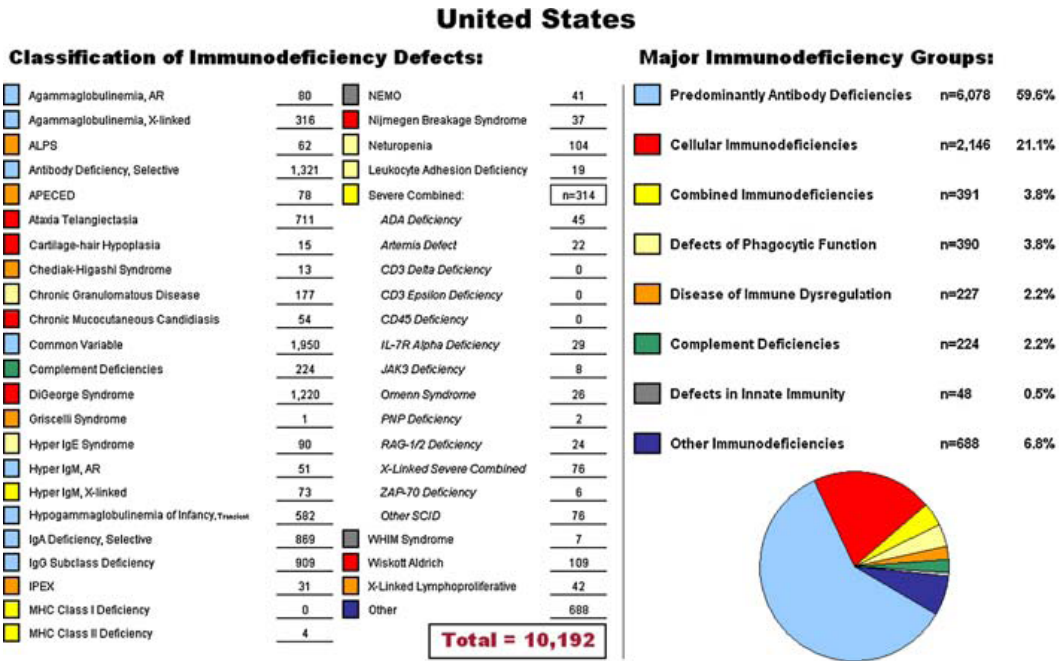
The results show the specific PI defects of 30,283 patients out of a total of 37,544 patients being followed at Jeffrey Modell Centers worldwide.

Table 1 Total of 30,283 patients worldwide identified with specific PI defects



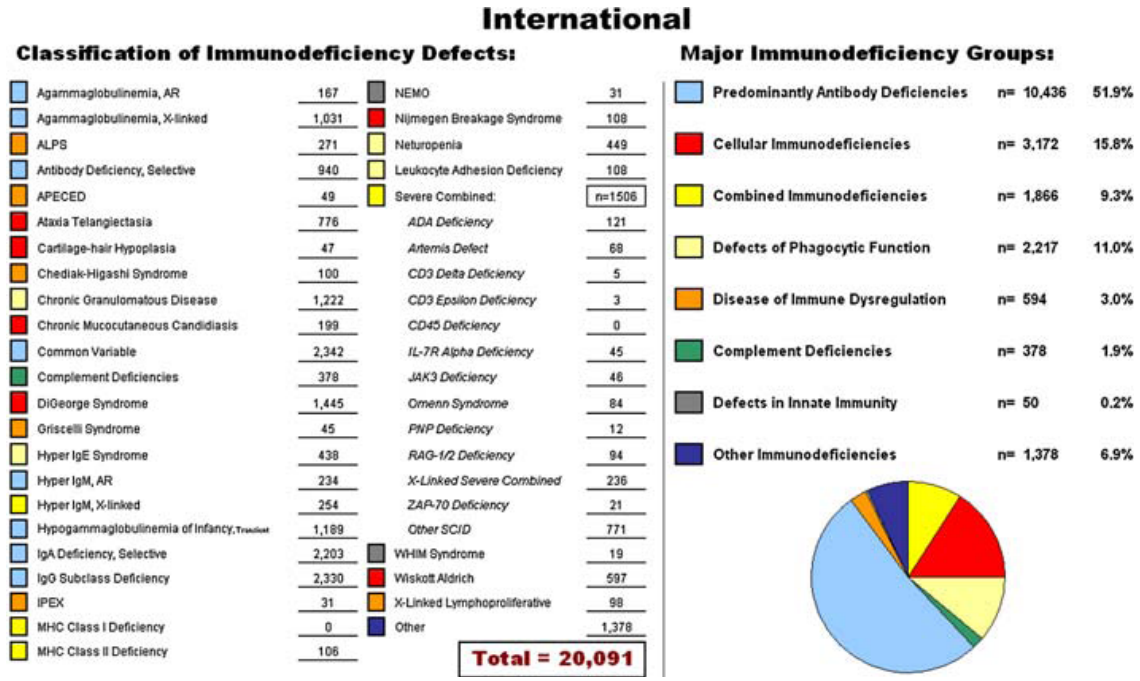
Source: Survey of Jeffrey Modell Centers

Table 2 Total of 10,192 patients in the United States identified with specific PI defects



Source: Survey of Jeffrey Modell Centers

Table 3 Total of 20,091 patients internationally (outside the United States) identified with specific PI defects



International

Classification of Immunodeficiency Defects:

Agammaglobulinemia, AR	167	NEMO	31
Agammaglobulinemia, X-linked	1,031	Nijmegen Breakage Syndrome	108
ALPS	271	Neturopenia	449
Antibody Deficiency, Selective	940	Leukocyte Adhesion Deficiency	108
APECED	49	Severe Combined:	n=1506
Ataxia Telangiectasia	776	*ADA Deficiency*	121
Cartilage-hair Hypoplasia	47	*Artemis Defect*	68
Chediak-Higashi Syndrome	100	*CD3 Delta Deficiency*	5
Chronic Granulomatous Disease	1,222	*CD3 Epsilon Deficiency*	3
Chronic Mucocutaneous Candidiasis	199	*CD45 Deficiency*	0
Common Variable	2,342	*IL-7R Alpha Deficiency*	45
Complement Deficiencies	378	*JAK3 Deficiency*	46
DiGeorge Syndrome	1,445	*Omenn Syndrome*	84
Griscelli Syndrome	45	*PNP Deficiency*	12
Hyper IgE Syndrome	438	*RAG-1/2 Deficiency*	94
Hyper IgM, AR	234	*X-Linked Severe Combined*	236
Hyper IgM, X-linked	254	*ZAP-70 Deficiency*	21
Hypogammaglobulinemia of Infancy, Transient	1,189	*Other SCID*	771
IgA Deficiency, Selective	2,203	WHIM Syndrome	19
IgG Subclass Deficiency	2,330	Wiskott Aldrich	597
IPEX	31	X-Linked Lymphoproliferative	98
MHC Class I Deficiency	0	Other	1,378
MHC Class II Deficiency	106		

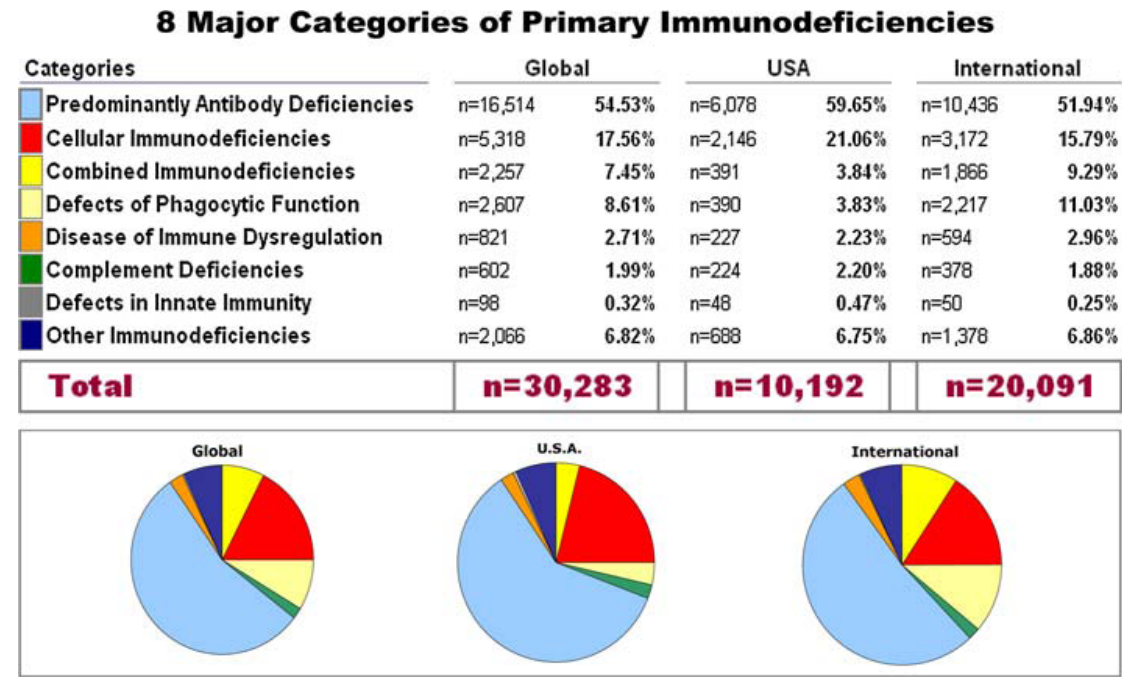
Total = 20,091

Major Immunodeficiency Groups:

Predominantly Antibody Deficiencies	n= 10,436	51.9%
Cellular Immunodeficiencies	n= 3,172	15.8%
Combined Immunodeficiencies	n= 1,866	9.3%
Defects of Phagocytic Function	n= 2,217	11.0%
Disease of Immune Dysregulation	n= 594	3.0%
Complement Deficiencies	n= 378	1.9%
Defects in Innate Immunity	n= 50	0.2%
Other Immunodeficiencies	n= 1,378	6.9%

Source: Survey of Jeffrey Modell Centers

Table 4 Eight major categories of Primary Immunodeficiencies



8 Major Categories of Primary Immunodeficiencies

Categories	Global		USA		International	
Predominantly Antibody Deficiencies	n=16,514	54.53%	n=6,078	59.65%	n=10,436	51.94%
Cellular Immunodeficiencies	n=5,318	17.56%	n=2,146	21.06%	n=3,172	15.79%
Combined Immunodeficiencies	n=2,257	7.45%	n=391	3.84%	n=1,866	9.29%
Defects of Phagocytic Function	n=2,607	8.61%	n=390	3.83%	n=2,217	11.03%
Disease of Immune Dysregulation	n=821	2.71%	n=227	2.23%	n=594	2.96%
Complement Deficiencies	n=602	1.99%	n=224	2.20%	n=378	1.88%
Defects in Innate Immunity	n=98	0.32%	n=48	0.47%	n=50	0.25%
Other Immunodeficiencies	n=2,066	6.82%	n=688	6.75%	n=1,378	6.86%
Total	**n=30,283**		**n=10,192**		**n=20,091**	

Global

U.S.A.

International

Source: Survey of Jeffrey Modell Centers

Study III: Identifying the 43 major PI diseases in 9 geographic regions reported by JMCN worldwide

The data was generated as follows:

- The number of patients with specific defects was ranked in order of incidence covering the 43 major PI diseases.
- The 30,283 patients reported by the JMCN with specific defects were identified in 9 major geographic regions.
- The 15 leading PI defects were summarized in each of the 9 regions.

Results

The total number of specific PI defects covering the 43 major PI diseases is represented in Table 5.

The total number of patients with identified PI defects in each of 9 geographic regions is represented by Table 6.

The 15 leading PI defects, identified by region, are shown in Table 7. The 15 leading PI defects totaled 27,811 of the 30,283 patients or 91.8% of the total patients identified with PI defects.

The results show the incidence and prevalence of the major PI disease in 9 geographic regions, as reported by the JMCN.

Table 5 Listing of all PI defects on JMF survey, ordered by prevalence

Listing of all PI Defects on JMF Survey

	Leading 15 PI Defects	Global	U.S.A.	Int'l
1	Common Variable	4,292	1,950	2,342
2	IgG Subclass Deficiency	3,239	909	2,330
3	IgA Deficiency, Selective	3,072	869	2,203
4	DiGeorge Syndrome	2,665	1,220	1,445
5	Other Pts	2,066	688	1,378
6	Antibody Deficiency, Selective	2,261	1,321	940
7	Hypogammaglobulinemia of Infancy, Transient	1,771	582	1,189
8	Ataxia Telangiectasia	1,487	711	776
9	Chronic Granulomatous Disease	1,399	177	1,222
10	Agammaglobulinemia, X-Linked	1,347	316	1,031
11	Severe Combined - Other	847	76	771
12	Wiskott Aldrich Syndrome	706	109	597
13	Complement Deficiencies	602	224	378
14	Neutropenia	553	104	449
15	Hyper IgE Syndrome	528	90	438
	Balance of the PI Defects			
16	Hyper IgM, X-linked	327	73	254
17	ALPS	333	62	271
18	X-Linked Severe Combined	312	76	236
19	Hyper IgM, AR	285	51	234
20	Agammaglobulinemia, AR	247	80	167
21	Chronic Mucocutaneous Candidiasis	253	54	199
22	SCID - ADA Deficiency	166	45	121

	Balance of the PI Defects	Global	U.S.A.	Int'l
23	X-Linked Lymphoproliferative	140	42	98
24	Nijmegen Breakage Syndrome	145	37	108
25	APECED	127	78	49
26	Leukocyte Adhesion Deficiency	127	19	108
27	SCID - Omenn Syndrome	110	26	84
28	MHC I/II Class I Deficiency	110	4	106
29	SCID - RAG1/2 Deficiency	118	24	94
30	Chediak-Higashi Syndrome	113	13	100
31	SCID - Artemis Defects	90	22	68
32	SCID-IL-7R Alpha Deficiency	74	29	45
33	NEMO	72	41	31
34	Cartilage-hair Hypoplasia	62	15	47
35	IPEX	62	31	31
36	SCID-JAK3 Deficiency	54	8	46
37	Griscelli Syndrome	46	1	45
38	WHIM Syndrome	26	7	19
39	SCID-ZAP-70 Deficiency	27	6	21
40	SCID-PNP Deficiency	14	2	12
41	SCID-CD3 Delta Deficiency	5	0	5
42	SCID-CD3 Epsilon Deficiency	3	0	3
43	SCID - CD45 Deficiency	0	0	0
	Total	**30,283**	**10,192**	**20,091**

Source: Survey of Jeffrey Modell Centers

Table 6 Number of patients with identified PI defects by region

Region	Number of patients with identified PI defects
United States	10,192
Western Europe	9,312
Eastern Europe	2,484
Asia	2,393
Middle East	2,029
Latin America	1,845
Canada	1,803
Africa	182
Australia	43

Source: Survey of Jeffrey Modell Centers

Table 7 15 leading PI defects identified by region. The number of patients identified with one of the leading PI totals 27,811

15 Leading PI Defects Identified by Region

Categories	U.S.A.	Canada	Latin America	Western Europe	Eastern Europe	Middle East	Asia	Australia	Africa	Total
(1) Common Variable	1,950	255	196	1,084	290	292	214	4	7	4,292
(2) IgG Subclass Deficiency	909	22	44	1,975	162	93	31	1	2	3,239
(3) IgA Deficiency, Selective	869	102	236	1,146	426	152	124	0	17	3,072
(4) DiGeorge Syndrome	1,220	361	82	635	225	37	100	2	3	2,665
(5) Antibody Deficiency, Selective	1,321	226	45	586	43	28	11	1	0	2,261
(6) Other Pis NOS*	688	19	145	756	129	166	133	3	30	2,069
(7) Severe Combined	314	101	95	867	82	158	175	12	16	1,820
(8) Hypogammaglobulinemia of Infancy, Transient	582	150	30	210	247	102	448	1	1	1,771
(9) Ataxia Telangiectasia	711	32	151	115	124	239	95	1	19	1,487
(10) Chronic Granulo-matous Disease	177	39	221	344	110	202	298	5	3	1,399
(11) Agammaglobulinemia, X-linked	316	65	162	336	110	110	237	3	8	1,347
(12) Wiskott Aldrich Syndrome	109	30	44	275	67	27	150	2	2	706
(13) Complement Deficiencies	224	43	73	103	59	53	36	0	11	602
(14) Neutropenia	104	77	90	113	76	76	12	2	3	553
(15) Hyper IgE Syndrome	90	37	50	158	43	50	75	0	25	528
Total # of Patients for 15 Leading PI Defects										**27,811**

*NOS - Not Otherwise Specified

KEY:
- Predominantly Antibody Deficiencies
- Cellular Immunodeficiencies
- Combined Immunodeficiencies
- Defects of Phagocytic Function
- Disease of Immune Dysregulation
- Complement Deficiencies
- Defects in Innate Immunity
- Other Immunodeficiencies

Source: Survey of Jeffrey Modell Centers

Study IV: Evaluating the quality and consistency of the data by comparing survey reports from the JMCN and the ESID registry

It is well established that the ESID (European Society for Immunodeficiencies) registry is the most comprehensive and respected source of information reflecting the incidence and prevalence of PI diseases. The ESID registry is the ‘‘gold standard,’’ and is a model utilized by physicians and government authorities throughout the world.

JMF sought to evaluate the quality and consistency of the data provided by the JMCN, comparing the survey report information to the ESID registry.

The data was generated as follows:

- The ESID registry data was examined by looking at the 8 major immunodeficiency groups and comparing the data common to the JMCN surveys and ESID registry.
- The JMCN survey reports were collected from 9 major geographic regions compared to ESID’s single region. The total identified defects in the JMF survey reports totaled 30,283 patients compared to 6,020 ESID patients registered.

Results

The data gathered from the ESID registry is shown in Table 8.

A comparison of the ESID data against the JMF survey reports is represented in Table 9 and Table 10.

The results show a remarkable consistency in the incidence and prevalence of PI, measured by the percentage of all patients identified within each major immunodeficiency category.

Table 8 ESID registry data of 6,020 patients worldwide identified with specific PI defects

ESID Registry

Classification of Immunodeficiency Defects:

Agammaglobulinemia, AR	65	MHC Class II Deficiency	43
Agammaglobulinemia, X-linked	388	NEMO	0
ALPS	55	Nijmegen Breakage Syndrome	69
Antibody Deficiency, Selective	0	Neturopenia	268
APECED	13	Leukocyte Adhesion Deficiency	27
Ataxia Telangiectasia	385	Severe Combined:	n=314
Cartilage-hair Hypoplasia	10	*ADA Deficiency*	26
Chediak-Higashi Syndrome	8	*Artemis Defect*	18
Chronic Granulomatous Disease	246	*CD3 Delta Deficiency*	0
Chronic Mucocutaneous Candidiasis	19	*CD3 Epsilon Deficiency*	0
Common Variable	1,287	*CD45 Deficiency*	0
Complement Deficiencies	105	*IL-7R Alpha Deficiency*	9
DiGeorge Syndrome	193	*JAK3 Deficiency*	16
Griscelli Syndrome	11	*Omenn Syndrome*	0
Hyper IgE Syndrome	97	*PNP Deficiency*	3
Hyper IgM, AR	144	*RAG-1/2 Deficiency*	53
Hyper IgM, X-linked	69	*X-Linked Severe Combined*	53
Hypogammaglobulinemia	180	*ZAP-70 Deficiency*	2
Hypogammaglobulinemia of Infancy, Transient	265	*Other SCID*	134
IgA Deficiency, Selective	404	WHIM Syndrome	7
IgG Subclass Deficiency	495	Wiskott Aldrich	231
IPEX	2	X-Linked Lymphoproliferative	27
MHC Class I Deficiency	0	Other	593
		Total = 6,020	

Major Immunodeficiency Groups:

Predominantly Antibody Deficiencies	n=3,228	53.6%
Cellular Immunodeficiencies	n=907	15.1%
Combined Immunodeficiencies	n=426	7.1%
Defects of Phagocytic Function	n=638	10.6%
Disease of Immune Dysregulation	n=116	1.9%
Complement Deficiencies	n=105	1.7%
Defects in Innate Immunity	n=7	0.1%
Other Immunodeficiencies	n=593	9.9%

Source: Survey of Jeffrey Modell Centers and ESID registry

Table 9 Comparison of the incidence and prevalence of PI gathered from JMCN survey reports and ESID registry data

Comparison of JMCN Survey Reports and ESID Registry Data

Major Primary Immunodeficiencies Categories:	JMCN 2007		ESID 2007	
Predominantly Antibody Deficiencies	n=16,514	54.5%	n=3,228	53.6%
Cellular Immunodeficiencies	n=5,318	17.6%	n=907	15.1%
Combined Immunodeficiencies	n=2,257	7.5%	n=426	7.1%
Defects of Phagocytic Function	n=2,607	8.6%	n=638	10.6%
Disease of Immune Dysregulation	n=821	2.7%	n=116	1.9%
Complement Deficiencies	n=602	2.0%	n=105	1.7%
Defects In Innate Immunity	n=98	0.3%	n=7	0.1%
Other Immunodeficiencies	n=2,066	6.8%	n=593	9.9%
TOTAL	n=30,283		n=6,020	

Source: Survey of Jeffrey Modell Centers and ESID registry

Table 10 Summary of number of patients with identified PI defects in the major immunodeficiency groups, reported by JMCN and ESID

Major immunodeficiency groups	JMCN reports		ESID registry	
Predominantly antibody deficiencies	16,514	54.5%	3,228	53.6%
Cellular immunodeficiencies	5,318	17.6%	907	15.1%
Combined immunodeficiencies	2,257	7.5%	426	7.1%
Complement deficiencies	602	2.0%	105	1.7%

Source: Survey of Jeffrey Modell Centers and ESID registry

Study V: Measuring clinical outcomes and quality of life data before and after diagnosis for patients with PI disease [8]

The data was generated as follows:

- Eighty-five Jeffrey Modell Diagnostic, Research, and Referral Centers responded.
- Each of the Centers was asked to examine patient records one year before diagnosis and subsequent to diagnosis and treatment.
- Fifty-two reports were provided by Centers in the US and 33 reports were provided by
- Centers in Canada, Western and Eastern Europe, the Middle East, Latin America, Asia, Australia, and Africa.

Results

The following Figs. (7, 8, 9, 10, 11, 12, 13, 14) represent the results of the number of acute and severe infections, the number of physician/hospital/ER visits, the number of incidents of pneumonia, the number of days with chronic infections, the number of days on antibiotics, the number of days in the hospital, and the number of school/work days missed.

The results show significant differences in the clinical outcomes and quality of life data comparing patients with PI the year before and the year after diagnosis.

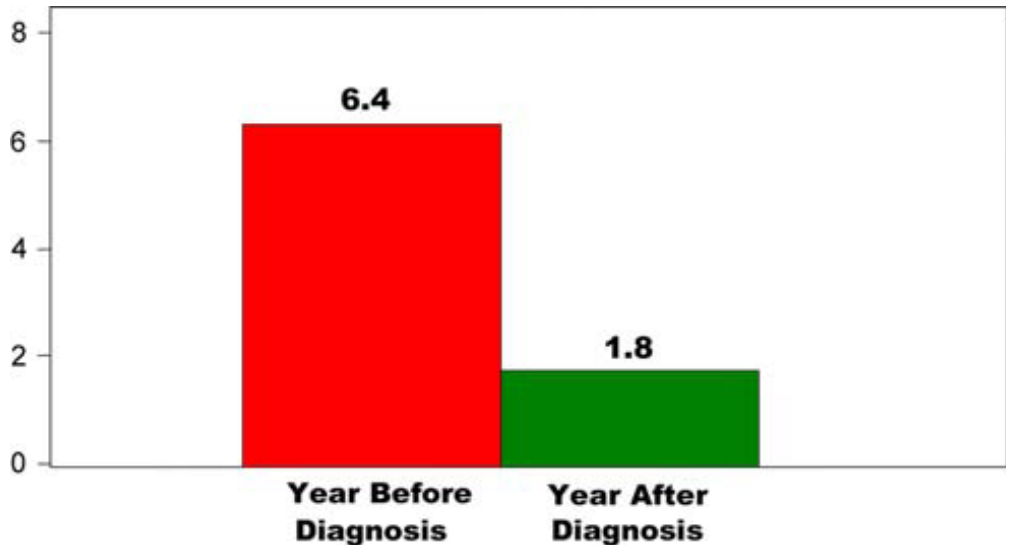


Fig. 7 Number of acute infections for patients with PI in the year before and the year after diagnosis. *Source:* Survey of Jeffrey Modell Centers

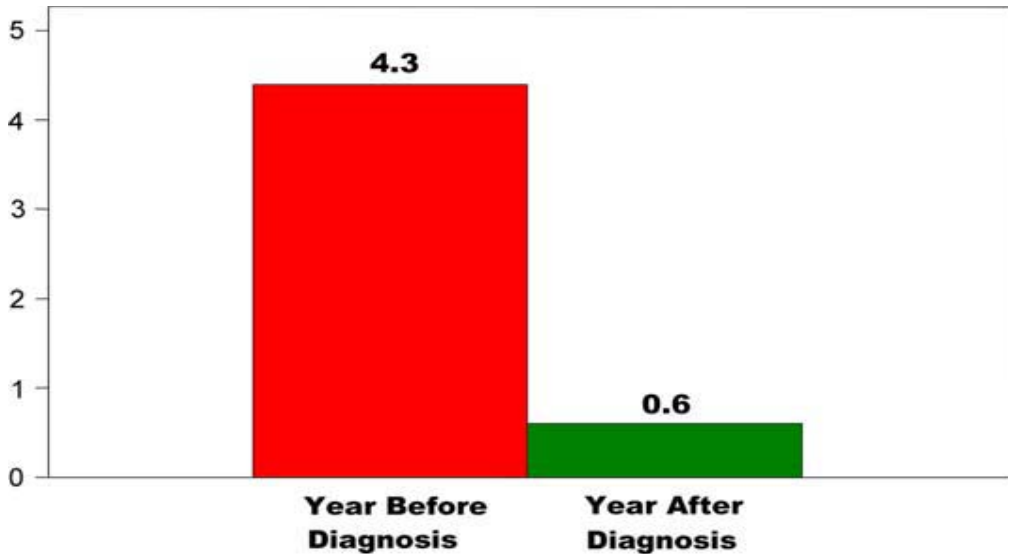


Fig. 8 Number of severe infections for patients with PI in the year before and the year after diagnosis. *Source:* Survey of Jeffrey Modell Centers

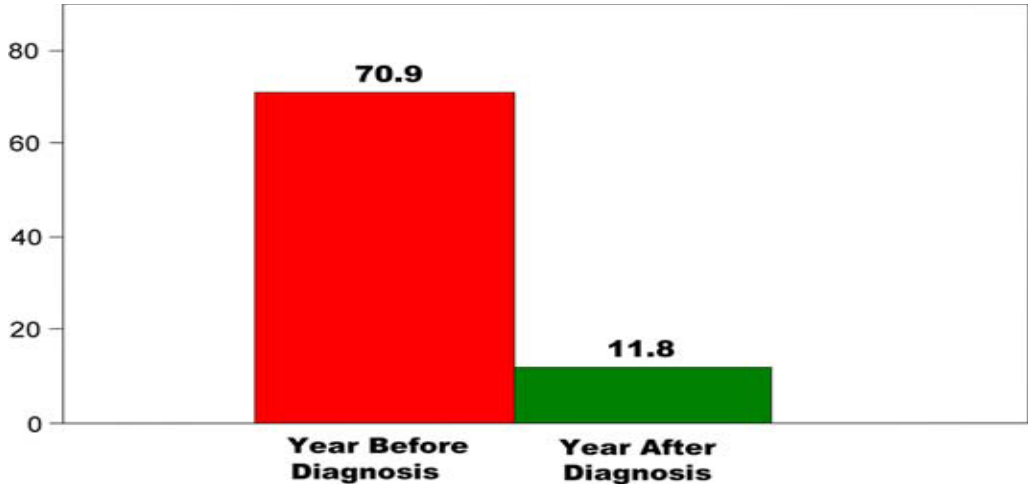


Fig. 9 Number of physician/hospital/ER visits for patients with PI in the year before and the year after diagnosis. *Source:* Survey of Jeffrey Modell Centers

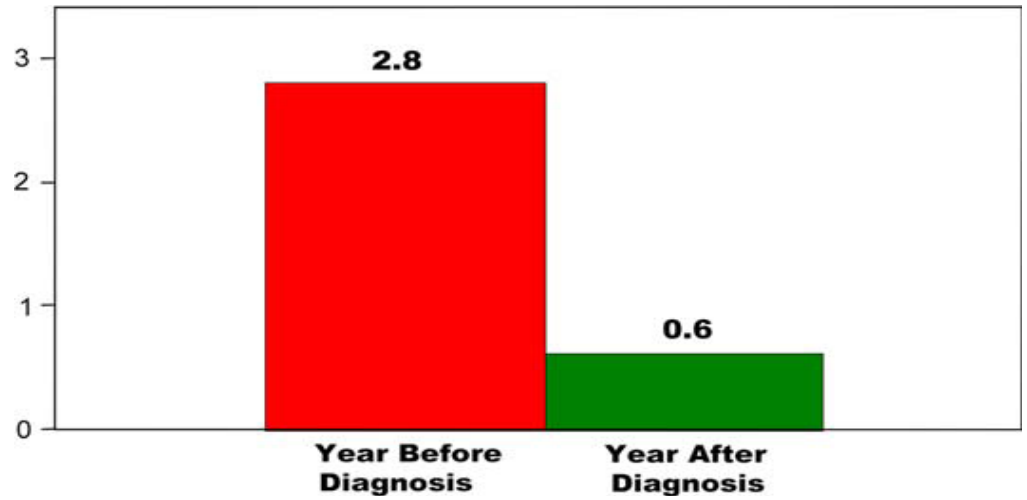


Fig. 10 Number of pneumonias for patients with PI in the year before and the year after diagnosis. *Source:* Survey of Jeffrey Modell Centers

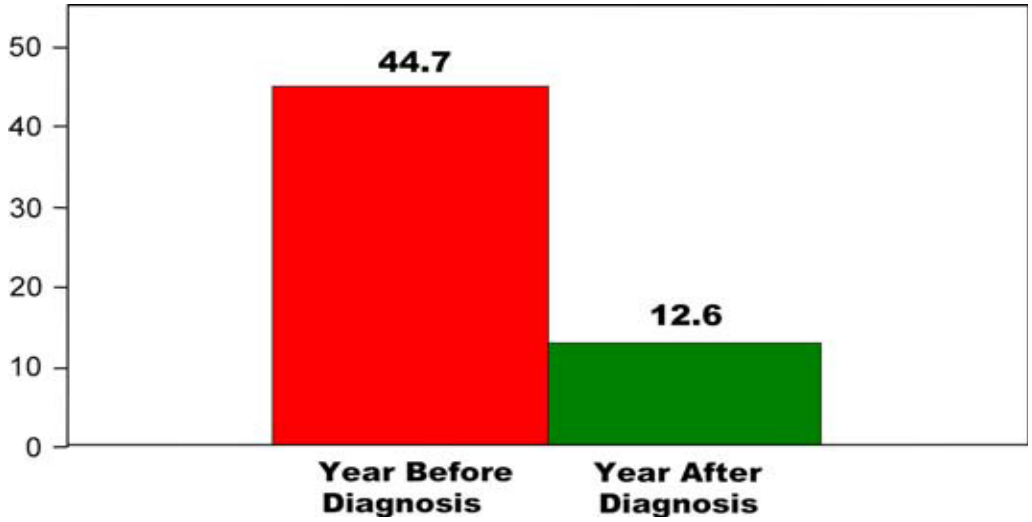


Fig. 11 Number of days with chronic infections for patients with PI in the year before and the year after diagnosis. *Source:* Survey of Jeffrey Modell Centers

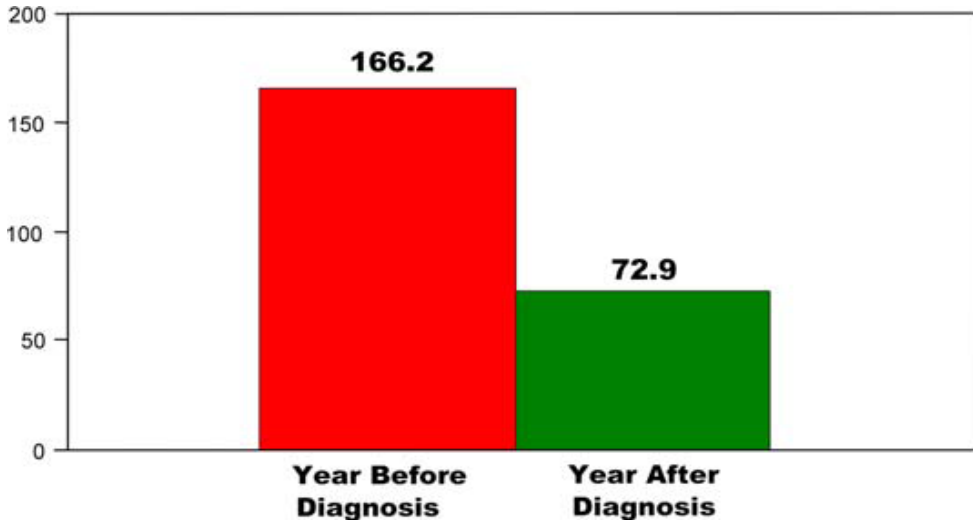


Fig. 12 Number of days on antibiotics for patients with PI in the year before and the year after diagnosis. *Source:* Survey of Jeffrey Modell Centers

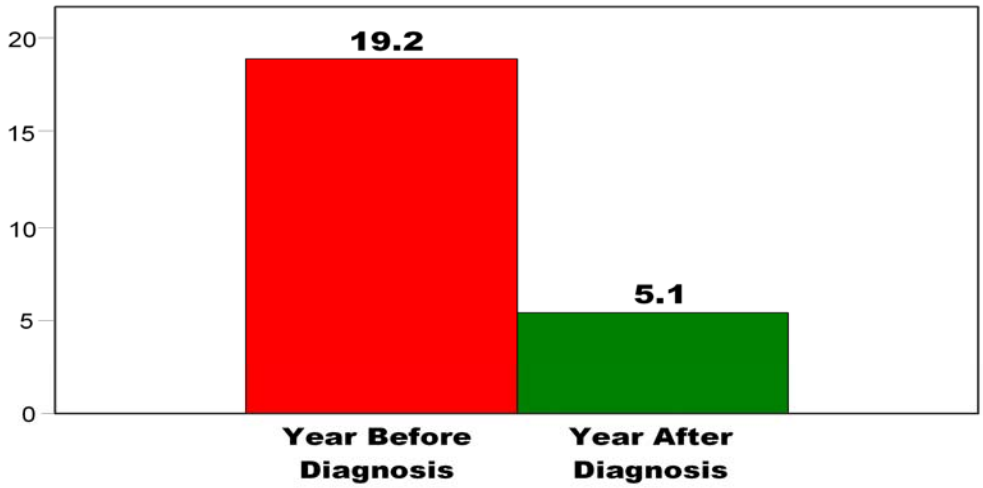


Fig. 13 Number of days in the hospital for patients with PI in the year before and the year after diagnosis. *Source:* Survey of Jeffrey Modell Centers

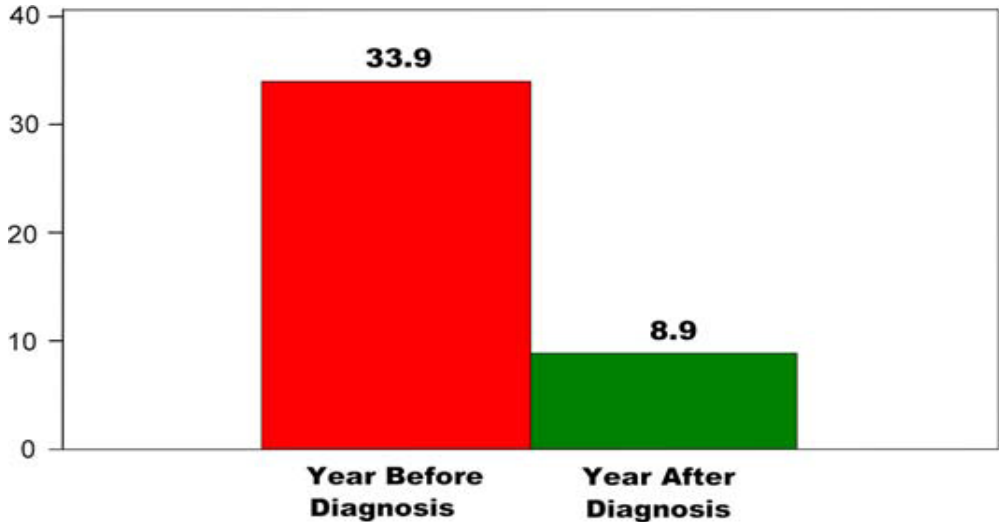


Fig. 14 Number of school/work days missed for patients with PI in the year before and the year after diagnosis. *Source:* Survey of Jeffrey Modell Centers

Study VI: Comparing the economic impact of undiagnosed and diagnosed patients with PI (in the US only)

JMF sought to ascertain the economic consequences of diagnosed and undiagnosed patients utilizing the quality of life data provided by the physicians. Due to the wide range of health care costs in countries and regions covered by the survey, this study only focused on costs in the United States.

The data was generated as follows:

- Hospital charges and length of stay data was obtained from the Hospital Cost and Utilization Project (HCUP), Nationwide Inpatient Sample, under the auspices of the Agency for Healthcare Research and Quality (AHRQ).
- Data was 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 hospital stay based on discharge data, per patient. A patient admitted to the hospital multiple times in one 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.
- Costs for antibody replacement therapy (IVIG) are not included in the study, as only a segment of the patients identified are treated with IVIG. However, assuming the IVIG treatment is warranted and effective, costs of infections, hospitalizations and related costs are substantially reduced.
- The study does not include costs of patient/parents' lost wages, diminished productivity, transportation, and other related costs of care for an undiagnosed child.
- The study does not include Quality Adjusted Life Years benefits or extended life expectancy accrued to diagnosed and treated patients.
- ''In-patient'' information was obtained from the HCUP website: www.hcup.ahrq.gov or www.hcupnet.asp.
- ''Outpatient'' information was obtained from the Aetna website: www.member.aetna.com/member. Charges are based on ''in network'' coverage. ''Out of network'' costs are 2–4 times greater.

Results

The data in Table 11 represents the economic impact of PI on patients in the United States in the year before and the year after diagnosis.

Table 11 Economic impact of the most frequent conditions affecting patients with PI - comparing the year before against the year after diagnosis (US only)

Condition	Cost per patient per episode/day	# of episodes pre-Dx	Annual cost per patient pre-Dx	# of episodes post-Dx	Annual cost per patient post-Dx	Annual savings per patient
Acute infections	$2,950 (per episode)	6.4	$18,880	1.8	$5,310	$13,570
Severe infections	$5,708 (per episode)	4.3	$25,544	0.6	$3,424	$21,119
Bacterial pneumonias	$7,529(per episode)	2.8	$21,081	0.6	$4,517	$16,564
Chronic infections	$36.33 (per day)	44.7	$1,623	12.6	$457	$1,166
Physician/Hospital/ ER visits	$125 (per visit)	70.9	$8,862	11.8	$1,475	$7,387
Hospitalizations	$1,158 (per day)	19.2	$22,233	5.1	$5,905	$16,328
Antibiotics	$4.25 (per day)	166.2	$706	72.9	$309	$397
School/Work days missed	$136.40 (per day)	33.9	$4,623	8.9	$1,213	$3,410
Totals per patient			$102,552		$22,610	$79,942

Source: Survey of Jeffrey Modell Centers

The results show significant differences in the economic consequences affecting patients with PI prior to diagnosis and post diagnosis. In summary:

1. Each undiagnosed patient with an underlying PI disease costs the healthcare system an average of $102,552 annually.
2. Each diagnosed patient with a recognized PI defect costs the healthcare system an average of $22,610 annually.
3. The economic impact to the healthcare system of diagnosing a patient with an underlying PI defect in contrast to not diagnosing a patient represents average savings of $79,942 per patient annually.
4. The US National Institutes of Health (NIH) estimates that at least 500,000 cases of PI remain undiagnosed in the United States.
5. The economic impact of undiagnosed PI patients to the healthcare system in the United States totals over $40 billion annually.

Summary of the 6 studies and conclusions

1. Data on PI disease was provided by 304 expert physicians at 138 academic teaching hospitals and medical schools in 39 countries and 120 cities, spanning 6 continents. All are participants in the JMCN.
2. The PEPAC generated substantial increases in diagnosis, referrals, and treatment of patients with PI disease.
3. The number of diagnostic tests performed by participating physicians at Jeffrey Modell Centers increased annually by nearly 5 times over a 4 year period.
4. The number of patients reported with a suspected PI disease totaled 37,544 and 30,283 of these patients were identified with specific PI defects.
5. The data was sorted and reported in the order of the 43 major PI diseases, and classified by the 8 major PI groups. The data was further organized by the 9 major geographic regions participating and the 15 leading defects by region.
6. The JMCN reports were compared to the ESID registry and there was little difference in the respective percentages for the major immunodeficiency groups.

Overall, JMF's PEPAC provided to the community:

1. The specific defect of 30,283 patients.
2. Where the patients were diagnosed and treated.
3. Who was diagnosing and treating the patients.

Furthermore, participating physicians reported dramatic changes in clinical outcomes and quality of life for diagnosed and undiagnosed patients. This was evidenced by decreases in rates of infection, reduced need for antibiotics, and reduced hospitalizations.

Finally, these clinical improvements, in the US alone, translate to an average economic savings of approximately $80,000 per patient per year.

The survey reports from the participants are secured at the JMF offices in NYC. The JMF encourages transparency and a robust exchange of data in connection with Jeffrey Modell Diagnostic, Research, and Referral Centers specializing in the diagnosis and treatment of PI. The recently established JMCN will hopefully contribute to continuing this dialogue and building on the data collected.

About the Jeffrey Modell Foundation

The Jeffrey Modell Foundation (JMF) was established in 1987 by Vicki and Fred Modell in memory of their son Jeffrey, who died at the age of 15 of a PI disease. The Foundation is dedicated to early and precise diagnosis, meaningful treatments, and ultimately cures of Primary Immunodeficiencies. Today there are 50 Jeffrey Modell Research and Diagnostic Centers and 120 Referral Centers worldwide. More information about PI can be found at www.info4pi.org or by contacting JMF at (212) 819–0200, or info@jmfworld.org.

About the Jeffrey Modell Centers Network

At the Jackson Hole (Wyoming) Expert Meeting on Primary Immunodeficiencies held in June 2007, 35 Jeffrey Modell Center Directors and industry supporters convened to review advances at our Diagnostic and Research Centers. There was a consensus reached to set up a Centers Network that would frame the scientific agenda and would include the specialized referral centers around the world. Areas of specific interest would include best practices, clinical guidelines, outcome measures and data capture, novel therapies, a research platform, an international fellowship program, and expansion of the Physician Education and Public Awareness Campaign.

Acknowledgments

The Jeffrey Modell Foundation acknowledges with gratitude the dedication of the physician experts who provided the documentation needed to complete this study of patients with PI. JMF also acknowledges with appreciation the European Society for Immunodeficiencies (ESID) and the data provided through their online registry at www.esid.org. This publication was supported in part by Grant/Cooperative Agreement Number 5H75DP225146-03 from the Centers for Disease Control and Prevention (CDC). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of CDC.

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