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ORIGINAL ARTICLE

Primary immunodeficiencies worldwide: an updated overview from the Jeffrey Modell Centers Global Network

Vicki Modell[1] · Jessica Quinn[1] · Jordan Orange[2] · Luigi D. Notarangelo[3] · Fred Modell[1]

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Abstract Primary immunodeficiencies (PI) are defects of the immune system that cause severe, sometimes life-threatening, infections if not diagnosed and treated appropriately. Many patients with PI are undiagnosed, underdiagnosed, or misdiagnosed. To raise awareness and assure earliest diagnosis, appropriate treatment, and proper care management, the Jeffrey Modell Foundation (JMF) implemented a physician education and public awareness program beginning in 2003. Data are requested annually from physician experts within the Jeffrey Modell Centers Network (JMCN), consisting of 602 expert physicians, at 253 academic institutions, in 206 cities, and 84 countries spanning six continents. Center Directors reported on patients' specific PI defects and treatment modalities including immunoglobulins, transplantation, and gene therapy as well as data on gender and age. Center Directors also provided physician-reported patient outcomes as well as pre- and post-diagnosis differences. Costs were assigned to these factors. In collaboration with the Network, JMF advocated, funded, and implemented population-based newborn screening for severe combined immunodeficiency and T cell lymphopenia, covering 96.2 % of all newborns in the US. Finally, 21 JMF Centers participated in a polio surveillance study of patients with PI who either received or have been exposed to the oral polio vaccine. These initiatives have led to an overall better understanding of the immune system and will continue to improve quality of life for those with PI.

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

Abbreviations

PI	Primary immunodeficiencies
JMF	Jeffrey Modell Foundation
JMCN	Jeffrey Modell Centers Network
SCID	Severe combined immunodeficiency
IUIS	International Union of Immunological Societies
HSCT	Hematopoietic stem cell transplantation
CVID	Common variable immunodeficiency
IG	Immunoglobulin therapy
IVIG	Intravenous immunoglobulin therapy
SCIG	Subcutaneous immunoglobulin therapy
PEG-ADA	Polyethylene glycol-conjugated adenosine deaminase
BM	Bone marrow
PBSC	Peripheral blood stem cell
Cord	Cord blood
WAS	Wiskott–Aldrich syndrome
MUD	Matched unrelated donor
mMUD	Mismatched unrelated donor
MRD	Matched related donor
PBSC	Peripheral blood stem cell
NBS	Newborn screening
OPV	Oral polio vaccine
VDPV	Vaccine-derived poliovirus
VAPP	Vaccine-associated paralytic poliomyelitis

✉ Fred Modell
fmodell@jmfworld.org

[1] Jeffrey Modell Foundation, 780 Third Avenue, 47th Floor, New York City, NY 10017, USA

[2] Texas Children's Hospital, Baylor College of Medicine, Houston, TX, USA

[3] Children's Hospital Boston, Harvard Medical School, Boston, MA, USA

Introduction

Primary immunodeficiencies (PI) [1, 2] are genetic defects of the immune system that result in chronic, serious, and often life-threatening infections, if not diagnosed and treated [3, 4]. There are at least 300 genetically defined single-gene inborn errors of immunity [5]. Recent studies have shown that PI may be more common than previously estimated [6] and that as many as 1–2 % of the population may be affected with a PI when all types and varieties are considered [7]. This includes monogenic detriments leading to common infectious diseases such as severe influenza, autoimmune diseases such as cytopenias and systemic lupus erythematosus, and inflammatory diseases [5]. Over the last decade, improvements in molecular diagnosis, genetic sequencing, and cutting edge research and treatments have led to a better understanding of the immune system, as well as improved quality of life for those living with PI. However, awareness of PI among physicians and the general public remains challenging, and there continues to be a need for improved and timely management of these conditions [8, 9].

In order to raise awareness of PI with the overall goal to reduce associated morbidity and mortality, the Jeffrey Modell Foundation (JMF) established a Physician Education and Public Awareness Campaign in 2003 [8, 9]. The Program has been expanded globally throughout the last decade. The main objectives of the Program are to (1) identify patients with PIs as early as possible; (2) refer "at-risk" patients to specialized healthcare institutions in the Jeffrey Modell Centers Network (JMCN) worldwide; (3) identify specific defects in order to offer precise and definitive diagnosis to patients; and (4) treat the defects effectively [8, 9]. JMF developed the "10 Warning Signs of Primary Immunodeficiency" in 1993, which has been revised, most recently in 2013. Two versions, for adults and children, have been generated, and over fifty countries have translated the Warning Signs into culturally appropriate languages and dialects.

The Program's target audience includes primary care physicians, family practitioners, pediatricians, medical subspecialists, emergency medicine physicians, school nurses, registered nurses, third-party payers, patients, government, and the public [8, 9]. Educational materials such as the 10 Warning Signs of PI, the physician algorithm for PI, and graphic posters of the immune system were developed and disseminated by JMF. Symposia and continuing medical education activities, informational websites, KIDS days, World Immunology Network (WIN) grant support for patients and clinical professionals, and public service advertising are all components of the program that assist in achieving the intended goals and objectives [8, 9].

JMF center surveys

The reach of these educational materials continues to expand and influence the number of patients identified with PI worldwide. The JMCN provides the infrastructure to accept referrals, provide diagnosis, and offer treatments. Currently, the Network consists of 602 Expert Physicians at 253 institutions, in 206 cities, and 84 countries spanning 6 continents. In order to provide data to measure effectiveness of the program, JMF developed a survey for physician experts within the JMCN to report on the number of patients identified with PI, and the treatment modalities, including immunoglobulins, transplantation, and gene therapy as well as data on gender and age. Center Directors also provided physician-reported outcomes and differentials pre- and post-diagnosis.

Newborn screening for severe combined immunodeficiency (SCID) and related T cell lymphopenia

An important development of the Centers Network was its integration of newborn screening for severe combined immunodeficiency (SCID) and related T cell lymphopenia consistent with the overall mission of earliest possible diagnosis. Infants born with SCID, and related conditions with T cell lymphopenia, suffer from serious, life-threatening infections and will likely not survive their first year of life without specific therapy to protect them from infections and restore their immune function [10–12].

SCID and related conditions can be detected by a simple screening test, the T cell receptor excision circles (TRECs) assay, using the same dried blood spot samples already collected from newborns to screen for other genetic disorders [11, 12]. The TRECs assay provides the earliest possible identification of babies with severe T cell lymphopenia before they develop serious infectious complications which may lead to irreversible organ damage or death. As compared to SCID infants identified based on clinical symptoms, those receiving HSCT in the first few months of life (after being identified through TRECs screening) have a higher probability of going to transplant without active infections; this difference translates into higher chance of survival for infants with SCID identified through the newborn screening program [10, 11, 13–17]. Furthermore, because of the lower incidence of serious infections before HSCT, it is likely that infants with SCID identified through newborn screening will also have a lower rate of long-term complications and will therefore enjoy a better quality of life. Center Directors in the US worked in harmony with state public health departments to identify SCID and related conditions using the TRECs

assay, and directing patients identified to leading experts to provide lifesaving HSCT. While additional laboratory methods are being developed, the current TRECs assay has proven to have outstanding specificity and sensitivity to accurately identify all infants affected with SCID (the primary targets) as well as additional infants with other T cell lymphopenia (secondary targets) [11, 12].

Economic analysis to screen or not to screen newborns for SCID and T cell lymphopenia

JMF further developed a working algorithm or "decision tree" that has been vetted using peer-reviewed scientific literature and harmonized for application to be used by public health departments and health ministries in states, countries, and regions throughout the world. Local or regional data can be applied to measure the threshold and economic impact of implementing or not implementing newborn screening for SCID. This decision tree provides the appropriate agency with a usable tool and understandable formula that will assist in deciding upon the willingness to pay for additional years of life utilizing criteria and costs specifically relevant to the locality.

Global polio surveillance study

JMF conducted a surveillance study of patients with PI who have either received the oral polio vaccine (OPV), a live-weakened form of the virus, or have been exposed to it. Physicians at twenty-one JMF Centers around the world participated in an actual surveillance study in PI patients in an effort to contribute to global polio eradication efforts. This study was conducted in collaboration with the World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), Task Force for Global Health (TFGH), and the Bill & Melinda Gates Foundation.

Due to inadequate immunity, when a patient with PI receives OPV, he/she is at risk of being unable to clear the intestinal vaccine strain viral infection, which is typically no longer excreted after 6–8 weeks by individuals with normal immune systems. After prolonged periods of viral replication and shedding, however, the virus may no longer be the same as the original vaccine-virus, as it can alter genetically, also known as vaccine derived poliovirus (VDPV). Although rare, patients with PI are at risk of developing vaccine-associated paralytic poliomyelitis (VAPP) and immunodeficient-associated VDPV (iVDPV) excretion, which could lead to possible additional exposure within the general population [18–20]. The objective of the study was to estimate the prevalence of poliovirus excretion in patients with B cell immunity defects known to be associated with prolonged poliovirus excretion and who have received OPV.

Methods

JMF survey identifying defects and treatments

The JMF survey on PI was developed using the categories and gene defects identified by the International Union of Immunological Societies (IUIS) Expert Committee for the Classification of PI [21]. Surveys were sent to all Center Directors, requesting data in 2015. The 2015 survey incorporated new gene defects known to cause PI and an optional demographics section. Each JMCN Center Director was asked to provide information on the number of patients seen and followed with a primary immunodeficiency, the number of patients diagnosed with specific defects, and the number of patients referred to each institution. Specific PI diagnoses were grouped according to the IUIS classifications. Physicians were given the opportunity to list "Unspecified" or "Other Deficiencies" for any additional disorders or gene mutations not listed in the survey. Physician-reported outcomes were analyzed regionally.

The JMF survey also included questions assessing immunoglobulin therapies. Specifically, the survey included data fields to determine the number of patients receiving immunoglobulin therapy intravenously (in the clinic or at home), by subcutaneous administration, or other methods of administration. Information was also requested on the number of patients treated by hematopoietic stem cell transplantation (HCST), including donor type and stem cell source. An optional demographics portion was included in the JMF survey. Physicians had the opportunity to report gender and age of patients treated at each Center.

Costs analysis to screen or not to screen newborns for SCID and T cell lymphopenia

JMF's "decision tree" was designed to serve as a practical tool and comprehensible formula that assists in deciding upon the willingness to pay for additional years of life utilizing criteria and costs specifically relevant to the locality. The decision to implement newborn screening for SCID and related T cell lymphopenia was considered based upon the cost and effectiveness of the screening test, the incidence of SCID and related T cell lymphopenia within a population, the cost ratio of the intervention, and the benefit of earliest possible treatment [22, 23]. If one makes an assumption that the number of births within a region is 100,000 per year, and the incidence of SCID or related T cell lymphopenia is approximately 1:33,000 newborns; this decision tree projects three cases per year.

Physician office waiting rooms

To measure the effect of a pilot program JMF introduced in 2015, which broadcasts a branded video in the waiting rooms of 350 primary care physician offices, a survey was disseminated. Physicians were asked questions including how many patients in their practice were already diagnosed with PI, whether there was an increase in the number of patients asking about PI since the JMF content began airing, and whether they thought the program was effective, among others. The survey was completed by 144 physicians.

Global polio surveillance study

Patients of all ages were enrolled into the surveillance study, with a target of 300 patients diagnosed with common variable immunodeficiency disease (CVID) and 300 patients diagnosed with agammaglobulinemia or SCID. The study is ongoing. To assess the fraction of patients excreting poliovirus, two stool samples were collected from each patient within a 4-day period and shipped to a designated WHO Global Poliovirus Laboratory Network site, where the samples were tested by virus culture for the presence of poliovirus or non-polio enterovirus [24]. Informed consent and/or assent were received from all patients and/or guardians, and the procedure was approved by all necessary institutional review boards.

Results

JMF center surveys

There was an increase in the physician-reported prevalence of patients with PI from 2013 to 2015. Tables 1 and 2 highlight the number of patients identified by year and region. JMF Centers joining the Network increased by 6.8 %. However, this increase was offset by existing Centers not reporting updated data since 2014. Thus, any reported increases (or decreases) were directly related to actual number of patients diagnosed and treated, and not attributed to the number of Centers reporting, which was essentially unchanged. "International" represents reporting Centers outside of the US. "Global" represents the total of all Center reports.

As shown in Tables 3 and 4, Center Directors reported on 34,481 patients with respect to gender and 30,829 patients with respect to age. Male patients accounted for 58.3 % globally, while female patients accounted for 41.7 %. In the US, 55.7 % of the patients were male and 44.3 % of patients were female. Globally, 63 % of the patients were 19 years of age or younger, while 37 % were 20 years of age or older.

Table 5 highlights the distribution of patients diagnosed with PI in 2015, using the categories defined by the IUIS Expert Committee for the Classification of PI. Predominantly Antibody Deficiencies are reported by physicians to be 63.4 % in the US, 47.7 % internationally, and 53 % globally. Well-defined Syndromes with Immunodeficiency was 16.3 % in the US, 11.2 % internationally, and 12.9 % globally.

Table 6 displays physician-reported variations within the fifteen most prevalent PI defects, the regional distribution, and percentage of each defect by region. For example, Selective IgA deficiency is the most prevalent with 16.4 % in the US, 13.0 % internationally, and 14.1 % globally. Common variable immunodeficiency (CVID) showed a prevalence of 15.4 % in the US, 11.2 % internationally, and 12.6 % globally. It is noteworthy that Canada and Australia had 25.5 and 39.5 % prevalence for CVID, respectively. The Middle East reported 30.5 % Familial Mediterranean fever compared to 3.3 % globally. Africa reports 6.5 % Ataxia telangiectasia (A-T) compared to 2.6 % globally, and 8.7 % "other combined immunodeficiencies" compared to 1.5 % globally.

As a percentage of all patients identified with a specific defect, Antibody Deficiencies account for 57 % of all patients identified with a specific defect. The distribution of these patients is shown in Table 7.

Table 1 Physician-reported prevalence of PI

	Patients evaluated and followed			Patients diagnosed with PI defects			Patients referred		
	2015	2013	% Change	2015	2013	% Change	2015	2013	% Change
US	52,713	40,560	30.0	27,194	22,781	19.4	26,447	14,869	77.9
International	104,741	98,287	6.6	56,549	54,412	3.9	54,892	49,952	9.9
Global totals	157,454	138,847	13.4	83,743	77,193	8.5	81,339	64,821	25.5

The number of patients followed, diagnosed with a specific PI defect, and referred in the US and internationally in 2015 compared with 2013

Table 2 Physician-reported prevalence of PI by region

	Patients evaluated and followed		Patients diagnosed with PI defects		Patients referred	
	2015	2013	2015	2013	2015	2013
US	52,713	40,560	27,194	22,781	26,447	14,869
Canada	3796	4058	2138	3880	1875	1575
Latin America	9197	5377	7726	5361	6740	4175
Western Europe	34,407	35,932	23,407	25,518	18,523	15,068
Eastern Europe	45,062	42,458	12,862	11,886	23,357	22,905
Middle East	5511	5520	5493	4370	994	562
Asia	3744	3373	2113	1843	1143	1019
Australia	1397	91	1209	91	0	0
Africa	1627	1478	1237	1463	2260	4648
Global totals	157,454	138,848	83,743	77,193	81,339	64,822

The number of patients followed, diagnosed with a specific defect, and referred by region in 2015 compared with 2013

Table 3 Gender and age

	US		International		Global	
	n	%	*n*	%	*n*	%
Gender						
Male	4293	55.7	15,820	59.1	20,113	58.3
Female	3411	44.3	10,957	40.9	14,368	41.7
Totals	7704	100	26,777	100	34,481	100
Age						
<1 year	386	5.4	1821	7.7	2207	7.2
1–4 years	1403	19.7	4400	18.6	5803	18.8
5–19 years	2146	30.2	9254	39.0	11,400	37.0
20–39 years	1593	22.4	4373	18.4	5966	19.4
≥40 years	1589	22.3	3864	16.3	5453	17.7
Totals	7117	100	23,712	100	30,829	100

The number of patients reported in 2015 by age and gender in the US and internationally

Table 4 Gender and age comparative report

	2015	2013
Number of patients reported by age	30,829	5993
Number of patients under 1 year of age	2207	149
Number of patients reported by gender	34,481	6343
Number of male patients reported	20,113	3540
Number of female patients reported	14,368	2803

The number of patients reported by age and gender, the number of patients under 1 year of age, and the number of reported male and female patients in 2015 compared to 2013

Treatment with IG

As Tables 8, 9, and 10 demonstrate, there was a 19 % overall increase in patients receiving IgG according to the physician report. There was an increase of 7 % in all patients receiving intravenous immunoglobulin therapy (IVIG) and a 100 % increase in patients receiving subcutaneous immunoglobulin (SCIG). Of all patients in the JMCN database diagnosed with a PI defect, 24.3 % are on immunoglobulin replacement therapy. As to all patients in the database with an Antibody Deficiency, 42.9 % are treated with IVIG/SCIG. It is noteworthy that there was a 27 % increase in the number of patients receiving IVIG in the hospital or clinic. There was a decrease of 49 % in the number of patients receiving IVIG at home. This decrease was more than offset by an increase of nearly 100 % in patients receiving SCIG. Latin America reported 87 % of their patients receiving IgG are treated in the clinic or hospital compared to 55 % globally. In the US, 30 % of patients receiving IgG are treated at home compared to 14 % globally. Western Europe reported 46 % of their patients requiring IgG receive SCIG compared to 28 % globally.

Other treatment modalities

Tables 11, 12, 13, 14, 15, and 16 show that there were commensurate increases in patients receiving other treatments for PI as well. The number of patients treated with PEG-ADA increased by 44 % (Table 11). There was a 22 % overall increase in patients treated by HSCT or thymus transplantation, with the number of patients receiving matched donor transplants, matched unrelated donor transplants, mismatched unrelated donor transplants, and parental haplo transplants increasing by 28.6, 17.6, 5.5, and 15.6 %, respectively (Table 15). Use of bone marrow as the source of stem cells increased by 17.4 %, while cord blood as the stem cell source increased by 66 % (Table 16). While there was a 22 % increase in the number of patients having received HSCT, specific stem cell

Table 5 Physician-reported prevalence of PI by categories

	US		International		Global	
	n	%	*n*	%	*n*	%
Combined Immunodeficiencies	996	3.3	3766	6.4	4762	5.3
Well-Defined Syndromes with Immunodeficiency	4999	16.3	6598	11.2	11,597	12.9
Predominantly Antibody Deficiencies	19,437	63.4	28,111	47.7	47,548	53.0
Diseases of Immune Dysregulation	750	2.4	1883	3.2	2633	2.9
Congenital Defects of Phagocyte #, Function, or both	1026	3.3	3628	6.2	4654	5.2
Defects in Innate Immunity	243	0.8	711	1.2	954	1.1
Autoinflammatory Disorders	797	2.6	5605	9.5	6402	7.1
Complement Deficiencies	790	2.6	4158	7.0	4948	5.5
Unspecified or Other Deficiencies	1605	5.2	4531	7.7	6136	6.8
Totals	30,643	100	58,991	100	89,634[a]	100

The distribution and percentages of patients diagnosed with PI in 2015, using the categories defined by the IUIS Expert Committee Classification of PI

[a] Global total does not match that of Tables 1 and 2 due to the inclusion of "Unspecified or Other Deficiencies"

sources varied significantly by region and source. Latin America reported 74 % of the transplants were bone marrow, as opposed to 61 % globally. Middle East reported 35 % of the transplants were peripheral stem cells as opposed to 22 % globally. There was a 65 % overall increase in cord blood transplants in the past 2 years. Asia reported 42 % of the transplants were cord blood, compared to 16 % globally (Table 14). This differential may call for further analysis going forward.

Physician-reported clinical outcomes

Network Center Directors were asked to examine records of PI patients 1 year before diagnosis and for the year subsequent to diagnosis and report on outcomes based upon their analysis. Eighty-five Centers in the JMCN responded. Table 17 contains the results of this survey. There were clear benefits ascribed to early diagnosis in terms of significantly decreased morbidity and mortality. There were also substantial cost savings (Table 18) for diagnosed patients compared to undiagnosed, even if regular IgG is required (i.e., accounting for the cost of providing IgG replacement therapy).

The cost of the most frequent conditions affecting patients with PI pre- and post-diagnosis, and the post-diagnosis average annual savings are shown in Table 18.

Cost analysis measuring outcome improvement

Cost analysis, reflecting the substantial differences in patient outcomes described in the previous section, was 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) [25]. 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, i.e., infections and hospitalizations. Costs related to 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 [25]; "outpatient" information was obtained from the Aetna Web site [26]. Charges are based on ''In network'' coverage, with ''Out of network'' costs 2–4 times greater [26]. Healthcare costs data for privately insured patients were included [27, 28]; healthcare costs data from the Centers for Medicare and Medicaid statistics were included [29, 30]; economic factors underlying growth in Medicare spending were determined by CBO, Congressional Budget Office data [31]; employer-sponsored coverage data were provided by the Employee Benefit Research Institute Issue: Washington, DC [32, 33].

Costs were updated using the Health Care Cost Institute (HCCI) data [34]. HCCI performed analysis on a subset of data for approximately 40 million insureds per year from 2010

Table 6 Physician-reported prevalence of 15 PI defects by region and percent of defect by region

	Canada	Latin Amer	West Euro	East Euro	Middle East	Asia	Australia	Africa	US totals	Int. totals	Global totals
1 IgA deficiency, selective											
Total number	166	1553	3015	2264	148	42	97	49	4458	7334	11,792
Percentage of diagnosis	1 %	13 %	26 %	19 %	1 %	0 %	1 %	0 %	38 %	62 %	100 %
Percent of defect by region	7.8 %	20.1 %	12.9 %	17.6 %	2.7 %	2 %	8 %	4.0 %	16.4 %	13.0 %	14.1 %
2 Common variable immunodeficiency (CVID)											
Total number	546	858	3064	844	272	178	477	113	4193	6352	10,545
Percentage of diagnosis	5 %	8 %	29 %	8 %	3 %	2 %	5 %	1 %	40 %	60 %	100 %
Percent of defect by region	25.5 %	11.1 %	13.1 %	6.6 %	5 %	8.4 %	39.5 %	9.1 %	15.4 %	11.2 %	12.6 %
3 DiGeorge anomaly (Chrom 22q11.2 deletion syndrome)											
Total number	333	312	1167	647	169	89	31	50	3212	2798	6010
Percentage of diagnosis	6 %	5 %	19 %	11 %	3 %	1 %	1 %	1 %	53 %	47 %	100 %
Percent of defect by region	15.6 %	4 %	5 %	5 %	3.1 %	4.2 %	2.6 %	4.0 %	11.8 %	4.9 %	7.2 %
4 Hypogammaglobulinemia (unspecified)											
Total number	49	418	1013	430	9	14	4	65	3244	2002	5246
Percentage of diagnosis	1 %	8 %	19 %	8 %	0 %	0 %	0 %	1 %	62 %	38 %	100 %
Percent of defect by region	2.3 %	5.4 %	4.3 %	3.3 %	0.1 %	0.7 %	0.3 %	5.3 %	11.9 %	3.5 %	6.3 %
5 Hypogammaglobulinemia of infancy (transient)											
Total number	188	488	525	1509	43	30	9	27	829	2819	3648
Percentage of diagnosis	5 %	13 %	14 %	41 %	1 %	1 %	0 %	1 %	23 %	77 %	100 %
Percent of defect by region	8.8 %	6.3 %	2.2 %	11.7 %	0.7 %	1.4 %	0.7 %	2.2 %	3.0 %	5.0 %	4.4 %
6 Specific Antibody Deficiency (normal Ig and B cells)											
Total number	78	411	605	56	4	16	42	6	2468	1218	3686
Percentage of diagnosis	2 %	11 %	16 %	2 %	0 %	0 %	1 %	0 %	67 %	33 %	100 %
Percent of defect by region	3.6 %	5.3 %	2.9 %	0.4 %	0 %	0.8 %	3.5 %	0.5 %	9.1 %	2.2 %	4.4 %
7 Familial Mediterranean fever											
Total number	14	19	536	285	1677	36	23	18	179	2608	2787
Percentage of diagnosis	1 %	1 %	19 %	10 %	60 %	1 %	1 %	1 %	6 %	94 %	100 %
Percent of defect by region	0.7 %	0.2 %	2.9 %	2.2 %	30.5 %	1.7 %	1.9 %	1.5 %	0.7 %	4.6 %	3.3 %
8 C1 inhibitor deficiency											
Total number	74	219	1628	408	30	16	0	13	323	2388	2711
Percentage of diagnosis	3 %	8 %	60 %	15 %	1 %	1 %	0 %	0 %	12 %	88 %	100 %
Percent of defect by region	0.4 %	2.8 %	7.0 %	3.2 %	0.5 %	0.8 %	0 %	1.1 %	1.2 %	4.2 %	3.2 %
9 PFAPA syndrome											
Total number	29	92	1050	391	667	25	8	0	353	2262	2615
Percentage of diagnosis	1 %	4 %	40 %	15 %	26 %	1 %	0 %	0 %	13 %	87 %	100 %

Table 6 continued

	Canada	Latin Amer	West Euro	East Euro	Middle East	Asia	Australia	Africa	US totals	Int. totals	Global totals
Percent of defect by region	1.4 %	1.2 %	4.5 %	3.0 %	12.1 %	1.2 %	0.6 %	0 %	1.3 %	4.0 %	3.1 %
10 IgG subclass deficiency, isolated											
Total number	35	102	2815	573	9	26	234	15	761	3809	4570
Percentage of diagnosis	1 %	2 %	62 %	13 %	0 %	1 %	5 %	0 %	17 %	83 %	100 %
Percent of defect by region	1.6 %	1.3 %	12.0 %	4.5 %	0.1 %	1.2 %	19.4 %	1.2 %	2.8 %	6.7 %	5.5 %
11 Ataxia telangiectasia (A-T)											
Total number	37	229	349	224	104	27	2	81	1130	1053	2183
Percentage of diagnosis	2 %	10 %	16 %	10 %	5 %	1 %	0 %	4 %	52 %	48 %	100 %
Percent of defect by region	1.7 %	3.0 %	1.5 %	1.7 %	1.9 %	1.3 %	0.1 %	6.5 %	4.2 %	1.9 %	2.6 %
12 TACI Deficiency (mutation TNFRSF13B)											
Total number	2	9	91	4	0	0	0	0	2041	106	2147
Percentage of diagnosis	0 %	0 %	4 %	0 %	0 %	0 %	0 %	0 %	95 %	5 %	100 %
Percent of defect by region	0 %	0.1 %	0.4 %	0 %	0 %	0 %	0 %	0 %	7.5 %	0.2 %	2.6 %
13 Agammaglobulinemia (XLA)—BTK deficiency											
Total number	57	282	600	255	128	245	86	47	466	1700	2166
Percentage of diagnosis	3 %	13 %	28 %	12 %	6 %	11 %	4 %	2 %	22 %	78 %	100 %
Percent of defect by region	26.7 %	3.7 %	2.6 %	2.0 %	2.3 %	11.6 %	7.1 %	3.8 %	1.7 %	3.0 %	2.6 %
14 Other combined immunodeficiencies											
Total number	22	174	275	162	113	113	63	108	202	1030	1232
Percentage of diagnosis	2 %	14 %	22 %	13 %	9 %	9 %	5 %	9 %	16 %	84 %	100 %
Percent of defect by region	1.0 %	2.3 %	1.2 %	1.3 %	2.1 %	5.3 %	5.2 %	8.7 %	0.7 %	1.8 %	1.5 %
15 IgA with IgG subclass deficiency											
Total number	16	21	457	279	4	15	0	20	326	812	1138
Percentage of diagnosis	1 %	2 %	40 %	25 %	0 %	1 %	0 %	2 %	29 %	71 %	100 %
Percent of defect by region	0.7 %	0.3 %	2.0 %	2.2 %	0 %	0.7 %	0 %	1.6 %	1.2 %	1.4 %	1.4 %

The distribution of the 15 most commonly identified PI globally by region

Table 7 Patients with Antibody Deficiency

	2015	2013
US	19,437	10,783
International	28,111	26,749
Global totals	47,548	37,532

The number of patients reported with an Antibody Deficiency in the US and internationally in 2015 compared with 2013

Table 8 Treatment with IG comparative reporting

	2015		2013	
	n	%	*n*	%
IVIG—clinic				
US	3098		2572	
International	8175		6285	
Global	11,273	55	8857	51
IVIG—home				
US	2415		2423	
International	447		418	
Global	2865	14	4298	25
SCIG				
US	2272		1631	
International	3416		2667	
Global	5688	28	2841	17
Other				
US	380		689	
International	224		540	
Global	604	3	1229	7
Totals for all IgG				
US	8165		7315	
International	12,262		9910	
Global	20,427	100	17,225	100

The total number of patients receiving immunoglobulin therapy (IgG) in the clinic intravenously, at home intravenously, subcutaneously, and by other reported treatment route or modality in 2015 compared with 2013

through 2014. This generated approximately 5 billion claim lines and represents one of the largest data sets on the privately insured ever assembled. Overall, healthcare spending increased 3.9 % over the past 2 years. Costs were constrained by additional outpatient care, limiting hospital costs. Another significant constraint on costs was that a greater number of Americans were covered under the Affordable Care Act, limiting the number of emergency room visits and hospital stays. Finally, in a study from the National Center for Biotechnology, information dated June 2014, entitled "Economic impact of infections among patients with primary immunodeficiency disease receiving IVIG therapy," the economic consequences are confirmed within 10 % [35].

Risk assessment SPIRIT Analyzer software

In an effort to utilize the JMF 10 Warning Signs, which are substantiated by the above-described physician-reported outcomes, JMF developed and continues to advance a new software Analyzer. The purpose is to identify patients at risk for PI in existing databases. While formal evaluations of the Analyzer are underway, JMF engaged payers and providers to beta test and pilot JMF's newly developed Analyzer, SPIRIT (Software for Primary Immunodeficiency Recognition, Intervention and Tracking). The software matches more than 350 weighted ICD-9 codes (currently transitioning to ICD-10) 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 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.

Functionality and efficacy of the SPIRIT Analyzer were tested on the IMS LifeLink database, comprised of 60 million unique patients from 90 health plans in the US [8]. 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 <30 min. Specificity and sensitivity tests were conducted, and risk assessment and economic consequences were quantified. Statistical analysis was conducted using two-way ANOVA and Student's *t* test for paired data. P values < 0.05 were considered significant.

Importance of outcomes analyzers

Amerisource Bergen/Xcenda developed the SPIRIT Analyzer in collaboration with JMF. Outcomes analyzers such as SPIRIT were surveyed at the Academy of Managed Care Pharmacy 26th Annual Meeting [36]. Fifty-eight participants from the Managed Care Network participated in the survey and provided their perspectives on SPIRIT (Fig. 1).

Table 9 Patients receiving IG by site of care regionally and by percentage

	US	Canada	Latin Amer	West Euro	East Euro	Middle East	Asia	Australia	Africa	Global totals
IVIG—clinic	3098	475	1354	2579	1511	594	422	855	385	11,273
	38 %	66 %	87 %	46 %	73 %	100 %	99 %	98 %	94 %	55 %
IVIG—home	2415	11	51	381	2	1	0	0	1	2862
	30 %	2 %	3 %	7 %	0 %	0 %	0 %	0 %	0 %	14 %
SCIG	2272	234	104	2566	472	0	4	19	17	5688
	28 %	33 %	7 %	46 %	23 %	0 %	1 %	2 %	4 %	28 %
Other	380	0	42	98	78	0	0	0	6	604
	5 %	0 %	3 %	2 %	4 %	0 %	0 %	0 %	1 %	3 %
Totals	8165	720	1551	5624	2063	595	426	874	409	20,427
	100 %	100 %	100 %	100 %	100 %	100 %	100 %	100 %	100 %	100 %

The total number of patients receiving immunoglobulin therapy (IgG) in the clinic intravenously, at home intravenously, subcutaneously, and by other reported treatment route or modality by region in 2015

Table 10 Patients receiving IG by region comparative report

	2015	2013
US	8165	7315
	40 %	42 %
Canada	720	756
	4 %	4 %
Latin America	1551	851
	8 %	5 %
Western Europe	5624	5343
	28 %	31 %
Eastern Europe	2063	1675
	10 %	10 %
Middle East	595	485
	3 %	3 %
Asia	426	322
	2 %	2 %
Australia	874	21
	4 %	0 %
Africa	409	457
	2 %	3 %
Global totals	20,427	17,225
	100 %	100 %

The number of patients receiving IgG by region in 2015 compared with 2013

Table 11 Treatment by gene therapy, PEG-ADA, and transplantation comparative report

	2015	2013
Patients treated by gene therapy	113	488
Patients treated with PEG-ADA	89	62
Patients treated by transplant	2493	2049
US	477	427
International	2016	1622

The total number of patients with severe forms of PI, such as SCID, that have received gene therapy, PEG-ADA, or a hematopoietic stem cell or thymus transplant in 2015 compared with 2013

Current results for screening of newborns for severe combined immunodeficiency (SCID) and related T cell lymphopenia

In the period of 2001–2007, the JMF advocated before the United States Congress to consider adding SCID to the National Newborn Screening Core Panel. In 2008, JMF funded the first pilot program, in the state of Wisconsin, to screen 10,000 newborns using the TREC assay [12]. In this initial pilot program, a newborn with a combined immunodeficiency was identified and was successfully treated with a cord blood transplant.

In 2010, soon after the implementation of this pilot program, JMF advocated before the US Secretary of Health and Human Services Advisory Committee on Heritable Disorders in Newborns and Children, making an impassioned plea to add SCID to the National Newborn Screening Core Panel. It was unanimously recommended that all newborns be screened for SCID and T cell lymphopenia, characterizing SCID screening using the TREC assay as "The National Standard for Newborn Screening Programs" [37].

In 2012, JMF announced that it would provide funding to every state for every baby to be screened for SCID, a total of approximately 4.1 million newborns.

As of the date of this manuscript, JMF has advocated, funded, and helped implement newborn screening for SCID and related T cell lymphopenia in 47 states, the District of Columbia, Puerto Rico, and the Navajo Nation. Based upon state population data from the most recent

Table 12 Treatment by gene therapy, PEG-ADA, and transplantation by region

	US	Canada	Latin Amer	West Euro	East Euro	Middle East	Asia	Australia	Africa	Global totals
Patients treated by gene therapy	23	2	4	76	5	3	0	0	0	113
Patients treated with PEG-ADA	38	4	1	35	6	2	0	0	3	89
Patients treated by transplant	477	64	182	1066	240	287	119	22	36	2492

The total number of patients with severe forms of PI, such as SCID, that have received gene therapy, PEG-ADA, or a hematopoietic stem cell or thymus transplant by region in 2015

Table 13 Stem cell donor type used for patients having received HSCT by region and percentage

Donor type	US	Canada	Latin Amer	West Euro	East Euro	Middle East	Asia	Australia	Africa	Global totals
MRD	94	25	57	271	89	115	32	0	22	705
	24 %	36 %	41 %	28 %	34 %	53 %	28 %	0 %	69 %	32 %
MUD	172	41	35	319	135	55	57	0	3	817
	43 %	59 %	25 %	33 %	52 %	25 %	50 %	0 %	9 %	37 %
mMUD	42	1	15	83	7	10	14	0	0	172
	11 %	1 %	11 %	9 %	3 %	5 %	12 %	0 %	0 %	8 %
Parental Haplo	88	3	31	290	28	39	10	0	7	496
	22 %	4 %	22 %	30 %	11 %	18 %	9 %	0 %	22 %	23 %
Totals	396	70	138	963	259	219	113	0	32	2190
	100 %	100 %	100 %	100 %	100 %	100 %	100 %	0 %	100 %	100 %

The distribution of the number of patients who received bone marrow transplants from matched related donors, matched unrelated donors, mismatched unrelated donors, and parental donors by region in 2015

Table 14 Stem cell source used for patients having received HSCT by region and percentage

Stem cell source	US	Canada	Latin Amer	West Euro	East Euro	Middle East	Asia	Australia	Africa	Global totals
BM	240	38	115	546	147	41	56	0	24	1207
	63 %	76 %	74 %	59 %	62 %	59 %	50 %	0 %	69 %	61 %
PBSC	64	5	9	251	70	24	8	0	8	439
	17 %	10 %	6 %	27 %	29 %	35 %	7 %	0 %	23 %	22 %
Cord	76	6	31	127	22	4	48	0	3	317
	20 %	12 %	20 %	14 %	9 %	6 %	42 %	0 %	9 %	16 %
Other	3	1	0	3	0	0	1	0	0	8
	1 %	2 %	0 %	0 %	0 %	0 %	1 %	0 %	0 %	0 %
Totals	383	50	155	927	239	69	113	0	35	1963
	100 %	100 %	100 %	100 %	100 %	100 %	100 %	0 %	100 %	100 %

The number of patients who received transplantation through the source of bone marrow, peripheral stem cells, cord blood, or other stem cell sources by region in 2015

National Vital Statistics Report [38], 3.8 million or 96.2 % of all newborns are screened for SCID annually in the US. Since inception of this program in 2010, more than 11 million newborns will have been screened for SCID in the US by the end of 2015. It is estimated that at least 4000 babies were affected over the past 5 years. Globally, pilot programs have started in Ontario, Canada; Norway; the Netherlands; Israel; and Taiwan. States reported back to JMF that in addition to the known gene defects causing SCID and related forms of combined immunodeficiencies, the following conditions were identified, utilizing the TRECs assay: Jacobsen syndrome, trisomy 18, trisomy 21, DiGeorge syndrome, chylothorax, and pulmonary hypoplasia with other anomalies, as well as degenerative

Table 15 Stem cell donor type used for patients having received HSCT comparative report

	2015		2013	
	n	%	*n*	%
MRD				
US	94		76	
International	611		472	
Global	705	32	548	30
MUD				
US	172		151	
International	645		544	
Global	817	37	695	38
mMUD				
US	42		29	
International	130		134	
Global	172	8	163	9
Parental haplo				
US	88		57	
International	408		372	
Global	496	23	429	23
Totals				
US	396		313	
International	1794		1522	
Global	2190	100	1835	100

The distribution of the number of patients who received bone marrow transplants from matched related donors, matched unrelated donors, mismatched unrelated donors, and parental donors in 2015 compared with 2013

Table 16 Stem cell source used for patients having received HSCT comparative report

	2015		2013	
	n	%	*n*	%
BM				
US	240		189	
International	967		839	
Global	1207	61	1028	61
PBSC				
US	64		53	
International	375		401	
Global	439	22	454	27
Cord				
US	76		47	
International	241		144	
Global	317	16	191	11
Other				
US	3		1	
International	5		8	
Global	8	0	9	1
Totals				
US	383		290	
International	1588		1392	
Global	1971	100	1682	100

The number of patients who received transplantation through the source of bone marrow, peripheral stem cells, cord blood, or other stem cell sources in 2015 compared with 2013

neuromuscular disease, cardiac anomalies, congenital heart defects, multiple congenital anomalies, and Ataxia Telangiectasia.

Comparative economic analysis to screen or not to screen newborns for SCID and T cell lymphopenia

If newborns are not screened at birth, they will likely sustain overwhelming infections and hospitalizations, averaging costs estimated to be at least $2 million in the first year of life [40, 41]. Importantly, experience with newborn screening in the US has permitted us to establish that SCID is twice more common than originally thought [39]. This means that in the pre-newborn screening era, many infants with SCID remained undiagnosed and presumably died. The costs associated with the care of these infants (many of which likely suffered from severe infections) were not taken into consideration. Our experience further emphasizes the positive cost–benefit ratio of newborn screening for SCID. Given the incidence and population, the total costs of care for the predicted three affected newborns, as shown in the "decision tree" (Fig. 2), will amount to $6 million in healthcare costs [40, 41].

In a previous analysis, Chan et al. [22] found that the incremental cost-effective ratio (ICER) was $27,907 per quality of adjusted life year (QALY), given 70 years of life saved [22]. This ratio is highly favorable and also compares closely with other metabolic diseases currently screened. Additionally, this analysis stated that assuming society is willing to pay $50,000 per QALY, preference for screening occurred if incidence of SCID was at least 1:250,000 [22]. In 2011, three US federal agencies estimated the value of one life saved to be $7.7 million [42]. This estimate is an average provided by the Environmental Protection Agency ($9.1 million), Food and Drug Administration ($7.9 million), and the Transportation Department ($6.1 million) [42]. Given this economic information, a newborn baby with SCID or T cell lymphopenia that is screened and treated in the first 3.5 months of life generates a contribution to society that is at least 15 times greater than the cost of screening and curative treatment.

Table 17 Physician-reported clinical outcomes

Condition	Pre-diagnosis average no. of episodes per patient	Post-diagnosis average no. of episodes per patient
Persistent otitis media	4.2	1.6
Serious sinus and upper respiratory infections	4.6	2.1
Viral infections	3.7	1.4
Acute bronchitis	3.1	0.8
Bacterial pneumonias	2.8	0.6
Chronic obstructive pulmonary disease and bronchiectasis	4.3	1.4
Hospitalization days	19.8	3.1
Physician/ER visits	70.8	11.7
Days on antibiotics	166.2	72.8
School/work days missed	33.9	8.9

The average number of specific physician-reported clinical outcomes pre- and post-diagnosis

Table 18 Costs of the most frequent conditions affecting patients with PI

Condition	Pre-Dx average no. of episodes	Pre-Dx cost per episode	Pre-Dx annual cost	Post-Dx average no. of episodes	Post-Dx cost per episode	Post-Dx annual cost	Post-Dx average annual savings
Persistent otitis media	4.2	$528	$2217	1.6	$528	$845	
Serious sinus and upper respiratory infections	4.6	$1125	$5175	2.1	$1125	$2362	
Viral infections	3.7	$1275	$4717	1.4	$1275	$1785	
Acute bronchitis	3.1	$1700	$5270	0.8	$1700	$1360	
Bacterial pneumonias	2.8	$3552	$9945	0.6	$3552	$2131	
Chronic obstructive pulmonary disease and bronchiectasis	4.3	$3165	$13,609	1.4	$3165	$4431	
Hospitalization days	19.8	$2480	$49,104	3.1	$2480	$7688	
Physician/ER visits	70.8	$180	$12,744	11.7	$180	$2106	
Days on antibiotics	166.2	$10	$1662	72.8	$10	$728	
School/work days missed	33.9	$195	$6610	8.9	$195	$1735	
Total cost annually per patient without IgG			$111,053			$25,171	$85,882 Annual savings per patient per year without IgG
Average annual cost of IgG						$30,000	
Total cost savings annually including 100 % on IgG (actual total 25.6 %)							$55,882 Annual savings per patient per year with IgG

The cost of the most frequent conditions affecting patients with PI pre- and post-diagnosis, and the post-diagnosis average annual savings

The TREC assay is inexpensive, highly sensitive, and has been effectively integrated into public health programs [12, 43, 44]. SCID is a fatal disease that causes accrual of exorbitant healthcare costs in just 1 year of life [40, 41]. The cost of care for just one infant with SCID could be more than the cost of screening for an entire regional population [41]. Implementation of screening through the TREC assay will provide the earliest possible identification and allow for intervention of early transplantation before infants suffer from severe infections, organ damage, and ultimately death [11]. Newborn screening for SCID and related T cell lymphopenia is cost effective, and most importantly, it is lifesaving and allows children with SCID the opportunity to live a healthy life.

There are increasingly more established, dedicated, and specialized treatment centers for affected patients to

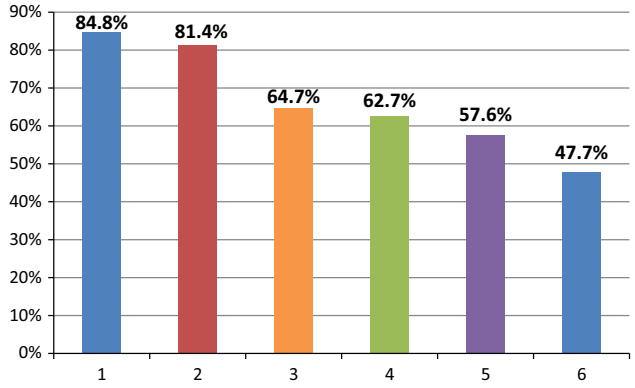

Fig. 1 Outcomes analyzers survey results. Figure 1 displays the results of the outcomes analyzer survey completed by 58 participants from the Managed Care Network. *1* 84.8 % of the respondents described outcome analyzers (OA) as moderately or highly credible. *2* 81.4 % described OAs to be transparent. *3* 64.7 % of the respondents stated that the OA will improve healthcare resource utilization. *4* 62.7 % of the respondents stated that the OA will improve quality of clinical care for patients. *5* 57.6 % of the respondents stated that the OA will have a positive net fiscal benefit. *6* 47.7 % of the respondents stated that the OA will improve physician adherence to clinical guidelines/good clinical practice

receive care [8]. The cost of the screen is $4–5 per infant. This includes equipment usage, labor, and reagents [22]. The actual incidence of SCID was found to be approximately 1:66,000 and T cell lymphopenia 1:20,000. The overall average reported was approximately 1:33,000 [43].

Results show that the cost to screen 100,000 newborns, at $4.25 per patient, totals $425,000 [22]. The cost to transplant one newborn is $120,000 [45, 46]. The cost of post-transplant care over the next 5 years may be as much as $200,000 for one newborn. Therefore, the cost to screen 100,000 newborns and treatment of one patient would be approximately $745,000. The cost to screen 100,000 newborns and treat three patients totals $1,385,000 (see Fig. 2).

Physician office waiting rooms

JMF introduced an effective new pilot program at the end of 2015, which broadcasts a branded video in the waiting rooms of 350 primary care physician offices, in 42 states and the District of Columbia, served by 1800 healthcare providers (HCPs). An initial survey was completed by 144 physicians. Figure 3 displays the results that were reported to JMF.

In the first 3 months of airing JMF content in physician office waiting rooms, survey data were analyzed by office location. Fifty percentage of the physician offices were in cities in which there is a Jeffrey Modell Diagnostic and Referral Center ("Control Group"), and 50 % were in cities or rural areas that do not have a Jeffrey Modell Diagnostic and Referral Center ("Non-control Group"). Since JMF content began airing in physician office waiting rooms, 49 % of the "Control Group" reported testing patients with two or more of the JMF 10 Warning Signs of PI, while 69 % of the "Non-control Group" offices reported testing patients with two or more of the JMF 10 Warning Signs of PI. Similarly, 16 % of the "Control Group" physician offices noted an increase in the number of patients asking about PI, while 30 % of the "Non-control Group" reported an increase in the number of patients asking about PI.

Global polio surveillance study

The JMCN provided a large patient population for this surveillance activity of vaccine strain poliovirus in vaccinated PI patients. To date, 620 patients with CVID, agammaglobulinemia, or SCID, who either received or have been exposed to the OPV, have been enrolled. A total of 13 patients excreting poliovirus have been identified, as well as 26 patients excreting non-polio enteroviruses (NPEV). Of the 13 patients identified as excreting poliovirus, three were diagnosed with agammaglobulinemia, three with CVID, and seven with SCID. Thus, overall vaccinated or exposed PI patients have a 1.5 % prolonged vaccine viral shedding rate.

In July 2015, JMF participated in the WHO Stakeholders' Meeting on Poliovirus surveillance among children with primary immunodeficiency in Geneva, Switzerland. This was a 2-day meeting focused on the success of surveillance efforts to date and strategies for moving forward, which included:

- Continuation of patient enrollment in current surveillance study,
- Expansion of efforts to additional study sites, to include not only low and middle-income countries but high-income countries as well,
- Broadening the criteria for patient enrollment,
- Longitudinal screening of PI patients for enterovirus excretion,
- Investigating transmission of iVDPV in household contacts,
- Public awareness and community outreach programs to help address risk reduction,
- Public health outreach to government health ministries to drive early diagnosis through the JMF 10 Warning Signs and other educational materials.

The JMCN will continue to play an integral role in iVDPV surveillance activities and contribute to the overall global polio eradication effort. The JMCN surveillance

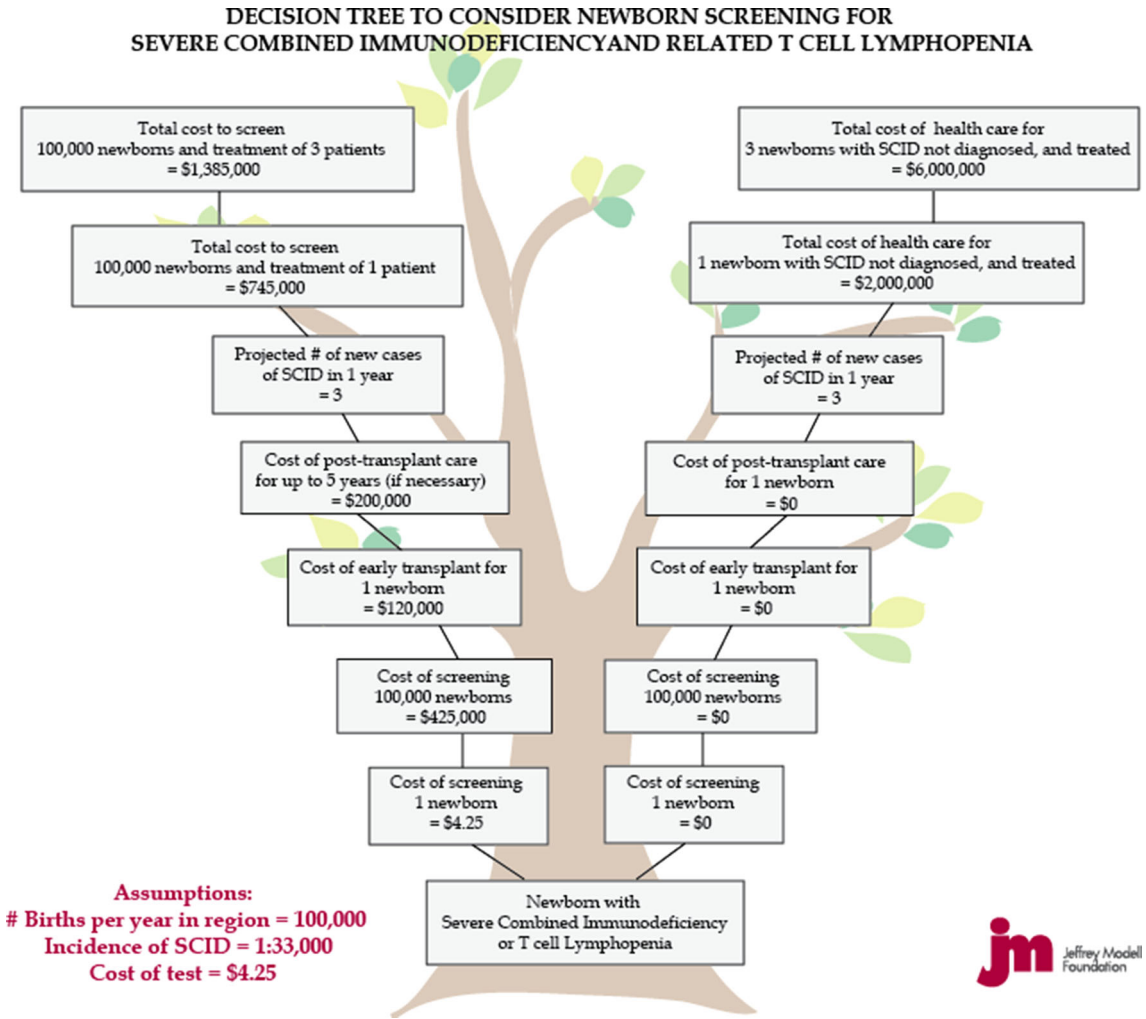

Fig. 2 Decision tool for implementation of newborn screening. Figure 2 displays a "decision tree," or working algorithm, developed by the JMF, substantiated by peer-reviewed scientific literature, and harmonized for application to be used by Public Health Departments and Health Ministries in states, countries, and regions throughout the world. The "decision tree" provides a usable tool and understandable formula that assists in deciding upon the willingness to pay for additional years of life utilizing criteria and costs specifically relevant to the locality

study for vaccine strain poliovirus shedding and development of iVDPV is ongoing, and results will be published upon completion.

Discussion

To our knowledge, this is the most comprehensive physician report on patients with PI around the world. The current physician-reported data reflect an increase in diagnosed patients, as well as those receiving treatment. Importantly, this is all despite there having not been a net increase in return of survey instruments to the JMF. Twelve years after the initiation of the Physician Education and Public Awareness Program and the inception of the JMCN, there has been a continued increase, reported by physicians, in the number of patients with PI identified, diagnosed, and treated. By expanding awareness and education, suspected patients are being identified and referred so that they can receive early and appropriate diagnosis. This program of earliest possible diagnosis has been integrated into newborn screening for SCID and related T cell lymphopenia. In the US, 96.2 % of all newborns are now being screened for this life-threatening disease. Treatment modalities have been enhanced and refined, in connection with IgG therapy and HSCT intervention. Physician-reported outcomes, pre- and post-diagnosis, have shown significant differentials reflected by independently documented cost analyses.

Over the past decade, improvements in diagnostics and implementation of newborn screening programs for SCID have led to a greater understanding of PI and allowed for clearer assessments of prevalence. Simultaneously, advancement in genomic technologies has led to a better

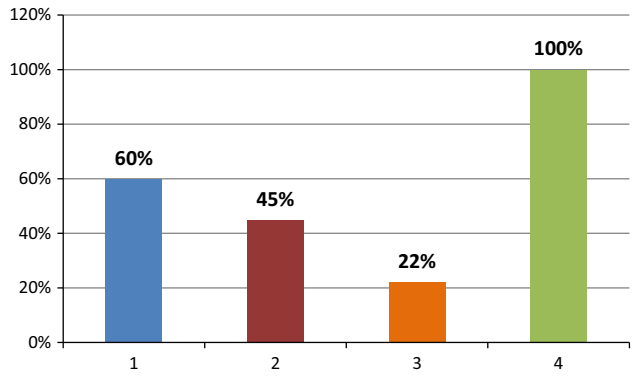

Fig. 3 PCP office waiting room video physician survey. Figure 3 displays the results of the initial survey completed by 144 physicians. *1* 60 % of HCPs reported patients in their practice with two or more of the 10 Warning Signs of PI just in the past year. *2* 45 % of HCPs already have patients diagnosed with PI. *3* 22 % of HCPs noted an increase in the number of patients asking about PI since JMF content began airing. *4* 100 % of the HCPs participating rated the waiting room program as an excellent or very good way to create awareness of PI

understanding of the underlying mechanisms that lead to monogenic defects of the immune system [47]. These advancements and new discoveries will continue to impact the field of immunology, as well as contribute to related fields such as genomics, infectious disease, and oncology [47].

There are many PIs that remain undiscovered. As genomic sequencing technologies advance, additional defects will be identified, contributing to an understanding of the mechanisms of diseases of the immune system, as well as basic cellular pathology [47]. It is important that as genetic technologies advance, access to these technologies also increases to reduce inequalities in diagnostics worldwide.

Currently, there are over 300 PI defects identified [5, 21, 48]. A review of the most recent IUIS Expert Committee Classification of PI found that nearly 100 new genes were discovered at Jeffrey Modell Centers during the period of 2012–2015, with specific focus on molecular diagnosis, whole genome and exome sequencing. Centers have reported advances re-programming SCID mutations in the cells employing new CRISPR technology and genome editing [49]. Antiviral immunotherapy by means of virus-specific cytotoxic T cells is underway at a number of JMF Centers in the Network [50]. The JMF survey report and resulting database include substantive numbers of various genotypes and aim to continue to provide a strong platform for collaboration, contributing to international coordination of studies to promote further gene discovery.

Our findings show that there are regional differences throughout the Network, which reflect greater prevalence of specific gene defects based on occurrences such as founder effect and consanguinity [8]. Because of this, awareness campaigns must be targeted to meet the unique needs in each of these diverse geographical regions. Furthermore, it is important to expand on epidemiological and demographic assessments of specific genes, which may lead to more targeted efforts, and lead to tailoring of continuing medical education, with more precise risk categories identified.

The JMCN continues to materially impact the field of immunology worldwide. The Network serves as a unique resource, creating greater awareness of PIs, conducting physician and patient education, and facilitating access to diagnosis and treatment. The Network infrastructure is in place, established, and matured. This platform will allow the PI community to leverage research advances, earlier diagnosis, improved treatments, and clinical care so that patients can experience healthier outcomes and a better quality of life.

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