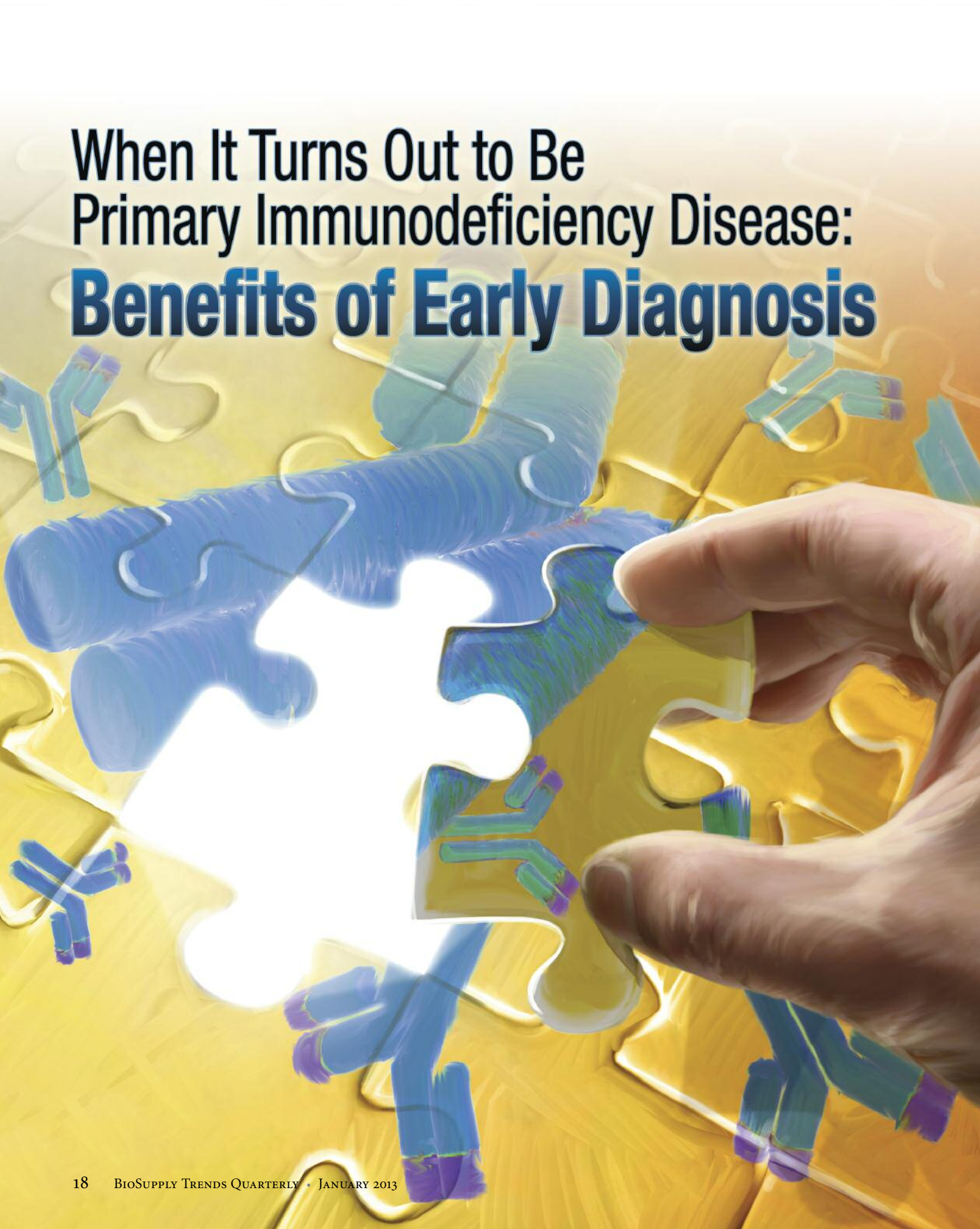
When It Turns Out to Be Primary Immunodeficiency Disease: Benefits of Early Diagnosis



Early referral for workup of patients with any of more than 150 occult primary immunodeficiency diseases can dramatically reduce hospitalizations, permanent disability and high costs of care.

By Keith Berman, MPH, MBA

Today in all 50 states in the U.S., every newborn is screened for cystic fibrosis with a genetic test or blood test so that treatment can begin almost immediately. The unusual excessive bleeding in infants or young children with hemophilia generally leads to a prompt referral to a hematologist and coagulation testing to identify the disorder. But for the more than 150 distinct genetically-based primary immunodeficiency diseases (PIDDs) characterized to date, nor for most are there any readily recognizable clinical manifestations.

For all but the most severely affected individuals, PIDD typically manifests as "ordinary" infections, most often involving the ears, lungs or sinuses. Consequently, it often takes years for infants born with a PIDD to be diagnosed and to start receiving immune globulin (IG) prophylaxis or other disease-appropriate therapy. In the meantime, repeated unusually severe or prolonged infections place many of these individuals at risk for permanent organ damage or death.

The specific genetic immune system defect at fault may variously involve compromised function of T cells, phagocytic cells, complement or, in roughly half of all cases, B cells responsible for production of protective antibodies. While disease expression is at least as variable as the range of disorders themselves, this increased susceptibility to infection manifests as:

- high infection recurrence rate,
- unusual severity of infection,
- unusual persistence or complicated course,
- clinical infections with organisms of relatively low virulence.

At the far extreme is severe combined immunodeficiency (SCID), a group of 10 very rare genetic disorders characterized by profound deficits in both T and B cell function; SCID is frequently fatal without bone marrow transplantation. By contrast, most patients with PIDD of mainly B cell origin have intact T cell immunity and some residual humoral immunity. The result is much variability in type, frequency and severity of mainly bacterial infections, but importantly a much less obvious serious infection history than one sees with SCID. With aggressive antibiotic therapy, patients usually recover, in effect further "masking" the underlying immune deficiency. But inevitably these patients are soon afflicted with a new infection or a recurrence of the same unresolved infection.

It often takes years for infants born with a PIDD to be diagnosed and to start receiving immune globulin prophylaxis or other disease-appropriate therapy.

Under the Umbrella of PIDD

Immunologists have defined nine categories to broadly classify the extraordinarily heterogeneous population of some 50,000 individuals labeled with the umbrella term "primary immunodeficiency."[1] According to a recent U.S. provider

*Currently, at least 12 states (including California, Colorado, Connecticut, Delaware, Florida, Iowa, Massachusetts, Michigan, Mississippi, New York, Texas and Wisconsin) test for severe combined immunodeficiency using T-cell receptor excision circle (TREC) assays, which identify infants with absent or extremely low numbers of T cells.

survey that captured 15,600 U.S. patients, the PIDD population is distributed among these disorders as follows:[2]

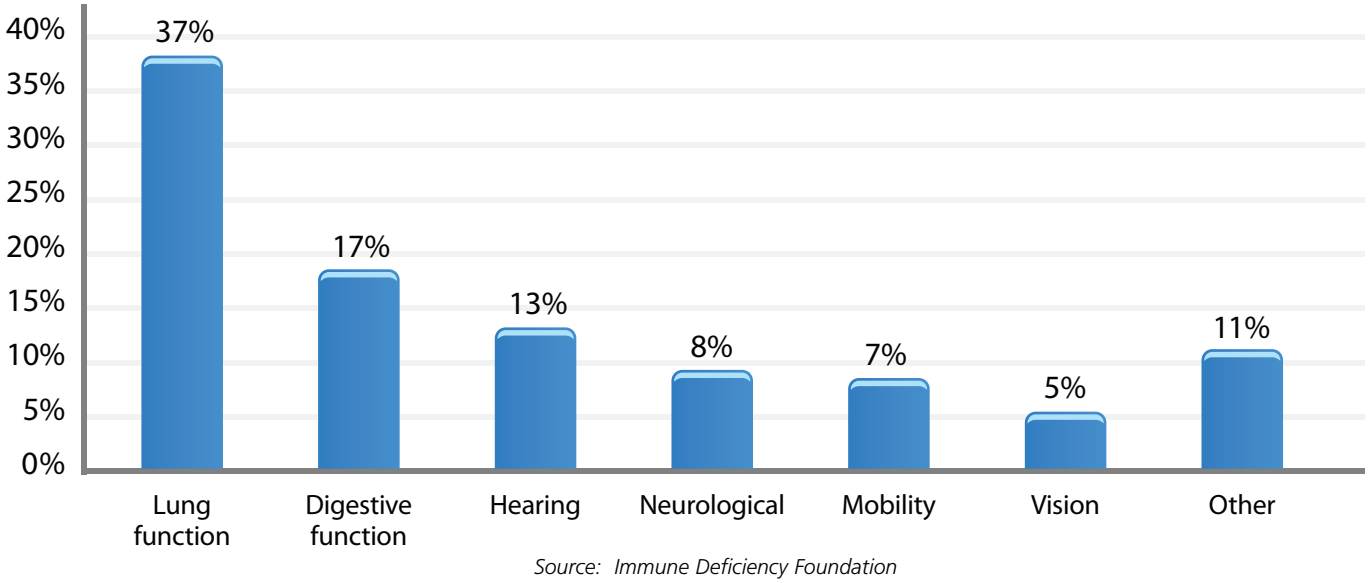
- Combined T- and B-cell immunodeficiencies: 3.9%
- Other well-defined immunodeficiency syndromes: 21.9%
- Diseases of immune dysregulation: 1.8%
- Congenital defects of phagocyte numbers and function: 2.9%
- **Predominantly antibody deficiencies: 53.8%**
- Defects in innate immunity: 0.8%
- Autoinflammatory disorders: 2.3%
- Complement deficiencies: 3.6%
- Other immunodeficiencies: 9.1%

Common variable immunodeficiency (CVID) disorders account for most of the roughly one-half of persons whose condition predominantly involves antibody deficiencies. These individuals have severe reductions in serum IgG and IgA, with normal, low or very low numbers of B cells. Their deficient IgG antibody production in particular puts them at high risk for recurrent bacterial infections. Depending on the specific genetic disorder, the underlying problem may be a deficiency in total Ig concentrations, or a significant inability to respond with IgG antibody production after an antigenic challenge (typified by a lack of response against diphtheria and tetanus toxoids, pneumococcal polysaccharide vaccine or both).

For CVID and certain other disorders involving impaired antibody production, adequate replacement with IVIG or subcutaneous IG (SCIG) has been shown to reduce the incidence of pneumonia and prevent the progression of lung disease.[3] A recent meta-analysis of 17 clinical trials evaluating

a total of 676 patients found that pneumonia incidence declined 27 percent with each 100 mg/L increment in patients' trough IgG level just prior to the next IG administration. The incidence of pneumonia with maintenance of 500 mg/dL IgG trough levels was 0.113 cases per patient-year, five-fold higher than the incidence with maintenance of a trough level of 1,000 mg/dL — 0.023 cases per patient-year.[4]

Figure 1. Percentage of persons with PI (n = 1,030) reporting permanent impairments or losses prior to diagnosis[8]



Source: Immune Deficiency Foundation

After more than 30 years of experience, accumulating evidence has prompted recommendations to approach or exceed the lower limit of IgG concentration for normal healthy adults, which is approximately 700 mg/L.[3]

Beyond dosing to achieve a recommended target IgG trough level, one additional step in individualizing IgG replacement therapy is to adjust dosage upward, if and as needed, to minimize infection in that patient.

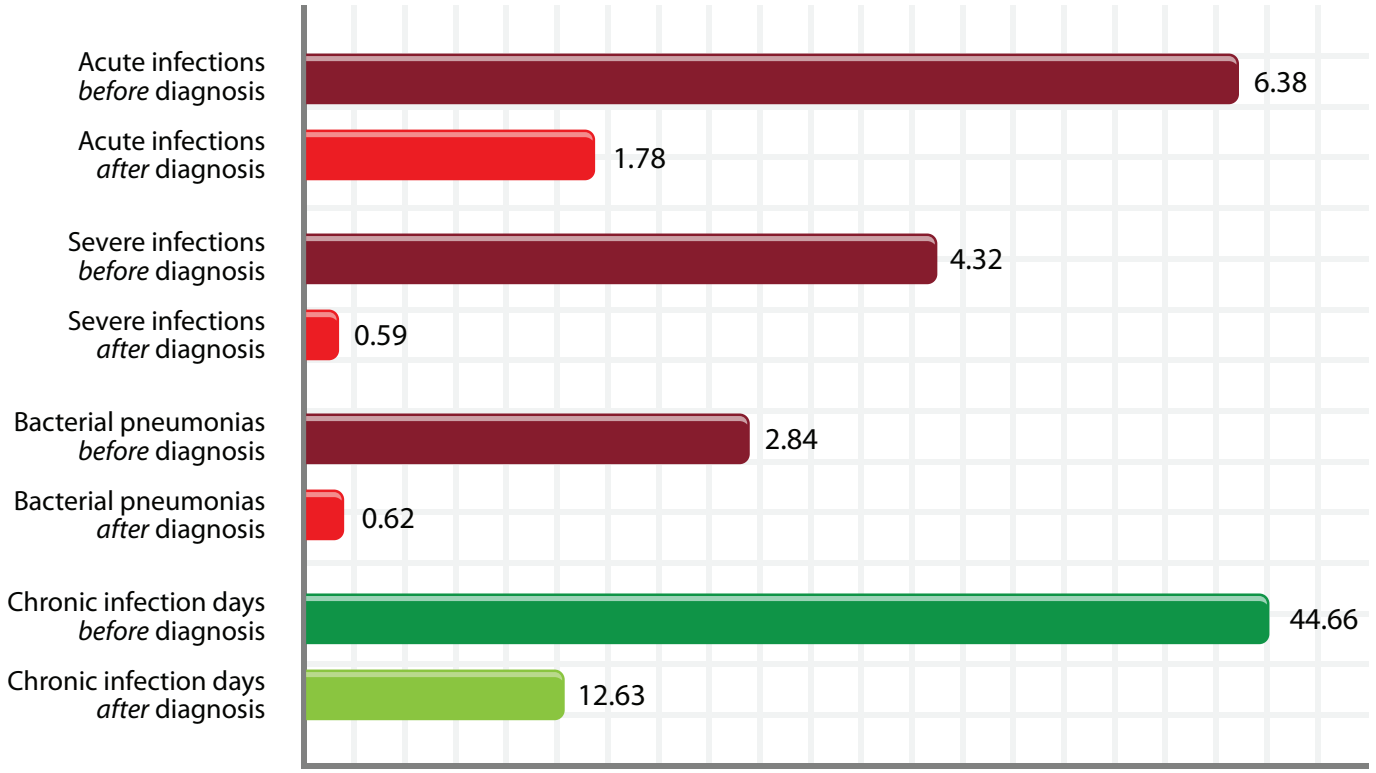
For some PIDD cases involving severe deficits in cell-mediated immunity, cellular therapy — most commonly hematopoietic stem cell transplantation — is the mainstay of treatment, with the goal of complete cure. Since the first bone marrow transplants for PIDD in 1968, stem cell transplantation for several life-threatening immunodeficiencies (including SCID) has enabled many hundreds of children with PIDD to live normal lives. Certain other patients, for example those with complete DiGeorge syndrome, benefit from thymus transplantation.[5] In a highly promising recent study, a small number of X-linked SCID patients appear to have been cured with gene therapy.[6]

The biggest problem that persists with PIDD remains the years-long delay in diagnosing these individuals in the first place.

Health Status Before, After PIDD Diagnosis

But the biggest problem that persists with PIDD remains the years-long delay in diagnosing these individuals in the first place. Despite public outreach and dissemination of provider education materials, today many more than half of all persons

Figure 2. Infection experience in U.S. patients with PI during the year prior to and the year following diagnosis[9]



Source: Jeffrey Modell Foundation

with PIDDs are not diagnosed until they are adolescents or adults.[7] According to a 2008 survey of more than 1,000 patients by the Immune Deficiency Foundation (IDF), the majority reported that they were hospitalized two or more times before a diagnosis was made, and about one-third were hospitalized four or more times.[8] Nearly one in 10 were hospitalized with serious infections 11 or more times before their underlying PIDD disorder was finally diagnosed.

IDF survey respondents also reported that, not including hospitalizations, they were too sick to attend work or school or to perform their usual activities an average of 36.8 days during the 12 months prior to diagnosis. Nearly one in five missed more than a month, and 7 percent missed more than 100 days over the year prior to diagnosis. These and other indicators, in particular very high reported antibiotic days and physician visits, underscore the huge burden in morbidity and healthcare costs of undiagnosed PIDD.

Of particular concern are the permanent adverse effects of severe and repeated infections prior to diagnosis. Slightly more than half of patients surveyed by IDF reported permanent impairment or losses prior to their initial diagnosis, including 37 percent, 17 percent and 13 percent with permanent loss of lung function, digestive function and hearing, respectively (see Figure 1).

The Jeffrey Modell Foundation (JMF), an internationally acclaimed nonprofit organization that advocates for early diagnosis of PIDD, recently screened more than 60 million U.S. medical and drug insurance claims to isolate persons diagnosed with a PIDD and examined several key infection-related health parameters over the year prior to and the year following their diagnosis.[9] Figure 2 presents a summary of those findings.

According to these data from JMF and academic collaborators, the year following PIDD diagnosis is accompanied by dramatic declines in the number of severe infections (-86 percent), number of bacterial pneumonias (-78 percent) and days with chronic infections (-72 percent). All differences between the diagnosed and undiagnosed groups were highly significant (P = 0.001). Thus in a quantifiable fashion, these crude before-and-after findings powerfully demonstrate the importance of early diagnosis of the PIDD condition that can underlie severe, recurrent and persistent infections.

Clearly, the responsibility for earlier diagnosis of PIDD ultimately resides with each primary physician who interfaces with patients every day.

The Cost of Treatment and Non-Treatment

In lock-step with those drops in infection rates following PIDD diagnosis are similar reductions in the number of physician/hospital/ER visits (-83 percent), hospitalization days (-74 percent) and days on antibiotics (-56 percent). Each directly translates, of course, into reduced costs (see Table 1).

Table 1. Selected estimated medical costs during the year prior to and the year following diagnosis of PI[9]

	Annual cost per patient before diagnosis	Annual cost per patient post-diagnosis	Annual cost savings per patient
Physician/hospital/ER visits	$11,875	$1,977	$9,899
Hospitalization	$29,792	$7,913	$21,880
Antibiotics	$946	$414	$532

Source: Jeffrey Modell Foundation

Altogether, the JMF investigators estimated total annual pre-diagnosis medical costs of $138,760. Over the year following diagnosis, estimated medical costs plunged to just under $30,300. For the roughly half of PIDD patients with primary humoral immunodeficiency, a very large annual savings remains even after the presumption of an additional $30,000 annual cost for IG replacement therapy.

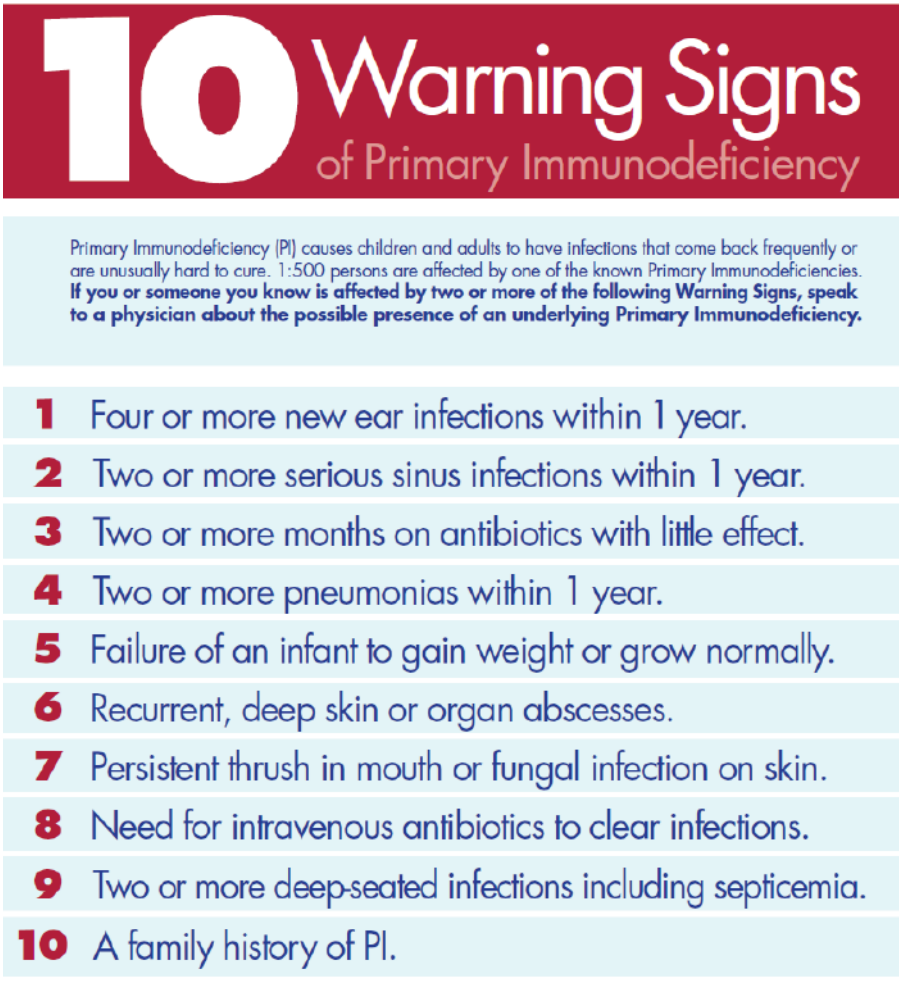
Working Toward Earlier Diagnosis

First developed in 1993 with support from the U.S. Centers for Disease Control and Prevention (CDC), JMF has disseminated a simple educational poster alerting physicians to the "10 Warning Signs of Primary Immunodeficiency" (see Figure 3).[10] Various other educational materials — patient brochures, wall posters for school and day care facilities, public service announcements to reach the general public through television, radio, print and the Internet — have and continue to be produced with funding support in part from the CDC and the National Institutes of Health. JMF reported more than 550,000 visits to its website last year and more than 23,500 calls to its information hotline.

But clearly the responsibility for earlier diagnosis of PIDD ultimately resides with each primary physician who interfaces with patients every day. Dr. Rebecca Buckley, a leading immunologist and researcher in this field, summed up the primary physician's role quite nicely: "You need a high index of suspicion." ❖

KEITH BERMAN, *MPH, MBA, is the founder of Health Research Associates, providing reimbursement consulting, business development and market research services to biopharmaceutical, blood product and medical device manufacturers and suppliers. Since 1989, he has also served as editor of* International Blood/Plasma News, *a blood products industry newsletter.*

Figure 3.



Source: Jeffrey Modell Foundation

References

1. Geha RS, Notarangelo LG, Casanova J-L, et al. The International Union of Immunological Societies (IUIS) Primary Immunodeficiency Diseases (PID) Classification Committee. *J Allergy Clin Immunol* 2007 Oct;120(4):776-94.
2. Modell V, Gee B, Lewis DB, et al. Global Study of Primary Immunodeficiency Diseases (PI) — Diagnosis, Treatment, An Economic Impact: An Updated Report from the Jeffrey Modell Foundation. *Immunol Res* 2011;51:61-70.
3. Orange JS, Hossny EM, Weiler CR, et al. Use of Intravenous Immunoglobulin in Human Disease: A Review of Evidence by Members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 2006;117:S525-53.
4. Orange JS, Grossman WJ, Navickis RJ, et al. Impact of Trough IgG on Pneumonia Incidence in Primary Immunodeficiency: A Meta-Analysis of Clinical Studies. *Clin Immunol* 2010 Oct;137(1):21-30.
5. Markert ML, Devlin BH, McCarthy EA. Thymus Transplantation. *Clin Immunol* 2010;135:236-46.
6. Hacein-Bey-Abina S, Hauer J, Lim A, et al. Efficacy of Gene Therapy for X-Linked Severe Combined Immunodeficiency. *New Engl J Med* 2010;362:355-64.
7. Buckley, RH. "Infections in PID Patients: Prevention of End-Organ Damage, Need for Practice Guidelines and Screening." April 13, 2005 presentation at FDA Workshop: Intravenous Immune Globulins in the 21st Century: Progress and Challenges in Efficacy, Safety, and Paths to Licensure.
8. Treatment Experiences and Preferences Among Patients with Primary Immunodeficiency Diseases: A National Survey of Patients (2008). Immune Deficiency Foundation. May 6, 2009.
9. Modell V, Gee B, Lewis DB, et al. Global Study of Primary Immunodeficiency Diseases (PI) — Diagnosis, Treatment, and Economic Impact: An Updated Report from the Jeffrey Modell Foundation. *Immunol Res* 2011;51:61-70.
10. Jeffrey Modell Foundation. 10 Warning Signs of Primary Immunodeficiency. Accessible as a pdf file at: http://www.info4pi.org/aboutPI/pdf/General10WarningSigns FINAL.pdf.