

# **PRIMARY IMMUNE DEFICIENCY DISEASES IN AMERICA**

**THE FIRST NATIONAL SURVEY OF PATIENTS AND SPECIALISTS**



**IMMUNE DEFICIENCY FOUNDATION**

*The National Organization Devoted To Research And Education For The Primary Immune Deficiency Diseases.*

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## **Background: Immune Deficiency Diseases**

Primary immune deficiency diseases represent a class of disorders in which there is an intrinsic defect in the human immune systems (rather than immune disorders that are secondary to infection, chemotherapy, or some other external agent). In some cases, the body fails to produce any or enough antibodies to fight infection. In other cases, the cellular defenses against infection fail to work properly. There are more than 80 different primary immune deficiency diseases currently recognized by the World Health Organization.

Medical recognition of primary immune deficiency disease is only fifty years old. Although these disorders may have existed in antiquity, it was not until the development of antibiotics that infections could be controlled long enough to recognize there was an underlying defect in the immune system. Also, the parallel development of gamma-globulin in World War II provided a replacement therapy for the antibody deficiency forms of immune deficiency.

Although primary immune deficiency diseases are often described as rare disorders, the true population prevalence of these diseases, either individually or in the aggregate, is not well established. The major health surveys conducted by the government in the United States, the National Health Interview Survey and the National Health and Nutrition Examination Survey, do not collect information on primary immune deficiency diseases. No comprehensive population survey has even been undertaken by the federal government to estimate the prevalence or the population characteristics of these diseases in the United States. Hence, although these diseases are clinically described in the medical literature, there is no comprehensive portrait available of the patient with primary immune deficiency disease.

## **Survey of Patients with Primary Immune Deficiency Diseases**

The Immune Deficiency Foundation undertook the first national survey of the state of primary immune deficiency diseases in the United States. The survey has a number of objectives. First, the survey sought to provide an estimate of the general magnitude of primary immune deficiency in the American population, if not a precise estimate of population prevalence. Second, the survey sought to describe the general population characteristics of persons with these disorders. Third, the survey sought to describe the health of persons with primary immune deficiency diseases, both with and without treatment. Fourth, the survey sought to identify problems in access to treatment in this population. All of these goals are related to the primary objective of the Immune Deficiency Foundation: improving the diagnosis and treatment of persons with primary immune deficiency diseases. The survey was designed for IDF by Schulman, Ronca and Bucuvalas, Inc. (SRBI), a national public opinion research organization. SRBI analyzed the survey data and prepared their report for the Foundation.

The survey was designed within the constraints of primary immune deficiency diseases. In the absence of a rigorous set of symptom criteria that would uniquely define primary immune deficiency disease, the survey population must be restricted to the sub-population who already has a diagnosis of primary immune deficiency disease. Many persons with immune deficiency diseases may be relatively asymptomatic. Others may have chronic and/or unusual infections that are the hallmark of immune deficiency, but have not yet been diagnosed with the underlying disorder. This survey is restricted to the population who have been tested and diagnosed with a primary immune deficiency disease. No clinical confirmation of the diagnosis has been incorporated into the study, so the survey is restricted to persons who report a physician diagnosis of a primary immune deficiency disease.

Since primary immune deficiency diseases are comparatively rare, and diagnosed cases of the condition will be rarer still, population screening to obtain a national sample of persons with these disorders was not feasible. However, it is possible to develop a relatively complete sampling frame for physicians who are most likely to treat these disorders. So, a multi-stage sampling strategy was developed to obtain a large, national sample of persons diagnosed with primary immune deficiency diseases.

The first stage in the sampling process was to construct a sampling frame of the specialists who were most likely to follow patients with primary immune deficiency diseases. This includes the major medical associations and societies of specialties related to immune diseases

(immunology and infectious diseases), chairmen of pediatric departments in medical centers, and previously identified treating physicians in IDF mailing lists and registries. The combined sampling frame included a total of 17,451 physicians (Figure 1).

Figure 1  
SAMPLING FRAME FOR SPECIALISTS

• APS/Society for Pediatric Research	2,448
• American Academy of Pediatrics (Allergy and Immunology Sections)	1,073
• American Academy of Allergy and Immunology	4,402
• American Society for Clinical Investigations	2,251
• Infectious Disease Society of America	3,839
• Clinical Immunology Society	956
• Pediatric Department Chairman	233
• IDF Mailing List Physicians	2,410
• CGD Registry Physicians	4,114
• <b>TOTAL UNDUPLICATED CASES</b>	<b>17,451</b>

The second stage in the sampling process was to conduct a systematic survey of this population to identify the sub-population who currently sees patients with primary immune deficiency diseases. The survey identified the most common of these disorders by name in order to reduce ambiguity about which disorders are primary immune

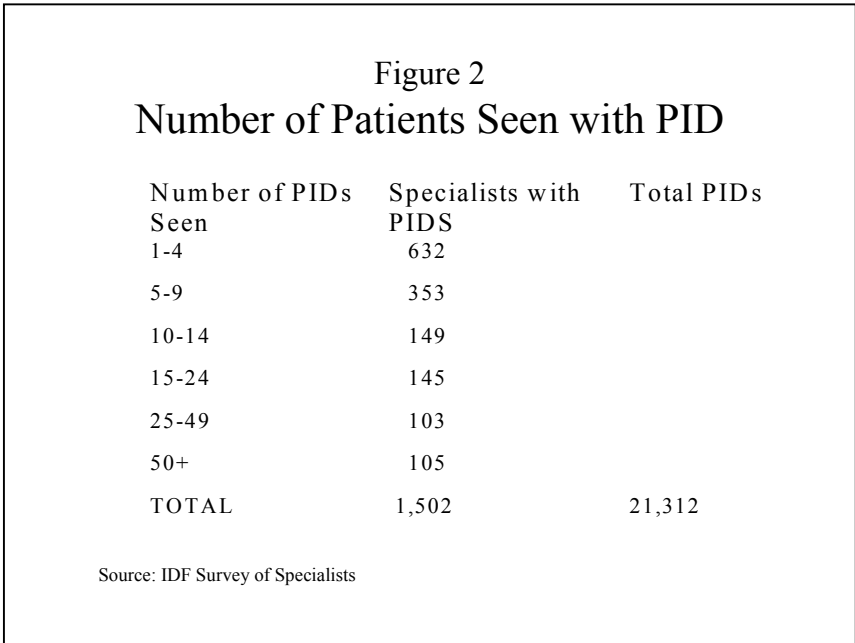
deficiency diseases. A total of 1,502 physicians from the sampling frame reported that they were currently treating one or more patients with these disorders.

The third stage in the sampling process was to send patient questionnaires to these physicians for distribution to their patients with primary immune deficiency disease. In addition, this questionnaire was sent to all self-identified patients in the IDF database. A total of nearly 3,000 questionnaires were completed and returned by unique patients. This includes 1,289 adult patients, 1,190 parents or guardians of children with primary immune deficiency diseases, and 335 where the respondent did not identify themselves as the patient or caregiver.

The sampling frame used for the survey does not provide complete coverage of physicians treating patients with primary immune deficiency diseases, nor by extension the patients themselves. The multi-stage sampling process introduces opportunity for non-sampling bias, even among the truncated sampling frame. In the absence of any denominator for the number of questionnaires distributed to eligible patients, we cannot estimate the response rate to the patient survey or adjust for non-response bias. Nonetheless, the sampling and field procedures produced a large, geographically diverse and relatively unclustered sample of persons with primary immune deficiency diseases in the United States. Although it is less than a perfect sample, it will remain the definitive sample until a better one can be obtained.

**Size of the Population of Primary Immune Deficiency Diseases**

The survey of specialists identified approximately 1,500 doctors who saw patients with primary immune deficiency diseases. Nearly half of these specialists reported that they saw four or fewer patients with these diseases. Two thirds of treating specialists reported that they followed less than ten of these patients. However, more than 100 specialists reported that they saw 50 or more primary immune deficient patients in their practice. In summary, 1,502 specialists in the United States reported that they were currently following a total of more than 21,000 patients with primary immune deficiency diseases (Figure 2).



A national survey of primary care doctors provides supplementary estimates of the number of patients with primary immune deficiency diseases. Among adult primary care specialties, approximately one in ten doctors in direct patient care on an outpatient

basis reported having one or more patients with primary immune deficiency diseases. One in five pediatricians reported having one or more patients with a primary immune deficiency disease. If we assume the minimum number of one patient per physician, this survey would yield an estimated 24,500 patients with primary immune deficiency disease being treated by primary care doctors (Figure 3).

Figure 3  
Primary Care Doctors and PID's

SPECIALTY	NUMBER IN DIRECT PATIENT CARE	PERCENT with PID*	Minimum estimate of PID's
General Practice	15,842	10%	1,582
Family Practice	49,902	10%	4,990
OB/GYN	30,296	12%	3,636
Internal Medicine	76,628	9%	6,897
Pediatrics	37,125	20%	7,425
<b>TOTAL</b>	<b>209,793</b>		<b>24,532</b>

Source: National Survey of Genetic Issues, National Center for Genome Resources, N=521.

How many persons within the United States have been diagnosed with a primary immune deficiency disease? The sample survey of specialists yields an absolute count of 21,000 patients followed by specialists. The sample survey of primary care doctors yields a population projection of 24,500 cases, assuming one patient per doctor. There may be some double counting of patients between specialists in group practices, as well as double counting of patients who are seen by both specialists and primary care doctors. At the same time, approximately half of the specialists known to the Immune Deficiency Foundation as treating patients did not respond to the survey. So, although the number of patients with primary immune deficiency diseases in the United States cannot be projected with any statistical certainty, a total of 50,000 diagnosed cases would be a reasonable estimate (Figure 4).

Figure 4  
How Many Persons with PID in US?

- Specialists report 21,312
  - May be some double counting within groups
  - Less than half of specialists with patients returned survey
- Primary care estimate is at least 25,000
  - Some may have more than one PID patient
  - Unlikely to be double counting within primary care
  - May be some double counting between primary care doctors and specialists

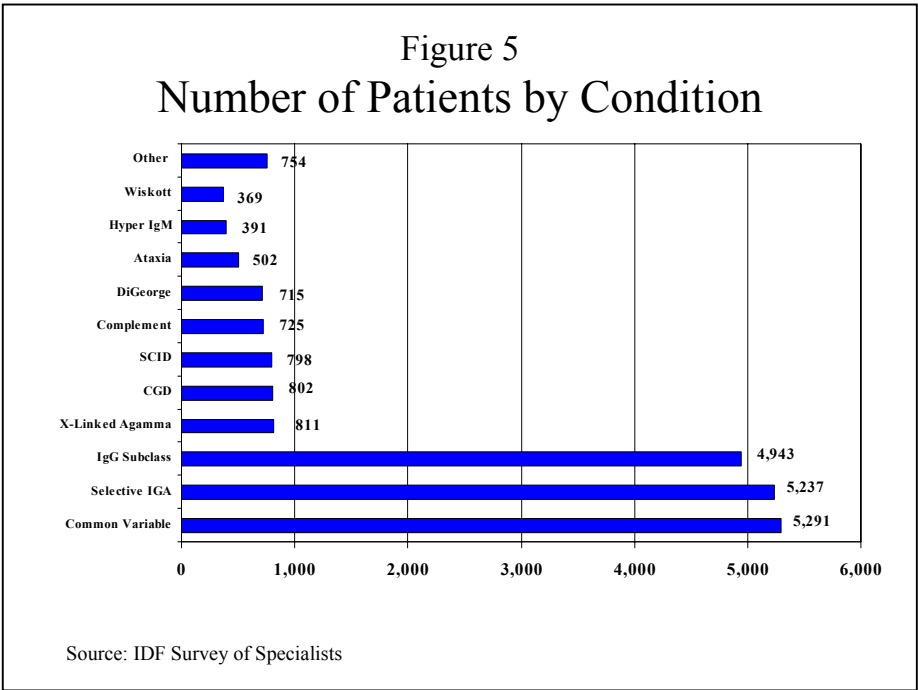
**BEST GUESS IS 50,000 DIAGNOSED CASES**

**Characteristics of the Patient Population**

An estimate of the relative distribution of the primary immune deficiency diseases by diagnosis is provided by the specialist survey. The specialists were asked how many patients they were seeing by major diagnosis.

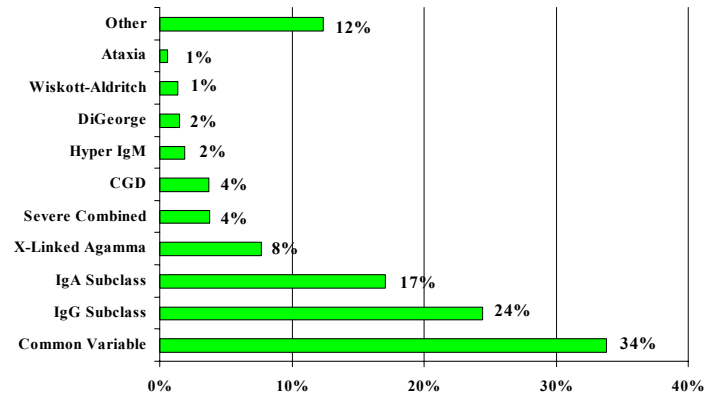
The most commonly reported primary immune deficiency diseases were: Common Variable Immune Deficiency (5,291), Selective IGA Deficiency (5,237) and IgG Subclass Deficiency (4,943). Nonetheless, specialists reported a substantial number of less common disorders such as X-linked Agammaglobulinemia (811), Severe Combined Immune Deficiency (798), Complement Disorders (725), Ataxia Telangiectasia (502), Hyper IgM (391) and Wiskott-Aldridge Syndrome (369). Since the survey of physicians is limited to a sample of specialists who see primary immune

deficiency diseases, these counts provide an estimate of the relative prevalence of the individual disorders, not a population count of these diseases. Moreover, since the sample is restricted to specialists, the more serious and complex disorders may be disproportionately represented in the sample (Figure 5).



The prevalence of specific diagnoses in the patient sample is similar to the specialist survey. The most common diagnosis is Common Variable Immune Deficiency, which accounts for a third (34%) of the patient sample. The next most common diagnoses are IgG Subclass Deficiency (24%) and IgA Subclass Deficiency (17%). X-linked Agammaglobulinemia is the fourth most common (8%) of the primary immune deficiency diseases in the patient sample. Smaller proportions of patients report Severe Combined Immune Deficiency (4%), Chronic Granulomatous Disease (4%), Hyper IgM (2%), DiGeorge Anomaly (2%), Wiskott-Aldrich Syndrome (1%) and Ataxia Telangiectasia (1%). Twelve percent report other diagnoses (Figure 6).

Figure 6  
Patients with PID by Reported Diagnosis

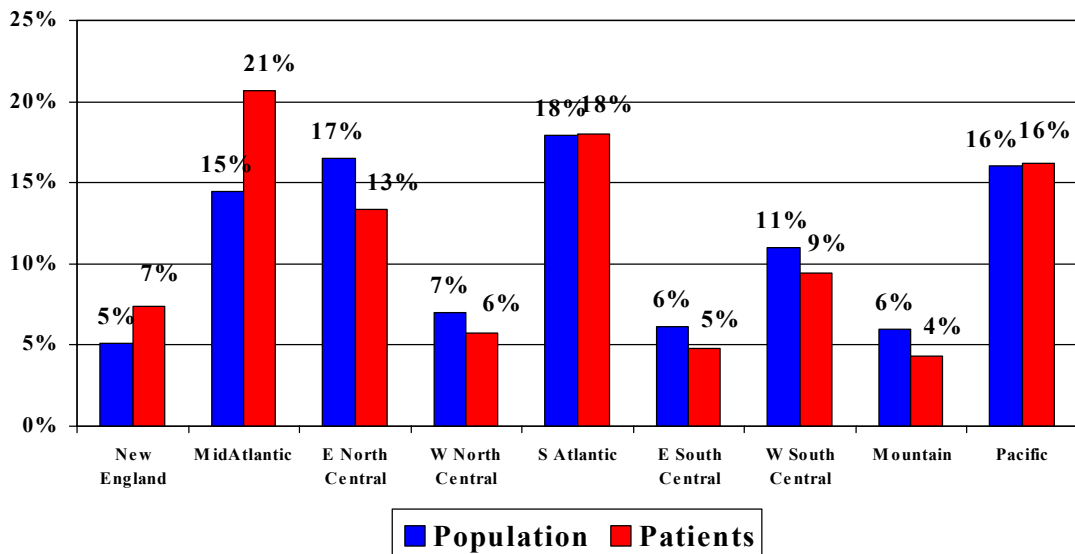


Source: IDF Patient Survey N=3,046

Despite the non-probability sampling procedures for the patient survey, the geographic distribution of the patient sample closely mirrors the total population of the United States. Among the nearly 3,000 patients in the sample, the place of birth is reported in all 50 states and the District of Columbia. There is a somewhat higher proportion of

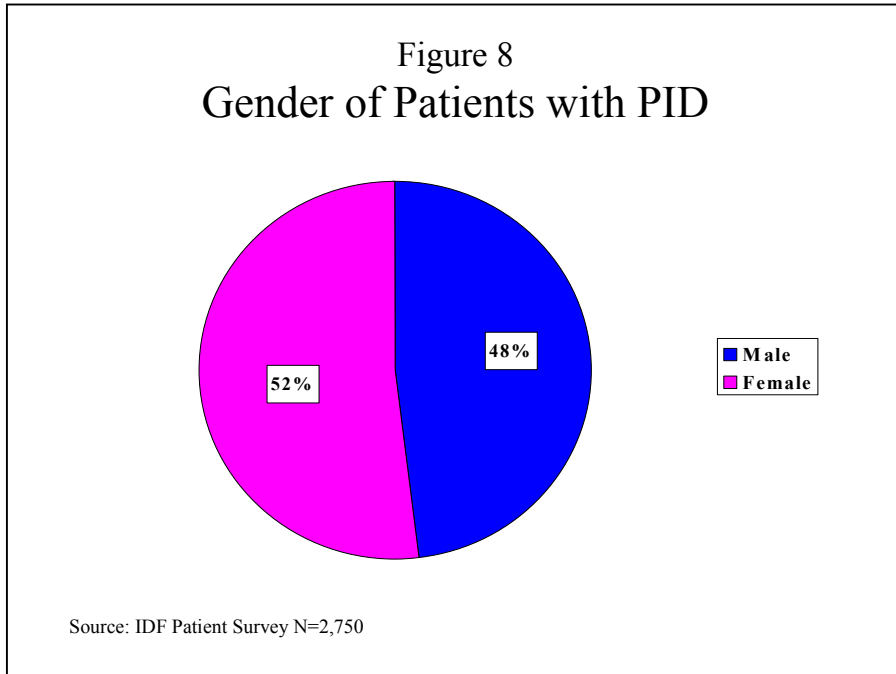
patients born in the Mid-Atlantic region (21%) than the total population (15%); while a somewhat lower proportion of patients from the East North Central region (13%) than the total population (17%). In the other seven Census divisions, the patient and population distributions are virtually identical. There are almost no cases in the sample of patients born outside of the United States (Figure 7).

Figure 7  
Patient and Population Distribution in USA

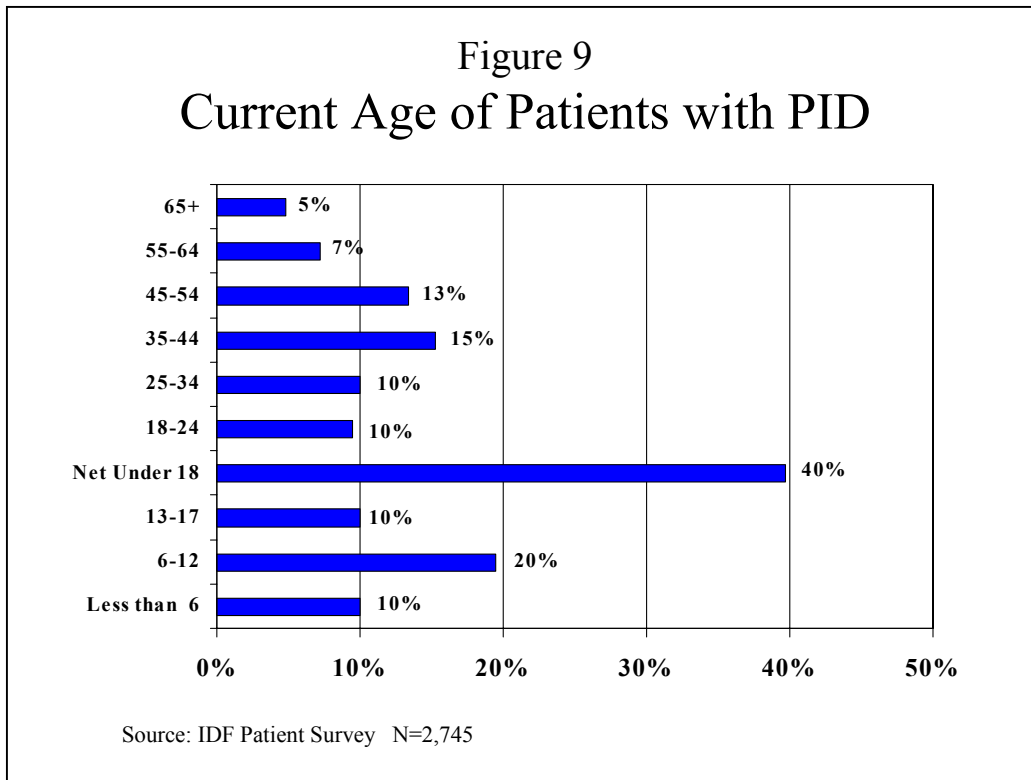


Source: US Census and IDF Patient Survey

Like the geographic distribution, the gender distribution of persons with primary immune deficiency diseases mirrors the general population. Among patients with primary immune deficiency diseases, 48% are male and 52% are female (Figure 8).



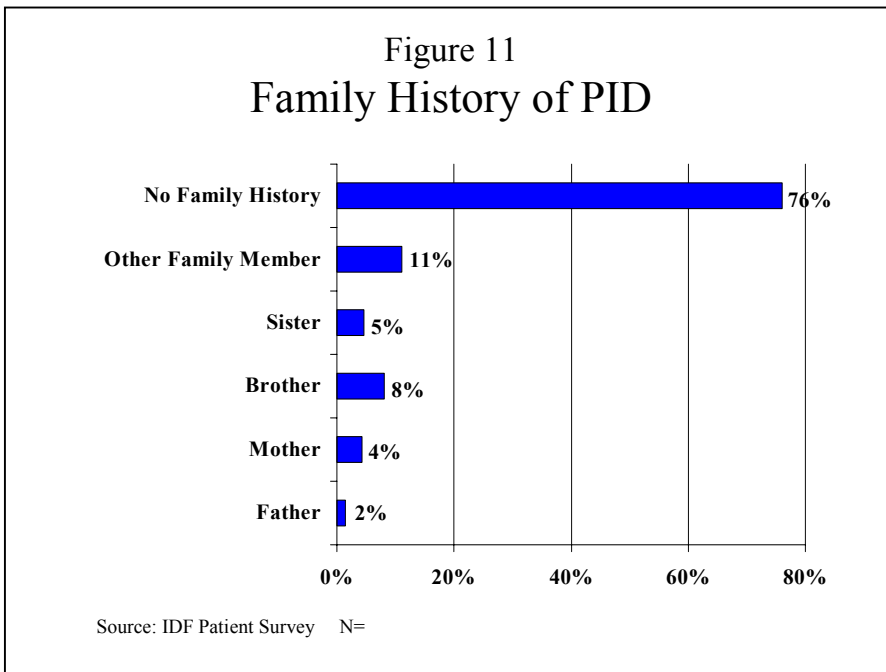
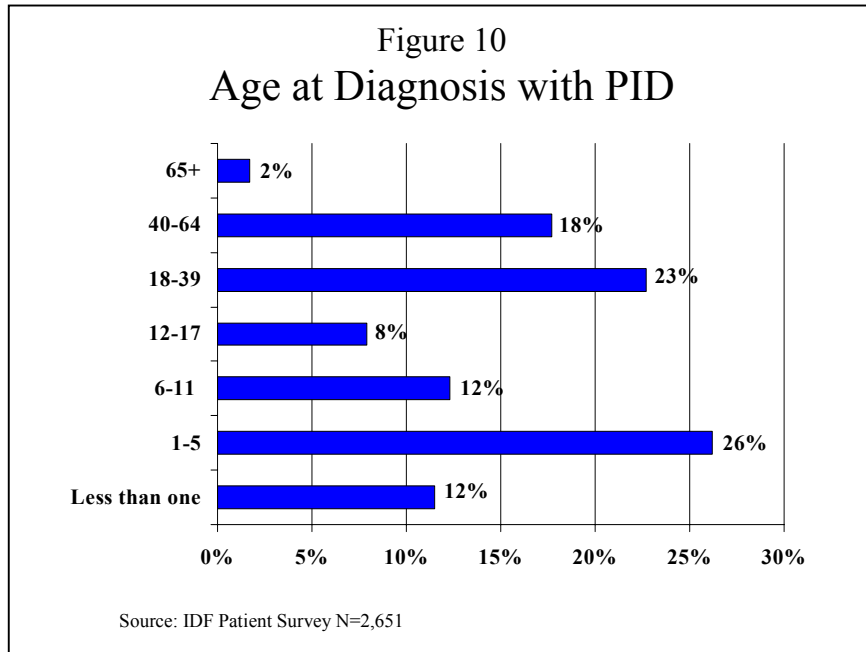
Primary immune deficiency diseases are no longer child disorders. About 10% of patients are under six years of age. Twenty percent are aged six to twelve. And, another 10% are adolescents, aged thirteen to seventeen. Sixty percent of patients with primary immune deficiency diseases are adults, aged 18 or older. Indeed, a quarter of patients are aged 45 or older. Five percent are aged 65 or older (Figure 9).





**Diagnosis**

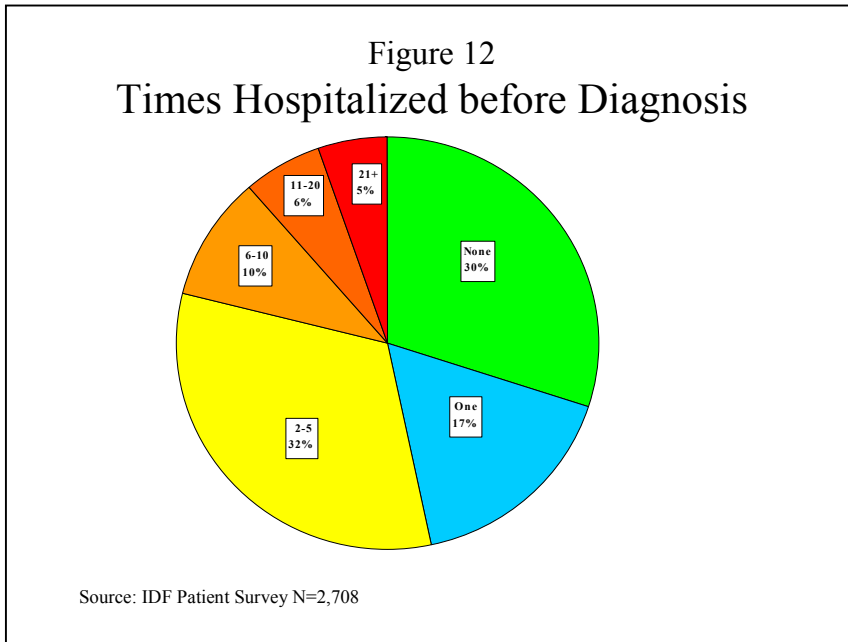
Only 12% of patients were initially diagnosed with a primary immune deficiency disease before one year of age. A total of 38% were diagnosed before age six. And a majority (50%) was diagnosed before they were twelve years of age. Nonetheless, 43% of persons with primary immune deficiency diseases were not diagnosed until they were an adult (Figure 10).



One reason for late diagnosis is the absence of a family history of these disorders. Only 2% of patients had a father with a primary immune deficiency disease and 4% had a mother with one of these diseases. It is somewhat more common for patients to have a brother (8%) or sister (5%) with this disorder.

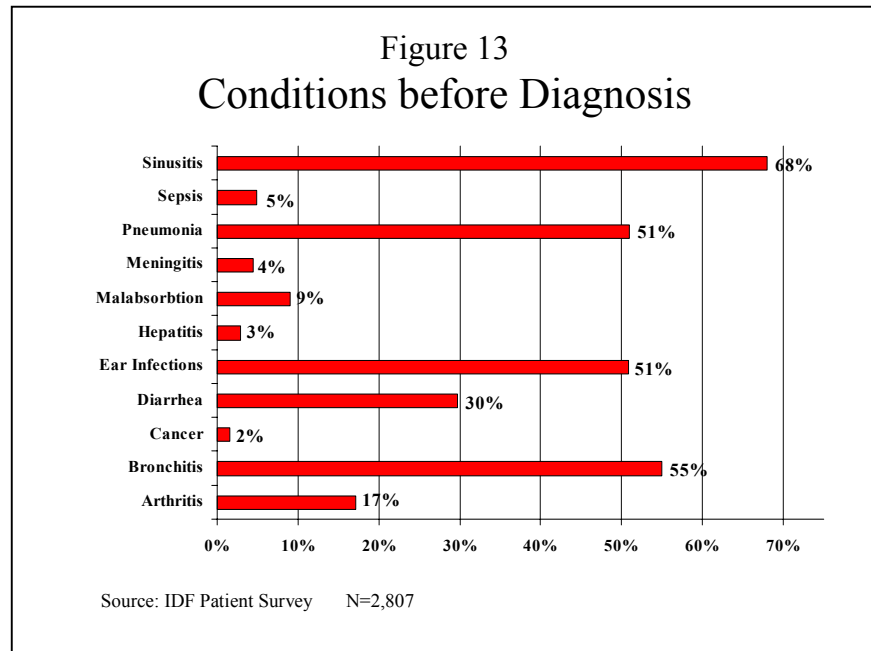
About one in ten patients (11%) report other family members with a history of these diseases. But, three quarters (76%) of patients with primary immune deficiency diseases have no family history (Figure 11).

The importance of early diagnosis of these diseases is demonstrated by medical history prior to diagnosis. Although most patients are diagnosed before age twelve, 70% of patients report being hospitalized prior to diagnosis. Seventeen percent were



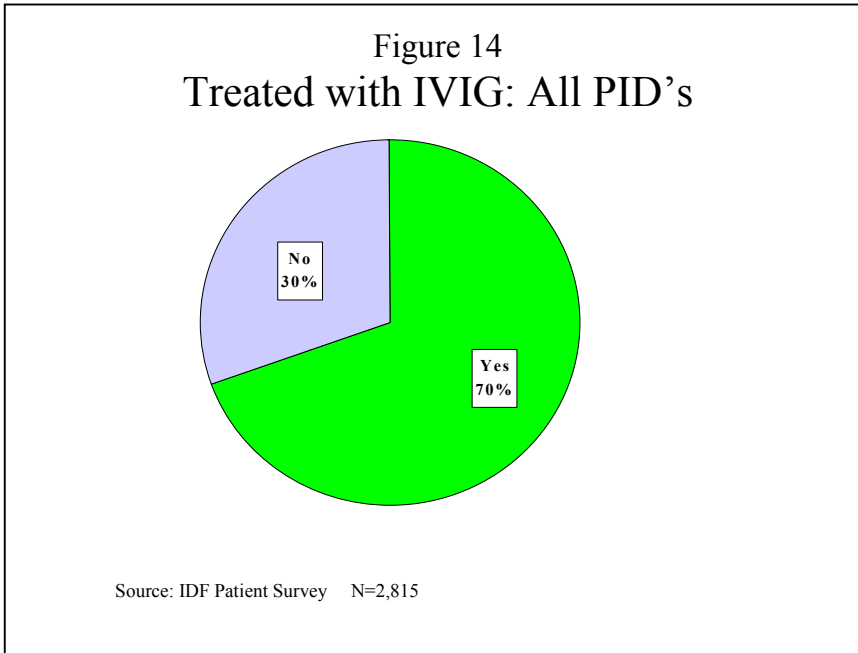
hospitalized only once prior to diagnosis. A third (32%) were hospitalized 2 to 5 times prior to diagnosis. Ten percent reported being hospitalized 6 to 10 times before diagnosis. And, twelve percent of persons with primary immune deficiency diseases report more than 10 hospitalizations before diagnosis (Figure 12).

Also, despite the relatively early age of diagnosis, many patients report the onset of serious or chronic health conditions prior to diagnosis. The majority of patients with primary immune deficiency diseases report sinusitis (68%), bronchitis (55%), pneumonia (51%) and repeated ear infections (51%) prior to diagnosis. Nearly a third (30%) report frequent diarrhea prior to diagnosis. Although far less common, relatively high rates of malabsorption (9%), sepsis (5%), meningitis (4%) and hepatitis (3%) are reported prior to diagnosis (Figure 13).

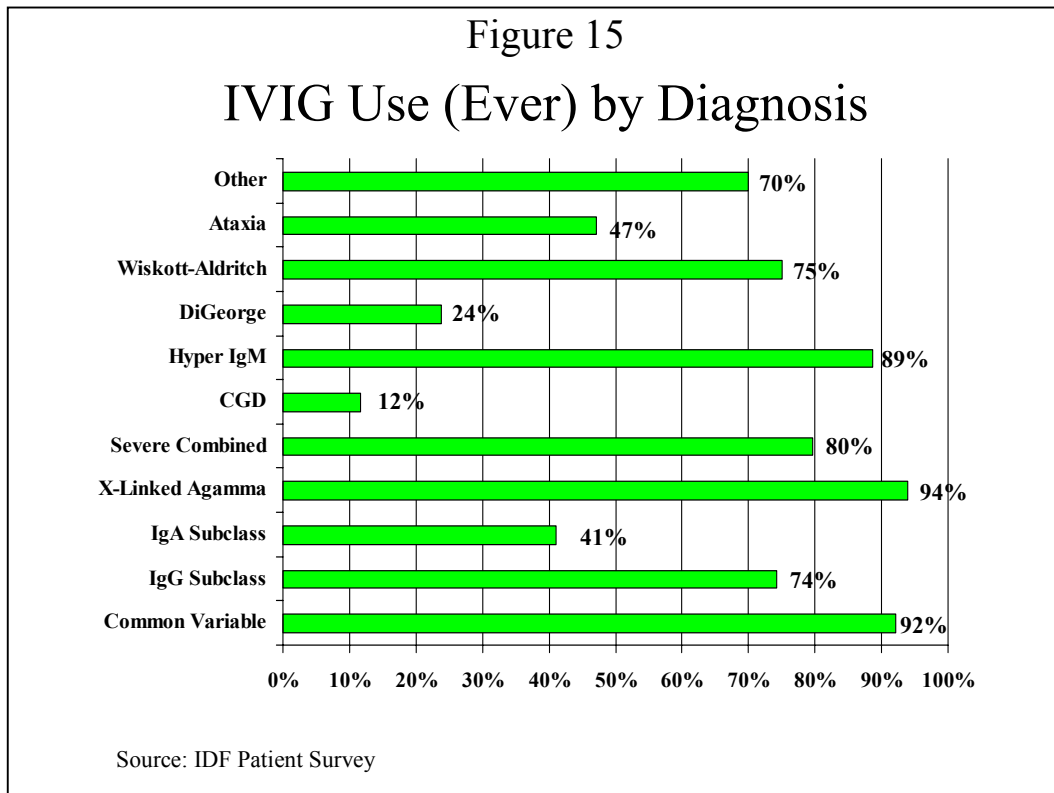


**Treatment**

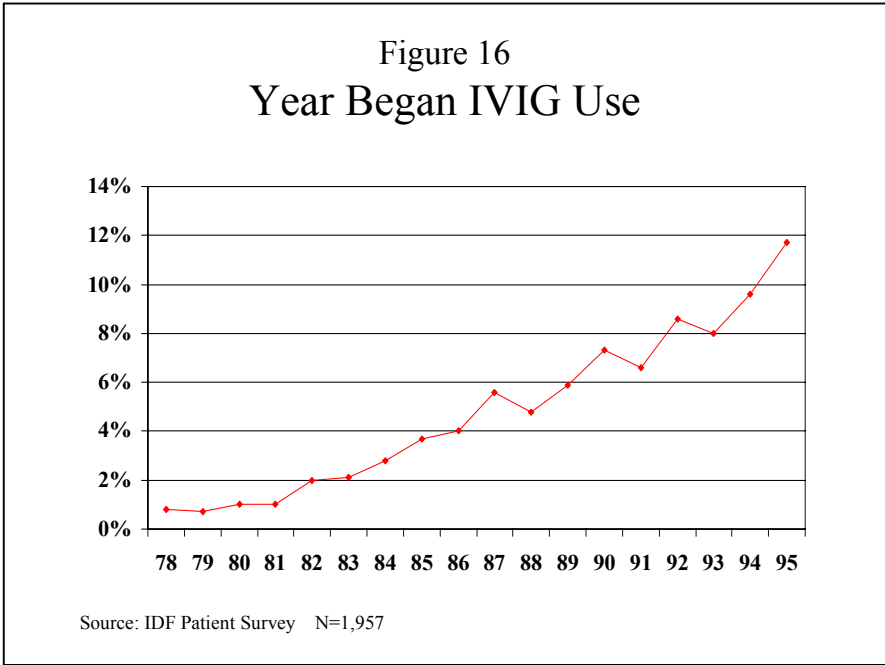
Seven out of ten (70%) patients with primary immune deficiency disease report that they have been treated with intravenous gammaglobulin (IVIG) for their disorder (Figure 14). IVIG use is most common for X-linked Agammaglobulinemia (94%),



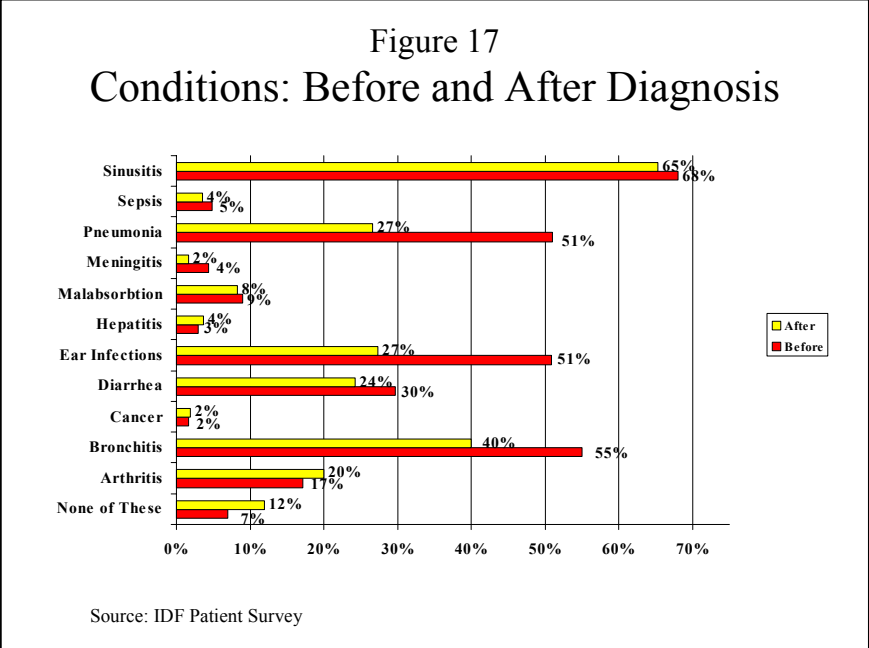
Common Variable Immunodeficiency (92%) and Hyper IgM (89%). It is also reported by a majority of patients with Severe Combined Immune Deficiency (80%), Wiskott-Aldrich Syndrome (75%), and IgG Subclass Deficiency (74%). It is least commonly used for DiGeorge Anomaly (24%) and Chronic Granulomatous Disease (12%) (Figure 15).



A small proportion of persons with primary immune deficiency diseases began IVIG use in the late 1970's and early 1980's in clinical trials. The chart of year began using IVIG reveals a strong rising demand for this product. In the three years prior to the survey, the proportion of immune deficient patients beginning IVIG use was 8%, 10% and 12% respectively. This represents an increase in the total population of immune deficient patients on IVIG at 15% per annum. This is probably identical to the annual increase in the immune deficient population in the United States (Figure 16).



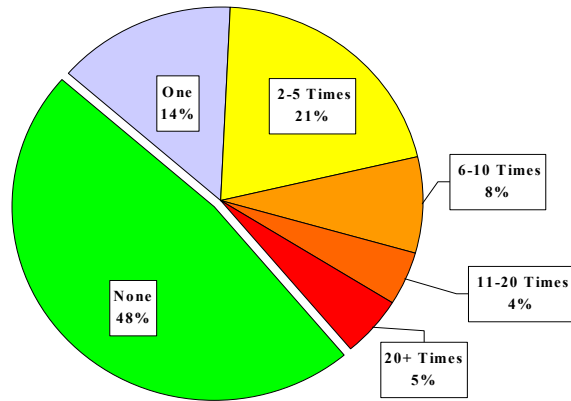
The impact of treatment, including IVIG therapy, on primary immune deficiency diseases is reflected in the prevalence of serious and chronic conditions before and after diagnosis. Arthritis (17%-20%), which is aged related, and hepatitis (2.9%-3.7%) are the only conditions that are more common after diagnosis than before. There is a small, but statistically significant decline in the rate of sinusitis (68%-65%), malabsorption (9%-8%), and sepsis (5%-4%) after diagnosis.



There is a much more dramatic decline after diagnosis in pneumonia (51%-27%), ear infections (51%-27%), bronchitis (55%-40%), and chronic diarrhea (30%-24%) (Figure 17).

Although seventy percent of patients had been hospitalized prior to diagnosis, nearly half (48%) reported no hospitalization since diagnosis. Another 14% reported only one hospitalization since diagnosis. By contrast, about one in ten patients reported 11-20 (4%) or more than 20 hospitalizations (5%) since diagnosis (Figure 18).

Figure 18  
Hospitalized since Diagnosis

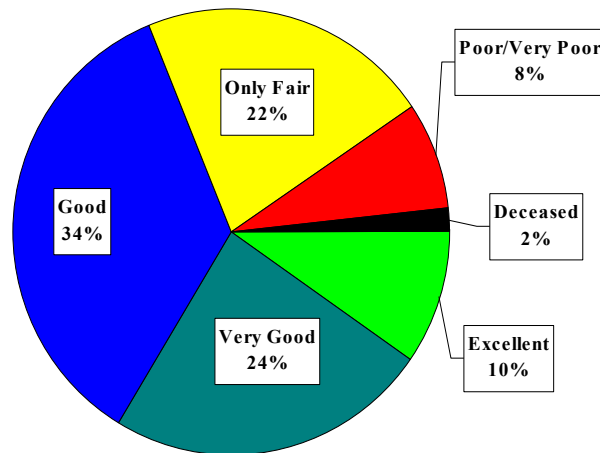


Source: IDF Patient Survey N=2,707

**Current Health**

More than two thirds of patients with primary immune deficiency diseases describe their current health status as good or better. Specifically, 10% describe their

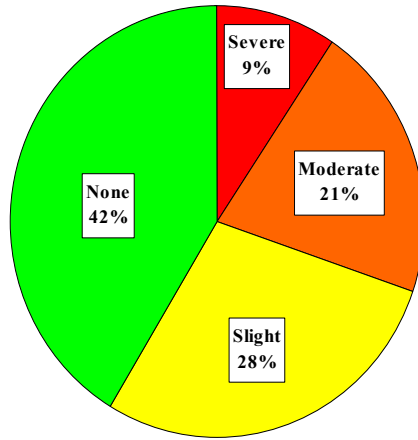
Figure 19  
Current Health Status



Source: IDF Patient Survey N=2,683

current health status as excellent, 24% as very good, and 34% as good. Twenty-two percent describe their current health as only fair. Only 8% of patients report their current health status as poor or very poor, while 2% are deceased (Figure 19).

Figure 20  
Current Physical Limitation



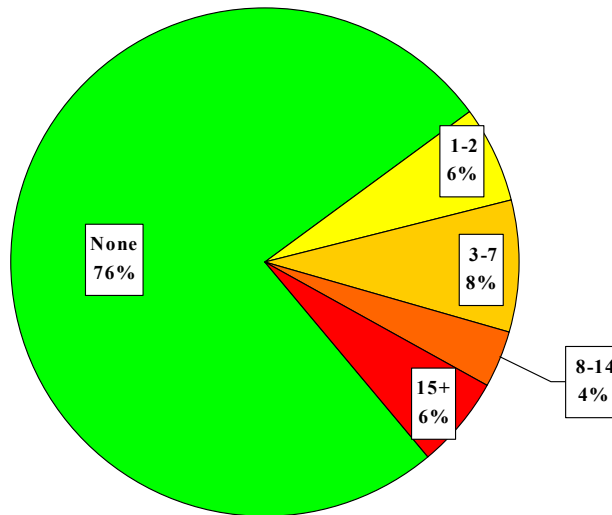
Source: IDF Patient Survey N=2,647

Most patients with primary immune deficiency diseases report only slight (28%) or no physical limitations (42%) as a result of health. A fifth (21%) report moderate limitations as a result of their health. One in ten (9%) reports severe physical limitations as a result of their health (Figure 20).

Three quarters of patients with primary immune deficiency diseases

(76%) report no hospital nights in the past year. Another 6% report one to two hospital nights in the past year. Eight percent report 3-7 hospital nights in the past year. And, 10% of patients with primary immune deficiency diseases report more than a week (8+ nights) in the hospital in the past year (Figure 21).

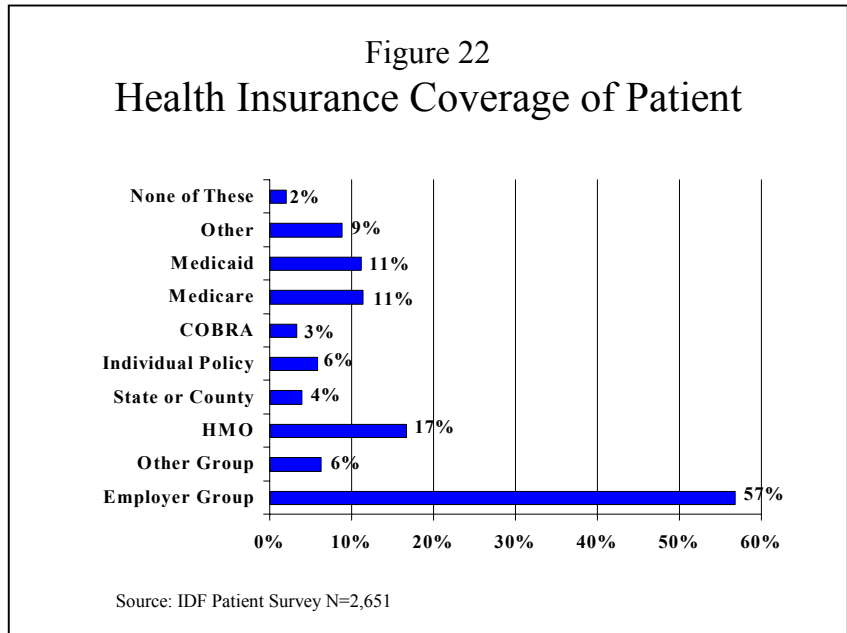
Figure 21  
Hospital Nights in Past Year



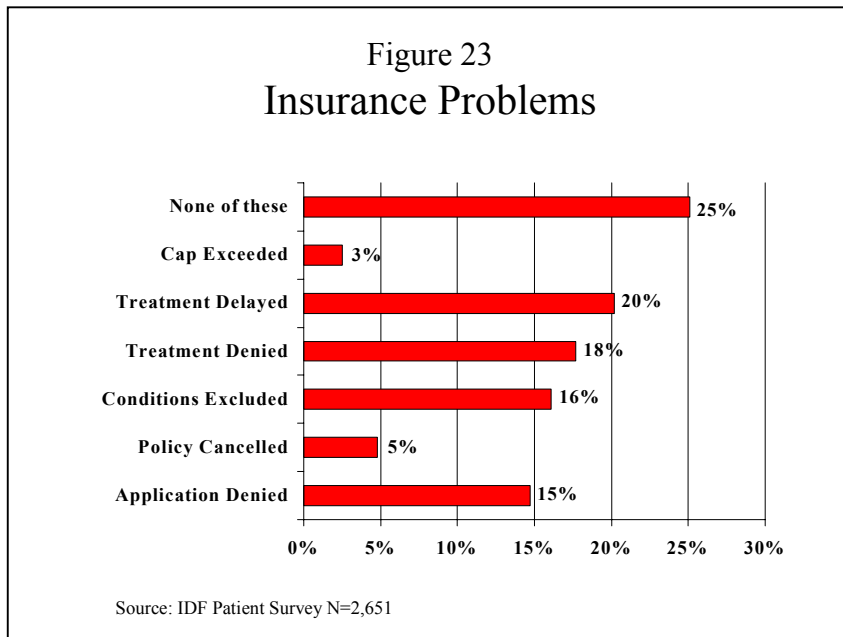
Source: IDF Patient Survey N=2,426

**Cost, Coverage and Barriers to Care**

Most persons with primary immune deficiency diseases have some form of health insurance coverage. The majority (57%) has insurance through an employer group policy. Seventeen percent belong to an HMO. And, another 6% belong to an other group policy, while 6% have an individual policy. Only 11% have Medicaid coverage, 11% have Medicare coverage, and 4% are covered by a state or county health program. Only two percent report none of these (Figure 22).

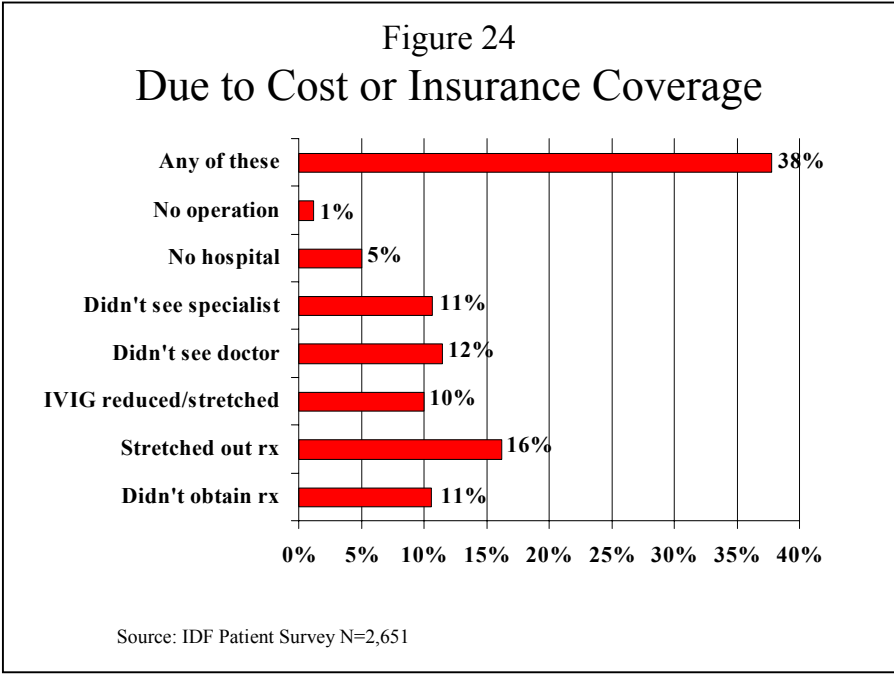


Although most patients are covered by some form of health insurance or public health program, many have experienced insurance problems. Fifteen percent have had a health insurance application denied, while 5% have had a policy cancelled. Sixteen percent have had conditions excluded from their coverage. Twenty percent have had

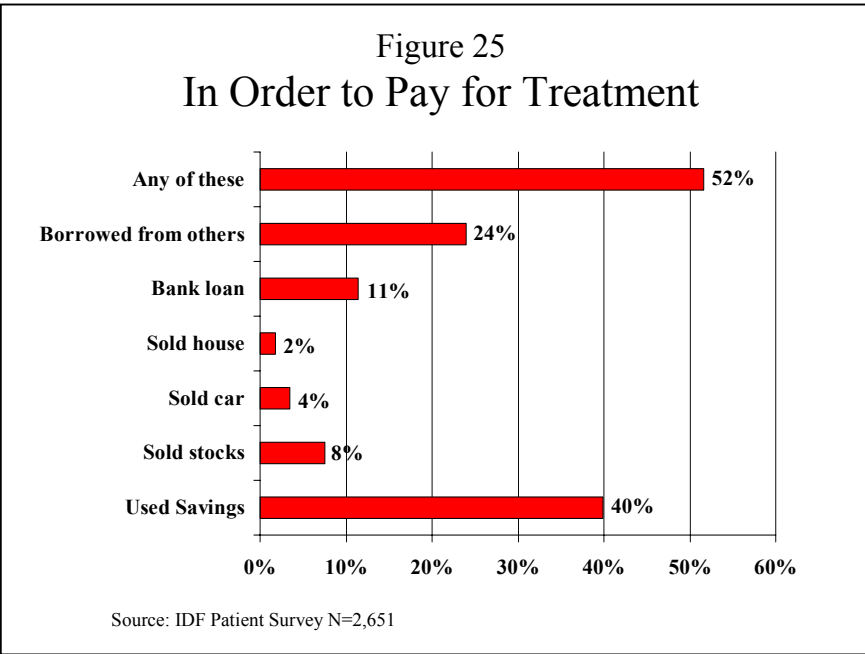


treatment delayed by their insurance carrier, while 18% have had treatment denied by their carrier. Three percent of patients with primary immune deficiency disease say that they have exceeded the lifetime cap of the insurance coverage. Only a quarter (25%) of persons with primary immune deficiency diseases have not experienced any of these health insurance problems (Figure 23).

The majority of persons with primary immune deficiency disease have experienced barriers to treatment as a result of cost or insurance coverage. Twelve percent have not seen a doctor, and 11% have not seen a specialist when they needed to because of cost or coverage. Five percent did not go to the hospital and one percent did not have an operation when needed because of cost or coverage. Even more commonly, 16% stretched out a prescription, 11% did not fill a prescription and 10% reduced the amount or stretched out the schedule for IVIG. Only 38% of persons with primary immune deficiency disease have not experienced any of these treatment problems as a result of cost or coverage (Figure 24).



In order to pay for their treatment, 40% of patients with primary immune deficiency disease have used their savings. A substantial proportion have taken out bank loans (11%) or borrowed from others (24%) to pay for treatment. Others have sold their stock (8%), sold their car (4%) or sold their house (2%) to pay for treatment. Barely half of patients with primary immune deficiency disease (52%) have never had to resort to using their savings, borrowing or selling their possessions to pay for treatment (Figure 25).





## Conclusions

Primary immune deficiency diseases are a set of comparatively rare genetic disorders. Nonetheless, the survey suggests that approximately 50,000 persons in the United States have been diagnosed with one of these diseases. Hence, primary immune deficiency diseases are more common in the United States than some better known genetic disorders, including hemophilia (less than 15,000), cystic fibrosis (30,000) and Huntington's Disease (30,000), among others.

Half of all persons with primary immune deficiency diseases are not diagnosed until they are adolescents or older. In some cases, this may represent adult or delayed onset of symptomatic disease. In other cases, however, this represents late diagnosis of the condition despite unusual, serious, or repeated infections. One problem for early diagnosis is that the vast majority of patients have no family history of immune deficiency disease.

The cost of late diagnosis is a heavy burden of disease on the patient. The majority of patients suffered two or more hospitalizations before diagnosis. The majority experienced repeated ear infections, bronchitis, and pneumonias before diagnosis, which may cause permanent limitations. In addition, some suffered serious infections and potentially life-threatening infections before diagnosis, including sepsis, meningitis and hepatitis.

Treatment significantly reduces the burden of disease among persons with primary immune deficiency diseases. The prevalence of pneumonia, bronchitis, diarrhea and repeated ear infections drops significantly after diagnosis. Nearly half of persons with primary immune deficiency diseases have had no hospitalizations since diagnosis.

Two thirds of persons with primary immune deficiency diseases describe their current health as good, very good or excellent. Most say their health causes no limitations or only slight limitations on work, play and other activities. Three quarters have had no hospitalizations in the past year.

The most common form of treatment for primary immune deficiency diseases is intravenous gammaglobulin (IVIG). Seven out of ten patients report being treated with IVIG for their condition. The proportion of PID patients being treated with IVIG has been increasing at a rate of about fifteen percent per annum in recent years.

Most patients are covered by some form of health insurance or health plan, most commonly through employer group insurance. Nonetheless, a quarter of persons with primary immune deficiency disease report experiencing insurance problems as a result of their condition. In addition, over half report using savings, selling property or borrowing to pay for treatment. As a result of cost or lack of coverage, nearly two out of five patients with primary immune deficiency disease has missed needed doctor or hospital visits, failed to fill prescriptions or reduced the amount or frequency of their treatment.

Despite a generally positive outlook after diagnosis for most patients with primary immune deficiency diseases, the survey finds that a significant portion of the patient population faces barriers to timely and effective treatment of their condition. In addition, a significant number of patients with primary immune deficiency disease are only diagnosed after multiple hospitalizations. The long-term outlook for most patients with primary immune deficiency diseases, while good, could be greatly improved by earlier diagnosis and better access to appropriate care and treatment.