1. **What is the Jeffrey Modell Foundation?**
   The Jeffrey Modell Foundation (JMF) is a 501(c)3 public charity established in 1987 by Vicki and Fred Modell in memory of their son, Jeffrey, who died at the age of 15 after struggling with a Primary Immunodeficiency (PI) disease.

   JMF is a global organization specifically dedicated to basic and clinical research, physician education, patient support, public awareness and advocacy.

   The Foundation’s overall mission is to reach early and precise diagnosis, provide meaningful treatments, and ultimately cures of the ever increasing known PI diseases.

2. **What is Primary Immunodeficiency (PI)?**
   Primary Immunodeficiency (PI) is a genetic defect in the immune system that causes increased susceptibility to infections that are often chronic, persistent, recurring, debilitating, and in some cases, fatal.

3. **What is the prevalence of PI?**
   - Experts estimate that **PI affects at least 10 million** people worldwide and more than **1 million** Americans.¹
   - **PI is more prevalent than childhood leukemia and lymphoma combined and four times the incidence of cystic fibrosis.**²
   - The National Institutes of Health (NIH) estimate 1:500 Americans have a PI and another 1:500 Americans have an underlying PI and don’t know they have it.³, ⁴
   - Recently, the National Institute of Allergy and Infectious Disease (NIAID) stated in a grant announcement: “While individual Primary Immunodeficiency diseases are rare, as a group they may affect 1-2% of the population.”¹ This translates to **3 million to 6 million Americans, a prevalence far greater than most health agencies have estimated in the past.**

4. **What do we know about PI?**
   - Primary Immunodeficiency diseases have long been neglected as medical conditions, but are now recognized as a worldwide health problem. The rapid progress of research in this field has widened the gap between cutting-edge
medical care and the lack of appropriate diagnosis and treatment of these conditions.⁵

- PI is not rare. It is just not very well known.⁴
- There are more than 200 PI diseases ranging in severity from Chronic Sinusitis to Severe Combined Immune Deficiency (SCID), commonly known as “Bubble Boy Disease.”¹,⁶
- PI can appear at any age, sometimes showing up in the 3rd or 4th decade of life. This disorder has no racial or ethnic boundaries.⁷
- 15 of the 200 diseases account for more than 90% of diagnosed cases. Approximately 80% of affected persons are under the age of 20.⁶,⁷
- The National Cancer Institute reports that individuals with PI have a 200-fold greater risk of developing cancer.⁸
- When PI is left undiagnosed, under-diagnosed or misdiagnosed, the immune system remains compromised leading to a lifetime of chronic illness, permanent organ damage or even death.

5. **How is PI expressed?**

   PI is often expressed by a lifetime of **chronic, persistent and recurring infections** including: ear infections, sinus infections, bronchitis, pneumonia, skin abscesses, and thrush.

   Related conditions may include: autoimmune disease, anemia, allergies, skin rashes, and chronic inflammatory diseases.

6. **Is PI a public health issue?**

   - A fact-finding Consensus Conference sponsored by the U.S. Centers for Disease Control and Prevention (CDC) concluded that Primary Immunodeficiency is a serious public health threat.⁹
   - Individuals with undiagnosed PI are reservoirs of severe infections – bacterial, viral, and fungal.⁹
   - Undiagnosed and unprotected, affected children and young adults become a “delivery system” of infection to the general public – a threat to schools, daycare centers, the workplace and even hospitals.⁹
   - Delayed diagnosis and insufficient treatment leads to increased morbidity, mortality, and inflated medical costs.⁹
7. **What is the public’s awareness of PI?**

   A national survey was conducted by Opinion Research Corporation (ORC) asking 1,064 American adults questions about PI.
   - One in three American adults (36%) state that they have heard of Primary Immunodeficiency.
   - Although many respondents claimed to be aware of PI, not one respondent could correctly name any of the diseases (not even “Bubble Boy” Disease).
   - Yet, three in ten adults (31%) know someone, child or adult, who suffers from repeated ear infections, sinusitis, pneumonia, or similar recurring infections that are listed on JMF’s 10 Warning Signs of PI, **without a clear diagnosis**.

8. **What is the physician’s awareness of PI?**

   A national survey was conducted by Opinion Research Corporation (ORC) asking 253 pediatricians and 249 family practice physicians questions about PI.
   - Virtually every physician (96%) responded that they have at least one patient with two or more of the 10 Warning Signs of PI, but without a clear diagnosis.
   - Physicians with patients having two or more of the 10 Warning Signs refer only 2% of them to an immunologist, and they suspect an underlying PI disease in only 1% of these patients.
   - Asked to rate the prevalence of PI, 85% of physicians consider PI as rare or extremely rare (1:5,000-10,000). The National Institutes of Health (NIH) cites prevalence of at least 1:500, a 10- to 20-fold disparity in perceived prevalence.³

9. **Is there really an issue of PI diseases being undiagnosed and unrecognized?**

   - **70% to 90% of all PI patients in the United States are undiagnosed.**¹⁰
     
     Delayed diagnosis and insufficient treatment leads to increased morbidity, mortality, and inflated medical costs – not to mention a miserable life of chronic illness and suffering.

10. **How do we reach early diagnosis?**

    - The diagnosis of PI can be relatively inexpensive.
    - A simple and inexpensive CBC can detect over 95% of the PI diseases.
    - In many instances, the earlier investigations are enough to confirm or rule out PI, while ambiguous cases may be referred to a clinical facility for more specialized laboratory evaluation.
11. **How does JMF measure clinical outcomes, quality of life, and economic impact data before and after diagnosis for patients with PI disease?**

Data was compiled from reports provided by 85 Centers from the Jeffrey Modell Centers Network (JMCN) of Diagnostic, Research, and Referral Centers. 9 of the top 10 and 24 of the top 30 pediatric hospitals in the United States are Jeffrey Modell Diagnostic, Research, and Referral Centers.\(^{11}\)

In order to measure clinical outcomes, quality of life, and economic impact data before and after diagnosis for patients with PI Disease, each of the Centers was asked to examine patient records one year before diagnosis and subsequent to diagnosis and treatment.

The results were published in the scientific peer-reviewed journal *Immunologic Research*, published by Humana Press, an imprint of Springer Publishers, NYC. The results showed a dramatic decrease in the number of acute and severe infections, the number of physician, hospital and ER visits, the number of incidents of pneumonia, the number of days with chronic infections, the number of days on antibiotics, the number of days in the hospital, and the number of school/work days missed, when comparing patients with PI the year before and the year after diagnosis.

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

- Each undiagnosed patient with an underlying PI disease costs the healthcare system an average of $102,552 annually.

- Each diagnosed patient with a recognized PI defect costs the healthcare system an average of $22,610 annually.

- The economic impact to the healthcare system of diagnosing a patient with an underlying PI defect in contrast to not diagnosing a patient represents average savings of $79,942 per patient annually.

- The US National Institutes of Health (NIH) estimates that at least 500,000 cases of PI remain undiagnosed in the United States.

- The economic impact of undiagnosed PI patients to the healthcare system in the United States totals over $40 billion annually.\(^{12}\)
About SPIRIT
(Software for Primary Immunodeficiency Recognition, Intervention and Tracking)

12. What is the reason for SPIRIT?
   ▪ Disease Prevention
   ▪ Electronic Recognition & Tracking
   ▪ Reduction of Healthcare Costs
   ▪ Improved Quality of Life for Patients

13. What does SPIRIT do?
   ▪ The SPIRIT Analyzer is a new software screening tool for use by healthcare organizations across the country to assist in the identification of undiagnosed patients with PI.

14. How does SPIRIT work?
   ▪ The 10 Warning Signs of PI were developed by the Jeffrey Modell Foundation in 1993 and have been used in more than 35 countries around the world as a primary screening tool for PI. The SPIRIT Analyzer is an expanded screening tool that matches more than 350 weighted ICD-9 Codes to the 10 Warning Signs and calculates risk points to establish low, medium, and high-risk categories. Patients that score in the medium and high-risk categories are flagged as potentially in need of further testing for PI.
   ▪ Healthcare organizations are able to alert the physicians of those patients with recurring infections and encourage appropriate assessment, thereby saving enormous healthcare costs.
   ▪ The SPIRIT Analyzer is designed to be a screening tool, not a diagnostic tool.

15. What data will SPIRIT generate?
   HIPAA-compliant, de-identified reports will describe the patient population via the following metrics related to PI:
   ▪ Population Overview (Gender and Age)
   ▪ Distribution by PI Warning Sign
   ▪ Distribution by Risk Category and by Number of Warning Signs
   ▪ Antibiotic Utilization
• Average Health Care Costs by:
  □ All patients screened by the SPIRIT Analyzer and by Risk Category and Number of Warning Signs
  □ Total Costs broken out as Medical Costs and Pharmacy Costs
• Provider Measure: Patients in each Risk Category (High, Medium, and Low)
• Patient Measure: Risk Category and Number of Warning Signs

16. What is the value proposition for a healthcare organization to use this tool?
The SPIRIT Analyzer will help healthcare organizations improve patient outcomes and reduce costs through early diagnosis and treatment of PI diseases:
  ▪ Average cost savings after diagnosis is approximately $80,000 annually per patient. Using the National Institutes of Health (NIH) estimates that at least 500,000 cases of PI remain undiagnosed, this represents a savings of over $40 billion annually to the U.S. healthcare system.¹²

17. If our organization is currently not pursuing identification of rare diseases, why should this tool be of interest?
  ▪ PI is not rare; it is just not very well known. A rare disease is one that affects fewer than 200,000 Americans at any given time.¹³ Recently, the National Institute of Allergy and Infectious Disease (NIAID) stated in a grant announcement: "While individual Primary Immunodeficiency diseases are rare, as a group they may affect 1-2% of the population."¹ This translates to between 3 million and 6 million Americans.
  ▪ PI is more common than childhood leukemia and lymphoma combined, and 4 times more prevalent than cystic fibrosis.²
  ▪ When PI is left undiagnosed, under-diagnosed, or misdiagnosed, the immune system remains compromised; leading to a life of chronic illness, permanent damage, or even death.

18. What do we do with these patients once we identify them from the output of the tool?
  ▪ Patients that score in the medium and high-risk categories are flagged as potentially in need of further testing for PI.
  ▪ Healthcare organizations are able to alert the physicians of these patients and encourage appropriate assessment. Template letters to send to physicians, along
with the 10 Warning Signs Poster and the 4 Stages of Testing for Primary Immunodeficiency Poster are provided in the tool.

- Additional follow up is a matter between the healthcare organization and the physician, as well as the patient and the physician.
- Some patients, even after definitive diagnosis, require no specific intervention or treatment, with the exception of periodic monitoring. Others require prophylactic antibiotics. More serious conditions may require more aggressive interventions.

19. **Is it appropriate for a healthcare organization to get into the business of making or even suggesting a diagnosis? How will physicians perceive this?**

- **The SPIRIT Analyzer is designed as a screening tool, not a diagnostic tool.**
  
  As such, healthcare organizations are not involved in diagnosing the patient using the SPIRIT Analyzer. SPIRIT is provided as a screening tool to alert physicians of those patients who are at high risk or medium risk of a PI disease, based on historical claims in the last 12 months, and encourage appropriate assessment.

- The information contained is provided as a public service and SPIRIT is not intended to dispense medical advice or make a diagnosis. Only direct examination by a physician should be used to determine the presence of a disease.

- Even the most vigilant physician may misdiagnose the presence of an underlying PI disorder.

- In the experience of the JMF over the past 26 years, physicians and clinicians welcome information that match up the 10 Warning Signs and the ICD-9 codes.

20. **Are the tool’s criteria evidence-based? Can we see the background evidence that was used?**

   The JMF Medical Advisory Board of Experts created the 10 Warning Signs in 1993. It has been disseminated and translated in more than 35 countries. The Medical Advisory has identified more than 350 ICD-9 codes as being related to a potential underlying PI disease. The Medical Advisory also assigned the weights and the inclusion and exclusion criteria.
21. What proportion of the patients identified through the SPIRIT Analyzer will be undiagnosed PI patients? Will our organization be using case management resources to outreach to a good number of patients who do not have PID? The NIH believes that 1:500 Americans have an underlying PI disease and don’t know they have it.\(^3\)

The SPIRIT Analyzer was designed to screen patients utilizing minimal staff resources. The tool was developed in an easy to use format and includes template letters and straightforward reporting to further simplify the process. **No additional personnel or resources are required to make use of the SPIRIT Analyzer!**

22. Will there be politically sensitive issues raised with finding undiagnosed patients with PI?

The SPIRIT project has received the support and encouragement of the United States Congress, the National Institutes of Health (NIH), the United States Centers for Disease Control and Prevention (CDC), and the physician community of expert immunologists.

It is anticipated that the SPIRIT Analyzer will have application for several other diseases that are under-diagnosed.

23. Is PI a real priority for healthcare organizations and is it the right disease to target for this type of activity?

- PI is a priority according to the U.S. government. The Centers for Disease Control and Prevention (CDC) in a Consensus Conference concluded that PI is a public health threat.\(^9\)
- The current administration in Washington D.C. is implementing healthcare reform focusing on:
  - Disease Prevention
  - Electronic Tracking & Recognition
  - Reduction of Healthcare Costs
  - Improved Quality of Life for Patients

**This is exactly the mission of SPIRIT!**
24. **Why would our organization focus on this disease vs. other diseases?**
   The first reason is economic! The data, which has been peer-reviewed and published in a scientific journal, indicates that the economic impact to the healthcare system of diagnosing a patient with an underlying PI defect in contrast to not diagnosing a patient represents average savings of $79,942 per patient annually.\textsuperscript{12} Clearly the cost savings, in addition to improved quality of life, disease prevention and related issues all contribute to make PI disease the appropriate candidate for the SPIRIT Analyzer.

25. **Will utilizing this Analyzer lead to requiring its application for many other diseases?**
   This will depend on the specificity and efficiency of the SPIRIT Analyzer being brought to private payers, government agencies, physician groups, and healthcare organizations. There is no reason to believe that third party payers would be reluctant to save more than $79,000 per patient per year.

26. **Is a pharmaceutical company behind this with the goal to “sell more IVIG”?**
   No! The JMF is a 501(c)3 public charity funded by thousands of individuals, many industries, and a number of federal agencies. The SPIRIT Analyzer program is owned exclusively by JMF, JMF holds all of the rights to its usage, and there are no commercial activities related to the SPIRIT Analyzer. JMF offers the Analyzer as a public service to the community.

27. **How accurate is the output of the tool?**
   The SPIRIT Analyzer has been successfully pilot tested by multiple sites whose data output is consistent with NIH and CDC estimates of incidence and prevalence. It has been successfully tested for specificity and sensitivity.
For additional information, please contact us:

Jeffrey Modell Foundation
780 Third Avenue
New York, NY 10017
212.819.0200
spirit@jmfworld.org
www.info4pi.org

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