SPRING 2023 | NUMBER 95

IDF ADVOCATE

THE NEWSLETTER OF THE IMMUNE DEFICIENCY FOUNDATION

Immune Deficiency Foundation

GRIFOLS

PRESIDENT'S LETTER

A letter to the PI community from IDF President & CEO, Jorey Berry

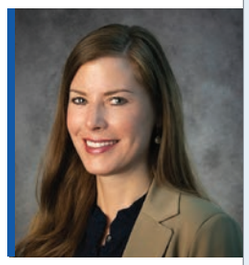
Throughout my career, I have learned that we often need to stop and take the time to reflect, to slow down, and truly look at what we're trying to achieve to see things from another perspective. This has been crucial for our team in understanding how to better serve our community. In our reflection, we've found that we can do more by looking at what has the largest impact and hearing from you, the people we're trying to serve.

When I had the privilege of being named IDF's President & CEO, I knew the role came with tremendous responsibility. More than 40 years of tradition, hard work, and success went into making the Immune Deficiency Foundation the leading national nonprofit for people with primary immunodeficiency (PI). There was–and still is–so much dedication from our community, volunteers, donors, and staff who allow us to truly make a difference in the lives of those with PI.

Our team is always ready to offer knowledge, skills, and resources to help you navigate the journey with PI, no matter where you are in that journey when you find us. Whether you're newly diagnosed or have been with us since the beginning, we are continuously improving our resources and support systems to offer you more in 2023 and beyond.

Looking to the months ahead, we are excited to have opportunities to meet with you, whether it's in person on April 27 at IDF Advocacy Day in Washington D.C. or at one of our IDF Walk for PI locations taking place across the country, or virtually at events like our 2023 Primary Immunodeficiency Conference, June 22-23.

While we aren't always able to be together, you can still stay connected to us. As part of the IDF podcast, the new "Bold Conversations" series hosted by Dr. Nicole Rochester, will tackle hard-hitting topics like the seeds of medical mistrust, and the lack of diversity in clinical trials. Another new podcast series, "Undiagnosed," provides a voice for people to share their journey to a PI diagnosis. We're also extending our reach by partnering with organizations, like the Jeffrey Modell Foundation, bringing together the two leading PI organizations in the U.S. for the first time ever to unite the PI community through social media challenges.



We're grateful to all those who are participating in our community, whether it's just by reading this newsletter or taking a more active role volunteering, donating, or attending events. Everything that we do here is to help ease your journey through life with PI.

Stay well,

Jorey Berry
IDF President & CEO

YOUR QUESTIONS, OUR ANSWERS

Someone told me IDF has a podcast that features stories from people with PI. How can I listen to it?

The IDF Podcast now has three distinct areas of focus: "IDF Podcast," which covers general information about PI and healthcare, "Bold Conversations," where Dr. Nicole Rochester, IDF's Medical Advisor for Health Equity, will tackle hard-hitting topics in health equity, and "Undiagnosed," where we tell true stories of the journey to diagnosis. The IDF podcast is available anywhere you typically listen to podcasts: Apple Podcasts, Spotify, Google Podcasts, Amazon Music, Stitcher, Pandora, and SoundCloud.

IDF PODCAST

I was hoping the 2023 conference was going to be in person. When will we all be together again?

While the 2023 Primary Immunodeficiency Conference will be virtual, June 22-23, we are excited to announce that in 2024, we will be together in person in Chicago! In the meantime, many IDF events have already returned to in-person meetings. You can find in-person events in your area by visiting our calendar of events.

2023 CONFERENCE

My doctor doesn't seem to understand PI. Where can I find someone near me who can help treat my PI?

The IDF Clinician Finder is an online tool that offers access to the names and addresses of providers with experience treating individuals with PI. The searchable provider database includes those not only in the field of immunology but also in other medical fields like family medicine, pediatrics, internal medicine, and more. To use the Clinician Finder, visitors create an account with IDF or log on to an existing account and go to the Clinician Finder page, where you can search for a specialist by distance from a specific location or within a state. Users can also search and filter by a clinician's name, specialty, and patient type (pediatric or adult).

IDF CLINICIAN FINDER

I want to encourage my friends and family to donate plasma. Are there any resources available for me?

Plasma Hero is an IDF initiative designed to guide individuals through the journey of plasma donation, encourage others to donate, and support those who rely on plasma-based products. Recently, Plasma Hero released a toolkit with resources to help individuals and organizations raise awareness for plasma donation. This toolkit includes printable versions of a flyer, a rack card, and stickers, and images to share on social media.

PLASMA HERO TOOLKIT

Is IDF doing anything for the month of April to promote PI?

Yes! April is Primary Immunodeficiency Awareness Month, and World PI Week is April 22-29, 2023. Throughout the month, we'll be sharing information about raising awareness for PI, as well as how to make a difference in the lives of those living with PI. Make sure you're following us on social media to learn more, and know that you can raise PI awareness throughout the year!

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Navigating young adulthood with PI

Even for the most conscientious adults, the responsibility of managing a chronic condition like primary immunodeficiency (PI) can be hard to shoulder. For teens and young adults, who are just beginning to find their way in the world, it can be completely overwhelming.

Casey Warford, who has chronic granulomatous disease (CGD), knows that newfound independence and a desire to be like everyone else can be a dangerous mix. As a college freshman, Warford was busy with classes and new friends, so he stopped taking his interferon gamma-1b medication. The summer after freshman year, he developed headaches but didn't tell his healthcare providers.

By the middle of his sophomore year, Warford's headaches were worse than ever. He eventually fell into a coma; doctors discovered a fungal infection in his brain. It took four surgeries to rid his brain of the fungus and repair the resulting hole in his skull.

Warford now uses the story to hammer home how important sticking with treatment and paying attention to symptoms is when he mentors young adults with PI.

"I tell them that when they get to college, they've got to have a health plan because they're not going to have a mother or father or nurse telling them to take their medication," Warford said.

Having a plan and being prepared are the central messages of IDF's newly revised *Guide for Young Adults* (formerly the *IDF Transition Guide: From Pediatric to Adult Care*), which eases teens and young adults with PI through the process of taking on adult responsibilities associated with their condition. The guide covers topics including taking charge of healthcare, understanding insurance, and considerations for work and higher education. It also contains checklists for gradually building skills like communicating with healthcare providers, keeping a personal health record, and evaluating and preparing for college.

Read Warford's full story online:
https://idf.primaryimmune.org/warford

IDF Guide for Young Adults

Download or request a hard copy of this guide for teens and young adults navigating the transition to adulthood.

REGISTER NOW!

The Escape Weekend

July 21-23, 2023
Grapevine, TX

The Escape Weekend is an opportunity for teens (13-17) and young adults (18-25) to connect in person with others their age living with PI.

A VIRTUAL EVENT | JUNE 22 & 23

PI CONFERENCE

Navigating the primary immunodeficiency journey

Join us as we bring together the PI community for two days of connection, learning, and networking. The 2023 PI Conference, June 22–23, 2023, will be held virtually, with a theme of "Navigating the Primary Immunodeficiency Journey." Sessions fall within one of three tracks:

- **Skimming the Surface:** This information is for those who are recently diagnosed and want to learn about broad topics that affect the PI community.
- **Deep Dive:** This information is geared toward those who are interested in more in-depth medical or scientific topics.
- **Rare of the Rare:** These sessions are targeted to the rarest of rare diagnoses and focus on topics outside of antibody deficiency.

The conference will feature world-class immunologists and life management experts providing sessions on topics related to PI like gene therapy and genetic testing, vaccines and PI, health insurance, navigating school systems and workplaces, and more. There will also be opportunities for connecting with peers and exhibitors, special events, and more. Register today!

REGISTRATION

The 2023 PI Conference is proudly supported by:

Takeda, CSL Behring, Grifols, Horizon Therapeutics, Octapharma, Pharming, Kedrion Biopharma, X4 Pharmaceuticals, Accredo, Enzyvant, and Ethical Factor RX.

JOIN US AT IDF WALK FOR PI

Make sure you register to join us at one of nine IDF Walk for PI events in 2023! Your support ensures that IDF can continue to provide educational resources and programs at no cost to individuals and families, fund critical patient-focused research, lead grassroots advocacy and fight to improve access to diagnosis and treatment, and bring together the entire PI community to remind you that you are not alone.

BOSTON: Saturday, September 09, 2023, at Franklin Park Zoo

CHARLOTTE: Saturday, July 29, 2023, at Discovery Place Science

COAST-TO-COAST: Saturday, December 02, 2023, Virtual

DALLAS: Saturday, October 21, 2023, at Dallas Zoo

MILWAUKEE: Saturday, August 05, 2023, at Milwaukee Zoo

PHILADELPHIA: Saturday, July 15, 2023, at Philadelphia Zoo

SAN FRANCISCO: Saturday, August 19, 2023, at San Francisco Zoo

ST. LOUIS: Saturday, September 23, 2023, at Saint Louis Science Center

TAMPA: Saturday, October 7, 2023, at ZooTampa at Lowry Park

www.walkforpi.org

2023

IDF WALK FOR PRIMARY IMMUNODEFICIENCY
An initiative of the Immune Deficiency Foundation

IDF Walk for PI is presented by

Takeda

Improving PI diagnosis with machine learning

In recent years, machine learning has jumped from science fiction into everyday life—voice assistants, translation apps, and fraud detection software all use machine learning technology. In healthcare, machine learning has been used to detect potential tumors on radiology images and transcribe clinical notes into electronic health records. Diagnosing conditions like primary immunodeficiency (PI) earlier and more accurately is next on the horizon.

Machine learning is a kind of artificial intelligence. The term covers a group of methods that allows software to develop its own algorithms and 'learn' how to perform specific tasks without being explicitly programmed to do so. Think of how a toddler learns what the word 'dog' means. The child may use all kinds of clues to develop and refine their understanding of 'dog,' including the context in which adults say 'dog' and the reaction of others when the child uses the word. In essence, machine learning methods combine these decision-making and analysis abilities of the human brain with the large processing power and fast recall of computers.

Immunologists agree that PI is underdiagnosed; IDF's own surveys show that patients often wait a decade or more for a diagnosis after they start exhibiting symptoms. In some ways, diagnosing PI is a perfect use case for machine learning—there are clearly patterns in symptoms, laboratory tests, and patient history that are regularly missed.

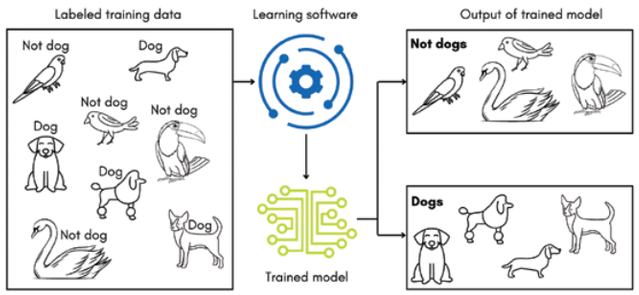
The quest to diagnose PI by harnessing computer power began almost two decades ago with the Study Targeting Recognition of Immune Deficiency and Evaluation (STRIDE) project. STRIDE researchers, led by Dr. Charlotte Cunningham-Rundles, developed a scoring system for patient hospital records based on ICD-9 diagnostic codes. ICD codes, now in their tenth edition, are standardized and used by all healthcare providers in the U.S. for insurance and billing purposes.

Using a set of predefined rules and a predetermined score threshold, the researchers programmed software to score thousands of records. Fifty-nine patients that met the threshold were then tested for PI and 17 (29%) were ultimately diagnosed. The original software did not use machine learning, as the scoring system and the score threshold were set by the researchers. But, STRIDE proved that indicators of PI were indeed hiding in patient records waiting to be found.

In more recent efforts, researchers at Texas Children's Hospital led by Dr. Nicholas Rider developed PI Prob. It also leverages ICD codes from electronic health records but uses machine learning to distinguish between records belonging to children with PI and records belonging to children without PI.

To build PI Prob, researchers first determined which ICD codes were more frequent in records for more than 1,500 children with confirmed PI diagnoses than in records for a control group of children without PI. These codes were further refined using expert knowledge in immunology. In contrast to the STRIDE project though, the codes were not given predetermined scores by the researchers. Instead, they were used for supervised machine learning.

A subset of machine learning technologies, supervised machine learning uses training datasets where every record has a known classification. The software must 'learn' how to correctly classify each record within the training set by adjusting the weight given to different features in the data. In the analogy of learning the word 'dog,' this is similar to an adult presenting the child with pictures of dogs mixed in with other animals. The child might learn that four legs, a tail, and overall size are features in the photos that help them correctly identify dogs.



Supervised machine learning uses training data where each record is labeled, allowing the learning software to develop and refine a model for correctly labeling each record in the training set. Once the model is trained, it can be used on real data.

For PI Prob, the training set was drawn from the previously described set of records, and the data features were the refined ICD codes. The software then experimented with how to weigh the codes to develop the best model for classifying the training records correctly. After training, the researchers then tested how well PI Prob could distinguish records it had not seen before.

Overall, it was 89% accurate in distinguishing records for children with PI from records for children without PI.

A related study from researchers at the University of Chicago, funded by Takeda, attempted to develop a model that works for both children and adults and expanded on the type of data features the software could consider in order to 'learn.' In addition to ICD codes, their software counts how many orders for laboratory tests, radiological tests, and prescriptions for medication meant to manage PI symptoms are in each record. The researchers showed that adding these clinical features improves the accuracy of their algorithm by 7% versus using ICD codes alone.

However, the accuracies of both PI Prob and the University of Chicago tool were tested only on known datasets—that is, records for individuals who were already known to either have a PI or not. The true test is to deploy such a tool proactively and determine if the individuals it flags are ultimately diagnosed with PI, as in the original STRIDE study.

In a paper published in October 2022, researchers, again led by Rider, got one step closer to truly testing machine learning for diagnosing PI. They developed a two-step pipeline using the Jeffrey Model Foundation's Software for Primary Immunodeficiency Recognition, Intervention, and Tracking (SPIRIT) Analyzer and a machine learning tool that triages high-risk children for immunology referrals based on the percentage of their medical visits that concern PI symptoms. The initial machine learning was done using a training set of records from children with PI diagnoses and from children with secondary or no immunodeficiency diagnoses.

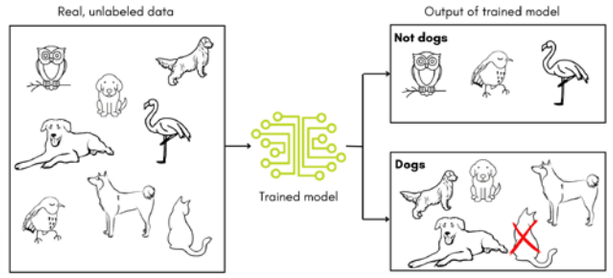
However, the group then deployed the pipeline within the Texas Children's Health Plan, which is a Medicaid program. Thirty-seven total children were proactively flagged for immunology referrals. Unfortunately, some of the individuals were lost to follow up and the authors did not know the referral outcomes for the rest at the time of publication.

X4 Pharmaceuticals, a company that focuses on chronic neutropenia, has taken a different tact. To align with their focus, they are using machine learning to identify individuals with one specific PI, warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome, rather than PIs in general.

To train their machine learning software, X4 used a decades-worth of medical records for 32 individuals with genetically confirmed diagnoses. By asking the software to construct a 'typical' medical record for WHIM syndrome and then looking for similar patient records within an insurance claims database, X4 estimates that there are between 1,800-3,700 individuals with WHIM syndrome in the U.S. Even the low estimate is substantially more than current prevalence numbers, which place the number at less than 1,000 individuals with WHIM syndrome living in the U.S. The company has not released information on whether they intend to use the software to identify specific individuals at high risk for a WHIM diagnosis.

Despite these successes, there are challenges ahead in using machine learning software to find individuals with PI. The U.S. healthcare system is fractured over many providers and insurers who all use their own data systems. Designing one tool that can operate across those systems, and convincing providers and insurers to implement it, will be difficult.

In addition, since the tools developed to date rely on training datasets, they may have to be trained and retrained depending on where they are deployed to account for differences in patient populations. After all, if a toddler is given a training set of pictures of dogs mixed in with pictures of birds, their definition of the word 'dog' might not hold up when pictures of cats are introduced. In other words, supervised machine learning tools are very sensitive to any biases in their training datasets and must be validated in new contexts.



If the training data used to develop a machine learning model doesn't closely match the real data that the model will be used to analyze, the model can make mistakes. In this example, the model was trained with data that only included dogs and birds, and therefore, mistakenly labeled a cat as "dog" because its model could not distinguish it from a dog.

The studies detailed above are a promising start to using machine learning in the diagnosis of PI. With luck and ingenuity, these tools will come into common clinical use, saving those with undiagnosed PI years of uncertainty.

Healing the trauma of a lifechanging PI diagnosis

Most people associate trauma with distressing events such as a natural disaster, the sudden loss of a loved one, or an instance of violence, but trauma can also result from chronic illness, including primary immunodeficiency (PI)—and that trauma has an impact on mental health.

"Typically, trauma is something that is happening outside of us, something that once the event is over, we can escape it, we can move forward, we can avoid it. Medical trauma is something that is happening within the body, that is not escapable," said Dr. Sacha McBain, a clinical psychologist who is an assistant professor at the University of Arkansas for Medical Sciences (UAMS) and associate director of the UAMS Psychiatric Institute's Center for Trauma Prevention, Recovery, and Innovation.

"Because the potential trauma cues and the threat to self are already contained within us, it can create this cycle of eliciting those reactions over and over again and maintain a level of distress."

Chronic illness can create an adversarial relationship between the mind and the body. A person with a chronic illness like PI may be motivated to do certain activities but is hampered by fatigue and infection.

"Sometimes the perceived failure of the body or the betrayal of the body can leave people feeling trapped, helpless, and losing control of themselves. Layered on that is how we live in a social and built world that does not accommodate people with chronic illness or disability," said McBain.

With the average time to diagnosis for PI being 9 to 15 years, some live with symptoms for decades before learning why they have constant respiratory, sinus, or gastrointestinal infections. Meanwhile, illness can interfere with important life goals such as performing well in school or advancing in a career.

"Many people experience internalized ableism, for example, 'I'm hearing so many messages that I should be doing more. Why aren't I doing more?' You can start to believe these negative messages about yourself. As a result, people can experience a very conflictual relationship between their mind and body that can lead to depression and anxiety," said McBain.

Feelings of invalidation, disempowerment, fear, and lack of control that can arise from a PI diagnosis create a stressful experience that can be overwhelming, said McBain.

"It's very easy for life to become illness and for the spotlight to get really starkly focused on this one aspect of life and its multiple impacts," said McBain.

Seek professional help

McBain encourages anyone living with PI to reach out to a mental health provider so they can receive an unbiased perspective on challenges they might face. She recommends finding a provider who has expertise in helping people adjust to chronic illness.

"You need your social support network and your caregivers, but your family members are also a part of your disease experience. They're going to come with their own feelings and experiences of your illness and their own reactions to it. For some, this can lead to fear of being a burden and result in not talking about emotions at all. Therapy can offer a space that is just yours to explore your thoughts and feelings around a life-changing diagnosis," said McBain.

If classic signs of depression like low mood, fatigue, and changes in sleep patterns present themselves and significantly diminish the quality of life, then it's imperative to find help. Some primary care offices have mental health professionals co-located within the clinic to offer support and your doctor can also help provide referrals.

"I think sometimes there can be this assumption of, 'Well, this is just going to be what it is, and I'm just going to feel depressed, that's just it,' but that doesn't have to be the case. Life will be different after a diagnosis, and there are strategies to help improve your quality of life when you're ready," said McBain.

"If people are struggling with making sense of a new diagnosis, are finding it difficult to manage their health, or are navigating losses associated with PI, they can reach out to a mental health professional and work together to process the grief associated with chronic illness and develop an approach to promote emotional wellbeing."

Rely on your social network

If a person with PI doesn't want to see a mental health professional but does want to take steps to ensure that they maintain a balance in life, they can make use of existing social networks.

"Positive social support is the number one protective factor against mental health concerns, and that's why leveraging the support you have within your existing network is important. If that's not available to you currently, it might mean reaching out for peer support and developing new social networks," said McBain.

The Immune Deficiency Foundation offers several resources for support, including Get Connected Groups, Peer Mentors, Virtual Caretaker Support Group, and IDF Friends.

Encourage loved ones to listen

Family and friends can support a person with PI by being available to talk, but also by being active listeners and refraining from offering comments that diminish the person's feelings. Comments such as, "At least it's not as bad as other illnesses," or "You just need to get over it" only serve to constrain opportunities for emotional disclosure.

"How we combat that is to make space in our relationships to just listen. What tends to happen with people, and for caregivers too, is that there is this pressure to fix it. And you are not going to fix it, and when you try it often leads people to feel more unheard and invalidated," said McBain.

"We're all seeking connection. So, when people are coming to us with their concerns or to process feelings related to their illness, first—believe them."

If people do need help with problem-solving, ask them whether they want you simply to listen or if they want feedback too.

"Then respect the answer and do the thing that they prefer. We tend to jump to problem-solving and appeasing our own anxiety after hearing someone tell us something that is uncomfortable or distressing. We just want to say, 'Well, have you tried this? Why don't you do this?' While it might help us feel we've done something as a listener, it actually suppresses disclosure and genuine connection," said McBain.

While caregivers, friends, and family should strive to adapt to the emotional needs of a person with PI, the person with PI must also have realistic expectations of their relationships.

"We all have the hope that the people in our lives will just read our minds, pre-empt every need that we have. We tell ourselves that this is what a relationship should be like. Unfortunately, that's a story we've been told about how relationships work. We have to be willing to acknowledge that although we may wish we didn't have to express our needs, in order to help people help you, you also need to be actively expressing how people can support you," said McBain.

IDF: THE EARLY YEARS

Dr. Michael Blaese

As a leading researcher and physician in immunology at the National Institutes of Health (NIH) in Bethesda, Maryland, Dr. Michael Blaese treated patients with primary immunodeficiency (PI) for 33 years, beginning in the late 1960s. About an hour away at Johns Hopkins University in Baltimore, Maryland, Dr. Jerry Winkelstein, a pediatric immunologist/allergist, also specialized in patients with PI. Winkelstein often referred patients to Blaese, and the two colleagues became close friends.

In the late 1970s Winkelstein began treating a little boy with X-linked agammaglobulinemia (XLA), John Boyle. At that time, his mother, Marcia Boyle, established a non-profit–the Immune Deficiency Foundation (IDF)–in 1980 to help families with PI, and Blaese appreciated the effort.

"There was a real lack of a support system for people with these rare diseases. Most of these folks have never even heard of what their children had, and most doctors didn't know a darned thing about it either, and that was certainly the experience of what I had at the NIH," said Blaese.

"When IDF was set up, I was very enthusiastic about it. It gave us some place patients could go to realize they were not the only ones with this rare problem. There were other people who were concerned about them, who they could talk to, and they could meet other parents."

When IDF asked Blaese, then-director of the National Human Genome Research Institute at the NIH, to speak at national conferences on topics related to PI, he gladly accepted the invitation. A global expert in PI, Blaese specialized in Wiskott-Aldrich Syndrome (WAS). Along with his team, he performed the first gene therapy treatment on two girls with adenosine deaminase severe combined immunodeficiency (ADA-SCID) in 1990.

At the IDF conferences, Blaese spoke on topics such as the shortage of immunoglobulin (Ig), a biologic essential for the treatment of PI patients; bone marrow transplant and gene therapy; treatments for patients with certain kinds of PI like SCID and WAS; and most recently provided a COVID-19 update presentation online for IDF.

Beginning in 2000, after his departure from NIH, Blaese served as the medical director of IDF for three years, and he served on the IDF Medical Advisory Committee. In 2022, IDF named the grant that funds the highest-ranking proposal for patient-centered research on PI after Blaese. The inaugural IDF Michael Blaese Research Grant Award went to Dr. Joud Hajjar to support research on the gut microbiome in patients who have common variable immunodeficiency (CVID), the most common PI.

Blaese said IDF's role is integral to the PI community.

"It's scary when you get the diagnosis of this disease you've never heard about, or that your child is dying because of it. When you have the resources provided by IDF, you realize you're not the only person in the world who is dealing with this. You can talk to people who are dealing with this, and it gives you reassurance," said Blaese, who is 84 and now retired.

"There are a lot of people I took care of that really bonded with other families who are going through the same stuff. Their own families don't understand what's going on and I think that's one of the great advantages of IDF—you can find a community of like-minded people out there."

WHY AND HOW TO COLLECT A FAMILY MEDICAL HISTORY

Primary immunodeficiencies (PIs) are inherited disorders, which means that they run in families. As with other inherited conditions, knowing whether family members have a PI, a related condition, or symptoms of undiagnosed PI, can give you and your healthcare provider important context for your health. And if you're already diagnosed with a PI, collecting your family's medical history can help future generations understand their health.

Collecting family medical history

The first step in collecting a family medical history is sketching out a family tree. Start with the person who's the focus of the history and map biological relationships out to third-degree relatives (e.g., first cousins, great-grandparents) if possible.

After drawing the family tree, collect information about the health of each identified relative and be as specific as possible for the information you collect. For example, if an aunt had cancer, you want to specify what type and stage of cancer, what age the person was when it was diagnosed, and the outcome.

There are several tools for collecting family medical history, including "*Does it run in the family?*" from the Genetic Health Alliance and "*My Family Health Portrait*" from the U.S. Surgeon General. There's no guide or tool specific to PI, but here's what is most important to capture if you suspect or want to document a family history of PI:

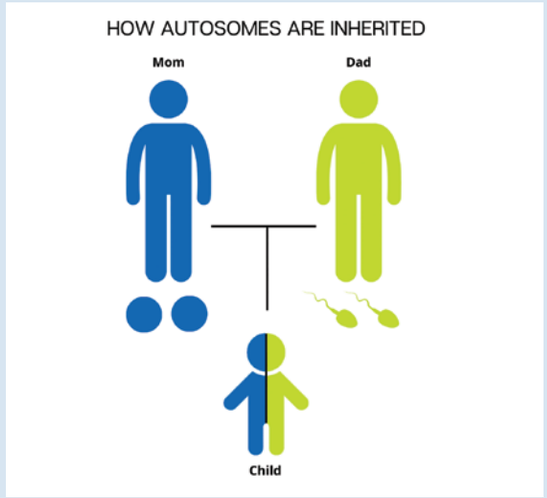
- Diagnoses of PI.
- Non-accidental infant or early childhood deaths.
- Relatives with a history of any of the following:
  - Enlarged spleen, liver, or lymph nodes without a known cause.
  - Low blood cell counts (e.g., neutropenia, anemia, thrombocytopenia) either due to autoimmunity or without a known cause.
  - Being considered "sickly," or reoccurring, unusually severe (i.e., requiring hospitalization or IV antibiotics in an otherwise healthy person), or uncommon infections.

    Note whether these individuals had/have healthy siblings, as this can indicate that the infections were not a result of shared environment.
- Diagnoses of autoimmune or autoinflammatory disease (e.g., lupus, arthritis, inflammatory bowel disease), particularly if diagnosed as a young child.
- Cancer diagnoses, particularly blood cancers (leukemia, lymphoma).

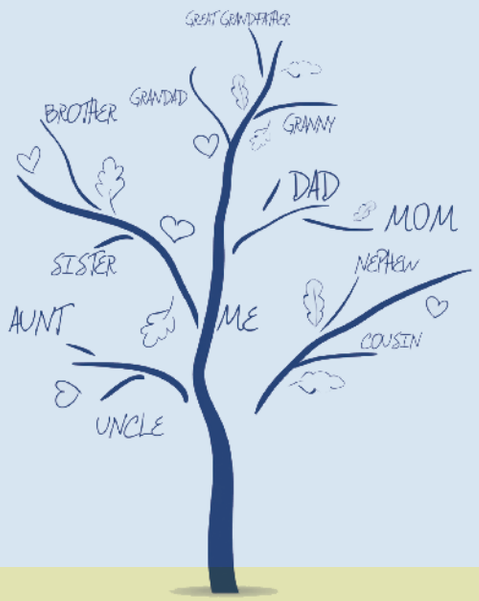
Family medical history can reveal patterns

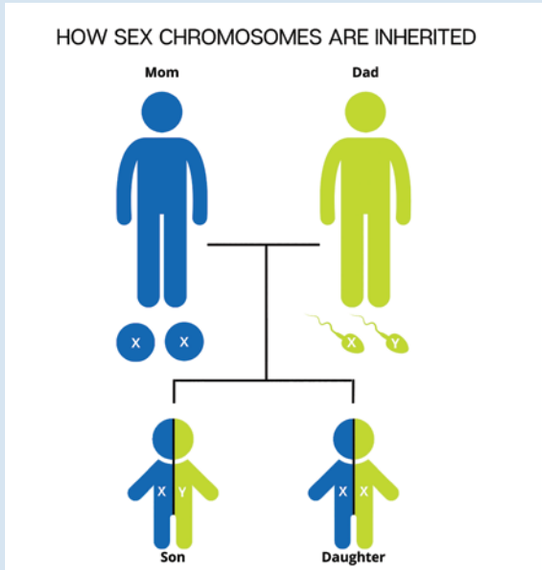
How does family medical history help in diagnosing PIs?

Many, but not all, PIs have a known genetic cause within a single gene (genetic variant) and show characteristic patterns in family medical history depending on how the genetic variant is inherited. There are three inheritance patterns for single-gene conditions: autosomal recessive, autosomal dominant, and X-linked recessive.



Every person has two copies of the genes on our autosomal chromosomes (all chromosomes except the X and Y sex chromosomes). One copy of each gene is inherited from the person's biological mother and the other copy is inherited from the person's biological father.





People who are genetically female have two copies of the X chromosome as well, again, one from their biological mother and one from their biological father. People who are genetically male have one copy of the X chromosome from their biological mother and one copy of the Y chromosome from their biological father.

Autosomal recessive means that an individual has to inherit two copies of the PI-causing genetic variant, one from each parent, in order to have the condition. 'Autosomal' means that the variant is not on a sex chromosome, so females and males have an equal chance of inheriting an autosomal recessive PI like adenosine deaminase (ADA) severe combined immunodeficiency (SCID).

PIs that are autosomal recessive are carried silently through the generations until someone who is a carrier—that is, who has one copy of the gene variant but does not have the PI itself—happens to have children with another carrier. Even then, a child of two carriers has a 25% chance of inheriting both copies of the variant and being affected by the condition. Unless there is intermarriage between people who are related, an autosomal recessive PI doesn't show up in every generation and multiple individuals with the PI in the same family tend to be siblings.

Like autosomal recessive PIs, the genetic variant that causes an autosomal dominant PI is not on a sex chromosome, so females and males are equally likely to inherit the condition. The difference is that an individual only has to inherit one copy of the variant, which can come from either parent, in order to have the disorder. Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome is an example of an autosomal dominant PI.

In a family medical history, an autosomal dominant PI can be traced through every generation and there are typically more family members with the disorder than in a family with an autosomal recessive PI.

X-linked recessive PIs like X-linked agammaglobulinemia (XLA) are a bit different. X-linked means that the PI-causing genetic variant is located on the X chromosome, which is a sex chromosome. Like an autosomal recessive PI, anyone with two X chromosomes (genetically female) has to inherit two copies of the variant to be affected.

But males only inherit one X chromosome, from their mothers. Males that inherit a single copy of the X-linked genetic variant are affected because, unlike females, they do not have another functional copy of the gene in question. In a family medical history, X-linked recessive conditions show up more often in males and can be traced back through male relatives of an affected male's mother, such as the maternal grandfather or maternal uncles. X-linked recessive PIs are never transferred from an affected male to his sons.

Unfortunately, experts don't yet know the genetic cause (or causes) for some of the most common PIs, like common variable immunodeficiency (CVID) and selective IgA deficiency (SIGAD). These disorders could be caused by a combination of genetic variants across multiple genes or a combination of environmental factors and genetic variants. The influence of multiple genes and/or non-genetic factors makes it more difficult to trace these conditions within a family. However, there is evidence that individuals with PIs that are not genetically defined are much more likely to have relatives with the same or similar disorders than the general public. So, even with disorders that have complex inheritance, a family medical history can be useful.

Family medical history has its limitations

Of course, family medical history is just one set of information and it isn't always helpful in considering or diagnosing PI in a particular person.

For example, some PIs show what's known as variable penetrance. That means that even for a disorder with a known cause in a single gene, people with the same variant in that gene don't have the same severity of the disorder. A PI with variable penetrance can make it harder to trace within a family because less-severely affected individuals may not even suspect that they have a PI.

Also, genetic variants aren't always inherited from parents. Sometimes, they happen spontaneously when an egg or sperm cell is formed, or early in fetal development. So, an individual with PI could have no family history of the disorder because they are the first person in their family to have the genetic variant that causes the disorder in all of their cells. In these cases, the PI does not show up in previous generations at all, although it is helpful to document for future generations.

Despite these limitations, family medical history can give healthcare providers crucial context and help them consider possibilities that they wouldn't otherwise. Proactively collecting family medical history, not just for PI, but for other conditions as well, is worth the time and effort.

AN INSIDE LOOK AT IDF

Chris Duckett

Chris Duckett

Director, Talent Management

I've been with the IDF team since November 2021, and in that time, there have been many changes to this organization, and all of them for the better. I joined IDF with more than 20 years of experience in the human resources (HR) profession as a manager, director, and vice president for employers in the retail, healthcare, and nonprofit industries. I enjoy finding the right fit for a job: someone who is dedicated and will work hard not just for IDF, but for the entire PI community.

Before coming to IDF, I served as the Director of Human Resources for the Center for Organ Recovery and Education (CORE). This experience gave me insight into the healthcare world and allowed me to understand the struggles that many individuals face when it comes to getting the care they need. A primary focus since joining this amazing team has been helping find individuals who will serve the PI community and brighten the future of this organization. I've had a hand in hiring many new employees who have proven their dedication and commitment, and I continue to search for those who are willing to go above and beyond to serve IDF.

Along with working towards a brighter future for IDF, I serve as our volunteer relations manager, working directly with the PI community to fulfill the needs for all of our volunteer initiatives; plasma ambassadors, peer support volunteers, community liaisons, and beyond. It's my goal to bring our community together through these volunteer positions. I truly believe that there is a way for each member of the PI community to be involved. Whether you visit a plasma center or support others living with PI through peer support, there's a way to make a difference and make an impact.

One of the most impactful things I've experienced during my time with IDF has been visiting a plasma donation center in person and thanking the donors there for being heroes to the PI community. I had the privilege of speaking one-on-one with individuals who had never heard of primary immunodeficiency but donate plasma to make a difference. They were thrilled to know that their donation helped save lives. This is one of the reasons we're working hard to build our Plasma Ambassador program.

Currently, we have plasma donation centers across the country that are looking for individuals who receive plasma-derived therapies to come in to talk to the donors, thank them for their donation, and encourage them to come back and donate again. By sharing your story and your journey, you inspire these donors to come back time and time again to donate and to encourage others to donate plasma.

There is a lot of work to be done to support the PI community, and I will continue to learn how to better serve the IDF mission of advocacy, education, and research to better the lives of those living with PI.

Become an IDF volunteer

MAKE A DONATION

Support critical resources and programs for the entire primary immunodeficiency community! Every donation counts.

Tackling policies that limit immunoglobulin therapy access

Fresh off of enacting a permanent Medicare benefit for home administration of intravenous immunoglobulin (IVIG), IDF's Policy team is tackling two additional issues related to immunoglobulin (Ig) therapy access. The first affects the ability of people receiving Ig therapy to also be admitted to skilled nursing facilities (SNFs) and the second concerns insurance providers dropping high-concentration Ig from their formularies.

Why skilled nursing facilities and Ig therapy don't mix

People are typically admitted to skilled nursing facilities (SNFs) when they need more care than they can receive at home (e.g., extensive physical therapy, changing of bandages, IV medication) but do not need to be hospitalized. For example, someone undergoing knee replacement surgery may be discharged to a SNF for recovery. SNFs can also serve as 'step-down' facilities for those recovering from hospitalization for acute medical needs, such as severe infections.

However, because of how Medicare pays these facilities for their services, SNFs will not administer Ig therapy intravenously (IVIG) or subcutaneously (SCIG). Since private insurance payers frequently model their own policies after Medicare, this flawed reimbursement scheme affects those insured through private plans as well.

When a Medicare beneficiary is admitted to a SNF, Medicare pays a bundled daily rate to the facility instead of reimbursing the SNF for each service or procedure, which is how Medicare reimburses hospitals. The per diem is intended to cover all medical care the patient receives at the SNF.

However, Ig is an expensive medication, so those who need Ig therapy cost the SNF more than the facility receives in per diem reimbursement. Because SNFs are not legally required to accept patients, they frequently turn away patients on Ig therapy. These individuals instead languish in hospitals, costing Medicare or their private insurance provider more money and increasing the patient's risk of contracting a hospital-acquired infection.

Sometimes, a SNF will accept a patient, but then refuse to administer their Ig therapy. In this case, the patient is at risk of infection because they are not receiving the necessary treatment for their PI.

Patients with hemophilia faced similar issues until legislation took effect in 2021 that allows SNFs to bill Medicare separately for bleeding disorder treatments on top of the standard per diem. IDF hopes to replicate this solution and is actively working with Congressional legislators to address the SNF and Ig access problem.

Why dropping high-concentration Ig from formularies is problematic

Recently, IDF has become aware of both private and public health insurance plans that have entirely removed 16.5% and/or 20% Ig formulations from their formulary lists. Individuals covered by these plans are essentially being denied the option to infuse subcutaneously because the high-concentration formulations preferred for SCIG are not covered by their insurance plans.

While three 10% Ig formulations are approved for SCIG in the U.S., these lower-concentration products require greater infusion volumes. Large infusion volumes are not tolerable for many SCIG users because they require more infusion sites and are not compatible with a biweekly SCIG regimen. IDF's 2018 Treatment Survey found that only 13% of PI patients using SCIG used 10% formulations.

There is no medical justification for dropping coverage of 16.5% and/or 20% Ig formulations, and payers seem to be dropping them solely because of cost. SCIG is an important option for patients when they don't tolerate IVIG well, when there is poor venous access (as in the elderly or in small children), or when the individual's lifestyle is not compatible with IVIG. When 16.5% and/or 20% Ig formulations are not covered, patients may be forced to switch to lower-concentration SCIG or to IVIG, increasing their risk of adverse events and negatively affecting their quality of life.

IDF is working with payers to emphasize the need to cover **all** Ig formulations and **all** routes of administration. Ig therapy is not interchangeable and access to the product that works best for each patient is essential.

"The choice of product and route of administration, e.g., intravenous or subcutaneous, should be determined by the prescribing physician in consultation with the patient, based on his/her individual needs."

– IDF Medical Advisory Committee, *Model Coverage Policy for Immunoglobulin Replacement Therapy for Primary and Secondary Immunodeficiency Diseases with Impaired Antibody Response*

Tell us your story

Please reach out via Ask IDF and tell us your story if you:

- Use SCIG or IVIG to treat your PI and have struggled to find a SNF that will admit you.
- Have been admitted to a SNF and then denied your SCIG or IVIG therapy.
- Have had to switch formulations/brands of Ig and/or route of administration due to insurance formulary changes for 2023.
- Are a healthcare provider who has struggled to find a SNF that will accept your PI patient.
- Are a healthcare provider who has patients that no longer have the option for 16.5% and/or 20% Ig formulations.

What you see on screen

Primary immunodeficiency in the media

When done correctly, the depiction of primary immunodeficiency (PI) in popular media can help raise awareness about this rare, chronic condition and destigmatize it. However, an inaccurate or sensationalized portrayal can be harmful to those with PI and their families because those who have seen it believe it to be true. Some are calling this phenomenon The "Grey's Anatomy" Effect–meaning there are a lot of misconceptions from what we see on the screen versus what happens in real life.

IDF has made statements about television episodes, films, and books that have portrayed those living with PI–each depiction getting some things right and some things wrong.

"The Boy in the Plastic Bubble"
1976

ON SCREEN: "The Boy in the Plastic Bubble" features Tod, who was born with an immune system that doesn't function properly. The audience is told that unfiltered air could kill him, and he is forced to spend his life in "incubator-like conditions." After years in the hospital, Tod finally finds a way to be allowed at home, restricted to his room. Eventually, he is enrolled in school and allowed to attend with a type of space suit that provides him the same protection as his room/incubator. Tod falls in love with his neighbor and has to choose between risking his life by leaving his bubble or staying in it forever. Tod chooses to leave his bubble and literally rides off into the sunset with Gina on her horse.

IN REAL LIFE: Tod's character was inspired by David Vetter, who is affectionately known as "the boy in the bubble." Vetter was born with SCID. At the time of his birth in 1971, a bone marrow transplant from an exact matched donor was the only cure for SCID, but there was no match available in Vetter's family. For 12 years, Vetter captured the world's attention as he lived in protected environments to maintain relatively germ-free surroundings at Texas Children's Hospital before his passing in 1984.

"Seinfeld"
1992

ON SCREEN: In season 4, episode 7, a fan of Jerry's tells him about his son who "lives in a plastic bubble" to create a germ-free and sterile environment. He convinces Jerry to agree to stop by on his way on a trip with George, Elaine, and George's girlfriend, Susan. George and Susan arrive first and begin to play Trivial Pursuit with Donald, which leads to a confrontation where Donald begins to strangle George. Susan defends George and punctures the bubble, causing Donald to collapse.

IN REAL LIFE: The reality is that people with SCID are not forced to live their lives in a sterile environment, which is an antiquated notion that has not been the case for many years. In fact, it was never a standard treatment, having only been used in a handful of cases. Most persons with SCID who have received treatment lead healthy and productive lives with no need to shield themselves from the world. In "Seinfeld," Donald's illness is treated as a joke for the audience.

Jerry Seinfeld: *He's a bubble boy!*
George Costanza: *A bubble boy?*
Jerry Seinfeld: *Yes, a bubble boy.*
Susan Biddle Ross: *What's a bubble boy?*
Jerry Seinfeld: *He lives in a bubble.*
George Costanza: *Boy!*

"Everything, Everything"
2017

ON SCREEN: Based on the book of the same name, "Everything, Everything" introduces Maddy, a teenager who has been forced to spend her life indoors at the recommendation of her mother and physicians due to her illness, which is supposedly SCID. Maddie says she is "allergic to the world." At the end of the movie, it is revealed that Maddy is a victim of Munchausen by proxy, which is a psychological disorder where a caregiver seeks attention by fabricating or inducing symptoms of a disease in those within their care.

IN REAL LIFE: Perhaps most troubling is that the twist ending of the movie informs us that Maddie never had SCID in the first place and was the victim of her mother's Munchausen syndrome by proxy. For anybody that has ever sought a PI diagnosis, this will be particularly upsetting, as being accused of hypochondriac behavior is a common form of medical gaslighting, and the film's reinforcement of this idea is worrisome and dangerous.

"The Sky Is Pink"
2019

ON SCREEN: Inspired by the book "My Little Epiphanies" by Aisha Chaudhary, "The Sky Is Pink" follows the story of Aditi and Niren, who fall in love and are trying to have a family. Their first child, Tanya, dies a few months after birth due to complications from SCID. Years later, they have a third child, Aisha, who also has SCID. After doctors in Delhi can no longer help Aisha, the family travels to London where they learn Aisha can be treated with a bone marrow transplant (BMT). The BMT is successful, but Aisha is later diagnosed with pulmonary fibrosis, which is a side-effect of the chemotherapy she had to undergo. With this diagnosis, Aditi sets out to fulfill all of Aisha's dreams–including publishing her own book. Aditi, unfortunately, suffers a breakdown and is hospitalized trying to make all of Aisha's dreams come true in her shortened life. After Aisha's death, the family is strained but comes together through memories of Aisha.

IN REAL LIFE: "The Sky Is Pink" was inspired by Aisha Chaudhary's real-life experience. Aisha was one of the youngest motivational speakers from India and was known for her positive and clear attitude toward life. Aisha's real life is represented in the movie and shows those with a PI are not confined to a bubble but are instead able to lead exciting or normal lives. Even when she was bedridden due to her pulmonary fibrosis, Aisha continued to pursue her passions by writing, and her book, "My Little Epiphanies," was published one day before her death.

The movie also shows an accurate portrayal of what life can be like for parents and caregivers of sick children and was directed by Shonali Bose, who lost her 16-year-old son in an accident.

We are PI

An IDF and JMF collaboration

We are proud to announce that for the first time ever, the Immune Deficiency Foundation and the Jeffrey Modell Foundation are teaming up to encourage the PI community to raise awareness for PI through monthly challenges! As two of the leading primary immunodeficiency patient organizations in the U.S., this partnership is an exciting opportunity to expand our reach to the PI community and beyond.

The first challenge went live on Rare Disease Day (February 28, 2023) and encouraged participants to share how they explain living with a rare disease to people who don't understand it.

"I don't know if people without an immunodeficiency or a close loved one with it can understand, as they lack the perspective. For most, our complications seem like something out of House or like we're being melodramatic. For many, they don't catch as many viruses and hardly ever worry about developing bacterial infections following. The public may need representation in the media of us they don't easily dismiss before they care for our perspective." — Sarah F.

"To live with a rare disease isolates you for a while because people don't have a clue how it is to live without an immune system. The only way is to spread information about it through publicity, social media, and maybe showing real cases on TV." — Paula P.

"I say a regular person gets a cold and is sick for a few days. I get a cold and it could get into my lungs and turn into pneumonia. I don't respond well to drugs, so it can be up to 8 weeks of antibiotics to be able to break well again. So if you have a cold, I'm leaving." — Linda C.

"It's difficult to explain and I find many physicians are not aware of it. I usually say I'm missing a protein in my blood to help me fight off infection." — Danielle

There will be more challenges coming each month! Be sure to follow us on social media to participate. #WeArePI

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Meet Plasma Hero Alice Drennon

Beginning in 2008, Alice Drennon experienced a multitude of severe infections—ear infections, sinus infections, pneumonia, bronchitis, upper respiratory infections, etc.—

that caused frequent trips to the emergency room and hospitalization. At the time, Drennon was working for a law firm in Houston, TX, and had to take 122 sick days. Her physician referred her to an immunologist. "My life was about to change forever," said Drennon.

Drennon was diagnosed with common variable immune deficiency (CVID), a type of primary immunodeficiency (PI) that affects roughly 1 in 250,000 individuals. There is no cure for it, only treatment. In this case, Drennon's immunologist recommended immunoglobulin (Ig) replacement therapy to provide her with the antibodies her body was not making. Drennon receives her Ig replacement therapy subcutaneously every 28 days at home with the help of a nurse. Each infusion lasts about 4-5 hours.

Realizing that not many people knew what CVID was and not knowing anyone else with the diagnosis, Drennon took matters into her own hands. "I decided to be my own advocate," she said. She became involved in the Immune Deficiency Foundation's (IDF) Get Connected Group in Houston, TX. These meetings bring together members of the PI community to discuss their diagnoses, build connections, and, sometimes, hear from medical professionals. At the meetings, Drennon learned that individuals with PI often visited plasma centers to thank donors and raise awareness for PI and the need for regular plasma donation.

"It's been almost five years since I began visiting multiple plasma centers in Texas," she says, the furthest one being 365 miles away. "The experience is humbling, to say the least. I can speak with the staff and donors, encouraging them to be kind to those who walk through the door, as we all have life challenges. These donors give the gift of life, which is priceless. They give, I live!"

In addition to her usual volunteer work for IDF, she volunteered to serve as a Spanish-language interpreter for interviews with Mexican plasma donors so that they could tell their stories for the Plasma Hero website and highlight the importance of plasma donation. Drennon is also featured in the U.S. Department of Health and Human Services (HHS) "Giving=Living" campaign to promote both blood and plasma donation.

"You can't imagine how honored and privileged I am," said Drennon. "I share my story with the purpose of [plasma donors] learning more about real patients. I thank each donor for their generosity and courage because their selfless act saves lives and one of them is standing in front of them—what an impact!"

In October 2022, Drennon received the Plasma Hero Award at the 2022 Primary Immunodeficiency Conference for her tireless efforts as an ambassador for plasma donation. We are thrilled to be able to feature her and all she's helped accomplish. To learn more about plasma donation and how you can raise awareness, visit **www.plasmahero.org**.