CMEO Snack

The Changing Face of Primary Immunodeficiency: Improving Diagnosis and Access to Treatment for All Patients

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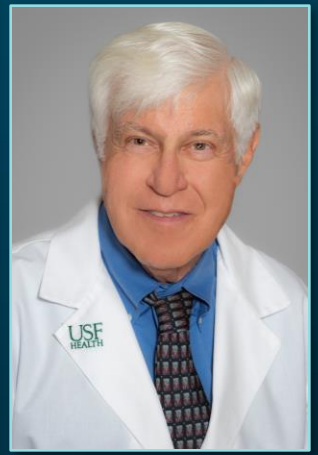

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LEARNING OBJECTIVE 1

Assess the various presentations of PI, including atypical presentations, to improve PI recognition and diagnosis.

Primary Immunodeficiency (PI) Overview, Impact, and Prevalence

Definition	• PIs comprise **over 559 inherited disorders** that impair normal immune function.
Cause	• Genetic defects affect immune system components, leading to increased susceptibility to infections.
Types/Phenotypes	• Infectious: characterized by recurrent or severe bacterial, viral, or fungal infections. • Non-infectious: includes autoimmune, autoinflammatory, allergic, or malignant manifestations.
Clinical Pattern	• Infections in PI patients tend to be more prolonged or severe than in immunocompetent individuals infected with the same organisms.
Diagnostic Challenges	• Non-infectious phenotypes are often under-recognized and diagnosed later due to atypical presentation or lack of infection history.
Epidemiology	• **Upwards of 700** different disorders genetically identified; ongoing genetic discoveries have expanded recognized disease spectrum. • Estimated prevalence of **1 in 1200 live births.**
Prognostic Impact	• Delayed diagnosis increases morbidity and mortality. • Early recognition and management markedly improve outcomes.
Clinical Priority	• HCPs must identify both infectious and non-infectious forms promptly for optimal short- and long-term management.

HCPs = health care professionals.

Perez EE, et al. *J Allergy Clin Immunol.* 2017;139(3S):S1-S46. Farmer JR, et al. *Front Immunol.* 2017;8:1740. Elsink K, et al. *Clin Immunol.* 2020;213:108359. Tangye SG, et al. *J Clin Immunol.* 2022;24:1-35. Kim VHD, et al. *Allergy Asthma Clin Immunol.* 2025;20(Suppl 3):76.

Secondary Immune Deficiencies (SIDs)

Definition and Epidemiology

- Acquired immune dysfunction from external causes (not genetic)
- More common than primary immunodeficiencies in adults
- ~6% of adults have an immune deficiency; most are secondary

Major Causes

- Medications: corticosteroids, chemotherapy, biologics (anti-TNF, rituximab, CAR-T)
- Malignancy: CLL or MM (up to 80% develop SID-related infections)
- Chronic illnesses (diabetes, renal/liver failure); HIV infection

Clinical Features

- Recurrent sinus/respiratory infections
- Poor vaccine responses
- Autoimmune cytopenias, bronchiectasis

Diagnostic Work-Up

- Immunoglobulin levels (IgG, IgA, IgM)
- Vaccine antibody titers
- Lymphocyte subsets and medication review

Management Principles

- Treat/remove underlying cause
- Prophylaxis: vaccinations, antimicrobials
- Consider IgRT/SCIG for recurrent infections

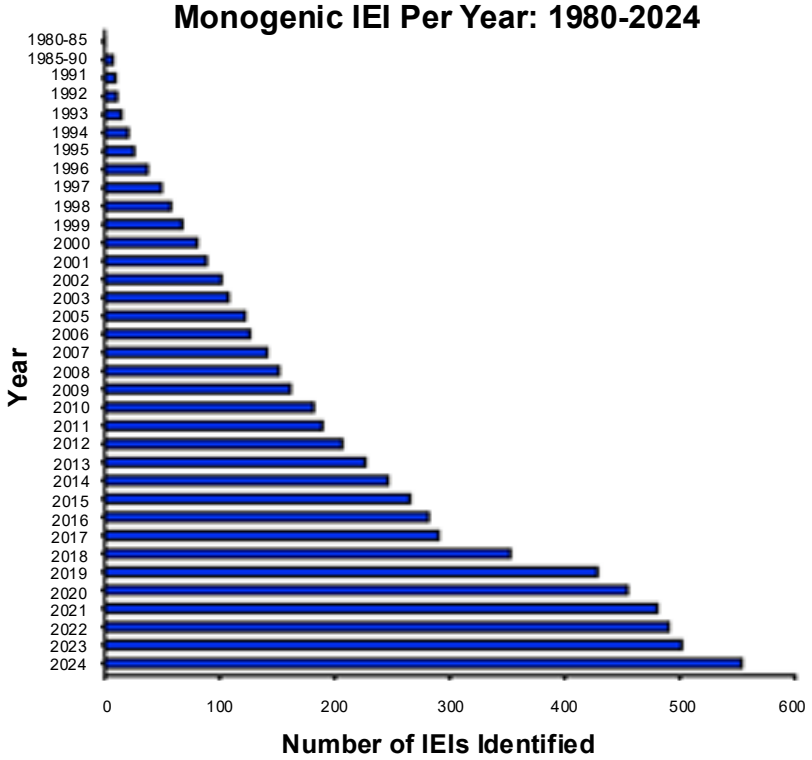
Emerging Issues

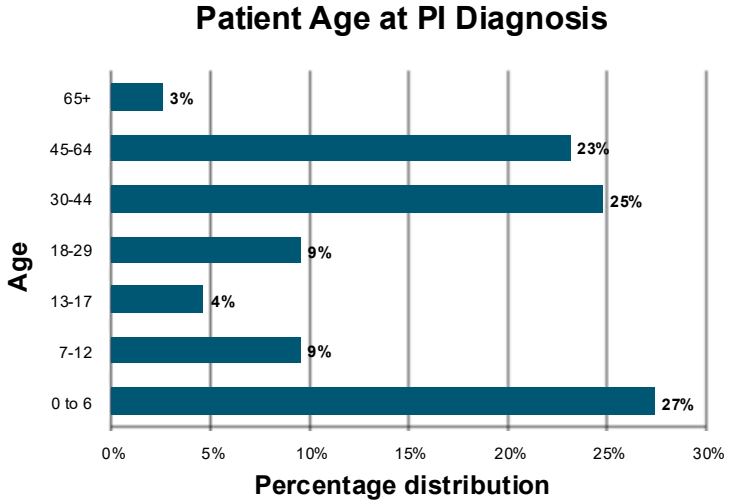
- CAR-T and bispecific antibody therapies increasing SID incidence
- Adult-onset immune defects blur PI vs SID boundaries

Anti-TNF = anti-tumor necrosis factor; CAR-T = chimeric antigen receptor-T; CLL = chronic lymphocytic leukemia; MM = multiple myeloma; HIV = human immunodeficiency virus; IgRT = immunoglobulin replacement therapy; SCIG = subcutaneous immunoglobulin.

Pourshahnazari P, et al. *J Allergy Clin Immunol Pract.* 2025;13(1):36-47. Cowan J, et al. *Front Immunol.* 2025;16:1528414. Regina J, et al. *Clin Rev Allergy Immunol.* 2025;68(1):92. Zo S, et al. *Tuberc Respir Dis (Seoul).* 2024;87(4):440-450. Wang JJF, et al. *Allergy Asthma Clin Immunol.* 2024;20(1):6.

Cumulative Discovery of IEI, Prevalence, and Types of Deficiencies





- **2024/2025 IUIS update: 559 distinct IEIs** formally classified, with new disorders and genes continually discovered every year
- **PIs** affect over **6 million** people worldwide, with ~70-90% remaining undiagnosed

IEIs = inborn errors of immunity.

International Union of Immunological Societies [IUIS]. 2025. https://iuis.org/committees/iei/.

Immune Deficiency Foundation 2023: Demographics for Patients with PI

Diagnoses	Number of Respondents
Common Variable Immunodeficiency	729
Hypogammaglobulinemia	117
Specific Antibody Deficiency	102
IgG Subclass Deficiency	76
Unspecified	43
Selective IgA Deficiency	37
Unclear	15
Combined Immunodeficiency	13
Hyper IgE Syndrome	8
Hyper IgM Syndrome	6
X-linked Agammaglobulinemia	6
Other	5
Complement Deficiency	4
Selective IgM Deficiency	4
Natural Killer Cell Def	4
Chronic Granulomatous Disease	3
Severe Combined Immunodeficiency	2
Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy	1
Hereditary Angioedema	1
Warts, Hypogammaglobulinemia, Infections, and Myelokathexis Syndrome	1
Total	**1177**

Respondent/Patient Demographics (N = 1177)

- Top 3 diagnoses were common variable immunodeficiency (CVID, ~62%), hypogammaglobulinemia (~10%), and specific antibody deficiency (~9%)
- The median age among patients at time of diagnosis was 52 years
- Wide age distribution, but most patients fell between 30 and 70 years old at time of diagnosis
- Time from initial infections to actual diagnosis was notably prolonged: median was 23 years, and the average was 25 years, with several patients experiencing extremely delayed diagnoses
- Out of 977 patients with infections preceding diagnosis, many waited more than 20 years for an accurate diagnosis
- The patient population was predominantly White (93%), with smaller percentages identifying as Black, Latine, two or more races, and other groups

Immune Deficiency Foundation [IDF]. 2025. https://primaryimmune.org/advancing-pi-research-and-clinical-care/idf-surveys/2023-national-patient-survey.

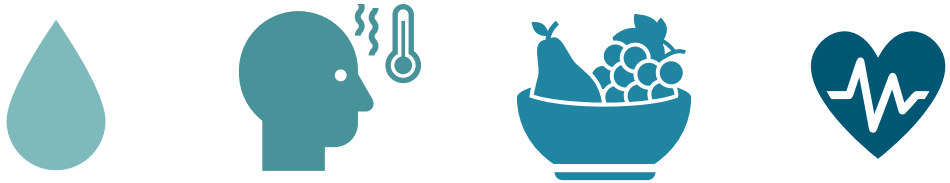
Different Phenotypes of PI

Classic Presentation

- Recurrent or severe infections
- Bacterial or sinopulmonary infections, ear infections, pneumonia, GI symptoms
- Early childhood onset
- Often humoral or combined immune defects
- Growth failure/delayed growth

Atypical/Non-Infectious Presentation

Emerging recognition in adolescents and young adults



Autoimmunity
- Cytopenias, autoimmune thyroiditis, lupus-like syndrome

Autoinflammation
- Recurrent fevers, rashes, arthritis without infection

Allergic/Atopic
- Severe eczema, food allergies, asthma

Lymphoproliferation/Malignancy
- Splenomegaly, lymphadenopathy, lymphoma

GI = gastrointestinal.
Soler-Palacín P, et al. *Front Immunol.* 2025;16:1593897.

Missed Phenotypes in PI: Diagnostic and Clinical Risks

Diagnostic Evaluation

- Adolescents increasingly present with “non-infectious” PI
- Genetic sequencing reveals immune dysregulation variants missed in infection-based screening
- Functional immune studies (lymphocyte subsets, cytokine profiling) help differentiate overlapping phenotypes

Clinical Implications

- Missed diagnosis risk:
  - Adolescent-onset autoimmune or inflammatory disease may mask underlying PI
- Therapeutic shift:
  - Biologic modulation (e.g., abatacept, JAK inhibitors) complements immunoglobulin replacement

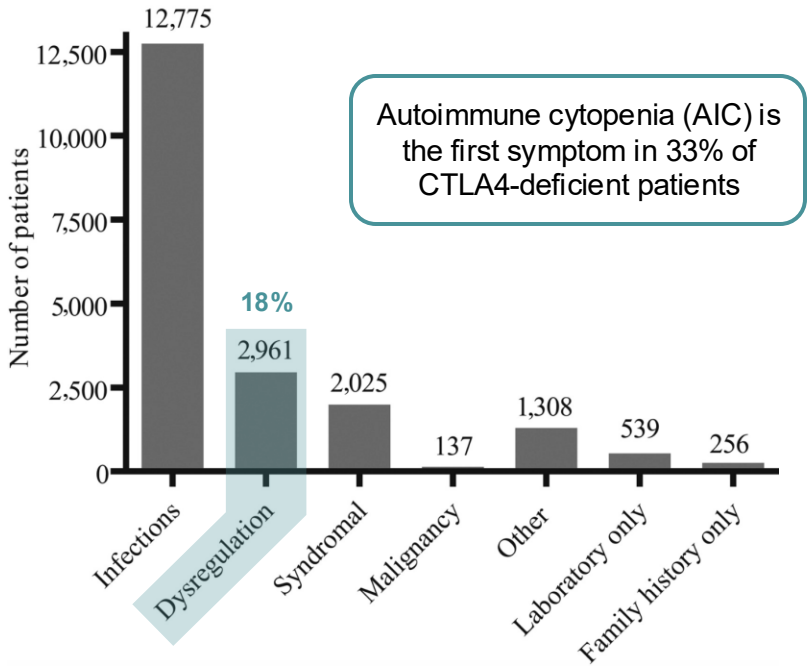
JAK = Janus kinase.

Soler-Palacín P, et al. *Front Immunol.* 2025;16:1593897.

Diverse Presentations for PI Beyond Infections

Autoimmunity as Initial Presenting Manifestation of IEI

N = 16,486 patients with PI of any kind (ESID)



- Roughly one in four patients with IEI first present with non-infectious symptoms, which can delay diagnosis if overlooked
- Recognizing non-infectious manifestations – immune dysregulation, autoimmunity, and laboratory abnormalities – is critical for timely PI diagnosis and optimal outcomes
- This evidence supports broadening PI "warning signs" beyond recurrent infections to include diverse clinical features

ESID = European Society for Immunodeficiencies.

Thalhammer J, et al. *J Allergy Clin Immunol.* 2021;148(5):1332-1341. Schwab C, et al. *J Allergy Clin Immunol*. 2018;142(6):1932-1946.

Ilana Jacqueline: Patient Planner

- 35 years old
- Patient Advocate and author of *Surviving and Thriving with an Invisible Chronic Illness*
- 19 years waiting for a diagnosis of CVID characterized by hypogammaglobulinemia
- 30 years waiting for a treatment plan
- Raised in a high-income, primarily White community less than one hour from an academic hospital system
- After her diagnosis, she struggled to find an immunologist who knew how to manage treatment with IgRT

Patient Journey

I am **Ilana Jacqueline,** and I have what we in the patient community call “lucky girl syndrome.” As in due to my social determinants of health, I was lucky enough to get diagnosed far sooner than many patients with PI – which might be a bit confusing to point out, as I was not diagnosed until I was 19 years old. In the general health sphere, this would seem extremely unlucky. However, beyond being a patient, I have also worked as a patient advocate for the last decade in the rare disease community. And if there's one thing that I've come to realize, it's that most patients do not have the resources, the finances, the connections, or the simple physical ability to endure what I had to endure to get this diagnosis.

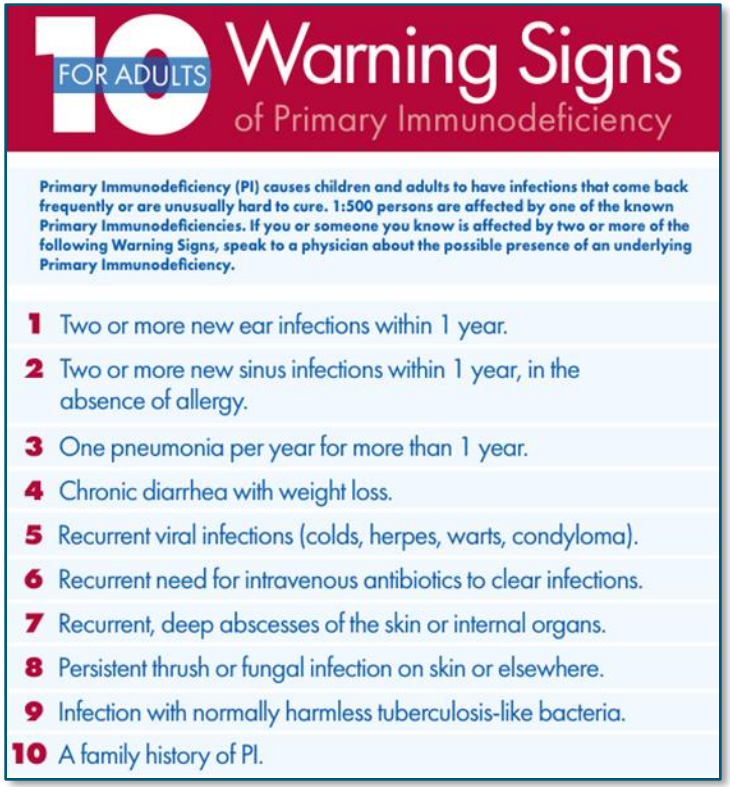
So, my story starts like this: I was born sick, constantly dealing with infections, mostly lung, bronchitis, mucosal sinus strep, and viruses. And they would not improve, not without aggressive intervention, and oftentimes without hospitalizations. I was fortunate in that I had a mother who was a great advocate for me, but who endured many instances of medical gaslighting where she was told she was being overprotective and paranoid, and that some children were just sickly children. Before the age of 18, with great insurance and access to a university hospital just one hour from my home in south Florida, I would see pediatricians, pulmonologists, allergists, and have many hospitalists who would look over my care and assess me as a patient, but none that would make the diagnosis. **And I slipped through the cracks.**

10 Warning Signs of PI: Pediatrics

- **Recurrent or severe infections** – frequent ear, sinus, or lung infections; poor response to antibiotics; need for IV therapy
- **Failure to thrive or unusual infection patterns** – deep abscesses, persistent fungal infections, or infections with uncommon organisms
- **Family history or genetic predisposition** – consider PI when there is a known familial immune disorder or unexplained recurrent illness

Jeffrey Modell Foundation. 2025. https://info4pi.org/library/educational-materials/.

10 Warning Signs of PI: Adults



- **Recurrent or persistent infections** – frequent ear, sinus, or lung infections; poor response to antibiotics; need for IV therapy
- **Unusual or severe infection patterns** – chronic diarrhea with weight loss, recurrent viral or fungal infections, or infection with normally harmless organisms
- **Family history or genetic predisposition** – consider PI in adults with relatives diagnosed with immunodeficiency or unexplained recurrent illness

Jeffrey Modell Foundation. 2025. https://info4pi.org/library/educational-materials/.

Audience Response

Which of the following reflects an atypical presentation of PI?

A. A child with severe combined immune deficiency (SCID) at birth presenting with failure to thrive
B. A child with severe eczema and multiple food allergies who develops recurrent skin infections
C. An adult presenting with recurrent pneumonia and sinus infections since childhood requiring frequent hospitalizations
D. A child experiencing recurrent viral upper respiratory infections while attending daycare
E. I don’t know

Maximizing Diagnostic Opportunities in the PI Disease Journey

Four Stages of PI Testing

Newborn Screening
Detects PI during the asymptomatic phase, targeting SCID and related disorders.

Family History and Early Symptoms in Primary Care
Relies on early recognition by primary care providers through family history and subtle symptom patterns.

Specialized Non-Immunological Secondary Care
Patients with persistent or complex symptoms are evaluated by non-immunology specialists (e.g., pulmonology, hematology, infectious disease).

Specialized Referral Units (Immunology Centers)
Patients receive comprehensive workups and confirmatory testing at tertiary immunology centers.

Patients should receive targeted evaluation based on clinical presentation and family history. Collaboration amongst pediatricians, internists, and relevant subspecialties (e.g., hematology, rheumatology, gastroenterology) is KEY!

Soler-Palacín P, et al. *Front Immunol.* 2025;16:1593897.

Comprehensive Laboratory Evaluation of PI

Humoral Immune Evaluation

Immune Function

Adaptive Immune System

1st Stage

- **CBC with differential**
- **Immunoglobulin production**: IgG, IgA, IgM, IgE
  - IgG subclasses (IgG1, 2, 3, 4) – sometimes

2nd Stage

- **Isohemagglutinins**: anti-ABO red blood cell antigens
- **Vaccine responses**
  - Vaccine-specific antibody responses
    - Tetanus, Hib, pneumococcal
    - Influenza A/B

Immune Evaluation

Immune Phenotyping/Cell Counts

3rd Stage

- **Lymphocyte subset counts:**
  - T (CD3, CD4, CD8), B (CD19) and NK (CD16/56) cell: **XLA, CVID**
  - Naïve vs memory (CD45RA vs CD45RO) CD4/CD8 T cells: **CID**

4th Stage (by an immunology specialist)

- **B cell panel**: B cell compartments (naïve, switched memory, plasma cells)
- **T cell panel**: Naïve/memory/effector/activated T cells; naïve recent immigrant T cells; regulatory T cells
- **Lymphocyte proliferative responses to mitogens/antigens**

CBC = complete blood count; Hib = haemophilus influenzae type b conjugate vaccine; NK = natural killer; XLA = X-linked agammaglobulinemia; CID = combined immunodeficiency.

Reust CE. *Am Fam Physician*. 2013;87(11):773-778. Kim VHD, et al. *Allergy Asthma Clin Immunol*. 2025;20(Suppl 3):76.

Patient Journey

I started to see every specialist I could get into, every single one. And we ran so many tests and I had so many doctors who just like couldn't wrap their heads around what it was that I was experiencing. And I started to feel like I was crazy. I got to a point where I did not wanna keep seeking answers, but I was also too sick to live like this. So, one day my stepfather went to synagogue and asked his congregation to pray for me out loud. And after he did that, one of the men in his temple introduced himself as an infectious disease doctor. Lucky. And he told him to bring me to his office and that he would try to figure me out. And my parents dragged me to that appointment. I mean, dragged. I was so scared to have another doctor gaslight me and make me feel silly and paranoid for being so sick. But he didn't. He took my history for over an hour. He looked through all the blood tests and scans that had already been performed. He did his own exam, and he said, you know, I think I know what's wrong with you. And I didn't wanna get my hopes up because I'd heard that before, but this time just seemed different. And not long after that, we went home and we waited for results. And he called and he said, "Hey, you have this disease. You have something called hypogammaglobulinemia, and your levels are critically low, **and you need to go to the hospital right now and start IVIG."**

The Long Road to Diagnosis

Average time to diagnosis
9-15 years on average from symptom onset to confirmed PI; varied by subtype and may be shorter in children.

Diagnosis in childhood
Severe or syndromic PI forms are often diagnosed in young children, but milder antibody deficiencies may not be recognized until adolescence or adulthood.

Functional impairments
Up to half of children with PI report lasting functional impairment or health complications by diagnosis.

Chronic infections
Recurrent respiratory, sinus, and ear infections are common presenting features in pediatric PI; these infections frequently lead to missed school and hospitalizations.

Autoimmune disease comorbidity
Approximately one-third of children with PI develop autoimmune complications such as cytopenias, thyroiditis, or juvenile idiopathic arthritis.

Hospitalizations/missed school
Children with PI experience frequent infections resulting in recurrent hospital admissions and significant school absences.

Adult PI impact
52% reported moderate to severe limitations in work or daily activity due to health problems.

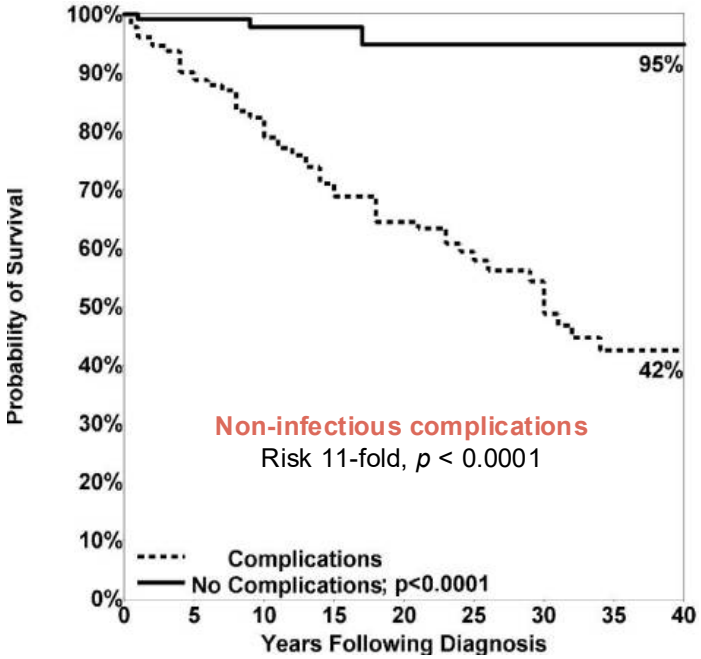
Nikzad S, et al. *J Clin Immunol.* 2025;45(1):69. Kim VHD, et al. *Allergy Asthma Clin Immunol.* 2025;20(Suppl 3):76. Ameratunga R, et al. *Clin Exp Immunol.* 2021;204(3):352-360. IDF. 2025. https://primaryimmune.org/advancing-pi-research-and-clinical-care/idf-surveys/2023-national-patient-survey.

Non-Infectious Complications and Mortality Risk in CVID

CVID with non-infectious phenotype:

- Less favorable outcome
- May be undertreated/misdiagnosed
- Increased mortality and morbidity
- **Risk of death is 11-fold higher in patients with complications**
  - Recognition and management are critical for improving survival in PI
- Increased mortality associated with:
  - Lymphoma
  - Hepatitis
  - Lung disease
  - GI disease

Mortality of 473 Patients with CVID



Resnick ES, et al. *Blood*. 2012;119(7):1650-1657.

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LEARNING OBJECTIVE 2

Differentiate among the immunoglobulin therapies available for the treatment of PI in order to provide patients with optimal, personalized care.

Clarifying Nomenclature for the Treatment of PI

IgRT	Immunoglobulin replacement therapy (preferred terminology)
IVIG	Intravenous immunoglobulin
SCIG	Subcutaneous immunoglobulin
fSCIG	Facilitated subcutaneous immunoglobulin (with rHuPH20 enzyme)

Additional treatments: hematopoietic stem cell transplantation, targeted therapies, enzyme replacement therapy, and gene therapy clinical trials

rHuPH20 = recombinant human hyaluronidase.

Yalcin Gungoren E, et al. *J Clin Immunol*. 2024;44(8):169. IDF. 2025. https://primaryimmune.org/understanding-primary-immunodeficiency/treatment/immunoglobulin-replacement-therapy.

IVIG: Efficacy, Safety, and Usage

Efficacy

- Regular IVIG reduces serious bacterial infection rates in PI, improving survival and quality of life
- Recent phase III trials report maintenance of IgG levels and a marked reduction in infections for both adults and children
- SBI rate: 0.02-0.05 events/patient/year ($p < 0.001$)
- All infections: 1.65 events/patient/year (95% CI: 0.7-3.2) in some studies

Safety

- Most adverse effects are mild and systemic (headache, fever, myalgia, chills, nausea), usually occurring early or in the first few infusions
- Rate-related reactions can be mitigated by slower infusion, premedication, and adequate hydration
- Severe reactions (anaphylaxis, thrombosis) are rare (< 1%), but vigilance is needed

Dosing

- Typical dose is 0.4-0.6 g/kg every 3-4 weeks IV infusion
- Adjusted according to IgG trough levels and infection frequency
- Doses may be increased for breakthrough infections or adjusted for body weight and clinical response

Contraindications

- IgA deficiency with anti-IgA antibodies (risk of anaphylaxis), prior severe reaction to IVIG product, and caution with heart disease, renal impairment, thrombosis risk, or diabetes

SBI = serious bacterial infection; CI = confidence interval.

Perez EE, et al. *J Allergy Clin Immunol.* 2017;139(3S):S1-S46. Wasserman RL. *Immunol Allergy Clin North Am.* 2019;39(1):95-111. Wasserman RL, et al. *Immunotherapy.* 2022;14(4):215-224.

SCIG: Efficacy, Safety, and Usage

Efficacy

- Achieves comparable infection prevention, higher steady-state IgG, and better patient-reported outcomes vs IVIG
- Results in fewer breakthrough infections and improved QoL
- Recent trials and long-term cohort studies confirm excellent efficacy in adults and children with PI
- SBI rate: 0.11 events/patient-year (99% upper CI: 0.38); $p < 0.001$
- All infections: 2.04 events/patient-year (95% CI: 1.04-3.56)

Safety

- Adverse reactions are mainly mild, local (redness, swelling, itching, discomfort), and decrease over time with repeated administration
- Systemic adverse events are less frequent than with IVIG (1.9% vs 12.4%), and long-term safety is strong

Dosing

- SCIG typically given at 0.1-0.2 g/kg/week (or 0.4-0.6 g/kg/month divided) via subcutaneous infusions, often at home
- Dose titrated to maintain IgG trough > 500-700 mg/dL (or as appropriate)

Contraindications

- History of severe allergic reaction to immunoglobulin, poor skin integrity at sites, significant coagulopathy, or severe thrombocytopenia

QoL = quality of life.

Perez EE, et al. *J Allergy Clin Immunol.* 2017;139(3S):S1-S46. Wasserman RL. *Immunol Allergy Clin North Am.* 2019;39(1):95-111. Wasserman RL, et al. *Immunotherapy.* 2022;14(4):215-224.

fSCIG: Efficacy, Safety, and Usage

Efficacy

- Hyaluronidase-fSCIG 10% has shown equivalent efficacy to IVIG and SCIG in PI, with convenient dosing schedule (every 3-4 weeks) and successful self-administration (94.9% at home)
- Real-world and long-term trials confirm robust infection prevention and IgG maintenance in adults and children
- SBI rate: 0.04 events/patient-year (99% upper CI: 0.20); $p < 0.001$
- All infections: 3.12 events/patient/year (95% upper CI: 3.95)

Safety

- fSCIG shares local reaction profile with standard SCIG (redness, swelling), but enables larger volume infusions with few systemic events
- Adverse reactions diminish with repeated use; serious adverse events are rare
- Elderly and patients with risk factors (thrombosis, comorbidity) require monitoring; otherwise, safety profile is favorable

Dosing

- Typical dose is 0.3-0.6 g/kg every 3-4 weeks (same as IVIG)
- 1-2 sites per month
- Individual titration based on IgG trough and infection recurrence

Contraindications

- Severe reaction to hyaluronidase or immunoglobulin, advanced age/comorbidities with thrombosis risk, history of severe local hemorrhage, history of hypersensitivity, allergy to excipients

Perez EE, et al. *J Allergy Clin Immunol.* 2017;139(3S):S1-S46. Wasserman RL. *Immunol Allergy Clin North Am.* 2019;39(1):95-111. Wasserman RL, et al. *Immunotherapy.* 2022;14(4):215-224. Patel NC, et al. *J Clin Immunol.* 2025;45(1):81.

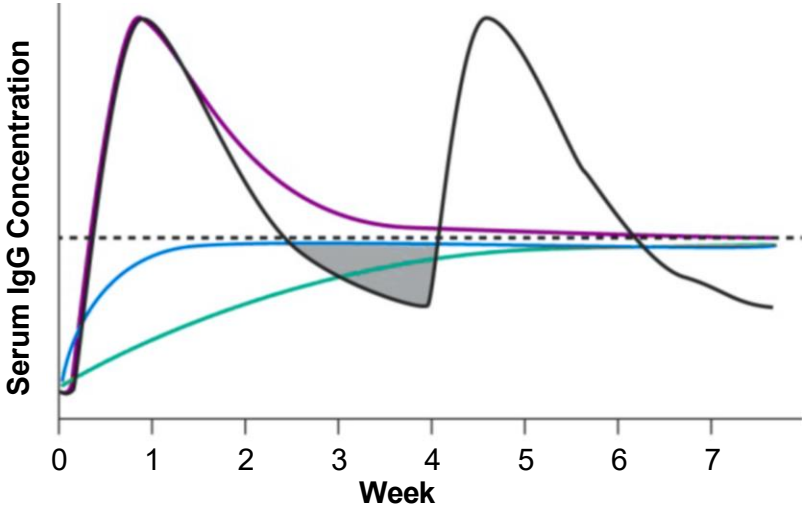
Advantages and Disadvantages: IV vs SC Immunoglobulin Therapy

	Advantages	Disadvantages
IVIG	• Less frequent infusions • Ability to give large volumes per infusion allows for intermittent dosing (every 21-28 days) • Rapid rise in IgG levels	• Travel to infusion centers • Home infusion possible, but demanding • Requires venous access and medical supervision during administration • Higher systemic side effects (e.g., nausea, headache, fatigue, fever = **"wear-off" phenomenon**)
SCIG	• Home-based flexibility and independence • Venous access not required • Steady IgG levels (avoids peaks/troughs) • Fewer side effects • Suitable for patients intolerant to IVIG	• Requires more frequent dosing • Multiple injection sites may be required • Local site reactions (e.g., redness, swelling, itching) • Self-infusion may require more patient involvement and training for adherence • Some equipment is complex • Loss of dexterity in elderly (prefilled syringes)

"Wear-off" refers to the decline of treatment effects toward the end of the dosing cycle (~3-4 weeks) due to ↓ in serum IgG levels

IDF. 2025. https://primaryimmune.org/understanding-primary-immunodeficiency/treatment/immunoglobulin-replacement-therapy. American Academy of Allergy Asthma & Immunology [AAAAI]. *Eight Guiding Principles for Effective Use of IVIG for Patients with Primary Immunodeficiency*. 2011. https://www.aaaai.org/Aaaai/media/Media-Library-PDFs/Practice%20Management/Practice%20Tools/IVIG-guiding-principles.pdf. Berger M. *Clin Immunol*. 2004;112:1-7.

The “Wear-Off” Effect of IVIG



Pharmacokinetic profile of IV and SC IgG administration illustrating the “wear-off” effect with IV administration

- IVIG
- Average daily IgG level with IVIG
- SCIG
- IVIG loading + SCIG maintenance
- Loading with SCIG
- Higher risk zone between two IVIG infusions

Jolles S, et al. *Biol Ther.* 2011;1(1):3.

Audience Response

Which of the following strategies is most effective for reducing Ig-associated adverse reactions during IVIG infusion?

A. Switch to another immunoglobulin product
B. Slow the infusion rate
C. Add high-dose corticosteroids
D. Start antibiotics
E. I don’t know

Considerations for IgRT in PI and SID

PI/IEI Category	IgRT	HSCT	Gene Tx
Antibody defects (agammaglobulinemia, CVID, others)	**YES**: Lifelong IgRT is standard of care for antibody deficiencies	No	No
CIDs/SCIDs (IL2RG, ADA, RAG1/2)	**YES**: Temporary IgRT while awaiting definitive therapy	Yes	Yes
Innate/signaling defects (NEMO deficiency, other NF-κB defects)	**YES**: But may be used conditionally, particularly if antibody defects coexist	Yes	No
Phagocytic defects (neutropenia, LAD, MSMD, CGD)	No	Yes	Yes: Indicated for CGD and LAD
Complement defects (C1q, C2, terminal C5-C9 deficiencies)	No	No	No
SID (drug-induced, malignancy, protein loss)	**YES**: Indicated when hypogammaglobulinemia + clinical infections coexist	Uncommon	No

Other Options*

- Antimicrobial prophylaxis
- Vaccines (avoid live vaccines in most patients with PI)
- Immunomodulators
- Enzyme replacement therapy

*Not currently FDA-approved for the treatment of PI. (Other options for comorbidities associated with PI may be FDA-approved in some cases.)

ADA = adenosine deaminase; CGD = chronic granulomatous disease; IL2RG = interleukin-2 receptor common gamma chain; LAD = leukocyte adhesion deficiency; MSMD = Mendelian susceptibility to mycobacterial disease; NF-κB = nuclear factor-kappa B; NEMO = nuclear factor-κB essential modulator; RAG1/2 = recombination-activating genes 1 and 2.

Bonilla FA, et al. *J Allergy Clin Immunol.* 2015;136(5):1186-205.e1-78.

IgRT Therapy: Considerations for Personalized Treatment Selection

	IVIG	SCIG	fSCIG
Who?	Indicated for adult and pediatric individuals with PI	Indicated for adult and pediatric individuals with PI	Indicated for adult individuals with antibody deficiencies
How?	Usually administered by a nurse	Self-administered	Either self-administered or given by a nurse
Where does it go?	Infused directly into the bloodstream intravenously	Infused or injected subcutaneously into the arms, belly, outer buttocks, or thighs	Infused subcutaneously into the belly, outer buttocks, or thighs
When?	Usually given every 3-4 weeks	Can be given on a flexible schedule from daily to every 2 weeks	Can be given every 3-4 weeks
How long?	Can take 2-6 hours to infuse	Can take 5 minutes to 2 hours to infuse or inject	Can take 1-2 hours to infuse
Where is it given?	At home, in a hospital, or an outpatient infusion center dependent upon insurance and patient preference	Usually administered in a home setting after the patient is trained to be independent	Can be infused at home (manual push or pump-assisted) or in an outpatient infusion center dependent upon insurance and patient preference
Side effects?	May be infusion rate-related and can be treated and prevented with medications prior to or after treatment	Skin can be red and irritated at the site of injections; this often improves with each injection	Skin may become red or irritated at the injection site, but this usually improves with each treatment; the larger volume of each injection can be visible under the skin and takes 2-3 days to absorb

IDF. 2025. https://primaryimmune.org/understanding-primary-immunodeficiency/treatment/immunoglobulin-replacement-therapy.

Switching Between IVIG and SCIG

Why Consider Switching?

From IVIG → SCIG

- "Wear-off" effect
- Systemic adverse events (headache, chills, fatigue) related to infusion rate or volume
- Venous access issues or home infusion preference
- Desire for steady-state IgG levels with fewer systemic peaks
- Improved convenience, flexibility, and independence

From SCIG → IVIG

- Inadequate disease control or frequent local reactions with SCIG
- Patient prefers less frequent infusions or simplified logistics
- Challenges with self-administration or multiple infusion sites
- Need for rapid IgG repletion (infection flare, acute setting)
- Preference for clinical supervision during infusions

The patient/caregiver experience is a KEY consideration!

Sil A, et al. *Front Pediatr.* 2024;12:1368755.

CMEO Snack

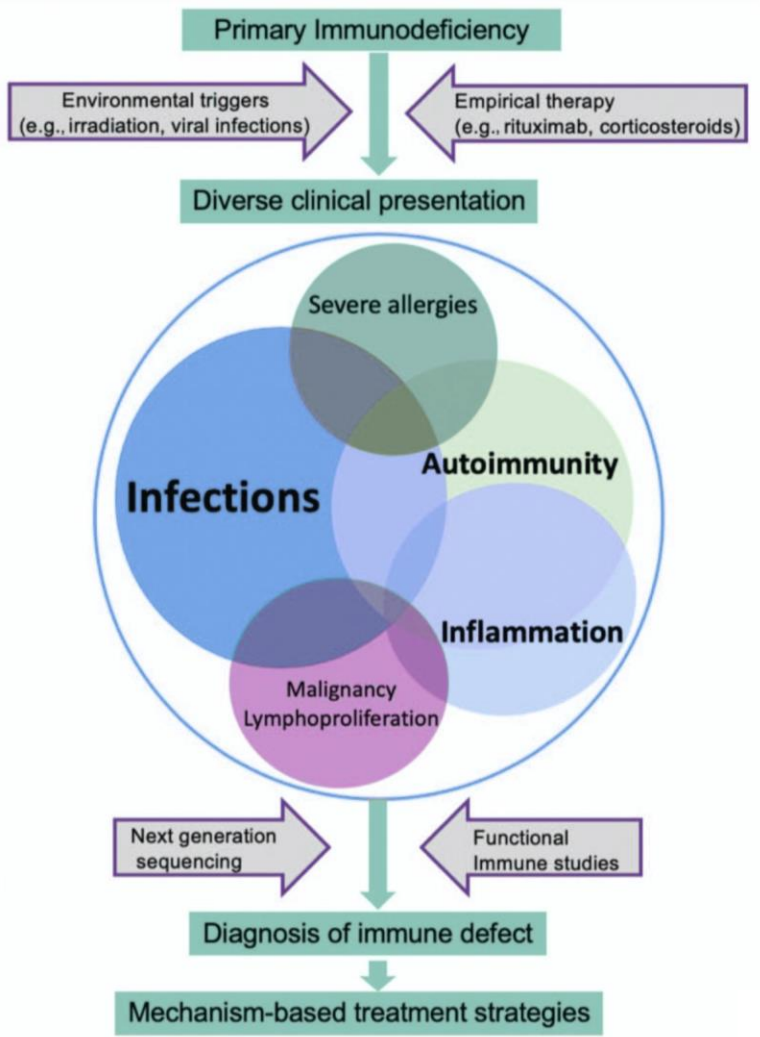
LEARNING OBJECTIVE 3

Implement multidisciplinary, team-based strategies and shared decision-making to optimize quality of care and outcomes for individuals with PI.

Interdisciplinary Management of PI

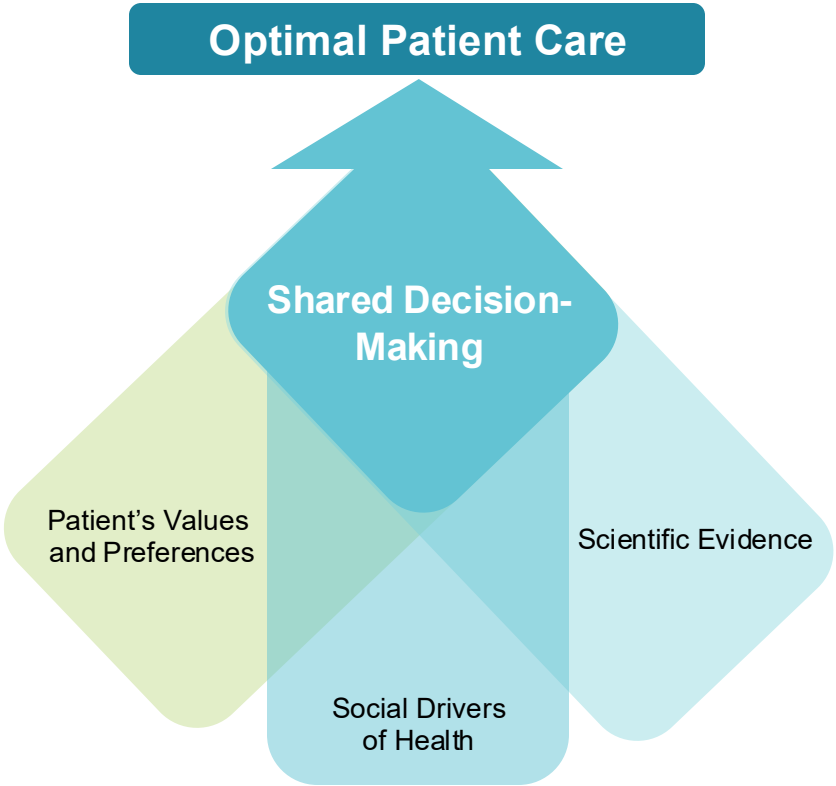
High Collaboration Amongst:

- Pediatricians
- Internists
- Hospitalists
- Relevant subspecialties:
  - Hematology
  - Infectious disease
  - Gastroenterology
  - Pulmonology
  - Rheumatology
  - Immunology



Walter JE, et al. *Curr Opin Pediatr.* 2019;31(6):851-862.

Shared Decision-Making (SDM) and the SHARE Approach



AHRQ. 2020. https://www.ahrq.gov/health-literacy/professional-training/shared-decision/tools/factsheet.html. Turkson-Ocran RAN, et al. *J Am Heart Assoc.* 2021;10:e018183.

Disparities and Social Drivers of Health (SDoH)

Factors to consider in SDM when discussing IgRT with patients/caregivers

Health literacy

- Limited understanding of PI and complications
- Medication nonadherence, reduced health care utilization

Financial resources

- Health care-related costs, inadequate access to health care and medical treatment, limited access to clinical trials

Social network

- Connectedness and social integration
- Digital health tools access
- Partner and caregiver support

Rurality and neighborhood

- Urban areas: higher environmental pollution
- Rural areas: transportation barriers, low-volume health care facilities, higher rates of un- or under-insured patients

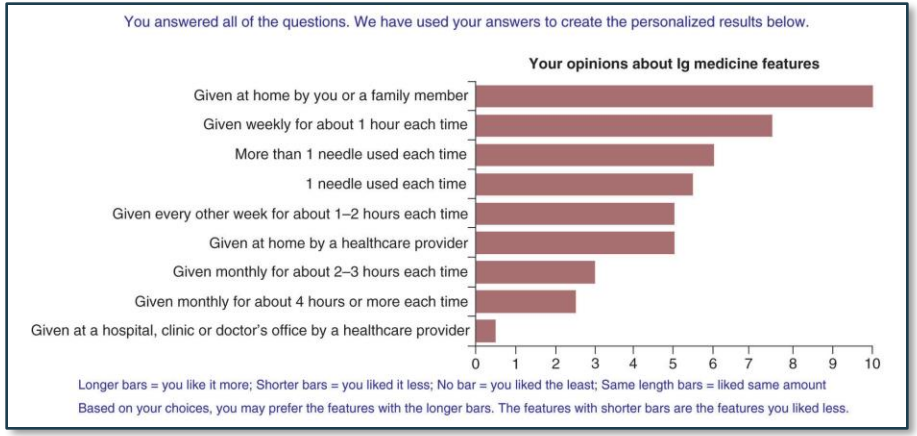
U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion. 2025. https://odphp.health.gov/healthypeople/priority-areas/social-determinants-health. Essien UR, et al. *Nat Rev Cardiol.* 2021;18(11):763-773.

Tools to Facilitate SDM for IgRT Treatment Selection

The tool uses **best-worst scaling** to help the patient/caregiver identify what features of the different modes of administration are **important** to the patient.

The patient/caregiver receives a **graphic output** of patient preferences.

I like this the most (please check one)	Things you could choose about the treatment	I like this the least (please check one)
	1 needle used each time	
	Given every other week for about 1–2 hours each time	
	Given monthly for about 2–3 hours each time	
	Given weekly for about 1 hour each time	
	Given at home by a healthcare provider	



Tzivelekis S, et al. *Immunotherapy.* 2023;15(9):647-656.

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Identify key benefits of newborn screening for PI and counsel families – especially those with a parental diagnosis – on current guideline-recommended testing and follow-up
- Identify typical and atypical presentations of PI in pediatric and adult populations
- Follow diagnostic pathways to confirm PI
- Utilize SDM approaches to treatment selection with consideration for patient/caregiver preferences, resources, access, and health literacy
- Evaluate and compare current IgRT strategies (IVIG, SCIG, fSCIG) for PI to guide individualized treatment choices and improve patient outcomes

PI Vigilance: Recurrent, Unusual, Persistent, Severe, Shared Infections

Do you have infections that are…

Recurrent: Keep coming back
Unusual: Caused by an uncommon organism
Persistent: Won't completely clear up or clears up very slowly
Severe: Requires hospitalization or intravenous antibiotics
Shared by family members: Others in the family have or have had a similar susceptibility to infection

Patient support:

What is PI?

Scan to learn more and get support.

Adapted from IDF. primaryimmune.org.

CME OUTFITTERS

Additional Resources

Visit www.cmeoutfitters.com for clinical information and certified educational activities

CME OUTFITTERS

Visit the

Immunodeficiency Disorders Hub

Free resources and education
for health care professionals and patients

https://www.cmeoutfitters.com/practice/primary-immunodeficiency-disorders-hub/

To Receive Credit

To receive CME/CE credit for this activity, participants must complete the post-test and evaluation online.

Participants will be able to download and print their certificate immediately upon completion.