Practical Updates in Primary Care

Primary Immunodeficiency: Streamlined Strategies for Timely Diagnosis, Optimal Treatment, and Improved Patient Outcomes

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Disclosures

- **Richard L. Wasserman, MD, PhD:** Consultant – Atheneum, Evolve Biologics, Gerson Lehrman Group, Grifols, Guidepoint Global, Third Bridge; Speaker's Bureau – EFACC, GSK, National Jewish Health; Advisory Board – GC Biopharma, Grifols, IgNS, Pfizer; Research Support – Takeda

Learning Objectives

Describe unmet needs in PID, as well as effective diagnostic strategies, evidence-based guidance, and best practices to reduce diagnostic delay and improve management of PID

Evaluate the latest safety and efficacy data associated with current and emerging evidence-based treatment options for PID

Assess strategies to improve care coordination among interprofessional team members to address healthcare disparities and optimize outcomes for patients with PID

PID = primary immunodeficiency.

Practical Updates in Primary Care

Patient AS – Medical History

- 23-year-old woman with CVID
- Infections began during the first year of life
- Multiple courses of antibiotics each year
- 7 episodes of X-ray-documented lobar pneumonia prior to CVID diagnosis
- Moderate to severe persistent asthma
- Diagnosis at age 13 after her 10-year-old brother was diagnosed

CVID = common variable immune deficiency.

PID Overview

- International Union of Immunological Societies (IUIS) 2024 Committee Report
  - Primary immunodeficiency (PID) now called inborn errors of immunity (IEI)
  - 10 major categories of IEI
  - 555 pathogenic mutations in 504 genes
- More than 2/3 of PIDs involve disorders of antibody production
- The prevalence of PID in the US may be as high as 1:1200
- >70% of patients with PID are undiagnosed
- The PID diagnostic odyssey averages 9-15 years
- ~75% of patients are diagnosed in adulthood

Poli MC, et al. *Human Inborn Errors of Immunity: 2024 Update on the Classification from the International Union of Immunological Societies Expert Committee*. Available at: https://wp-iuis.s3.eu-west-1.amazonaws.com/app/uploads/2025/01/08170257/IEI-Final-Update-of-2024-Report-Jan-2025.pdf. Rezaei N, et al. *Primary Immunodeficiency Diseases: Definition, Diagnosis, and Management*. 2nd ed. Springer; 2017. Boyle JM, Buckley RH. *J Clin Immunol*. 2007;27(5):497-502. Immune Deficiency Foundation. Accessed March 22, 2025. https://primaryimmune.org/advancing-pi-research-and-clinical-care/diagnosing-pi.

Why Is PID Diagnosis Delayed; Often Missed?

- PID comprises dozens of phenotypes and >500 genotypes
  - Each PID phenotype, considered separately, is rare and not thought of
  - Taken collectively, PID prevalence is comparable to well-recognized diagnoses
    - Cystic fibrosis, sickle cell disease, hemophilia

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  - Tests of immunocompetence are hard to order
  - Test results take a long time to come back
  - Immunologic testing is costly

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- Healthcare disparities present significant barriers to PID diagnosis
  - Racial barriers to genetic testing persist even when testing is done at no charge
  - Disparities have been identified in access to diagnosis, specialty care, and treatment of PID

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Diagnostic History and Physical Exam of PIDs

- Patient infection history
  - Frequency
  - Location
  - Persistence
  - Response to treatment
  - **Is the infection history out range for your patient population?**
- Co-morbidities
  - Atopic conditions
  - Autoimmune diatheses
  - Malignancy
- Family history
  - Consanguinity, infections, atopy, autoimmunity, malignancy
- Physical examination is often normal

Red Flags for PID

Mandates Laboratory Testing

- One episode
  - Vaccine-preventable disease
  - Pneumocystis jirovecii
  - Serratia marcescens
  - Periodontal disease in a pre-teenager
  - Liver or brain abscess
  - Disseminated/CNS Neisseria
- Multiple episodes
  - Lobar pneumonia
  - Giardia lamblia

Testing Will Be Normal or Negative

- Recurrent viral upper respiratory tract infections – colds
- Recurrent tonsillitis or pharyngitis – strep throat or viral
- Wheezy bronchitis or pneumonia – asthma
- Chronic rhinitis – allergy or non-allergic rhinitis
- Recurrent urinary tract infections – usually a structural problem

CNS = central nervous system.

Jeffrey Modell Foundation

10 Warning Signs of Primary Immunodeficiency

Primary Immunodeficiency (PI) causes children and adults to have infections that come back frequently or are unusually hard to cure. 1:500 persons are affected by one of the known Primary Immunodeficiencies. If you or someone you know is affected by two or more of the following Warning Signs, speak to a physician about the possible presence of an underlying Primary Immunodeficiency.

1. Four or more new ear infections within 1 year.
2. Two or more serious sinus infections within 1 year.
3. Two or more months on antibiotics with little effect.
4. Two or more pneumonias within 1 year.
5. Failure of an infant to gain weight or grow normally.
6. Recurrent, deep skin or organ abscesses.
7. Persistent thrush in mouth or fungal infection on skin.
8. Need for intravenous antibiotics to clear infections.
9. Two or more deep-seated infections including septicemia.
10. A family history of PI.

10 FOR ADULTS Warning Signs of Primary Immunodeficiency

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1. Two or more new ear infections within 1 year.
2. Two or more new sinus infections within 1 year, in the absence of allergy.
3. One pneumonia per year for more than 1 year.
4. Chronic diarrhea with weight loss.
5. Recurrent viral infections (colds, herpes, warts, condyloma).
6. Recurrent need for intravenous antibiotics to clear infections.
7. Recurrent, deep abscesses of the skin or internal organs.
8. Persistent thrush or fungal infection on skin or elsewhere.
9. Infection with normally harmless tuberculosis-like bacteria.
10. A family history of PI.

Jeffrey Modell Foundation. Accessed March 29, 2025. https://info4pi.org/library/.

Laboratory Evaluation for PID

About 80% of PIDs involve disorders of antibody production	
Identifying disorders of antibody production	Quantitative immunoglobulins; IgA, IgG, IgM vs age-related normals Quantitating anti-protein and anti-carbohydrate vaccine responses
T-cell and combined immunodeficiencies	Quantitate peripheral blood lymphocyte subsets Measure *in vitro* responses to mitogens and antigens
Phagocytic cell disorders	CBC Oxidative burst
Complement defects	CH_{50} – classical pathway components AH_{50} – alternate pathway components

CBC = complete blood count.

Kobrynski L, et al. *J Clin Immunol*. 2014;34(8):954-961.

Why Do Genetic Testing for PID?

- Provides a diagnosis, particularly if the presentation is atypical
- Predicts problems that have yet to be expressed
- Leads to precision management not previously considered
- May identify undiagnosed family members
- Informs genetic counseling, prenatal/preimplantation diagnosis, and preconception carrier testing
- Concludes the diagnostic odyssey

- Genetic testing will provide a diagnosis in about 30% cases
- The yield of genetic testing improves significantly if there is consanguinity

Heimall JR, et al. *J Clin Immunol*. 2018;38(3):320-329. Al-Herz W, et al. *Front Immunol*. 2019;9:3146. Chinn IK, et al. *J Allergy Clin Immunol*. 2020;145(1):46-69.

Routinely Available Genetic Testing Methods

Type	Description
Sanger “direct” sequencing	Useful when the family variant is known
Gene panels	Rapid, low-cost, most commonly used
Whole exome sequencing (WES)	Detects coding region variants only
Whole genome sequencing (WGS)	Use when WES is negative and a defect is highly suspected
Copy number variant analysis	Karyotype, FISH, CMA (CGH, SNP chip), structural variants

FISH = fluorescence in situ hybridization; CMA = chromosomal microarray analysis; CGH = comparative genomic hybridization; SNP = single nucleotide polymorphism.

Stray-Pedersen A, et al. *J Allergy Clin Immunol*. 2017;139(1):232-245. Chinn IK, Orange JS. *Expert Rev Clin Immunol*. 2020;16(9):897-909. Heimall JR, et al. *J Clin Immunol*. 2018;38(3):320-329. Meienberg J, et al. *Hum Genet*. 2016;135(3):359-362. Levy B, Burnside RD. *Prenat Diagn*. 2019;39(3):157-164.

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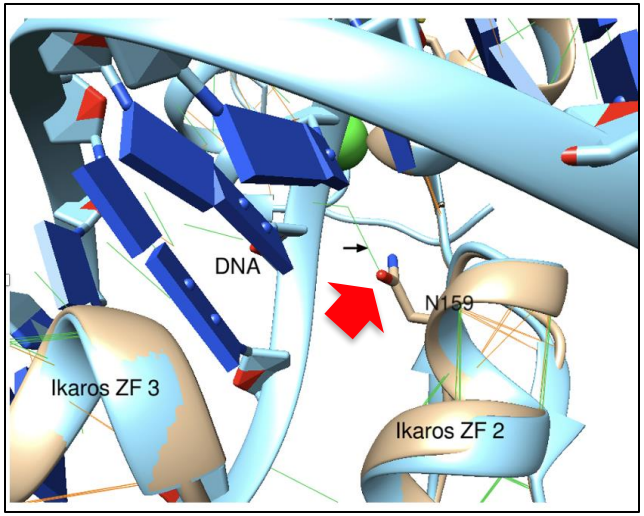
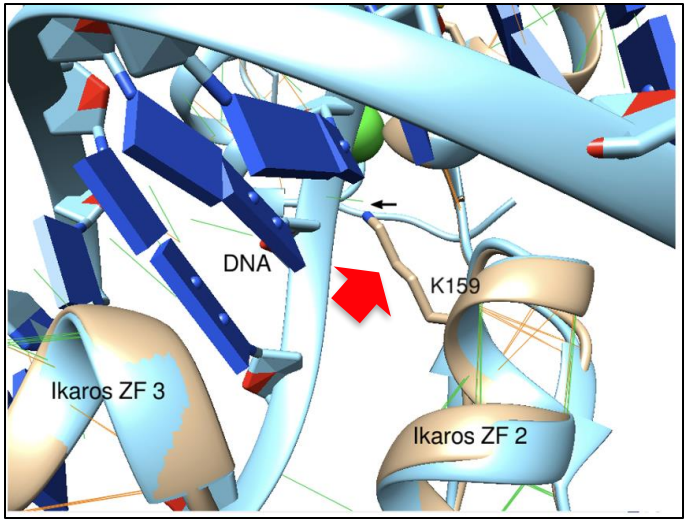
Patient AS



Wild Type



Patient AS

Ikaros mutation present in the patient, her sibling, and her father

Available and Emerging Treatment for PIDs

- Immunoglobulin replacement therapy (IgRT)
  - Intravenous immunoglobulin (IVIG)
  - Subcutaneous immunoglobulin (SCIG)
  - Hyaluronidase-facilitated SCIG (fSCIG)

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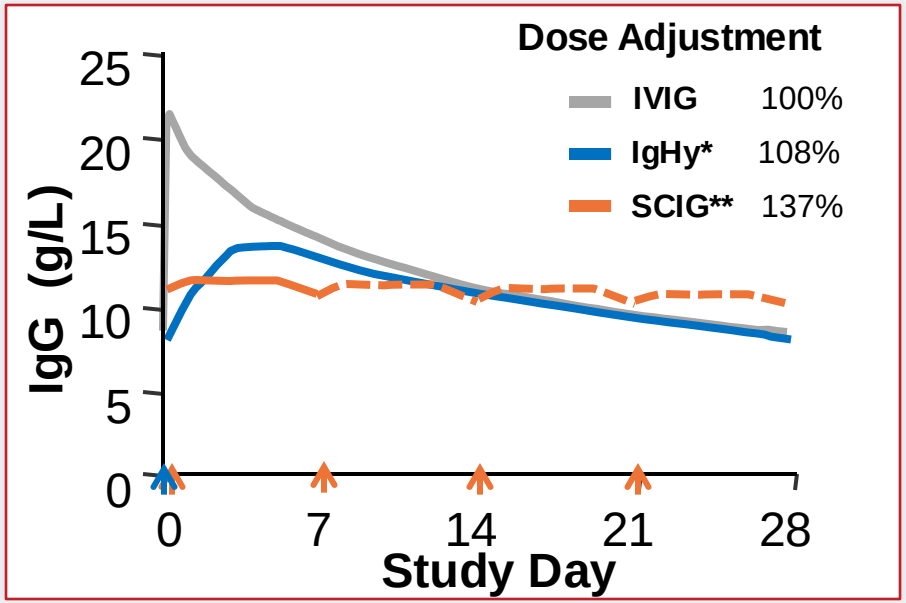
- Gene therapies in clinical trials
  - X-linked SCID
  - Adenosine deaminase (ADA) deficiency SCID
  - Wiskott-Aldrich syndrome
  - Chronic granulomatous disease (CGD)

SCID = severe combined immunodeficiency.

IgG Levels by Mode of Administration

- IVIG
  - High initial peak
  - Redistribution
  - Catabolism
- Conventional SCIG
  - No high peak
  - Re-dosed before a significant fall
- fSCIG
  - Enzyme-facilitated subcutaneous
  - Shoulder instead of a peak
  - Redistribution and catabolism like IVIG



***108% was considered bioequivalent per FDA guidance (interval should fall within a bioequivalence limit, usually 80-125%); **IVIG and IgHy data at 28-day dosing interval. SCIG data at 7-day dosing interval. SCIG dotted line shows weekly dose extrapolated over 21 additional days.**

Wasserman RL, et al. *J Allergy Clin Immunol*. 2012;130(4):951-957.e11. FDA. *Guidance for Industry: Statistical Approaches to Establishing Bioequivalence*. January 2001. Available at: https://www.fda.gov/media/70958/download.

Modes of IgG Administration

Attribute	IVIG	Conventional SCIG	IgHy
Infusion frequency	Every 3-4 weeks	Daily to biweekly	Every 3-4 weeks
Treatment options	Medical supervision Venous access	Self-infusion No venous access	Self-infusion or HCP No venous access
Relative dose	100%	137% of IV	100%
Sites / month	1	2-16	1-2
Infusion time	2-4 hours	1 hour	1-2 hours
Systemic AEs	3-15%	<1%	~7%
Local AEs	Very uncommon	Very common	Very common

AEs = adverse events.

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. FDA. Accessed March 29, 2025. https://www.accessdata.fda.gov/scripts/cder/daf/.

IgRT Adverse Events

Safety – Serious Adverse Events	Tolerability – "Rate-Related" AEs
• Renal failure – Carbohydrate-containing products – Risks – age, renal compromise, diabetes • Thrombosis – Activated factor 11 contamination – Risks – age, previous thrombotic event, thrombophilia, hyperviscosity • Hemolysis – anti-A and anti-B titers • Aseptic meningitis – history of migraine • TRALI – rare, no known risk factors	• Causes – hypothetical – High IgG peaks – Chronic bacterial colonization • Most common – migraine headache, myalgias, malaise, fatigue • Less common – fever, diarrhea, rash, cough, chest tightness, sinus tenderness • More frequent on the first or second infusion or after a hiatus in treatment

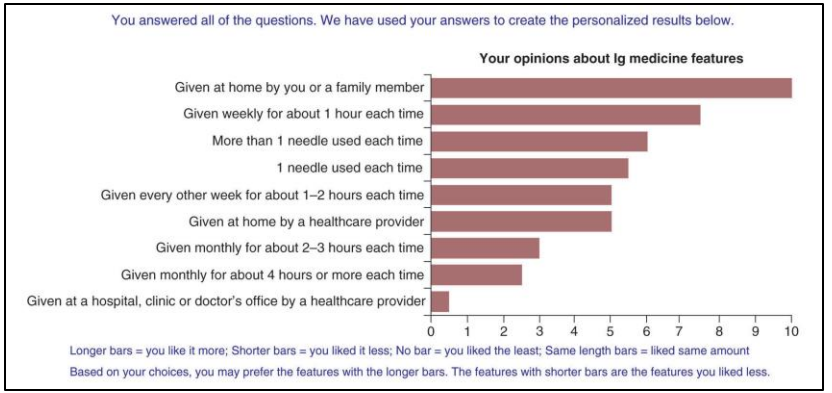
TRALI = transfusion-related acute lung injury.

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.

Shared Decision-Making Aid for IgRT Choices

- The tool uses best-worst scaling to help patients identify what features of the different modes of administration are important to them
- Patients receive a graphic output of their 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.

AS – Burdens of Disease before Diagnosis

- Frequent infections
- Never acquired a sense of what is normal – sword of Damocles
- Infections are painful, pneumonia, cough, sinusitis, otitis
- Chronically fatigued between infections
- “At any given time, there was always something going on”
- Frequent illnesses result in a loss of resiliency
  - “Minor” problems have an exaggerated effect
  - Often difficult to distinguish minor from major problems
- Unable to conduct the “business” of being a child – school, sports, social activities

Burdens of Disease after Diagnosis

- Despite appropriate therapy, infections occur
- Residual end-organ damage – bronchiectasis, chronic sinusitis
- Immunoglobulin replacement therapy
  - Long term – “basically, it’s for life”
  - IgRT takes time no matter how you do it
  - IgRT side effects
- Risk of co-morbid conditions
- Psychologic impact
  - Having a chronic illness
  - Having an antibody deficiency
  - Requiring a parenteral therapy indefinitely

Burdens of Care – Immunoglobulin Replacement

Non-Medical Burdens

- Arranging one's schedule around infusions
  - Travel, parking, etc at the infusion center
  - Regularly having a stranger in the home
- Frequent infusions
- Limitations on travel
- Financial access to treatment
  - Insurance coverage
  - Co-pays
  - Step care/formularies
  - Insurance transitions

Medical Burdens

- Needle sticks
- Local adverse events
- Systemic adverse events
- Serious adverse event risks
- Effect of IVIG on veins or SCIG on skin

Multidisciplinary Team Care

- The care of patients with PID often requires multiple specialties in addition to primary care
  - Because most physicians are unfamiliar with PID, the immunologist should be the “Captain of the Ship”
  - Good communication among collaborating physicians is crucial

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- In a practice setting, the team is usually the doctor and the nurse
  - Nurses play key roles in care of patients with PID – Immunoglobulin Nursing Society
    - Education about PID – Immune Deficiency Foundation resources
    - Education about treatment – teaching self-administration
    - Administering IVIG
    - Patient assessments – patients tell nurses about problems they may not tell doctors

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- Transitions of care
  - Institutions will often segregate patients by age
  - Most immunologists in practice take care of "children of all ages"

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Patient AS Outcomes

- Failed fSCIG because of needle phobia
- IgRT by IVIG every 3 weeks
  - Intermittent post-infusion migraine
  - No end-of-cycle deterioration
  - Needle phobia improved but still a problem
- No hospitalizations, no pneumonias, antibiotics <once/year
- No autoimmunity, no malignancy, normal PE, chronically fatigued
- No need for asthma controller medications
- Graduated from high school and college, starting grad school
- Socially active
- Distrustful of the medical system

PE = physical exam.

Key Learning Points

- Primary immunodeficiencies, taken as a group, are as prevalent as more commonly recognized disorders such as cystic fibrosis or hemophilia
- Any patient with an infection history out of the standard range for your practice should be evaluated for primary immunodeficiency
- Simple, inexpensive testing (CBC, IgA, IgG, IgM) will identify the majority of immunodeficiencies
- There are many treatments available for PID, from IgG supplementation to gene therapy
- The mode of IgG replacement should be chosen based on shared decision-making
- Delivering appropriate treatment employing a team-based approach can lessen the burden of disease and mitigate the burden of care