Primary Immunodeficiency in Pediatric Care:

When It's More Than "Just an Infection"

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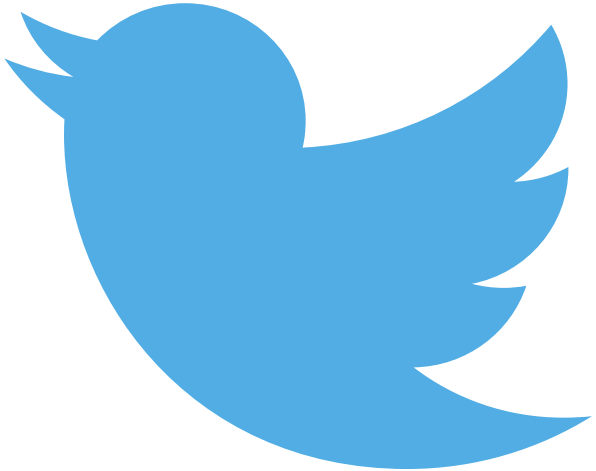
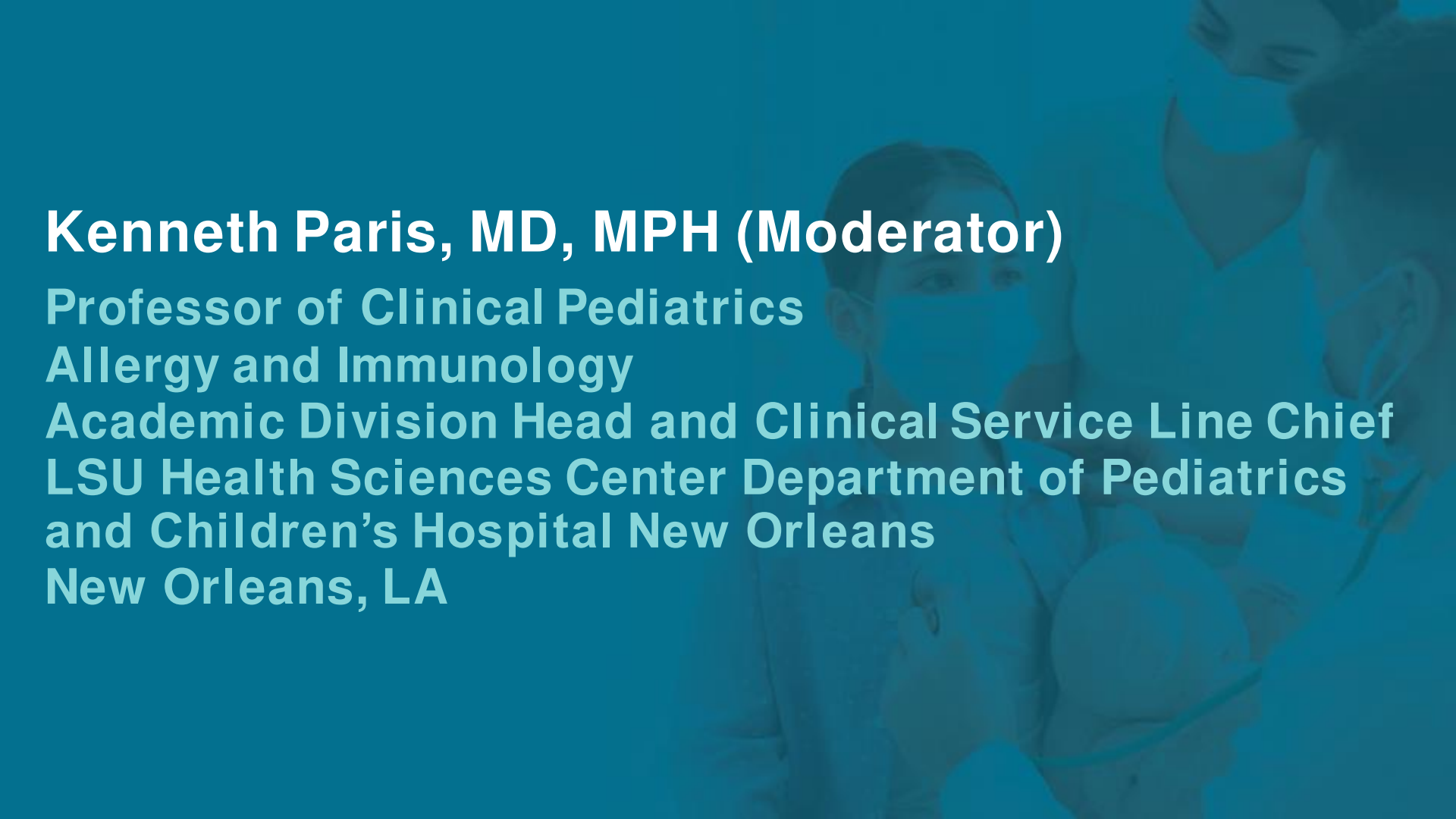




Kenneth Paris, MD, MPH (Moderator)

Professor of Clinical Pediatrics
Allergy and Immunology
Academic Division Head and Clinical Service Line Chief
LSU Health Sciences Center Department of Pediatrics
and Children's Hospital New Orleans
New Orleans, LA

Kristin Epland, MSN, FNP-C

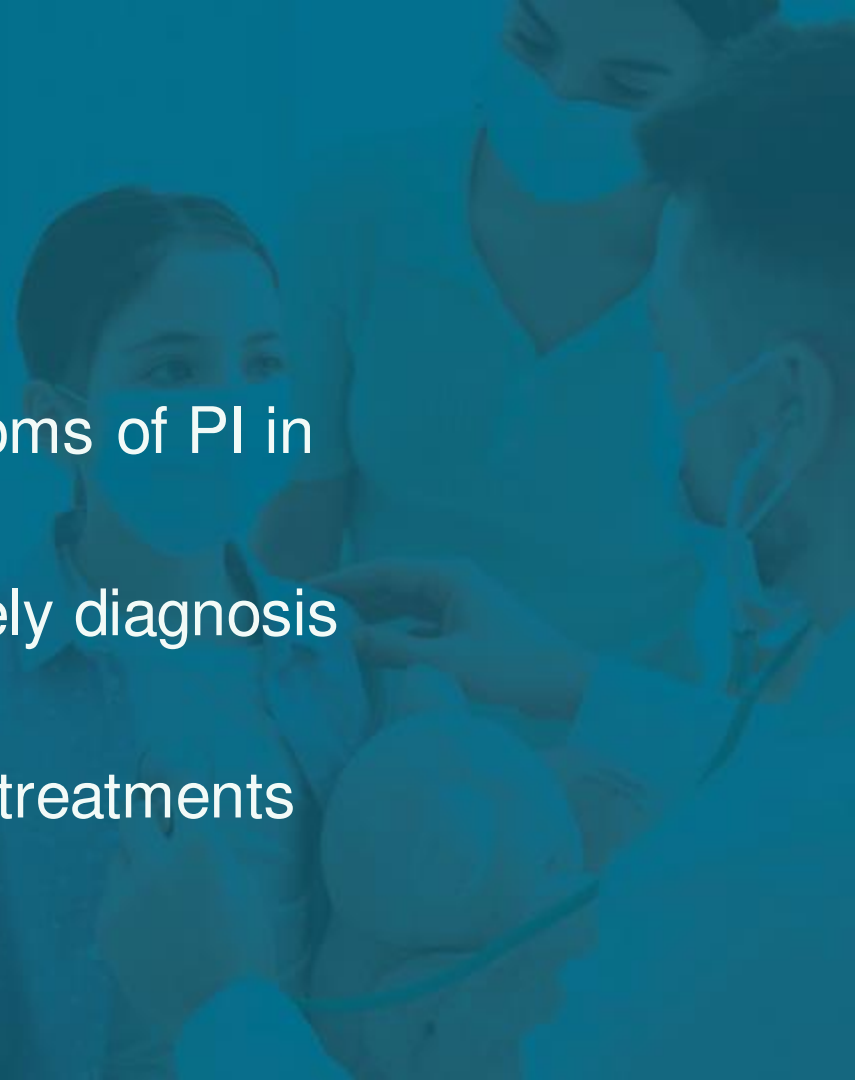
Family Nurse Practitioner
Infectious Disease Associates, PLLC
Minneapolis, MN

Hey Jin Chong, MD, PhD, FAAAAI

Division Director, Allergy & Immunology
Medical Director, Inborn Errors of Immunity Clinic
Associate Professor of Pediatrics
UPMC Children's Hospital of Pittsburgh
Pittsburgh, PA

LEARNING OBJECTIVES

1. Assess the signs and symptoms of PI in pediatric patients
2. Implement strategies for timely diagnosis of PI
3. Incorporate evidence-based treatments for patients with PI



PI Overview

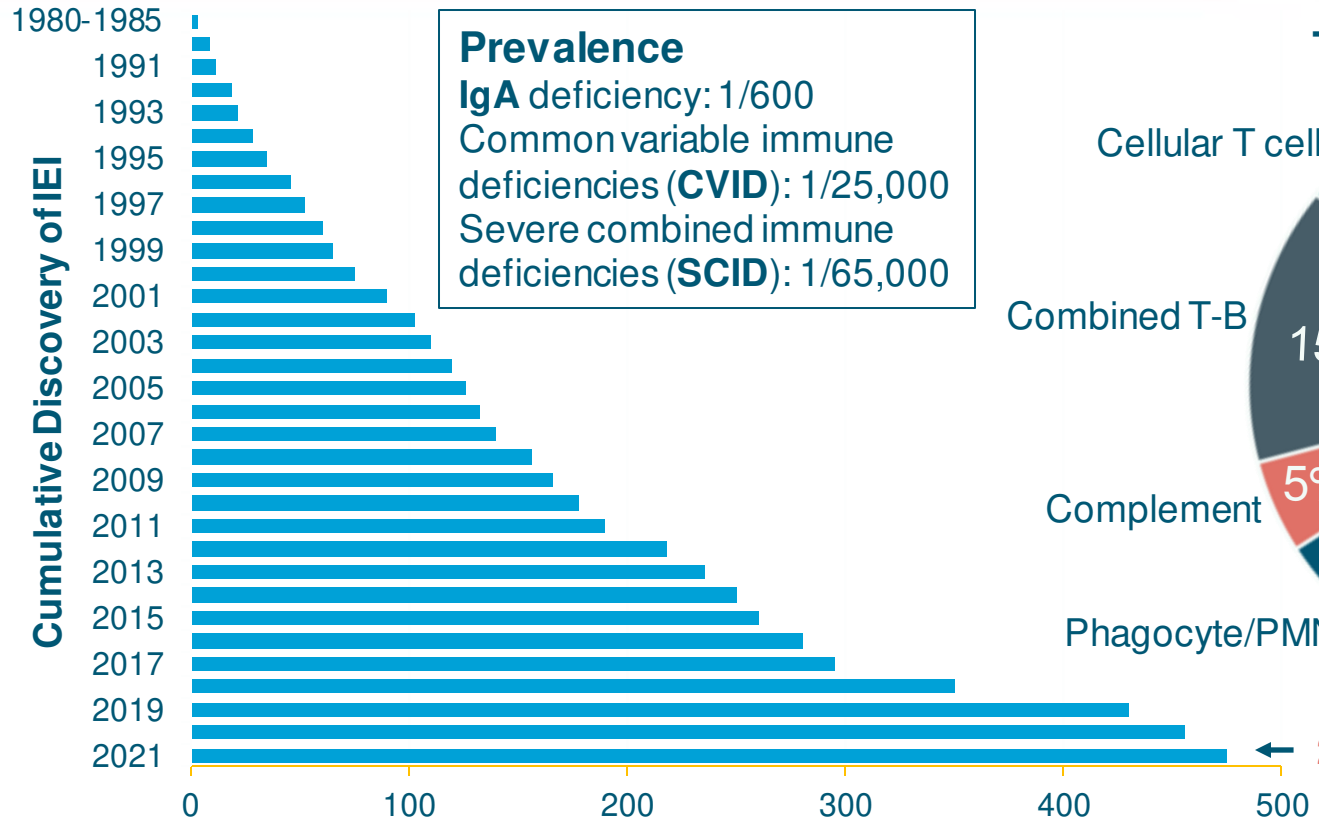
Kenneth Paris, MD, MPH

Primary Immunodeficiency

- Group of genetic disorders affecting development and function of the immune system
- Frequent, severe, and unusual infections
- Delayed diagnosis common (more so in underserved)
- Abbreviations:
  - **PI** (**P**rimary **I**mmunodeficiency)
  - **PID** (**P**rimary **I**mmuno**d**eficiency)
  - **PIDD** (**P**rimary **I**mmunodeficiency **D**isease)
  - **IEI** (**I**nborn **E**rrors of **I**mmunity)

Raje N, et al. *Immunol Allergy Clin North Am*. 2015;35(4):599-623. Kobrynski L, et al. *J Clin Immunol*. 2014;34(8):954-961.

Cumulative Discovery of IEI, Prevalence, and Types of Deficiencies

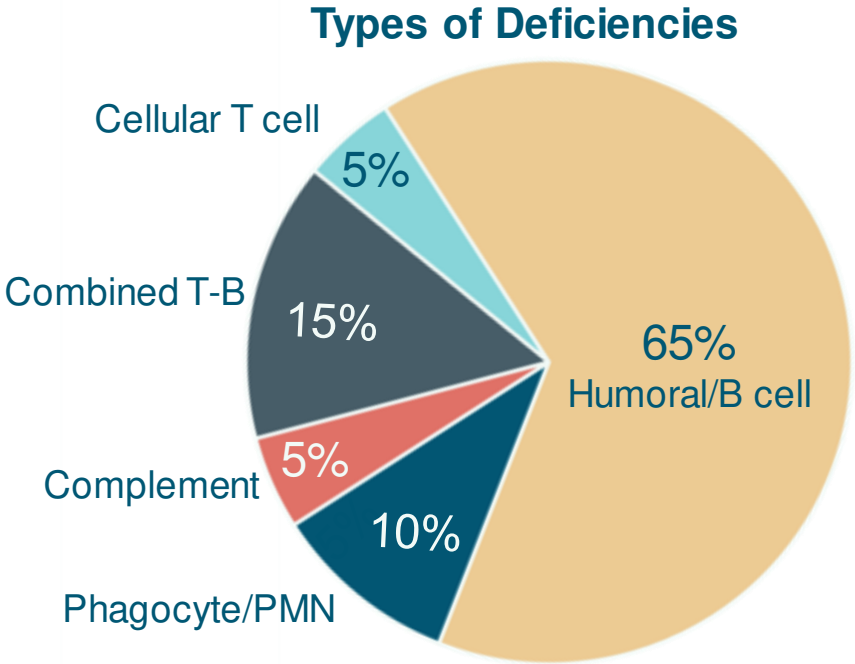


Prevalence

IgA deficiency: 1/600

Common variable immune deficiencies (**CVID**): 1/25,000

Severe combined immune deficiencies (**SCID**): 1/65,000



Tangye SG, et al. *J Clin Immunol*. 2022;42:1473-1508. Dorsey MJ, et al. *Immunol Allergy Clin North Am*. 2019;39(1):1-11.

Audience Response

According to the Jeffrey Modell Foundation guidance, which of the following is a warning sign for PI in pediatric patients?

A. ≥ 4 new ear infections in 1 year
B. ≥ 2 new ear infections in 1 year
C. 3 weeks of antibiotics with little effect
D. 1 sinus infection within 12 months
E. I'm not sure

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Audience Response

According to the Jeffrey Modell Foundation guidance, which of the following is a warning sign for PI in pediatric patients?

A. **≥ 4 new ear infections in 1 year**

B. ≥ 2 new ear infections in 1 year

C. 3 weeks of antibiotics with little effect

D. 1 sinus infection within 12 months

E. I'm not sure

LEARNING OBJECTIVE 1

Assess the signs and symptoms of primary immunodeficiency in pediatric patients

Kenneth Paris, MD, MPH

Diagnosing PI: Warning Signs

Jeffrey Modell Foundation. 2021. https://info4pi.org/library/educational-materials/.

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

Do you have infections that are...

Recurrent keeps coming back

Unusual caused by an uncommon organism

Persistent won't completely clear up or clears very slowly

Severe requires hospitalization or intravenous antibiotics

Shared by Family Members others in family have or have had a similar susceptibility to infection

Patient Support: Scan to learn more

Adapted from Immune Deficiency Foundation. primaryimmune.org; idf@primaryimmune.org

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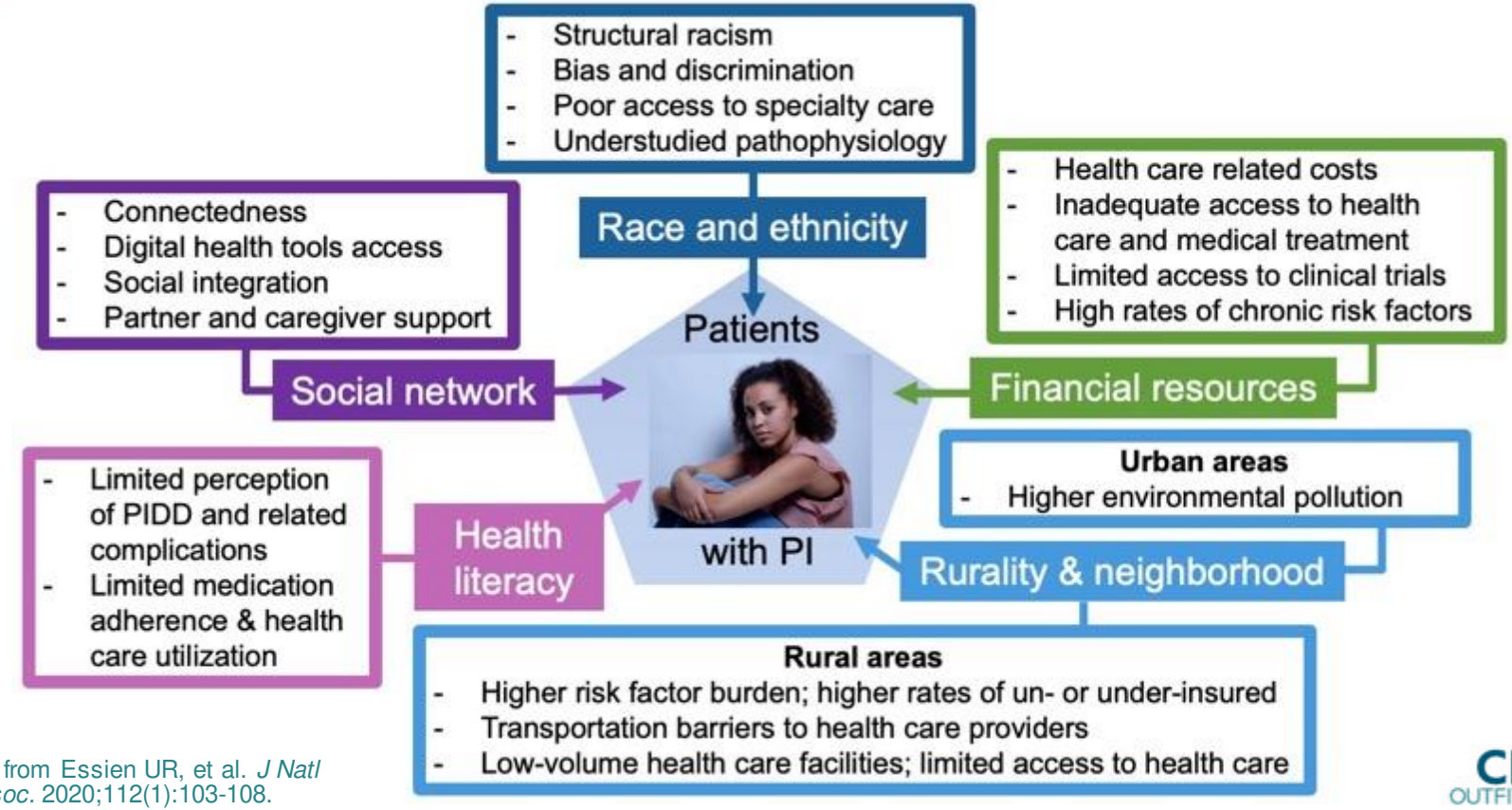
Racial, Ethnic, and Socioeconomic Disparities in the Diagnosis of PI

- Few studies address disparities in patients with PI
- Report by AAAAI Committee on Underserved:
  - Patients with private insurance in administrative databases → highest rates of PI diagnosis
  - White patients >2X more likely to be diagnosed with PI than Black or Hispanic patients
  - Under-representation among racial/ethnic underserved populations in clinical studies
- Important to assess patient social determinants of health (SDoH) to provide optimal, tailored care

AAAAI = American Academy of Allergy, Asthma & Immunology

Davis CM, et. al. *J Allergy Clin Immunol*. 2021;147(5):1579-1593.

Social Determinants of Health in PI



Adapted from Essien UR, et al. *J Natl Med Assoc*. 2020;112(1):103-108.

Audience Response

On average, how long does it take for PI to be properly diagnosed?

A. 5 years
B. 10 years
C. 15 years
D. 20 years
E. I'm not sure

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Audience Response

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A. 5 years

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D. 20 years

E. I'm not sure

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LEARNING OBJECTIVE 2

Implement strategies for timely diagnosis of primary immunodeficiency

Kristin Epland, MSN, FNP-C

The Long Road to Diagnosis

- IDF survey: on average, diagnosis of PI can take 15 years
- More than 50% of people are diagnosed > age 30
- In IDF survey, nearly half of respondents reported some type of functional impairment:
  - Chronic infection (bronchiectasis)
  - Autoimmune disease
  - Days in the hospital
  - Days missed from work or school

Immune Deficiency Foundation [IDF]. 2013 IDF National Immunoglobulin Treatment Survey. www.primaryimmune.org/sites/default/files/2013_IDF_National_Immunoglobulin_Treatment_Survey.pdf

Prompt Diagnosis Matters: Ilana's Story

- Ilana Jacqueline

- Patient Advocate and Author of *Surviving and Thriving with an Invisible Chronic Illness*
- 19 years waiting for a diagnosis of hypogammaglobulinemia
- www.IlanaJacqueline.com

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Initial Immune Evaluation: 4 Stages of Testing

- History and physical are essential in making the diagnosis
- Review growth parameters in children
- CBC with differential and serum immunoglobulins

1
- History and physical examination, height and weight
- CBC and differential
- Quantitative Immunoglobulin levels IgG, IgM, IgA (related to age)

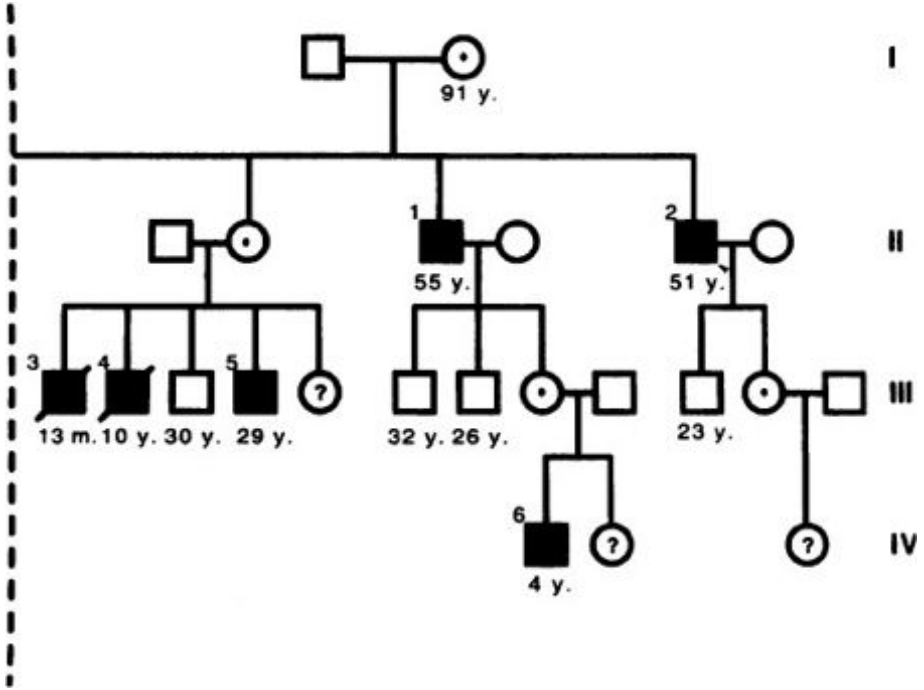
2
- Specific antibody responses (tetanus, diphtheria)
- Response to pneumococcal vaccine (pre/post) (for ages 3 and up)
- IgG subclass analysis

3
- Candida and Tetanus skin tests
- Lymphocyte surface markers CD3/CD4/CD8/CD19/CD16/CD56
- Mononuclear lymphocyte proliferation studies (using mitogen and antigen stimulation)
- Neutrophil oxidation burst (if indicated)

4
- Complement screening CH50, C3, C4
- Enzyme measurements (adenosine deaminase, purine nucleoside phosphorylase)
- Phagocyte studies (surface glycoproteins, mobility, phagocytosis)
- NK cytotoxicity studies
- Further complement studies AH50
- Neo antigen to test antibody production
- Other surface/cytoplasmic molecules
- Cytokine receptor studies
- Family/genetic studies

Jeffrey Modell Foundation. 2021. https://info4pi.org/library/educational-materials/.

Family History



Autoimmunity

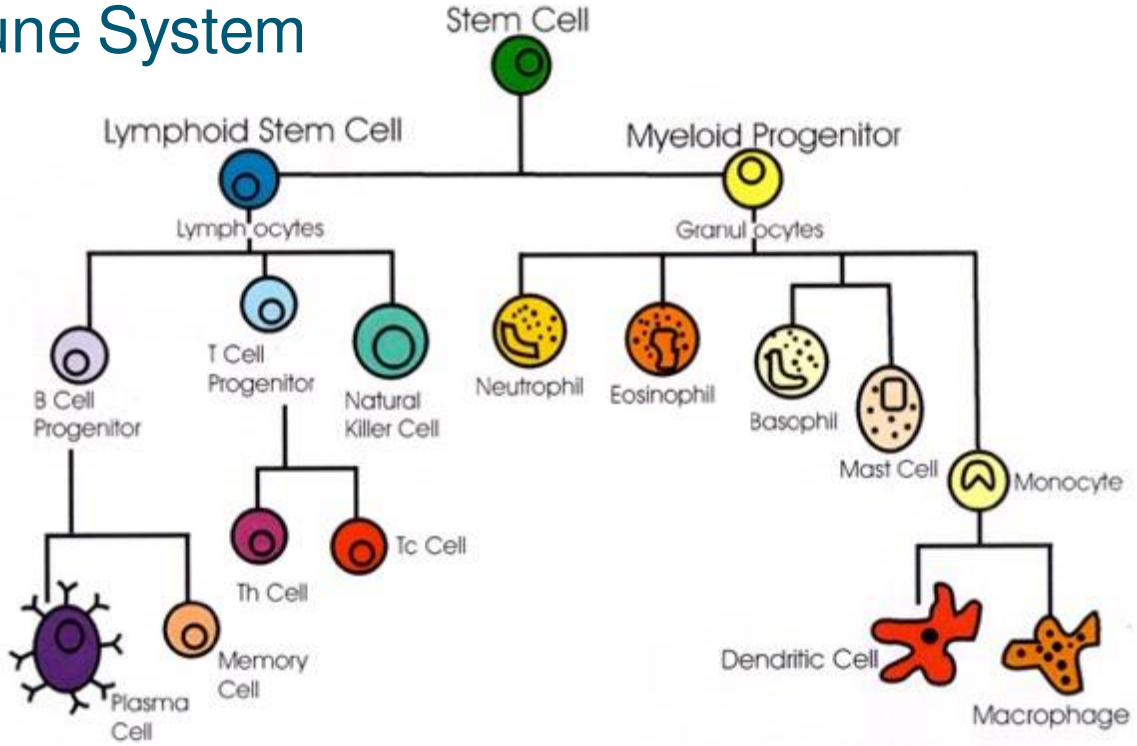
- Exclusively focusing on infection-centered warning signs **will miss ~25% of patients with PI** who initially present with other manifestations
- Most common autoimmune conditions: cytopenias, including immune thrombocytopenic purpura and hemolytic anemia
- Organ-specific autoimmune/inflammatory complications involve the gastrointestinal tract, skin, joints, connective tissue, and respiratory tract

Bastos S, et al. *Int J Mol Biol.* 2019;4(5):174-180.

Laboratory Analysis: Start with the Lymphocyte

Cells of the Immune System

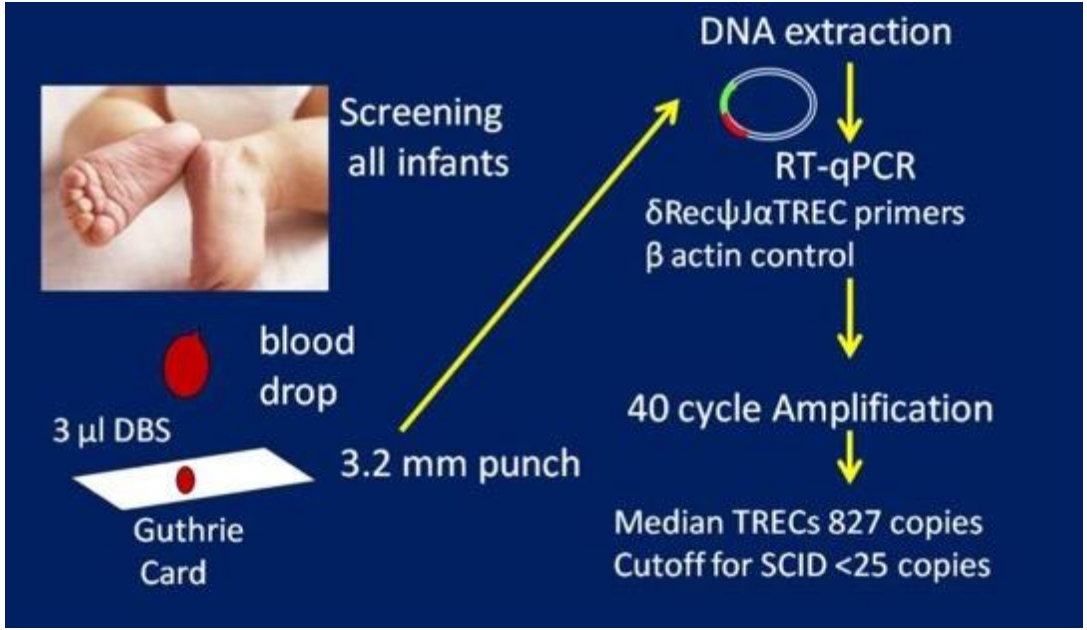
- **Test Cost: $20**



Adapted from Todar's Online Textbook of Bacteriology. https://textbookofbacteriology.net/adaptive_2.html.

T-Cell Receptor Excision Circle (TREC) Analysis

- Screening for SCID using TREC available in all 50 states
- Inexpensive assay effectively integrated into public health programs
- Without timely treatment, SCID is fatal, with exorbitant healthcare costs even in just 1 year of life



Cancer Therapy Advisor. 2017. https://www.cancertherapyadvisor.com/home/decision-support-in-medicine/pediatrics/scid-syndromes/

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Every Abnormal TREC is not SCID

- Other causes of positive SCID screening include:
  - Leaky SCID/Omenn syndrome
  - Prematurity
  - Trisomy 21
  - DiGeorge Syndrome
  - Idiopathic lymphocytopenia
  - Infants of mothers with immunosuppression
- Confirmatory tests are necessary with T and B lymphocyte and Natural Killer cell profile.
  - **Cost $698**

Cancer Therapy Advisor. 2017. https://www.cancertherapyadvisor.com/home/decision-support-in-medicine/pediatrics/scid-syndromes/

Screening Immunoglobulins

- **Immunoglobulin G (IgG):** most abundant type of antibody, found in all body fluids
- **Immunoglobulin A (IgA):** found in the mucous membranes (airway, GI tract, saliva, tears)
- **Immunoglobulin M (IgM):** found in blood and lymph fluid, first antibody made by the body to fight a new infection
- **Immunoglobulin E (IgE):** associated mainly with allergic reactions, found in lungs, skin, and mucous membranes

Test cost: $98

Justiz Vaillant AA, et al. Immunoglobulin. [Updated 2022 Nov 24]. In: *StatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2023. https://www.ncbi.nlm.nih.gov/books/NBK513460/

Pitfalls of Testing

- Reference ranges
  - Be aware that a normal Ig level for a 3-month-old is different than that for an 18-month-old
  - Quantitative deficiency does not mean a qualitative deficiency

Ig = immunoglobulin

Ludwig-Kraus B, et al. *J Clin Lab Anal.* 2017;31(6):e22146.

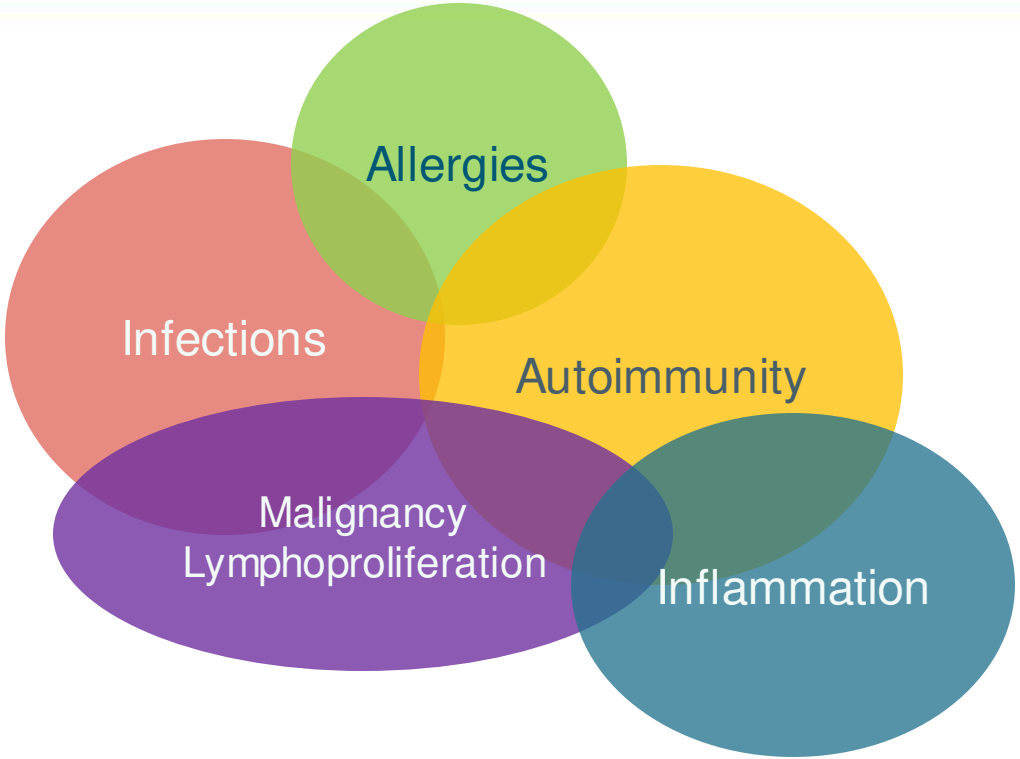
When to Refer to a Specialist

- Abnormal laboratory results
- Poor response to conservative management
  - Antibiotics
  - DMARDs
- Reproductive considerations
  - Genetics counseling

DMARDs = disease-modifying antirheumatic drugs

Bonilla FA, et al. *J Allergy Clin Immunol.* 2015;136(5):1186-1205.

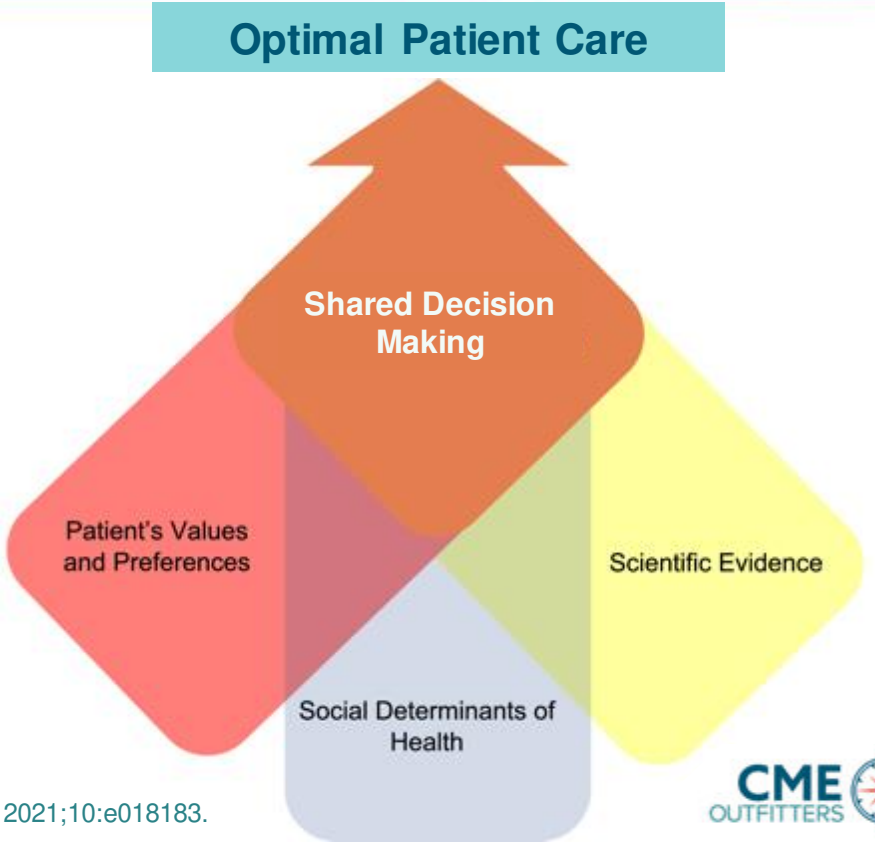
Interdisciplinary Management of PI



- Primary care
- Allergy/immunology
- Pulmonology
- Hematology
- Gastroenterology
- Infectious disease
- ENT
- Nutritionists/dieticians

Bonilla FA, et al. *J Allergy Clin Immunol.* 2015;136(5):1186-1205.

Shared Decision-Making and the SHARE Approach



AHRQ Publication 14-0034-1-EF. Turkson-Ocran R-A, et al. *J Am Heart Assoc.* 2021;10:e018183.

Audience Response

Which of the following IgRTs can be dosed in pediatric patients every 3-4 weeks?

A. IVIg
B. SCIg
C. fSCIg
D. IVIg and fSCIg
E. I'm not sure

fSCIg = hyaluronidase facilitated immunoglobulin; IgRT = immunoglobulin replacement therapy; IVIg = intravenous immunoglobulin; SCIg = subcutaneous immunoglobulin

Audience Response

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LEARNING OBJECTIVE 3

Incorporate evidence-based treatments for patients with primary immunodeficiency

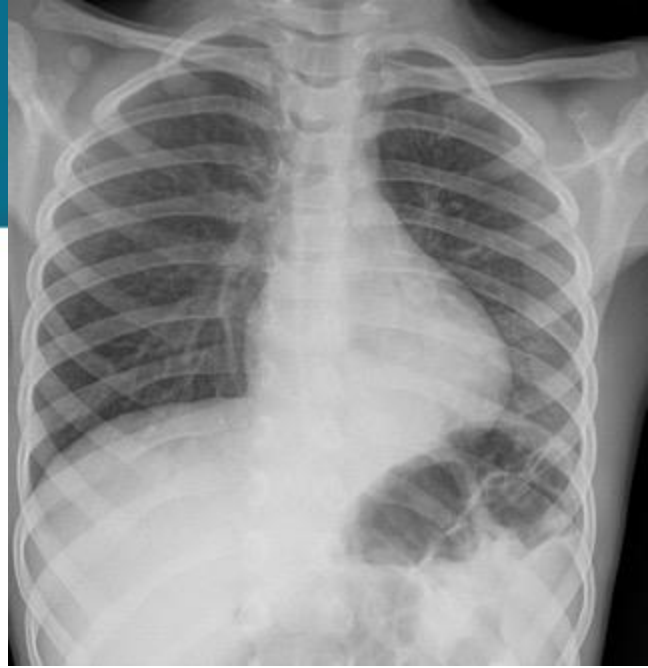
Hey Jin Chong, MD, PhD

Case Study: RS

- **17-year-old high school student**
- Lifelong history of pneumonias
- First few years of life: recurrent ear infections
- **At 6 years old** admitted to ICU with pneumonia
  - Required thoracoscopic decortication and pericardial window during this admission

Case Study: RS (cont'd)

- **Age 7**:
  - Direct laryngoscopy and bronchoscopy
  - Pus noted from trachea
  - Unable to be extubated; ventilation for 1 day
  - Chest x-ray consistent with left lower lobe pneumonia
  - Culture grew *Streptococcus pneumoniae*

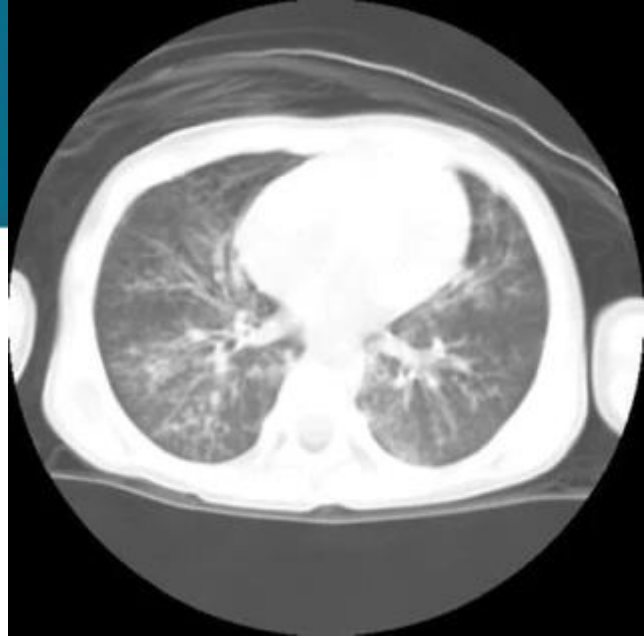


Left Lower Lobe Pneumonia at Age 7

Photo: McEniery J, Left lower lobe pneumonia. Case study, Radiopaedia.org. https://doi.org/10.53347/rID-76746.

Case Study: RS (cont'd)

- **Age 8:** Developed LLL and RUL PNA with reactive hilar and mediastinal adenopathy; no organism identified
- **Age 8-10:** Several (7-8) other CXR positive PNAs which would clear with antibiotics and recur within 1-2 months
- **Age 9:** Bronchiectasis on chest CT as well as restrictive airway disease on PFTs; chest physiotherapy, albuterol inhaler started
- **Age 10:** Referred to immunology; **started on IVIg** for recurrent infections and low pneumococcal titers; also **started on trimethoprim-sulfamethoxazole** for PJP prophylaxis due to severe T cell lymphopenia



Bronchiectasis on Chest CT at Age 9

CT = computed tomography; CXR = chest x-ray; LLL = left lower lobe; PFTs = pulmonary function tests; PJP = *Pneumocystis jirovecii* pneumonia; PNA = pneumonia; RUL = right upper lobe

Selecting Therapies for PI

	IgRT	HSCT	Gene Tx
Antibody Defects (agammaglobulinemia, others)	**YES**	No	No
CIDs (SCID [*IL2RG*, ADA])	**YES**	Yes	Yes
Innate Defects (NEMO deficiency, other NF-κB defects)	**YES**	Yes	No
Phagocytic defects (neutropenia, LAD, MSMD)	No	Yes	No
Complement defects	No	No	No

Other Options*

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

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

CIDs = combined immunodeficiencies; G-CSF = granulocyte colony stimulating factor; HSCT = hematopoietic stem cell transplantation; IFN = interferon; *IL2*RG = interleukin-2 receptor common gamma chain; IgRT = immunoglobulin replacement therapy; LAD = leukocyte adhesion deficiency; MSMD = Mendelian susceptibility to mycobacterial disease; NEMO = nuclear factor κB essential modulator; NF-κB = nuclear factor κB. Bonilla FA et al. *J Allergy Clin Immunol.* 2015;136(5):1186-205.

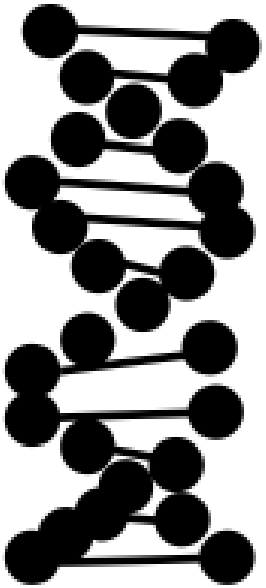
Patient Experience: IVIg, SCIg, fSCIg

Intravenous Immunoglobulin (IVIg)	Subcutaneous Immunoglobulin (SCIg)	Hyaluronidase Facilitated Immunoglobulin (fSCIg)
Indicated for adult and pediatric patients with PI	Indicated for adult and pediatric patients with PI	Indicated for adult and pediatric patients with PI **(new indication)**
Usually given every 3-4 weeks	Flexible schedule daily to every 2 weeks	Can be given every 3-4 weeks
Fewer needle sticks, less frequent	No need for venous access No wear-off effect Self administration Less/no pre-medication Fewer adverse effects Flexibility (dosing, frequency) Improved quality of life (QoL) Decreased healthcare costs	
Patient preference/comfort level 		

Epland K, Perez E. IDF Guide to Ig Therapy. https://primaryimmune.org/sites/default/files/publications/IDF%20Guide%20to%20Ig%20Therapy.pdf. U.S. Food and Drug Administration [FDA]. Prescribing Information (HYQVIA/Immune Globulin Infusion 10% [Human] with Recombinant Hyman Hyaluronidase) Solution, for subcutaneous administration. https://www.fda.gov/media/89844/download.

Enzyme Replacement Therapy (ERT)

- Approved therapy for ADA-SCID
- Adenosine deaminase: enzyme in the purine salvage pathway that modifies the DNA breakdown product deoxyadenosine into non-toxic deoxyinosine
- Treatment cost: up to $400,000/year
- Half of patients continue to need IgRT
- Despite low immune cells, patients tend to do well without infection



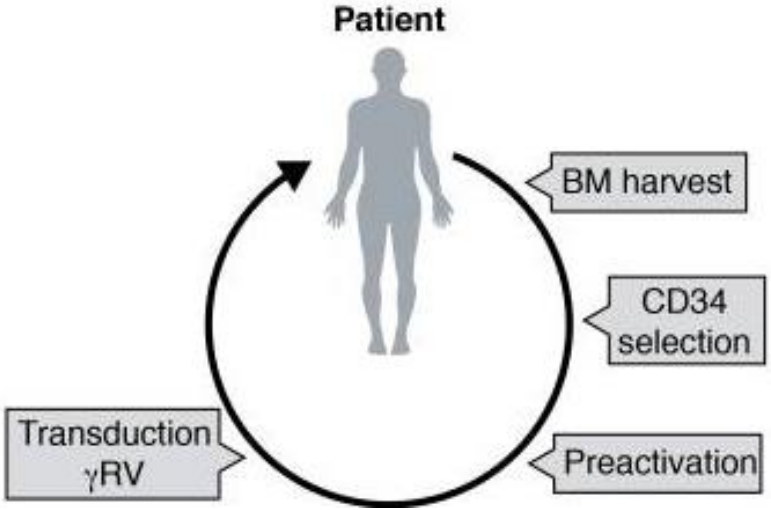
Ferrua F, Aiuti A. *Hum Gene Ther*. 2017;28(11):972-981. Markert ML, Hershfield MS, et al. *J Clin Immunol*. 1987;7(5):389-399. Hershfield MS. *Immunodeficiency*. 1993;4(1-4):93-97. Murguia-Favela L, et al. *Clin Exp Immunol*. 2020;200(2):176-184.

Gene Therapy

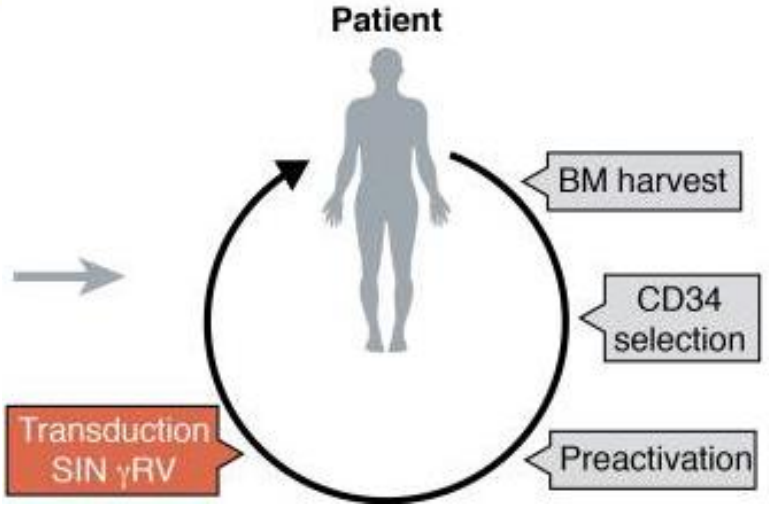
- Gene therapy for PI
  - SCID
  - Wiskott-Aldrich
  - Chronic granulomatous disease
  - Immune dysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome

Arlabosse T, et al. *J Allergy Clin Immunol Pract.* 2023;S2213-S2198(23)00403-9.

Gene Therapy: X-SCID



X-SCID gene therapy trials (20 patients) in Europe used gamma retroviral vectors: 6 patients developed leukemia (insertional oncogenesis)

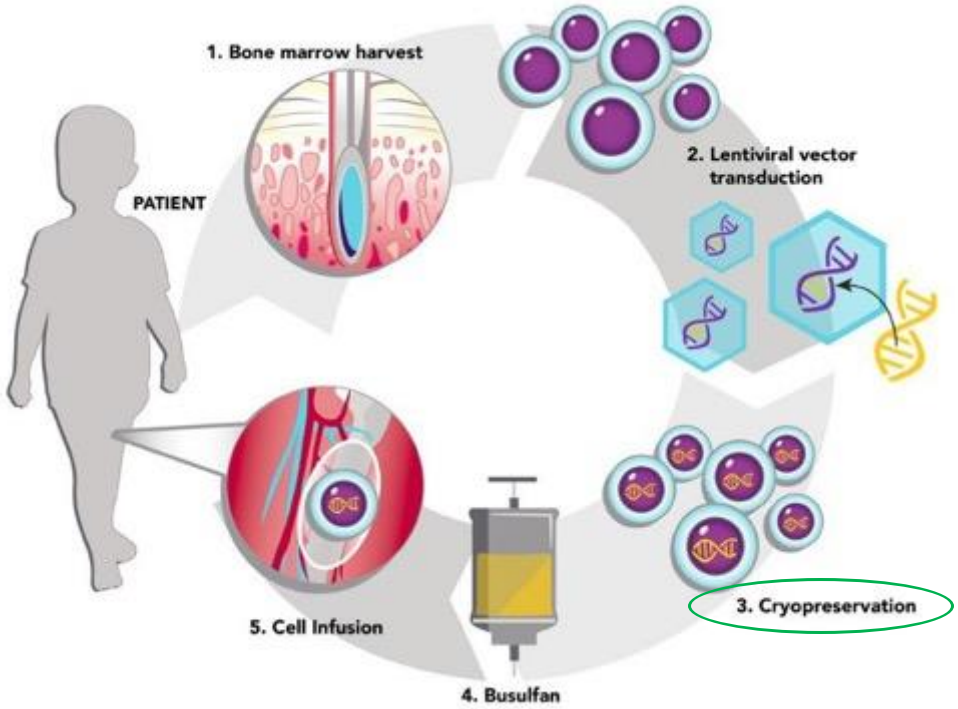


Gene therapy used **self-inactivating retroviral vectors (SIN)** – recent trials switched to SIN lentiviral vectors to be even safer

Fischer A, Hacein-Bey-Abina S. *J Exp Med.* 2020;217(2):e201. Kohn LA, et al. *Front Immunol.* 2021;12:648951.

Gene Therapy: X-SCID (cont'd)

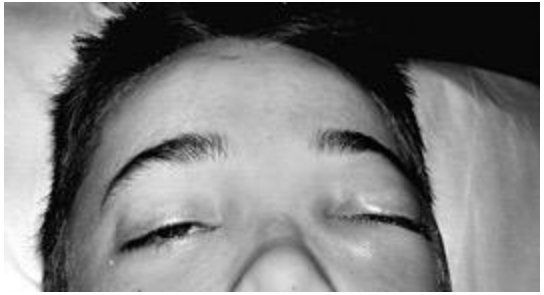
- Recent trials also cryopreserve cells, allowing for testing before re-introduction to patients, before being sent elsewhere; and to facilitate patient conditioning
- Ongoing research is promising



Kohn LA, et al. *Front Immunol.* 2021;12:648951.
Image: St. Jude Gene Therapy for X-Linked SCID. Ewelina Mamcarz, MD; Designer: Ashley Durand. www.stjude.org

Case Study: (cont'd) RS History After IVIg

- **Age 12:** normal mitogen response, persistent hyper IgM 574 and normalization of CH50, C4, but undetectable CS, C6
- **Age 13:** RS reports periorbital edema occurring in early June each year for several years; hospitalized for initial 3 infections and treated with IV antibiotics for 5 days, but no organisms ever grew
- **Age 15:** Appointment with ENT specialist – CT sinus showed chronic sinus disease; underwent successful sinus surgery, but symptoms continued to recur

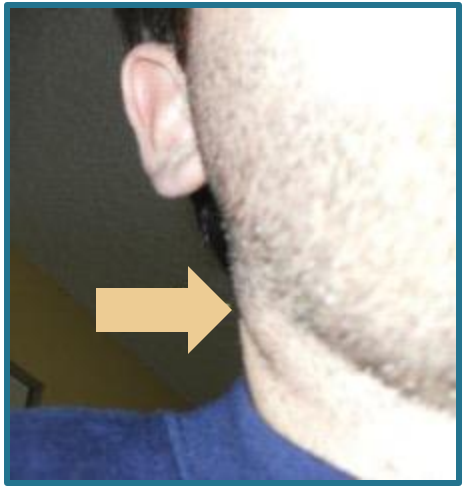


Periorbital Edema

ENT = ear, nose, and throat
Photo: Goodyear, P, et al. *Emerg Med J.* 2004;21:240-242.

Case Study: RS (History After IVIg)

- **Age 17**: Admitted 1 week for bilateral cervical lymphadenopathy of unknown etiology
- Biopsy showed reactive lymph node with follicular, paracortical, and sinus patterns, negative CMV, EBV, Bartonella, and negative bacterial cultures
- Imaging showed persistent cervical lymphadenopathy with suppuration, bronchiectasis, atelectasis/scarring in RLL/RUL/LUL, hepatosplenomegaly, bowel wall thickening in terminal ileum/cecum



Suppurative Cervical Lymphadenopathy

CMV = cytomegalovirus; EBV = Epstein-Barr virus; LLL = left lower lobe; RLL = right lower lobe
Photo: Hernandez M, et al. *J Am Osteopath Assoc*. 2011;111(1):49-51.

Case Study (cont'd): More History After IVIg

- What's unusual? Why is he different? Does he warrant further genetic testing? Why isn't this just CVID?
- Hyper IgM – cannot class switch
- Low complement does not fit CVID
- Severe lymphopenia not typical for CVID
- No more pneumonias (thanks IVIg!) but still having HSM, LAD

LAD = lymphadenopathy; HSM = hepatosplenomegaly

Case Study (cont'd): More History After IVIg

- What's unusual? Why is he different? Does he warrant further genetic testing? Why isn't this just CVID?
- Hyper IgM – cannot class switch
- Low complement does not fit CVID
- Severe lymphopenia not typical for CVID
- No more pneumonias (thanks IVIg!) but still having HSM, LAD
- Genetic testing is warranted
- Sent for whole exome sequencing (WES)

LAD = lymphadenopathy; HSM = hepatosplenomegaly

Case Conclusion: RS Responds to "Precision Medicine"

- WES reveals mutation in Pi3Kinase p110 delta gene
  - Diagnosis: Activated Pi3K delta syndrome (APDS)
- RS entered into clinical trial at NIH
  - Leniolisib/CDZ173 – small molecule inhibitor of Pi3K delta
  - Spleen decreased in size, no recurrence of periorbital swelling or LAD
  - Able to stop IgRT
  - Cough resolved
  - For the first time in his life, he walked 4 miles without stopping (while playing Pokemon Go)
  - RS says he "feels full of life" for the first time

Precision Medicine in PI

Primary Immunodeficiency	Gene Defect	Biologic
APDS (Activated PI(3)K delta syndrome)	PI3K (p110d) GOF	Leniolisib
CGD (Chronic granulomatous disease)	CYBB (gp91^{phox})	ɣ-interferon
CTLA-4 (Cytotoxic lymphocyte antigen 4) haploinsufficiency	CTLA4	Abatacept
LAD1 (Leukocyte adhesion deficiency 1)	ITGB2	Ustekinumab
LRBA (Lipopolysaccharide-responsive and beige-like anchor)	LRBA	Abatacept
STAT 1 GOF (Signal transducer and activator of transcription 1)	STAT1	Ruxolitinib
STAT 3 GOF (Stat 3 gain of function)	STAT3	Tocilizumab
WHIM (warts, hypogammaglobulinemia, infections, myelokathexis)	CXCR4	Plerixafor

Note: Partial list. These therapies are currently not FDA-approved for PI.

Pinto M, Neves J. *Front Immunol*. 2022;13:1029560. Hoyos-Bachiloglu R, Platt C. *Immunol Genet J*. 2019;2(4):8-22.

Audience Response

According to the Jeffrey Modell Foundation guidance, which of the following is a warning sign for PI in pediatric patients?

A. ≥ 4 new ear infections in 1 year
B. ≥ 2 new ear infections in 1 year
C. 3 weeks of antibiotics with little effect
D. 1 sinus infection within 12 months
E. I'm not sure

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Audience Response

On average, how long does it take for PI to be properly diagnosed?

A. 5 years
B. 10 years
C. 15 years
D. 20 years
E. I'm not sure

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Audience Response

Which of the following IgRTs can be dosed in pediatric patients every 3-4 weeks?

A. IVIg
B. SCIg
C. fSCIg
D. IVIg and fSCIg
E. I'm not sure

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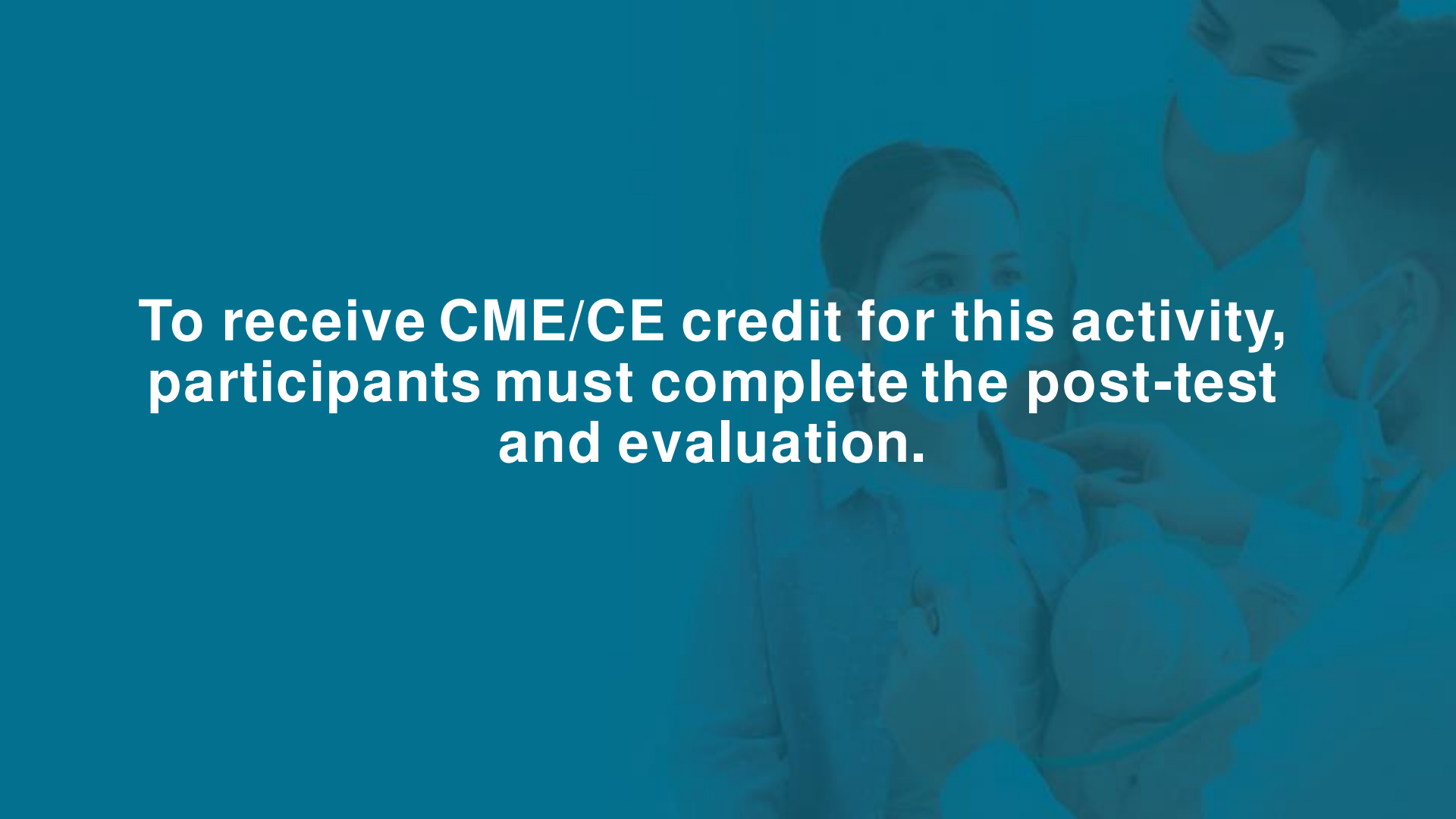
QUESTIONS
&
ANSWERS
Thank you for joining us.
Don’t forget to collect your credit.

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Consider PI in pediatric patients with frequent, severe, and/or unusual infections
- Follow diagnostic pathways to confirm PI
- Initiate (or refer) pediatric patients with PI for IVIg, SCIg, and now fSCIg, which can be life-saving and life-sustaining
- Keep abreast of new and emerging “precision medicine” strategies
- Provide patient-centered care that includes shared decision-making and considers social determinants of health



To receive CME/CE credit for this activity, participants must complete the post-test and evaluation.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Primary Immunodeficiency in Pediatric Care:

When It's More Than "Just an Infection"

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