Primary Immune Deficiency Treatment Consortium

Severe Combined Immunodeficiency (SCID) Data Collection

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RARE CLINICAL DISEASES RESEARCH NETWORK
National Institutes of Health

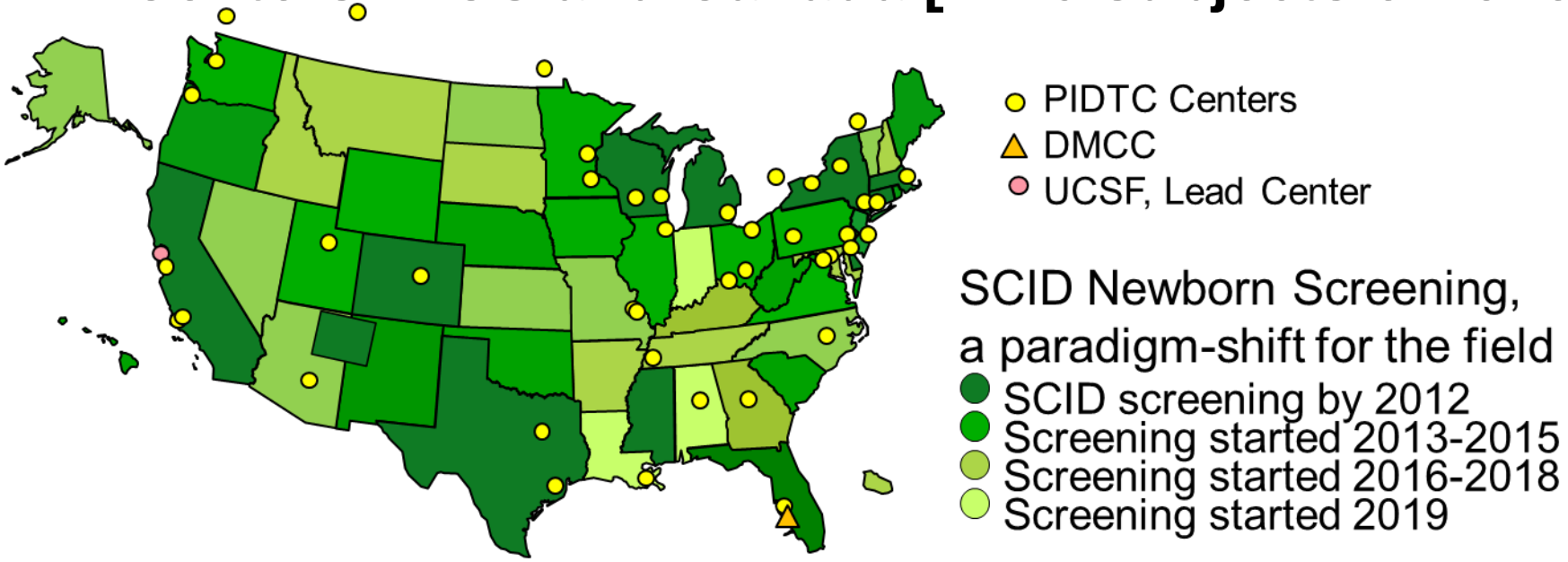
National Institute of Allergy and Infectious Diseases
Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases.

PIDTC History

- The **Primary Immune Deficiency Treatment Consortium** is part of the Rare Diseases Clinical Research Network (RDCRN), a group of consortia and a Data Management and Coordinating Center, united by the NIH Office of Rare Diseases Research, National Center for Advancing Translational Sciences (NCATS).
- Major support for PIDTC is from NIH NIAID.
  - First U54 6-year Award 9/1/2009, Competitive renewal 9/1/2014
  - Upcoming renewal for 3rd cycle, if funded, to start 9/1/2019
- PIDTC goals are to conduct natural history studies in SCID, Wiskott-Aldrich syndrome and Chronic Granulomatous Disease.
- Sites apply for membership, which is based on experience and commitment.
- Patient Advocacy Groups have been critical collaborators, from the start, including Jeffrey Modell Foundation, Immune Deficiency Foundation, SCID Angels for Life Foundation.

PIDTC Organization

- **44 Centers in US and Canada [1749 subjects enrolled]**



- **PIDTC Protocols**

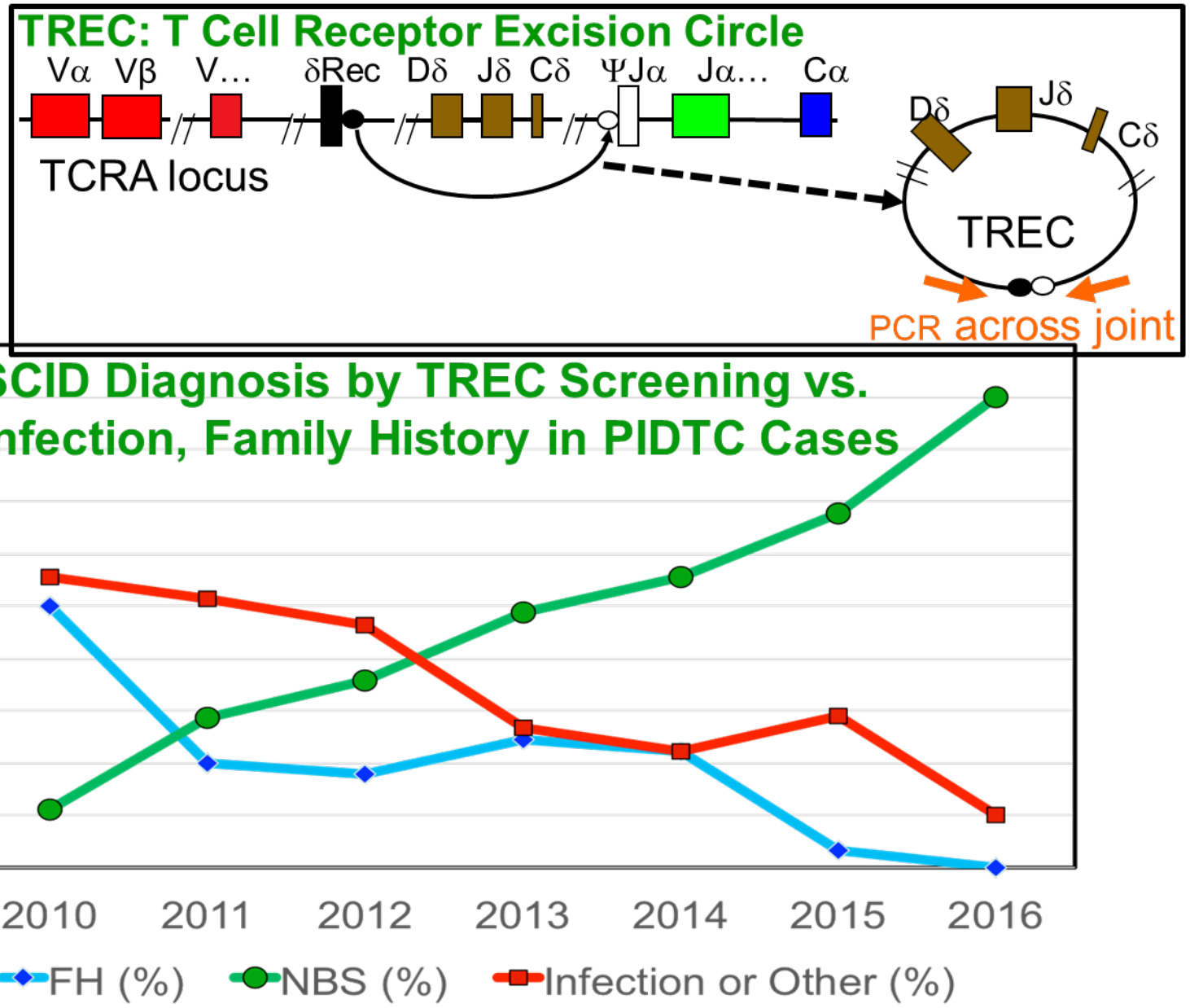
  6901 SCID Prospective, Longitudinal [293 enrolled]

  6901 SCID Retrospective, Cross-sectional [743 enrolled]

  6903 CGD Prospective and retrospective [406]

  6904 WAS Prospective and retrospective [307]

SCID Paradigm Shift with Newborn Screening



Central IRB

- Single IRB is now mandated by NIH for multicenter clinical studies (non-U.S. sites exempt).
- UCSF IRB is the IRB of record for PIDTC, thanks to Tara Bani, UCSF PIDTC, and Laurie Herraiz, UCSF IRB.
- Reliance agreements are in place for nearly all U.S. Sites (not the 5 Canadian sites).

PIDTC SCID Definitions

Shearer WT, Dunn E, Notarangelo LD, et al. *Establishing diagnostic criteria for severe combined immunodeficiency disease (SCID), leaky SCID, and Omenn syndrome: the Primary Immune Deficiency Treatment Consortium experience. J Allergy Clin Immunol. 2014;133(4):1092-1098.*

SCID Definitions

Typical SCID

<300 (autologous) CD3 T cells/uL
<10% of normal proliferation to PHA
Supported by detectable maternal T cells in peripheral blood
proven deleterious defect(s) in a known SCID gene.

Leaky (Atypical) SCID

300-1500 or more CD3 T cells, but few naive T cells
Reduced (10%-50% of normal) proliferation to PHA
No maternal T cells detectable
Supported by incomplete defect(s) in a known SCID gene

Omenn syndrome

Oligoclonal T cells
Reduced proliferation to PHA (10%-50% of normal)
Erythroderma, hepatosplenomegaly, eosinophilia, and elevated serum IgE antibody

Prospective SCID Data Collected

CIBMTR (legal requirement to report all USA transplants)

SCID *Research* Form has extensive transplant details

- SCID Genotype
- Phenotype
- Donor/recipient HLA
- Conditioning (agents, dose/exposure)
- Cell dose
- GVHD

PIDTC Case report forms

- Eligibility (voting panel, geneotype, mutation police)
- Demographics, study withdrawal or death
- Early life features (NBS, dx trigger, nursing, infections)
- Hematopoietic cell transplant
- Enzyme replacement therapy (ADA)
- Gene therapy (XSCID, ADA)
- Subsequent treatment (HCT, boost, ERT)
- Follow up at 100 d; 6 m; 1, 2, 3, 4, 5 and 8 y

PIDTC
NBSTRN DMCC Database

Prospective SCID Samples Collected

All SCID enrollees

DBS for TRECs

RNA (PaxGene tube) for spectratyping to measure T cell diversity

Baseline, 100 d, 6 m, 1 and 2 y

Special studies through Pilot Program

B cell development

T cell exhaustion

Host and donor HLA restriction for patients with EBV, CMV infection

PIDTC

NBSTRN DMCC Database

Sample of Case Report Form

PIDTC 6901
Day 100
Post Hematopoietic Cell Transplantation (HCT) Worksheet

22Sep2017
Version 3.0
Page 1 of 8

Center: _____ Person Completing Form: _____

Participant ID: _____ Local ID: _____

Date of Visit: __ __/__ __ __/__ __ __ __ (DAY MONTH YEAR) Date of HCT: __ __/__ __ __/__ __ __ __ (DAY MONTH YEAR)

This Day 100 Assessment form captures history within ±2 weeks of the scheduled visit date.

DATE OF CONTACT WITH PATIENT

Date of actual contact with the recipient to determine the medical status for this Visit Date's follow-up report: __ __/__ __ __/__ __ __ __ (dd/mmm/yyyy)

HEALTH ASSESSMENT

1. **Current Treatment**

a. Is the patient on enzyme replacement therapy at the present time?

- ○ Yes
  - If yes, what date was the treatment initiated? __ __/__ __ __/__ __ __ __ (dd/mmm/yyyy)
- ○ No

b. If patient was previously on enzyme replacement therapy, what was the date of the final treatment? __ __/__ __ __/__ __ __ __ (dd/mmm/yyyy)

c. Has the patient received gene therapy?

- ○ Yes
  - If yes, what was the date? __ __/__ __ __/__ __ __ __ (dd/mmm/yyyy)
- ○ No

2. **Additional Health Assessment**

Head circumference:	__ __.__	cm	__ __	to __ __ __	%ile for age	○ Not done
Height:	__ __ __.__	cm	__ __	to __ __ __	%ile for age	○ Not done
Weight:	__ __ __.__	kg	__ __	to __ __ __	%ile for age	○ Not done

Nutritional source (check all that apply)

- ☐ Enteral supplementation (NG, G-tube, oral)
- ☐ Parenteral nutritional support
- ☐ PO

Does the patient have lymphadenopathy?

- ○ Yes
- ○ No

Does the patient have a rash (other than GVHD)?

- ○ Yes
- ○ No

3. **Infectious Disease Assessment**

Did the patient have any infection(s) prior to initiation of conditioning for HCT therapy?

- ○ Yes
- ○ No

If yes, have all infection(s) resolved?

- ○ Yes
- ○ No (Please enter any unresolved infection on CIBMTR Form 2131)

4. **Autoimmune Disease Assessment**

Was the patient diagnosed with any of the following autoimmune diseases? (check all that apply)

- ☐ None
- ☐ Hypothyroidism
- ☐ Thrombocytopenia
- ☐ Neutropenia (ANC <500)
- ☐ Arthritis
- ☐ Myositis
- ☐ Nephritis
- ☐ Bronchiolitis obliterans or other pulmonary autoimmune disease
- ☐ Vitiligo
- ☐ Alopecia
- ☐ Inflammatory bowel disease
- ☐ Neurodegeneration
- ☐ Vasculitis
- ☐ Other; Specify: _____

5. **Brain**

Selected PIDTC Publications on SCID

Haddad E, Logan BR, Griffith LM, et al. SCID genotype and 6-month posttransplant CD4 count predict survival and immune recovery. Blood. 2018;132(17):1737-1749.

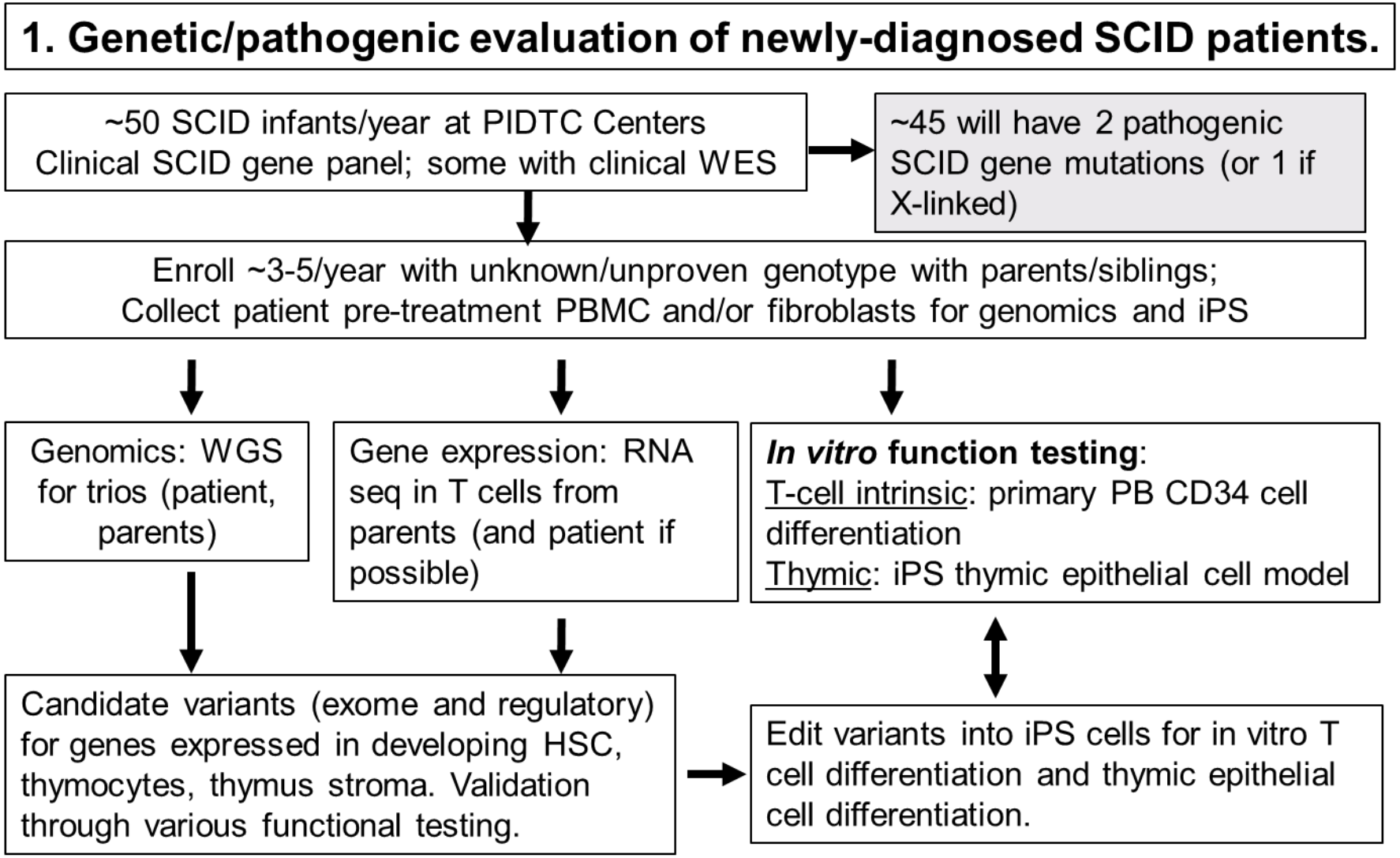
Heimall J, Logan BR, Cowan MJ, et al. Immune reconstitution and survival of 100 SCID patients post-hematopoietic cell transplant: a PIDTC natural history study. Blood. 2017;130(25):2718-2727.

Heimall J, Buckley RH, Puck J, et al. Recommendations for screening and management of late effects in patients with severe combined immunodeficiency after allogenic hematopoietic cell transplantation: a consensus statement from the Second Pediatric Blood and Marrow Transplant Consortium International Conference on Late Effects after Pediatric HCT. Biol Blood Marrow Transplant. 2017;23(8):1229-1240.

Pai SY, Logan BR, Griffith LM, et al. Transplantation outcomes for severe combined immunodeficiency, 2000-2009. N Engl J Med. 2014;371(5):434-446.

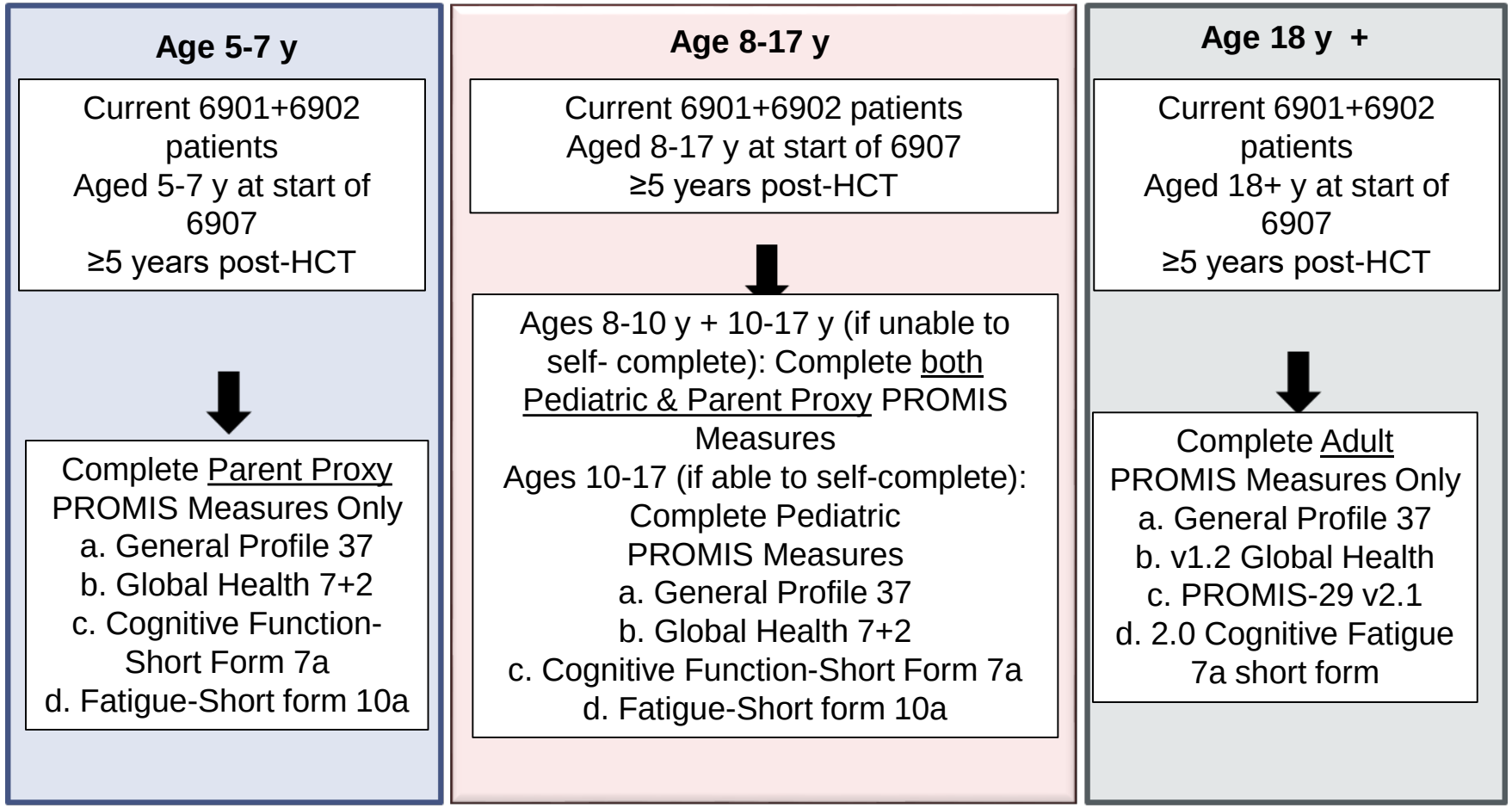
Dvorak CC, Cowan MJ, Logan BR, et al. The natural history of children with severe combined immunodeficiency: baseline features of the first fifty patients of the primary immune deficiency treatment consortium prospective study 6901. J Clin Immunol. 2013;33(7):1156-1164.

Selected Goals for Future



Selected Goals for Future

2. Quality of life assessments with validated PROMIS Pediatric self- and proxy-reported health measurements.



Goals for Future

3. CMV evaluation and natural history sub-study.

SCID diagnosed via Newborn Screening

↓

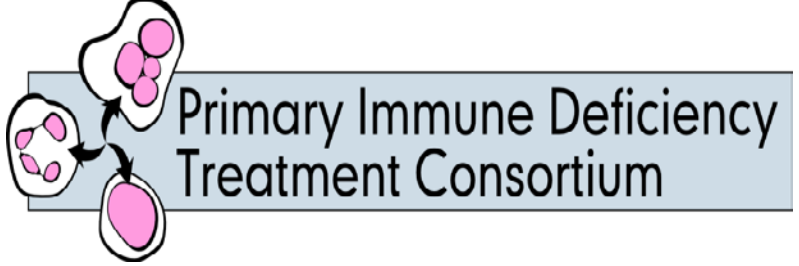
Infant managed according to local protocol with isolation (either in hospital or at home). Breast-feeding held or not per local site. Infant age will be about 5-21 d, at consent, study d 0.

↓

Baseline CMV Samples:

Mother	**Infant**
Serum CMV IgG, IgM; CMV PCR.	Blood, Urine, & Saliva for CMV PCR.
Breastmilk CMV PCR.	Liver function tests, bilirubin.
Saliva CMV PCR.	Request newborn screen DBS for CMV PCR.

Mother CMV IgG, IgM neg: **Infant not CMV exposed.**	Mother CMV IgG pos: **Infant CMV exposed.**	**Infant CMV PCR positive: Infected**
Allow nursing; continue surveillance. • Maternal milk & saliva CMV PCR at 1 wk; if neg stop. • Infant serum CMV PCR at 1, 3 wk, then per local SOC until engrafted >50 CD4 T cells/uL.	**Local protocol for nursing; continue surveillance.** • Maternal milk, saliva CMV. • Infant serum CMV PCR & LFTs; if neg then per local protocol until engrafted with >50 CD4 T cells/uL.	**Most sites stop nursing.** • Maternal studies as with exposed infant. • Infant serum CMV PCR, LFTs, CBC/diff q wk.
↓	↓	↓
If (+) move to CMV positive	**If (+) move to CMV positive**	**Infant ophtho, neuro, &audio exams. Treatment per local SOC with anti-virals +/- CTLs.**



Acknowledgments

- The Primary Immune Deficiency Treatment Consortium (U54-AI082973) is part of Rare Diseases Clinical Research Network (RDCRN), an initiative of the Office of Rare Diseases Research (ORDR), National Center for Advancing Translational Sciences (NCATS)
- The PIDTC is funded through collaboration between NCATS-ORDR, and the National Institute of Allergy and Infectious Diseases (NIAID)

Mort Cowan, first PI of the PIDTC, is dedicated to raising a new generation of leaders in Primary Immune Deficiencies.