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# **Selection/Enrollment/Consent for Gene Therapy for Severe Combined Immunodeficiency (SCID) in the Navajo, a Founder Population in the USA**

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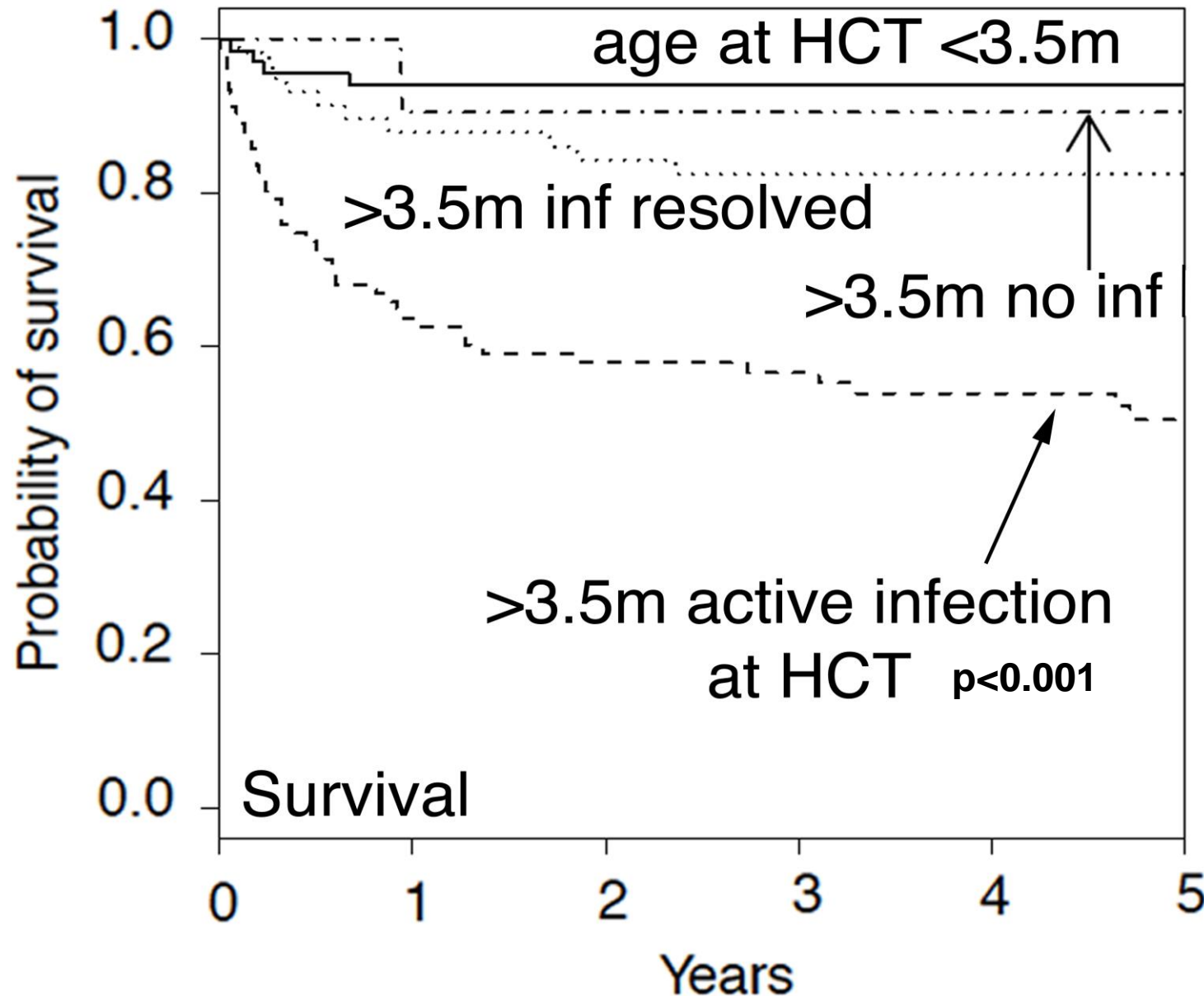
# Severe Combined Immunodeficiency, SCID

- Inability to fight infections, no T lymphocytes or antibodies.
- Recurrent infections and weight loss from age 2-4 months.
- Severe infections with microbes that do not harm healthy people.
- Defects in many genes can lead to SCID.
- Affected babies do not survive unless they can be given a working immune system.

# **Bone Marrow Transplant Can Rescue SCID Patients**

- 1968: first successful bone marrow transplant with HLA-matched sibling
- Alternative donors can be parents, matched unrelated donors, or cord blood
- ADA deficient SCID patients can be treated with ADA enzyme replacement
- Gene therapy has been developed for ADA and X-linked SCID

# Survival Compromised by Infections at Time of Treatment



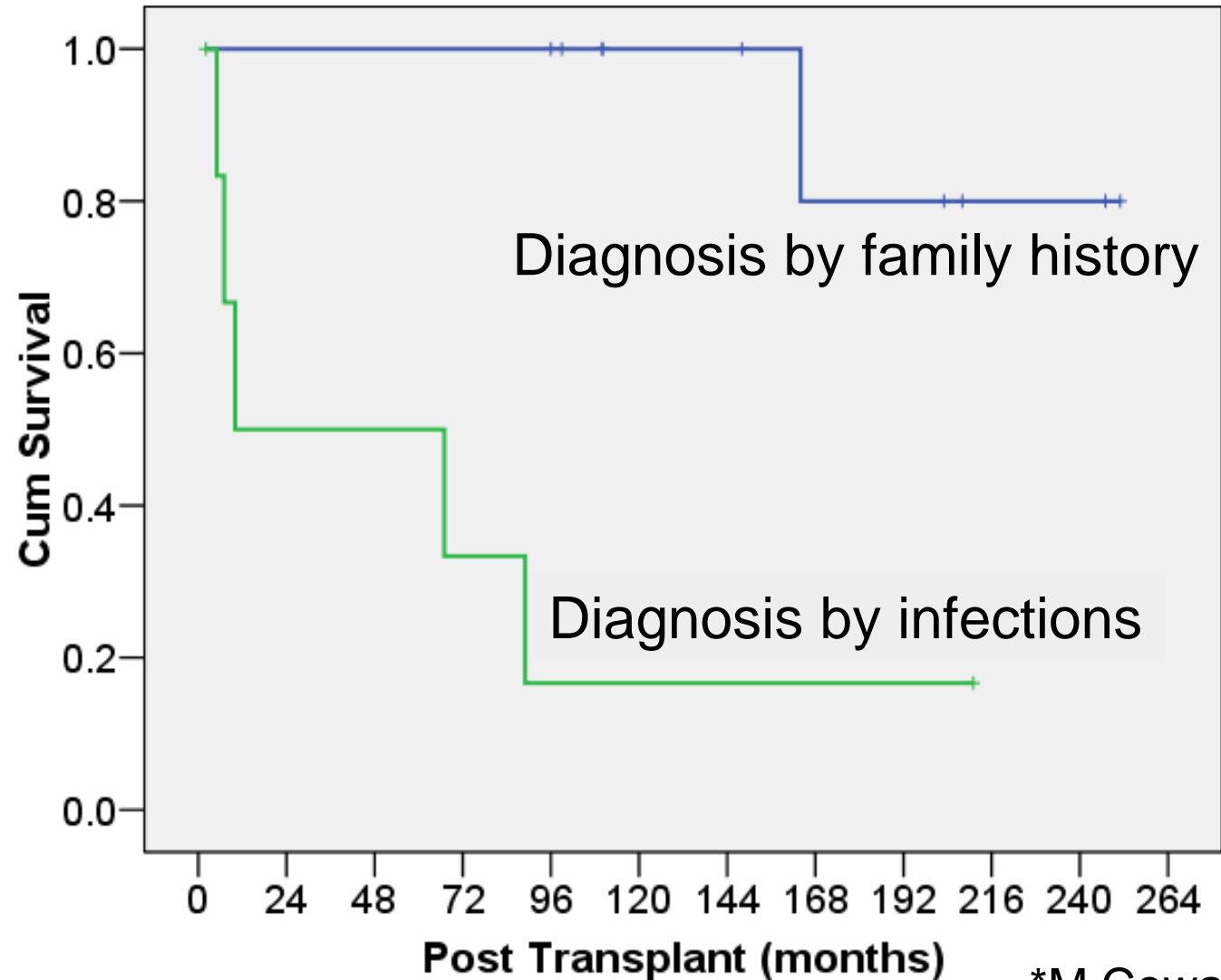
Since most SCID cases are sporadic, newborn screening would be needed to identify infants prior to developing infectious complications.

Pai et al, NEJM 2014 371:434-46.

# Navajo and Apache Indians Have Artemis *DCLRE1C*-Deficient SCID

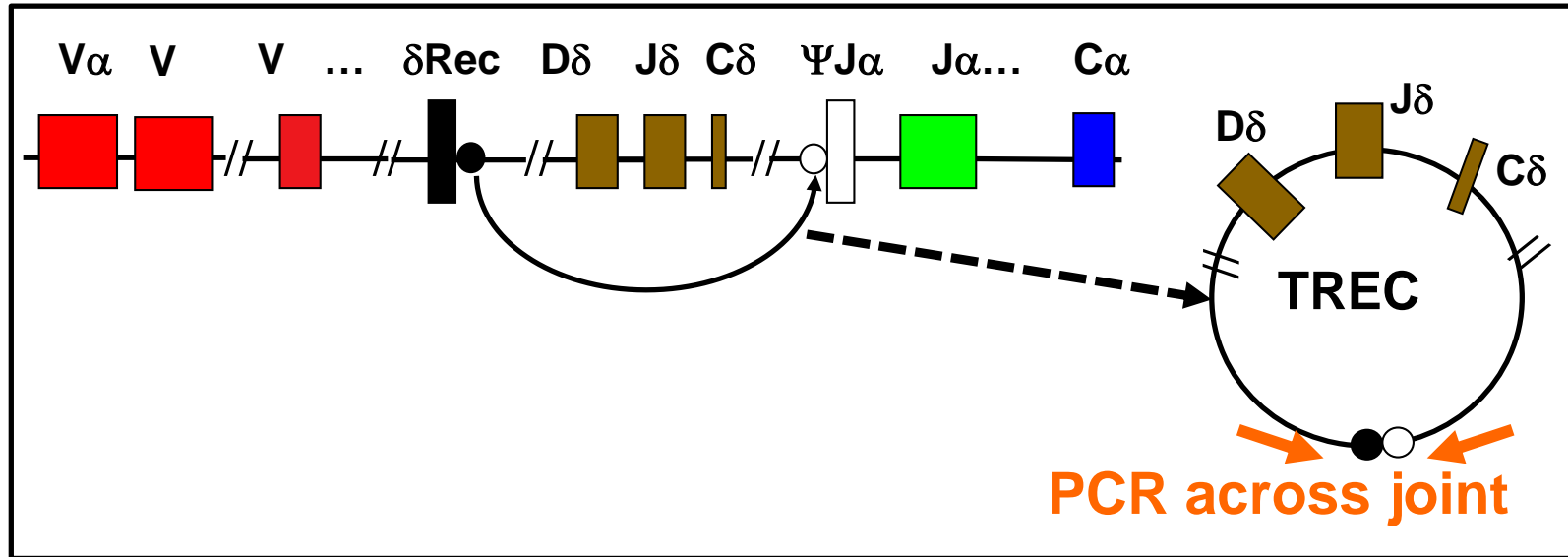
- Recessive SCID mutation, Artemis *DCLRE1C* Y192X, was carried by survivors of the Long Walk in 1864, from Fort Defiance, Arizona, to Fort Sumner, New Mexico, a forced relocation by the U.S. government. The ensuing population bottleneck and subsequent recovery may have contributed to the high SCID allele frequency.
- Hayward, Hu et al, 1980: frequent SCID, 1/2000 births, in the Navajo and Apache, who are related and share the Athabascan language.
- Artemis protein functions in VDJ recombination of T and B cells, and double-strand DNA repair; affected patients have no T or B cells and sensitivity to irradiation and alkylating agent chemotherapy.

# Navajo SCID Patients Treated at UCSF by Bone Marrow Transplant, 24 Years\*



\*M Cowan, UCSF

# Newborn Screen for SCID with T Cell Receptor Excision Circles (TRECs), a Byproduct of T Cell Maturation



# Navajo SCID Screening Study

- AIM: Screen infants; identify any SCID cases early and refer them for immediate treatment.
- Initial project in 2 hospitals: Tuba City, Chinle.
- Approved by Navajo Nation IRB, which has a moratorium on genetic testing. **NO genetic testing on study samples.**
- Written, face-to-face consent.
- For babies enrolled, 1 extra drop of blood was placed on a SCID Test card when routine newborn screening was done.
- Samples sent to UCSF for testing.
- Consent forms filed on Reservation.



# Introducing SCID Newborn Screening to Navajo Communities and Providers



**SILLY RABBIT,  
TREC'S ARE FOR  
SCIDS !**

## **SCID TESTING STUDY**

### **Voluntary Newborn Screening for Severe Combined Immunodeficiency (SCID)**

Babies can look very healthy at birth and still have a serious disease. That is why all babies are tested for certain conditions that cannot be seen, but need to be treated. The tests are done by a heel-stick, with drops of blood being collected on a paper blotter.



**SCID  
Testing  
Study**

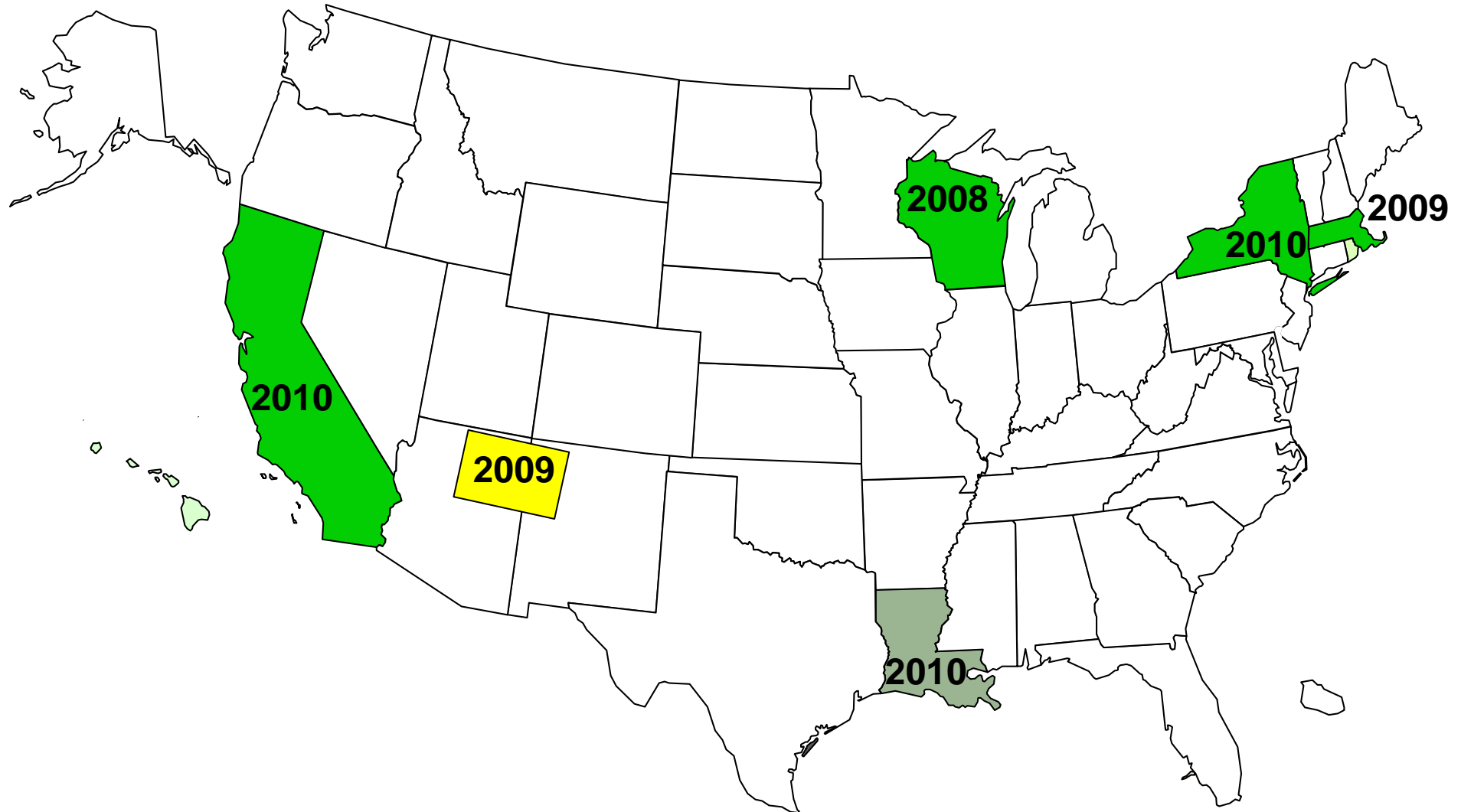
The **SCID Testing Study** is trying out a new blood-drop test that is not yet part of routine newborn screening everywhere, but is used in Wisconsin and Massachusetts. The study is being done by Dr. Puck and Dr. Cowan of the University of California in San Francisco, Dr. Hu of the Tuba City Regional Health Care Corporation, and their study teams at Tuba City and the Chinle Comprehensive Health Care Facility.

The new test is to find babies who may not be able to fight infections. The problem these babies have is called Severe Combined Immune Deficiency, or SCID. These babies need treatment right away.

You and your new baby are invited to join the **SCID Testing Study**. This study is only for babies whose parents give permission. A study worker will tell you about the study and ask if you wish join. Before you decide you may talk it over with your family and your doctor.



# Early SCID Newborn Screening Pilot Programs, 2008-2010





DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NOV 01 2011

Navajo Area  
Indian Health Service  
P.O. Box 9020  
Window Rock, Arizona 86515-9020

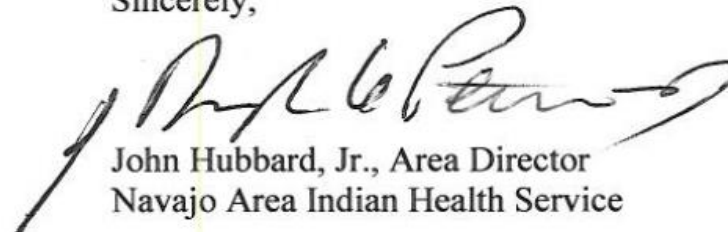
William Slimak  
Vice President and General Manager  
PerkinElmer Genetics  
90 Emerson Lane  
Bridgeville, PA 15017

Dear Mr. Slimak:

On behalf of the Navajo Area Indian Health Service (NAIHS), I am pleased to accept your donation of 6,000 TREC (T cell Receptor Excision Circle) immunodeficiency screening tests.

Your gift will support our mission to screen newborns for early detection of T-cell immunodeficiency. Thank you and your organization for supporting our goal to ensure that comprehensive, culturally acceptable, personal and public health services are available to the AI/AN population.

Sincerely,



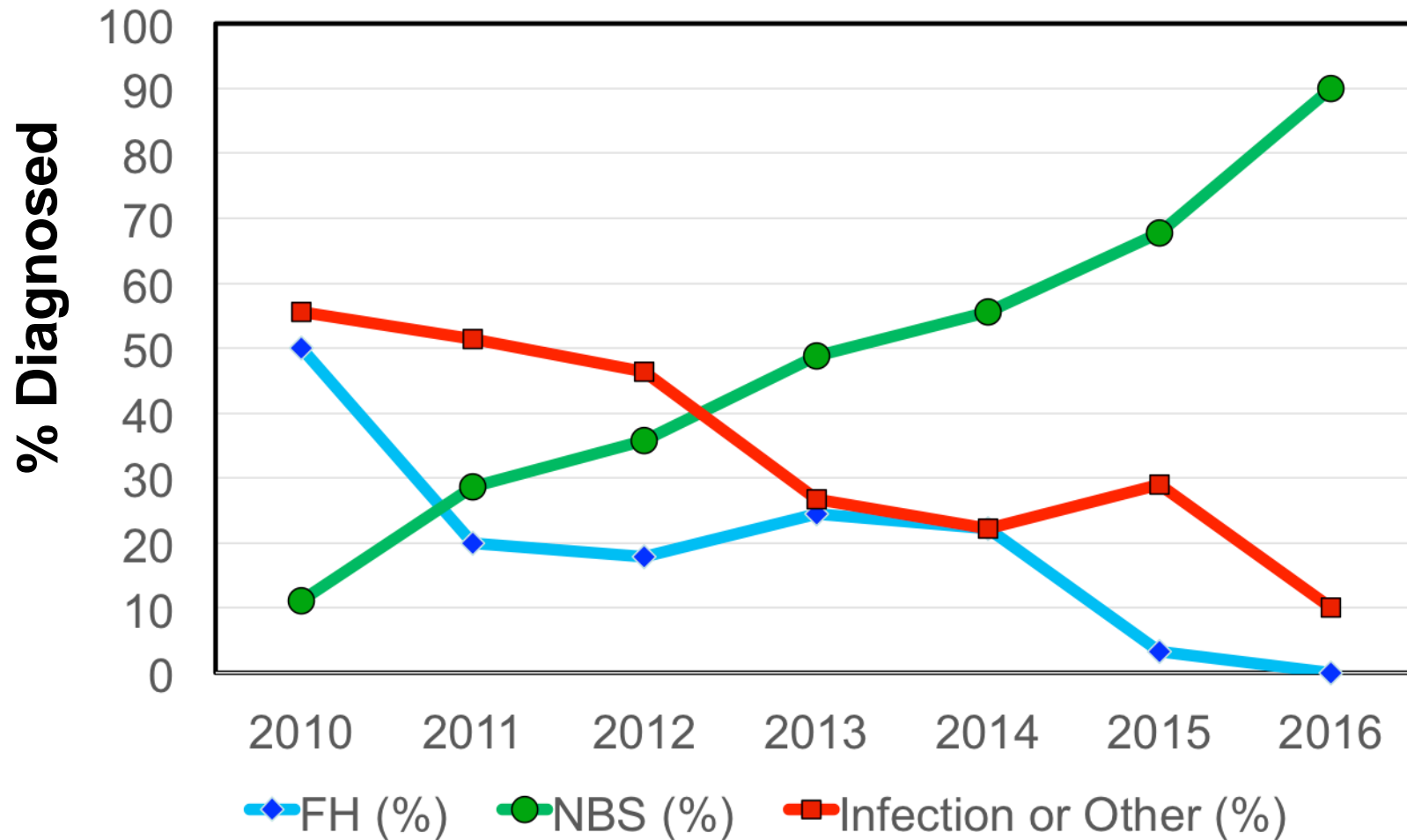
John Hubbard, Jr., Area Director  
Navajo Area Indian Health Service

Cc: Dr. Diana Hu, MCH Consultant/Peds, TCHRCC  
Gerald Jochem, HR, NAIHS

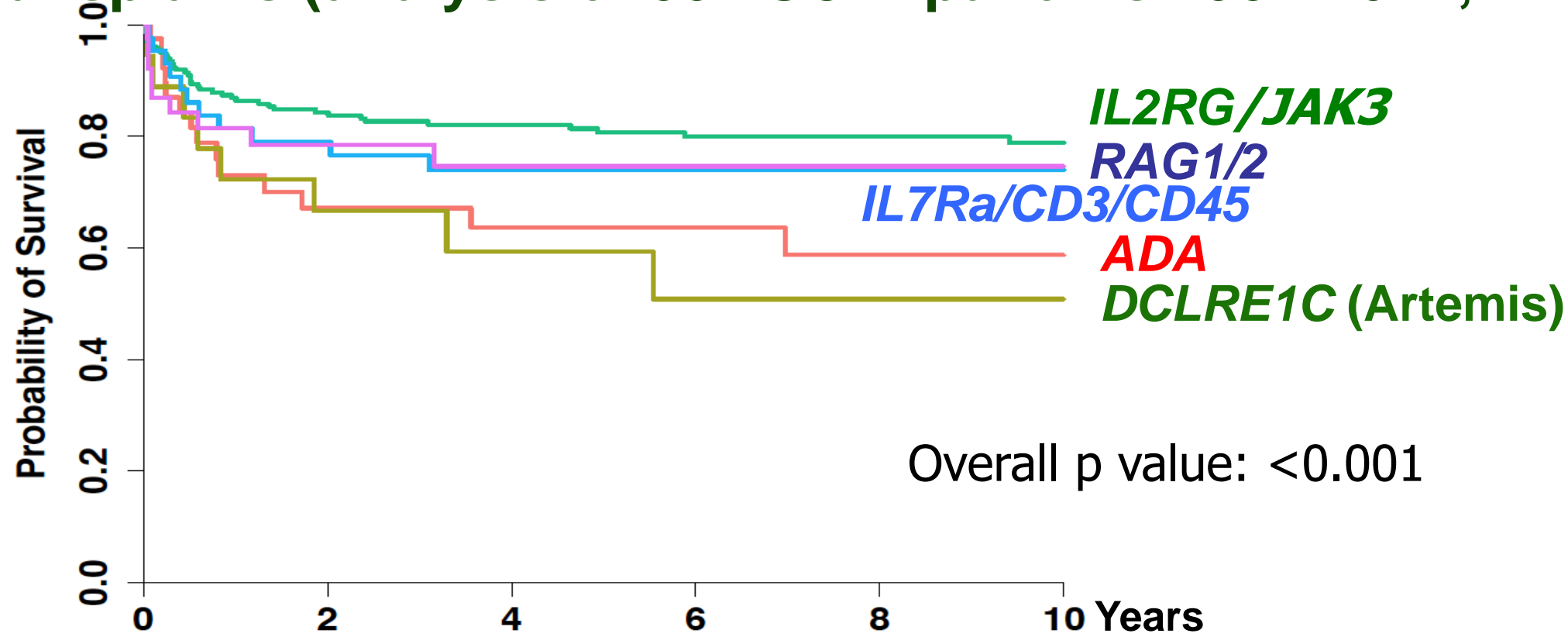
***After 1800 research samples, the test was adopted reservation-wide as standard care in 2011, with 6,000 TREC tests donated by PerkinElmer.***



# PIDTC SCID Diagnosis by Screening vs. Infection, Family History



# Impact of SCID Genotype on Survival with Alternative Donor Transplants (analysis of 337 SCID patients 1982-2012, PIDTC)



	p-value
<i>ADA vs IL2RG/JAK3</i>	0.020
<i>DCLRE1C vs IL2RG-JAK3</i>	<.001
<i>DCLRE1C vs IL7Ra, CD3, CD45</i>	0.008
<i>DCLRE1C vs RAG</i>	0.020

Haddad et al, *Blood* 2018 132:1737



Primary Immune Deficiency  
Treatment Consortium

# **ART-SCID is the most difficult form of SCID to treat with allogeneic HCT**

- Even with matched sibling, T cell recovery often incomplete, B cell recovery rare.
- With alternative donors, increased rejection & poor immune reconstitution.
- When high dose alkylator conditioning used late effects are short stature, poor tooth development, endocrinopathies & increased mortality.

**Autologous Gene Therapy may be a better approach.**

# First in Human Gene Therapy for ART-SCID: AProArt



- Self-inactivating lentiviral vector containing the human *DCLRE1C* promoter and cDNA, made with Scott McIvor, UMN.
- Low dose busulfan to make space in bone marrow, following lead of XSCID and ADA SCID trials.
- Newly diagnosed infants and previously transplanted older patients with insufficient immunity.
- Trial opened June, 2018. By October, 2019, have treated 4 infants, 3 older patients, of whom 2 infants, 2 older children are Navajo.



# Unbiased, population-based newborn screening

- identifies infants with rare, serious conditions.
- promotes fair access to treatment, including cutting-edge clinical trials.





# Elements of Success in Enrollment



- Navajos embrace SCID screening and early treatment, but optimal outcomes are challenged by distance from medical facilities, poverty and social difficulties.
- Network of trusted local physicians is critical (Dr. Diana Hu, Navajo Indian Health Service; PIDTC network).
- UCSF SCID team travels to Reservation annually to hold SCID Clinics.
- Some families contact each other for mutual support.
- Navajos bring traditions, including cradleboards, but endure high levels of stress, far from their home environment during long hospital stays.

*1940 photo, Princeton U Library*

# Thanks to Many Collaborators

## UCSF

Mort Cowan, Janelle Faccino,  
Chris Dvorak, Jason Yu,  
Carol Frazer-Browne, Ukina Sanford,  
Shivali Chag, Diana Gonzalez-Espinosa,  
Antonia Kwan

## U Minn

Scott McIvor

## Tuba City Regional Health Care Corporation, AZ

Diana Hu, Miran Song, Denise Brown

## Chinle Service Unit, Navajo Area Indian Health Services, AZ

Heidi Gomes, Trudy Bourque

## Support

**California Inst. for Regenerative  
Medicine (CIRM)**

## **NIH**

NIAID and ORD, Primary Immune  
Deficiency Treatment  
Consortium (PIDTC)

**DHHS** Maternal and Child Health  
Bureau

**CDC** Newborn Screening Branch,  
Division of Lab Sciences

**Jeffrey Modell Foundation**