NORD
National Organization for Rare Disorders

Rare Disease Scientific Symposium

Registries & Real-World Data as Development Platforms

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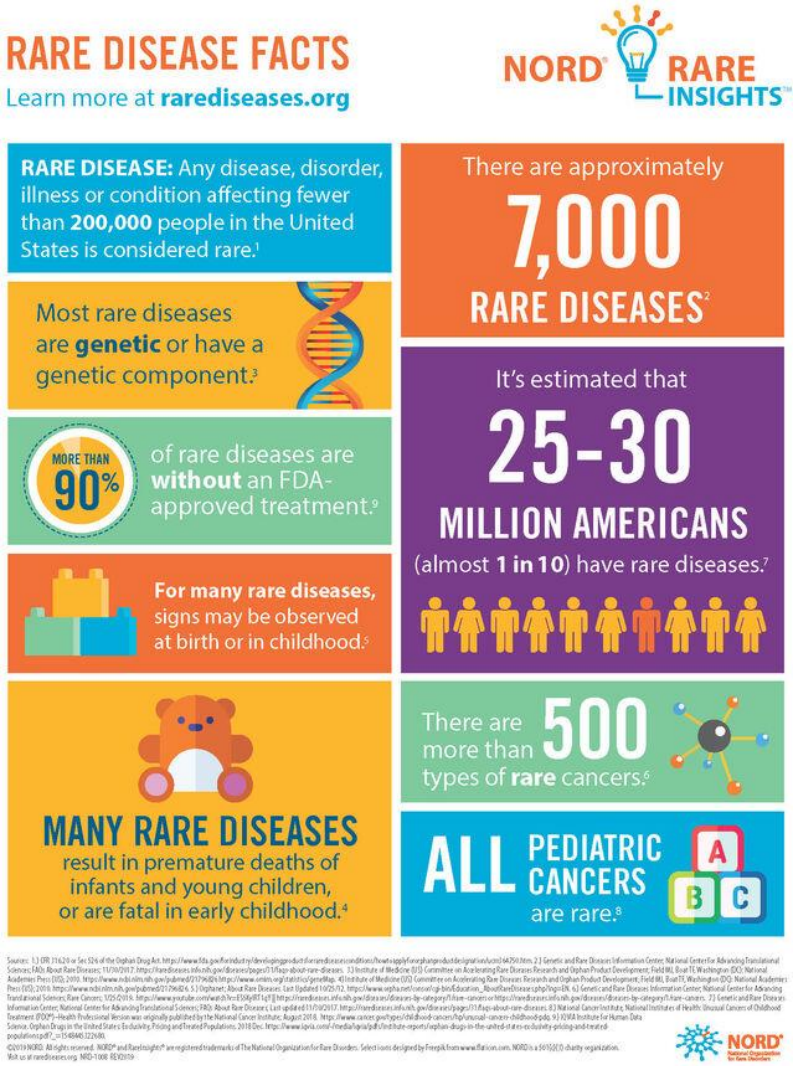
Biobanks in Rare Disease Research: Insights from *All of Us*

Srilakshmi Raj, Ph.D.
Albert Einstein College of Medicine
15-April-2026

Rare Disease is collectively common



Economic impact:

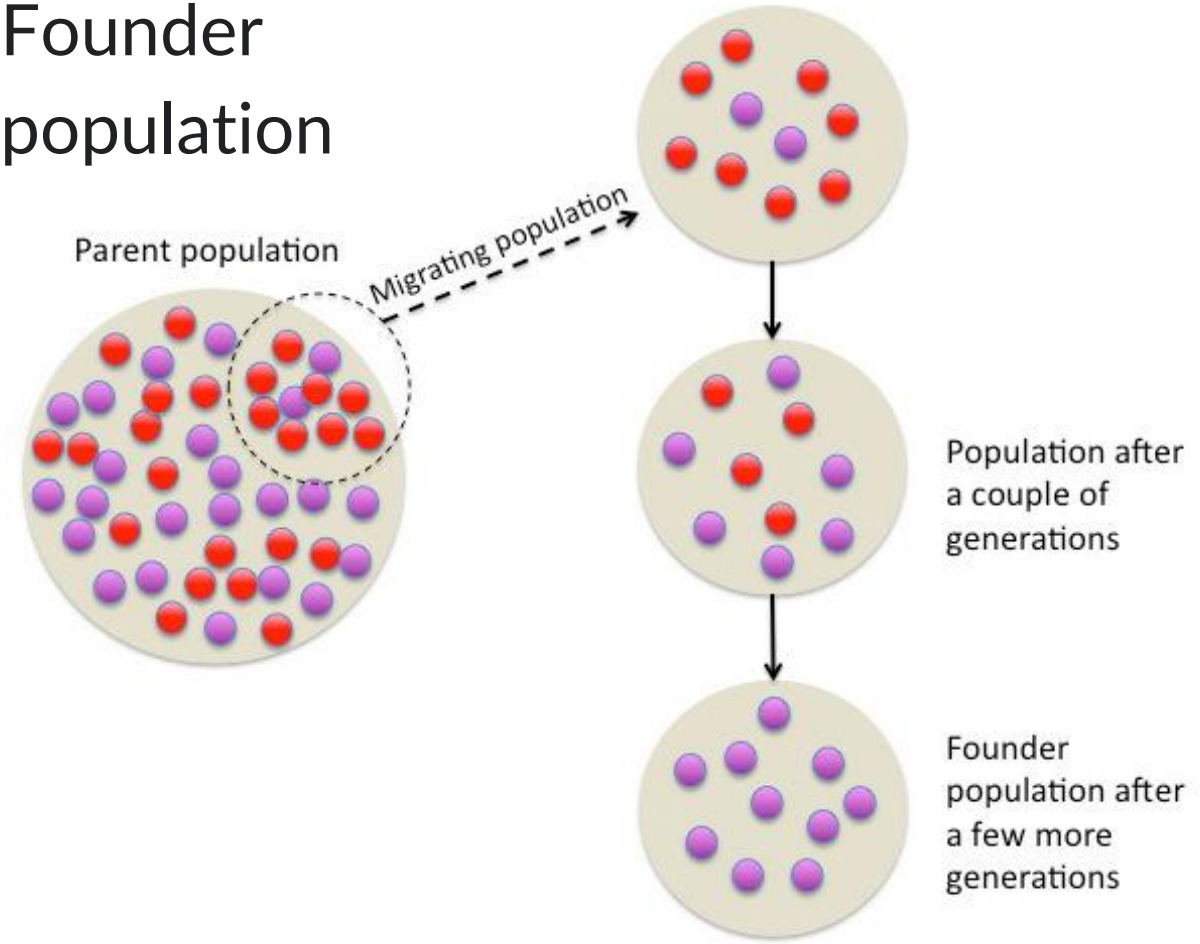
- $1 trillion/year in the US
- 10x higher costs per person than common disease
- Early diagnosis and treatment can save $500,000/person

What if a disease that is rare globally is common locally?

Known: family level

Patterns observable at the population level?

Founder population



Wikipedia (2015)

What if a disease that is rare globally is common locally?

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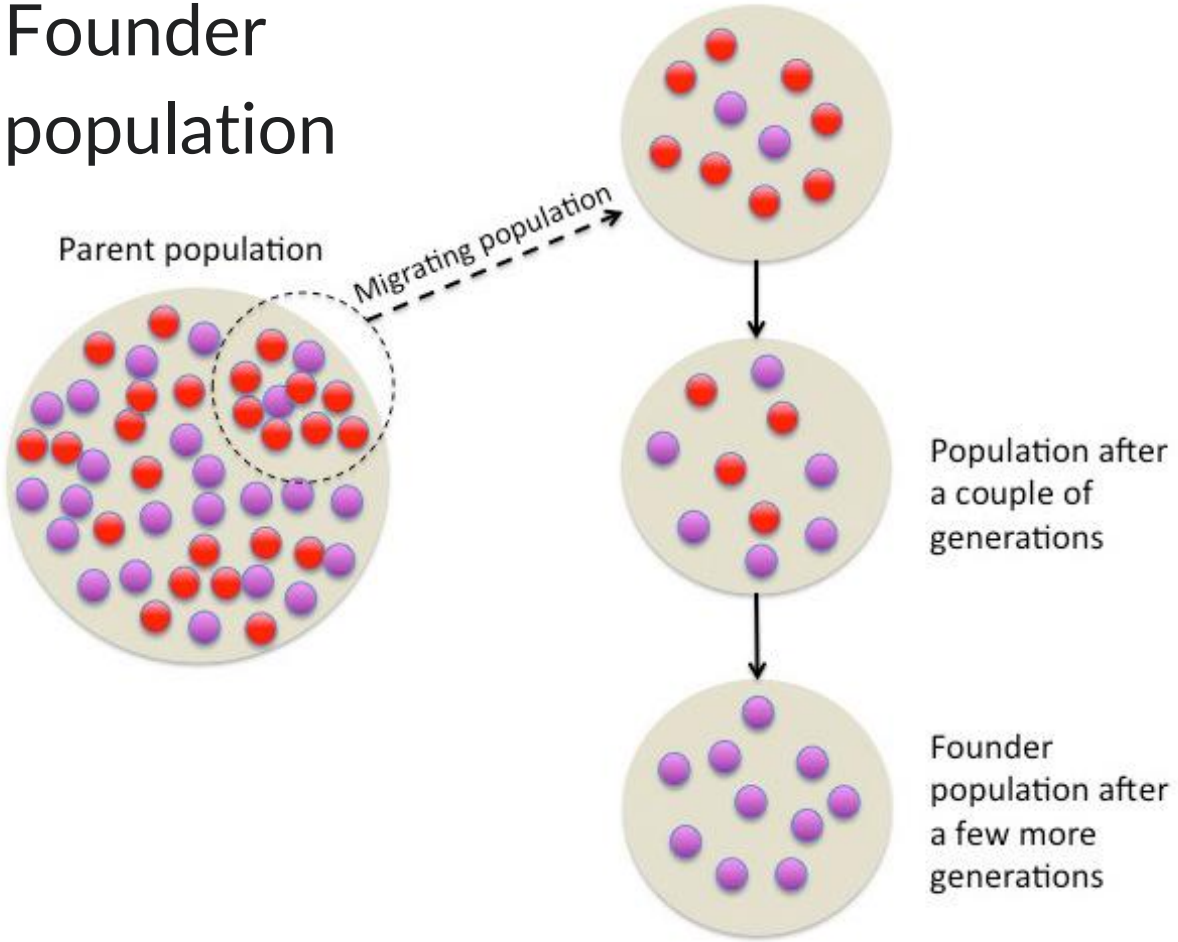
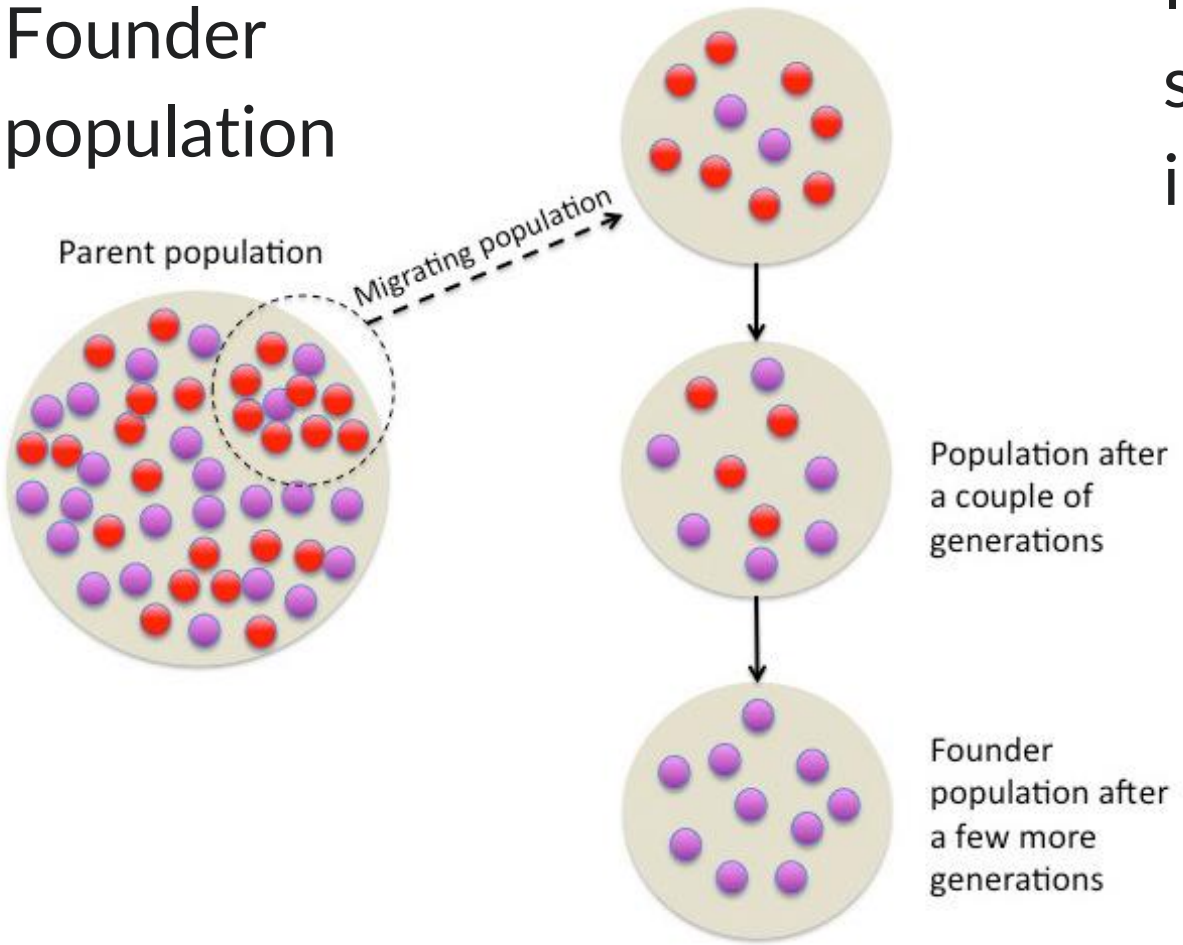


Population genetics is key to identifying these patterns

Wikipedia (2015)

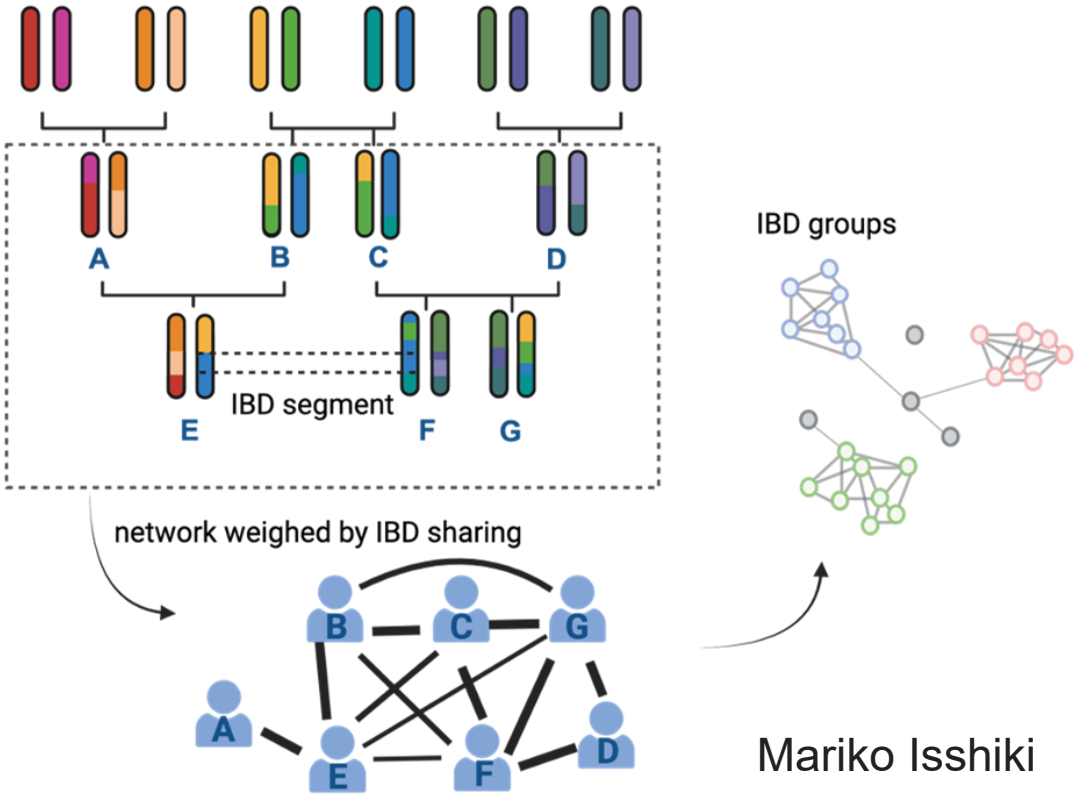
What if a disease that is rare globally is common locally?

Founder population



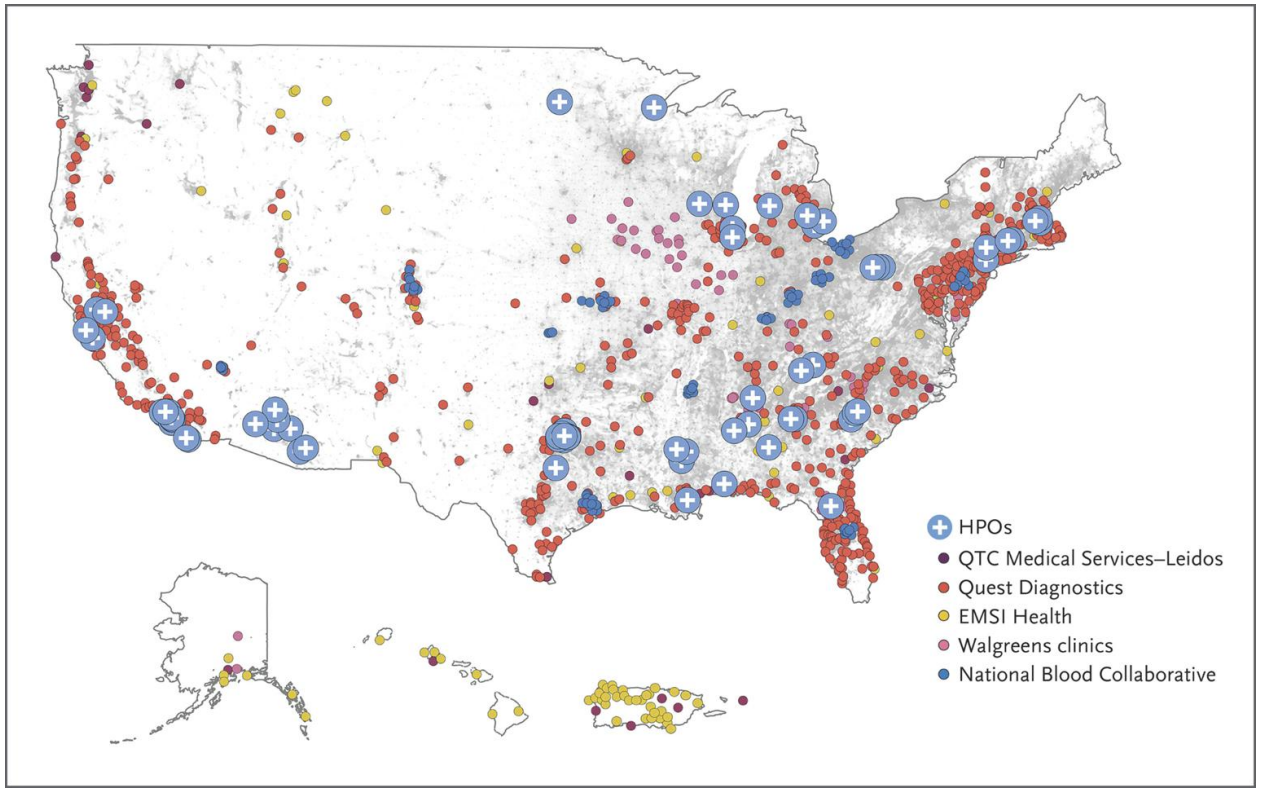
Wikipedia (2015)

Identity-by-descent: DNA sequences shared between two individuals inherited from a common ancestor



Mariko Isshiki

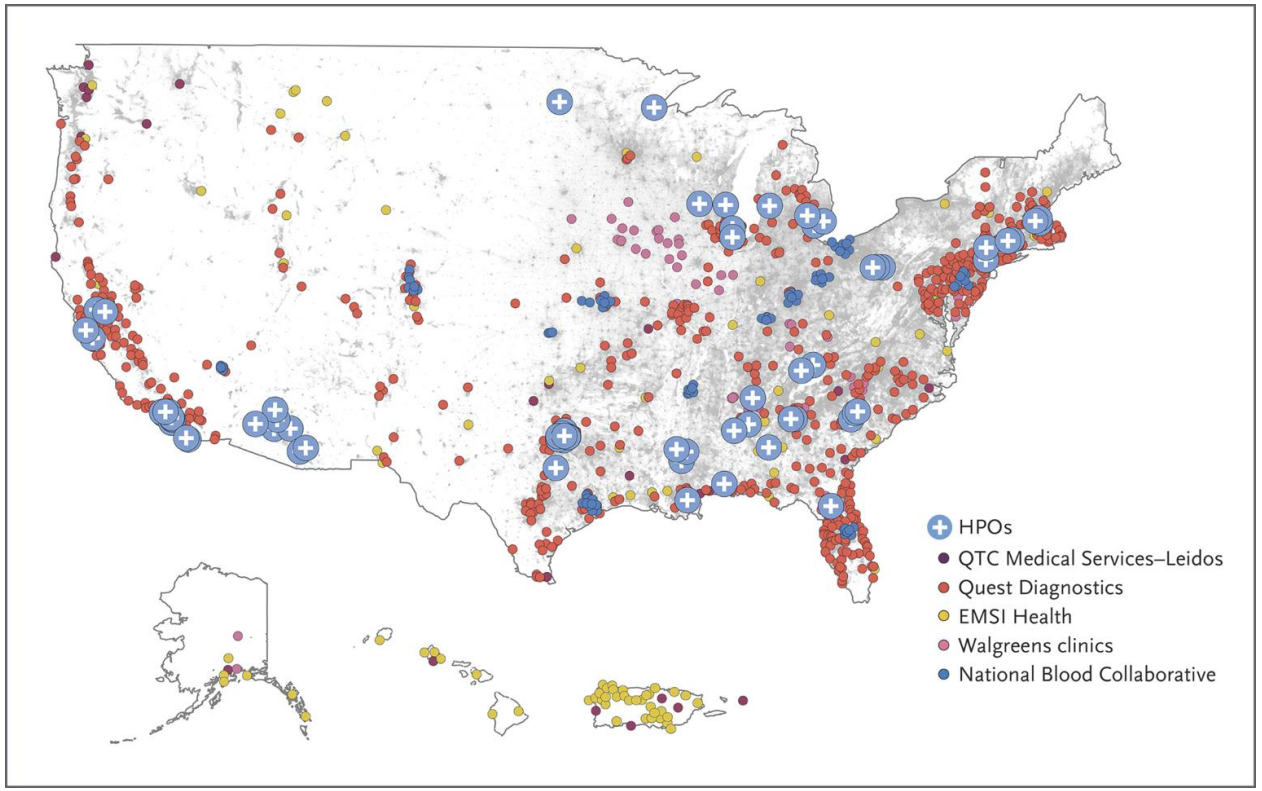
Leverage biobanks to identify rare disease risks particularly in founder populations



Current data (2025):

- >633,000 participants
- >393,000 EHR
- >414,000 short-read WGS

Leverage biobanks to identify rare disease risks particularly in founder populations



Dr. Mariko Isshiki (Segawa)

Dr. John Greally

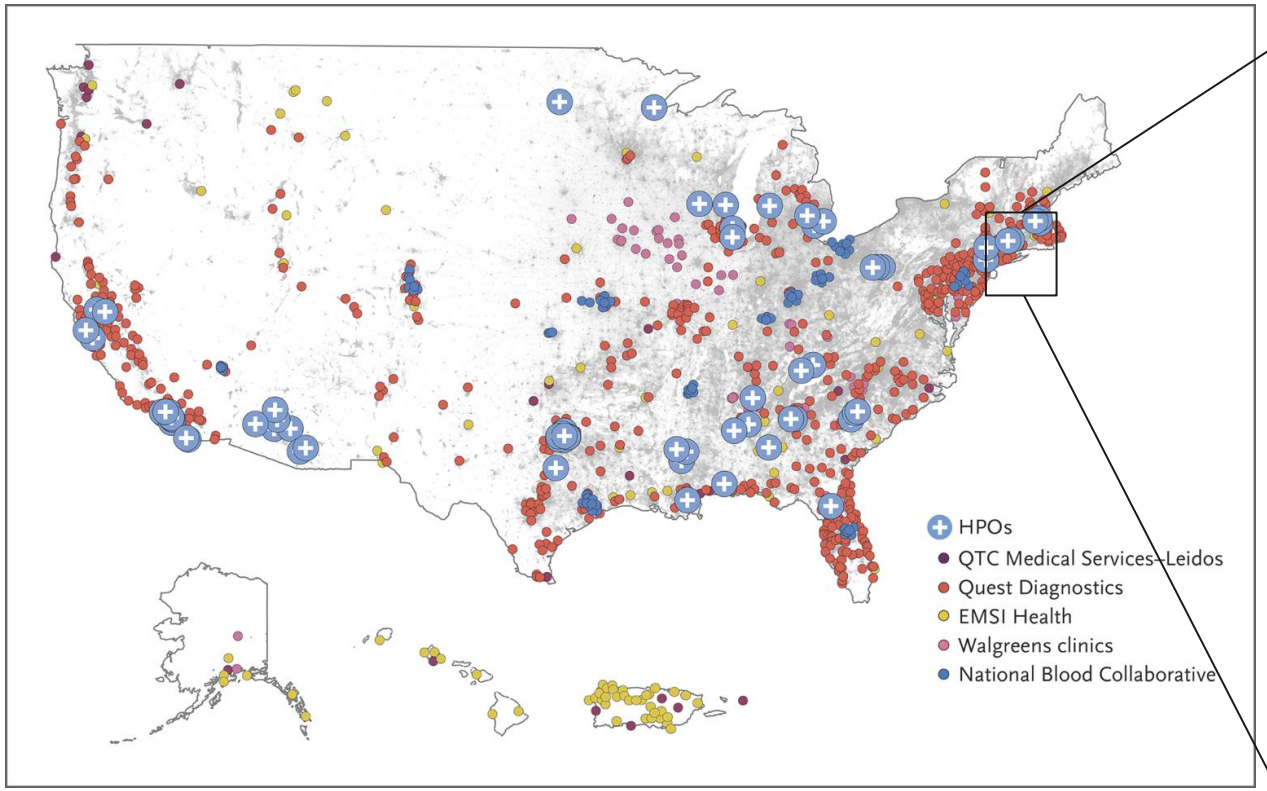
NYCRD
The New York Center for Rare Diseases

IBD across New York City

Genetic disease risks of under-represented founder populations in New York City

Mariko Isshiki, Anthony J. Griffen, Paul Meissner, Paulette Spencer, Michael D. Cabana, Susan D. Klugman, Mirtha Colón, Zoya Maksumova, Shakira Suglia, Carmen R. Isasi, John M. Greally, Srilakshmi M. Raj

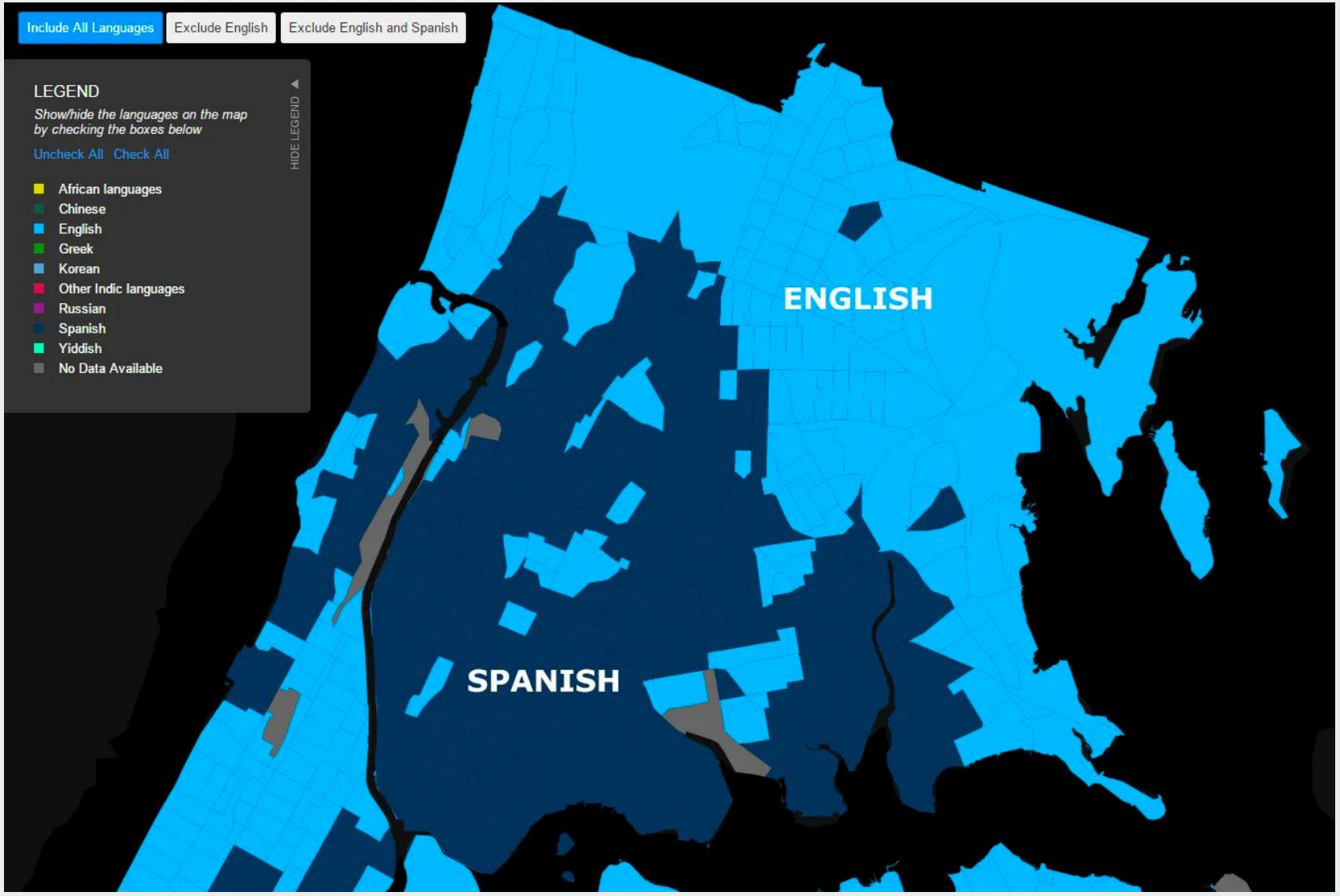
Version 2 Published: June 24, 2025 • https://doi.org/10.1371/journal.pgen.1011755



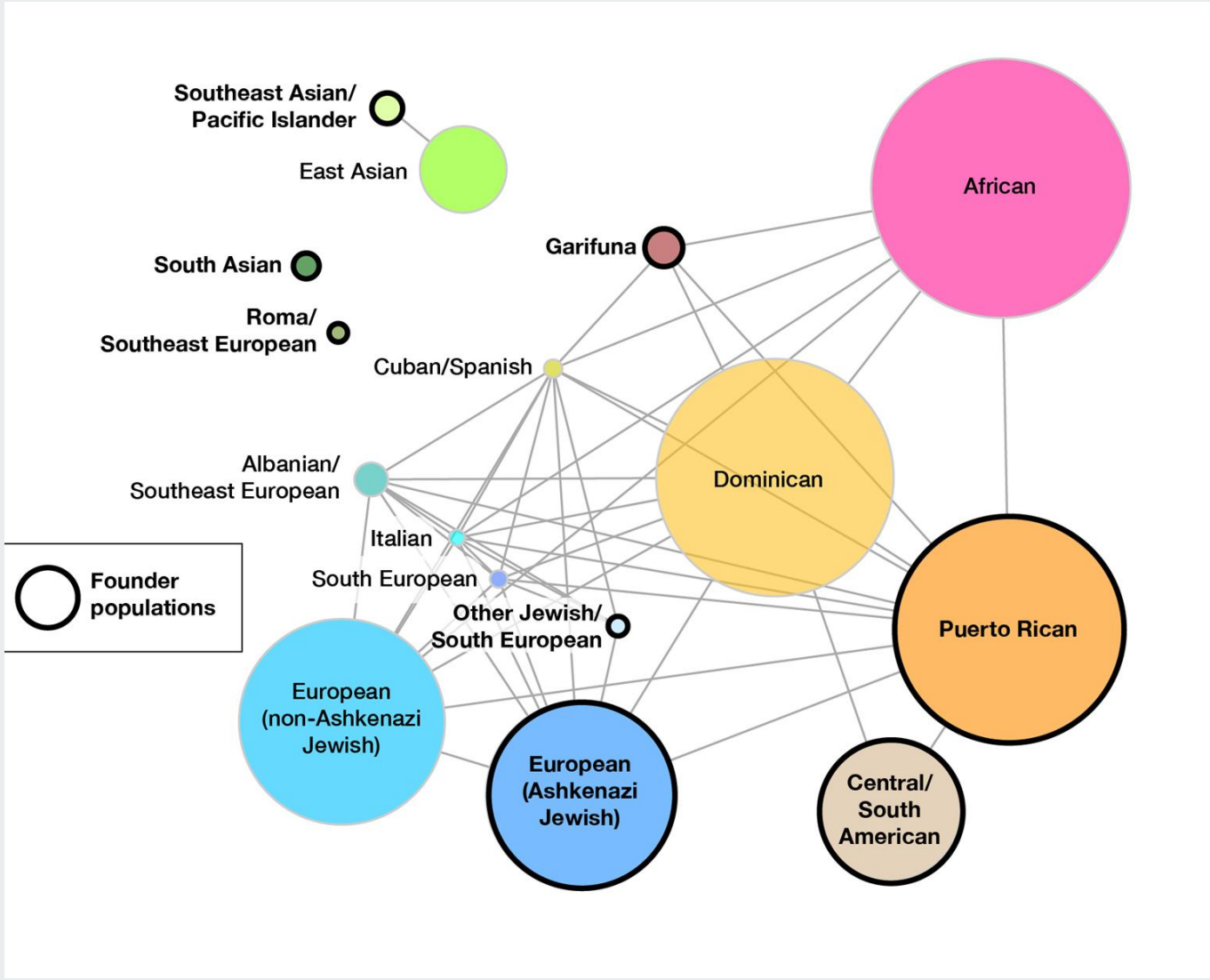
PMID: 40554605

Why New York? New York City is immense and diverse

- >800 languages spoken
- 8.6 million residents



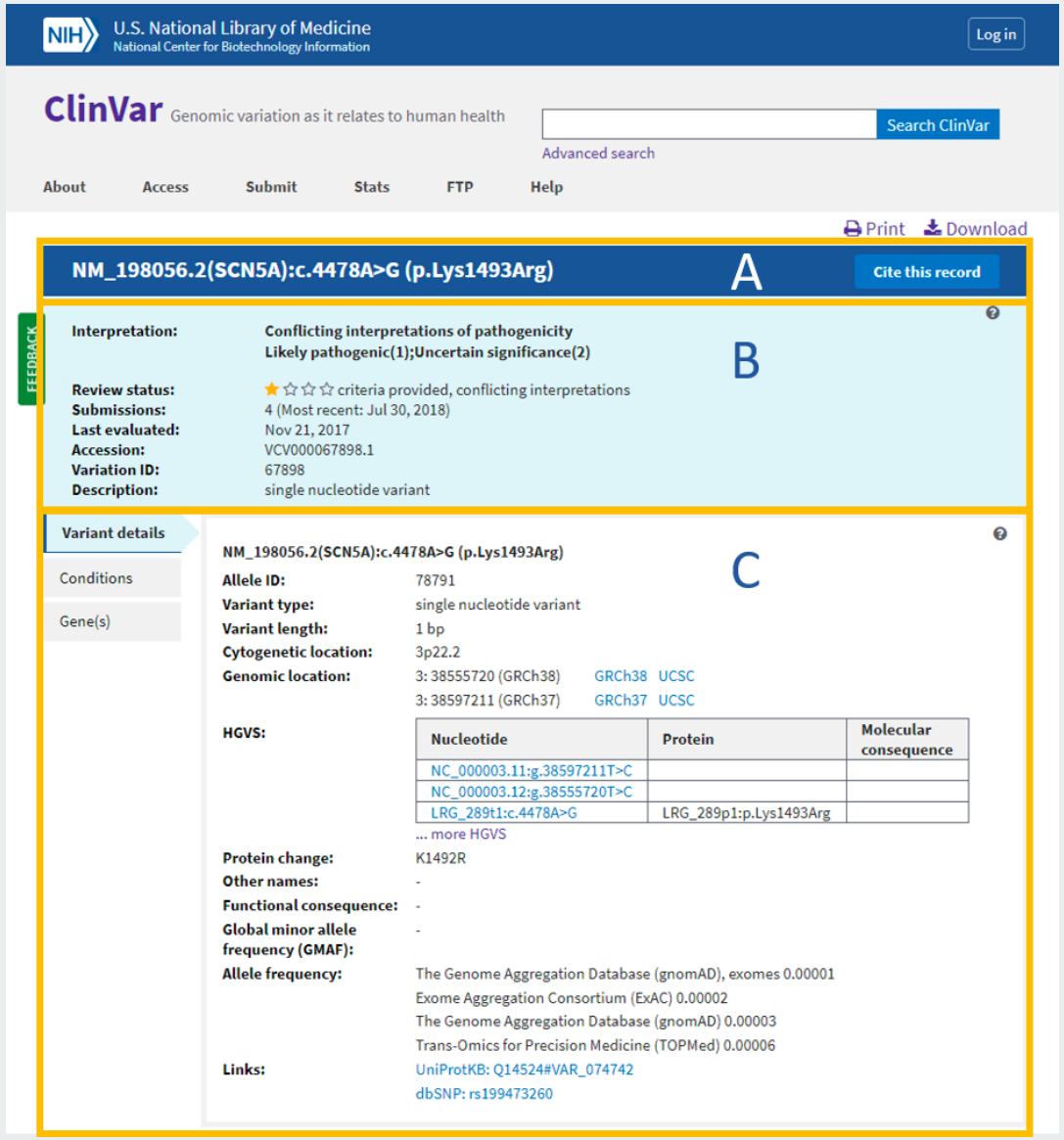
We identified 17 IBD groups in New York City



Identifying a strong founder effect in the Bronx

Who are the Garifuna?

Defining rare disease risk - ClinVar P/LP variants



ClinVar - 3,616 Pathogenic/Likely Pathogenic (P/LP) variants

-genotype rate > 0.9

- appear > 1x in NYC dataset

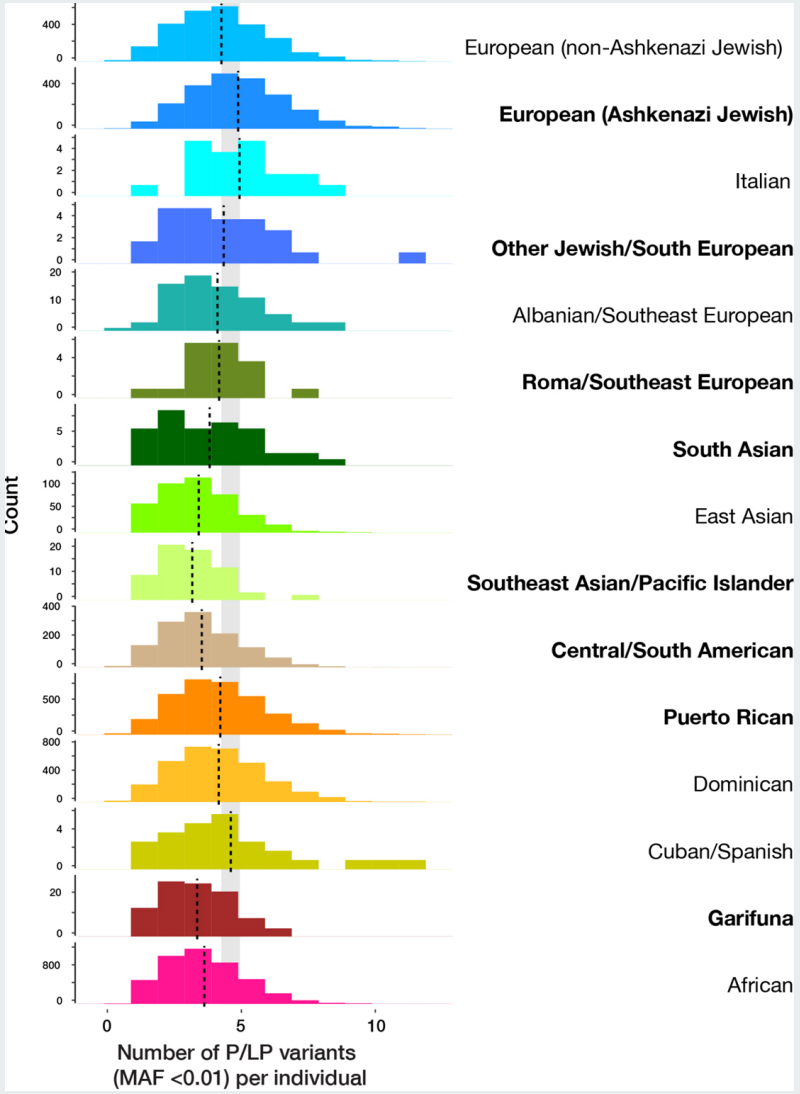
Uncovering founder effects for clinical pathogenic variants

Ashkenazi Jewish

Gene	Condition	Frequency in founder	Frequency in everyone else (~20k people)
F11	Hereditary factor XI deficiency	0.0248	0
KRT18	Cryptogenic cirrhosis	0.0098	0
CFTR	Cystic Fibrosis	0.0094	0

Puerto Rican

Gene	Condition	Frequency in founder	Frequency in everyone else (~20k people)	Ancestral origin
HPS1	Hermanski-Pudlak syndrome 1	0.0097	5.77E-05	AFR
RSPH4A	Primary ciliary dyskinesia	0.0096	2.89E-05	EUR
COL27A1	Steele syndrome	0.0091	5.77E-05	AMR



Discovering new founder effects

Garifuna

Gene	Condition	Frequency in founder	Frequency in everyone else (~20k people)	Ancestral origin
MYBPC3	Hypertrophic Cardiomyopathy	0.0245	2.38E-05	AMR
DUOX2	Thyroid dyshormonogenesis	0.0098	0	AFR
CNGB1	Retinitis pigmentosa	0.0147	2.38E-05	AFR

Discovering new founder effects

Garifuna

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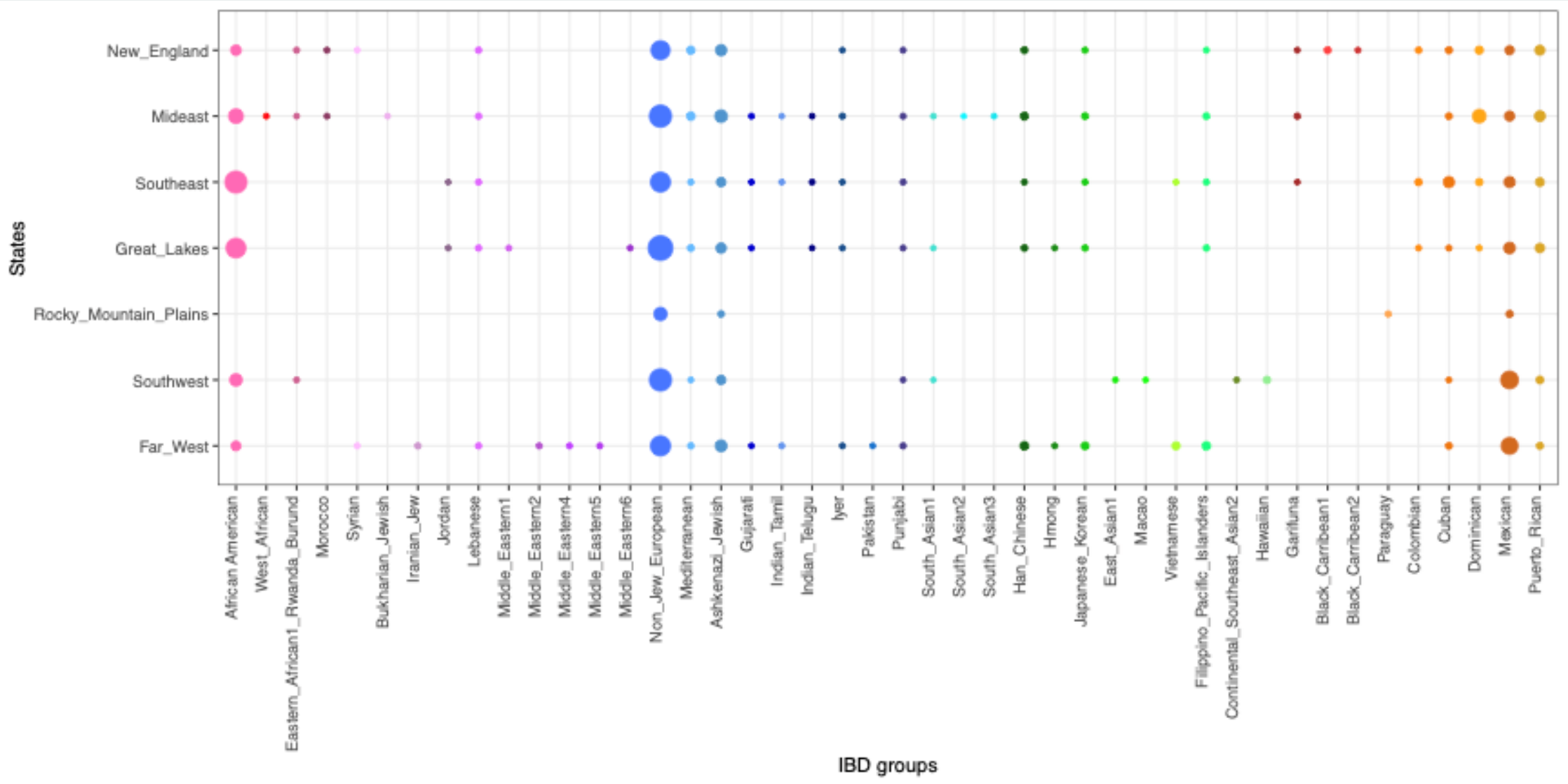
CNGB1	Retinitis pigmentosa	0.0147	2.38E-05	AFR

1 in 20 Garifuna have this variant

Closing the therapeutic loop - NYCRD colleagues involved in inherited hypertrophic cardiomyopathy treatment

Collaborating with community leaders and researchers

58 populations identified, who vary across the USA



Summary

Population-wide rare disease diagnostics: Biobanks allow expansion from family-based to population-based rare disease study

Community partnership is more important than ever to make genetic medicine accessible and reduce medical mistrust

Einstein's All of Us analysis team

MD-PhD students,
PhD students,
Bioinformaticians,
Postdocs,
Medical students

Acknowledgements

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Mirtha Colon
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The New York Center for Rare Diseases

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gencove
Gillian Belbin

VE RI TAS HARVARD
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Eimear Kenny
Alex Charney

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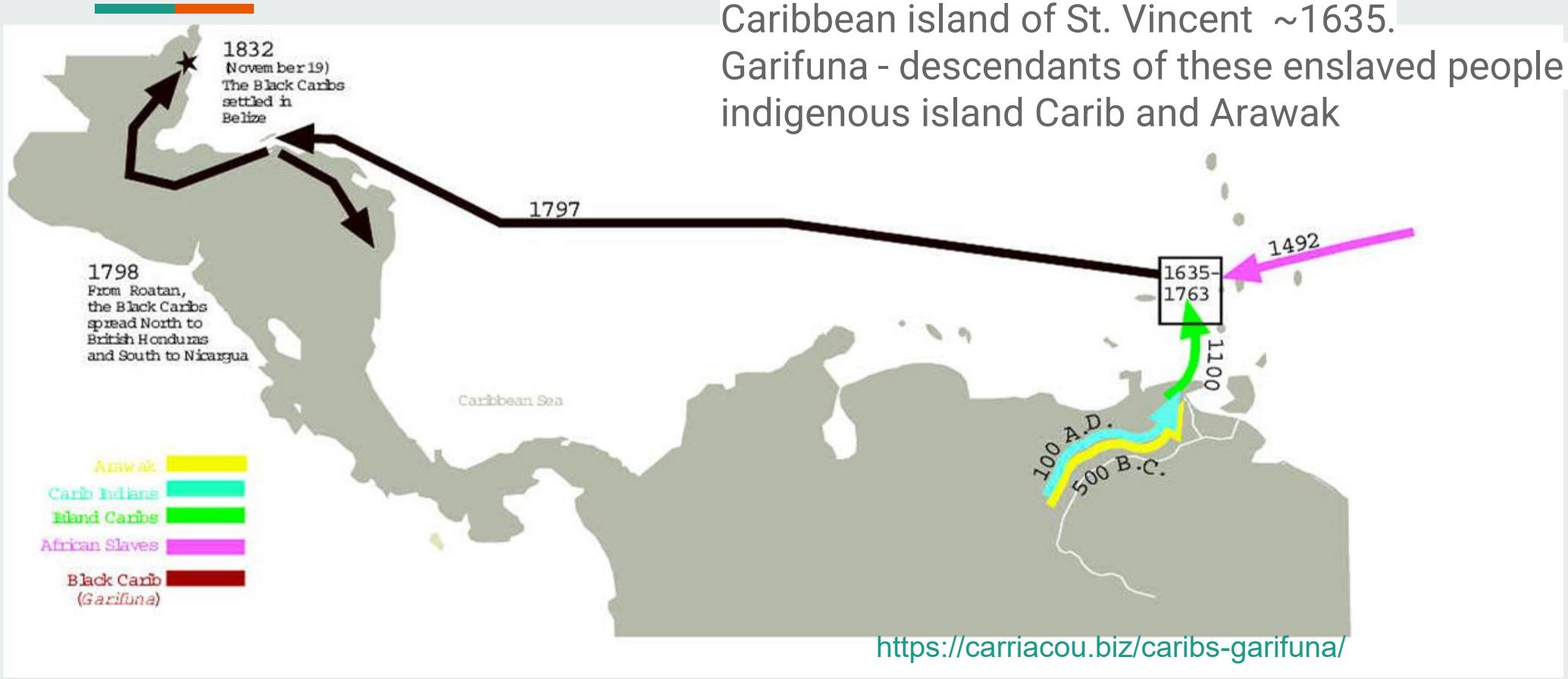
National Institutes of Health

-NIH for funding
-Cancer Center and Department of Genetics for support
-all the participants of the All of Us program, Bio*Me*, and other biobanks

Who are the Garifuna?

West African enslaved people who shipwrecked on the Caribbean island of St. Vincent ~1635.
Garifuna - descendants of these enslaved people and indigenous island Carib and Arawak



https://carriacou.biz/caribs-garifuna/

Garifuna have a strong presence in the Bronx

>200-300K in NYC, most in Crotona, South Bronx

Race vs ancestry: Self-defined race is helpful for social determinants of health, misleading and often wrong for biological determinants of health

-especially problematic for admixed individuals

Challenges to the physician - what is a population?

African?
African-American?
Afro-Caribbean?
Brazilian?
Creole?

American or Latino -
Cuban?
Mexican?
Puerto Rican?
Indigenous?

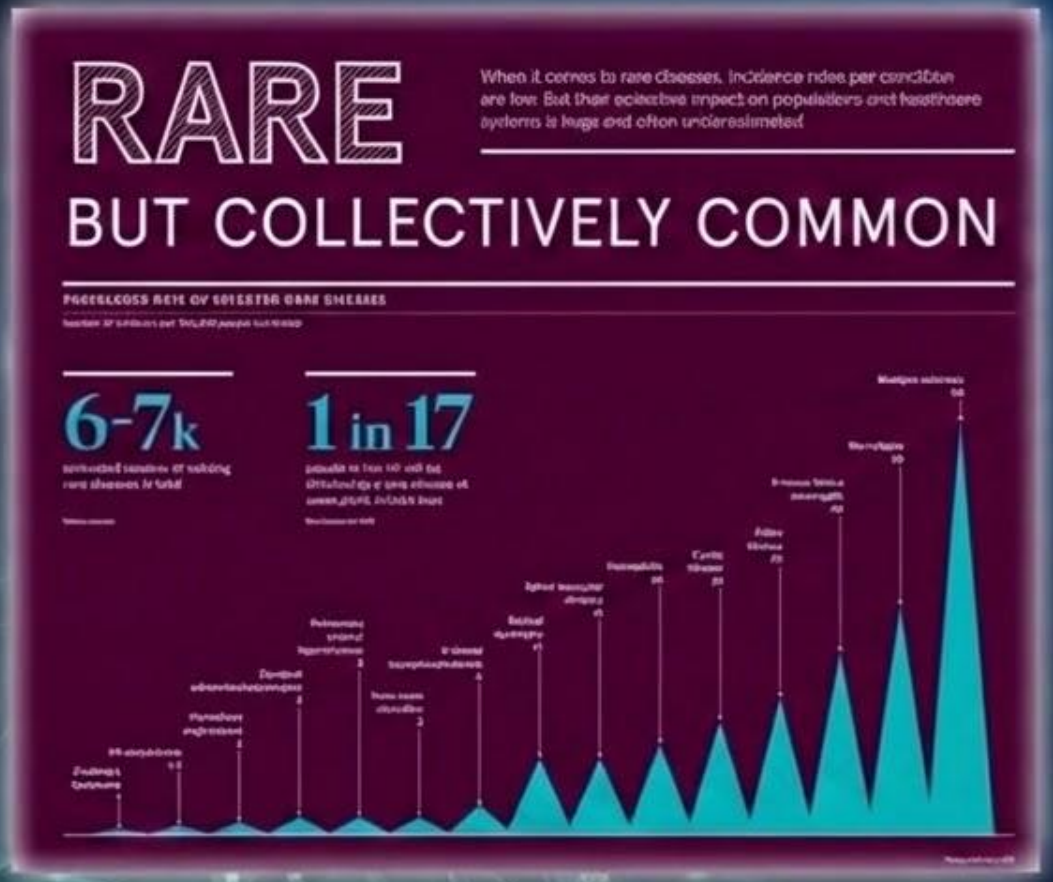
Northern European white?
Ashkenazi Jewish?
Hutterite?
Amish?
Italian?

Chinese?
Japanese?
Hmong?
Filipino?
Vietnamese?

Biobanks in Rare Disease Research - lessons from All of Us

Srilakshmi Raj, PhD
Albert Einstein College of Medicine

Rare disease is collectively common



Economic burden:

- ~$1 trillion/yr in USA (379 diseases)
- Per-patient costs: 10x higher than common diseases
  (National Economic Burden of Rare Disease study (2021)

- Early diagnosis of rare diseases - saves $500,000 per patient
  (Cost of Delayed Diagnosis in Rare Disease (2023)

Wikipedia (2015)

https://www.visualcapitalist.com/which-rare-diseases-are-the-most-common/

FOUNDATION FIGHTING BLINDNESS
CLINICAL CONSORTIUM

“If We Build It, They Will Come”

Amy Laster, PhD
Chief Scientific Officer

Retinal Degenerations

- **Rare:** less common than 1:3,500 worldwide
- **Inherited:** families may be concentrated in areas with limited access to specialist care
- **Extreme genetic heterogeneity:** caused by genetic changes in over 300 genes, with variable and widely ranging clinical manifestations associated with each gene
- **Relentless:** genetic changes cause progressive dysfunction and death of rod and cone photoreceptors
- **No effective treatments for most**

Challenges to Developing Treatments

- **Uncommon: few patients available for study, limited information exists**
- **Wide range of phenotypes requires evaluation using specialty testing and expert clinical evaluation**
- **Limited standardized prospective natural history data on IRDs**
- **Unclear what outcome measures will be most likely to demonstrate change over time, or safety and efficacy of treatments**

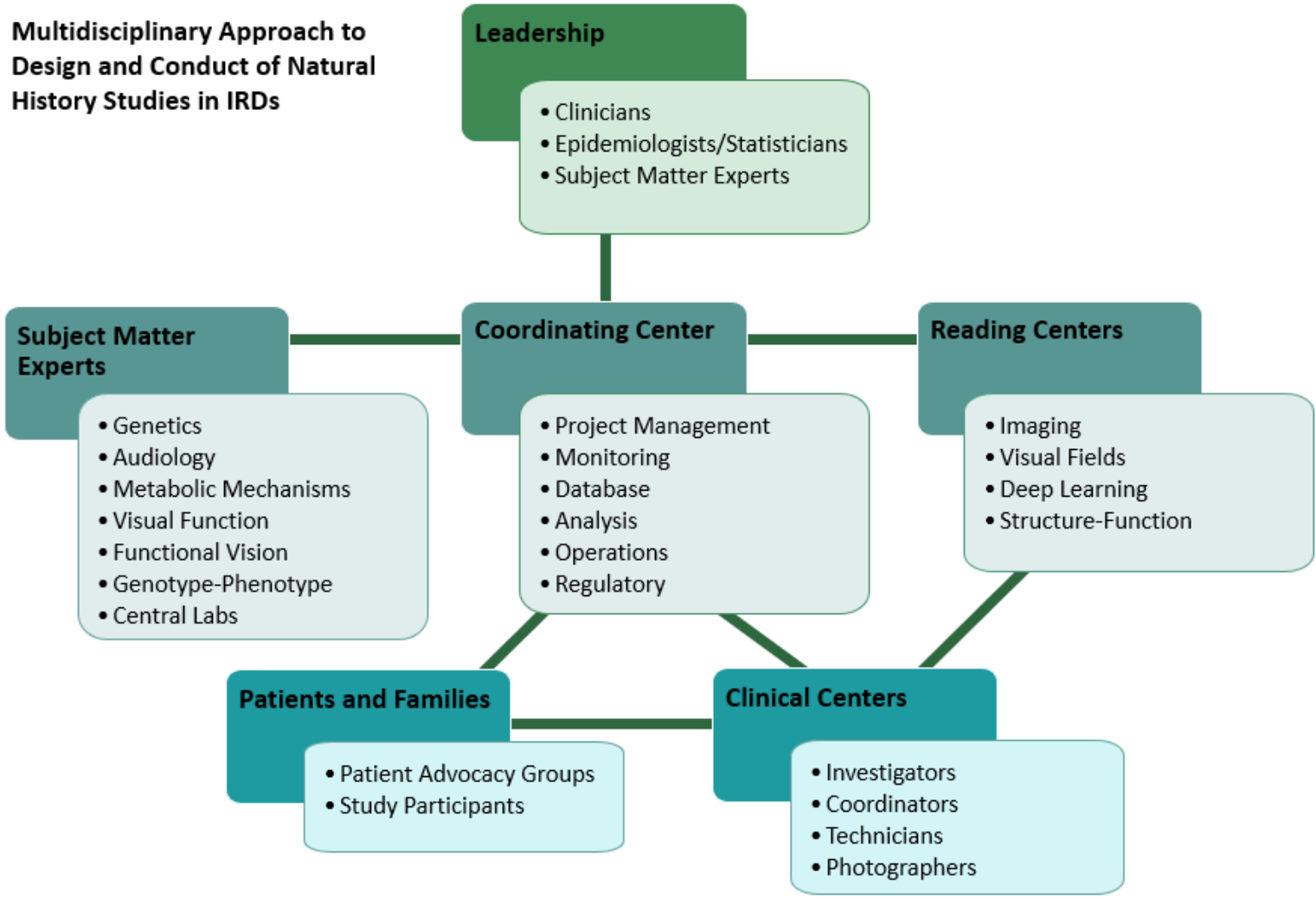
Consortium Model

- Goal: Accelerate development of treatments for IRDs
- Investigators collaborate on ideas for hypotheses, study designs, and publications
- Consortium Natural History Studies (NHS):
  - Provide prospective, standardized, longitudinal data on disease progression
  - Identify sensitive structural and functional outcome measures for future clinical trials
- Data from completed studies will be archived in an open central repository to stimulate further hypothesis generation and innovation

Consortium Overview

Consortium of clinical centers with expertise in inherited retinal degenerations (IRDs)

Goal: Accelerate development of treatments for IRDs



Ayala et al., The Importance of Natural History Studies in Inherited Retinal Diseases, Cold Spring Harbor Laboratory Press, 2023

Consortium Strengths

- **Feasible recruitment**
  - Due to large number of international sites
- **Data quality**
  - Enforced by standardized procedures
- **Efficiencies**
  - Gained from existing infrastructure
- **Collaboration**
  - Of ideas and expertise from multidisciplinary team
- **Sharing**
  - Of datasets further our mission to advance IRD research

Consortium Efficiencies

- Master Agreements
- IRB Reliance Agreements
- Technician Certification
- Standardized Data Collection Forms
- Standardized Procedures

Downstream efficiencies – monitoring procedures, reports, checks, and statistical coding become standardized and based on templates

Objectives of our NHS

- Estimate rates of progression
- Investigate structure-function relationships
- Explore properties of candidate endpoints (e.g., signal-to-noise, reproducibility, symmetry)
- Identify factors related to progression
- Define genotype-phenotype associations
- Provide a source of historical control data
- Inform the design and practical challenges of clinical trials

Outcome Measures in our NHS

- **Structural**

  Spectral-domain optical coherence tomography (SD-OCT) volume and V/H, fundus autofluorescence (FAF), color photos
- **Functional**

  Static perimetry (SP), microperimetry (MP), full-field stimulus threshold (FST), electroretinography (ERG), best corrected visual acuity (BCVA), low luminance visual acuity (LLVA), contrast sensitivity, color vision
- **Patient Reported Outcomes (PROs)**

  Visual function questionnaires (MRDQ, ViSIO)

  Quality-of-life questionnaires (PROMIS-29)
- **Performance Based Tests (PBTs)**

  MObility STandardized Task in Virtual Reality (MOST-VR)

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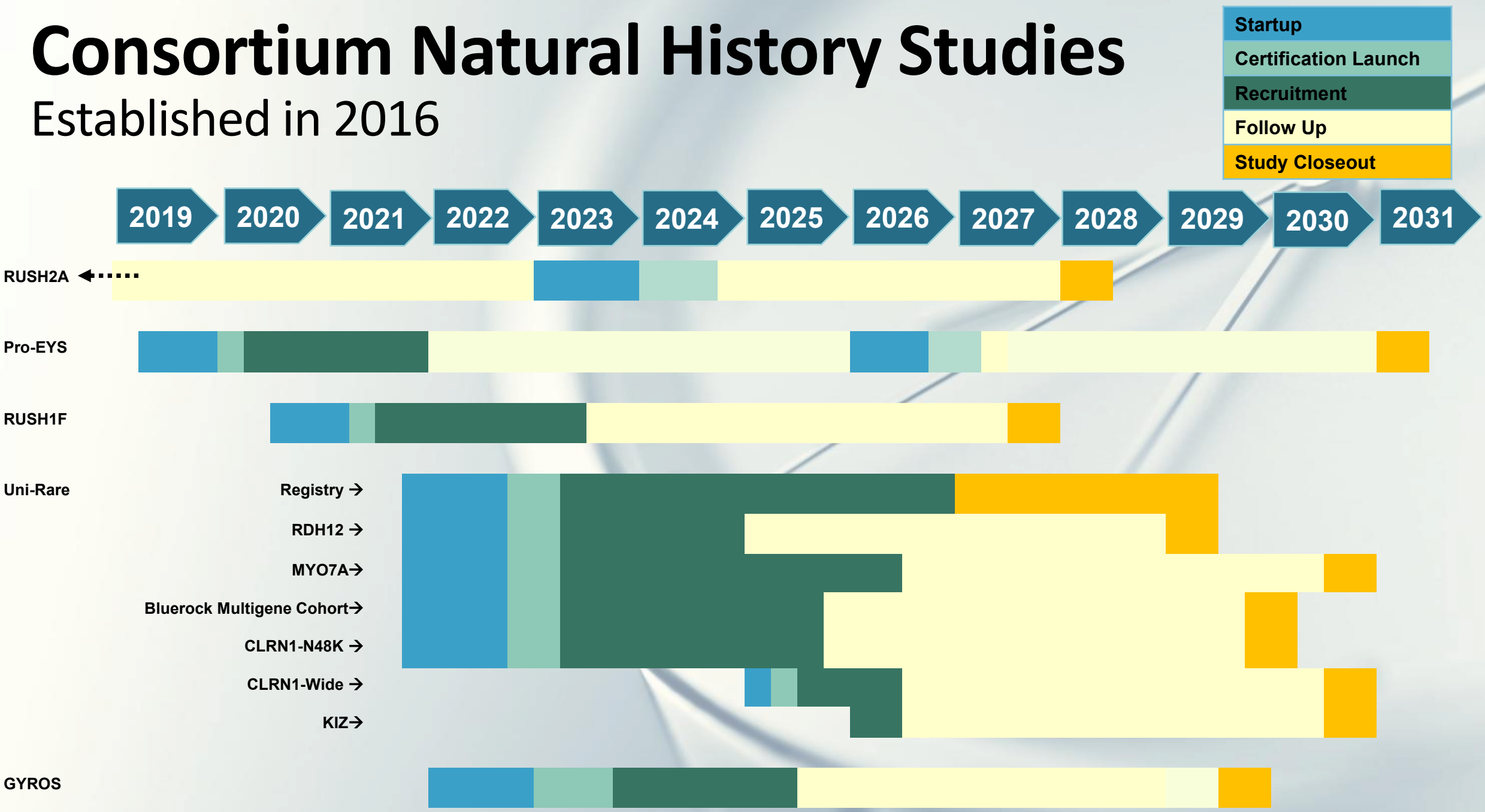
Studies

Consortium Natural History Studies

Established in 2016



Universal Rare Gene Study (Uni-Rare)

- **Study Chair:** José-Alain Sahel
- **Registry Component**
  - Prospective, standardized, cross-sectional clinical data collection
  - Open to >300 rare IRD genes
  - N=1500
- **Natural History Study (NHS) Component**
  - Prospective, standardized, longitudinal (4 years) clinical data collection
  - A platform to move participants from the registry as each gene opens
  - N=100 cap per gene

→ Genotype Characterization
Cross-Sectional Phenotype Characterization

→ Natural History using Functional, Structural, PRO Measures
Structure-Function Relationship
Risk Factors for Progression

Co-funded: *Co-funded by Foundation Fighting Blindness, AAVantgarde, Allen B. Cutting Foundation, Anonymous Donors, Atsena Therapeutics, BlueRock Therapeutics, Cove Therapeutics, Eli Lilly and Company, Jackie and David Marlin, Maryrose Sylvester, Max and Minnie Tomerlin Voelcker Fund, Octant Inc., Opus Genetics, Sarah de Coizart Trust, Save Sight Now, Usher III Initiative*

Status: Registry recruitment goal December 2026

NCT05589714

Uni-Rare Impact

Part 1 – Cross-sectional registry

The registry will establish genetically and clinically well-characterized cohorts of patients across hundreds of genetic variants associated with retinal dystrophy.

Characterization of these patients will:

- **Provide cross-sectional data on phenotype-genotype associations**
- **Contribute to our knowledge of pathogenicity of these rare disease-causing variants**
- **Accelerate eligibility screening for subsequent natural history studies**

Part 2 – Prospective, natural history

The natural history study will accelerate the identification of sensitive, reliable outcome measures for clinical trials, which will facilitate development of treatments for retinal dystrophies due to disease-causing genetic variants. The expected impact of the natural history study is to:

- **Describe the natural history of retinal degeneration in patients with rare disease-causing genetic variants**
- **Define sensitive structural and functional outcome measures for future multicenter clinical trials of rare inherited retinal degeneration**
- **Identify well-defined subpopulations for future clinical trials of treatments for rare inherited retinal degeneration**

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Thank you

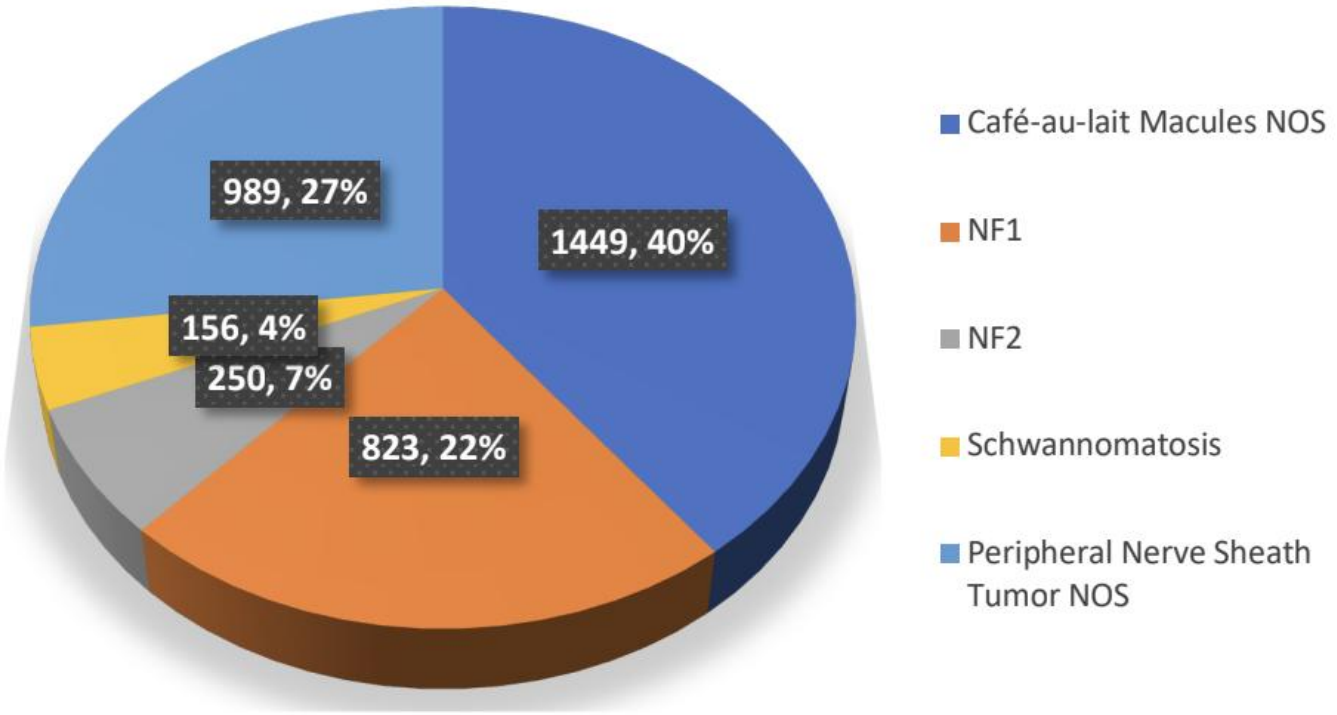
Amy Laster, PhD
alaster@FightingBlindness.org

MAYO CLINIC

Supplementing Patient Registries with Electronic Health Record (EHR) Dataset: Challenges and Opportunities

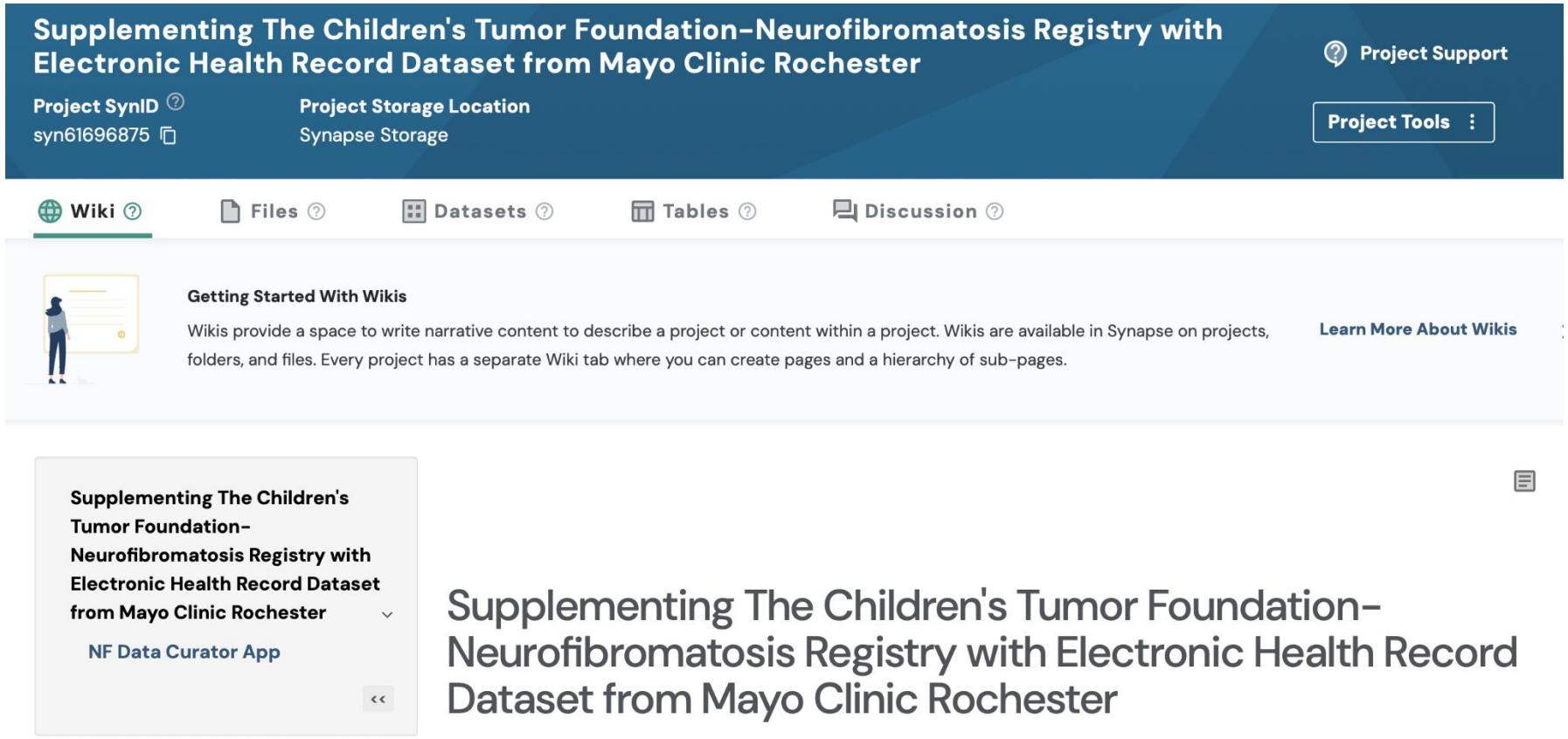
Mayowa Osundiji, MBBS, PhD, FACMG, FADLM, HCLD (ABB)
Clinical Geneticist
Department of Clinical Genomics

Supplementing Patient Registries with Electronic Health Record (EHR) Dataset: Exemplified by Neurofibromatosis (NF) and Schwannomatosis (SCHWN)

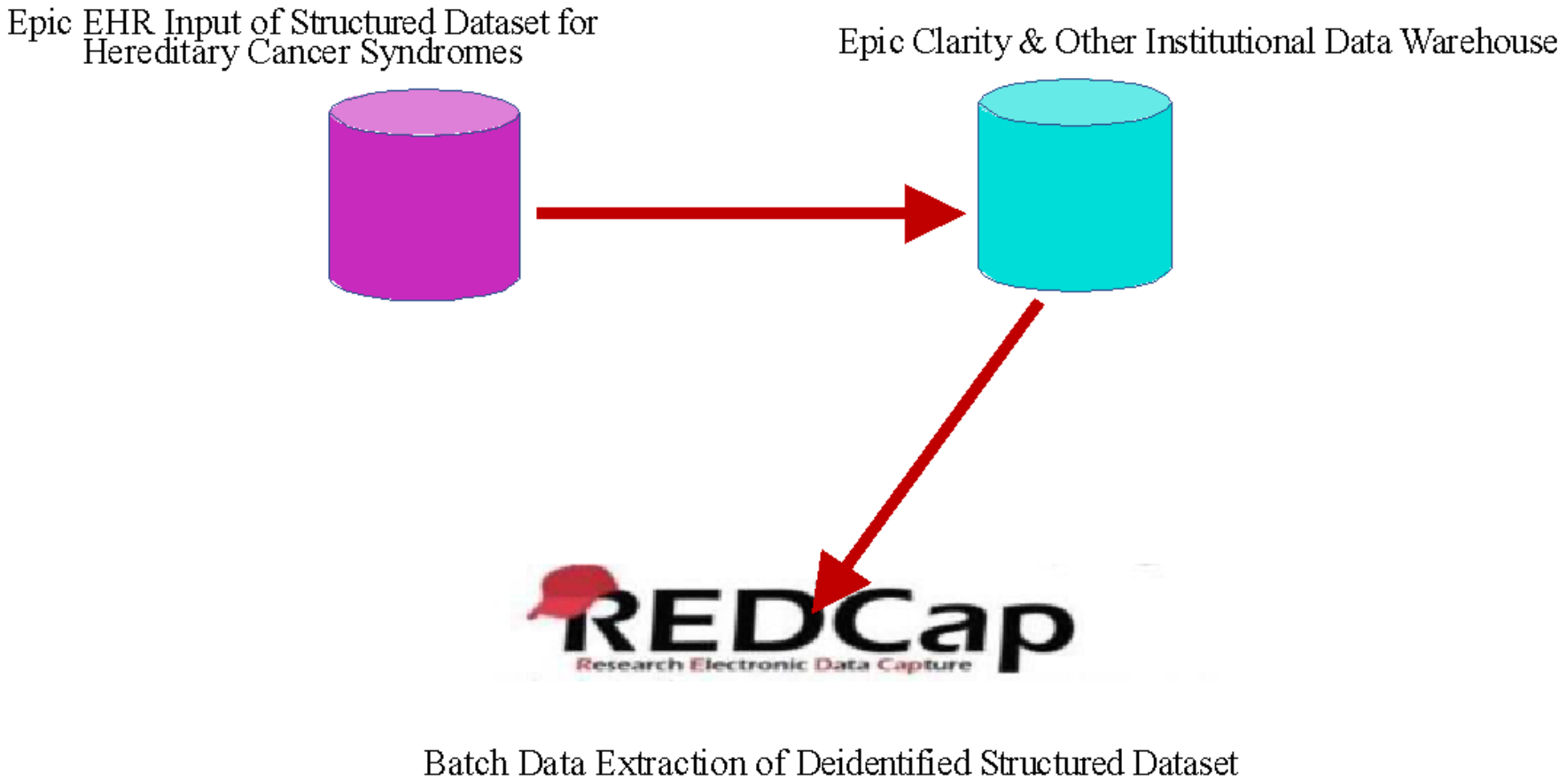


Proportion (number and percentage) of patients with neurofibromatosis (NF) type 1 and 2 as well as schwannomatosis across Mayo Clinic. Also included are patients who are being followed for suspected NF1, NF2 or schwannomatosis in the context of a history of peripheral nerve sheath tumor or multiple café-au-lait macules. NOS means not otherwise specified. Total n=3,667.

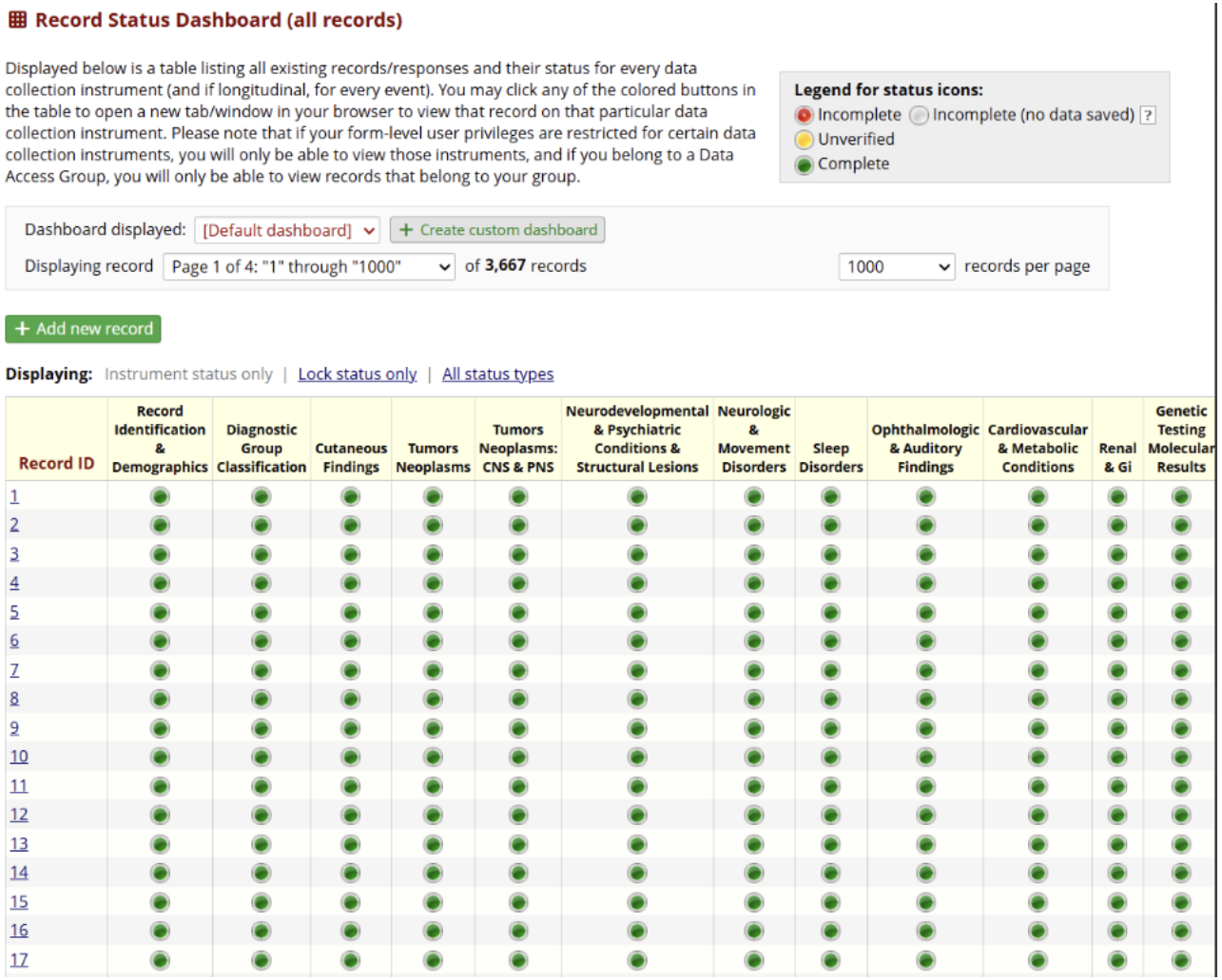
EHR Driven NF and SCHWN Registry



EHR Driven NF and SCHWN Registry



REDCap NF and SCHWN Registry



Record Status Dashboard (all records)

Displayed below is a table listing all existing records/responses and their status for every data collection instrument (and if longitudinal, for every event). You may click any of the colored buttons in the table to open a new tab/window in your browser to view that record on that particular data collection instrument. Please note that if your form-level user privileges are restricted for certain data collection instruments, you will only be able to view those instruments, and if you belong to a Data Access Group, you will only be able to view records that belong to your group.

Legend for status icons:
Incomplete | Incomplete (no data saved) | Unverified | Complete

Dashboard displayed: [Default dashboard] + Create custom dashboard

Displaying record Page 1 of 4: "1" through "1000" of **3,667** records 1000 records per page

+ Add new record

Displaying: Instrument status only | Lock status only | All status types

Record ID	Record Identification & Demographics	Diagnostic Group Classification	Cutaneous Findings	Tumors Neoplasms	Tumors Neoplasms: CNS & PNS	Neurodevelopmental & Psychiatric Conditions & Structural Lesions	Neurologic & Movement Disorders	Sleep Disorders	Ophthalmologic & Auditory Findings	Cardiovascular & Metabolic Conditions	Renal & Gi	Genetic Testing Molecular Results
1												
2												
3												
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11												
12												
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16												
17												

REDCap NF and SCHWN Registry

1. Improved understanding of clinical manifestations, disease characteristics and progression, can help guide surveillance

2. Genotype-phenotype associations and management outcomes

3. Improved molecular diagnostic processes via resolution of variants of uncertain significance

Questions

Registries and Real-World Data to Support Therapeutic Development: Empowering Patient Advocacy Groups

Theresa Strong, PhD

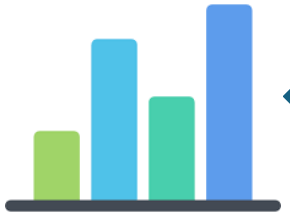
Director of Research Programs
Foundation for Prader-Willi Research
Daniel's mom

GLOBAL PRADER-WILLI SYNDROME REGISTRY

NORD® IAMRARE®
Registry Platform

FOUNDATION FOR PRADER-WILLI RESEARCH

PAGs are uniquely suited to:



Bring quantitative data to support anecdotal evidence - documenting the unmet medical needs of our patient community

Collaboratively develop tools to support efficient, meaningful clinical trials

Build knowledge to inform clinical development for pharmaceutical companies, regulatory agencies

Prader-Willi Syndrome

- Complex neurodevelopmental disorder that occurs in ~1/15,000 births; affects males/females, all races and ethnicities
- Loss of paternally expressed, imprinted set of genes on chromosome 15q11-13
- Major features:
  - Hypotonia, FTT → hyperphagia, obesity
  - Clinical problems: endocrine deficiencies, orthopedic problems (scoliosis), sleep disturbances, respiratory issues, GI problems, incr. risk of mortality across lifespan
  - Challenging behavioral profile: anxiousness, temper outbursts, OCD behaviors, cognitive rigidity; highly susceptibility to mental illness
  - Mild to moderate intellectual disability

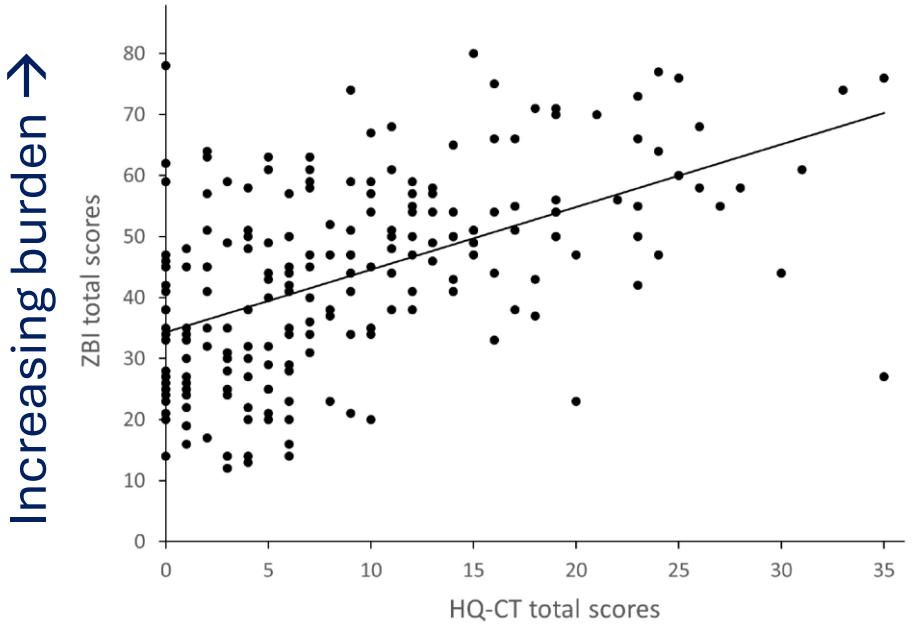






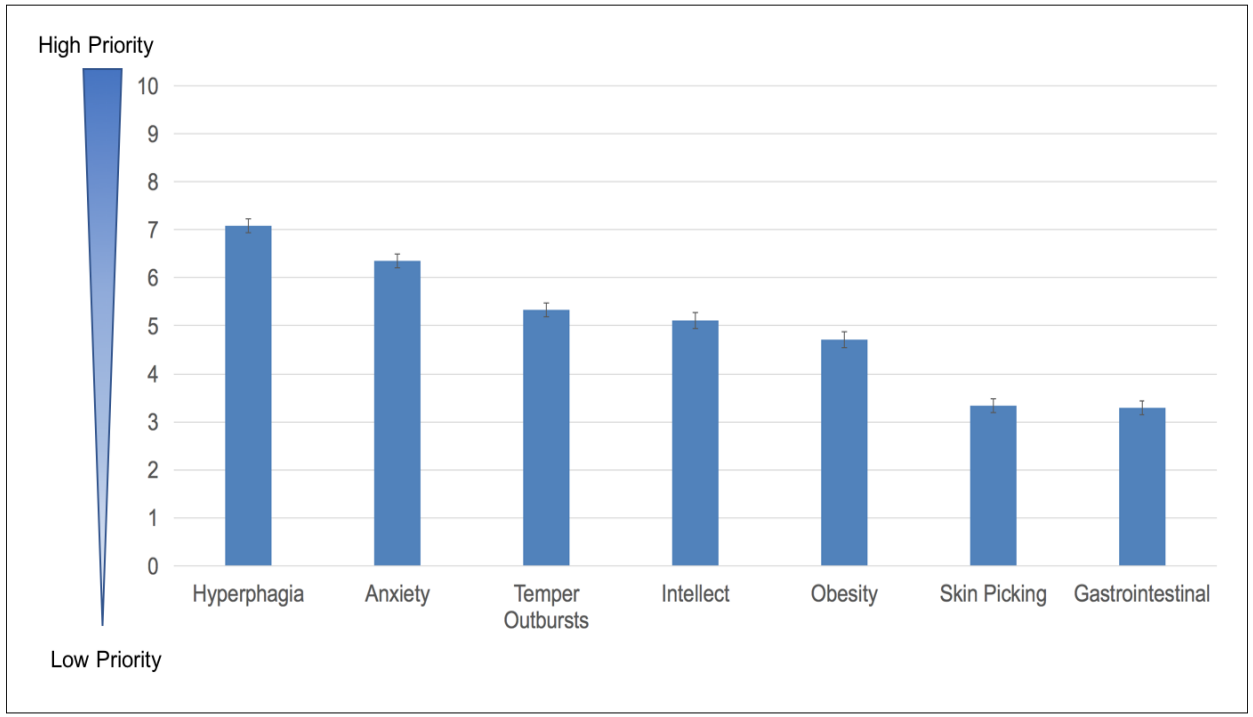
Impact of PWS on the Family

- Hyperphagia and behaviors limit the person's ability to achieve independence, reach life goals and engage in the community
- Caregiver burden as measured by the Zarit Burden Interview (ZBI) is very high, even compared to other challenging disorders: sleep, family relationships, and ability to work impacted
- ZBI score is higher for those families experiencing more severe hyperphagia
- ZBI scores stable over time in the absence of effective treatment



https://doi.org/10.1371/journal.pone.0248739.g002

What do families want to see treatments for?
What level of risk are they willing to accept?

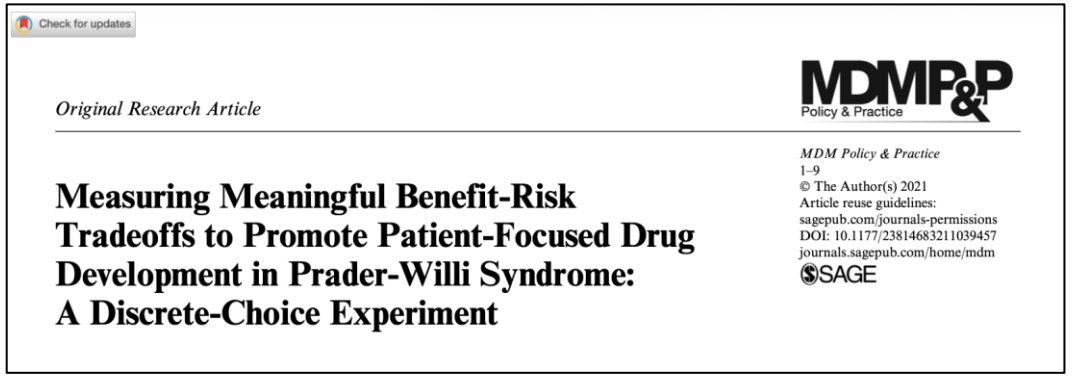


Families are willing to accept risk for a modest improvement in hyperphagia

Caregiver priorities for endpoints to evaluate treatments for Prader-Willi syndrome: a best-worst scaling

Jui-Hua Tsai, Ann O. Scheimann, Shawn E. McCandless, Theresa V. Strong & John F.P. Bridges

Journal of Medical Economics, DOI: 10.1080/13696998.2018.1528980


Check for updates

Original Research Article

MDMP&P Policy & Practice

Measuring Meaningful Benefit-Risk Tradeoffs to Promote Patient-Focused Drug Development in Prader-Willi Syndrome: A Discrete-Choice Experiment

MDM Policy & Practice
1–9
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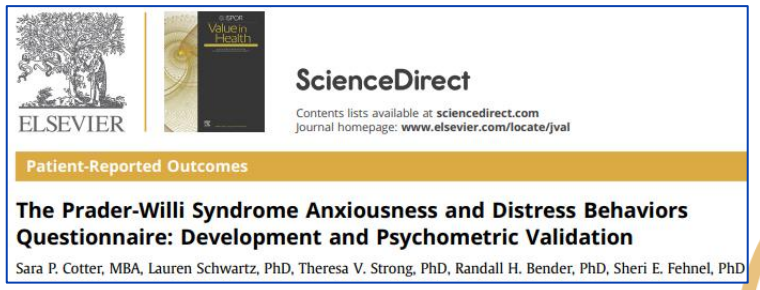
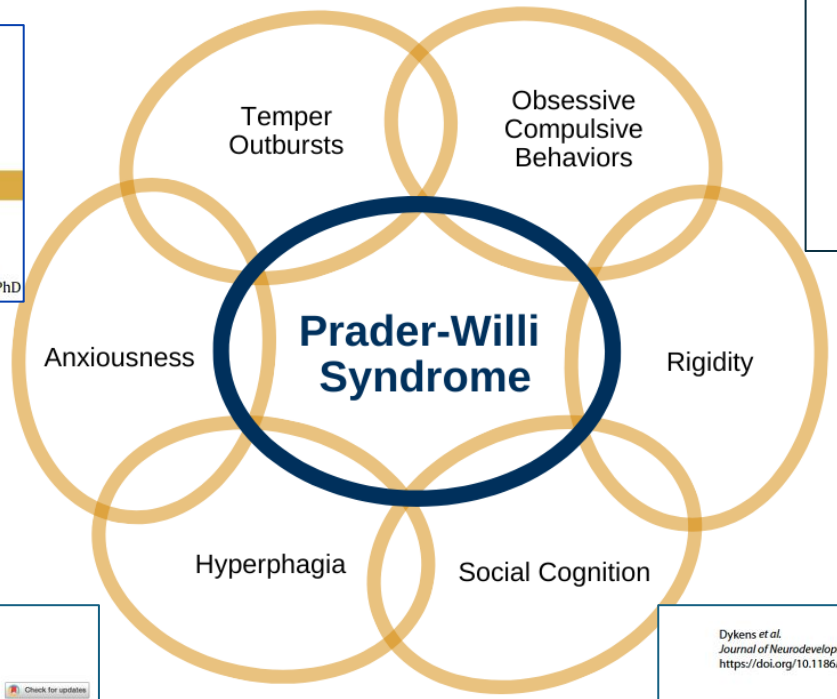
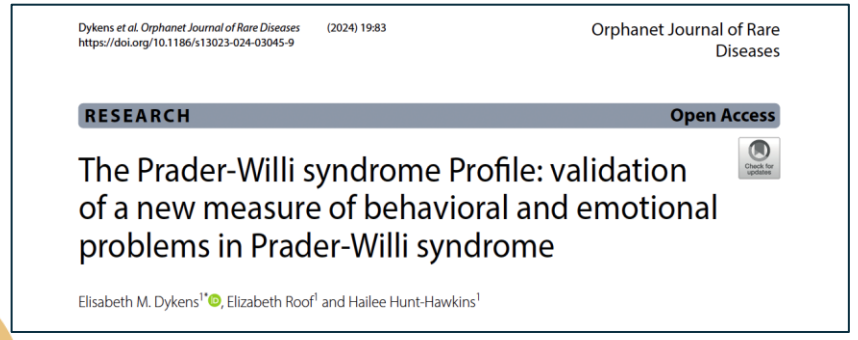
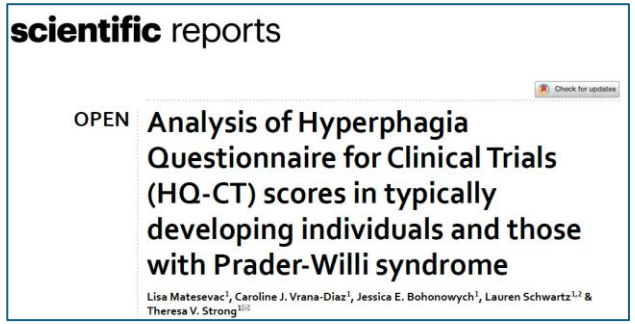
Measuring the PWS-specific features that matter to families: Characterizing new clinical outcome assessments

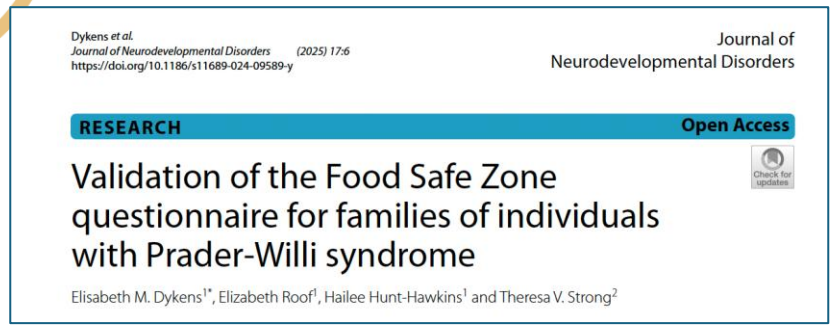
400-640 participants for each study
Longitudinal data over 4+ years



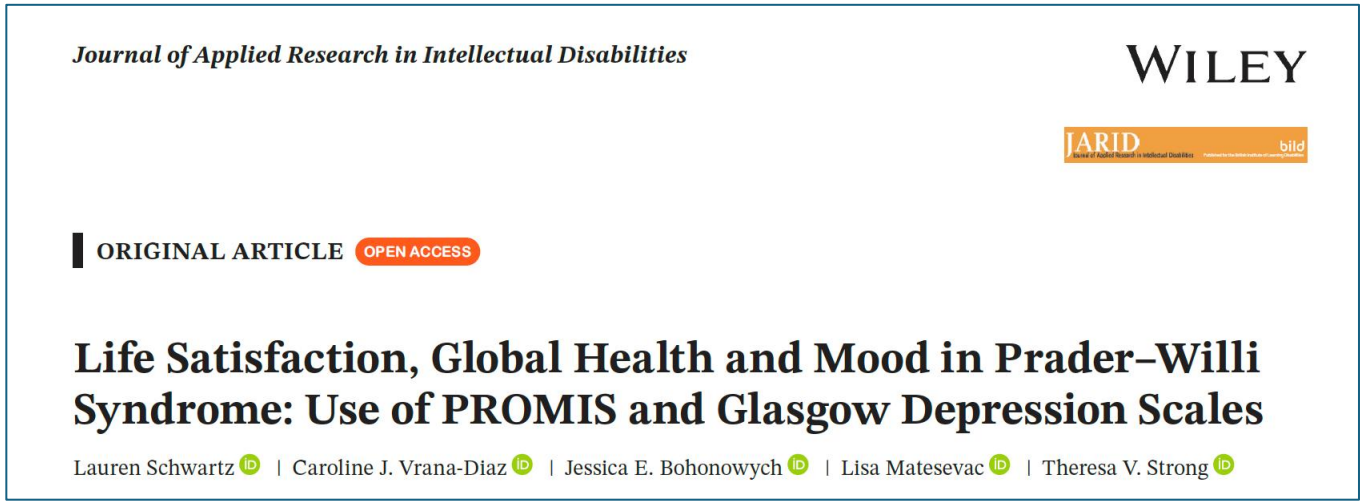








Evaluation of Validated Measures in PWS



Journal of Applied Research in Intellectual Disabilities

WILEY

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ORIGINAL ARTICLE OPEN ACCESS

Life Satisfaction, Global Health and Mood in Prader–Willi Syndrome: Use of PROMIS and Glasgow Depression Scales

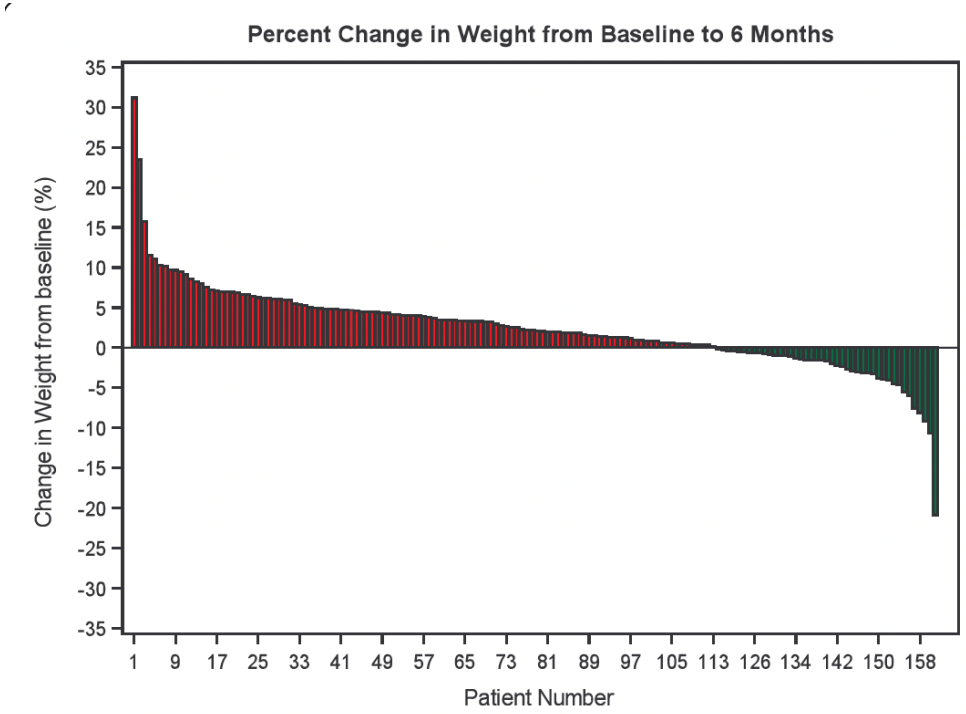
Lauren Schwartz | Caroline J. Vrana-Diaz | Jessica E. Bohonowych | Lisa Matesevac | Theresa V. Strong

PROMIS Parent Proxy Global Health
PROMIS Parent Proxy Life Satisfaction
Glasgow Depression Scale – Carer Supplement

Useful for assessing quality of life in the PWS population

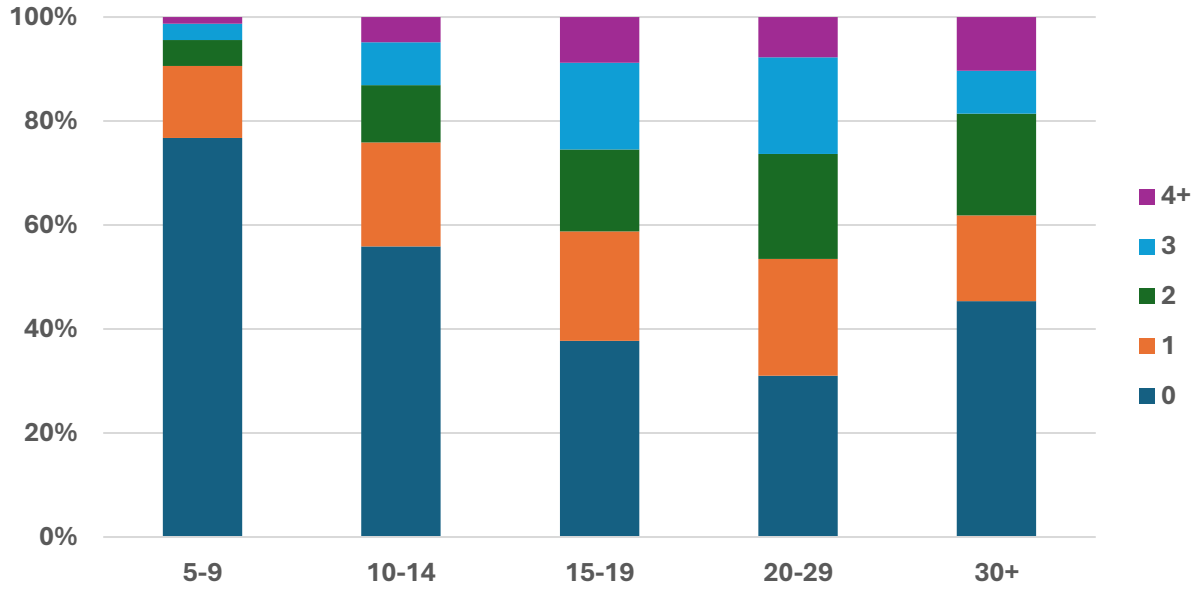
Natural History Studies to Inform Clinical Trial Design

What % of the PWS population has >5% change in weight over 6 mo?



Change in weekly weight over 6 mo, collected via HIPPA-compliant text messaging

What % of the population are taking psychotropic medication?



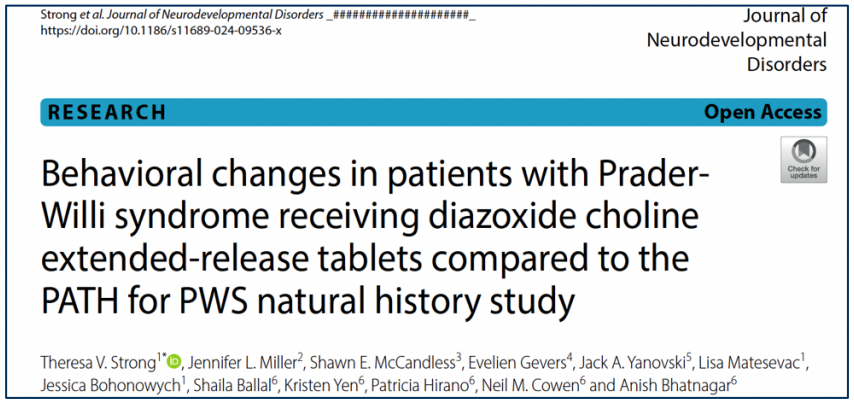
n=644

PATH for PWS
Paving the way for Advances in Treatments & Health for PWS

Natural History Studies to Support Drug Approvals

Compared to participants in *PATH for PWS* Natl Hx Study who were not receiving the drug, matched participants treated with VykatXR for 6 months or 1 year showed:

- Highly significant improvements in hyperphagia ($p < 0.001$)
- Significantly greater improvements in PWS associated behaviors - aggression, anxiety, compulsivity, rigidity/irritability, depression and disordered thinking



Strong *et al. Journal of Neurodevelopmental Disorders* _####################_
https://doi.org/10.1186/s11689-024-09536-x

Journal of Neurodevelopmental Disorders

RESEARCH Open Access

Behavioral changes in patients with Prader-Willi syndrome receiving diazoxide choline extended-release tablets compared to the PATH for PWS natural history study

Theresa V. Strong[1*], Jennifer L. Miller[2], Shawn E. McCandless[3], Evelien Gevers[4], Jack A. Yanovski[5], Lisa Matesevac[1], Jessica Bohonowych[1], Shaila Ballal[6], Kristen Yen[6], Patricia Hirano[6], Neil M. Cowen[6] and Anish Bhatnagar[6]

PATH for PWS™
Paving the way for Advances in Treatments & Health for PWS

SOLENO THERAPEUTICS

March 2025 approval

PAG's are increasingly sophisticated in using registries and real-world data to support therapeutic development

Ideally situated to collaborate / lead these studies:

- understand disease-specific issues / landscape
- highly motivated to generate and share data
- long-term commitment

Challenges

- Are we collecting data from a representative population?
- How can we better integrate multiple data sources (e.g., clinician reported data with patient reported data)?
- How can we ensure that PAGs have a meaningful seat at the table?