National Human Genome Research Institute

National Institutes of Health

U.S. Department of Health and Human Services

NHGRI's Genomic Medicine Research Portfolio

U.S. Department of Health and Human Services
National Institutes of Health
National Human Genome Research Institute

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Division of Genomic Medicine, NHGRI
August 30, 2016

NACHGR Genomic Medicine Working Group Members

NHGRI defines genomic medicine as *"an emerging medical discipline that involves using genomic information about an individual as part of their clinical care and the health outcomes and policy implications of that clinical use."*

Mary Relling	St. Jude
Dan Roden	Vanderbilt
Marc Williams	Geisinger
Eric Green	NHGRI
Teri Manolio	NHGRI
Laura Rodriguez	NHGRI

Genomic Medicine Colloquium Report
June 2011, Chicago, IL

REVIEW | Genetics inMedicine

Open

Impl linic:

- Much more than anticipated
- Largely in isolation
- Common barriers

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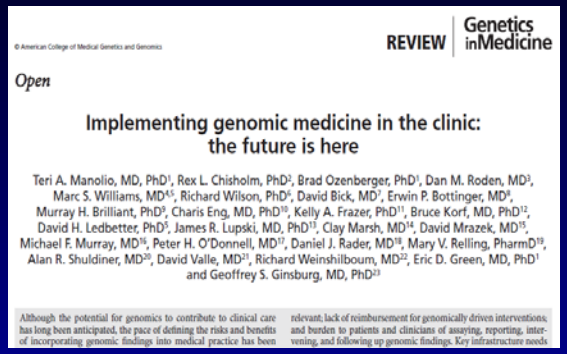
and Geoffrey S. Ginsburg, MD, PhD[23]

Although the potential for genomics to contribute to clinical care has long been anticipated, the pace of defining the risks and benefits of incorporating genomic findings into medical practice has been relevant; lack of reimbursement for genomically driven interventions; and burden to patients and clinicians of assaying, reporting, intervening, and following up genomic findings. Key infrastructure needs

Genet Med 2012; 15:258-67.

GM VIII: NHGRI's Genomic Medicine Programs, June 2015

Genomic Medicine Colloquium, June 2011



GM II: Forming Collaborations, Dec 2011

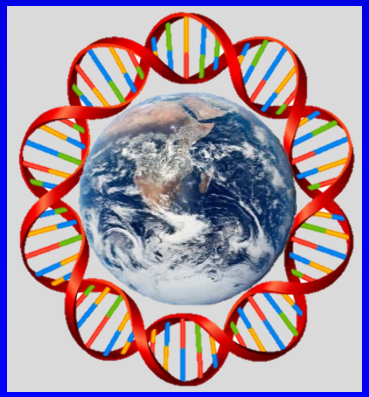
GM VII: Genomic CDS, Oct 2014

GM IX: Bedside Back to Bench, April 2016

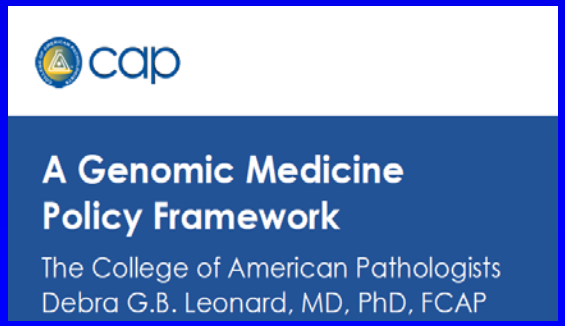
GM III: [illegible] 2

Google "NHGRI Genomic Medicine"

GM VI: Global Leaders, Jan 2014



GM V: Federal Strategies, May 2013



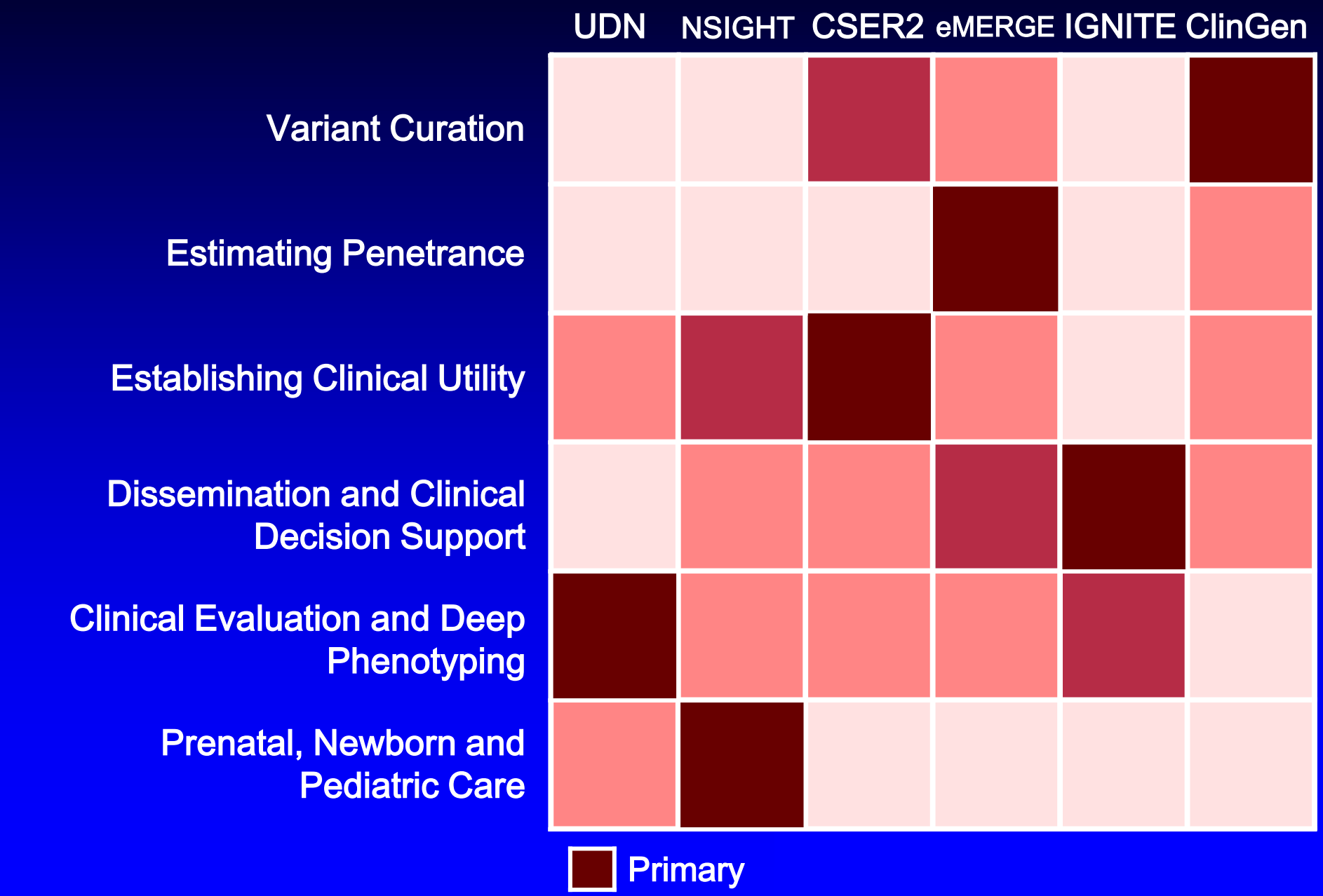
GM IV: Physician Education, Jan 2013

NHGRI's Genomic Medicine Research Program

Program	Goal	Σ$M	Years
UDN[1]	Diagnose rare and new diseases by expanding NIH's Undiagnosed Diseases Program	121	FY13-17
NSIGHT[2]	Explore possible uses of genomic sequence information in the newborn period	25	FY13-17
CSER[3]	Explore infrastructure, methods, and issues for integrating genomic sequence into clinical care	83	FY12-16
eMERGE[4]	Use biorepositories with EMRs for genomics; (III) assess penetrance of 106 clinically relevant genes in 25,000 individuals, develop e-phenotypes, CDS	135	FY07-18
IGNITE[3]	Develop and disseminate methods for incorporating patients' genomic findings into their clinical care	28	FY13-17
ClinGen[4]	Develop and disseminate consensus information on genes and variants relevant to clinical care	28	FY13-16

[1]NIH Common Fund; [2]Co-Funded by NICHD; [3]Co-Funded by NCI; [4]Co-Funded by OD.

Emphasis Areas of Genomic Medicine Programs



Share Print

NIH Undiagnosed Diseases Program

- Overview
- Program Background
- Program Information

See Also:

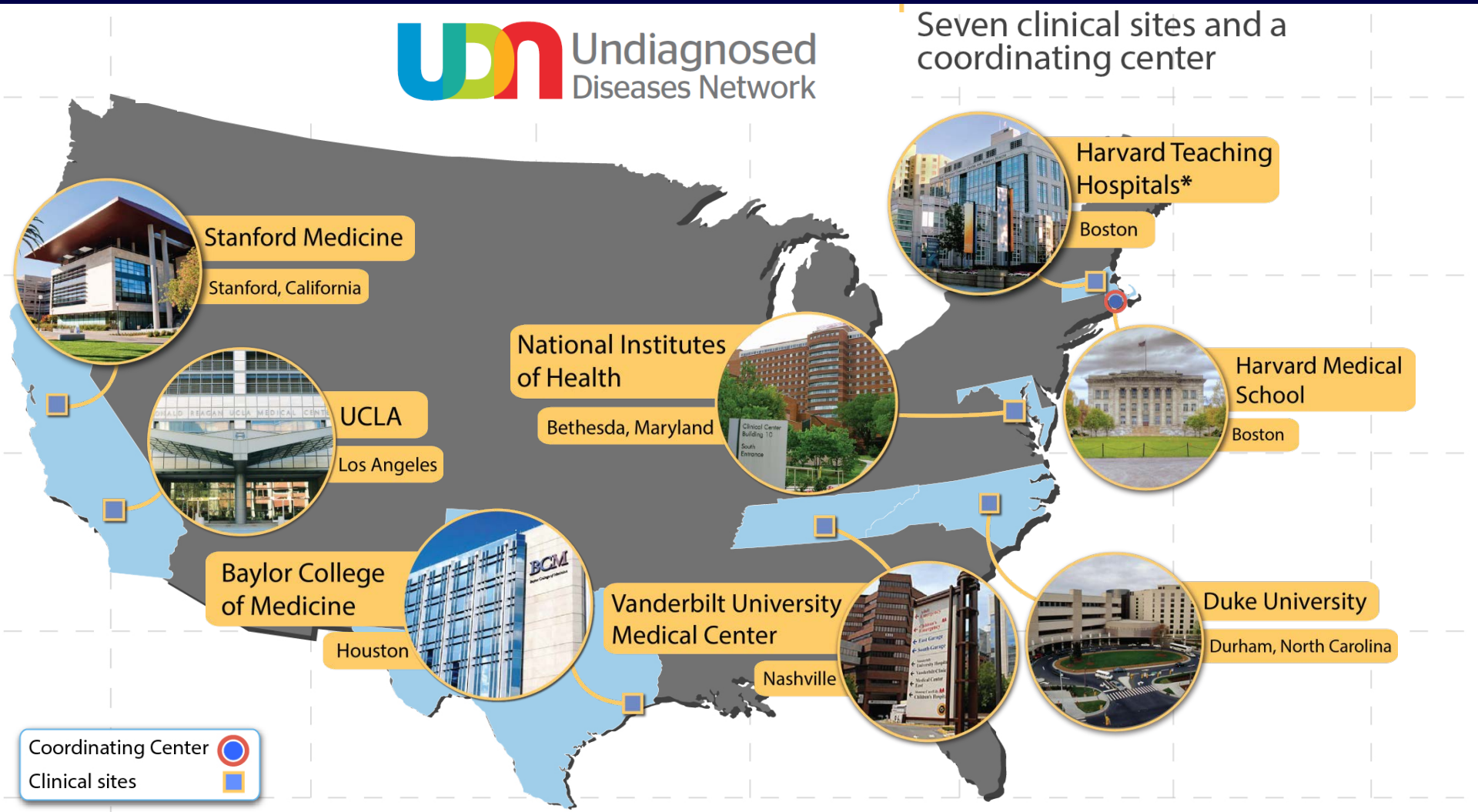
Undiagnosed Diseases

Overview

The NIH Undiagnosed
that focuses on the mo
Bethesda, Md. It was o
the NIH Office of Rare D
research centers and in
oncology, dermatology

A longstanding medical
interest to this clinical r
number will be invite
general, it takes 8 to 1

Undiagnosed Diseases Network (UDN)



The NIH site will continue to enroll about 150 patients per year; each of the clinical sites will ultimately enroll about 50 patients per year. A DNA sequencing core facility to be announced in the coming weeks.

*Boston Children's Hospital, Brigham and Women's Hospital and Massachusetts General Hospital participate jointly in the Harvard Center for Integrated Approaches to Undiagnosed Diseases

Newborn Sequencing in Genomic Medicine and Public Health (NSIGHT) Program

- Robert Green, Alan Beggs, Brigham
  NICU and healthy newborns, 240 exomes, NBS vs. NBS + genomic NBS
- Stephen Kingsmore, Children's Mercy Hospital
  NICU, 1000 genomes, NBS vs NBS + sequencing
- Jennifer Puck, UCSF
  1620 exomes, added value to NBS program
- Cynthia Powell, UNC
  400 exomes including 200 unselected infants; consented in pregnancy

Clinical Sequencing Exploratory Research (CSER)

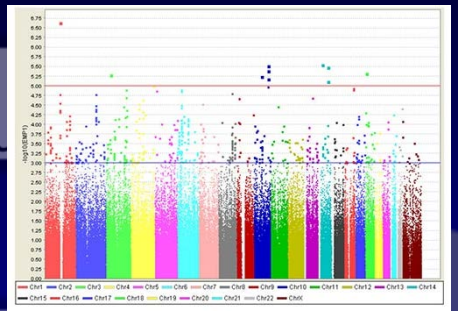
- Investigate challenges in applying sequence data to clinical care, including:
  - Implementing clinical workflow
  - Interpreting and translating data for clinicians
  - Communicating findings to patients
- Develop best practices for WGS/WES
- Further develop evidence base for implementation

CSER Projects

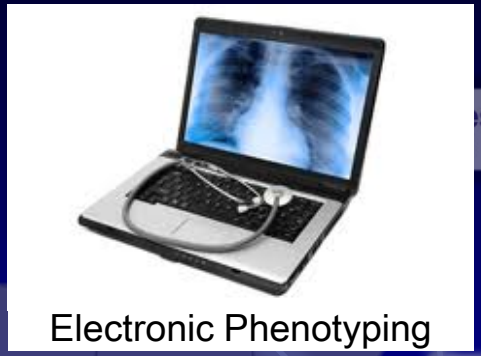
Site	Disease/Condition
Baylor*	Pediatric Cancer
Brigham	Healthy Pts, Hypertrophic Cardiomyopathy
CHOP	Pediatric Diseases (Intellectual Disability)
Dana-Farber	Solid Tumors
Hudson-Alpha	Children with Intellectual Dysfunction
Kaiser Portland	Preconception Carrier Screening
U Michigan*	Adults and Children with Advanced Cancer
U N Carolina	Cardiomyopathy, Cancer
U Washington*	CRC and Polyposis

*Co-funded by NCI.

Electronic Medical Records and Genomics (eMERGE) Network – Phase III



GWAS Discovery



Electronic Phenotyping

Consent Methodology

Clinician/Pt Education

Decision Support

Community Consultation

Pharmacogenomics

Pediatrics

Data Privacy

eMERGE III Goal and Aims

Continue genomic medicine discovery and implementation research utilizing large biorepositories linked to EMRs

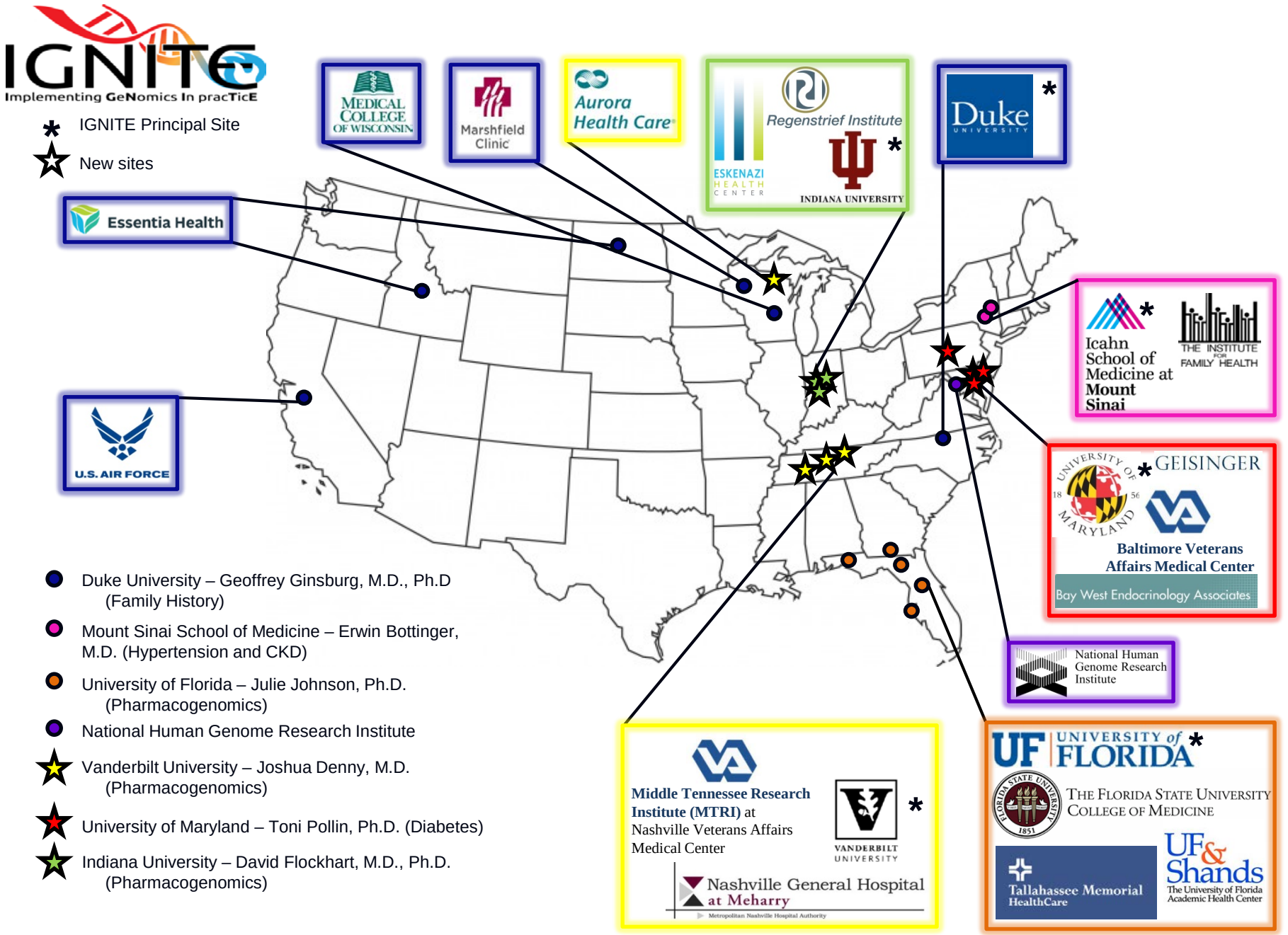
- Identify rare variants with presumed major impact on function of ~100 clinically relevant genes
- Assess phenotypic implications of variants by leveraging well-validated EMR data or re-contact
- With appropriate consent and education, report actionable variants to pts, (families), clinicians
- Assess impact to pts, clinicians, and institutions on pt outcomes and cost of care

Implementing Genomics Into Clinical Practice (IGNITE) Network

- Expand and link existing genomic medicine efforts
- Develop new collaborative projects and methods, in diverse settings and populations
- Contribute to evidence base regarding outcomes of incorporating genomic information into clinical care
- Define and share processes of genomic medicine implementation, diffusion, and sustainability

www.ignite-genomics.org

IGNITE
Implementing GeNomics In pracTicE



Weitzel K *et al.*, *BMC Med Genom* 2016; 9:1.

Clinical Genome Resource (ClinGen)

Improving our knowledge of genomic variation requires a massive effort in data sharing and collaborative curation

ClinGen
Clinical Genome Resource

Courtesy Erin Ramos, NHGRI

ClinGen: Purpose and Goals

Create centralized resource of clinically annotated genes and variants to improve understanding of genomic variation and optimize its use in medicine.

- **Standardize** clinical assessment of variants and deposition into ClinVar
- Develop a **consensus process** for identifying clinically relevant variants
- **Curate** genes and variants within multiple domains
- Develop **machine learning algorithms** to improve accuracy and throughput for interpretation
- **Disseminate** and explore integration with EHRs
- Grants awarded mid-Sept 2013

Courtesy E. Ramos, NHGRI

ClinGen
Clinical Genome Resource

Clinical Actionability

Official Journal of the American College of Medical Genetics and Genomics **ORIGINAL RESEARCH ARTICLE** Genetics inMedicine

Open

A standardized, evidence-based protocol to assess clinical actionability of genetic disorders associated with genomic variation

Jessica Ezzell Hunter, MS, PhD[1], Stephanie A. Irving, MHS[1], Leslie G. Biesecker, MD[2], Adam Buchanan, MS, MPH[3], Brian Jensen, MD[4], Kristy Lee, MS[5], Christa Lese Martin, PhD[6], Laura Milko, PhD[5], Kristin Muessig, MS[1], Annie D. Niehaus, BA[7], Julianne O'Daniel, MS[5], Margaret A. Piper, PhD, MPH[1], Erin M. Ramos, MPH, PhD[7], Sheri D. Schully, PhD[8], Alan F. Scott, PhD[9], Anne Slavotinek, MBBS, PhD[10], Nara Sobreira, MD, PhD[9], Natasha Strande, PhD[5], Meredith Weaver, ScM, PhD[11], Elizabeth M. Webber, MS[1], Marc S. Williams, MD[3], Jonathan S. Berg, MD, PhD[5], James P. Evans, MD, PhD[5], Katrina A.B. Goddard, PhD[1]; on behalf of the ClinGen Resource

Purpose: Genome and exome sequencing can identify variants unrelated to the primary goal of sequencing. Detecting pathogenic variants associated with an increased risk of a medical disorder enables clinical interventions to improve future health outcomes in patients and their at-risk relatives. The Clinical Genome Resource, ... can College of Medical Genetics and Genomics for return as secondary findings from clinical genome-scale sequencing. We also describe the challenges that arose during the development of the protocol that highlight important issues in characterizing actionability across a range of disorders.

Clinical Genome Resource

Genet Med. 2016 Apr 28 (epub ahead of print).

Many Thanks…

GenomMed Programs Investigators and Participants!

Ebony Bookman
Joy Boyer
Lisa Brooks
Erin Currey
Cecilia Dupecher
C. Fletcher-Hoppe
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Simona Volpi
Robert Wildin
Ken Wiley
Anastasia Wise

Carol Bult

Rex Chisholm

Geoff Ginsburg

Howard Jacob

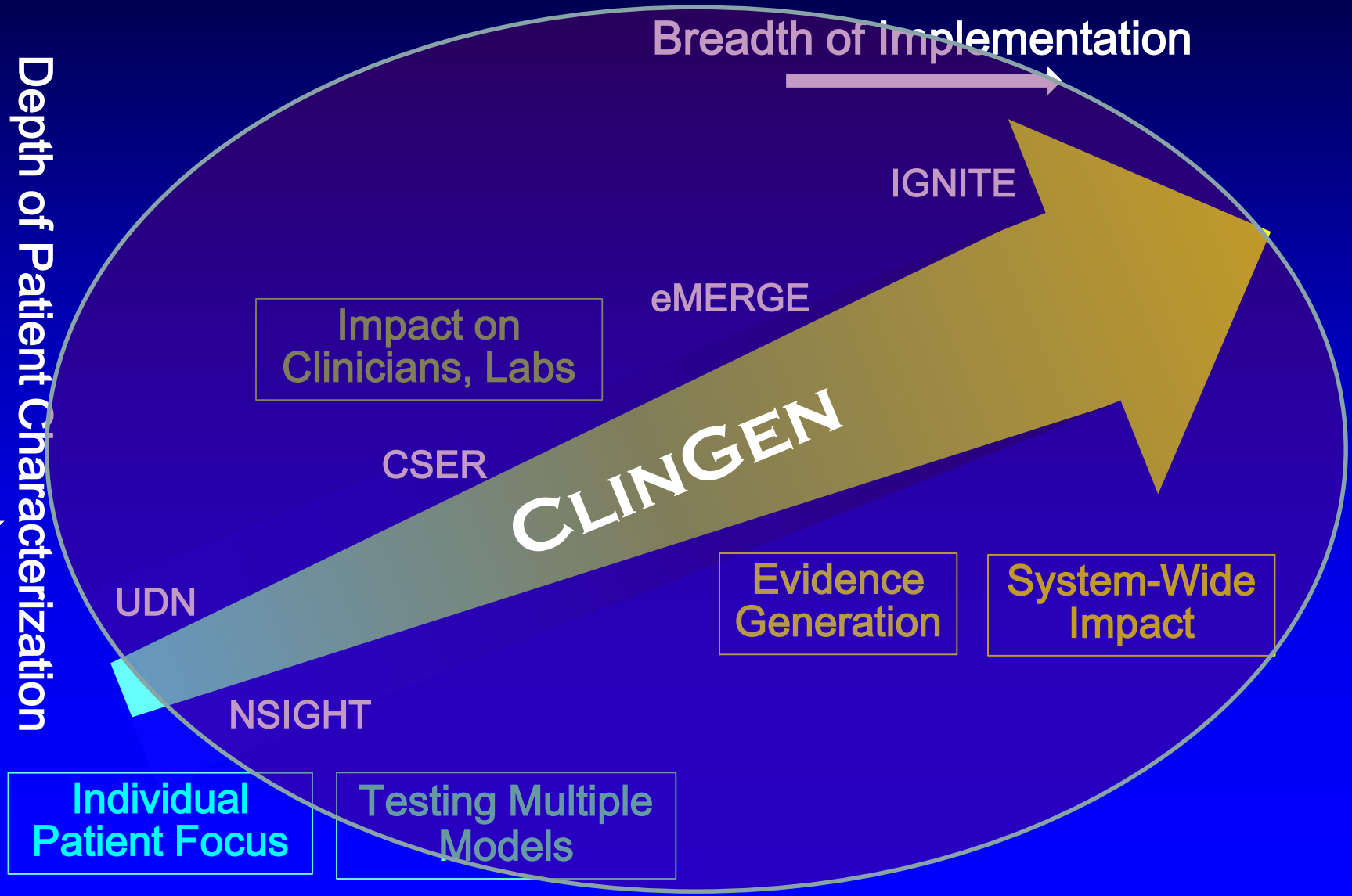
Howard McLeod

Mary Relling

Dan Roden

Marc Williams

Spectrum of Genomic Medicine Implementation: Intensity vs. Breadth



Gene-Disease Validity

Definitive	Repeatedly demonstrated in research & clinical settings.
Strong	Excess of pathogenic variants in cases vs. controls & supporting experimental data.
Moderate	≥3 unrelated probands with pathogenic variants & supporting experimental data.
Limited	<3 probands w/ pathogenic variants.
No Evidence Reported	"Candidate" genes based on animal models or disease pathways, but no pathogenic variants reported.
Disputed	Significant evidence *refuting* a role for gene in this disease.
Evidence Against	Evidence refuting the role of the gene significantly outweighs any supporting evidence.

Courtesy Erin Ramos, NHGRI

High Yield of Whole Genome Sequencing in Critically Ill Infants

Whole-genome sequencing for identification of Mendelian disorders in critically ill infants: a retrospective analysis of diagnostic and clinical findings

Laurel K Willig, Josh E Petrikin, Laurie D Smith, Carol J Saunders, Isabelle Thiffault, Neil A Miller, Sarah E Soden, Julie A Cakici, Suzanne M Herd, Greyson Twist, Aaron Noll, Mitchell Creed, Patria M Alba, Shannon L Carpenter, Mark A Clements, Ryan T Fischer, J Allyson Hays, Howard Kilbride, Ryan J McDonough, Jamie L Rosterman, Sarah L Tsai, Lee Zellmer, Emily G Farrow, Stephen F Kingsmore

- 35 infants < 4mo age in NICU/PICU
- 26 hour sequencing, infant + parents
- 20 (57%) diagnosed with sequencing, 3 (9%) with standard genetics
- 65% of diagnoses had immediate impact on clinical management

Willig L *et al.*, *Lanc Resp Hlth* 2015; 3:377-87.

Incorporating a Genetic Risk Score Into Coronary Heart Disease Risk Estimates

Effect on Low-Density Lipoprotein Cholesterol Levels (the MI-GENES Clinical Trial)

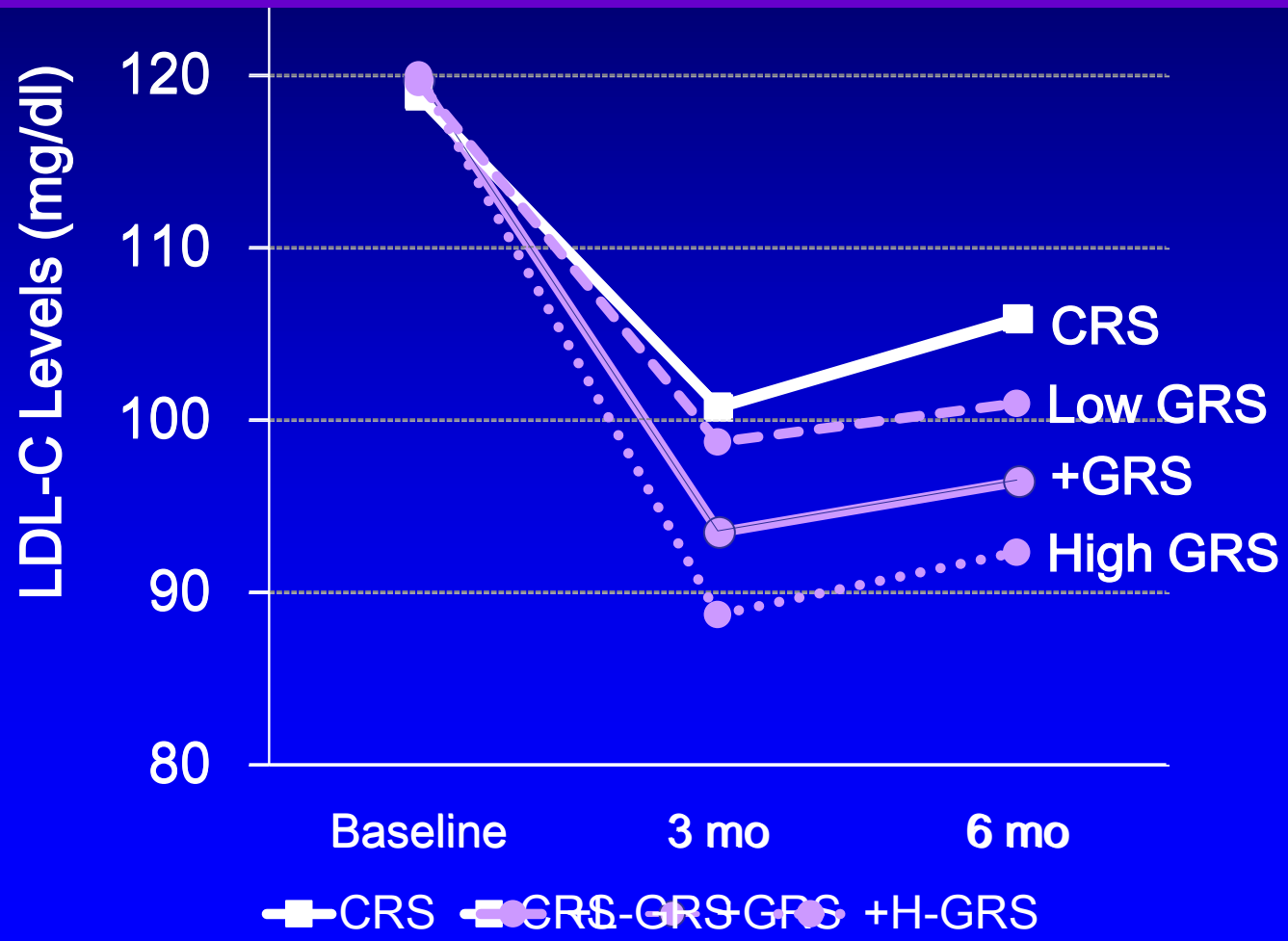
Iftikhar J. Kullo, MD; Hayan Jouni, MD; Erin E. Austin, PhD; Sherry-Ann Brown, MD, PhD; Teresa M. Kruisselbrink, GCS; Iyad N. Isseh, MBBS; Raad A. Haddad, MBBS; Tariq S. Marroush, MD; Khader Shameer, PhD; Janet E. Olson, PhD; Ulrich Broeckel, MD; Robert C. Green, MD, MPH; Daniel J. Schaid, PhD; Victor M. Montori, MD; Kent R. Bailey, PhD

- 203 middle-aged adults at intermediate risk
- Randomized to receive 10-yr CHD risk estimates from clinical risk alone (CRS) or clinical risk + genetic risk (+GRS)
- Compared LDL-C at 6 mos
- Any differences due to diet, activity, statins

Kullo I *et al.*, *Circulation.* 2016;133:1181-88.

LDL-C Lowering in Patients Given Clinical and

"…Disclosure of CHD risk estimates that incorporated genetic risk information led to lower LDL-C levels than disclosure of CHD risk based on conventional risk factors alone."



Kullo I *et al.*, *Circulation.* 2016;133:1181-88.

Exome Sequencing and Targeted Therapy

GCH1 heterozygous mutation identified by whole-exome sequencing as a treatable condition in a patient presenting with progressive spastic paraplegia *J Neurol* 2014; 261:622-24.

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