Precision Medicine: Coming to a Clinic Near You?

Martin Tristani-Firouzi, MD
Professor, Pediatric Cardiology
Associate Director, Nora Eccles Harrison CVRTI

First, a few definitions

- **Genetics:** genes (coding regions, exons); WES
- **Genomics**: genes + non-coding regions (promoters, enhancers, repressors, etc); WGS
- **Epigenetics**: modifications to DNA that alter ability to turn on/off genes (DNA methylation, histone modifications)

Overview

- Barriers to the practical implementation of Precision Medicine in the clinic

- Moving beyond genomics in Precision Medicine: Big Data

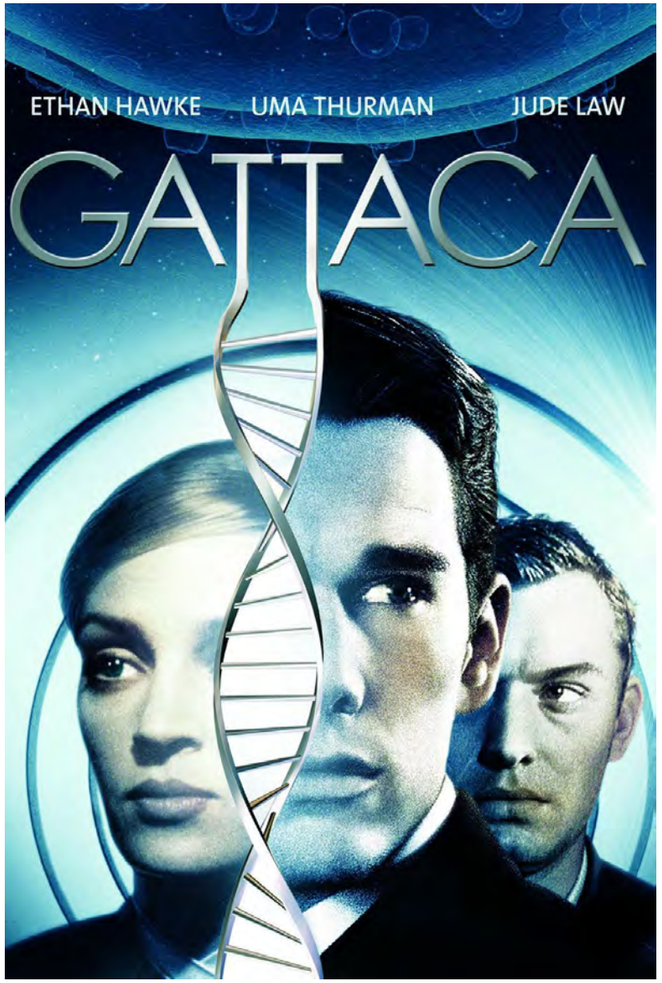
WHAT IS PRECISION MEDICINE?

- *"Providing the right treatment to the right patient, at the right dose and at the right time."*
- *"Combining an individual's genomic profile with clinical information to guide diagnosis, therapy and intervention."*
- Pharmacogenomics is the most practical application of Precision Medicine

WHAT PRECISION MEDICINE IS NOT:

The New York Times

Scientist Who Edited Babies' Genes Is Likely to Face Charges in China

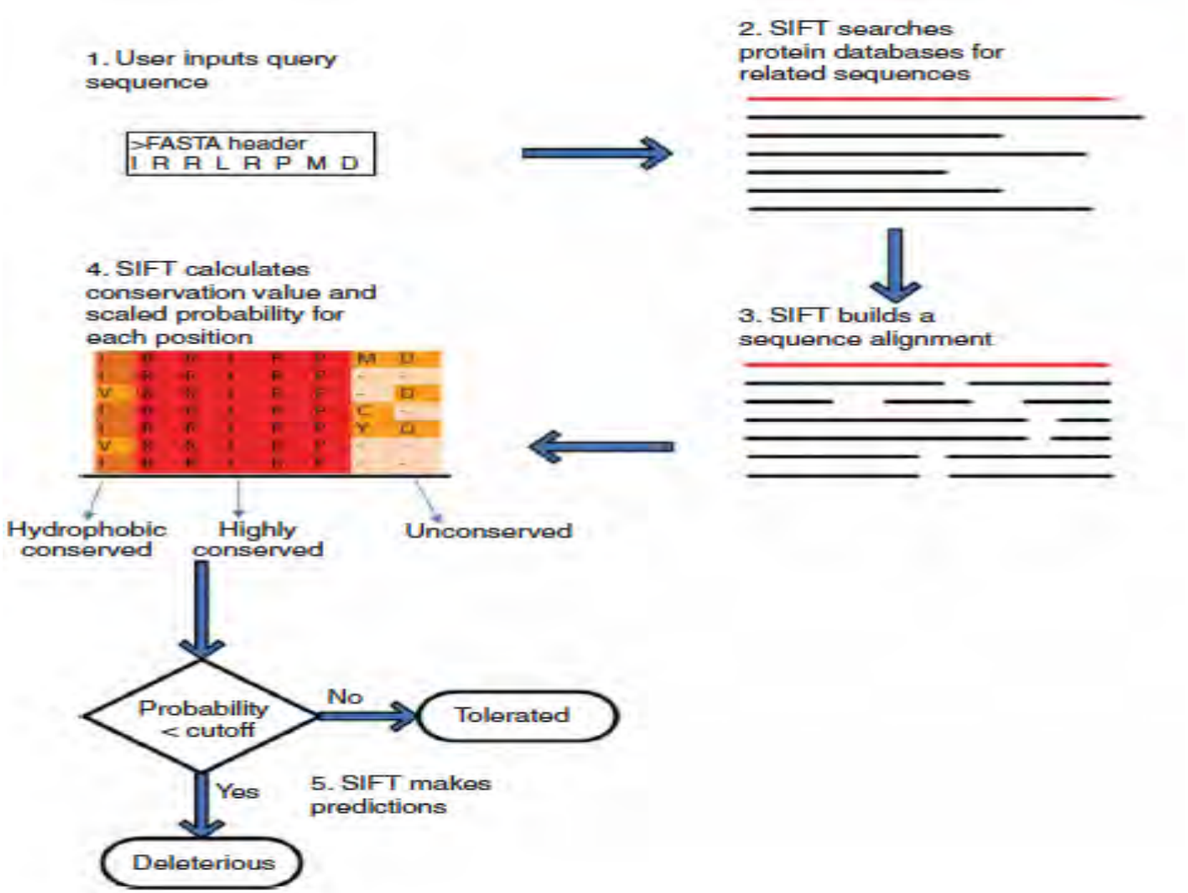


WHAT ARE THE BARRIERS TO PRECISION MEDICINE IMPLEMENTATION?

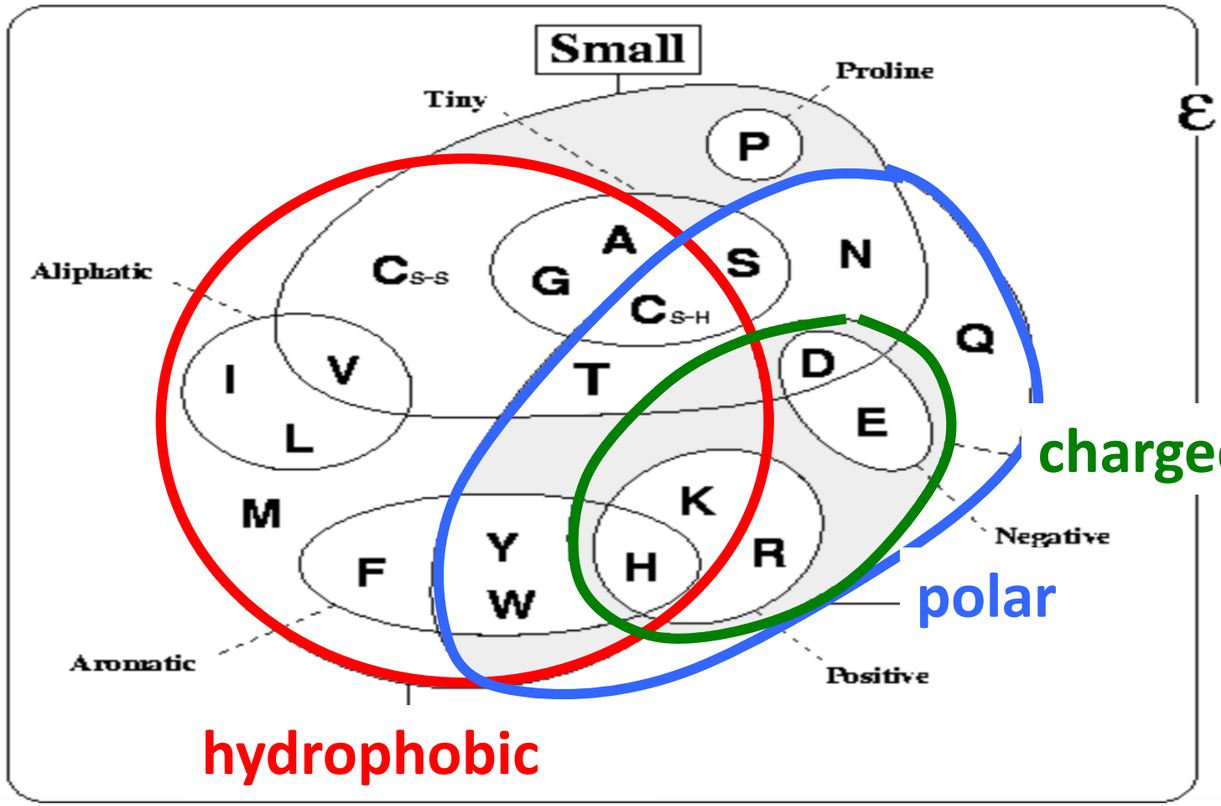
- **Variant adjudication**
- Clinician education
- Paucity of easy-to-use bioinformatic tools
- Functional validation

VARIANT ADJUDICATION: IS THIS GENETIC VARIANT PATHOGENIC?

Conservation-based method
SIFT: Sorting Tolerant from Intolerant tool



Physico-chemical properties of amino acid substitution: predicted mutation effect



Livingstone & Barton, *CABIOS*, **9**, 745-756, 1993

ENSEMBLE PREDICTION TOOLS: MORE IS BETTER?

Comparison and integration of deleteriousness prediction methods for nonsynonymous SNVs in whole exome sequencing studies

Chengliang Dong[1,2,†], Peng Wei[4,6,†], Xueqiu Jian[5], Richard Gibbs[7], Eric Boerwinkle[4,5,7], Kai Wang[1,2,3,*] and Xiaoming Liu[4,5,*]

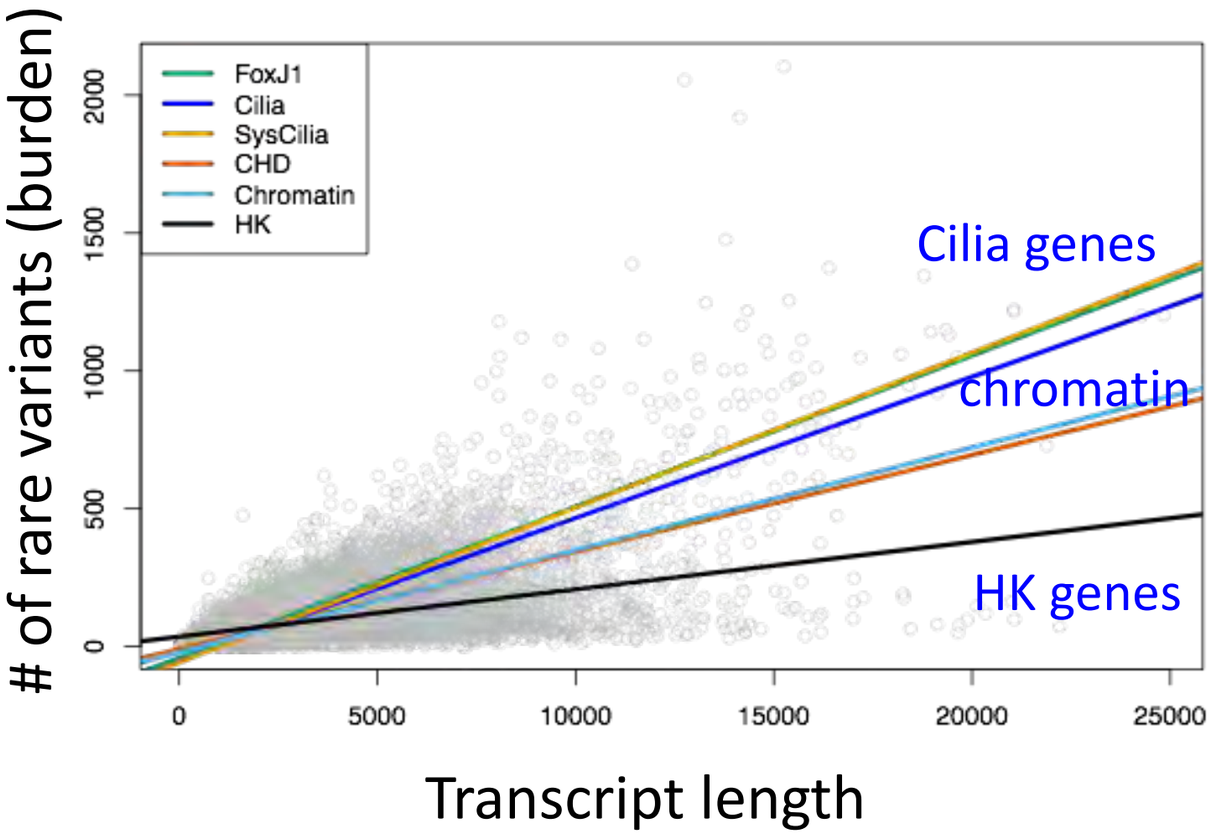
Meta-SVM

ARTICLE

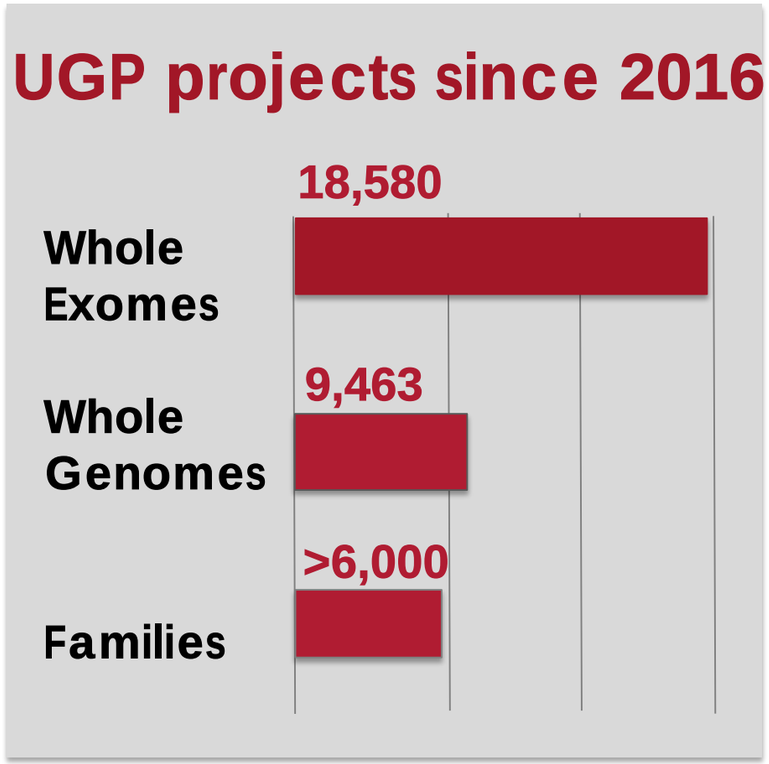
REVEL: An Ensemble Method for Predicting the Pathogenicity of Rare Missense Variants

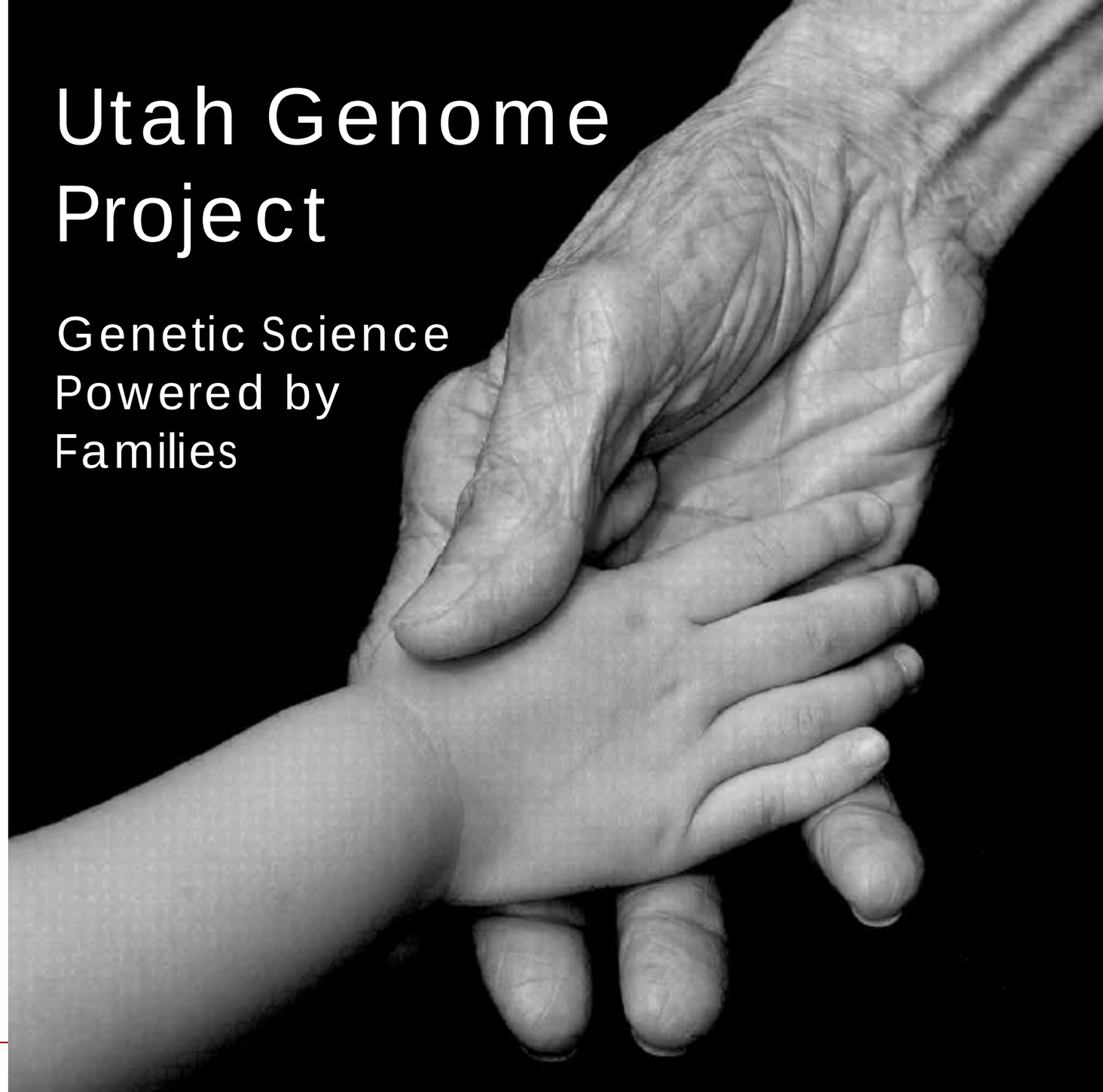
REVEL

Burden increases with increasing transcript length and different gene classes have different degrees of burden



The Utah Genome Project is designed to advance precision medicine in Utah





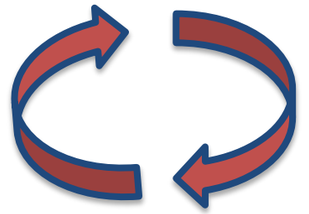
HEALTH
UNIVERSITY OF UTAH

VAAST: VARIANT ANNOTATION, ANALYSIS & SEARCH TOOL

A probabilistic disease-gene finder that employs a burden test to identity disease-genes using:

1. Population frequency of the variant
2. Phylogenetic sequence conservation
3. Frequency of that amino acid substitution among disease-causing mutations (OMIM)

$$\lambda = \sum_{i=1}^{k} \ln\left(\frac{n_i \hat{p}_{Yi}^{B_{Yi}+T_{Yi}}(1-\hat{p}_{Yi})^{B_{Xi}+T_{Xi}}}{a_i \hat{p}_{BYi}^{B_{Yi}}(1-\hat{p}_{BYi})^{B_{Xi}} \hat{p}_{TYi}^{T_{Yi}}(1-\hat{p}_{TYi})^{T_{Xi}}}\right)$$

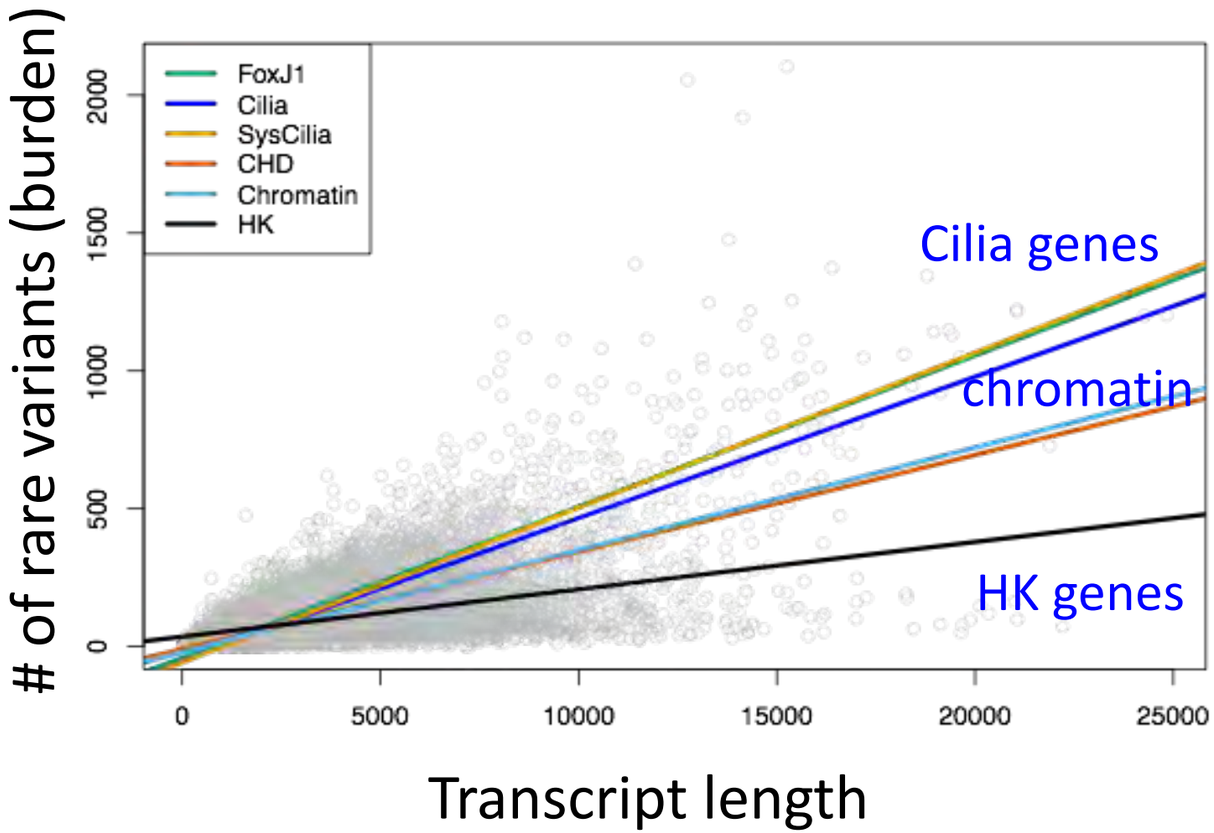


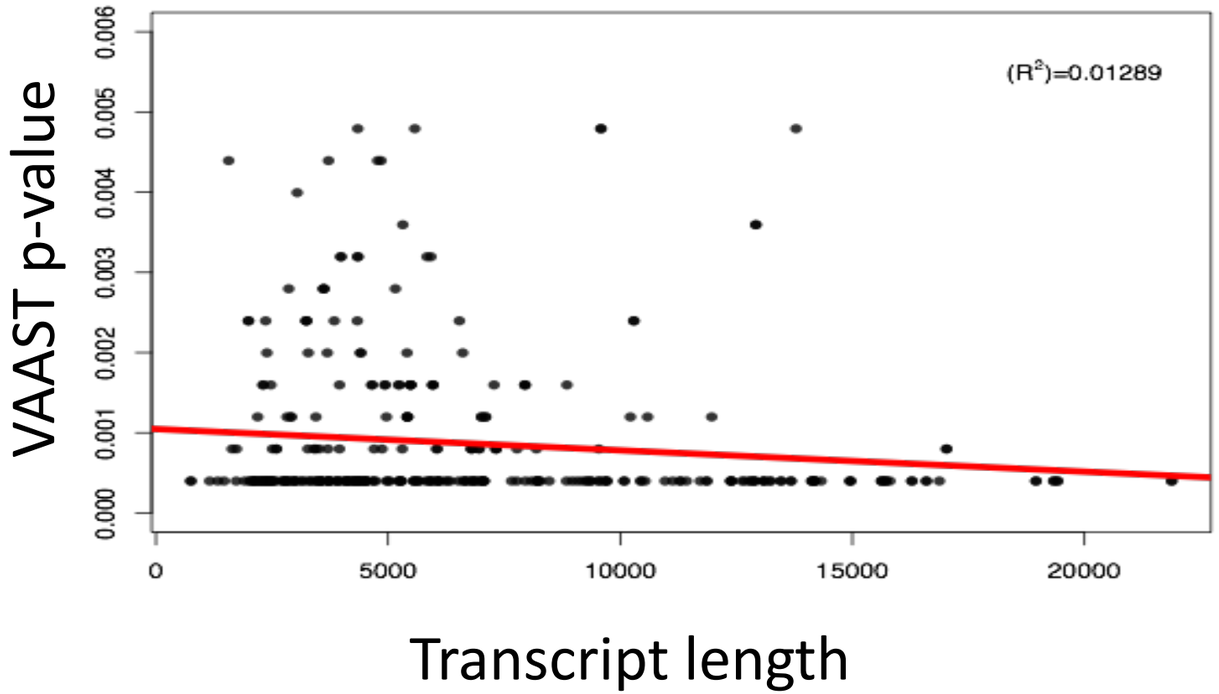
Derives an **empirical p value** for each variant by comparing the degree of burden at that locus to a background population that encompasses 26 ethnicities.

Yandell M, et al, Genome Res. 2011.

Hu H et al, Nat Biotechnol. 2014.

While burden increases with increasing transcript length, VAAST permutation p-value is independent of transcript length (or gene burden)





WHAT ARE THE BARRIERS TO PRECISION MEDICINE IMPLEMENTATION?

- Variant adjudication
- **Clinician education**
- **Paucity of easy-to-use bioinformatic tools**
- Functional validation

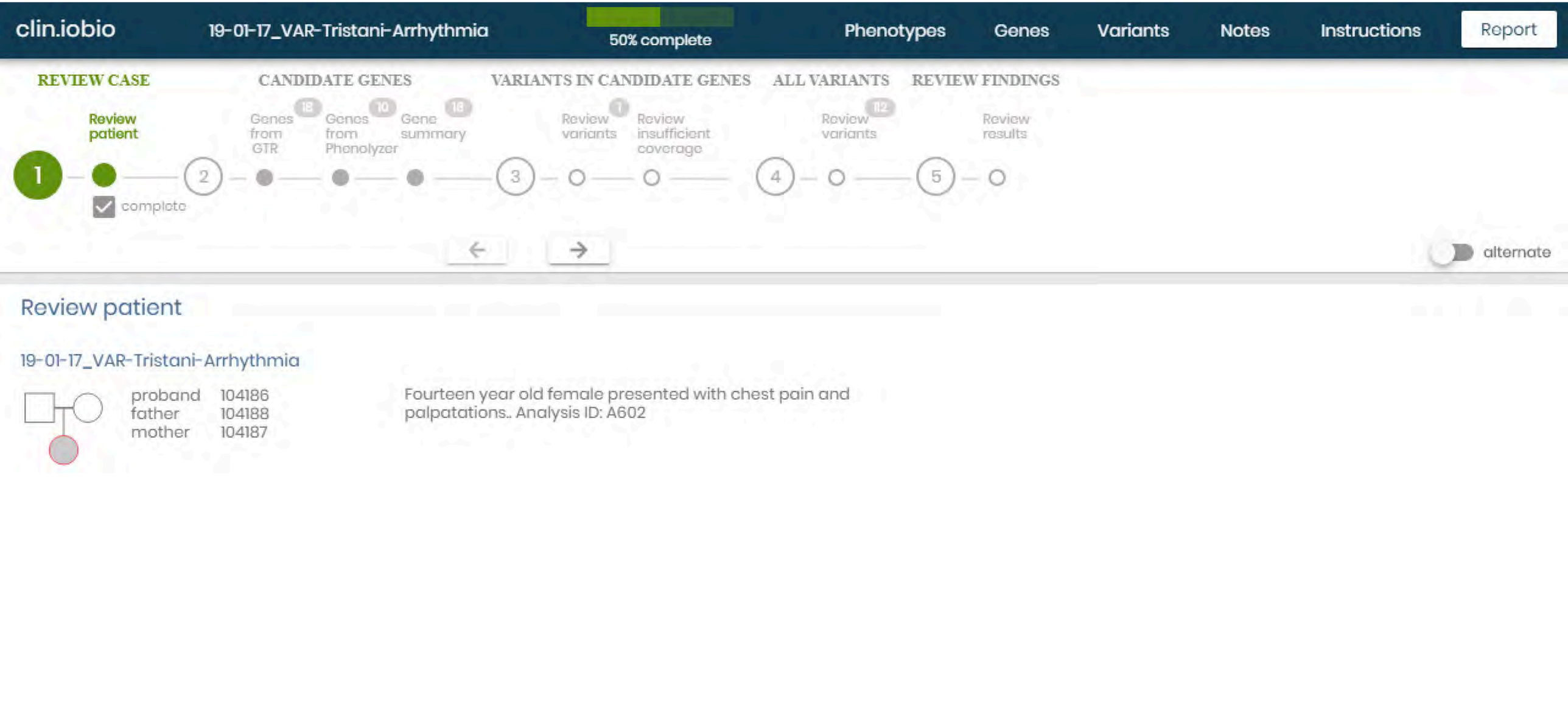
WHY CLINICIAN EDUCATION IS SO IMPORTANT

EDITORIAL COMMENTARY

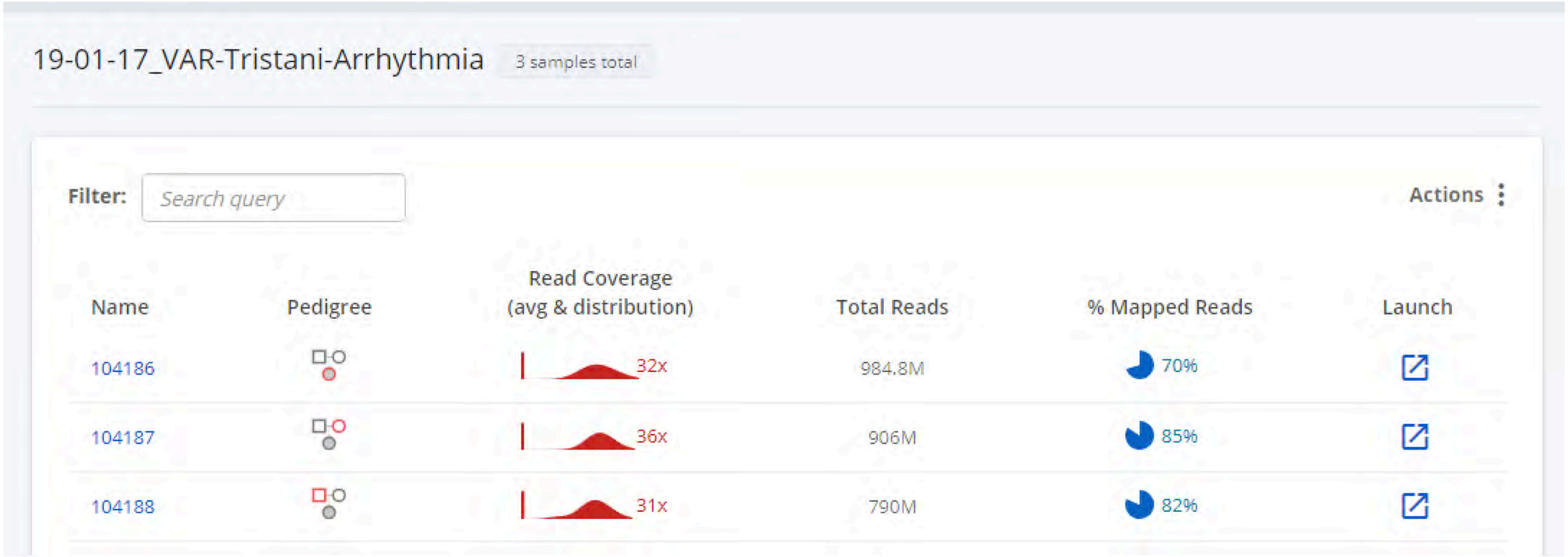
The phenotype is equally important in promoting variants from benign to pathogenic as well as in demoting variants from pathogenic to benign

Ahmad S. Amin, MD, PhD,* Arthur A.M. Wilde, MD, PhD, FHRS*†

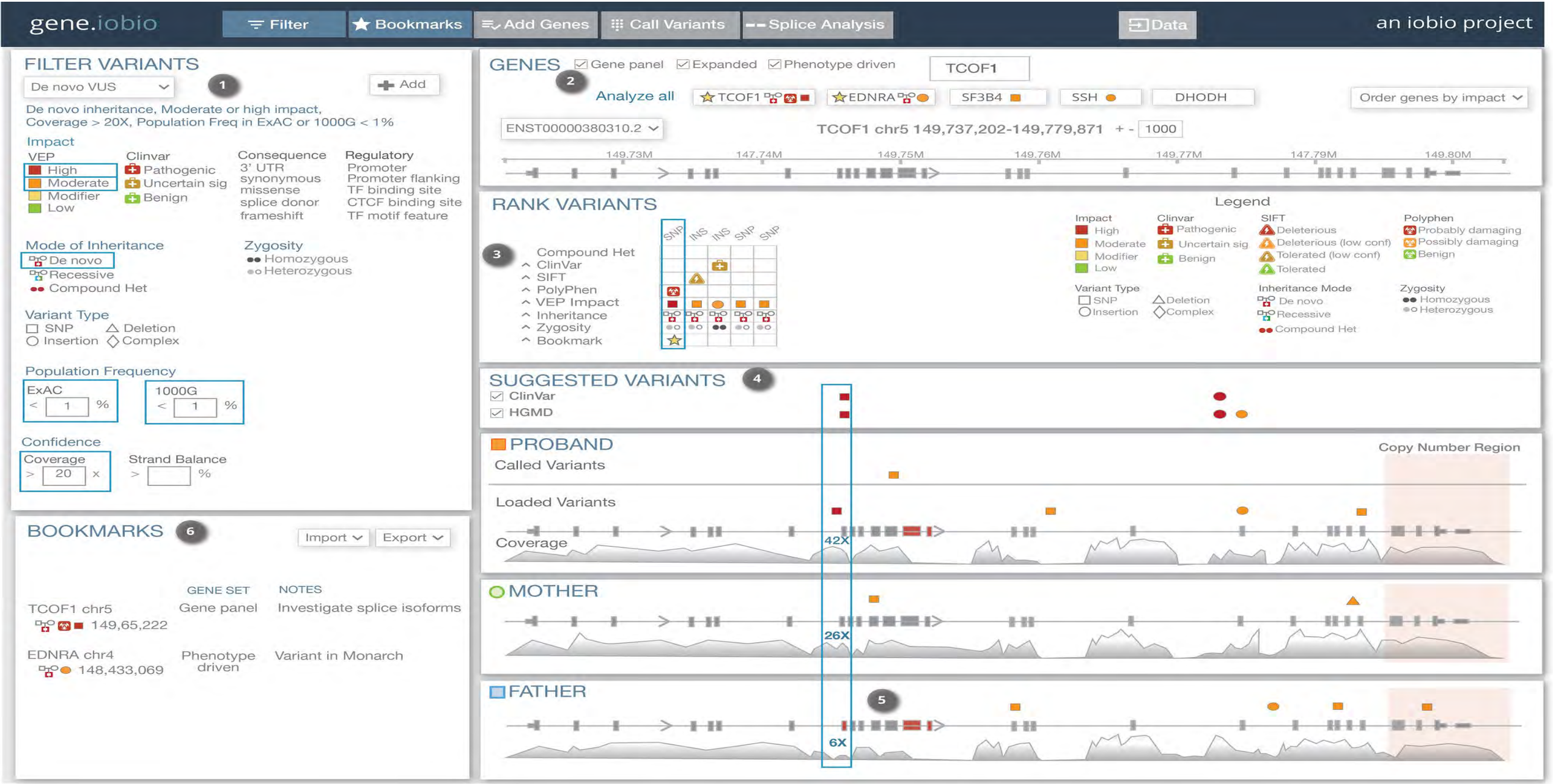
Point of care genomic analysis tools



Point of care genomic analysis tools: Assessment of quality of WES/WGS



Point of care genomic analysis tools

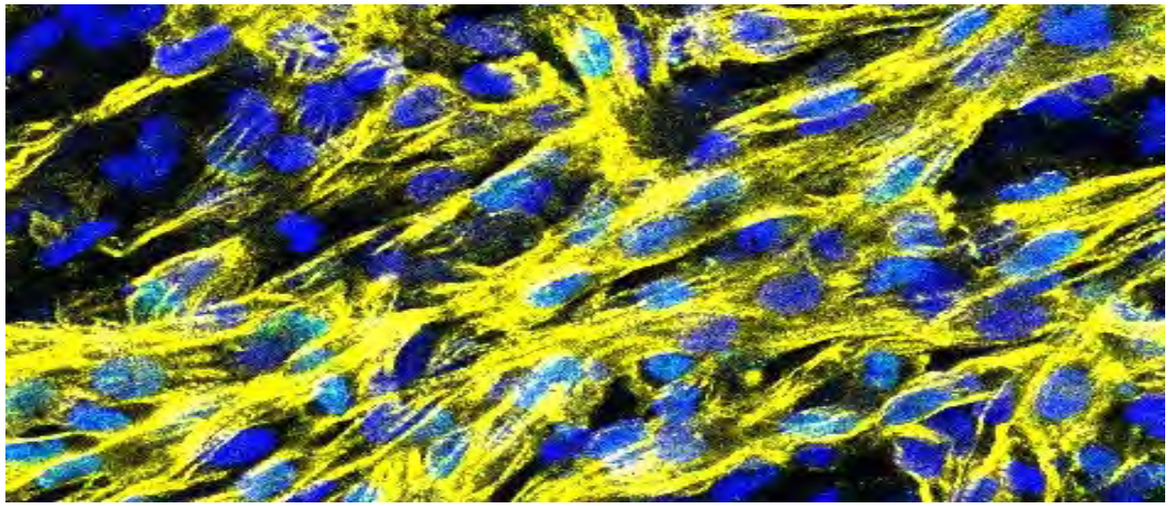


What are the barriers to Precision Medicine implementation?

- Variant adjudication
- Clinician education
- Paucity of easy-to-use bioinformatic tools
- **Functional validation**

Model organisms for functional validation

zebrafish



Human iPSC-CMs

Validating pathogenicity of genetic variants in zebrafish

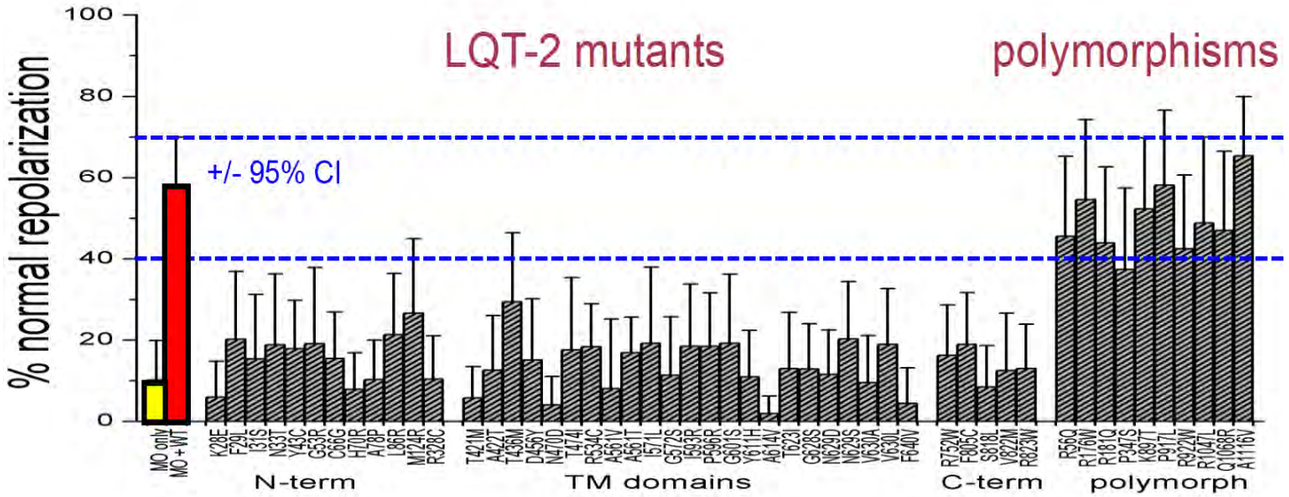
Cellular Physiology and Biochemistry

Original Paper

A Functional Assay for Sick Sinus Syndrome Genetic Variants

Chuanchau J. Jou[a] Cammon B. Arrington[b] Spencer Barnett[b] Jiaxiang Shen[c]
Scott Cho[b] Xiaoming Sheng[d] Patrick C. McCullagh[b] Neil E. Bowles[b]
Chase M. Pribble[b] Elizabeth V. Saarel[a] Thomas A. Pilcher[b] Susan P. Etheridge[b]
Martin Tristani-Firouzi[b,e]

Functional validation of 50 *KCNH2* variants



Circulation Research

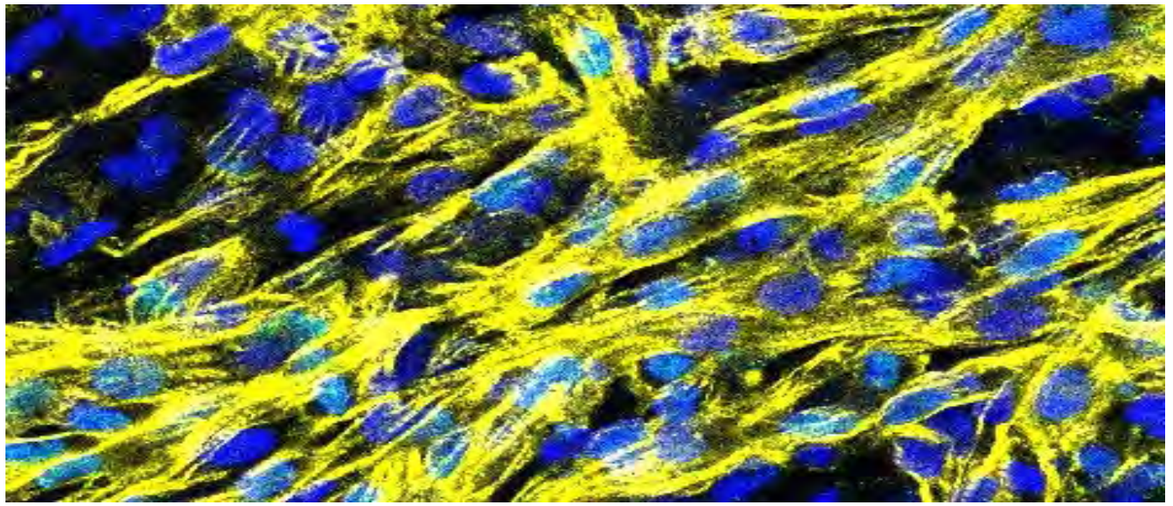
JOURNAL OF THE AMERICAN HEART ASSOCIATION

An In Vivo Cardiac Assay to Determine the Functional Consequences of Putative Long QT Syndrome Mutations

Chuanchau J. Jou, Spencer M. Barnett, Jian-Tao Bian, H. Cindy Weng, Xiaoming Sheng and Martin Tristani-Firouzi

HEALTH UNIVERSITY OF UTAH

Model organisms for genetic analyses



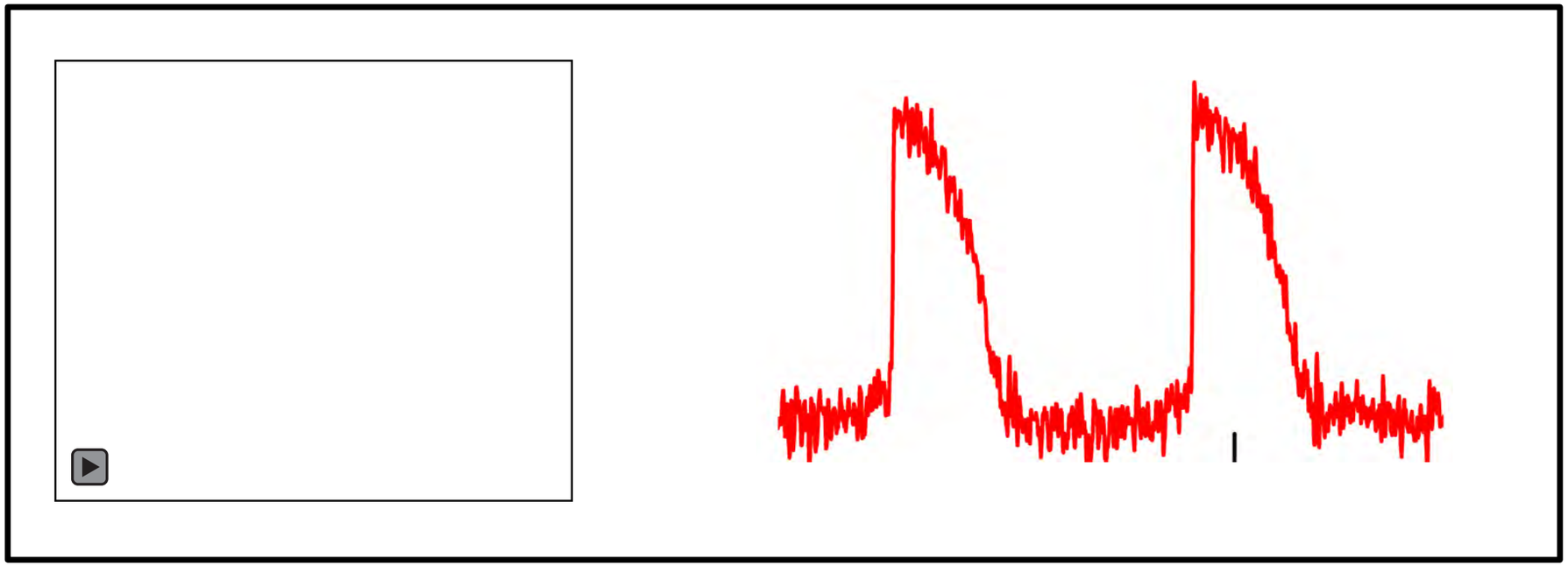
Human iPSC-CMs

Stem Cell Reports
Article

ISSCR

OPEN ACCESS

Functional and Pharmacological Analysis of Cardiomyocytes Differentiated from Human Peripheral Blood Mononuclear-Derived Pluripotent Stem Cells



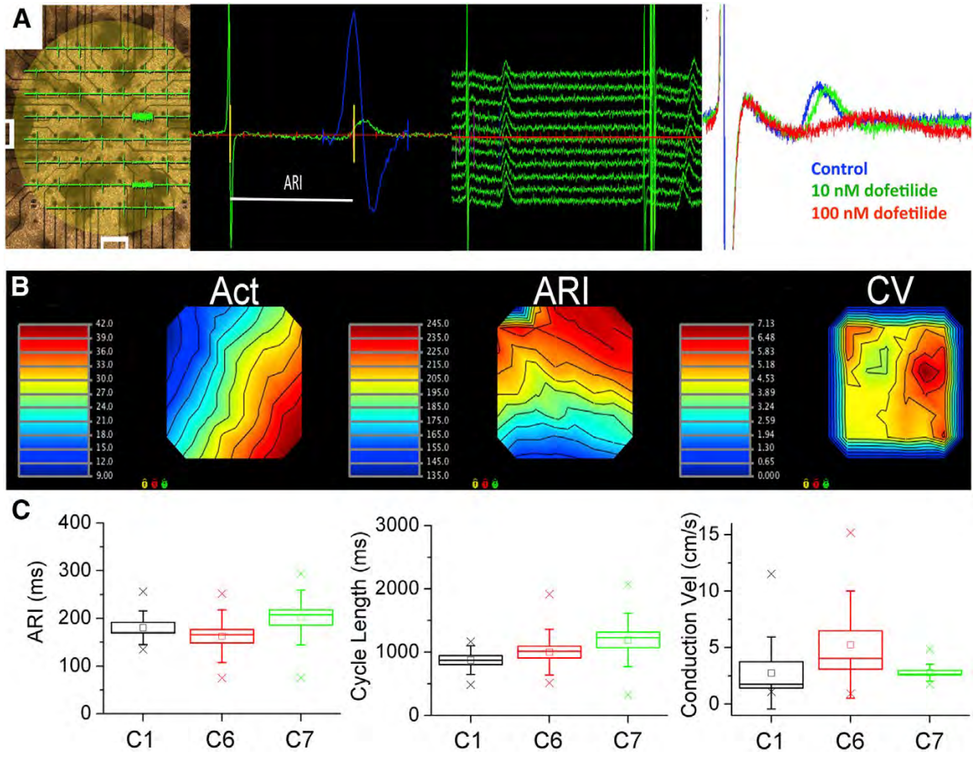
AMERICAN JOURNAL of PHYSIOLOGY
Heart and Circulatory Physiology®

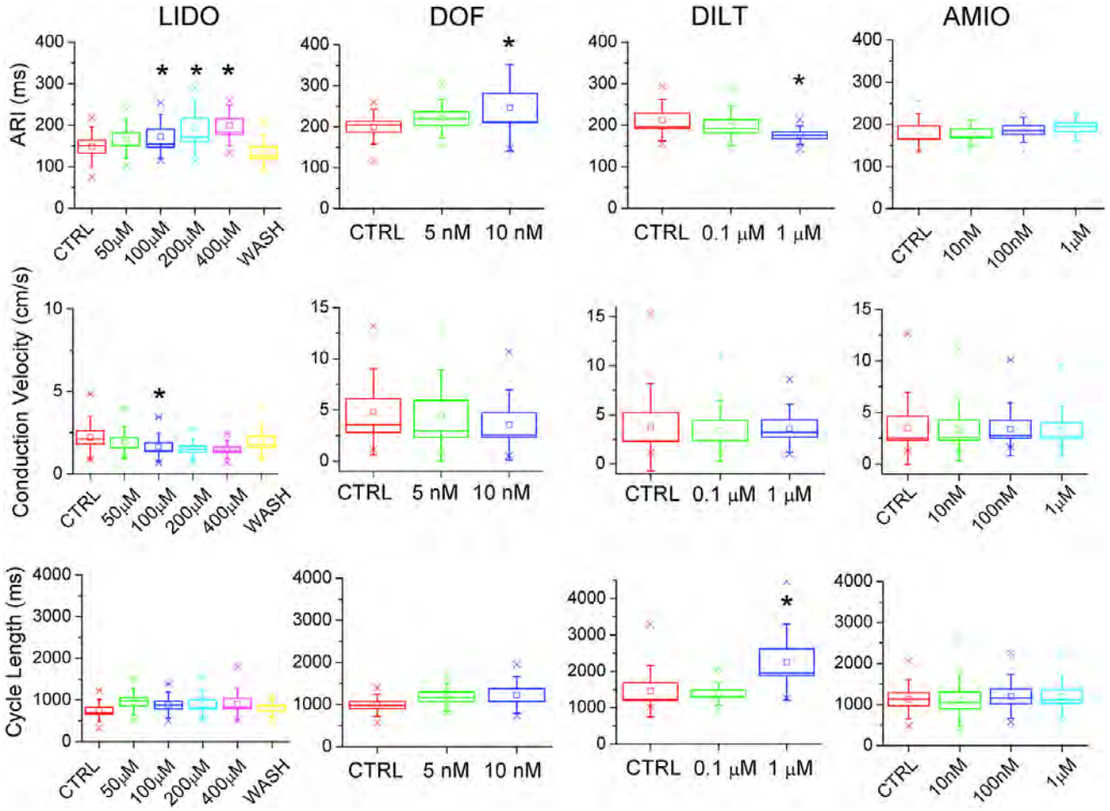
A near-infrared fluorescent voltage-sensitive dye allows for moderate-throughput electrophysiological analyses of human induced pluripotent stem cell-derived cardiomyocytes

Functional analyses of iPSC-CM using multi-electrode arrays (MEA)

Stem Cell Reports
Article
OPEN ACCESS

Functional and Pharmacological Analysis of Cardiomyocytes Differentiated from Human Peripheral Blood Mononuclear-Derived Pluripotent Stem Cells





PRECISION MEDICINE REQUIRES GETTING IT RIGHT

Reappraisal of Reported Genes for Sudden Arrhythmic Death

Evidence-Based Evaluation of Gene Validity for Brugada Syndrome

Systematic re-evaluation of *SCN5A* variants associated with Brugada syndrome

Nathan C. Denham BM[1,2,3] | Charles M. Pearman MBChB, PhD[1,2,3] | Wern Yew Ding MBChB[1] | Johan Waktare MD[1] | Dhiraj Gupta MD[1] | Richard Snowdon MD[1,2] | Mark Hall MD[1] | Robert Cooper MBChB, PhD[2] | Simon Modi MD[1,2] | Derick Todd MD[1,2] | Saagar Mahida MD, PhD[1,2]

Using the genome aggregation database, computational pathogenicity prediction tools, and patch clamp heterologous expression studies to demote previously published long QT syndrome type 1 mutations from pathogenic to benign

Daniel J. Clemens, BS,* Anne R. Lentino,* Jamie D. Kapplinger, BA,*† Dan Ye, MD,*‡ Wei Zhou, MD,*‡ David J. Tester, BS,*‡ Michael J. Ackerman, MD, PhD*†‡§

Still a long way to go to make Precision Medicine a practical reality

https://www.mskcc.org

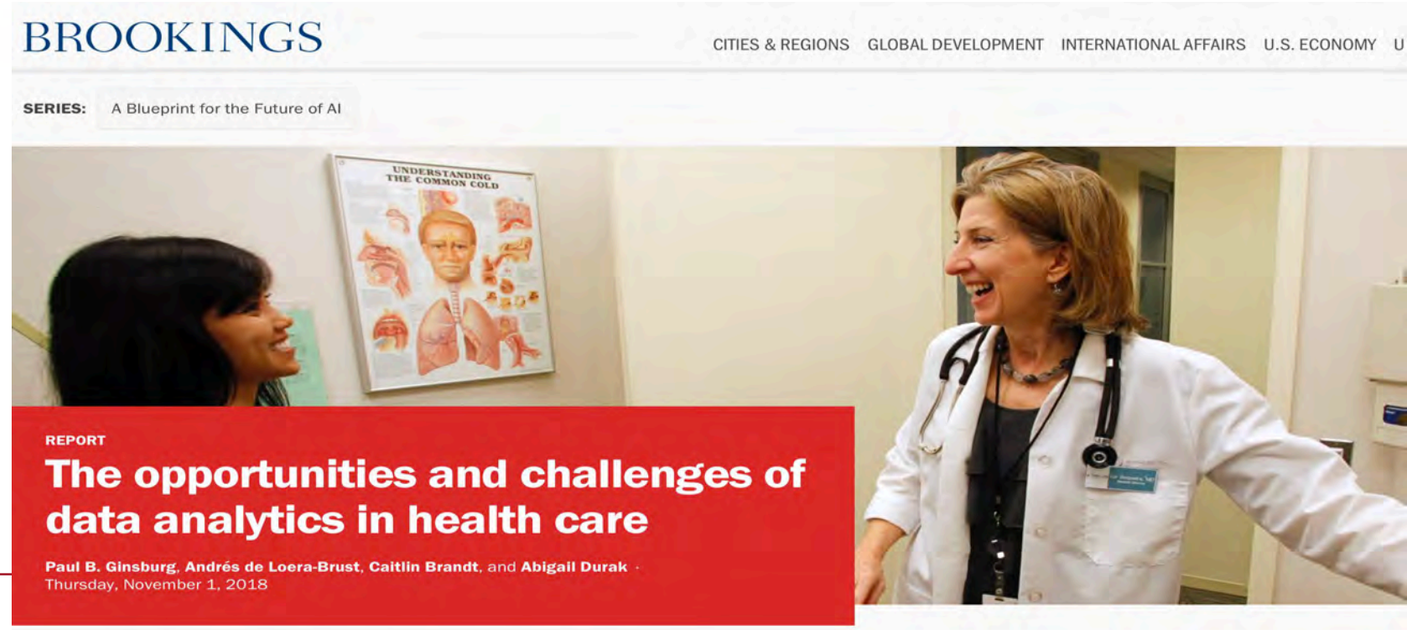
Moving beyond genomics in Precision Medicine: Predictive Analytics using Big Data

HEALTH INFORMATION SCIENCE AND SYSTEMS

REVIEW Open Access

Big data analytics in healthcare: promise and potential

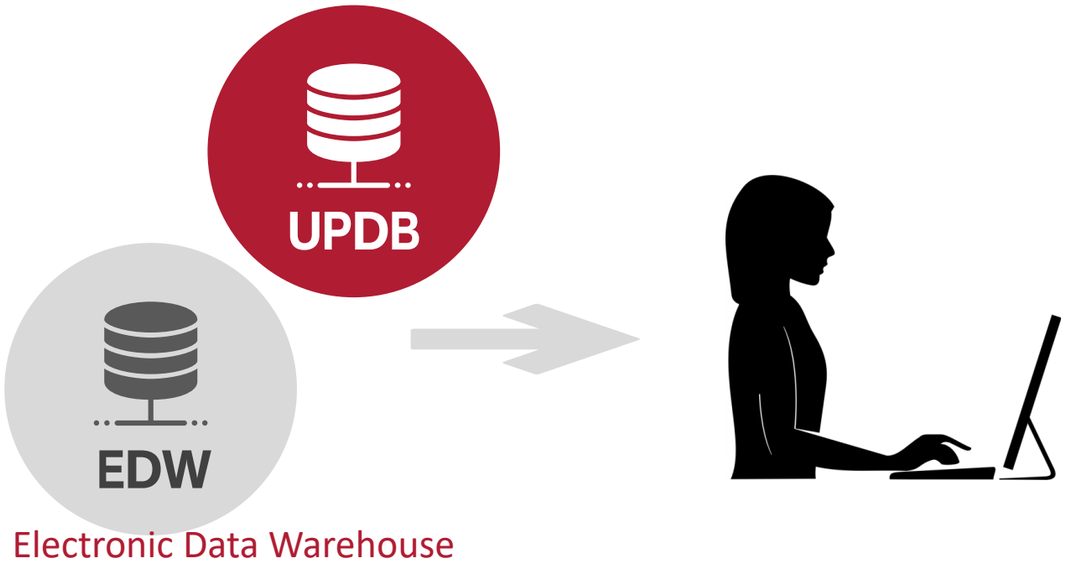
Wullianallur Raghupathi[1*] and Viju Raghupathi[2]



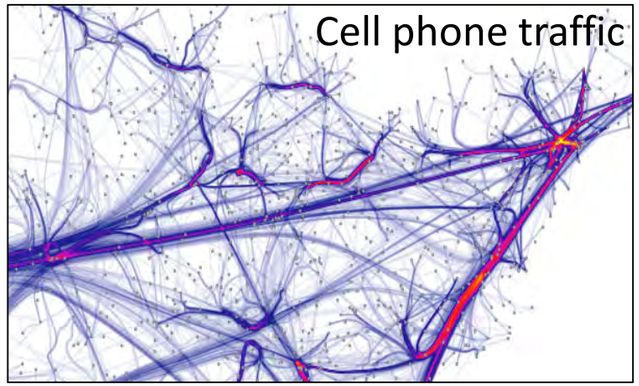
HEALTH
UNIVERSITY OF UTAH

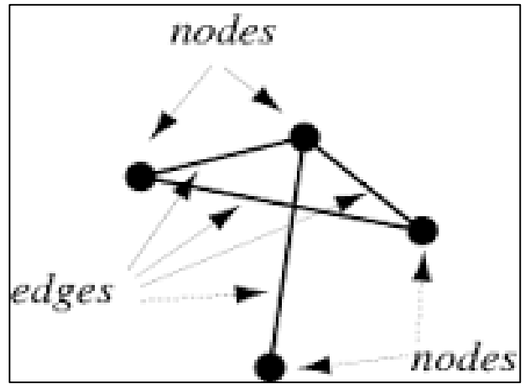
A BIG-DATA APPROACH TO BETTER UNDERSTAND CHD AND OUTCOMES

Utah Population Database

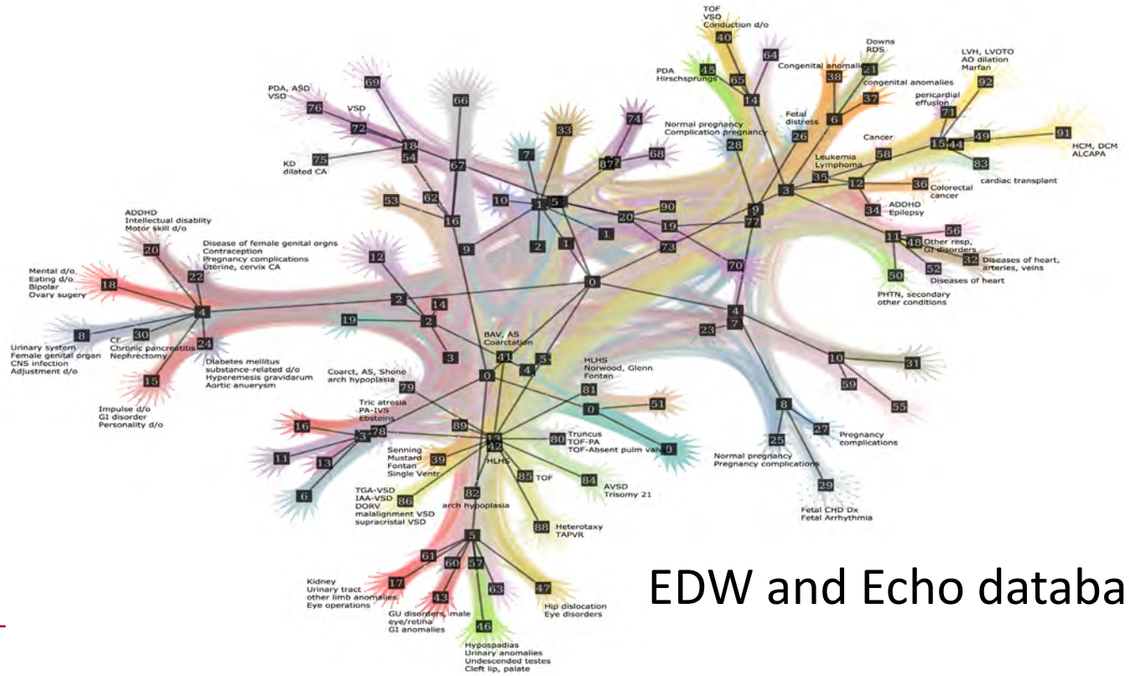


Electronic Data Warehouse



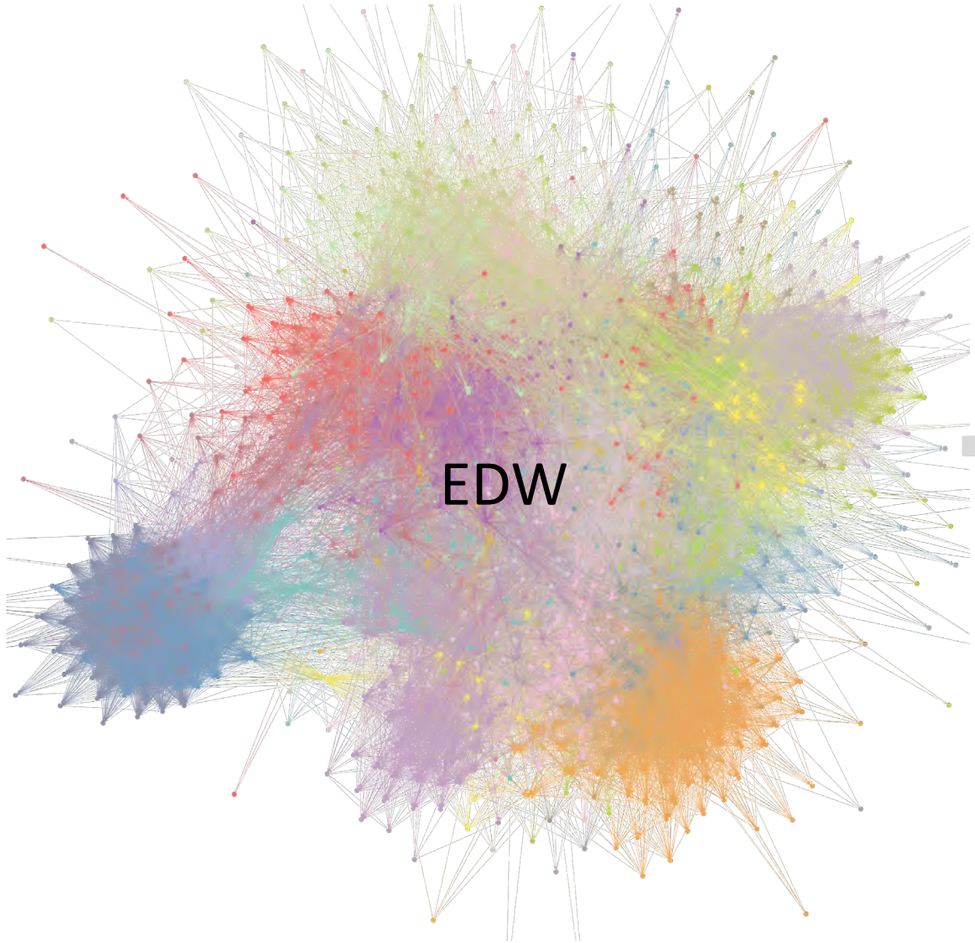


How to harness the power of big data for discovery and outcomes research?



EDW and Echo database

Intersecting the EDW with other clinical databases to empower outcomes research



Syngo

Echo database

STS

30 day surgical outcomes

NLP

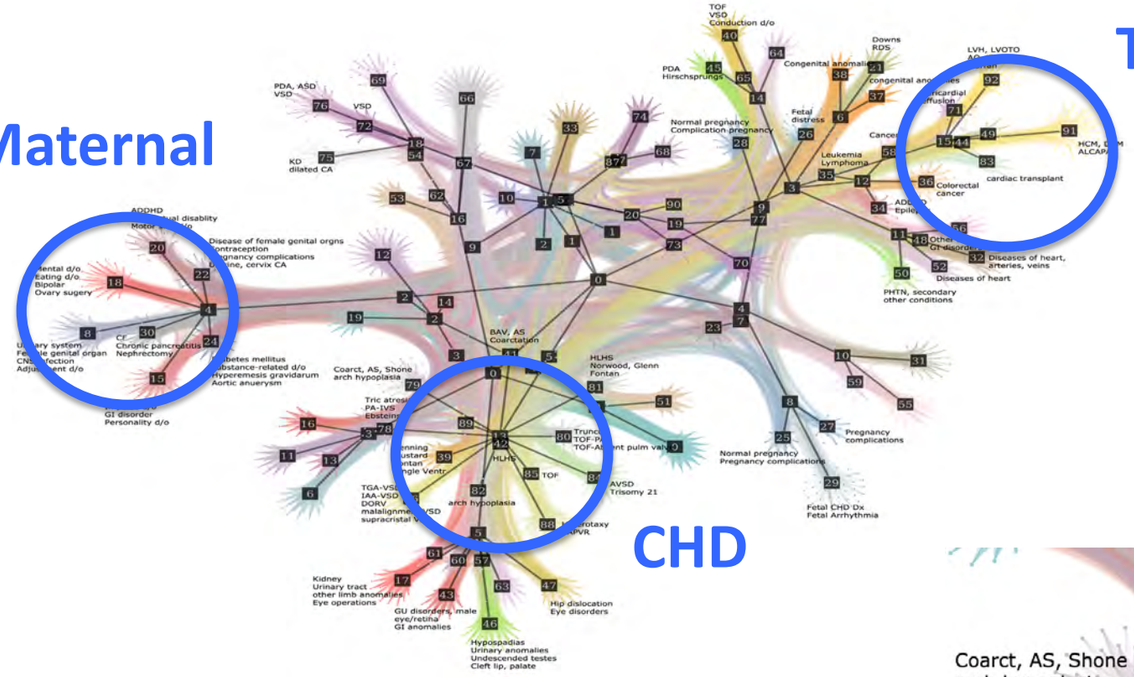
NLP restructuring of clinical notes

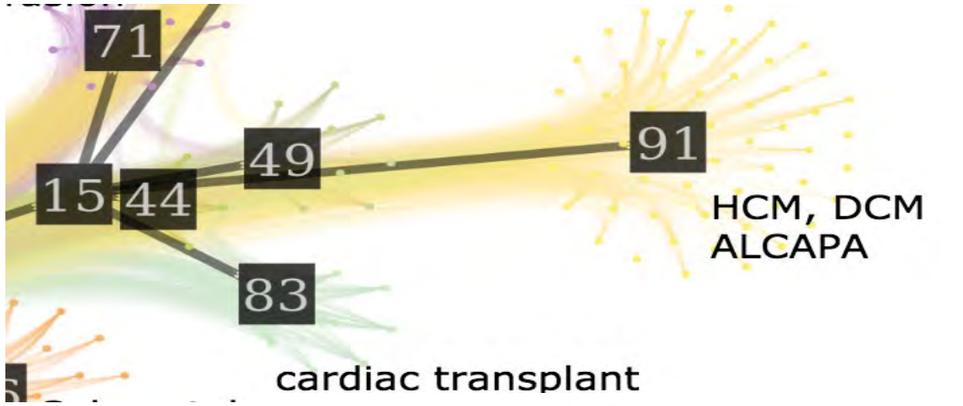
CONNECTIONS BETWEEN TERMS IN EDW AND ECHO DATABASE

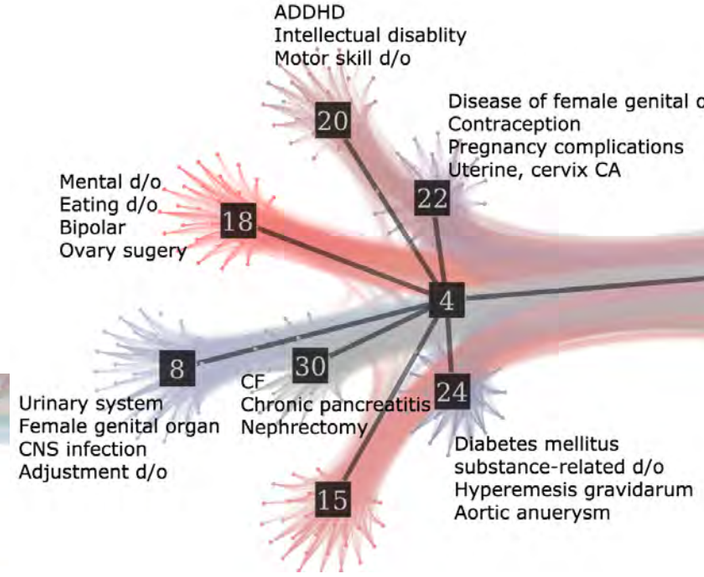
Maternal

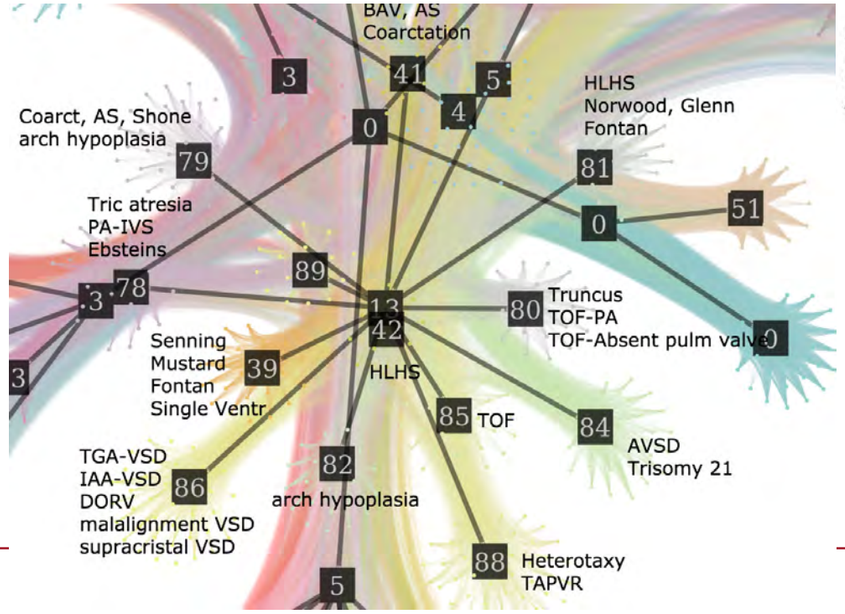
Tx

CHD





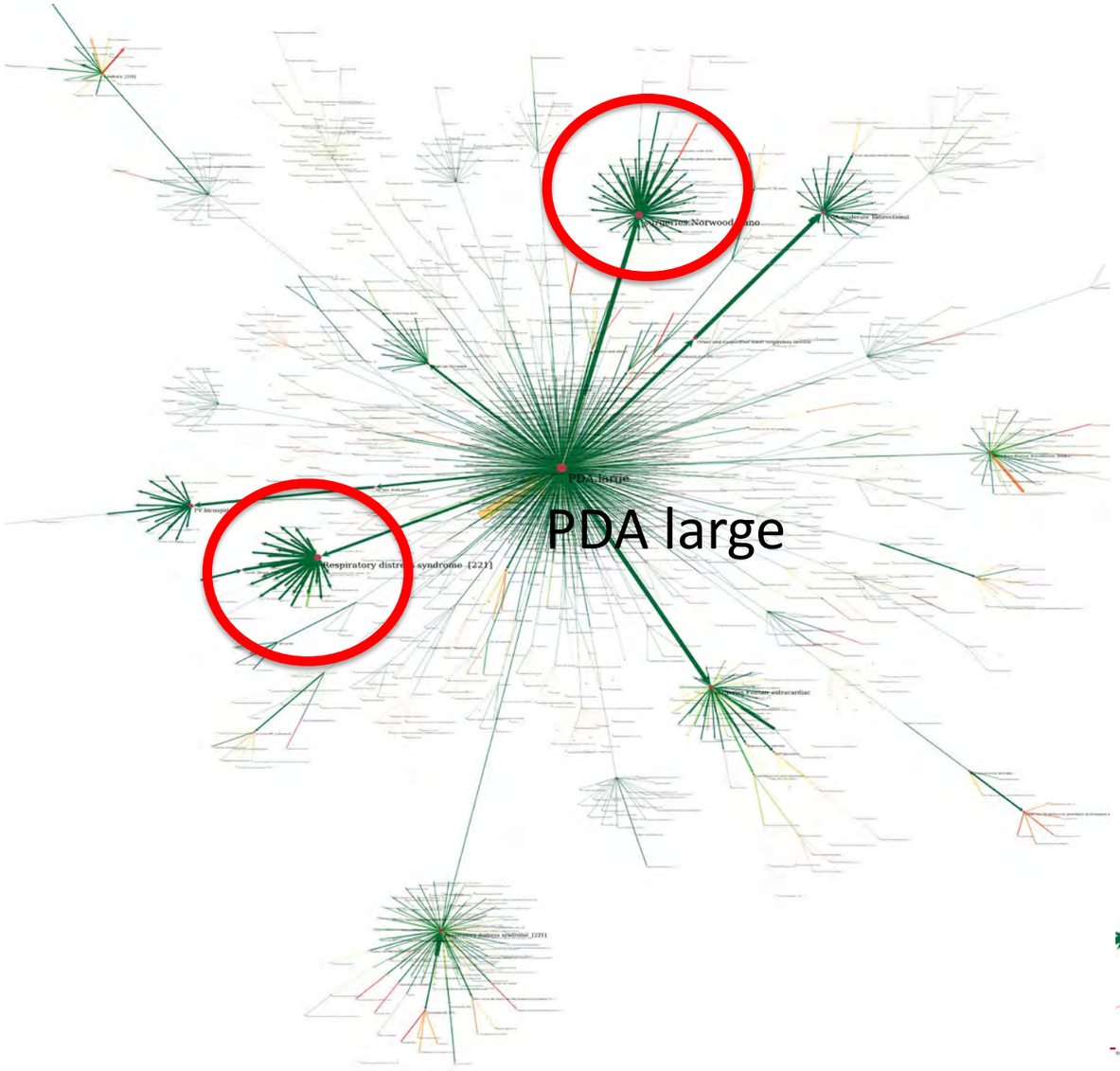


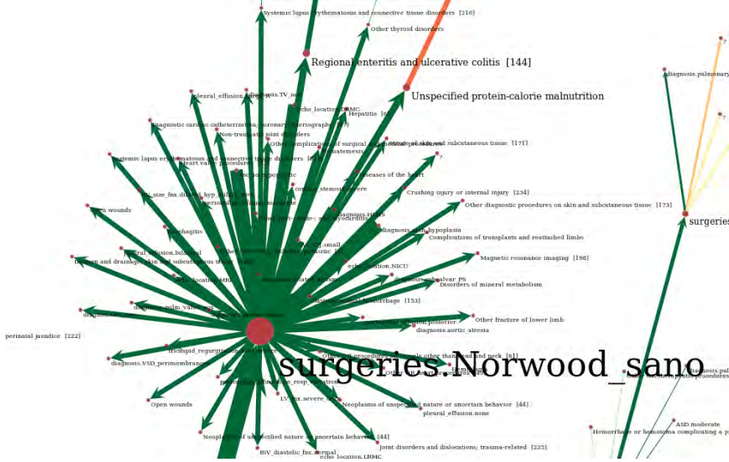


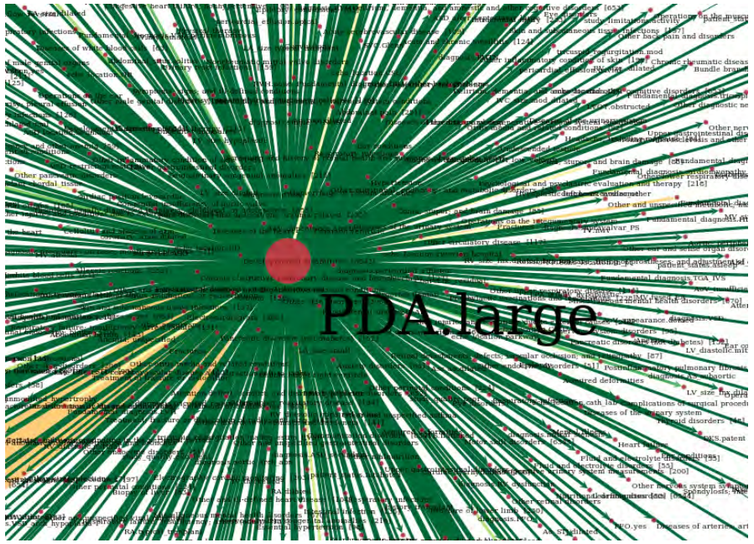
EDW

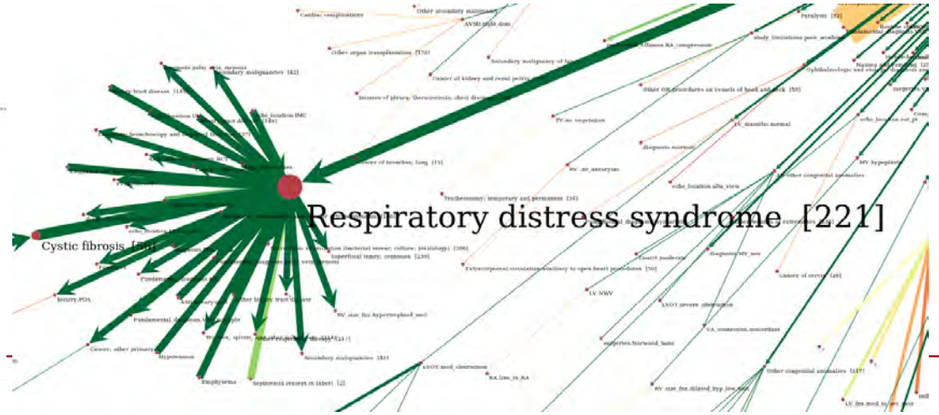
Syngo

HEALTH
UNIVERSITY OF UTAH


PDA_large
PDA large
Respiratory distress syndrome [221]


Regional enteritis and ulcerative colitis [144]
Unspecified protein-calorie malnutrition
surgeries
surgeries.Norwood_sano


PDA large


Respiratory distress syndrome [221]
Cystic fibrosis

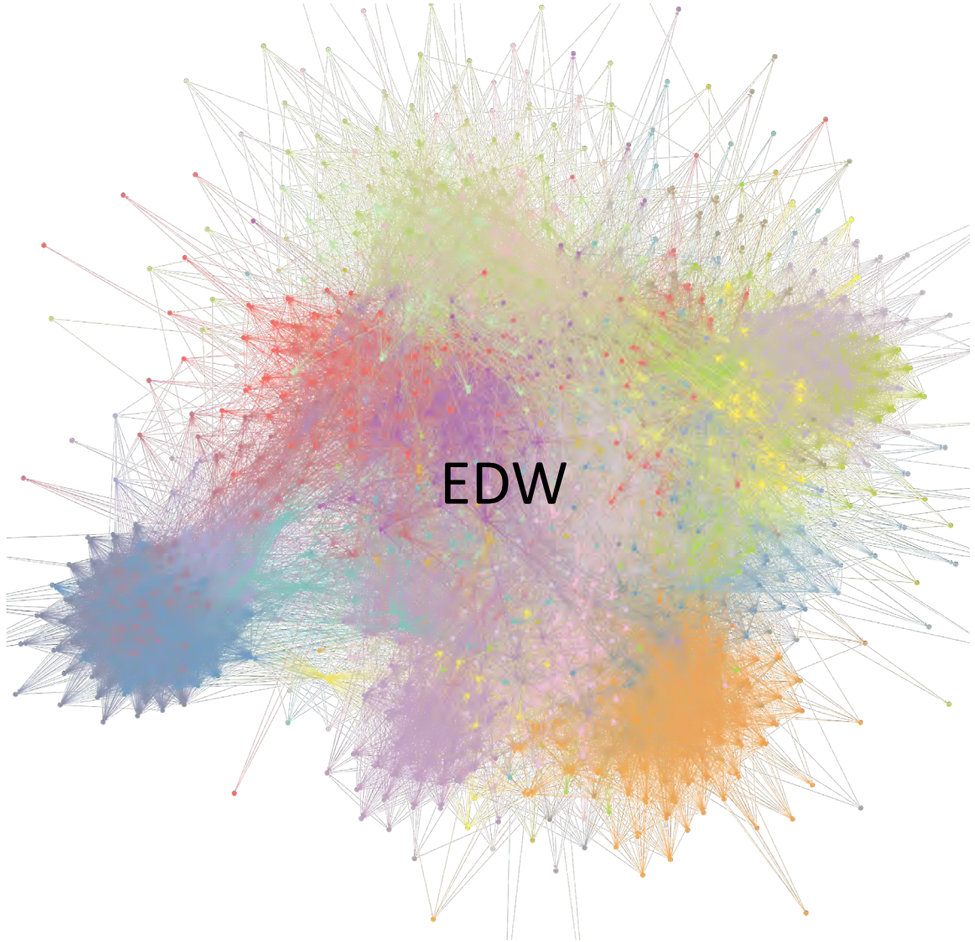
Risk calculations based on EDW terms

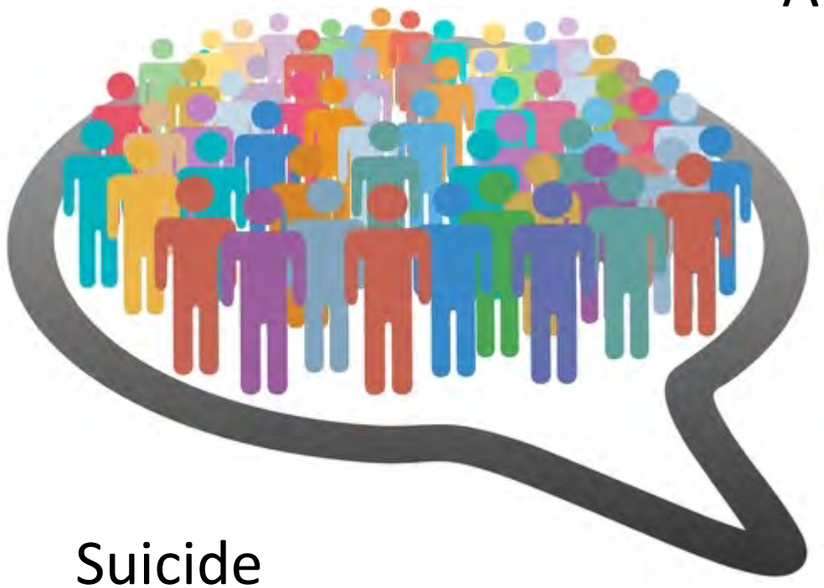
RISK TERM	TRISOMY 21 (YES)	TRISOMY 21 (NO)
AVSD	0.093	0.0002
TOF AVSD	0.030	0.00002
TOF	0.016	0.0003

CONDITION	SAN dysfunction
Fontan	0.20
Glenn	0.09
Norwood	0.07
HLHS	0.08
BAV	0.005

RISK TERM	MATERNAL Child w/CHD (YES)	MATERNAL Child w/ CHD (NO)
Hypertension	0.102	0.072
Diabetes	0.084	0.046
Mental Health d/o	0.271	0.182

Estimating individual risk for any medical disorder across the UU Health System





Atrial fibrillation

Diabetes mellitus

Stroke

Sudden cardiac death

Congenital heart disease

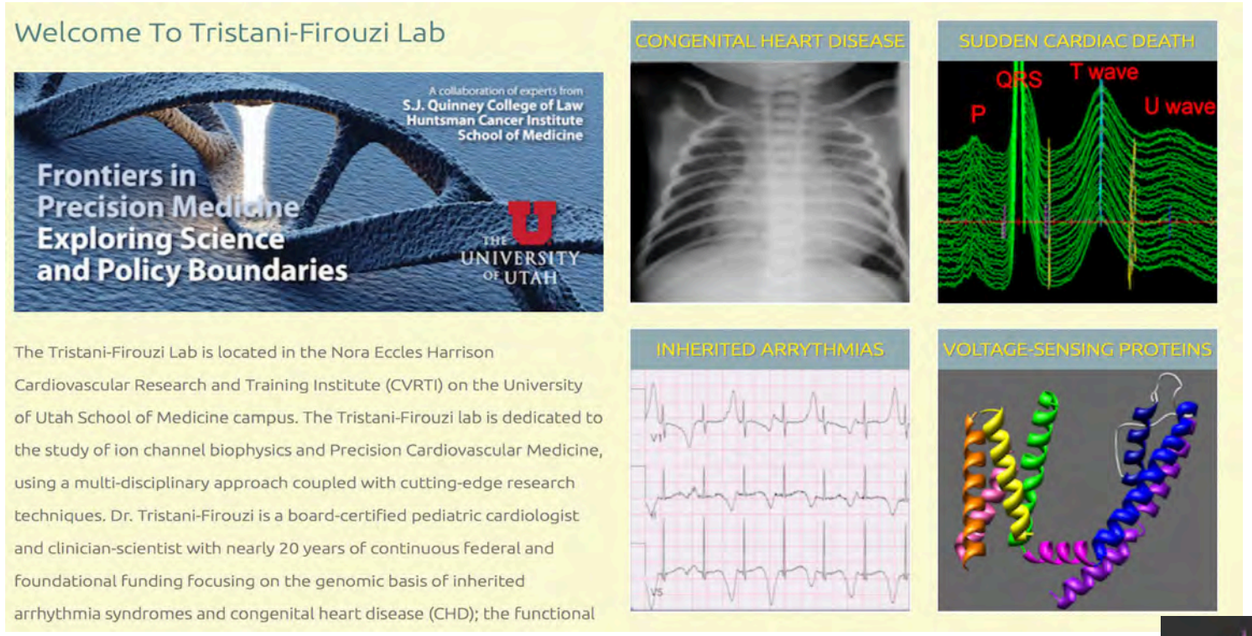
Schizophrenia

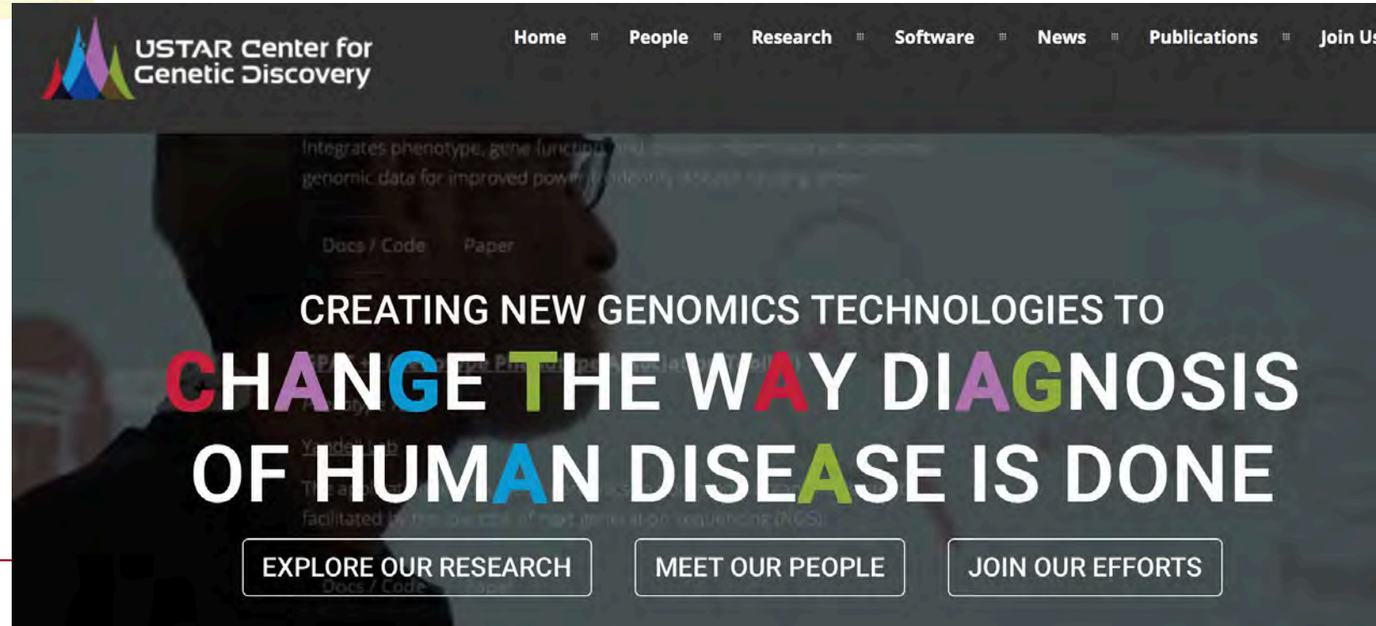
Suicide

WHERE DO WE GO NEXT?

Leveraging Big-Data and Precision Medicine to improve outcomes and health care value

THANK YOU…





HEALTH
UNIVERSITY OF UTAH