



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:

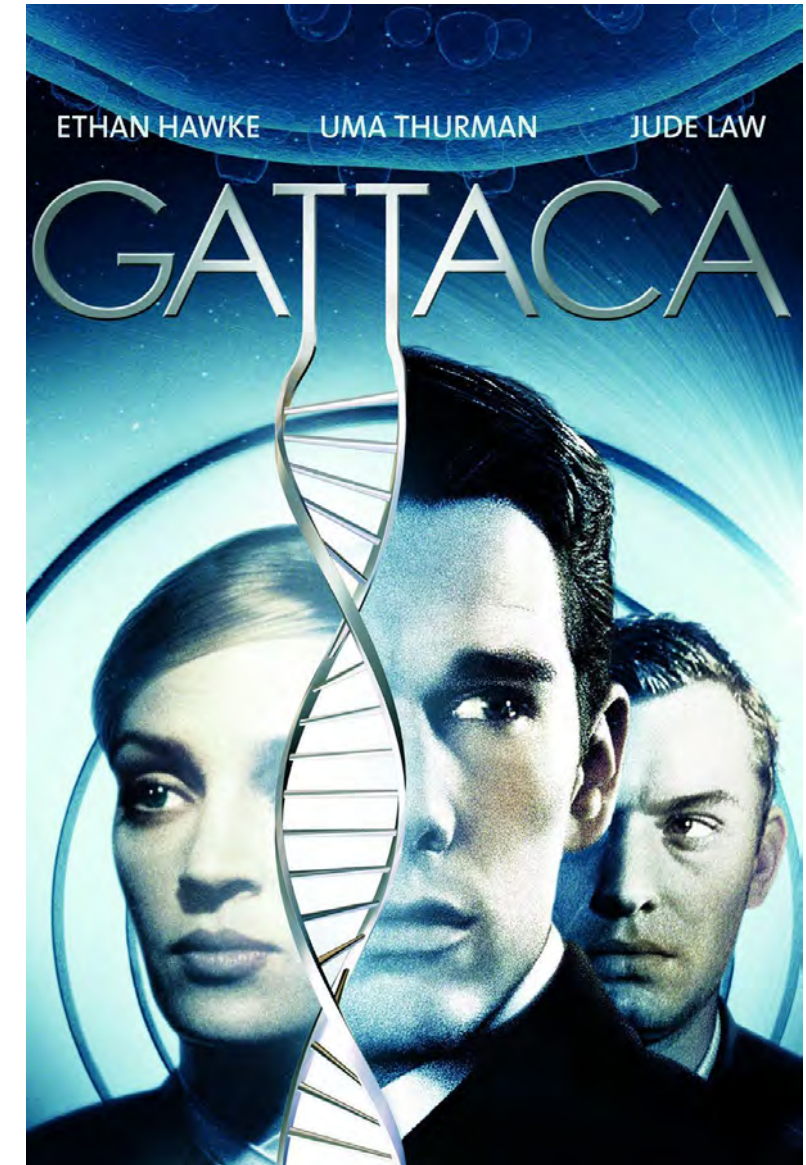
The New York Times

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



ATCAGCTACGGCAC
TGGTTTGCATTAGT
AGATTACAAGCTAT
GCTAGCTAGCCATA
CCTACCCTAGAAAG
GAATTACGGATCTA
TTACCGATCACAGA
AAATCGCTAGCTAC
ACCATGATCGAGTG
CAGATCGAGCCTAT
ACGTAGCGAGTAAA
TGTCGATGCGGTCC
AACGTAGCTTCAAC
GGATCTGCTAGAAT

An Andrew Niccol Film



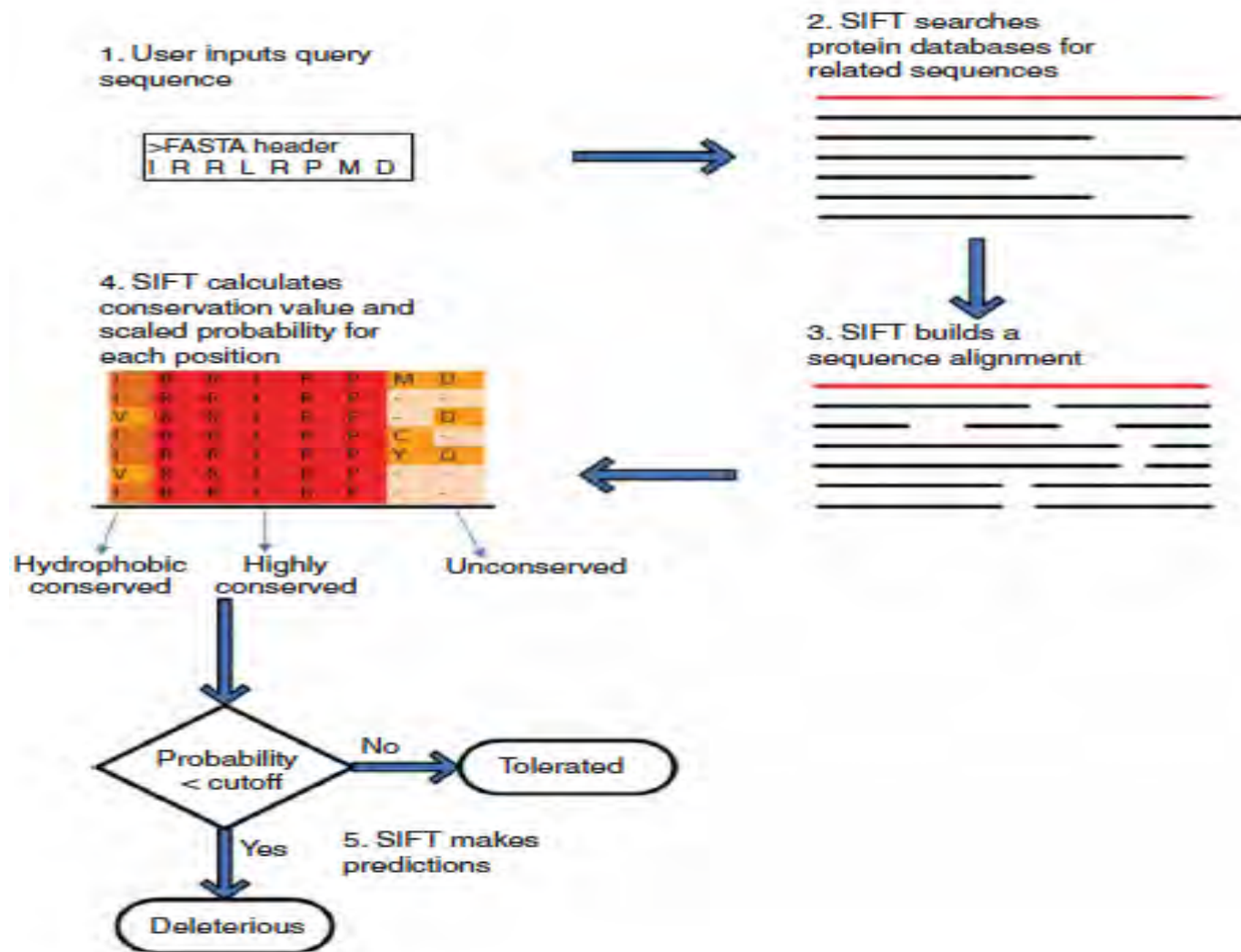
WHAT ARE THE BARRIERS TO PRECISION MEDICINE IMPLEMENTATION?

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

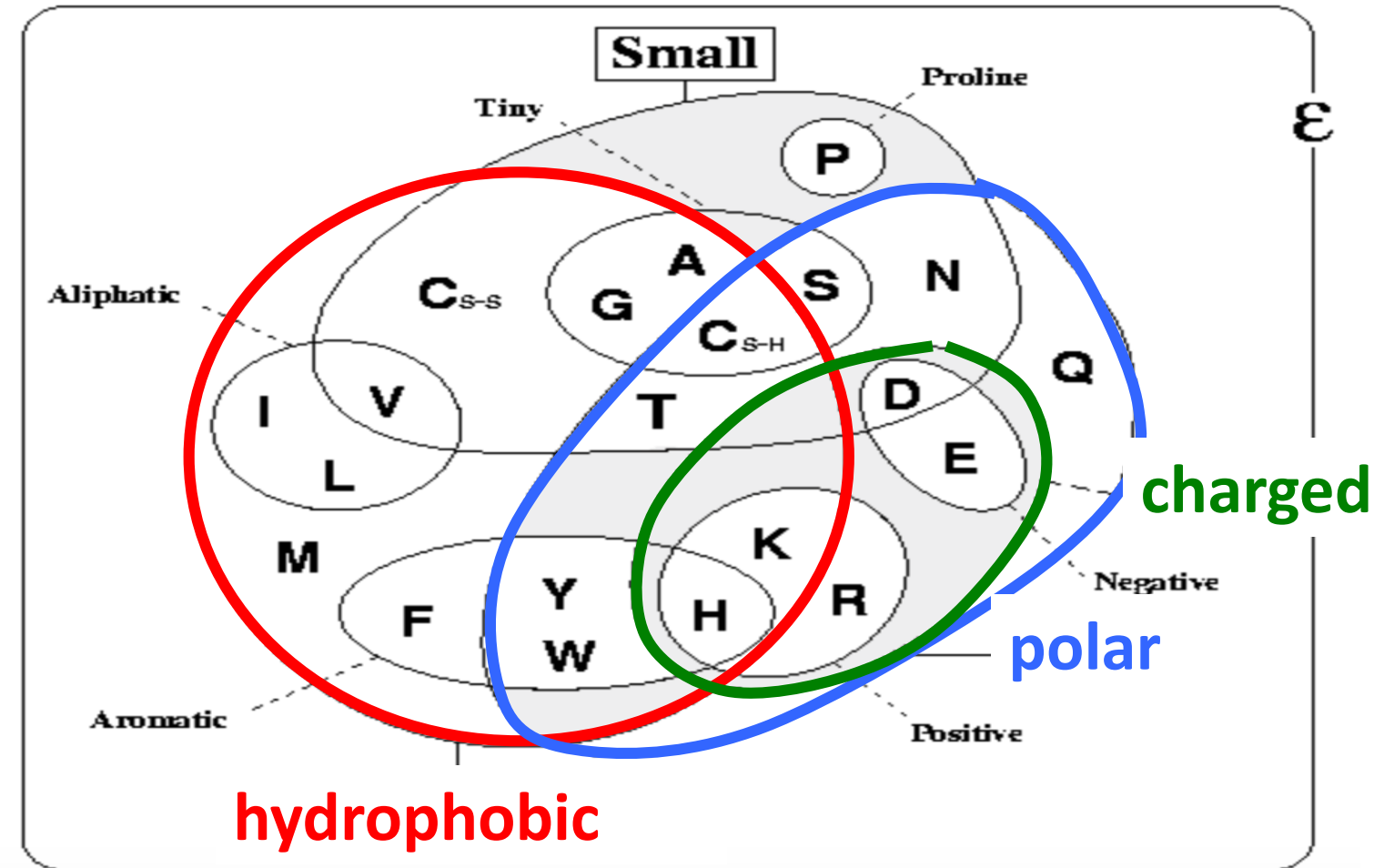


VARIANT ADJUDICATION: IS THIS GENETIC VARIANT PATHOGENIC?

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 Jian⁵, Richard Gibbs⁷, Eric Boerwinkle^{4,5,7}, Kai Wang^{1,2,3,*} and Xiaoming Liu^{4,5,*}

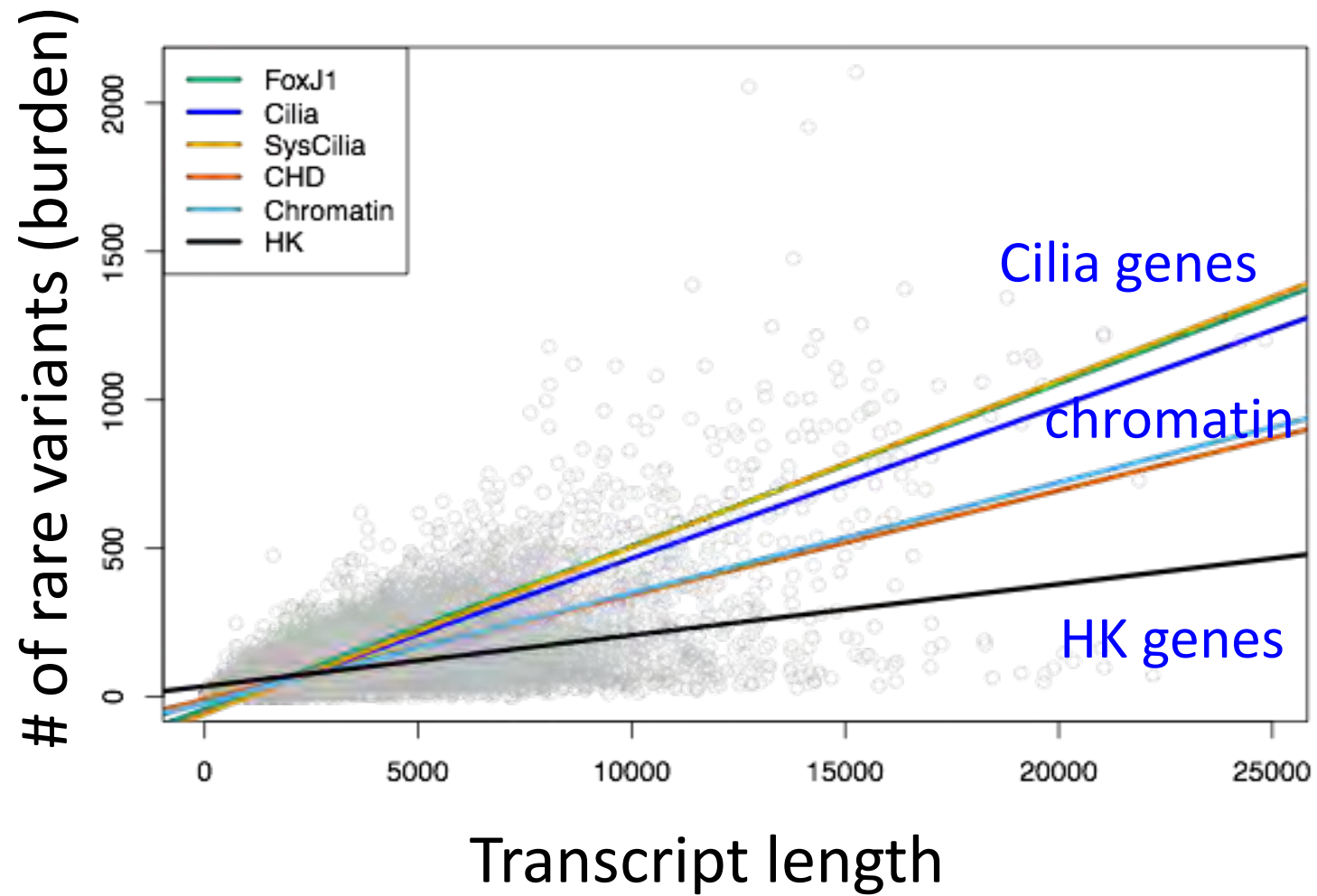
Meta-SVM

ARTICLE

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

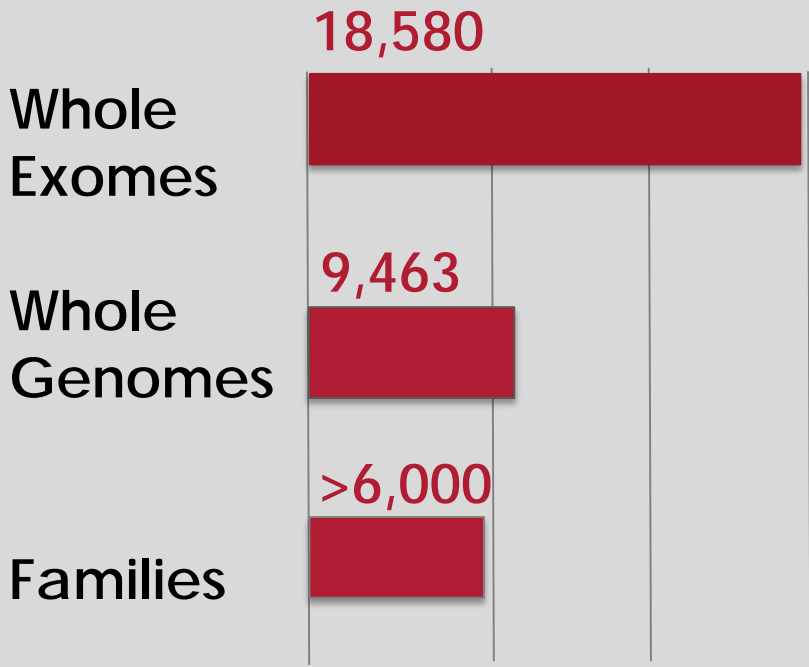
REVEL

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



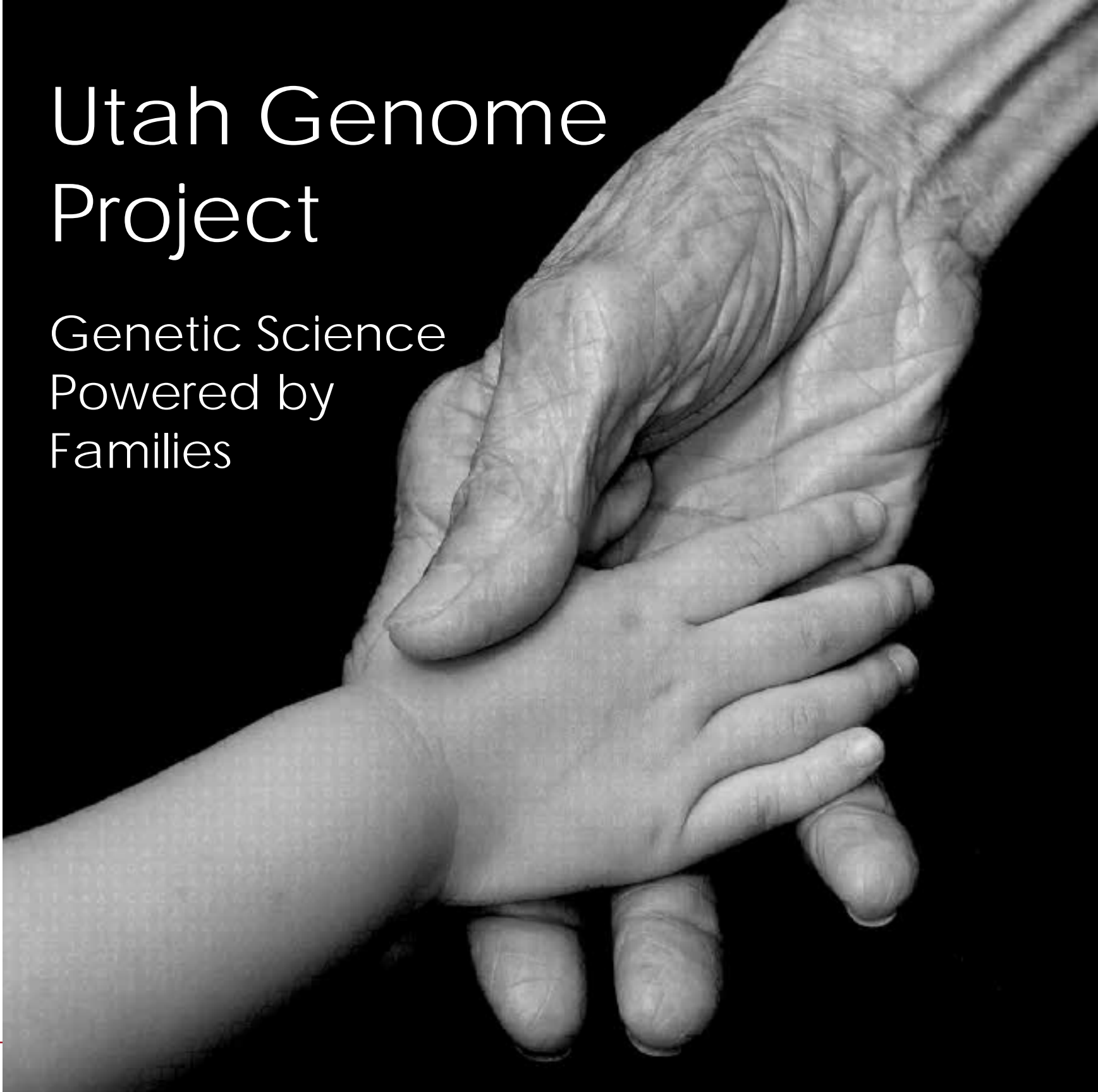
The Utah Genome Project is designed to advance precision medicine in Utah

UGP projects since 2016



Utah Genome Project

Genetic Science
Powered by
Families

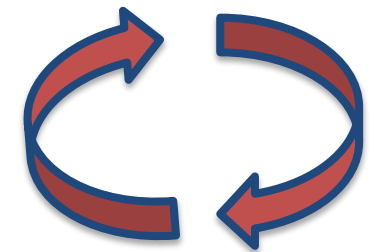


VAAST: VARIANT ANNOTATION, ANALYSIS & SEARCH TOOL

A probabilistic disease-gene finder that employs a burden test to identify 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)

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



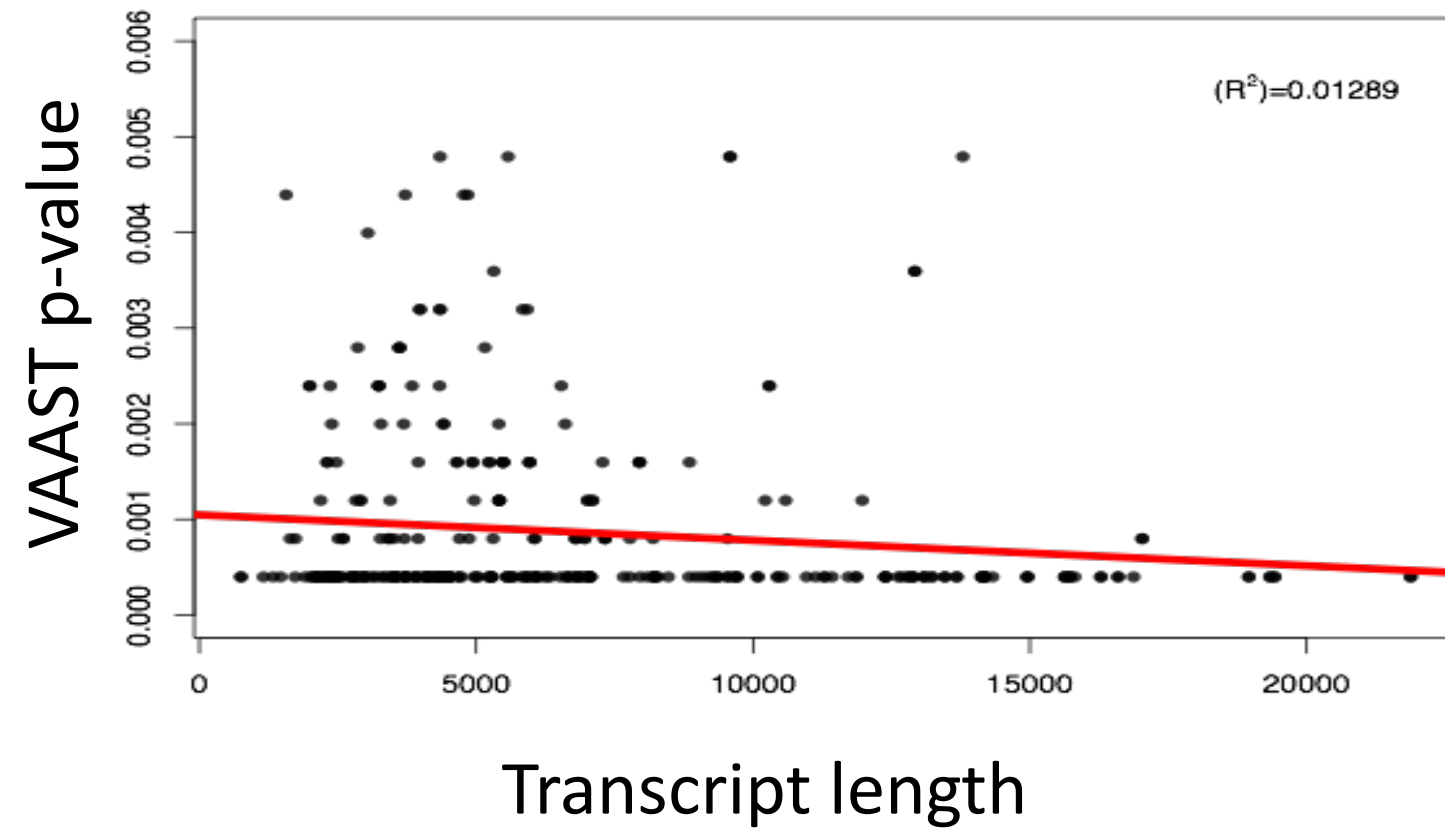
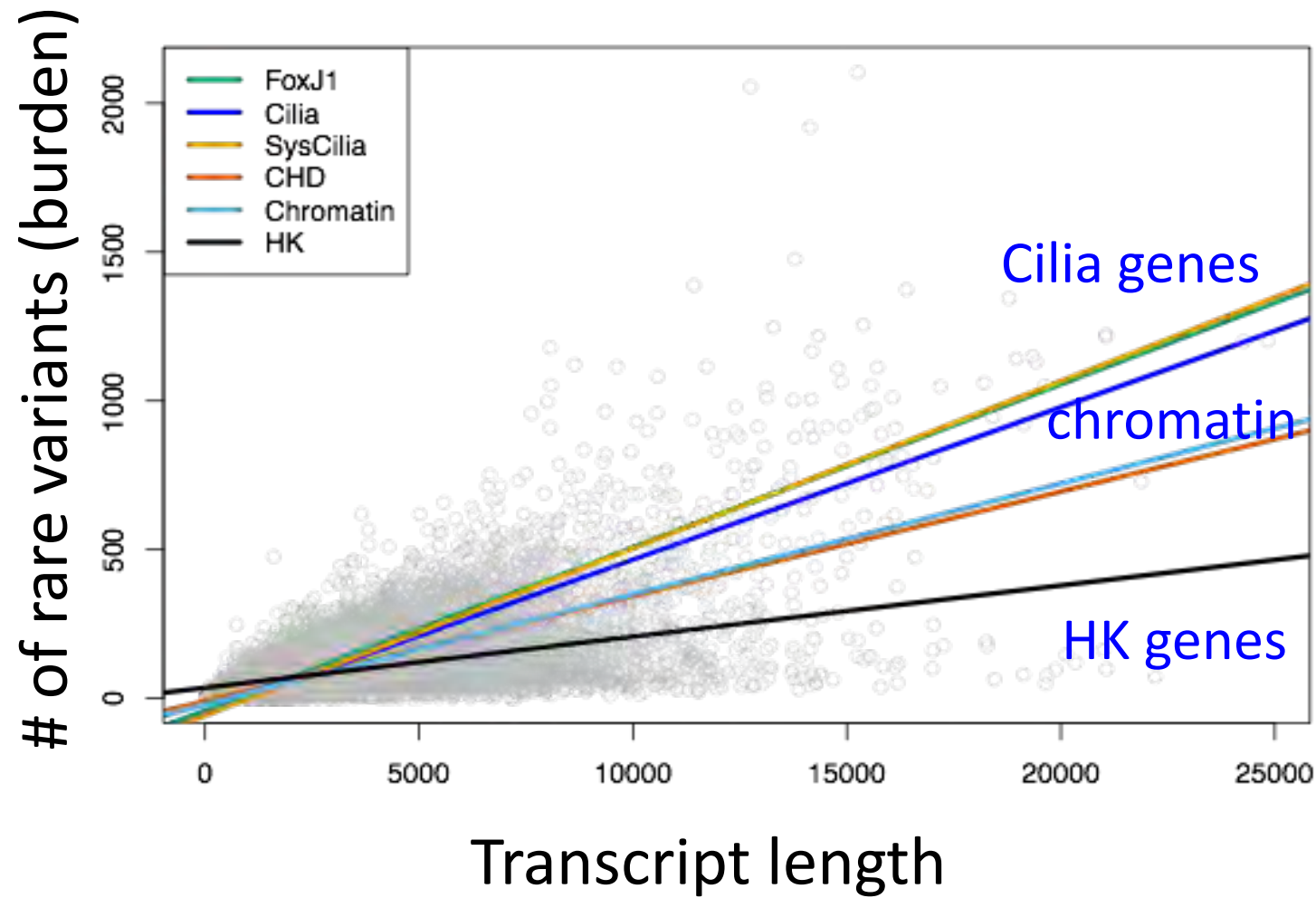
Derives an **empirical p value** for each variant by comparing the degree of burden at that locus to a background population that encompasses 26 ethnicities.



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



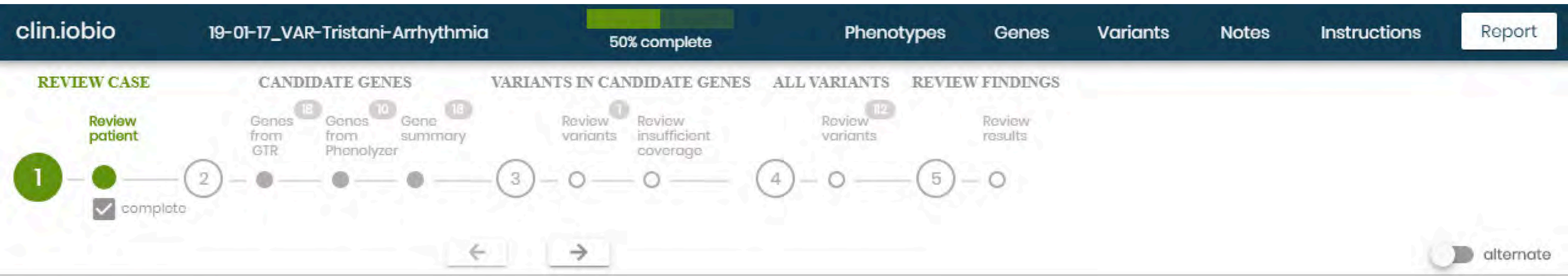
WHY CLINICIAN EDUCATION IS SO IMPORTANT

EDITORIAL COMMENTARY

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

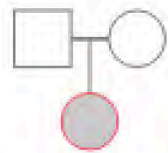
Ahmad S. Amin, MD, PhD,^{*} Arthur A.M. Wilde, MD, PhD, FHRS^{*†}

Point of care genomic analysis tools



Review patient

19-01-17_VAR-Tristani-Arrhythmia



proband	104186
father	104188
mother	104187

Fourteen year old female presented with chest pain and palpitations.. Analysis ID: A602

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

19-01-17_VAR-Tristani-Arrhythmia 3 samples total

Filter: Actions ⋮

Name	Pedigree	Read Coverage (avg & distribution)	Total Reads	% Mapped Reads	Launch
104186		32x	984.8M	70%	
104187		36x	906M	85%	
104188		31x	790M	82%	

Point of care genomic analysis tools

gene.iobio Filter Bookmarks Add Genes Call Variants Splice Analysis Data an iobio project

FILTER VARIANTS

1 + Add

De novo VUS

De novo inheritance, Moderate or high impact, Coverage > 20X, Population Freq in ExAC or 1000G < 1%

Impact

VEP: High, Moderate, Modifier, Low

Clinvar: Pathogenic, Uncertain sig, Benign

Consequence: 3' UTR, synonymous, missense, splice donor, frameshift

Regulatory: Promoter, Promoter flanking, TF binding site, CTCF binding site, TF motif feature

Mode of Inheritance

De novo, Recessive, Compound Het

Variant Type

SNP, Insertion, Deletion, Complex

Population Frequency

ExAC < 1%, 1000G < 1%

Confidence

Coverage > 20x, Strand Balance > %

BOOKMARKS

6 Import Export

GENE SET	NOTES
TCOF1 chr5 149,65,222	Gene panel Investigate splice isoforms
EDNRA chr4 148,433,069	Phenotype driven Variant in Monarch

GENES

2 Analyze all TCOF1 EDNRA SF3B4 SSH DHODH Order genes by impact

ENST00000380310.2 TCOF1 chr5 149,737,202-149,779,871 +- 1000

RANK VARIANTS

3

Variant Type	Impact	Clinvar	SIFT	PolyPhen	Inheritance Mode	Zygoty
SNP	High	Pathogenic	Deleterious	Probably damaging	De novo	Homozygous
INS	Moderate	Uncertain sig	Deleterious (low conf)	Possibly damaging	Recessive	Heterozygous
INS	Modifier	Benign	Tolerated (low conf)	Benign	Compound Het	
SNP	Low		Tolerated			
SNP						

SUGGESTED VARIANTS

4 ClinVar HGMD

PROBAND
Called Variants

Loaded Variants

Coverage

42X

MOTHER

26X

FATHER

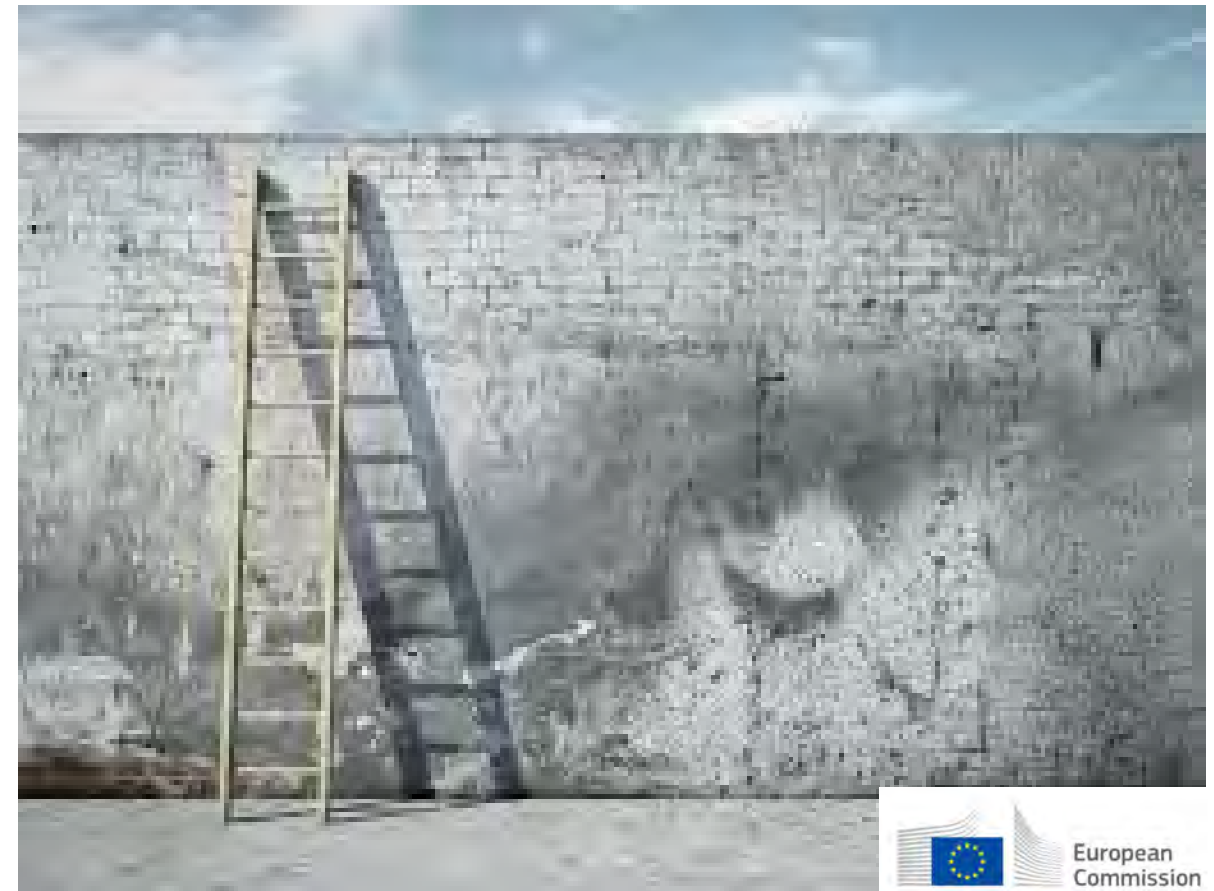
6X

5

Copy Number Region

What are the barriers to Precision Medicine implementation?

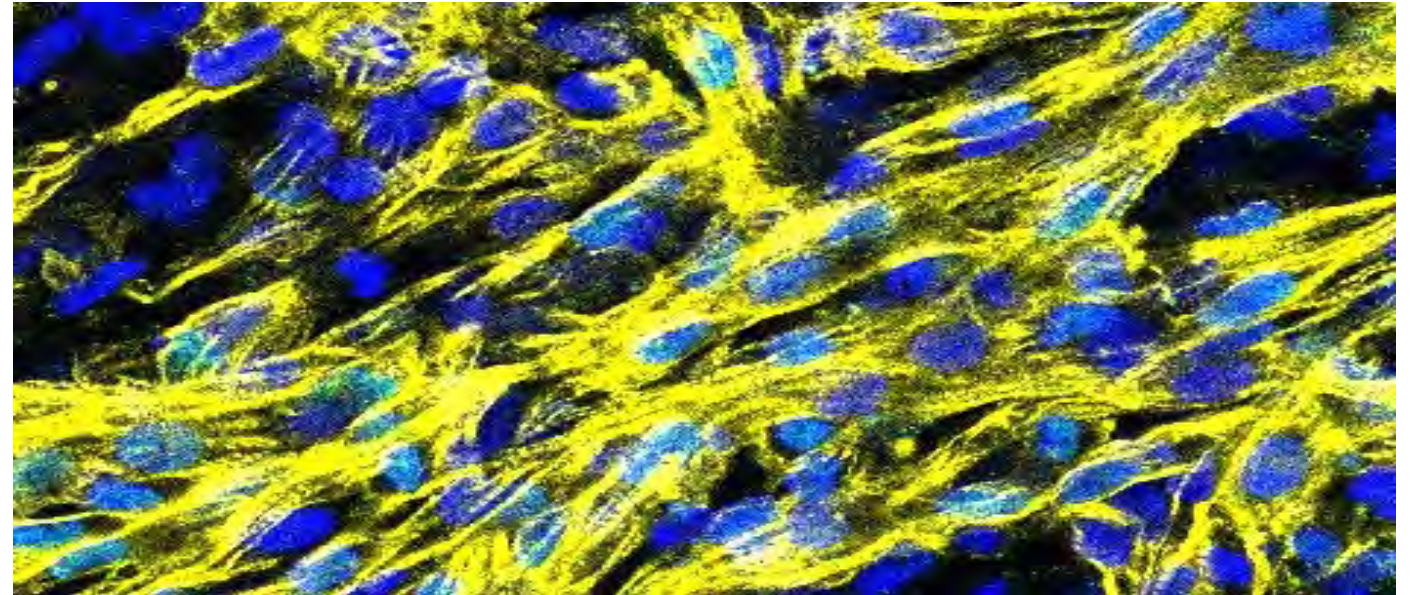
- Variant adjudication
- Clinician education
- Paucity of easy-to-use bioinformatic tools
- **Functional validation**



Model organisms for functional validation



zebrafish



Human iPSC-CMs

Validating pathogenicity of genetic variants in zebrafish

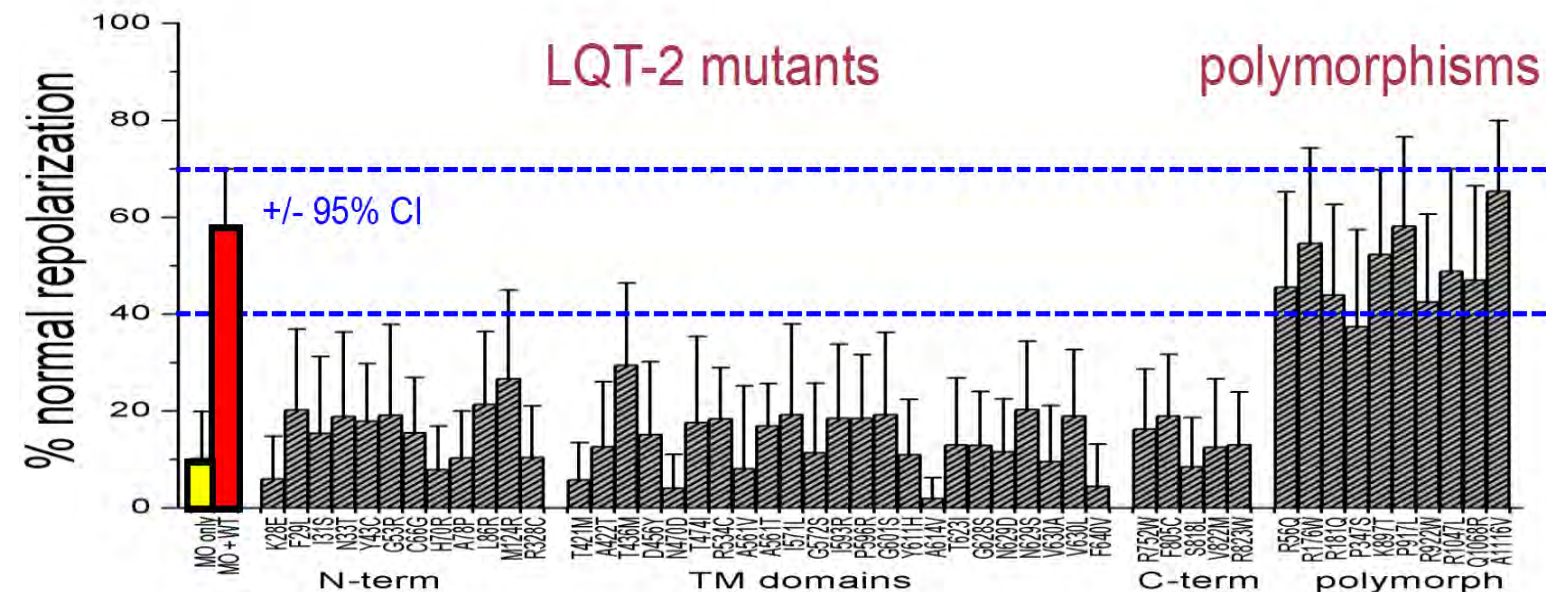
Cellular Physiology
and Biochemistry

Original Paper

A Functional Assay for Sick Sinus Syndrome Genetic Variants

Chuan Chau 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

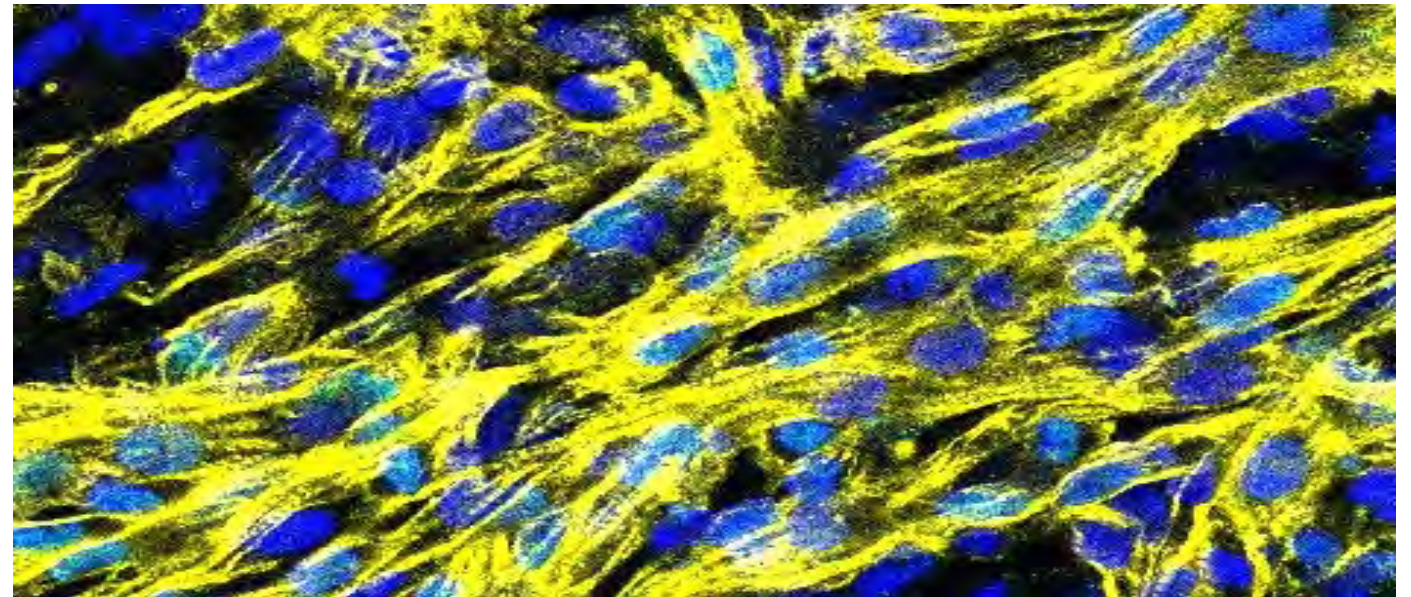
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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

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

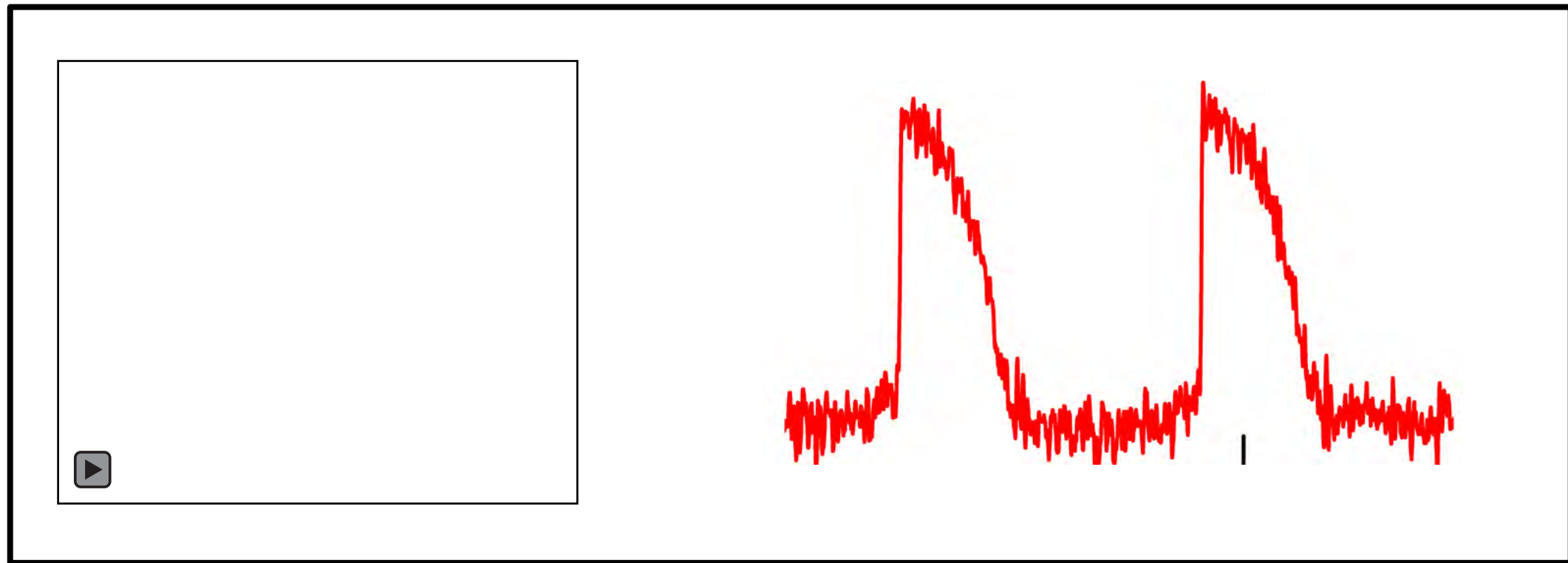


Model organisms for genetic analyses



Human iPSC-CMs

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

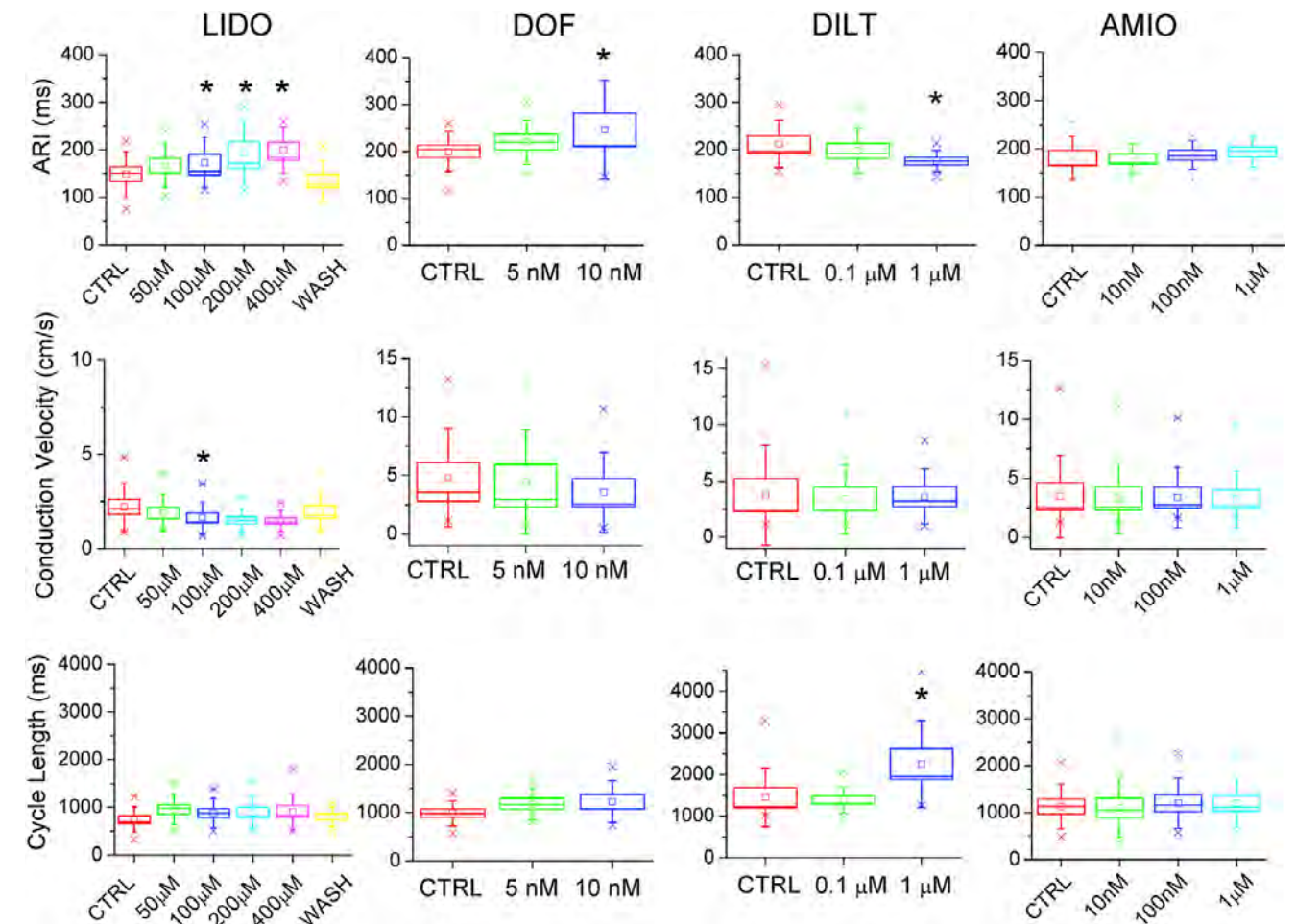
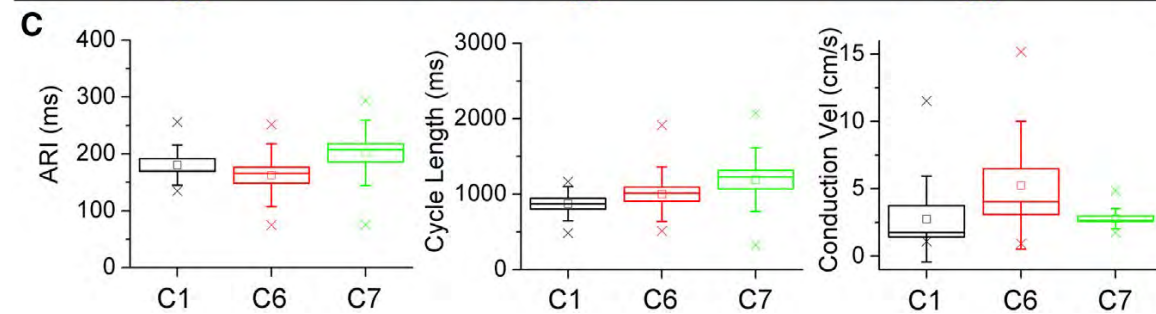
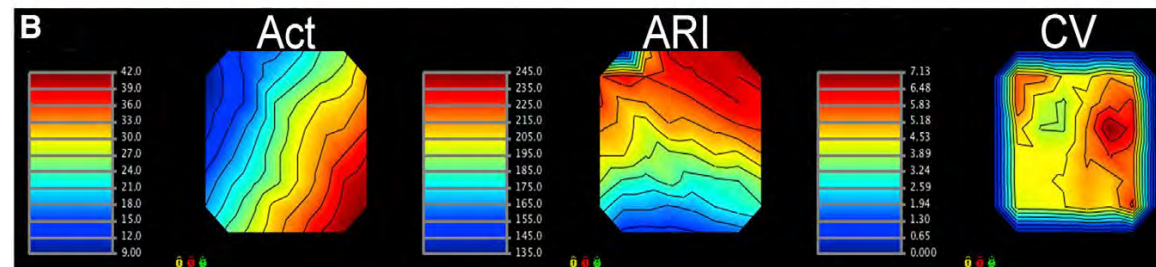
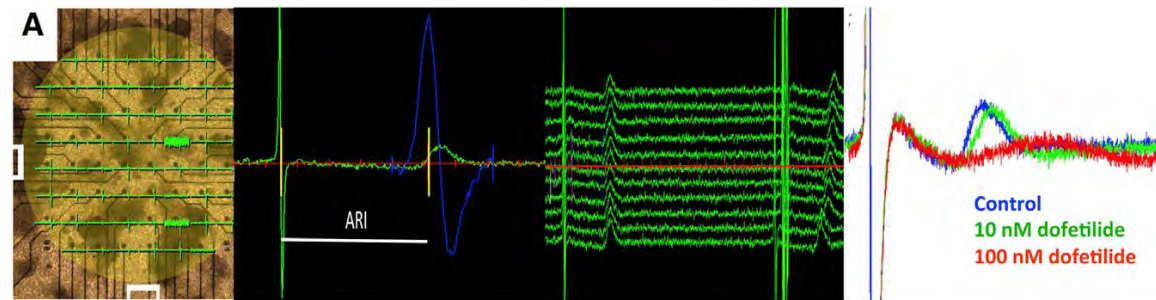


AMERICAN JOURNAL of PHYSIOLOGY
**Heart and Circulatory
Physiology**[®]

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)

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

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 ^e

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^{*†‡§}

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 MBChB¹ | Johan Waktare MD¹ | Dhiraj Gupta MD¹ |
Richard Snowdon MD^{1,2} | Mark Hall MD¹ | Robert Cooper MBChB, PhD² |
Simon Modi MD^{1,2} | Derick Todd MD^{1,2}  | Saagar Mahida MD, PhD^{1,2}

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



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



REVIEW

Open Access

Big data analytics in healthcare: promise and potential

Wullianallur Raghupathi^{1*} and Viju Raghupathi²

BROOKINGS

CITIES & REGIONS GLOBAL DEVELOPMENT INTERNATIONAL AFFAIRS U.S. ECONOMY U

SERIES: A Blueprint for the Future of AI

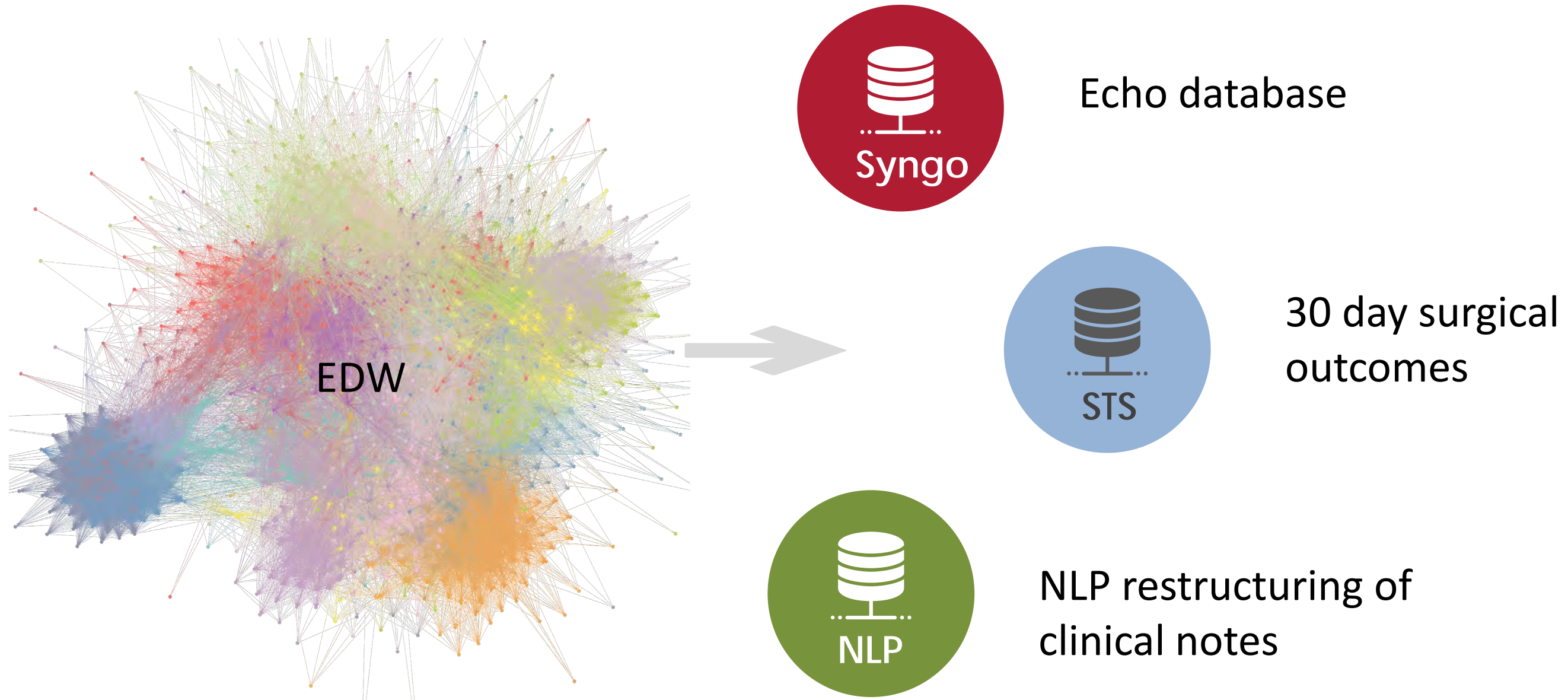


REPORT

The opportunities and challenges of data analytics in health care

Paul B. Ginsburg, Andrés de Loera-Brust, Caitlin Brandt, and Abigail Durak
Thursday, November 1, 2018

Intersecting the EDW with other clinical databases to empower outcomes research

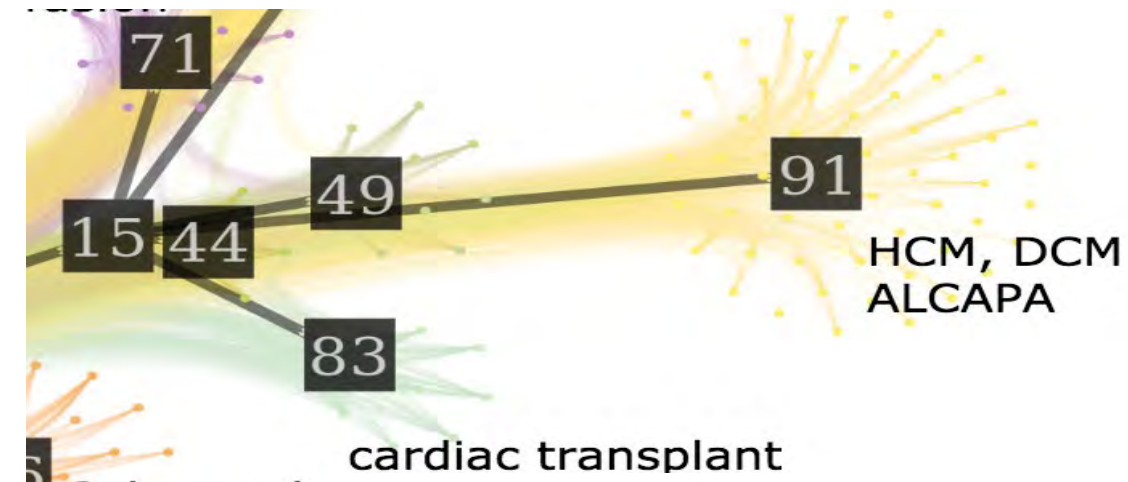
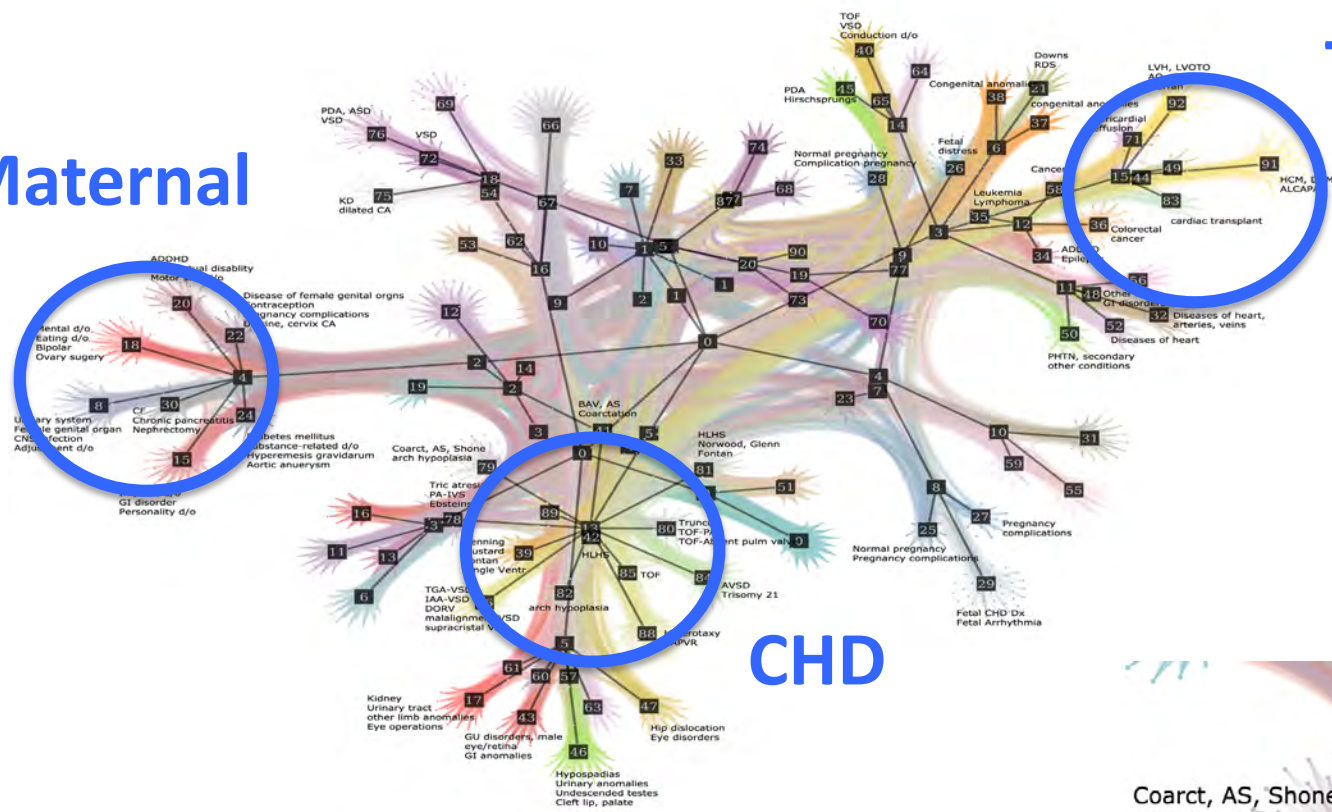


CONNECTIONS BETWEEN TERMS IN EDW AND ECHO DATABASE

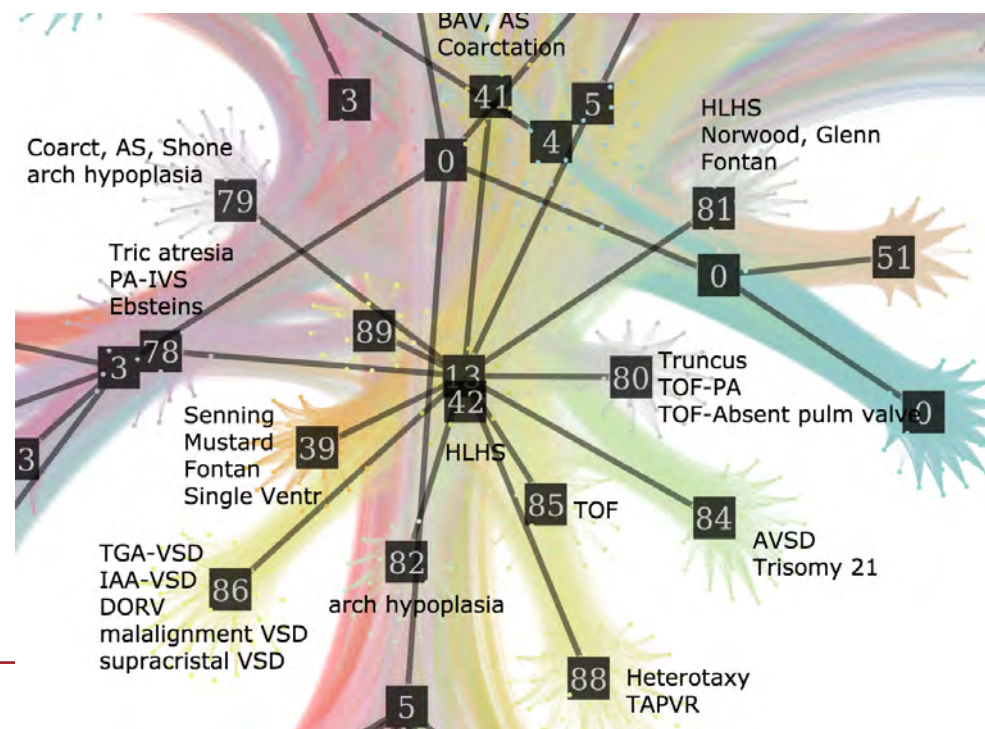
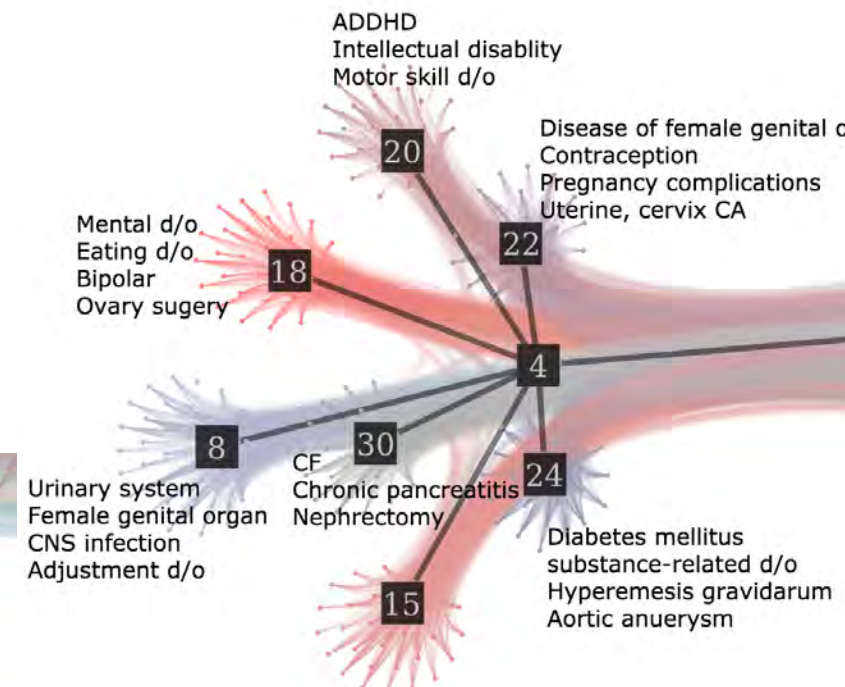
Maternal

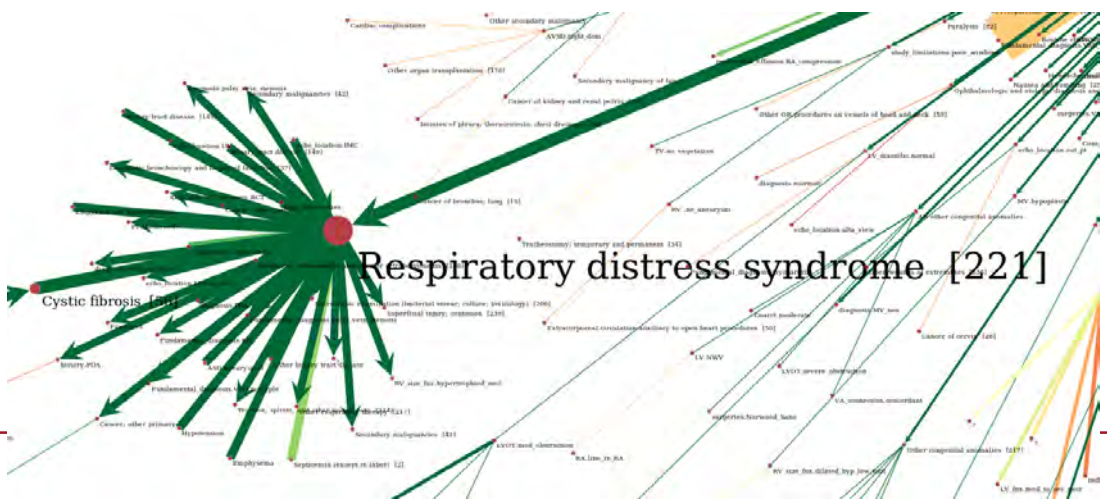
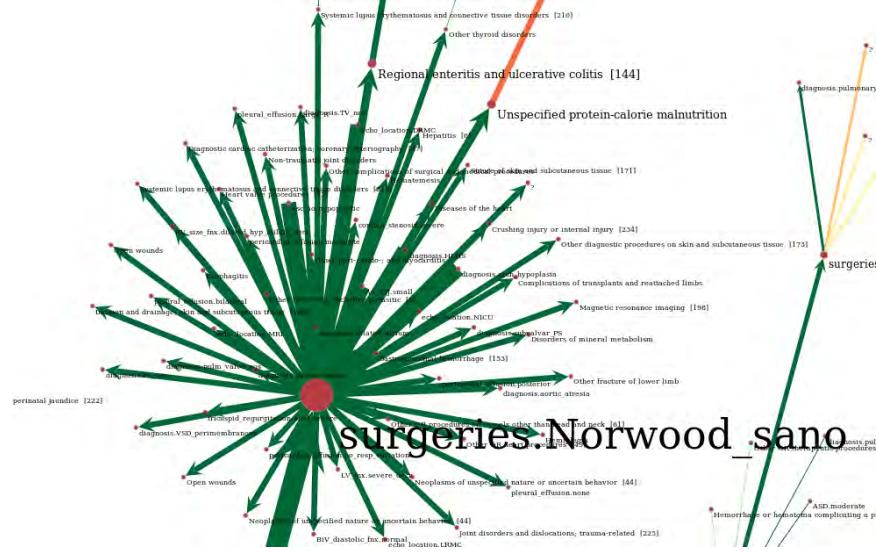
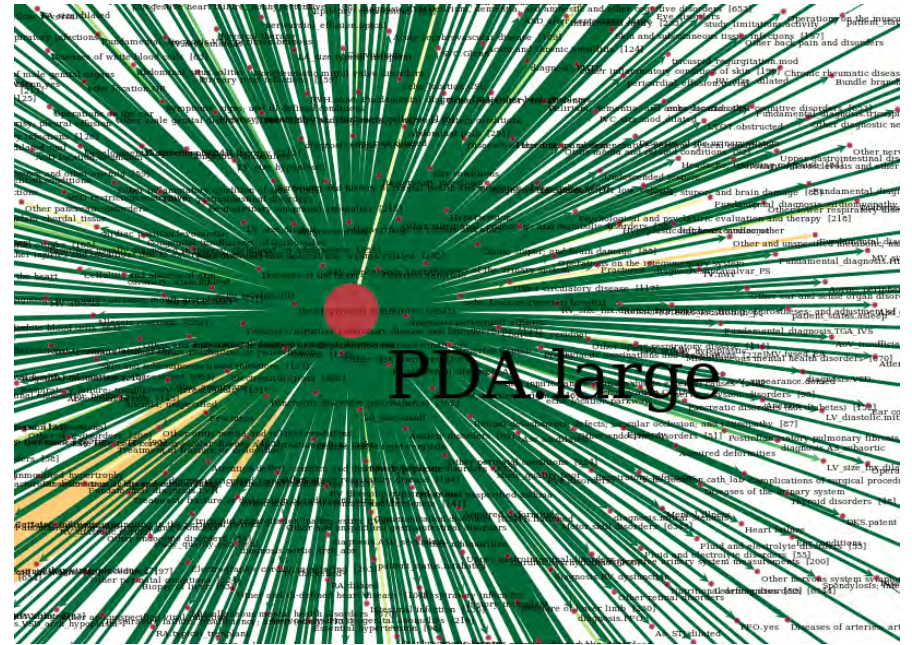
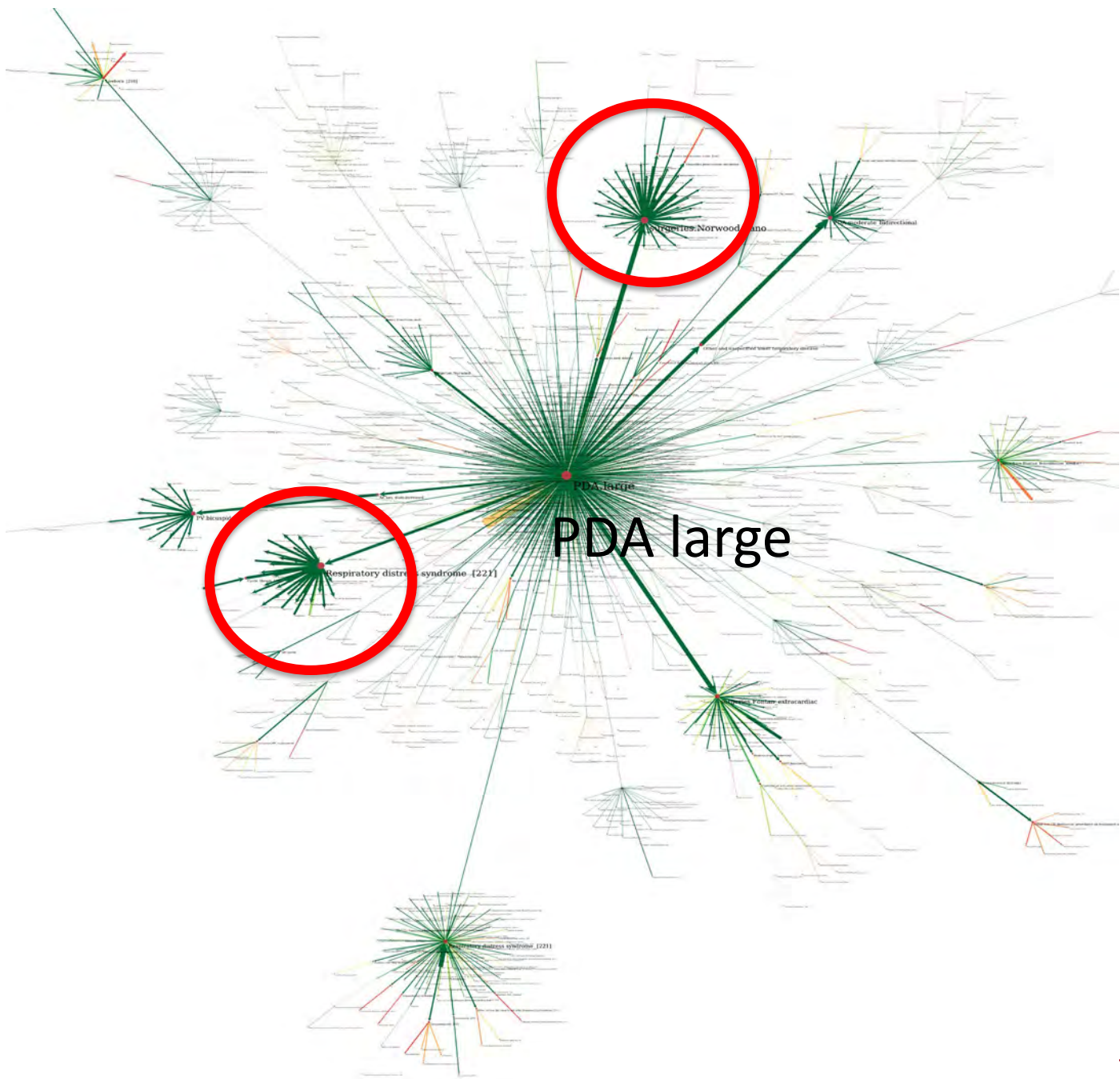
Tx

CHD



cardiac transplant





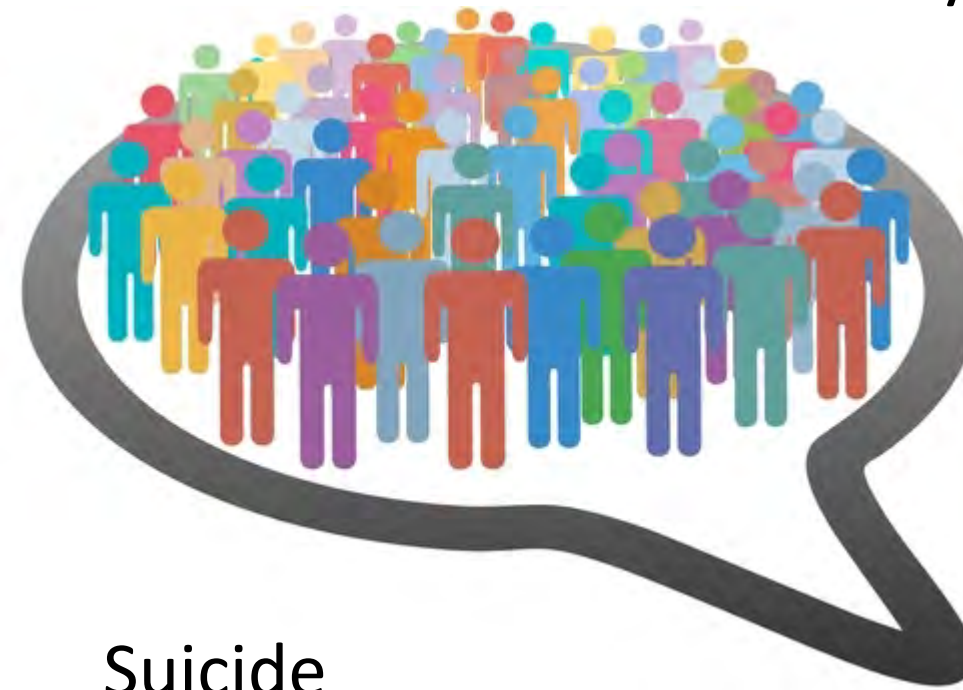
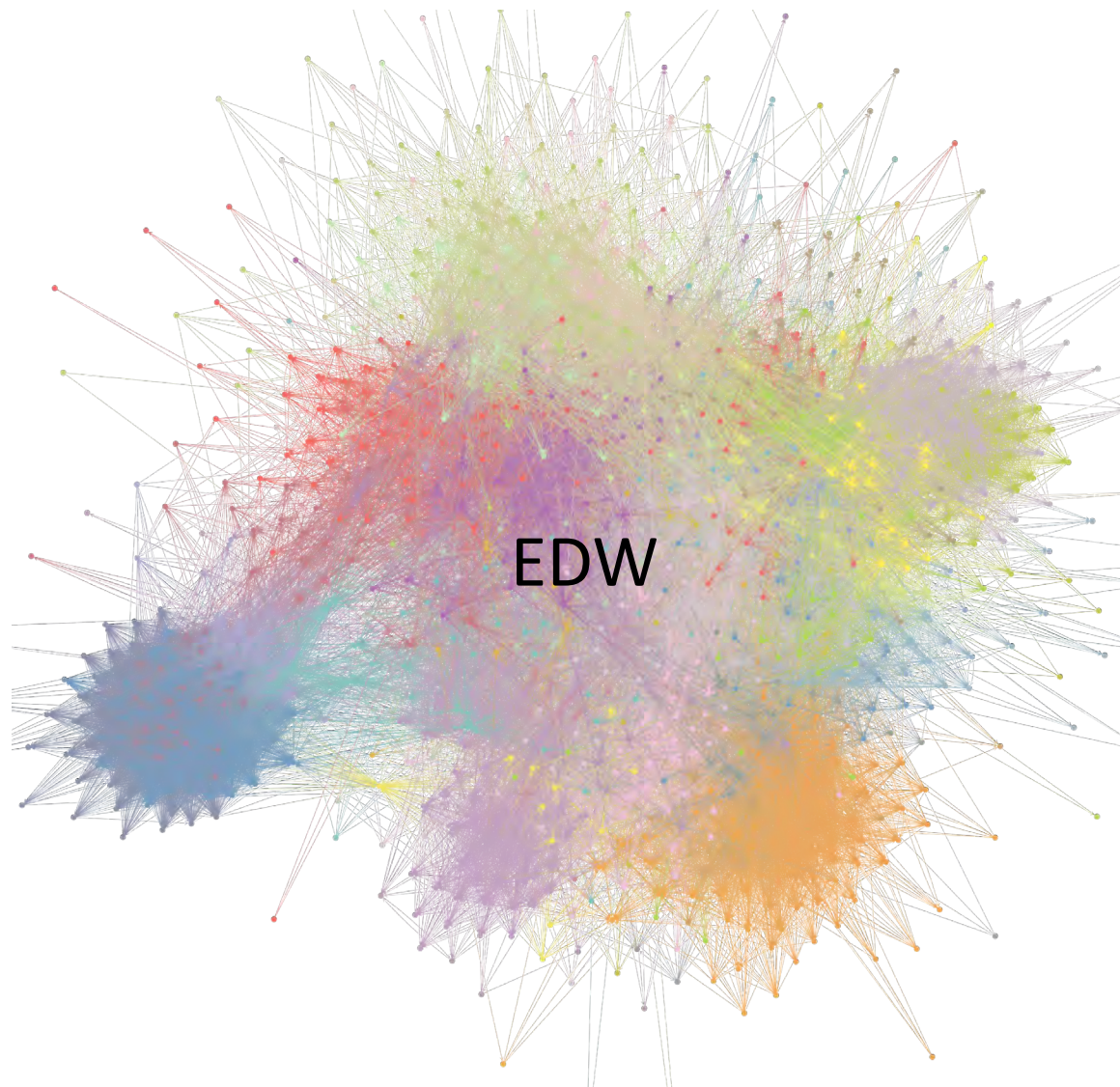
Risk calculations based on EDW terms

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



Suicide

Schizophrenia

Atrial fibrillation

Diabetes mellitus

Stroke

Sudden cardiac death

Congenital heart disease

WHERE DO WE GO NEXT?



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



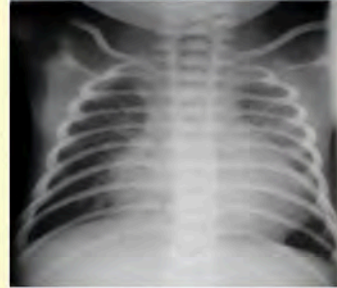
THANK YOU...

Welcome To Tristani-Firouzi Lab

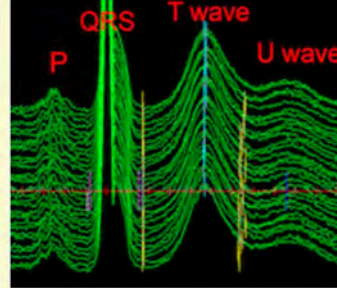


The Tristani-Firouzi Lab is located in the Nora Eccles Harrison Cardiovascular Research and Training Institute (CVRTI) on the University of Utah School of Medicine campus. The Tristani-Firouzi lab is dedicated to the study of ion channel biophysics and Precision Cardiovascular Medicine, using a multi-disciplinary approach coupled with cutting-edge research techniques. Dr. Tristani-Firouzi is a board-certified pediatric cardiologist and clinician-scientist with nearly 20 years of continuous federal and foundational funding focusing on the genomic basis of inherited arrhythmia syndromes and congenital heart disease (CHD); the functional

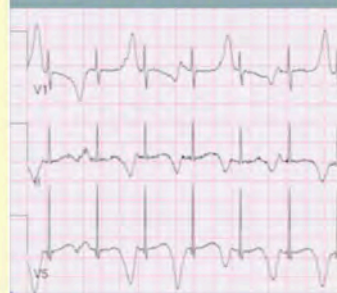
CONGENITAL HEART DISEASE



SUDDEN CARDIAC DEATH



INHERITED ARRHYTHMIAS



VOLTAGE-SENSING PROTEINS



USTAR Center for Genetic Discovery

Home People Research Software News Publications Join Us

Integrates phenotype, gene function, and genomic data for improved power, accuracy, and discovery.

Docs / Code Paper

CREATING NEW GENOMICS TECHNOLOGIES TO
CHANGE THE WAY DIAGNOSIS
OF HUMAN DISEASE IS DONE

EXPLORE OUR RESEARCH MEET OUR PEOPLE JOIN OUR EFFORTS