Personalizing Care using Genomics – Opportunities and Challenges

Robb Rowley, M.D.

24 June 2021
1155 - 1255 ET

Presenter

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Robb Rowley, M.D.

Dr. Robb Rowley is an Internal Medicine Physician and is the newly appointed Program Director for the National Human Genome Research Institute (NHGRI) Electronic Medical Records and Genomics (eMERGE) Network. The national Network combines DNA biorepositories with electronic medical record (EMR) systems for large scale, high-throughput genetic research in support of implementing genomic medicine.

Prior to starting at NHGRI, he spent thirteen years in private practice and hospital management, where he provided clinical assessments and medical care for adult diseases influenced by genetically influenced conditions to improve patient risk stratification and individualize treatments. Dr. Rowley previously served in the United States Air Force Surgeon General's Office in Washington DC as the Chief of Medical Bioinformatics and Genomics. During this time, he established genomic policy and conducted genomic research for the United States Air Force. Dr. Rowley has also been instrumental in establishing national and international plans and policies for incorporating genomics into biosurveillance systems and biotechnology for the Department of Defense (DoD) and North American Trade Organization (NATO). Dr. Rowley has experience with managing multiple Food and Drug Administration (FDA) clinical trials, along with presenting original research at international scientific and medical meetings.

Disclosures

- Dr. Rowley has no relevant financial or non-financial relationships to disclose relating to the content of this activity.
- The views expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of the Department of Defense, nor the U.S. Government.
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- Commercial support was not received for this activity.

Learning Objectives

At the end of the presentation, participants will be able to:

1. Describe genomic medicine opportunities and challenges.
2. Explain how genomics can be used for clinical care: assessing risk, pharmacogenomics, undiagnosed disease, and somatic variation.
3. Summarize emerging concepts in genomics and how clinicians are needed for implementation.

DoD demonstrates value of genomic medicine

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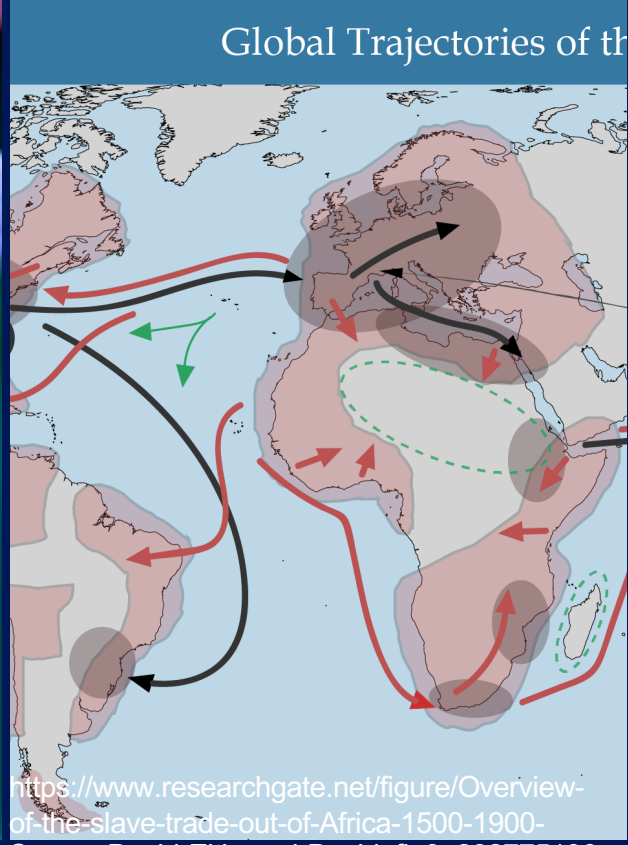
https://www.stripes.com/air-force-expands-basic-training-course-to-focus-on-readiness-lethality-1.555371

https://www.cdc.gov/coronavirus/2019-ncov/downloads/COVID19-symptoms.pdf

https://Wikipedia.com



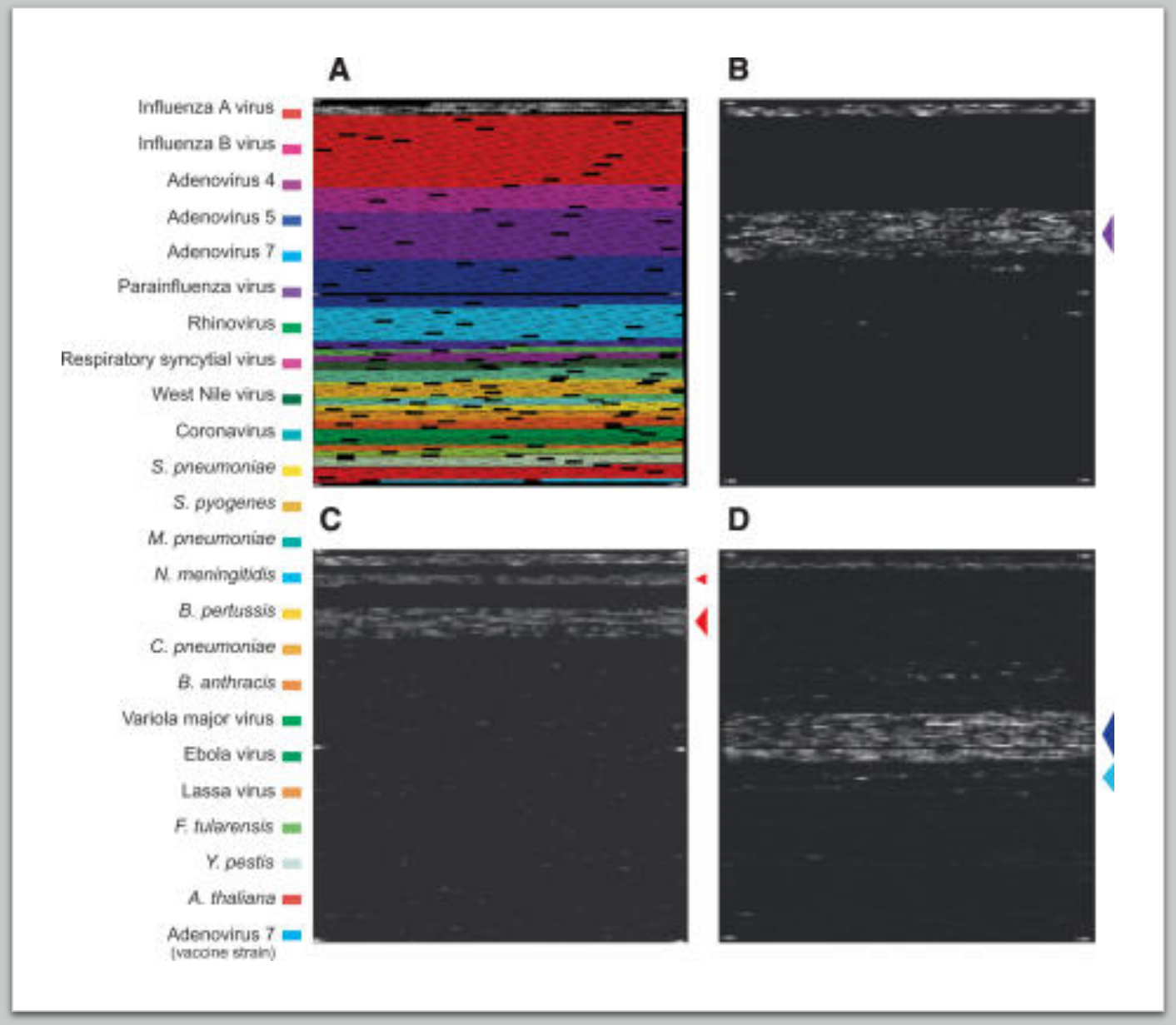
https://www.researchgate.net/figure/Overview-of-the-slave-trade-out-of-Africa-1500-1900-Source-David-Eltis-and-David_fig3_282775196

DoD at the forefront of Genomic Medicine

- In 1999 basic trainees had “flu-like” symptoms with loss of Adenovirus vaccine
- Recognized that many pathogens present with these symptoms
  - Adenovirus, Influenza, Anthrax, SARS, coronavirus…
- Understood the limitations of current approach of suspect and test
- Limited ability to monitor and track pathogens

Tackling Challenge

- 2001 DoD started the epidemic outbreak surveillance program
- Developed and validated a microarray to identify 100's of strains of pathogens at the sequence level in a single test
- Allowed the tracking and monitoring of pathogens by digitizing biology
- Conducted a genomic medicine clinical trial



https://Wikipedia.com

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Tackling Challenge

Table 1. Pathogens identified for 424 matched specimens-overall microarray vs. reference methods.

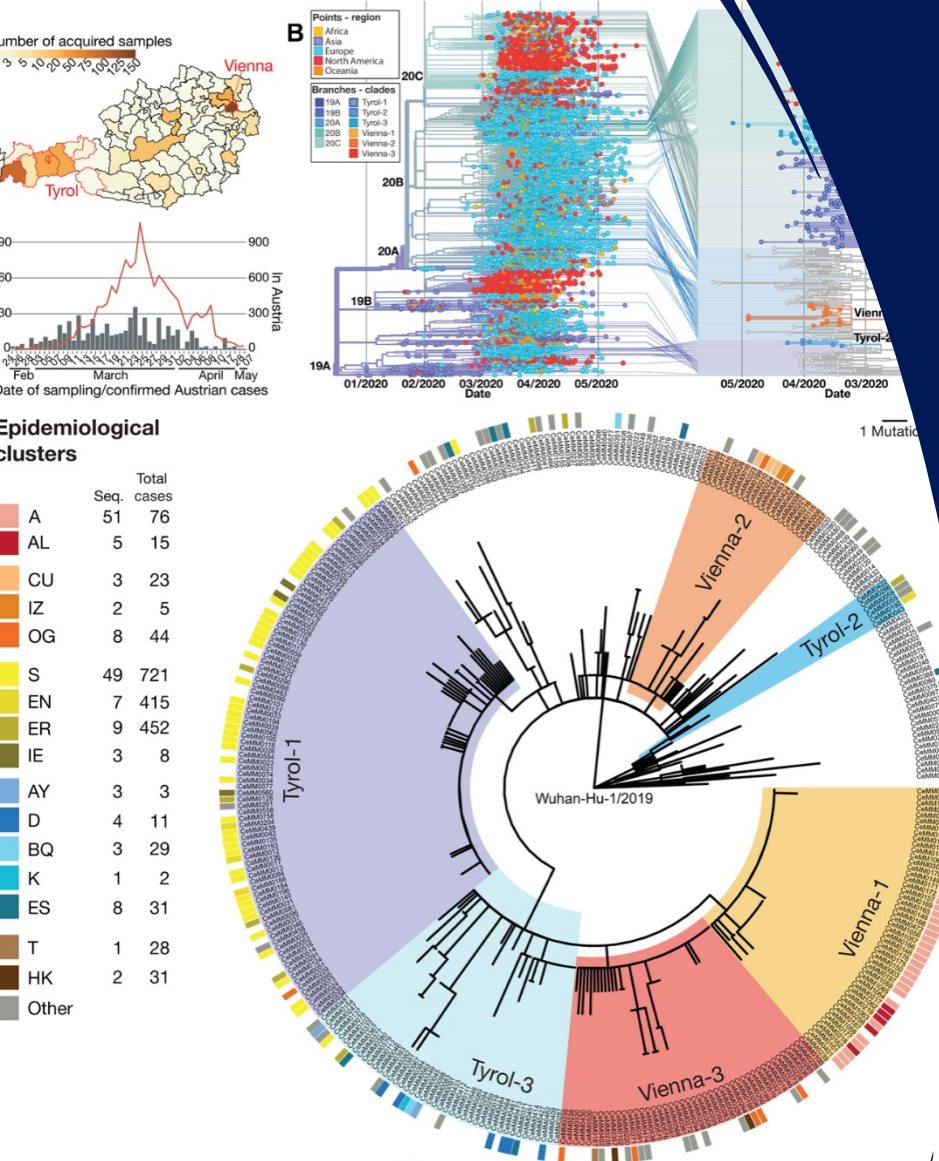
Organism	Culture (+)	Ref© (+)	RPM v.1 (+)	Ref© (+), RPM v.1 (−)	Ref© (−), RPM v.1 (+)
Adenovirus	2	8	9	0	1
Coronavirus	28*	29	24	6	2
Influenza A	176	263	269	1	7
Influenza B	28	41	46	1	6
PIV 1	0	0	1	0	1
PIV3	0	0	2	0	2
Rhinovirus	0	1	2	1	1
M. pneumoniae	0	2	3	0	1
S. pneumoniae	8	40	38	3	1
S. pyogenes	9	13	13	0	0
Negative	176	52	59	0	7

Note: *Coronaviruses were identified through CAP-certified PCR method, Ref©: reference assays-culture and/or RT-PCR/PCR positive.

doi:10.1371/journal.pone.0000419.t001

(Lin, et al., 2007)

Lessons from COVID



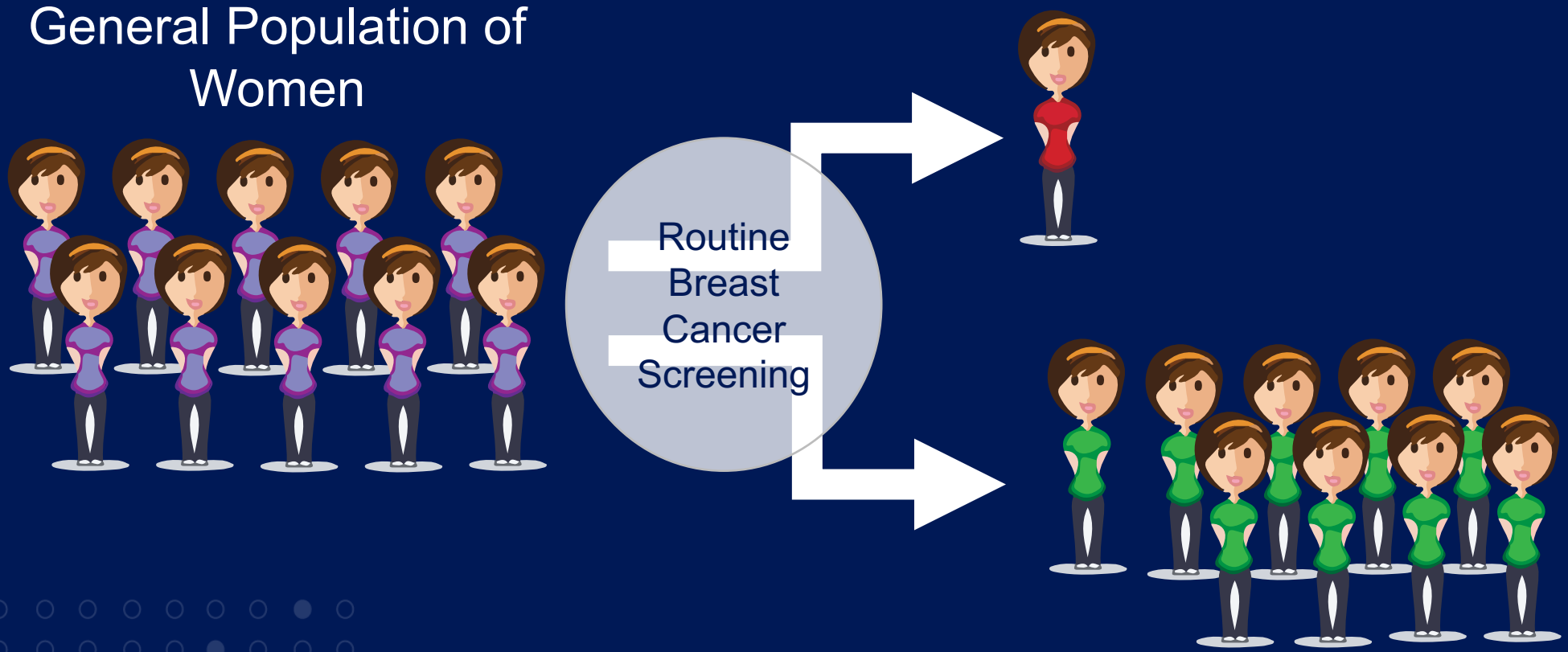
- What is an appropriate threshold for positivity?
- How do we manage the improved resolution of the outbreak for clinical decisions?
- What constitutes significant change in the genome?
- How do we manage the rapid identification and dissemination of information?
- Explaining transmissibility

(Popa et al., 2020)

Science Translational Medicine
AAAS

Assessing Risk

Rationale behind genetics for risk



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Rationale behind genetics for risk

General Population of Women

High Risk

Lower Risk

High Risk

Screening

Identify Early

https://www.pinterest.co.uk/gloriagiganti/angelina-jolie/

(Frost, 2011)

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Monogenic Risk

- Found in ~3.2% of the general population
- Average risk significantly different than monogenic conferred risk e.g.
  - 12.9% risk of a woman in the general population
  - ~70% risk in woman with Breast Cancer (BRCA) 1 variant

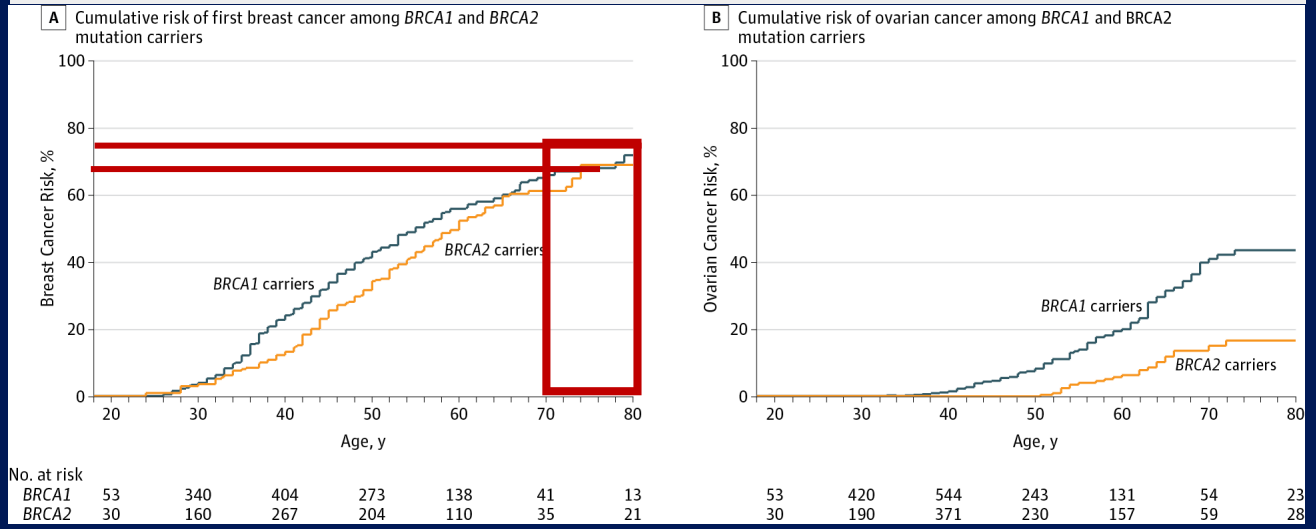
Cancer Statistics, 2021

Siegel, R. L., Miller, K. D., Fuchs, H. E., & Jemal, A. (2021). Cancer Statistics, 2021. *CA: a cancer journal for clinicians*, *71*(1), 7–33. https://doi.org/10.3322/caac.21654

	BIRTH TO 49	50 TO 59	60 TO 69	70 AND OLDER	BIRTH TO DEATH
Breast					
Female	2.1 (1 in 49)	2.4 (1 in 42)	3.5 (1 in 28)	7.0 (1 in 14)	12.9 (1 in 8)

From: **Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers**

JAMA. 2017;317(23):2402-2416. doi:10.1001/jama.2017.7112



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Using an Individual Patient's Genomic Variants in their Clinical Care– Germline Cancer Mutations

Syndrome	Gene	Tumors
Hereditary breast and ovarian cancer	*BRCA1/2*	Breast, ovarian, prostate, pancreatic, other cancers
Li-Fraumeni	*TP53*	Multiple
Cowden	*PTEN*	Breast, thyroid, endometrial other cancers
HNPCC (Lynch)	*MLH1, MSH2, MSH6*	Colon, endometrial, ovarian, other cancers
Von Hippel-Lindau	*VHL*	Hemangioblastomas, renal cell, other cancers
Retinoblastoma	*RB1*	Retinoblastoma
Hereditary paraganglioma	*SDHD, SDHC, SDHB*	Paraganglioma, pheochromocytoma
Multiple endocrine neoplasias	*MEN1, RET*	Multiple

(Garber, 2005)

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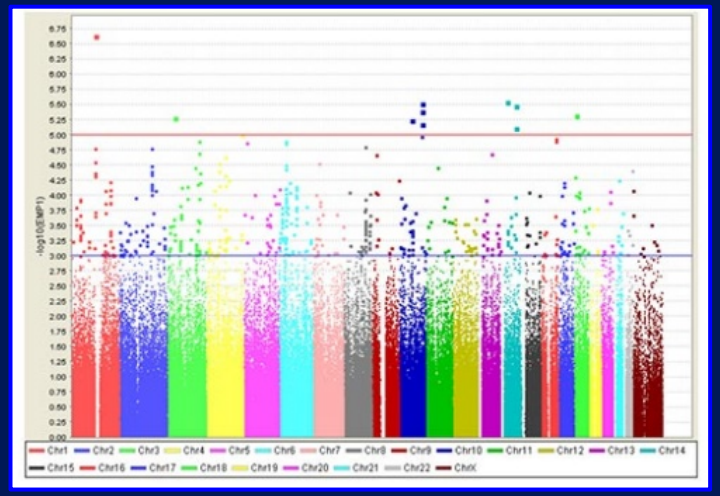
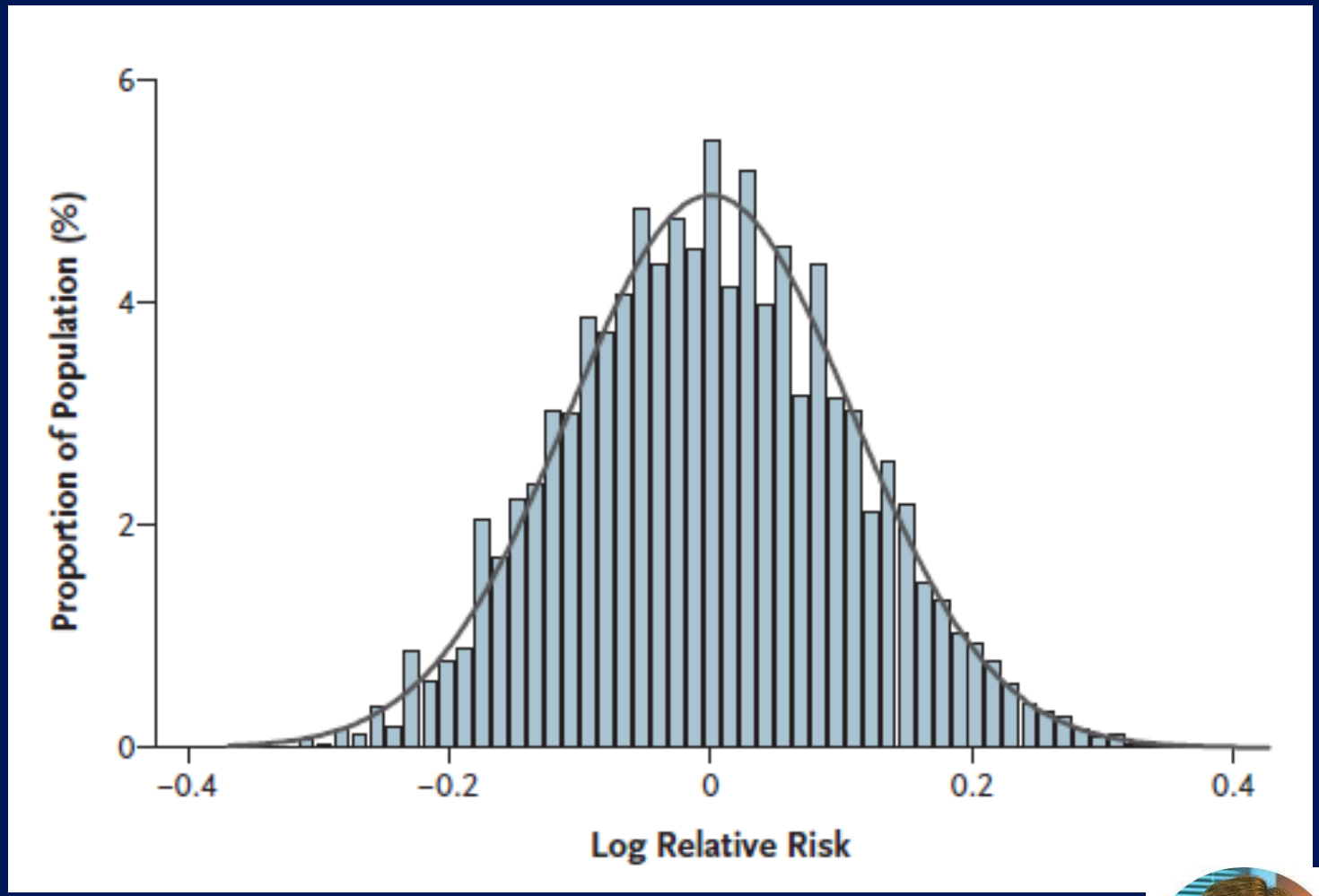
Polygenic Risk Scores (PRS)



$$Y = \sum_{m=1}^{M_1} \beta_m X_m + \sum_{m=M_1+1}^{M} 0 \times X_m + \varepsilon$$



(Pharoah, 2008)

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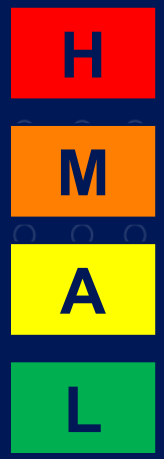
Clinical Factors



High

Moderate

Average

Low

How do we improve on the standard of care for risk stratifying patients?

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Incorporating a Genetic Risk Score Into Coronary Heart Disease Risk Estimates

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

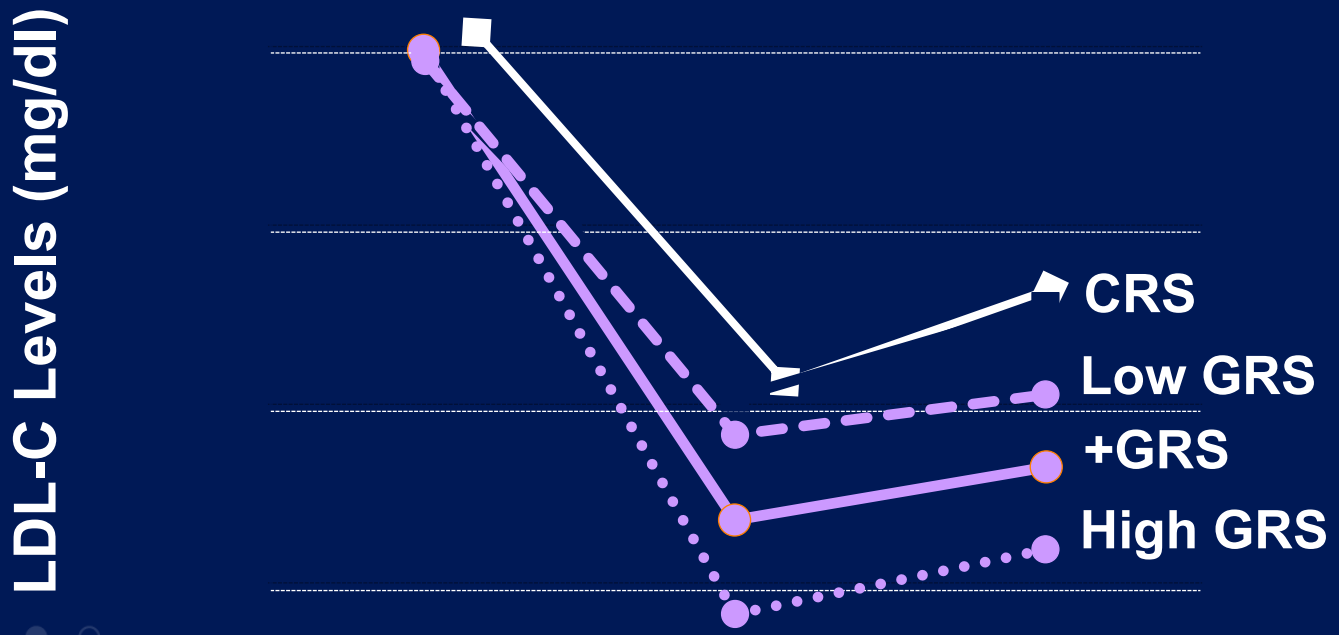
Iftikhar J. Kullo, MD; Hayan Jouni, MD; Erin E. Austin, PhD; Sherry-Ann Brown, MD, PhD; Teresa M. Kruisselbrink, GCS; Iyad N. Isseh, MBBS; Raad A. Haddad, MBBS; Tariq S. Marroush, MD; Khader Shameer, PhD; Janet E. Olson, PhD; Ulrich Broeckel, MD; Robert C. Green, MD, MPH; Daniel J. Schaid, PhD; Victor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

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

(Kullo, 2016)

LDL-C Lowering in Patients Given Clinical and Genomic Risk Information

"…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, 2016)

Applying Risk

- Using monogenic risk with clinical factors
- Combine PRS with clinical factors
- Combine monogenic and PRS to understand risk

Association of Lifestyle and Genetic Risk With Incidence of Dementia

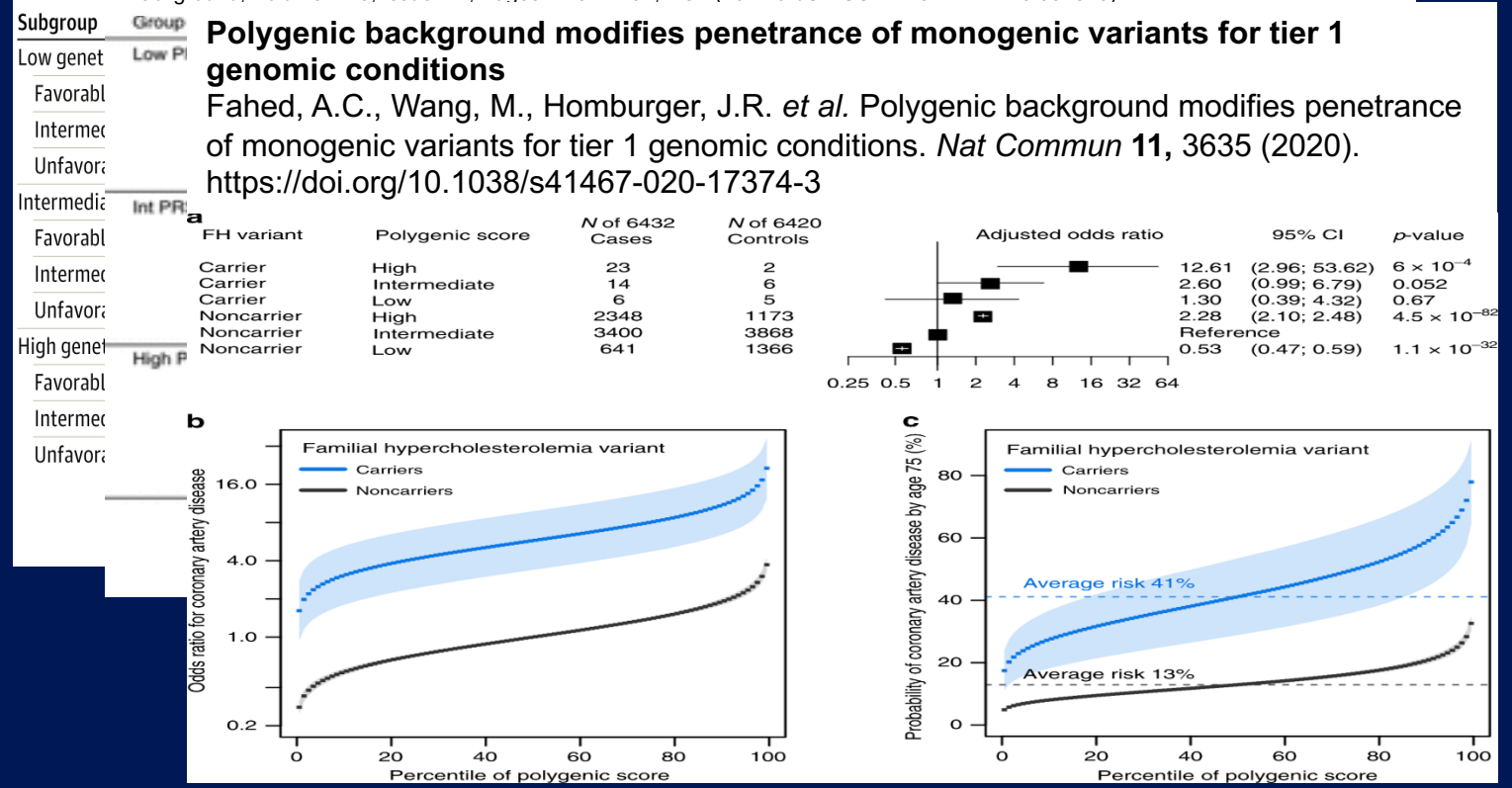
JAMA

Risk of Coronary Artery Disease Conferred by Low-Density Lipoprotein Cholesterol Depends on Polygenic Background

Alessandro Bolli. Circulation. Risk of Coronary Artery Disease Conferred by Low-Density Lipoprotein Cholesterol Depends on Polygenic Background, Volume: 143, Issue: 14, Pages: 1452-1454, DOI: (10.1161/CIRCULATIONAHA.120.051843)

Polygenic background modifies penetrance of monogenic variants for tier 1 genomic conditions

Fahed, A.C., Wang, M., Homburger, J.R. *et al.* Polygenic background modifies penetrance of monogenic variants for tier 1 genomic conditions. *Nat Commun* **11,** 3635 (2020). https://doi.org/10.1038/s41467-020-17374-3



(Bolli et al., 2021)
(Lourida, 2019)
(Fahed et al., 2020)

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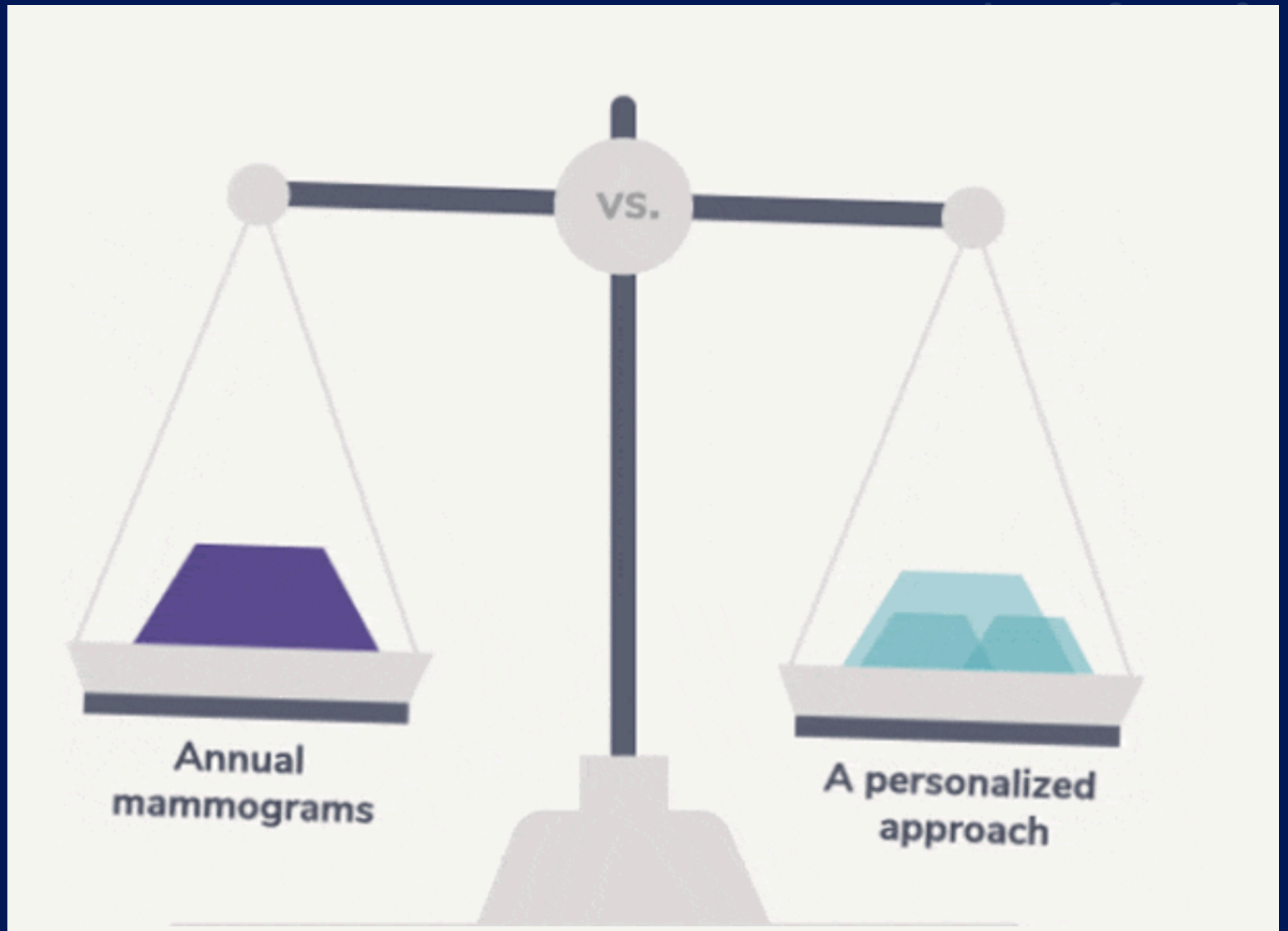
Risk Stratifying

- Highly penetrant low prevalence conditions for primary prevention
- Highly prevalent low penetrance conditions
- Shared decision making to help decide how to manage risk



(Esserman, et al., 2017)

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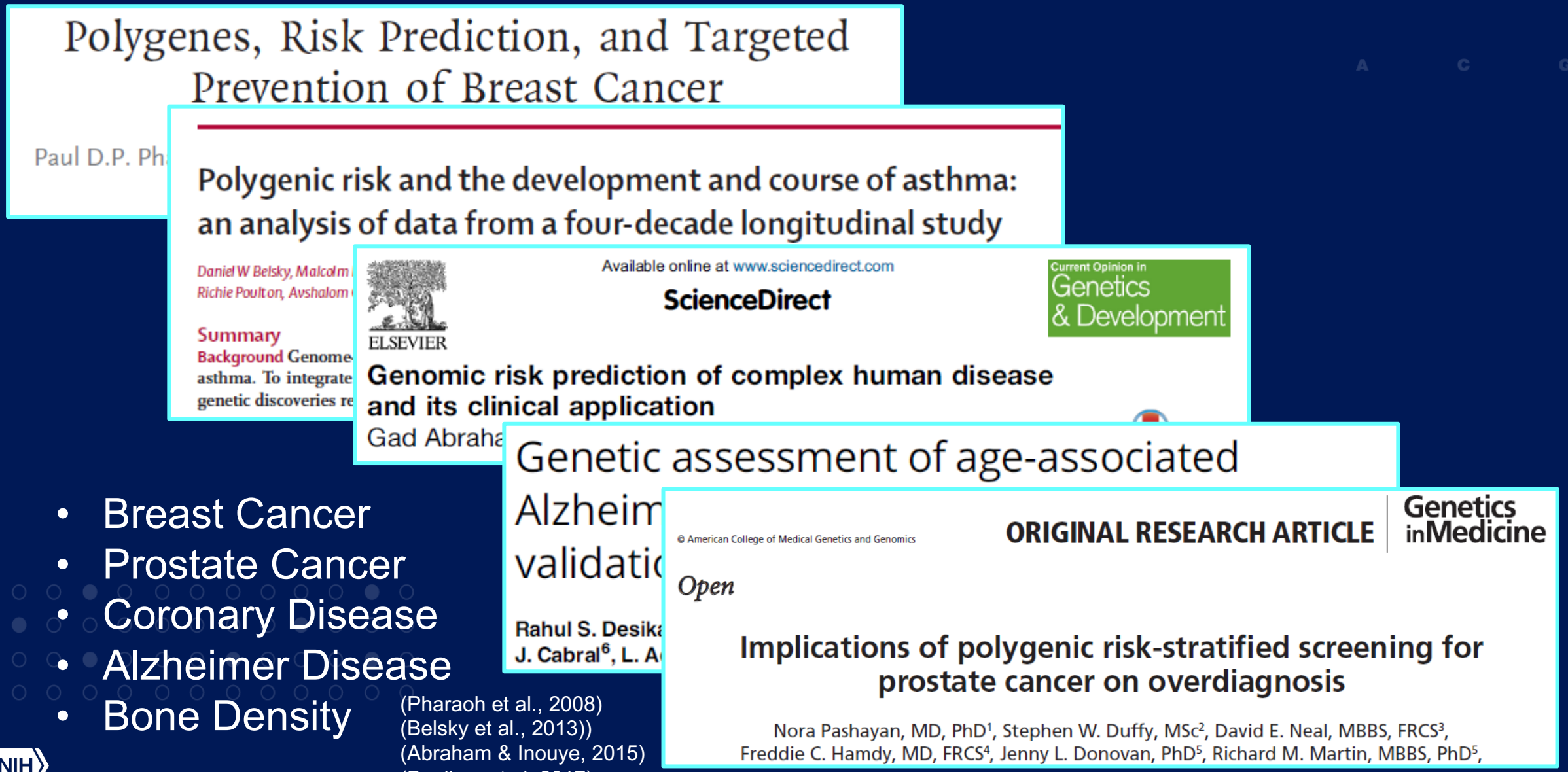
Polygenic Risk Scores (PRS)



- Breast Cancer
- Prostate Cancer
- Coronary Disease
- Alzheimer Disease
- Bone Density

(Pharaoh et al., 2008)
(Belsky et al., 2013))
(Abraham & Inouye, 2015)
(Desikan et al, 2017)
(Pashayan, 2015)

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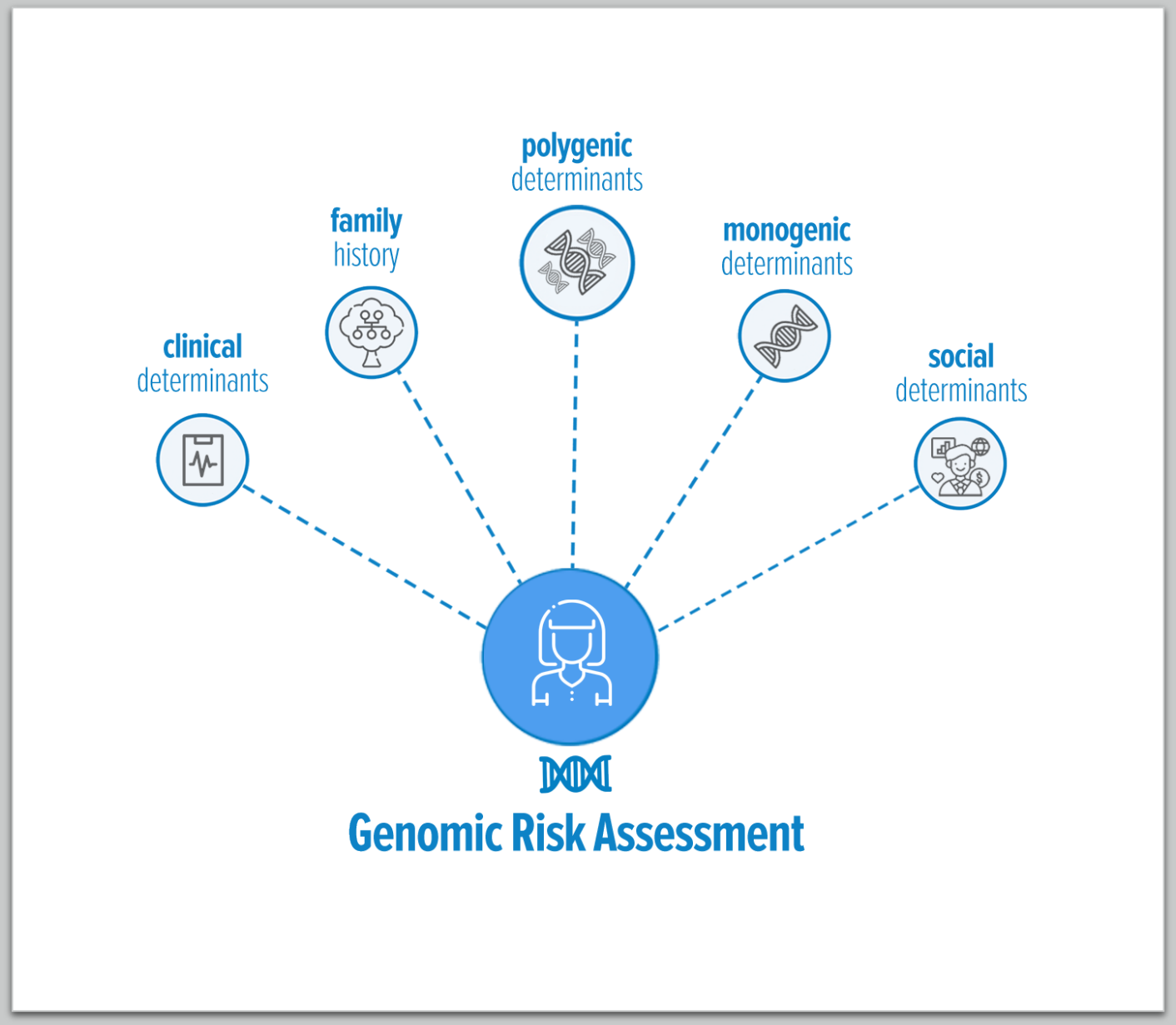
eMERGE

- Prospective clinical study assessing genome informed risk assessments for ~10 conditions
- Provide management recommendations
- Participants will be followed for 2-3 years
- Assess impact has on clinician and patient behavior



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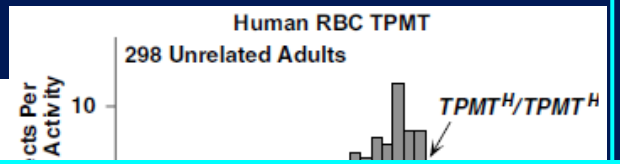
Pharmacogenomics

Beginnings of Genomic Medicine

Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells

Mercaptopurine Pharmacogenetics:



Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing

MV Relling[1], EE Gardner[1], WJ Sandborn[2], K Schmiegelow[3,4], C-H Pui[5], SW Yee[6], CM Stein[7], M Carrillo[8], WE Evans[1] and TE Klein[8]

(Druker et al. 2001)
(Relling et al. 2011)

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TPMT (thiopurine methyltransferase)

- 6-mercaptopurine, 6-thioguanine, and azathioprine used to treat acute leukemia, autoimmune disorders, inflammatory bowel disease, transplant rejection
- Relatively narrow therapeutic index, major toxicity is life-threatening myelosuppression
- Metabolized by S-methylation catalyzed by the thiopurine methyltransferase enzyme
- TPMT activity levels controlled by a common genetic polymorphism; 89% homozygous for high activity, 11% heterozygous (intermediate), 0.3% low

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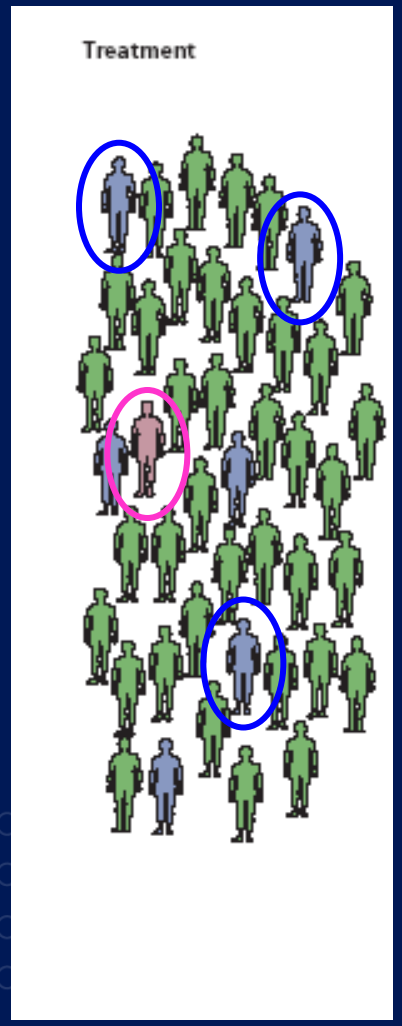
TPMT



(Cheok, 2006)

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Common *TPMT* Variants

mal" activity

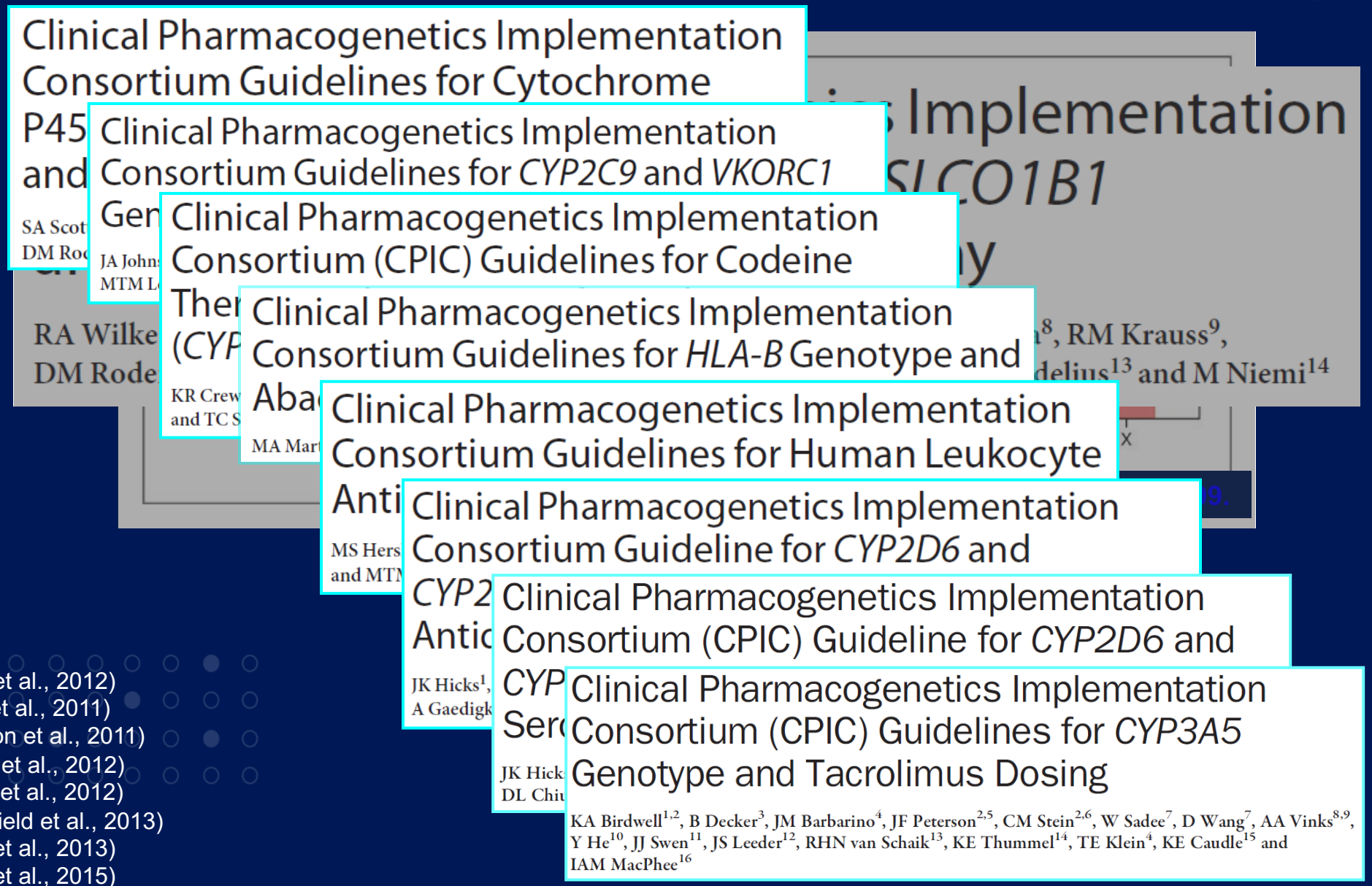
lete absence

ld reduction

old reduction

(Weinshilboum, 2001)

SLCO1B1 and Statin Myopathy



(Wilke et al., 2012)
(Scott et al., 2011)
(Johnson et al., 2011)
(Crews et al., 2012)
(Martin et al., 2012)
(Hershfield et al., 2013)
(Hicks et al., 2013)
(Hicks et al., 2015)
(Birdwell et al., 2015)

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Table 4 Pharmacogenomic markers for SJS/TEN in clinical practice

Drug	Marker[a]	Result	Clinical interpretation	Clinical recommendation	High-risk ethnicities[b]	Additional remarks for positive carriers
Carbamazepine	*HLA-B*15:02*	Positive	Increased risk for SJS/TEN	Do not use carbamazepine or oxcarbazepine	Han Chinese, Thai, Malaysian, Indian, Singaporean, and Vietnamese	If the patient is carbamazepine or oxcarbazepine naive, do not use carbamazepine or oxcarbazepine, respectively. If the patient has previously used carbamazepine or oxcarbazepine for longer than 3 months without a cutaneous adverse drug reaction, continuously consider using carbamazepine or oxcarbazepine.
		Negative	Normal risk for SJS/TEN	Use carbamazepine or oxcarbazepine		
	*HLA-A*31:01*	Positive	Increased risk for SJS/TEN	Do not use carbamazepine or oxcarbazepine	Japanese, Korean, and European	If the patient is carbamazepine or oxcarbazepine naive, do not use carbamazepine or oxcarbazepine, respectively. If the patient has previously used carbamazepine or oxcarbazepine for longer than 3 months without a cutaneous adverse drug reaction, continuously consider using carbamazepine or oxcarbazepine.
		Negative	Normal risk for SJS/TEN	Use carbamazepine or oxcarbazepine		
Allopurinol	*HLA-B*58:01*	Positive	Increased risk for SJS/TEN, DRESS, and MPE	Do not use allopurinol	Asian and Caucasian	If the patient is allopurinol naive, do not use allopurinol. If the patient has previously used allopurinol for longer than 3 months without a cutaneous adverse drug reaction, continuously consider using allopurinol. A starting dose of less than 200 mg should be considered. Screening should be considered for elderly patients and patients with renal abnormal function.
		Negative	Normal risk for SJS/TEN, DRESS, and MPE	Use allopurinol		

Abbreviations: DRESS, drug reaction with eosinophilia and systemic symptoms; HLA, human leukocyte antigen; MPE, maculopapular exanthema; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

[a]These variants confer risk in both the heterozygous and homozygous states.

[b]The risk alleles are common in these ethnicities.

(Sukasem, 2018)

Undiagnosed disease

Share Print

NIH Undiagnosed Dise

Overview

See Also:

Overview

The NIH Undiagnosed Disea
that focuses on the most puz
Bethesda, Md. It was organize
the NIH Office of Rare Disease
research centers and institutes
oncology, dermatology, dentis

A longstanding medical conditi
interest to this clinical researc
number will be invited to pr
general, it takes 8 to 12 week

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Undiagnosed Diseases Network

Seven clinical sites, a coordinating center, two DNA sequencing cores, a metabolomics core, a model organisms screening center, and a central biorepository

Objectives:

Improve the level of diagnosis and care for patients with undiagnosed diseases

Facilitate research into the etiology of undiagnosed diseases

Create an integrated and collaborative research community to identify improved options for optimal patient management

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Undiagnosed Diseases Network

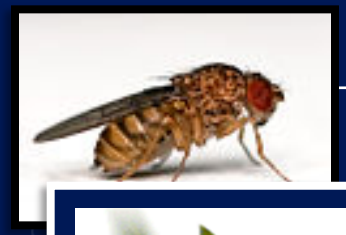
APPLY

http://udnconnect.org/apply/

[4516]	[373]	[1703]	[1401]	[417]
Applications Received	Applications Under Review	Applications Accepted	Participants Evaluated	Participants Diagnosed

Clinical Evaluations

Sequencing
(exome and genome)



Model Organisms
(fly and fish)

Metabolomics

Working Together for Diagnoses

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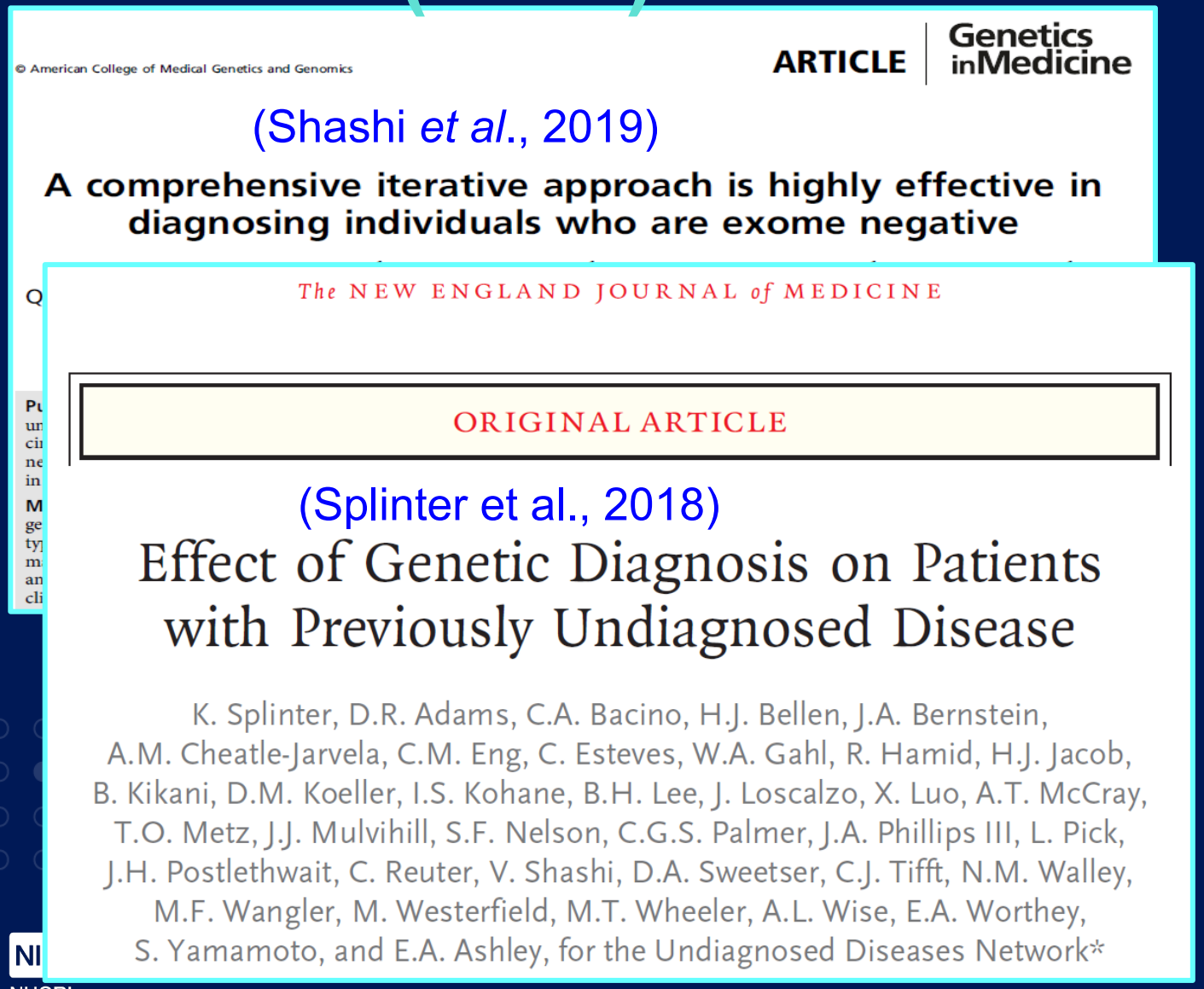
Genetic Diagnosis in Undiagnosed Disease Network (UDN)



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ARTICLE | Genetics inMedicine

(Shashi *et al.*, 2019)

A comprehensive iterative approach is highly effective in diagnosing individuals who are exome negative

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

(Splinter et al., 2018)

Effect of Genetic Diagnosis on Patients with Previously Undiagnosed Disease

K. Splinter, D.R. Adams, C.A. Bacino, H.J. Bellen, J.A. Bernstein, A.M. Cheatle-Jarvela, C.M. Eng, C. Esteves, W.A. Gahl, R. Hamid, H.J. Jacob, B. Kikani, D.M. Koeller, I.S. Kohane, B.H. Lee, J. Loscalzo, X. Luo, A.T. McCray, T.O. Metz, J.J. Mulvihill, S.F. Nelson, C.G.S. Palmer, J.A. Phillips III, L. Pick, J.H. Postlethwait, C. Reuter, V. Shashi, D.A. Sweetser, C.J. Tifft, N.M. Walley, M.F. Wangler, M. Westerfield, M.T. Wheeler, A.L. Wise, E.A. Worthey, S. Yamamoto, and E.A. Ashley, for the Undiagnosed Diseases Network*

- 382 evaluated patients
- 132 received diagnosis (35%)
  - 98 diagnoses made by sequencing (74%)
  - 21% led to recommended changes in therapy
  - 37% led to changes in diagnostic testing
  - 36% led to variant-specific genetic counseling

Undiagnosed Diseases Network

Solving Medical Mysteries Through Team Science

Undiagnosed Diseases Network (UDN)

CLINICAL REPORT

WILEY Molecular Genetics & Genomic Medicine Open Access

Whole genom
leading to u
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[1]De
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[2]De
Uni
Ten

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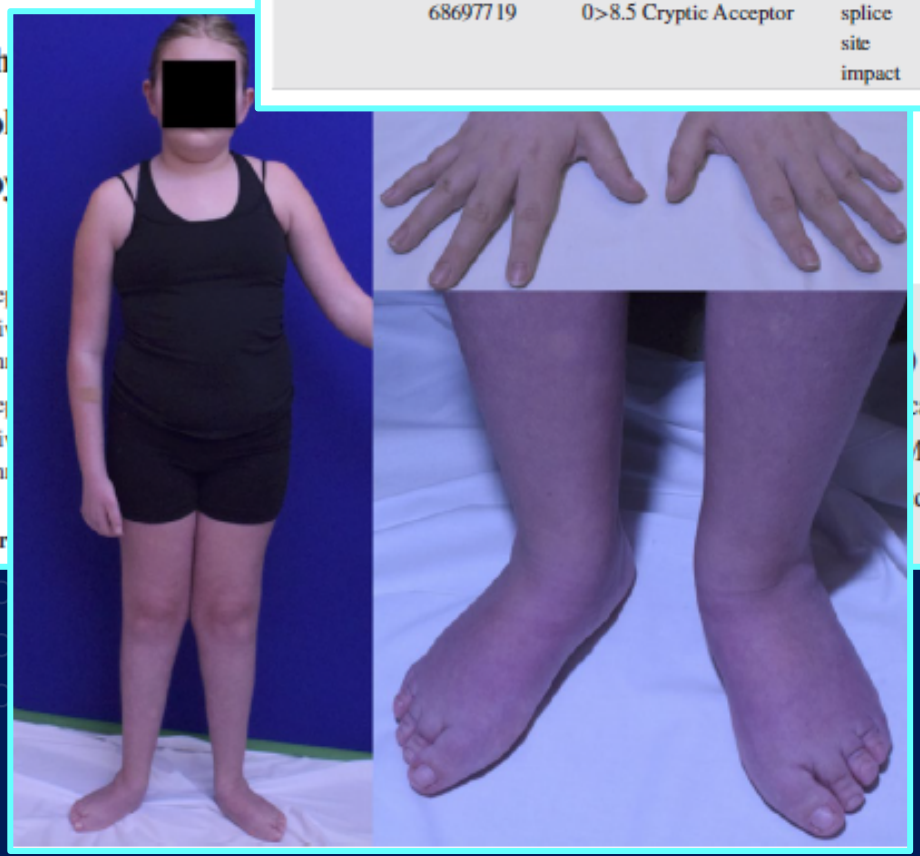
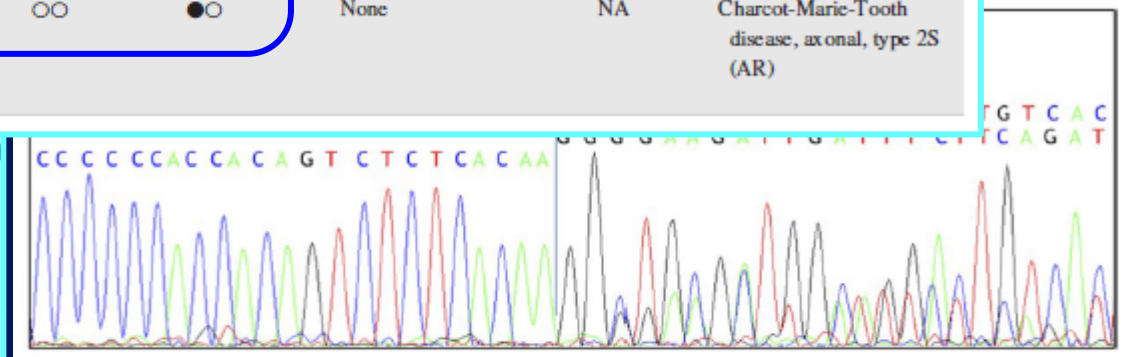
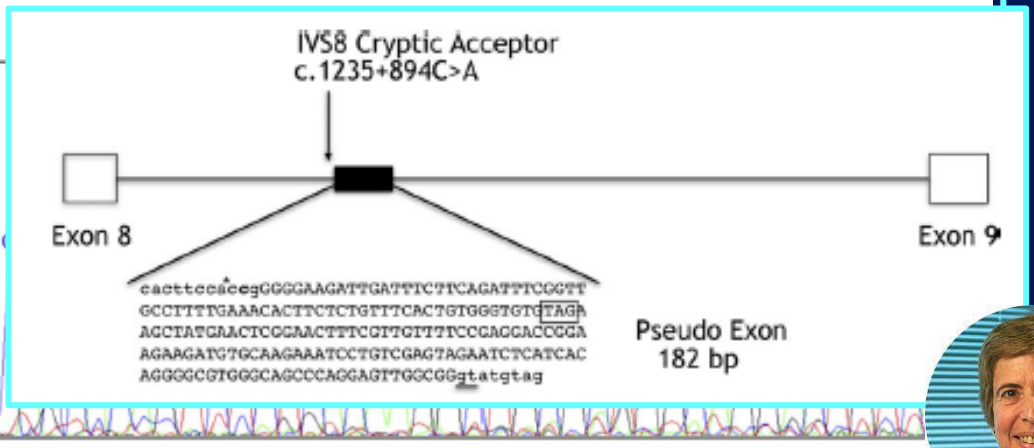
M 616155], a
d with CMT,

TABLE 1 WGS identified a previously reported pathogenic variant in maternal allele and a novel deep-intronic variant in paternal allele

Gene	Position	Change	Effect	Proband Zygosity	Mother Zygosity	Father Zygosity	1KG AF EVS AF ExAC AF gnomAD AF	SIFT Polyphen GERP	Condition
IGHMBP2	chr11: 68702864	T → C c.1730T>C p.Leu577Pro	Missense	●○	●○	○○	None	0.002 1 4.91	Charcot-Marie-Tooth disease, axonal, type 2S (AR)
IGHMBP2	chr11: 68697719	C → A c.1235+894C>A 0>8.5 Cryptic Acceptor	Intron splice site impact	●○	○○	●○	None	NA	Charcot-Marie-Tooth disease, axonal, type 2S (AR)







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

- Robert Green, Alan Beggs, Brigham and Women's Hospital
  NICU and healthy newborns, 240 exomes, Newborn Screen (NBS) vs. NBS + genomic NBS
- Stephen Kingsmore, Rady Children's Hospital
  Clinical and Social Implications of 2-day Genome Results in Acutely Ill Newborns
- Jennifer Puck, Barbara Koenig, University of California San Francisco (UCSF)
  Sequencing of Newborn Blood Spot DNA to Improve and Expand Newborn Screening
- Cynthia Powell, Jonathan Berg, University of North Carolina (UNC) North Carolina Newborn Exome Sequencing for Universal Screening

NIH 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 neonatal intensive care unit Neonatal/Pediatric Intensive Care Unit (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, 2015)

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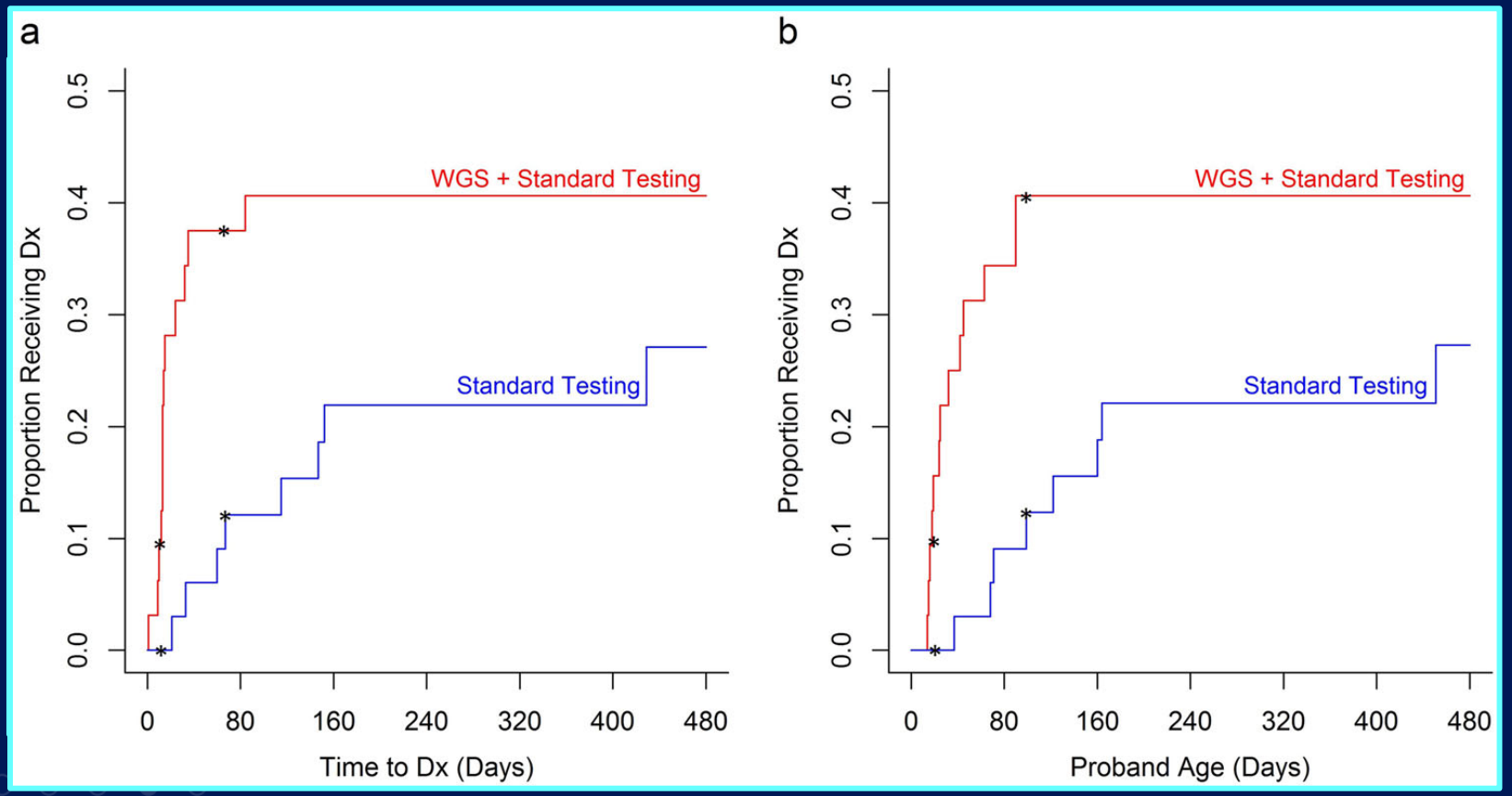
Yield and Speed of Genome Sequencing Diagnosis in Critically Ill Infants



- 65 infants < 4moth age in NICU/PICU, trios
- 31% diagnoses in “cases,” 3% “controls”
- Time to diagnosis: 13 days [1-84] vs. 107 days [21-429]

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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

(Fan et. al., 2014)

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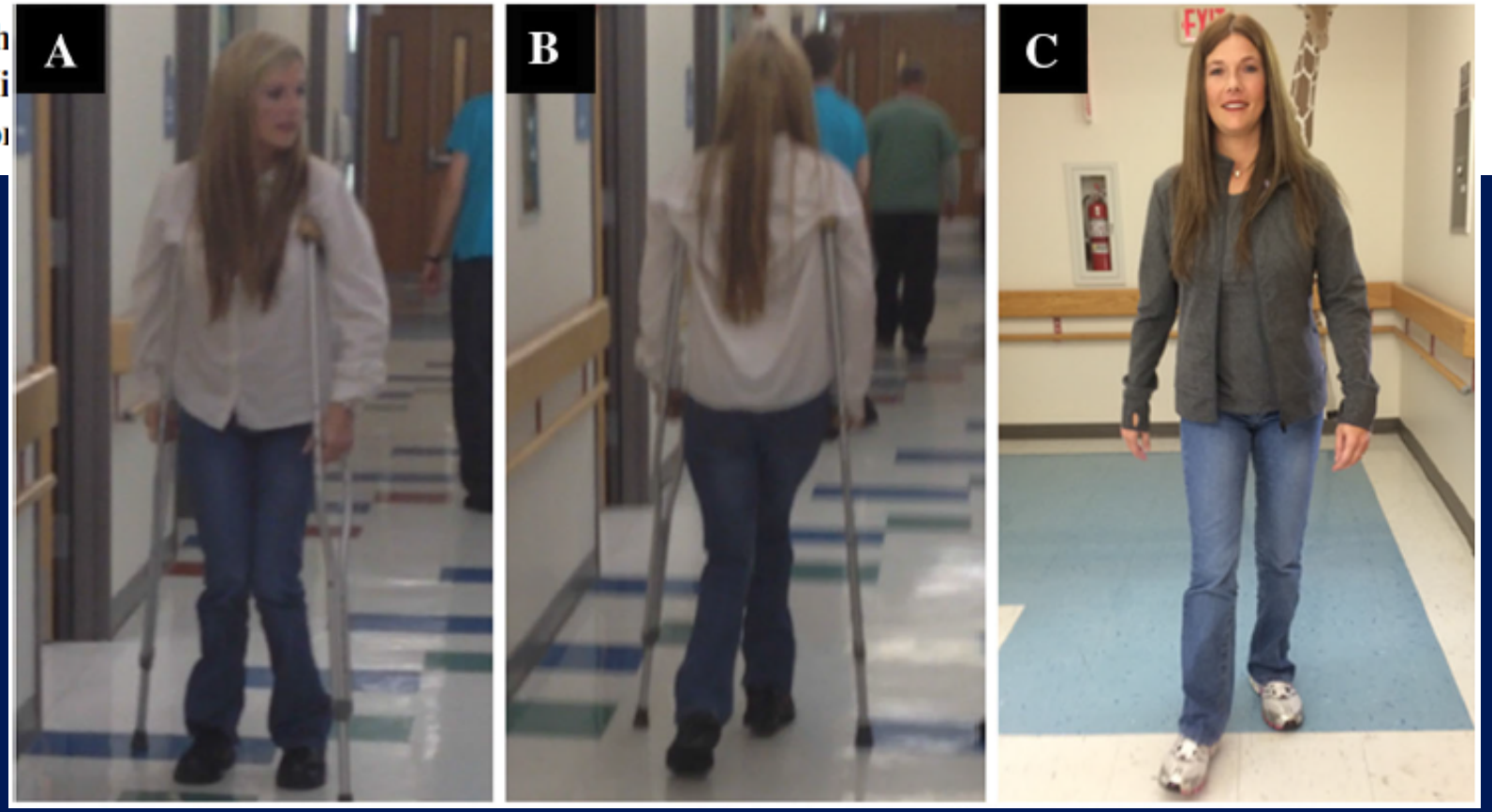

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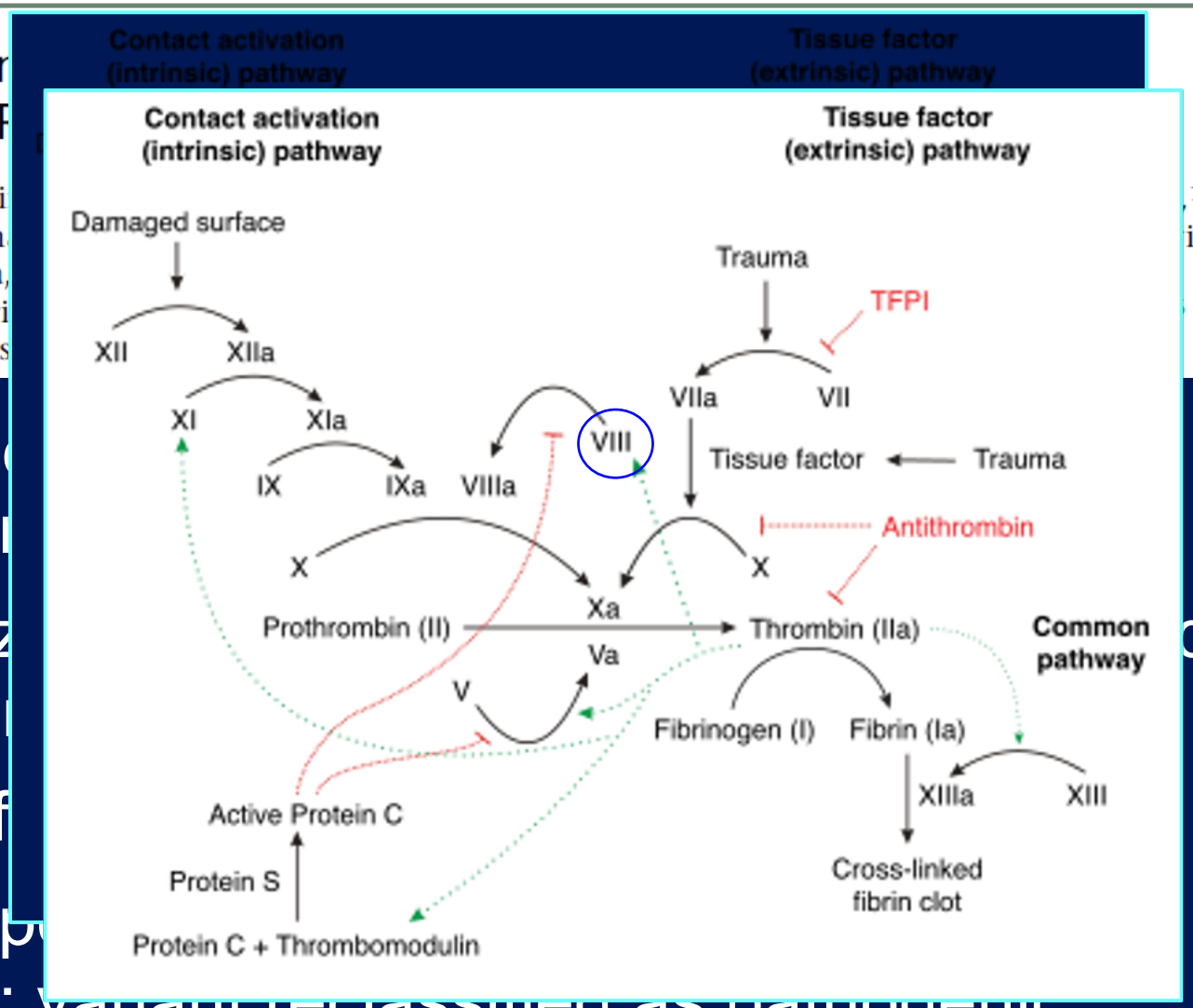
Carrier Testing and Care of Newborns

ARTICLE

Preconceptio
Sequencing: F

Sumit Punj,[1] Yassmi
Amiee Potter,[1] Mich
Laura M. Amendola,
Tia Kauffman,[6] Mari
and C. Sue Richards



- Precon
  pregnar
- Heteroz
  with he
- Opted f
- Develop
  treated; variant reclassified as pathogenic

(Punj et al, 2018)

cser
Clinical Sequencing Evidence-Generating Research

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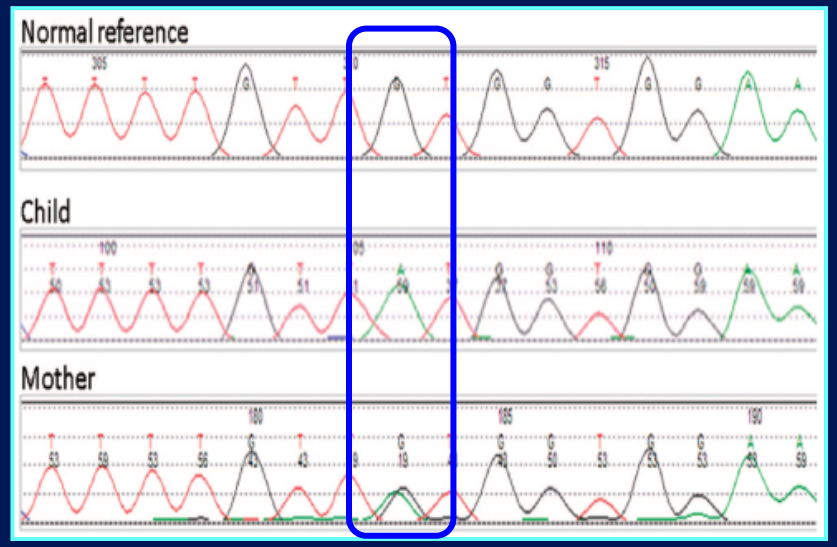
Research to Clinic and Back Again



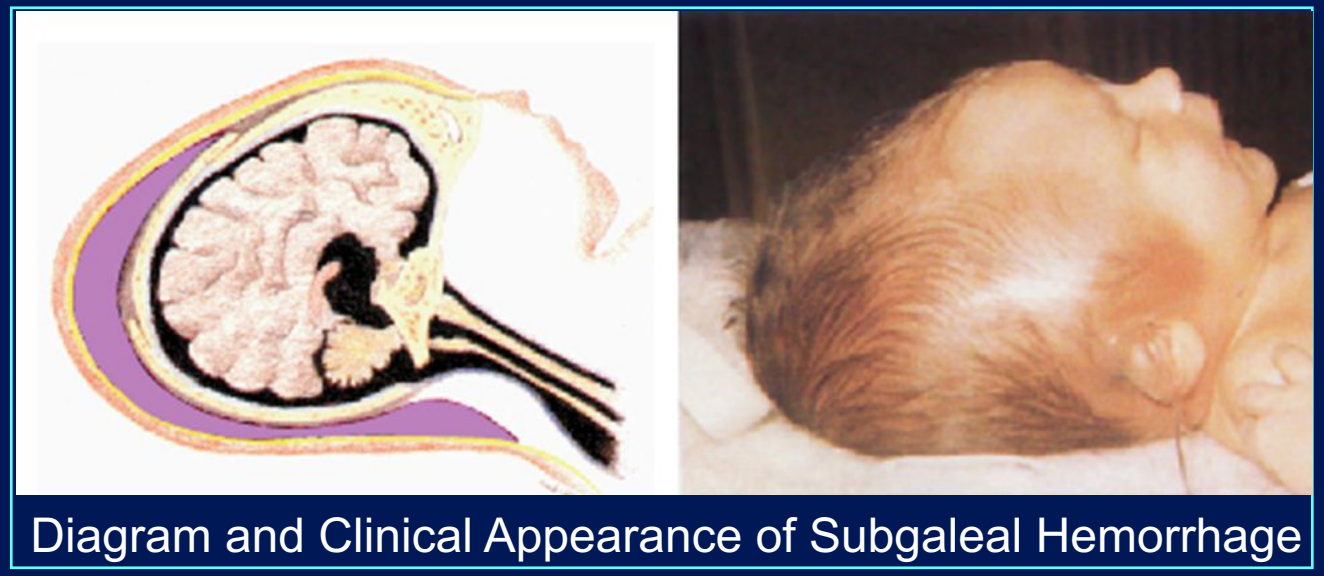


Diagram and Clinical Appearance of Subgaleal Hemorrhage

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Clinical Sequencing Evidence-Generating Research

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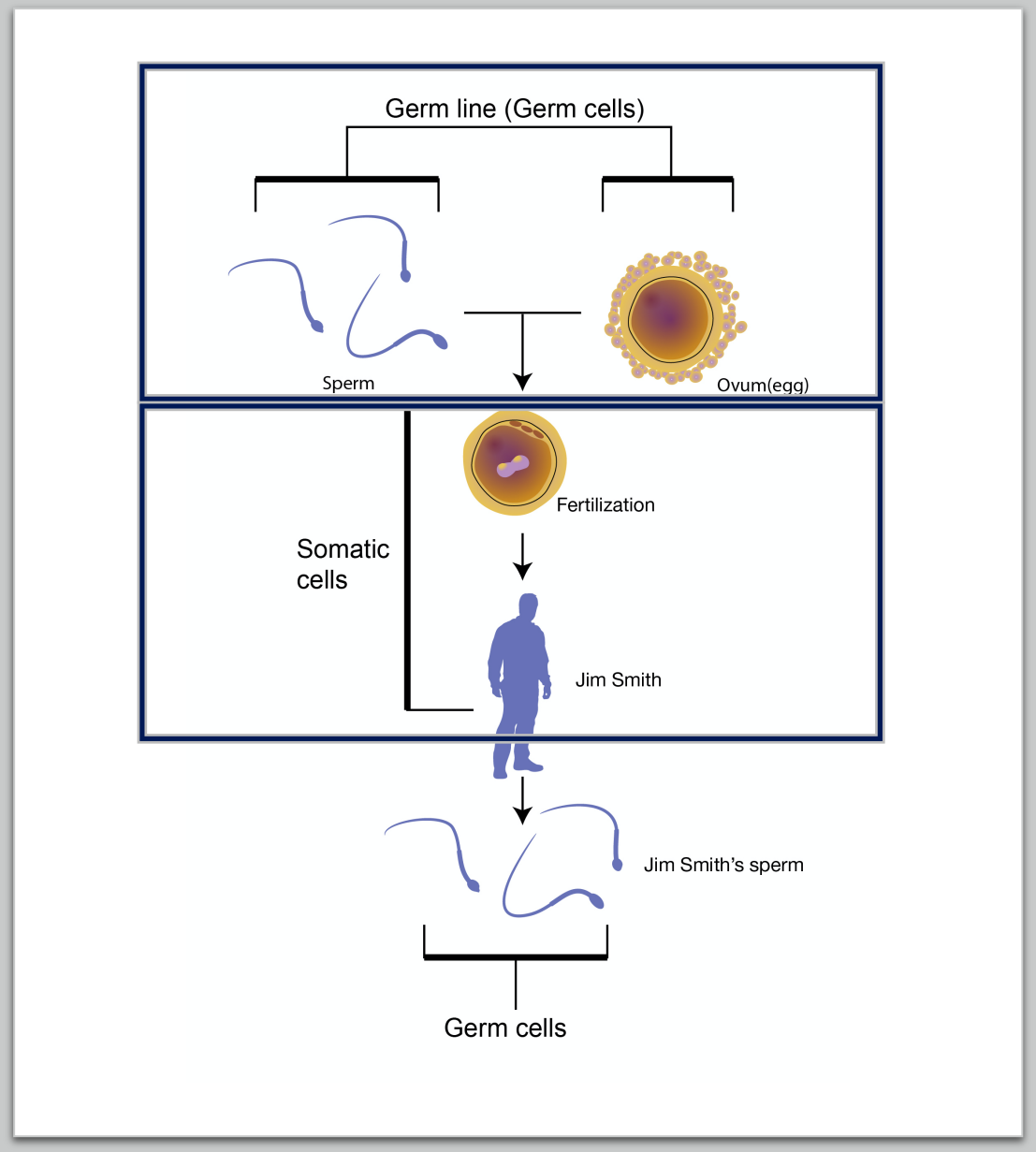
Somatic Variation

Somatic vs. Germline variation

- Germline genetic variants are the changes that can impact generations
- Somatic genetic variants are the changes that occur starting after conception
- **How do these changes affect health and disease?**



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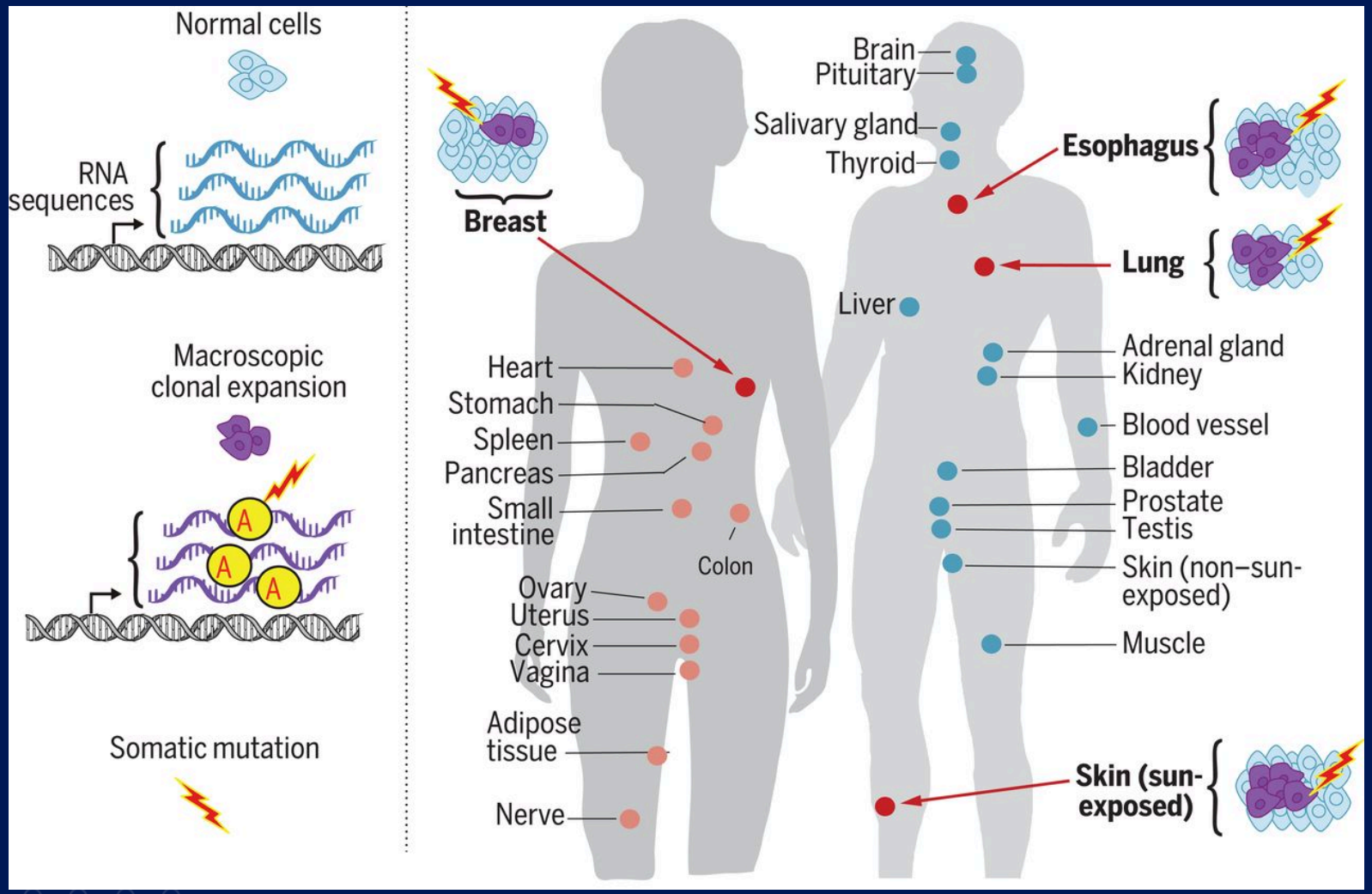
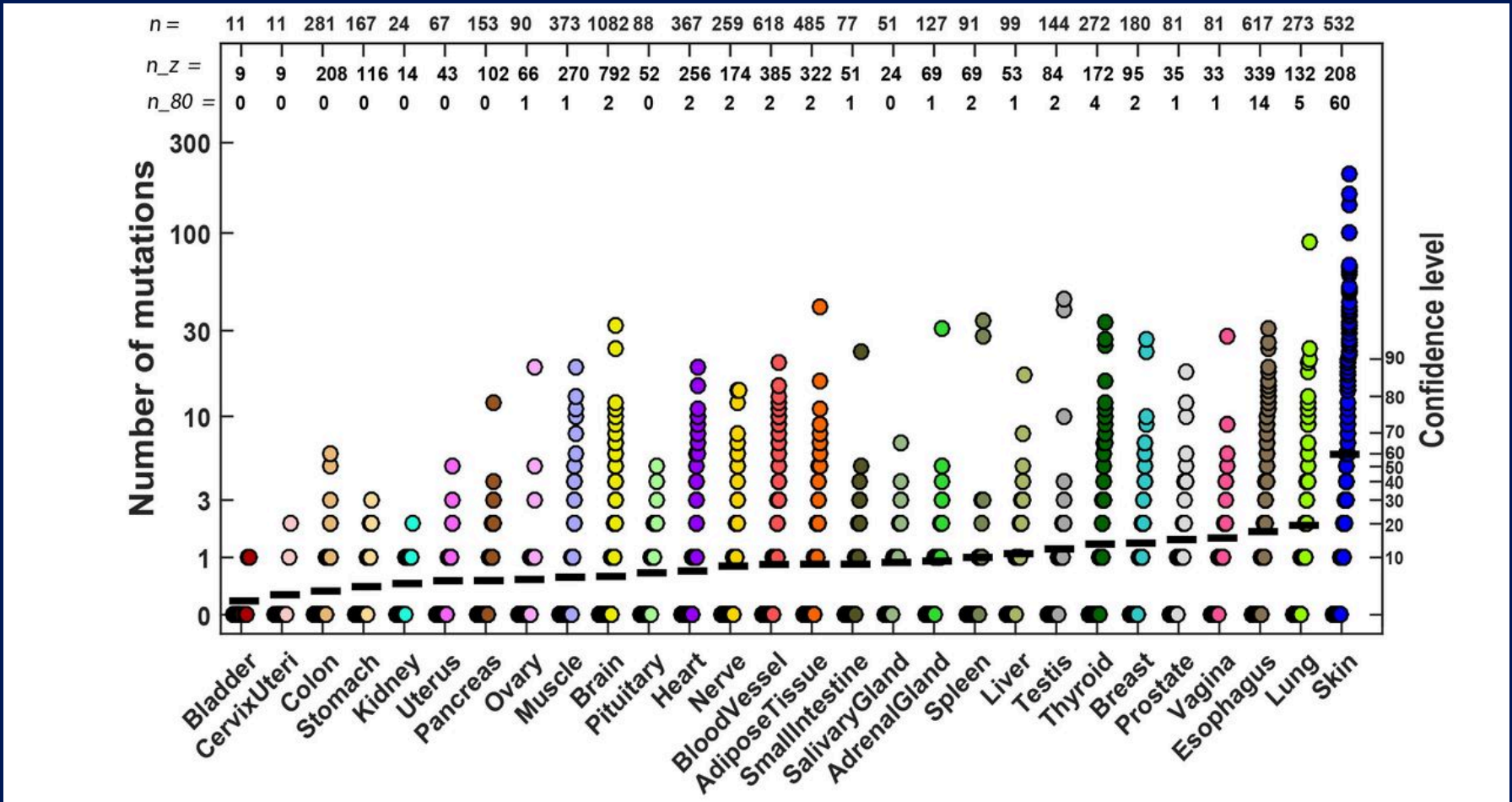
Somatic clonal expansions in normal human tissues.



(Yizhak, 2019)

Fig. 2 Somatic clonal expansion in normal tissues



(Yizhak, 2019)

Using an Individual Patient's Genomic Variants in their Clinical Care – Somatic Cancer Mutations

Agent	Target(s)	Indications
Bevacizumab (Avastin)	*VEGF* ligand	Colorectal cancer Glioblastoma, others…
Ceritinib (Zykadia)	*ALK*	Non-small cell lung cancer
Cetuximab (Erbitux)	*EGFR (HER1/ERBB1)*	Colorectal cancer
Crizotinib (Xalkori)	*ALK, MET, ROS1*	Non-small cell lung cancer
Erlotinib (Tarceva)	*EGFR (HER1/ERBB1)*	Non-small cell lung cancer
Imatinib (Gleevec)	*KIT, PDGFR, ABL*	Philadelphia chromosome-positive ALL and CML
Trastuzumab (Herceptin)	*HER2 (ERBB2/neu)*	Breast cancer (*HER2*+) Gastric cancer (*HER2*+)
Vemurafenib (Zelboraf)	*BRAF*	Melanoma (with *BRAF* V600E mutation)

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MyCancerGenome.org

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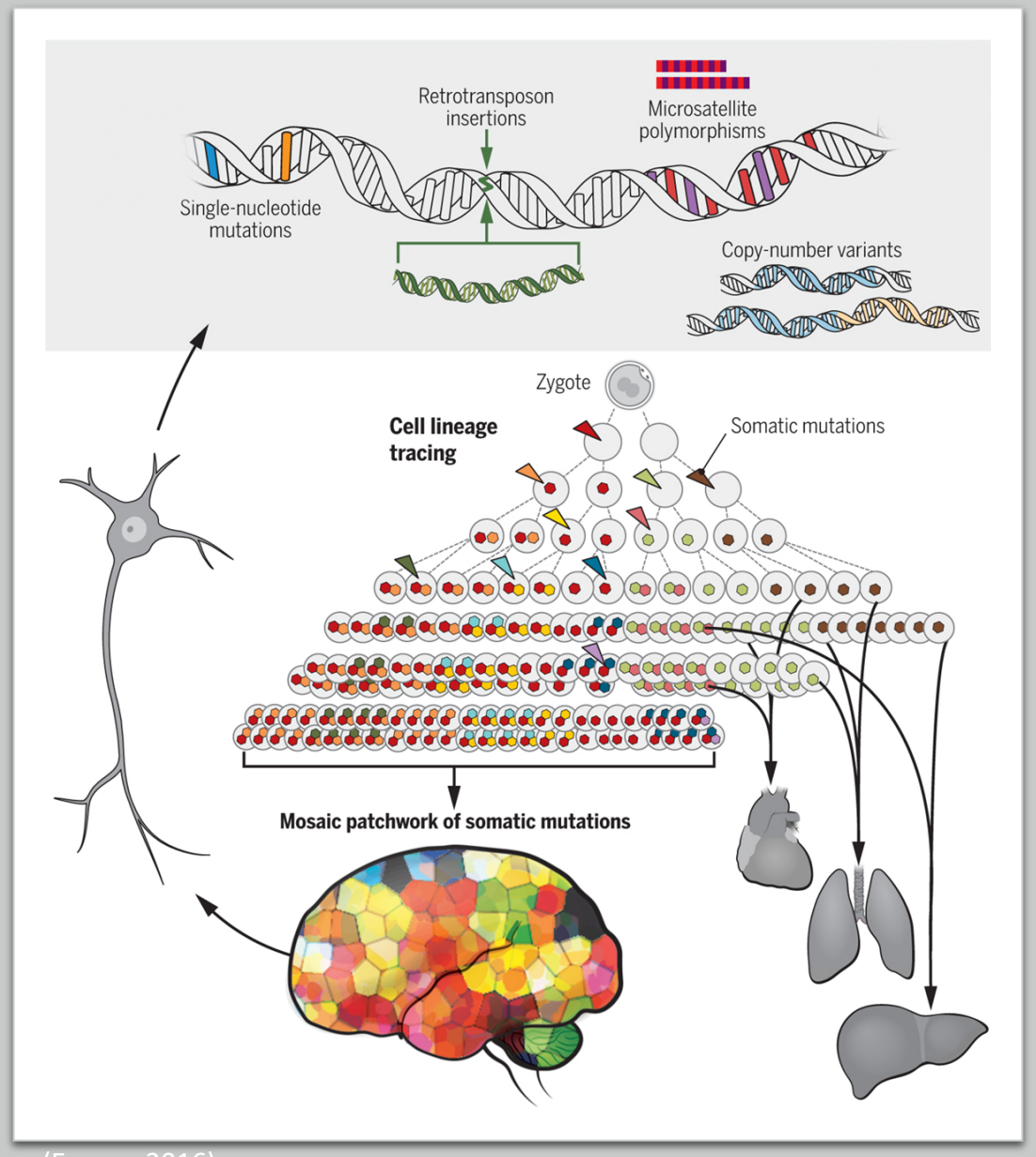


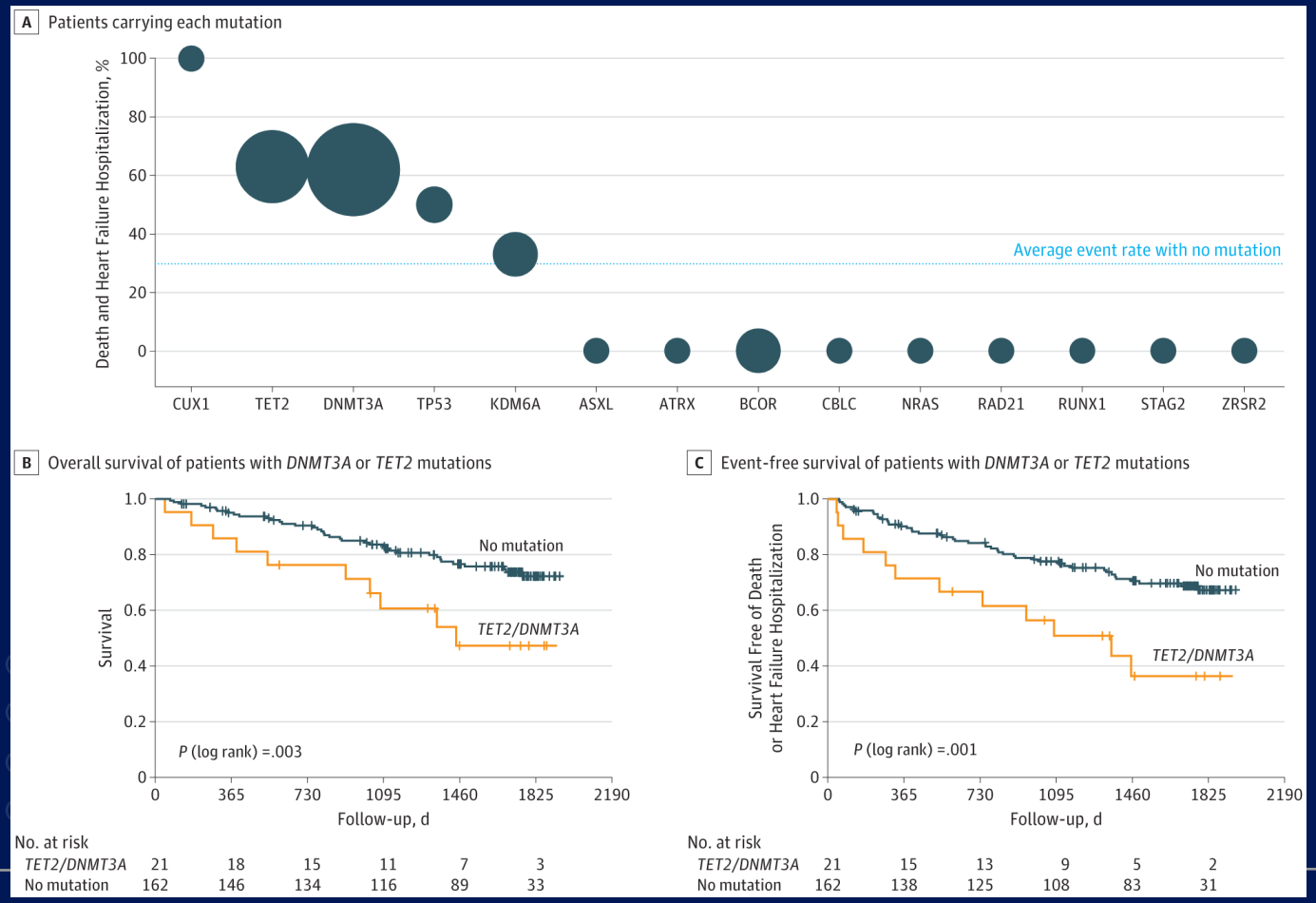
(Evrony, 2016)

Somatic variation

- Somatic mutations accumulate over the lifespan and expand clonally
- Adjacent cells can have different genomes
- Linked with cancer, placental development, Amyotrophic Lateral Sclerosis (ALS), Systemic lupus erythematosus (SLE), Multiple Sclerosis (MS), Rett, substance use disorders, aging pathologies

From: **Association of Mutations Contributing to Clonal Hematopoiesis With Prognosis in Chronic Ischemic Heart Failure**

(Dorsheimer, 2019)



Clinician Involvement

Genomic Medicine: On the Threshold

- Identify risk
- Prevent disease
- Improve diagnostics
- Improve treatments
- Increase access

PERSPECTIVE

doi:10.1038/nature09764

Chart … nomic medicine from … de

Eric D. Green[1], M… te*

There has been … sequence of the human genome was published. Opportunities … ented, as advances in genomics are harnessed to obtain robust … on of the human genome and about the genetic contributions … vision for the future of genomics research and describe the p…

Since the end of the Human Genome Project (HGP) in 2003 and the publication of a reference human genome sequence[1,2], genomics has become a mainstay of biomedical research. The scientific community's foresight in launching this ambitious project[3] is evident in the broad range of scientific advances that the HGP has enabled, as shown in Fig. 1 (see rollfold). Optimism about the potential contributions of genomics for improving human health has been fuelled by new insights about cancer[4–7], quickly. Although genomics has already begun to improve diagnostics and treatments in a few circumstances, profound improvements in the effectiveness of healthcare cannot realistically be expected for many years (Fig. 2). Achieving such progress will depend not only on research, but also on new policies, practices and other developments. We have illustrated the kinds of achievements that can be anticipated with a few examples (Box 2) where a confluence of need and opportunities should

(Green, 2011)

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nature > perspectives > article

Perspective | Published: 28 October 2020

Strategic vision for improving human health at The Forefront of Genomics

Eric D. Green, Chris Gunter, [...]Teri A. Manolio

Nature **586**, 683–692 (2020) | Cite this article

https://www.clinicalgenome.org/

ClinGen
Clinical Genome Resource

Get Started | About Us | Curation Activities | Working Groups | Expert Panels | Documents & Annoucements | Tools

ClinGen - Clinical Genome Resource

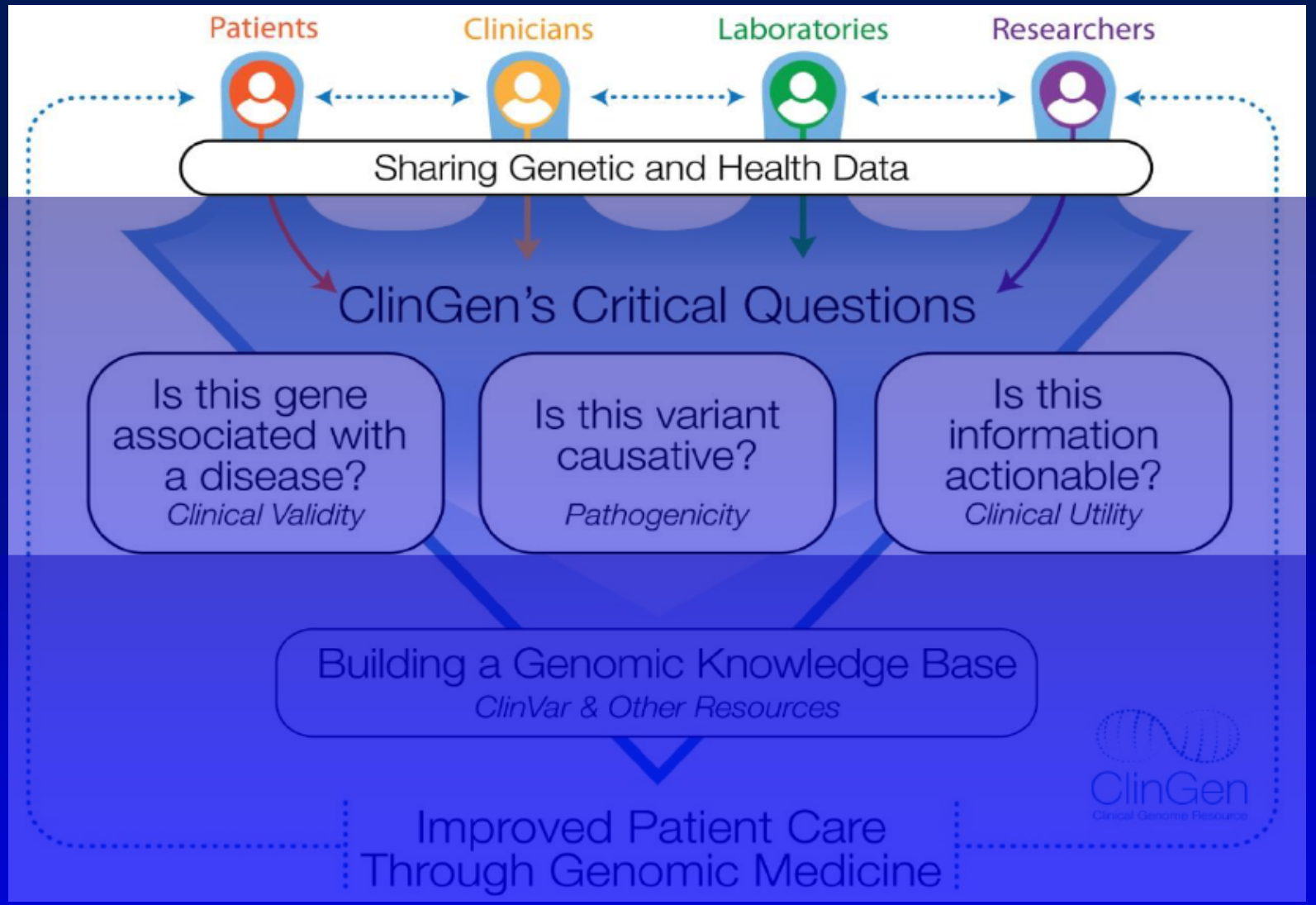
ClinGen is a National Institutes of Health (NIH)-funded resource dedicated to building an authoritative central resource that defines the clinical relevance of genes and variants for use in precision medicine and research.

ClinGen
Clinical Genome Resource

Goals

- Share genomic and phenotypic data among clinicians, researchers, and patients through centralized and federated databases for clinical and research use.
- Develop and implement standards to support clinical annotation and interpretation of genes and variants.
- Develop data standards, software infrastructure and computational approaches to enable curation at scale and facilitate integration into healthcare delivery.
- Enhance and accelerate expert review of the clinical relevance of genes and variants.
- Disseminate and integrate ClinGen knowledge and resources to the broader community.

What is the Clinical Genome Resource (ClinGen)?



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American College of Medical Genetics and Genomics (ACMG) Evidence Framework for Variant Interpretation

	Benign		Pathogenic			
	Strong	Supporting	Supporting	Moderate	Strong	Very strong
Population data	MAF is too high for disorder BA1/BS1 **OR**			Absent in population databases PM2	Prevalence in affecteds statistically	
Computational and predictive data		Multiple lines of computational evidence suggest no impact on gene	Multiple lines of computational evidence support a	Novel missense change at an amino acid residue where a different	Same amino acid change as an established	Predicted null variant in a gene where LOF is a
Functional data	Well-established functional studies show no deleterious effect BS3		Missense in gene with low rate of benign missense variants and path. missenses common PP2	Mutational hot spot or well-studied functional domain without benign variation PM1	Well-established functional studies show a deleterious effect PS3	
Segregation data	Nonsegregation with disease BS4		Cosegregation with disease in multiple affected family members PP1	Increased segregation data →		
De novo data				De novo (without paternity & maternity	De novo (paternity and maternity confirmed)	
Allelic data		Observed in *trans* with a dominant variant BP2		For recessive disorders, detected		
Other database		Reputable source w/out shared data = benign BP6	Reputable source = pathogenic PP5			
Other data		Found in case with an alternate cause BP5	Patient's phenotype or FH highly specific for gene PP4			

(Richards, 2015)

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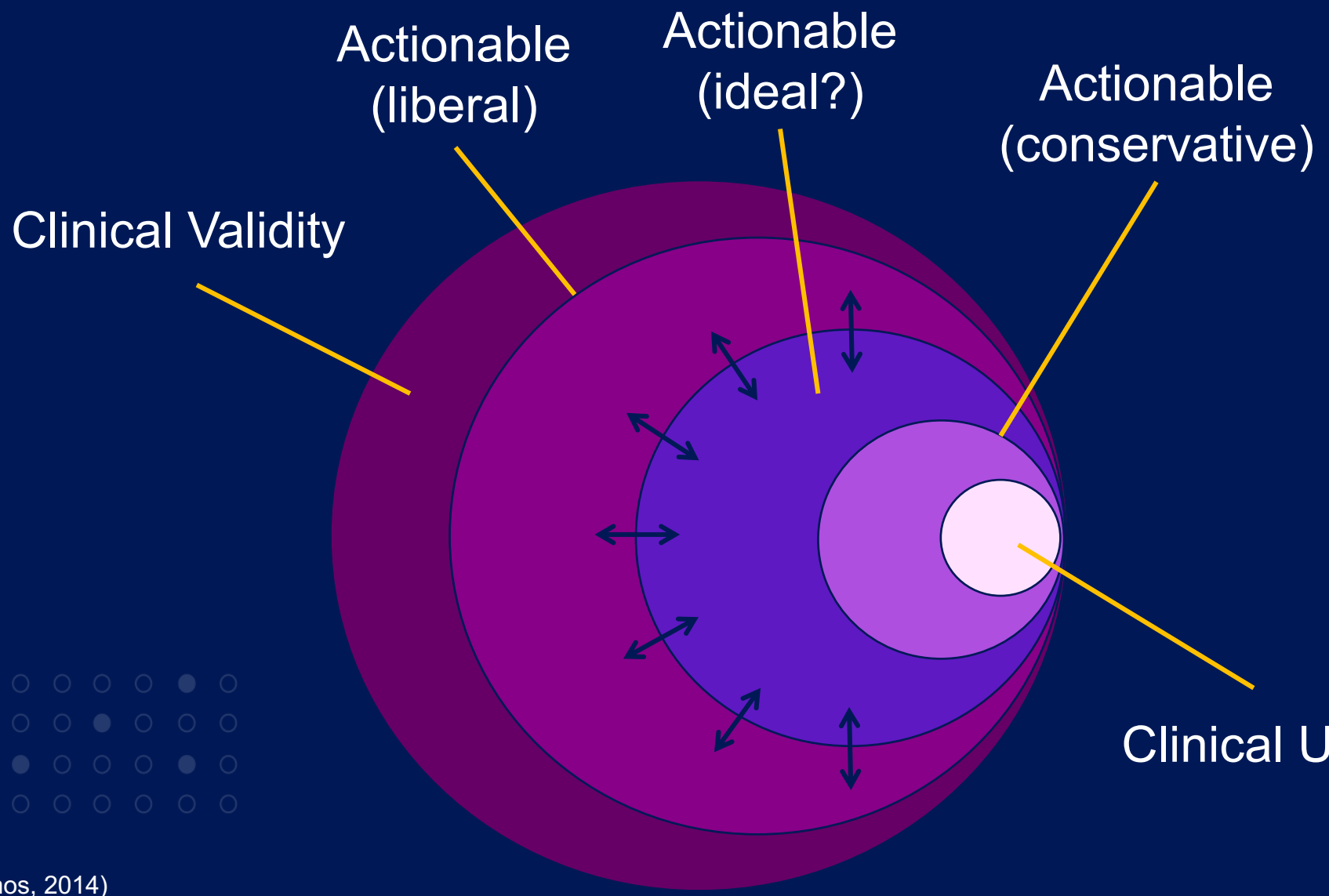
Range of Clinical Actionability?



(Ramos, 2014)

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Clinical Actionability

- Develop clear and robust criteria to guide decisions regarding actionable secondary findings:

1. Severity
2. Likelihood of disease
3. Efficacy of intervention

} Level of Evidence

4. Nature of intervention

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(Hunter, 2016)

ClinGen Clinical Genome Resource

Topics of ClinGen Variant and Gene Curation Expert Panels

- *ACADVL*
- Aminoacidopathy
- Arrhythmogenic RV Cardiomyopathy
- Brain Malformations
- Breast/Ovarian Cancer
- Brugada Syndrome
- Cardi
- *CDH*
- Cereb
  Syndr
- Coagulation Factor Deficiency
- Colon Cancer
- Congenital Myopathies
- DICER1 and miRNA-Processing
- Epilepsy
- Familial Hypercholesterolemia
- Familial Thoracic Aortic Aneurysm and Dissection
- Fatty Acid Oxidation Disorders
- *FBN1*
- Glauc
- Hearing Loss
- [illegible]asis/ Thrombosis
- Hereditary Breast, Ovarian and Pancreatic Cancer
- Hereditary Cancer
- Hereditary Hemorrhagic Telangiectasia
- Hypertrophic Cardiomyopathy
- Intellectual Disability and Autism
- *KCNQ1*
- Long QT Syndrome
- Lysosomal Storage Disorders
- Malignant Hyperthermia Susceptibility
- Mitochondrial Dy
- Myeloid Malignancy
- Peroxisomal Disorders
- Phenylketonuria
- Platelet Disorder
- *PTEN*
- RASopathy
- Rett and Angelman-like Disorders
- *TP53*
- *VHL*

Volunteer to Curate

Please take a brief survey to tell us more about your interests and desired level of involvement so we can pair you with an appropriate curation activity and/or Expert Panel.

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ClinGen Work Group and Expert Panel representation includes 1,423 investigators from 35 countries

Updated June 2020 by Natalie Pino

Teri Manolio

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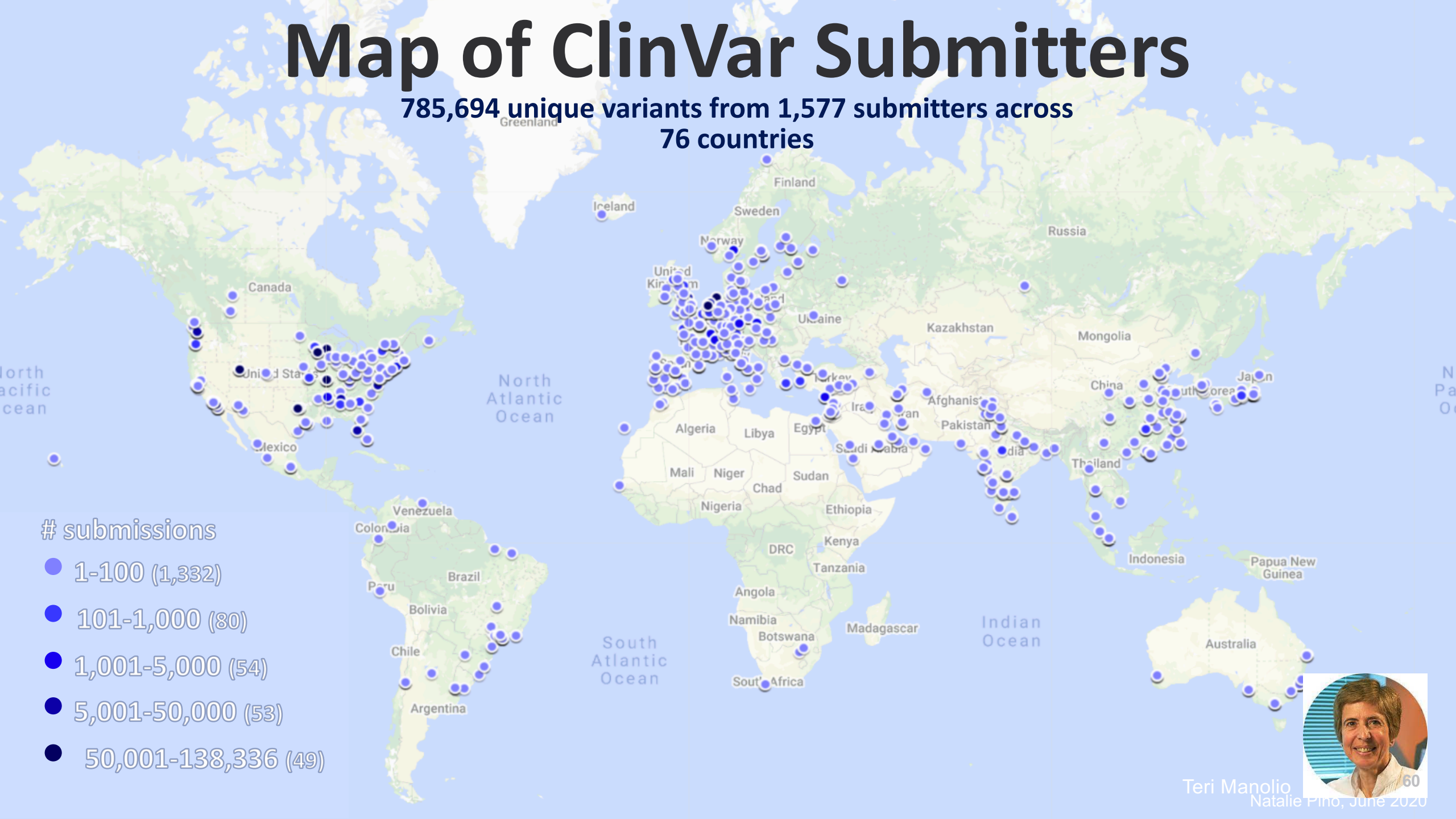
Map of ClinVar Submitters

785,694 unique variants from 1,577 submitters across 76 countries



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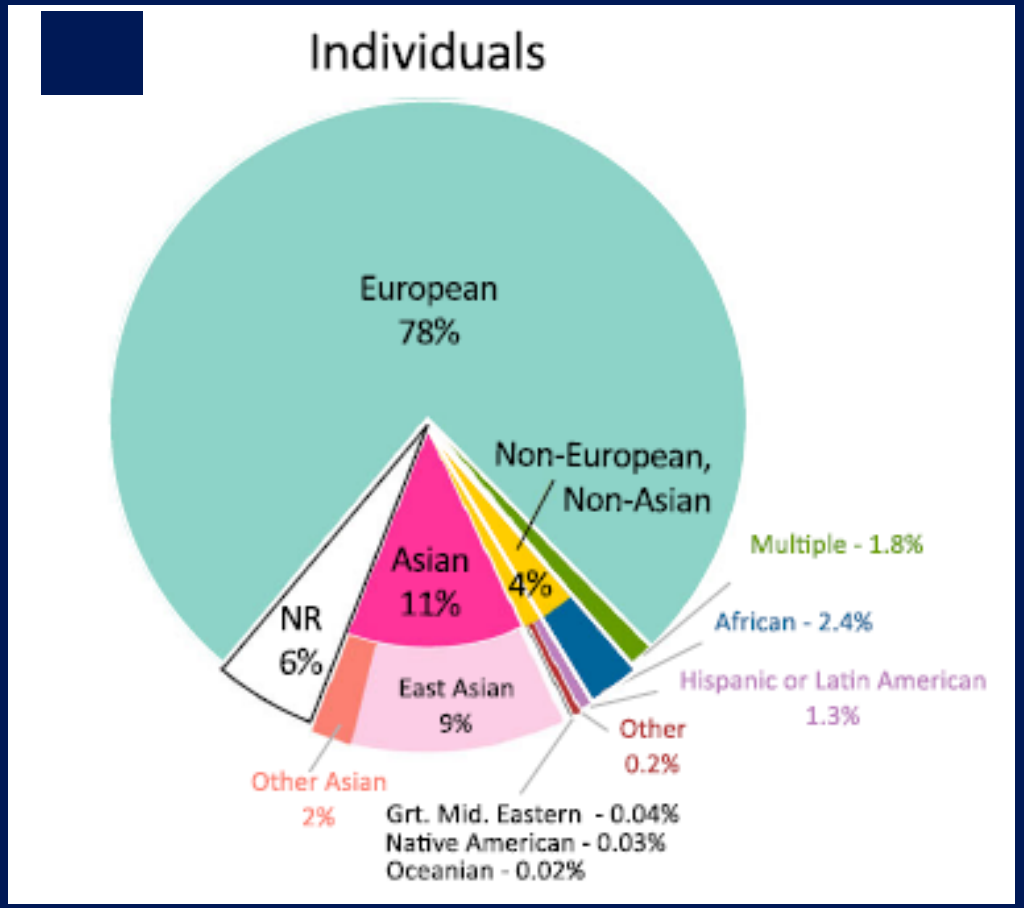
Natalie Pino, June 2020

Diversity and Genomics

Certain drugs may be less effective, or even unsafe, in some populations because of genetic differences.

Genomics is failing on diversity



(Popejoy, 2018)

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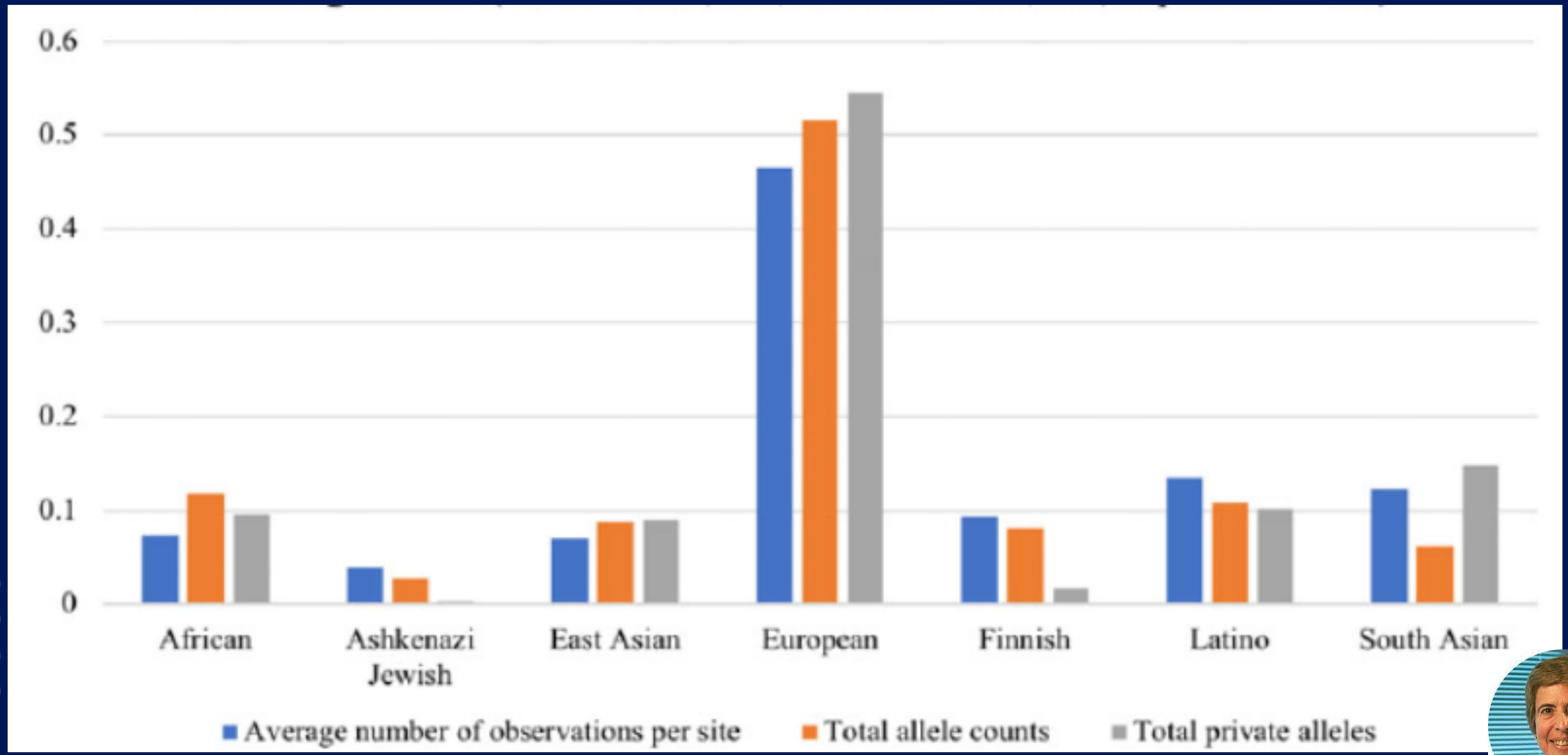
Distributions Across Populations: Information About Clinically Relevant Sites in gnomAD (>225K Observations)



(Popejoy, 2018)

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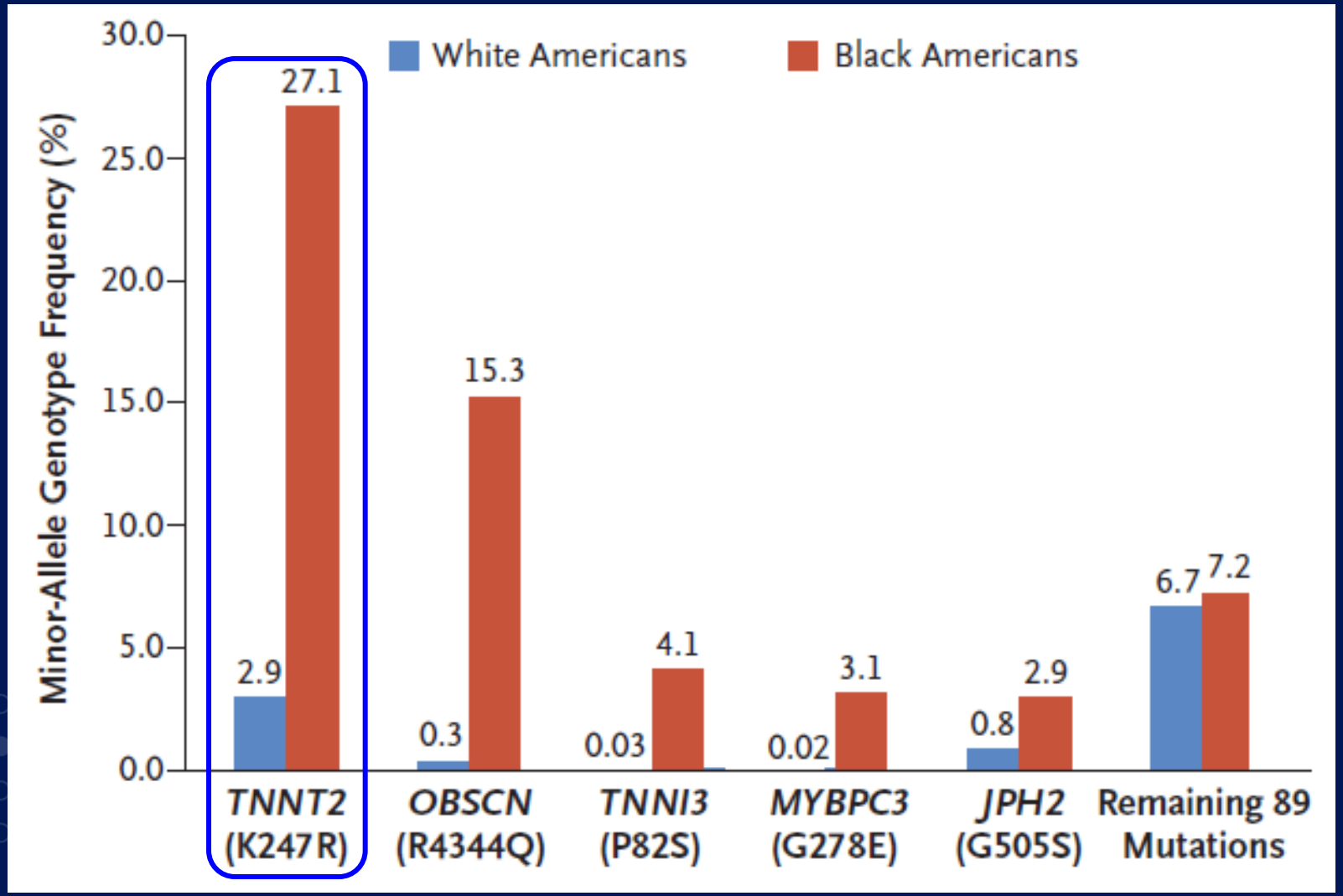
Frequency of Genetic Variants Misassociated with Cardiomyopathy in Black and White Americans



(Manrai, 2016)

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Key takeaways

- Genomics offers a way to personalize care but need to understand long-term outcomes
- Genomics can help with risk assessment, avoid adverse drug events, diagnose undiagnosed disease, and improve efficacy
- Clinicians are needed in implementation research projects to help understand impact

Many Thanks…

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Lucia Hindorff
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Rongling Li
Nicole Lockhart
Ebony Madden
Ebony Madden
Teri Manolio
Donna Messersmith
Erin Ramos
Baergen Schultz
Heidi Sofia
Dave Stenger
Clark Tibbetts
Simona Volpi
Ken Wiley

Carol Bult, Rex Chisholm, Pat Deverka, Geoff Ginsburg, Gail Jarvik, George Mensah, Mary Relling, Dan Roden, Marc Williams

NHRC Naval Health Research Center — Readiness Through Research
U.S. Naval Research Laboratory
eMERGE network — Electronic Medical Records and Genomics
IGNITE — Implementing GeNomics In practicE
NSIGHT Newborn Sequencing
cser — Clinical Sequencing Evidence-Generating Research
Undiagnosed Diseases Network
ClinGen — Clinical Genome Resource
GWAS Catalog — The NHGRI-EBI Catalog of published genome-wide association studies

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The **Forefront** of **Genomics**®

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