Defining high risk of CKD: Genetic Risk Scores as New Players

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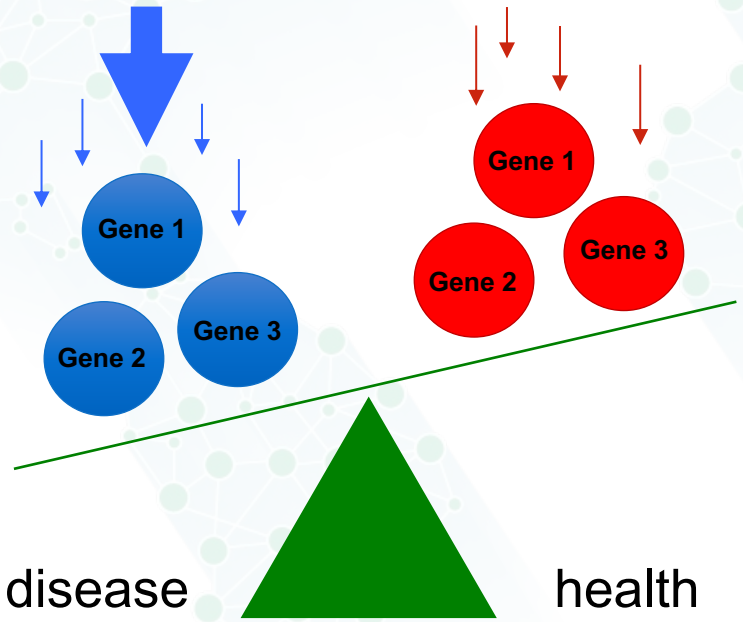
DISCLOSURES

- Research collaborations: AstraZeneca, Visterra, Vanda, Aevi Genomics
- Consulting or advisory boards: HiBio, Vera, Travere

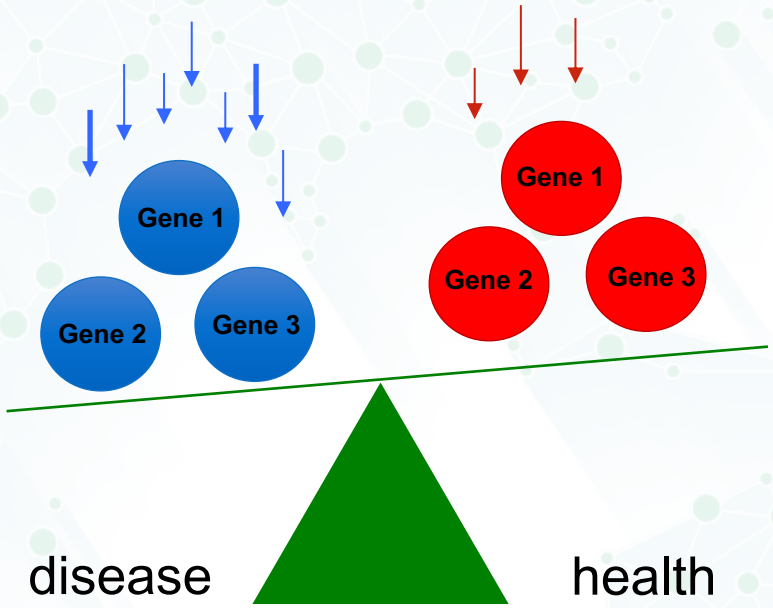
Genetic Architecture of Human Disease

Mendelian Traits



Rare variants
Large effects

Complex Traits

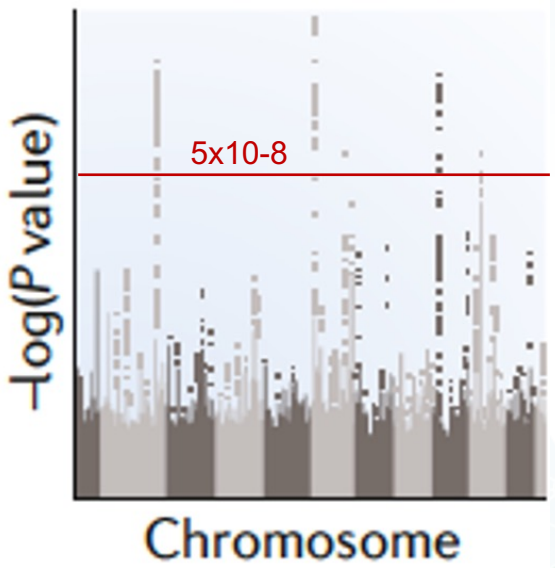


Common variants
Small effects

Thousands of GWAS Loci for Complex Traits

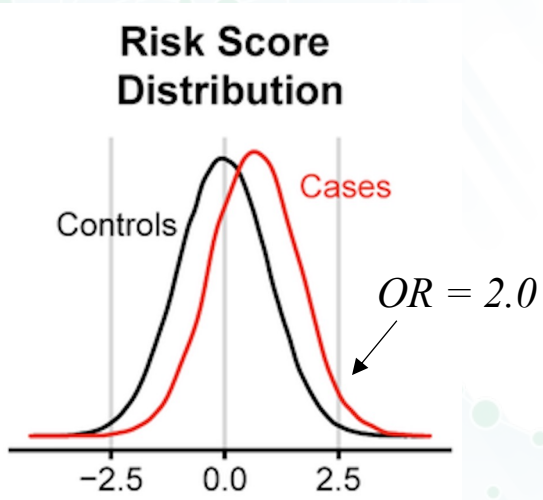
Buniello et al. The NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted arrays and summary statistics. Nucleic Acids Research, 2019, Vol. 47 (Database issue): D1005-D1012. www.ebi.ac.uk/gwas

Genetic Risk Score (GRS)

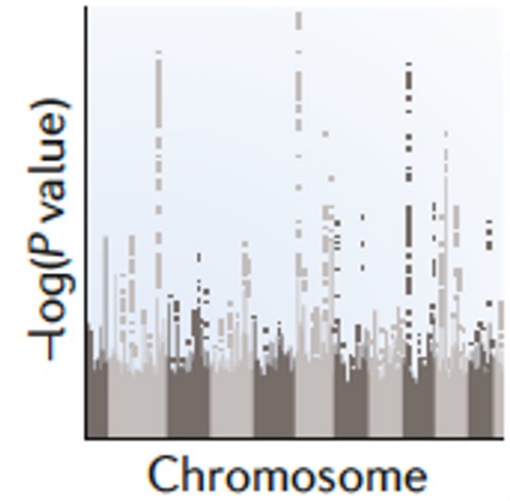


$$GRS = \beta_1 * snp_1 + \beta_2 * snp_2 + \ldots + \beta_n * snp_n$$

$$Standardized\ GRS = (GRS - mean_{ctr}) \ / \ sd_{ctr}$$



Genome-wide Polygenic Score (GPS)



Extended PRS formulation captures the effects of all ~10M common variants across the genome

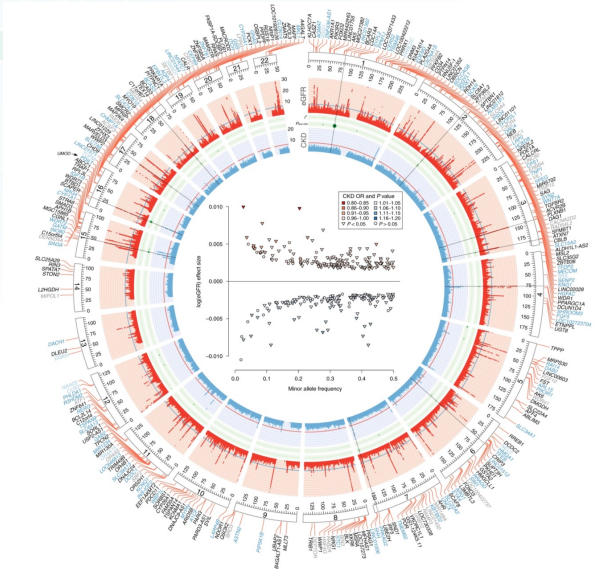
$$GPS_i = \sum_j^M \hat{\beta}_j \times dosage_{ij}$$

Methods to account for linkage disequilibrium (LD):

- P+T – P-value thresholding and LD pruning to select independent SNPs
- LD Pred – adjusts SNP weights to account for non-independence

Polygenic Risk Models are Phenotype-specific

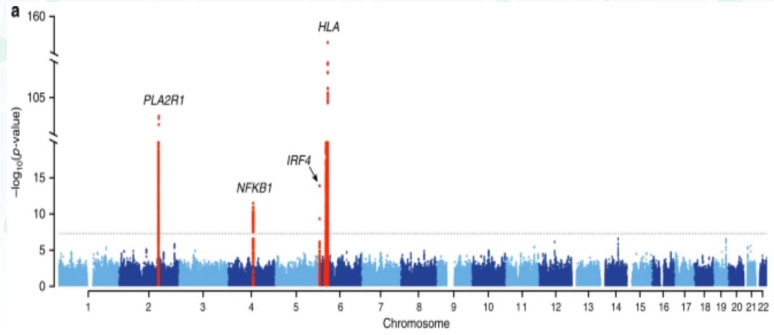
GWAS for eGFR and CKD
N ~ 1 million



308 genome-wide significant loci
~7% of variance in eGFR

Wuttke et al. *Nature Genetics* 2019

GWAS for Membranous Nephropathy
3K cases/9K controls

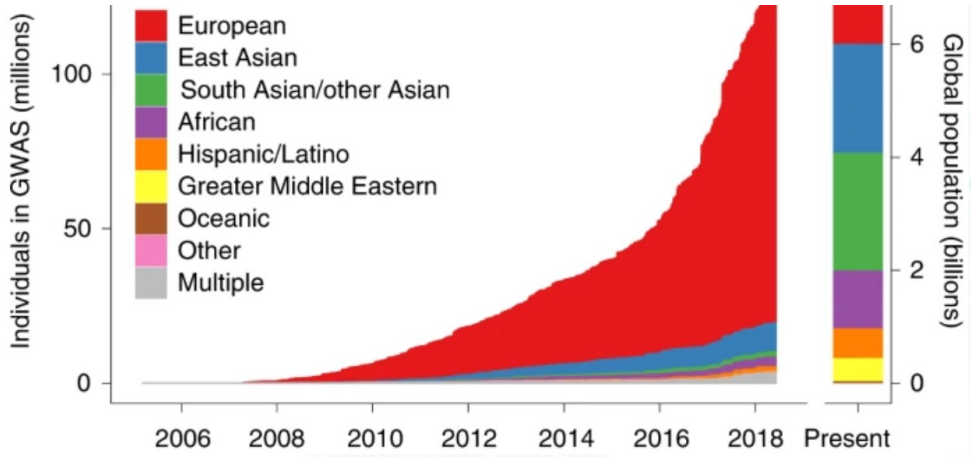


4 genome-wide significant loci
~30% of disease risk

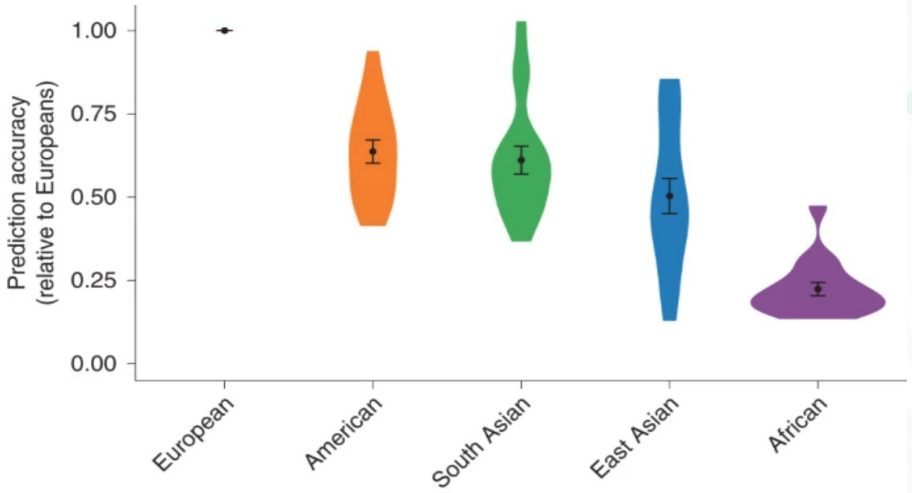
Xie et al. *Nature Commun.*2020

Major Limitation: Ancestry Bias

80% of GWAS participants are of European ancestry
(Europeans represent only 16% of the global population)



GPS accuracy by ancestry relative to Europeans
(17 quantitative traits from UKBB)



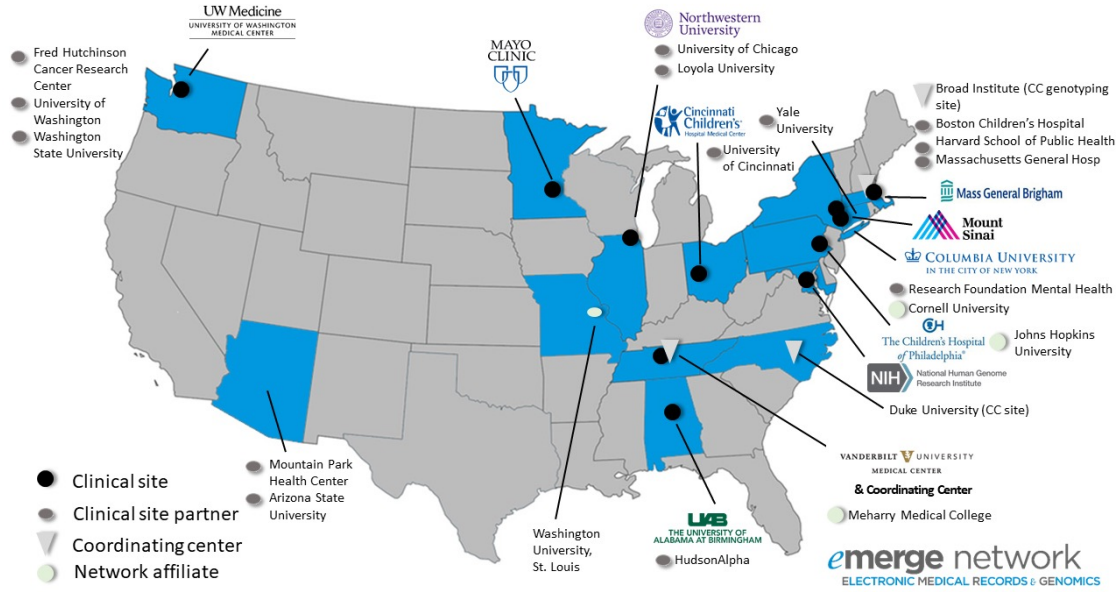
Reasons for poor cross-ancestry transferability:

- European over-representation in GWAS, bias in array design, bias in imputation
- LD differences between populations
- Differences in the environment (via GxE interactions)
- Actual differences in the genetic architecture (e.g., *APOL1*)

Martin et al. *Nature Genetics* 2019.

Electronic Medical Records & Genomics Phase IV (eMERGE-IV)

- Optimization of polygenic scores for 10 common diseases
- Recruitment of 25,000 participants of diverse ancestries for PRS + Monogenic screening
- Return of results with prospective collection of outcomes



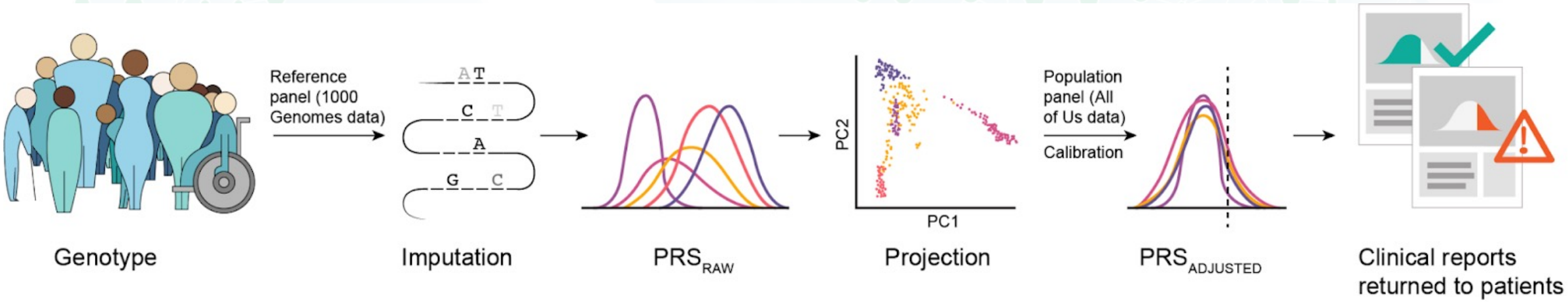
Coronary Artery Disease
Chronic Kidney Disease
Type 1 Diabetes
Type 2 Diabetes
Atrial Fibrillation
Obesity
Asthma
Breast Cancer
Colorectal Cancer
Prostate Cancer

emerge network
ELECTRONIC MEDICAL RECORDS & GENOMICS

KDIGO KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES

eMERGE-IV PRS Testing Process (CLIA Lab)

Major challenge: to implement standardized GPS calculations in CLIA-certified testing labs, establish actionable thresholds and standardize reporting.



Genotype | Imputation | PRS_{RAW} | Projection | $PRS_{ADJUSTED}$ | Clinical reports returned to patients

DNA is genotyped with Global Diversity Array (1.8M SNPs).

Genotyping data is phased and imputed (*1000G* reference)

Raw PRS scores are calculated for each condition

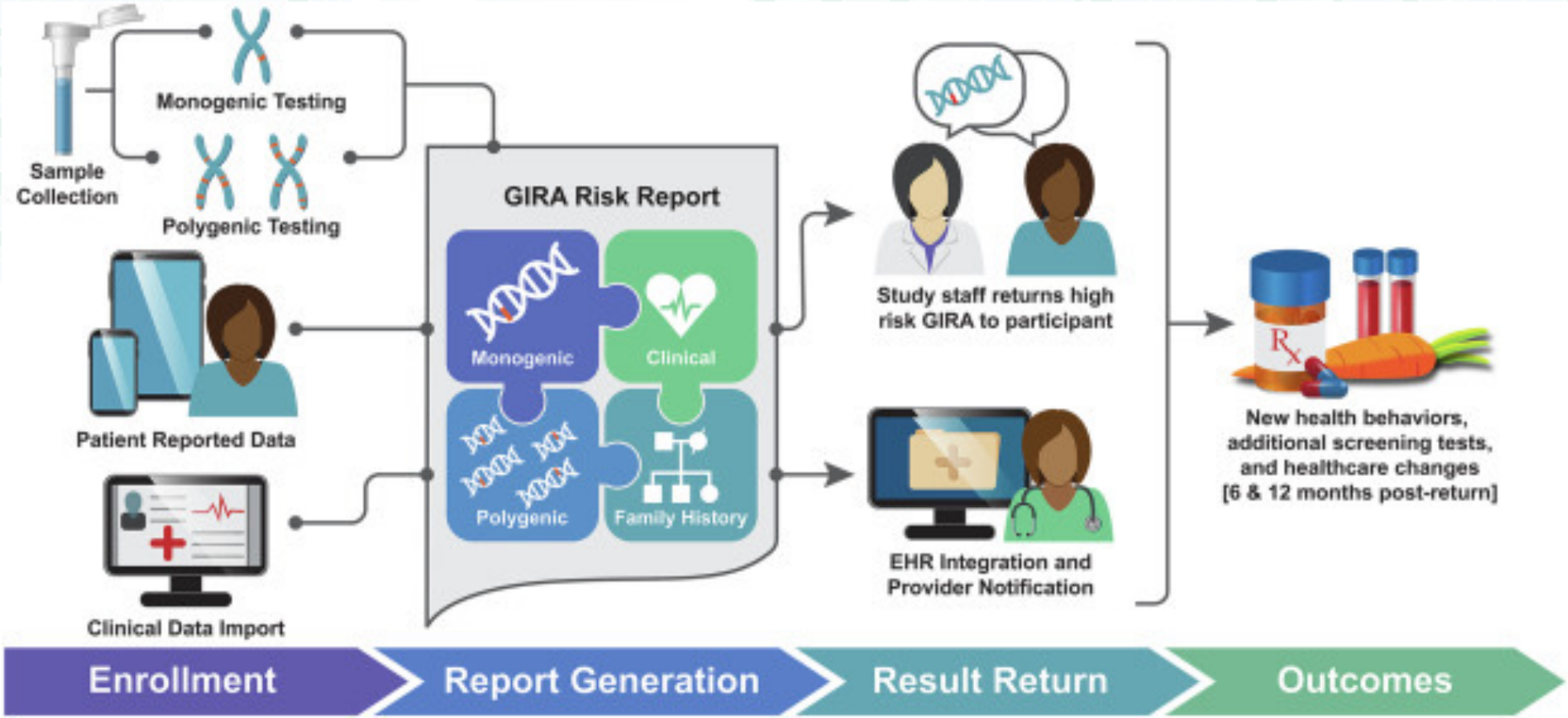
Ancestry calibration based on AoU

'high risk' defined for adjusted scores crossing the threshold

Clinical report is generated, signed and delivered to the study portal

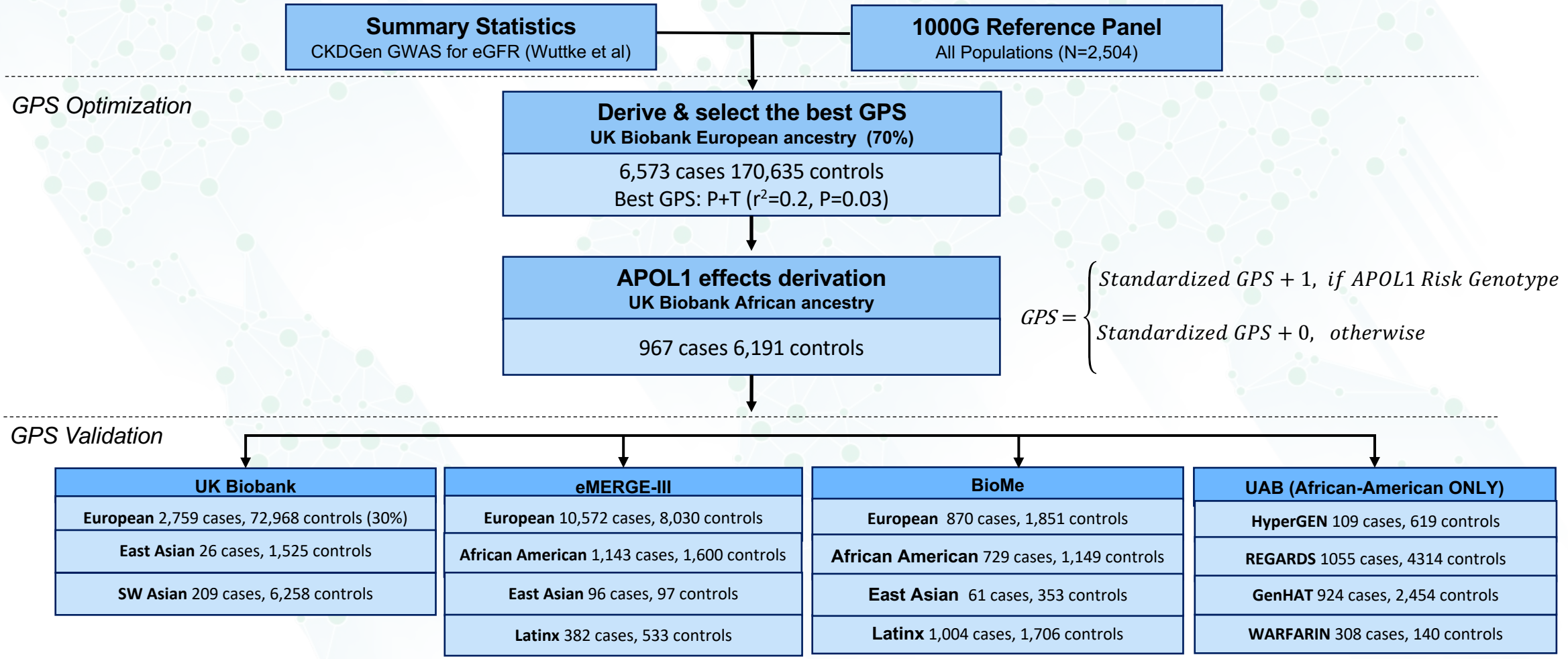
Lennon et al. *Nature Med (in press)*

Genomic Integrative Risk Assessment (GIRA)



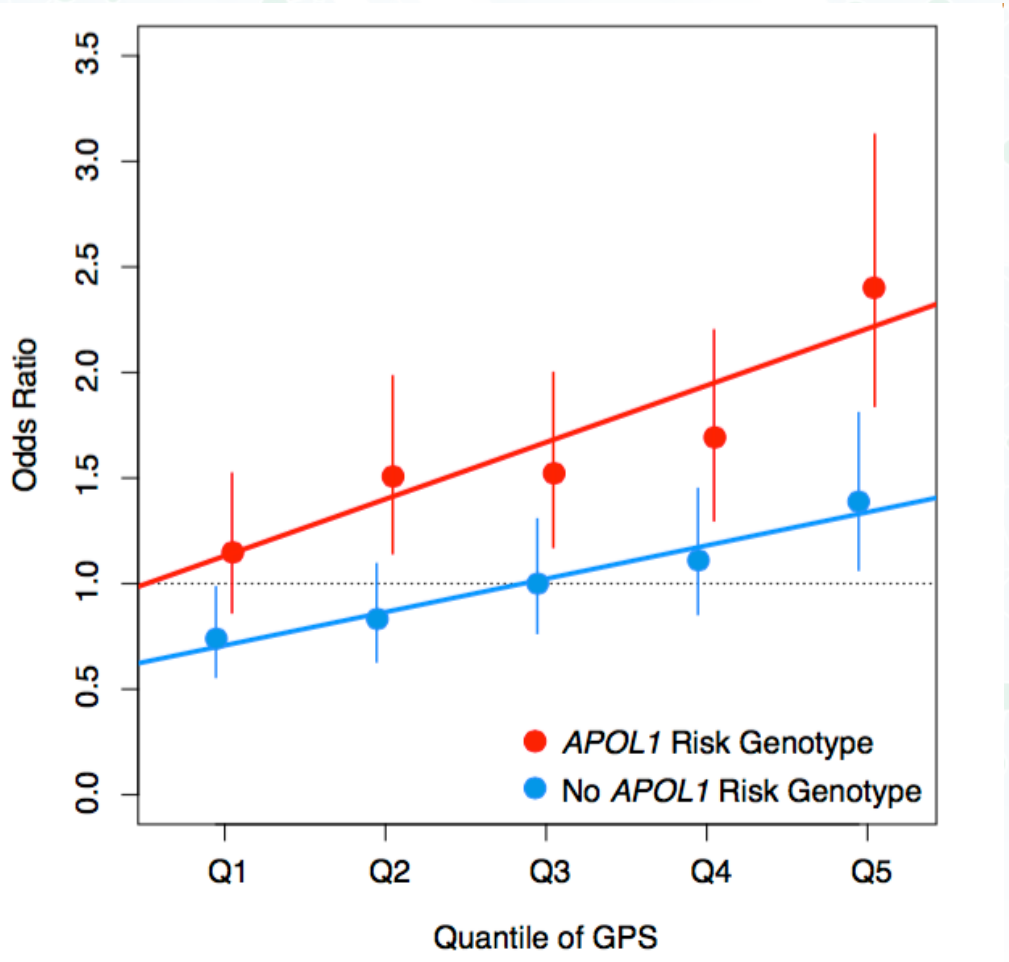
Lennon et al. *Nature Med (in press)*

Genome-wide Polygenic Score (GPS) for CKD



Khan et al. *Nature Medicine* 2022

Additive effects of *APOL1* and polygenic background

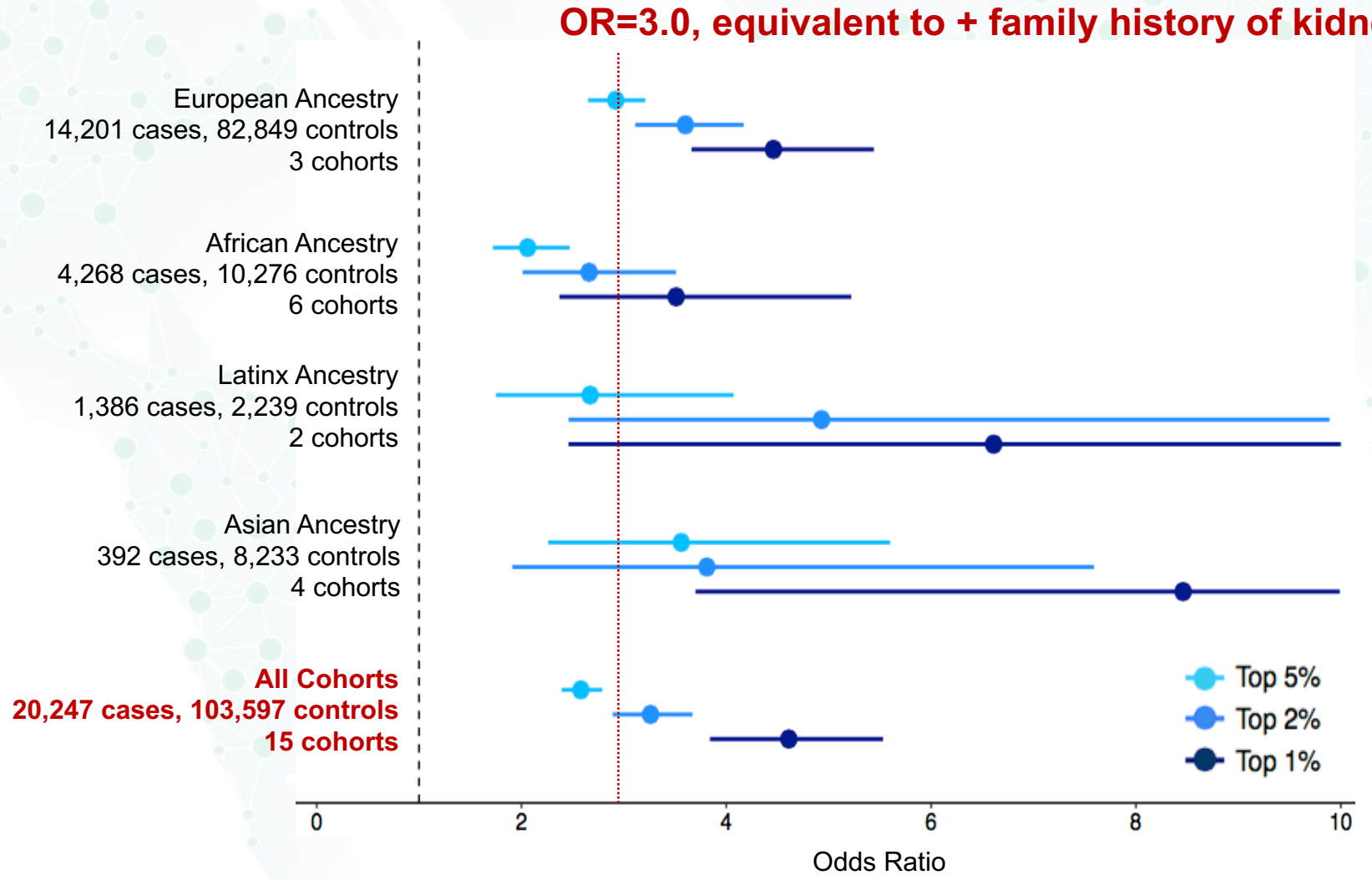


Six validation cohorts of African ancestry (4,268 cases and 10,276 controls)

Outcome of CKD stage 3+, covariates: age, sex, diabetes, cohort, and ancestry PCs

Khan et al. *Nature Medicine* 2022

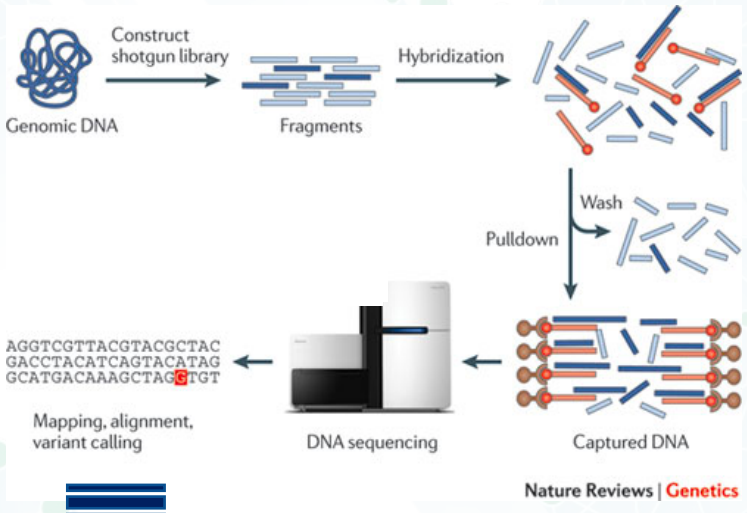
GPS for CKD: tail cut-off selection



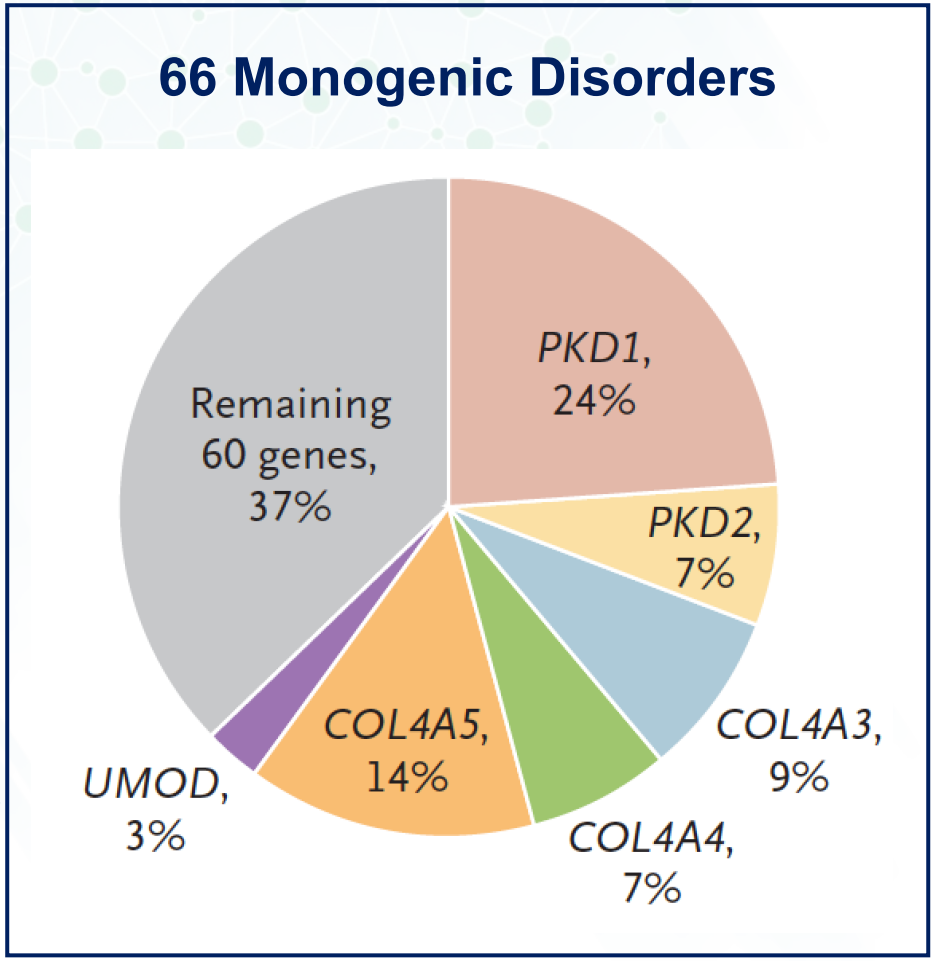
Khan et al. *Nature Medicine* 2022

Monogenic risk of CKD

Diagnostic ES
N=3,315
CKD patients

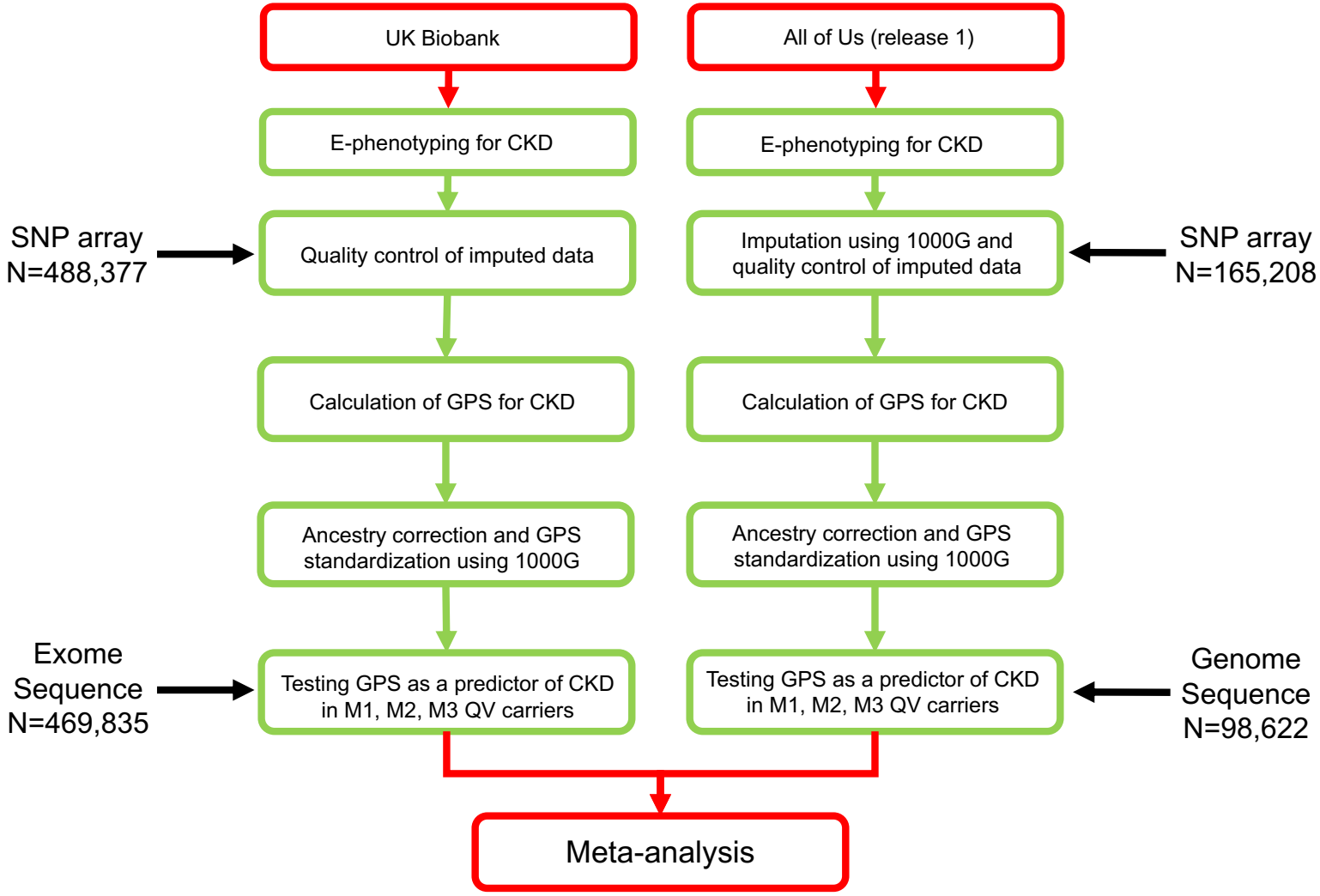


307 with Monogenic Disease
(9.3% diagnostic yield
by ACMG criteria)



Groopman at al. *NEJM* 2019

Interplay of polygenic and monogenic risk for CKD



Khan et al. *Nature Comm (in press)*

Polygenic risk and ADPKD

UKBB + All-of-Us
~600K individuals with ES/GS

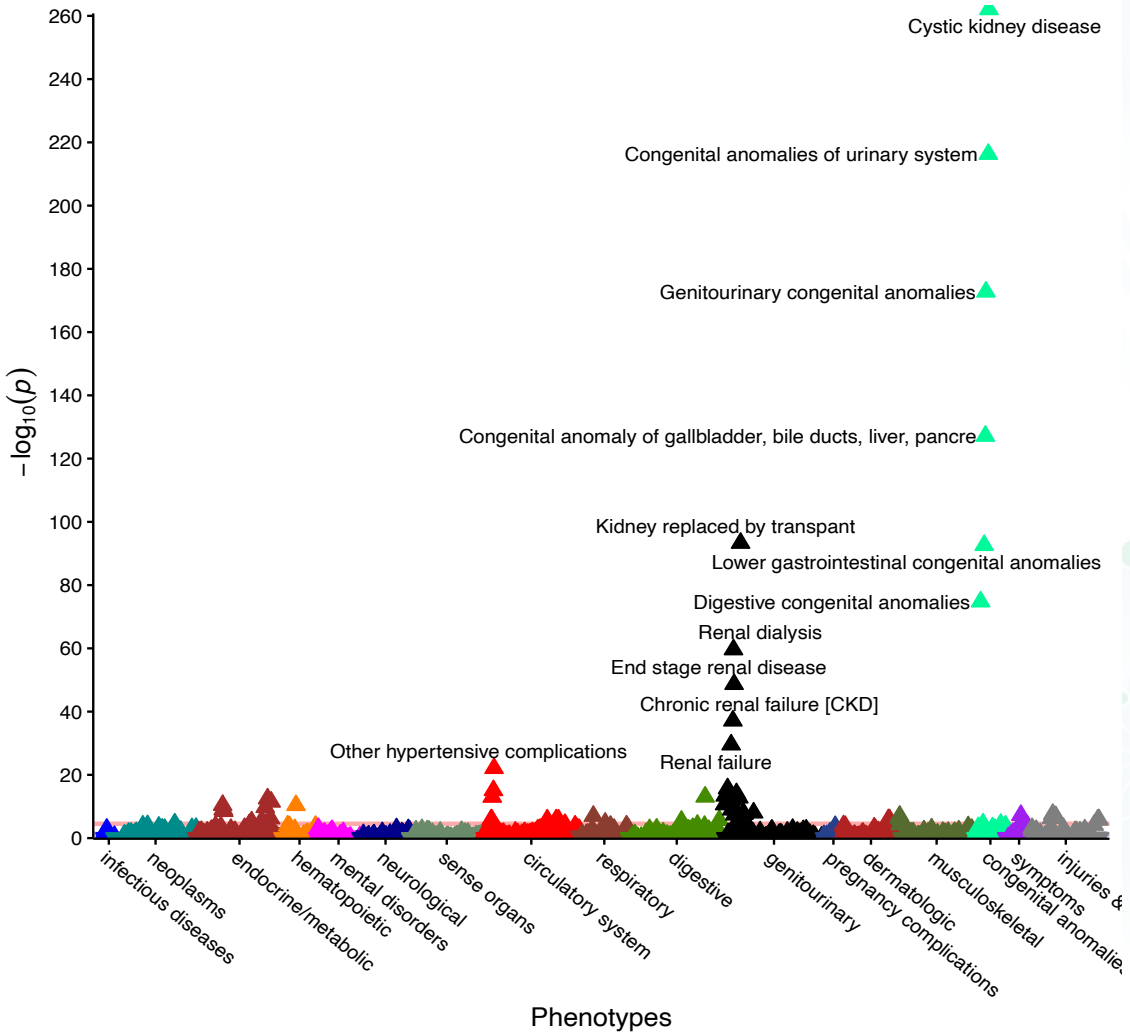
pLOF and ClinVar 'Pathogenic' variants
PKD1 and *PKD2* genes

Exclude:

1. MAF>10-5 in any ancestry (UKBB, AoU, gnomAD)
2. Single submitter 'Pathogenic' in ClinVar
3. Conflict of pathogenicity in ClinVar

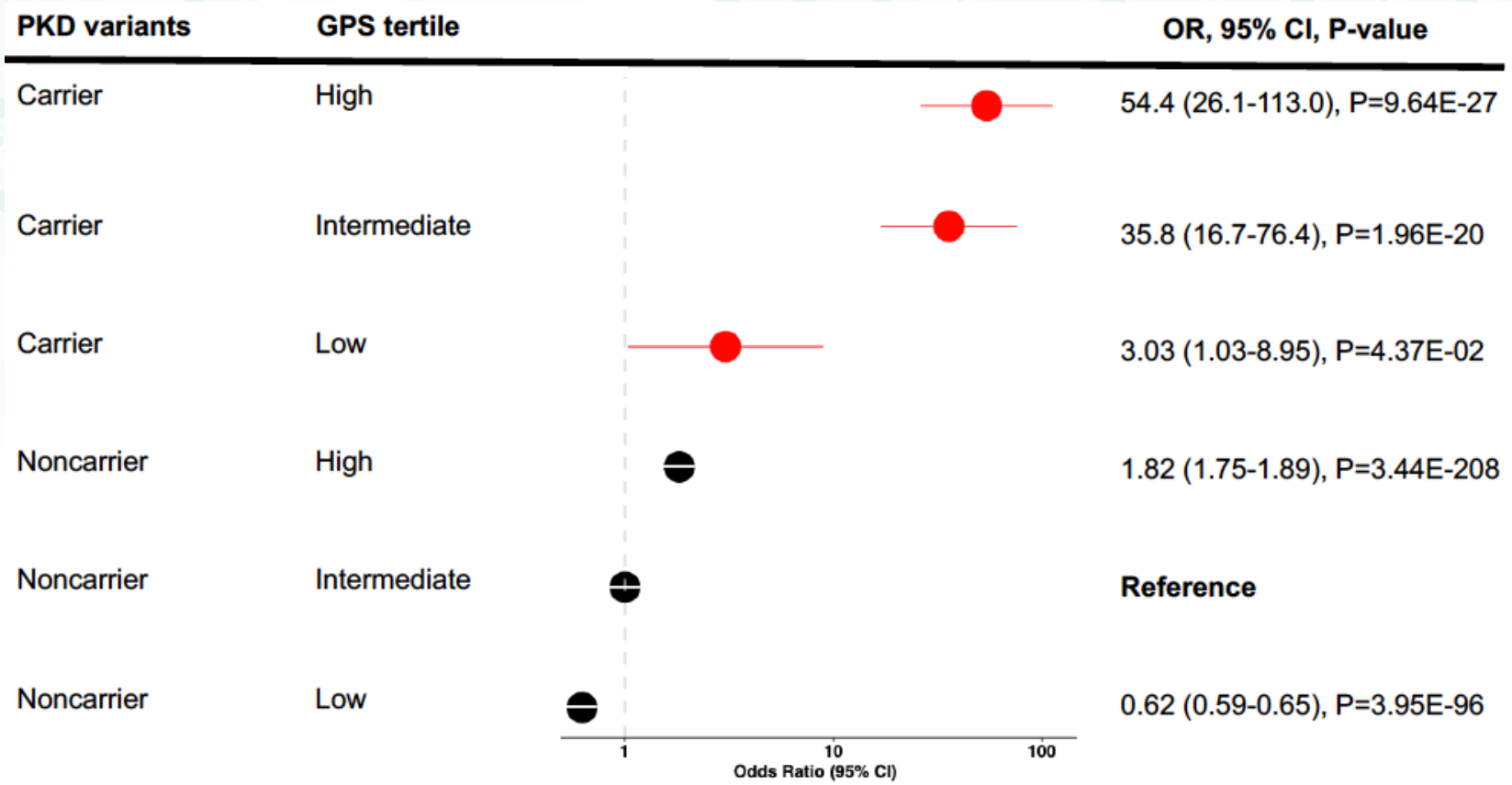
Monogenic ADPKD variants used in the analysis (**Model 1**)

N=206 carriers (0.03%)



Khan et al. *Nature Comm (in press)*

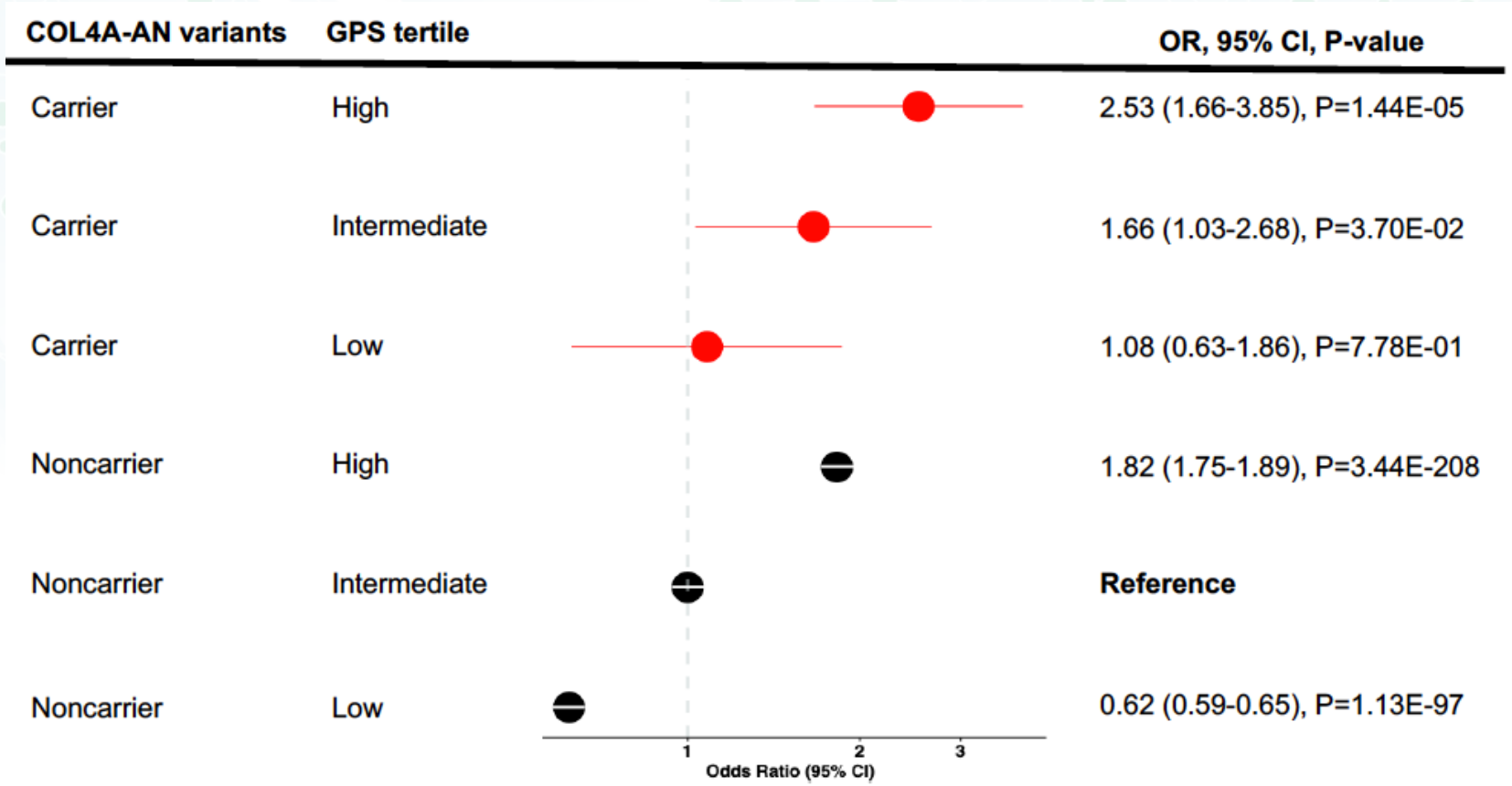
Polygenic risk and ADPKD



Outcome of CKD stage 3+, covariates: age, sex, diabetes, cohort, and ancestry PCs

Khan et al. *Nature Comm (in press)*

Polygenic risk and COL4A-AN



Outcome of CKD stage 3+, covariates: age, sex, diabetes, cohort, and ancestry PCs

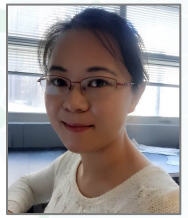
Khan et al. *Nature Comm (in press)*

Summary:

- GPS offers a promising tool for kidney disease risk stratification: top 2% associated with >3-fold higher risk (a family history risk equivalent)
- Monogenic risk, *APOL1*, and polygenic risk appear to have additive effects; Added value of polygenic risk over family history and other known risk factors still unknown for kidney disease.
- Ongoing work includes improvements in the overall predictive performance and cross-ancestry portability (new GWAS, new methods) and prospective testing of clinical utility (prospective eMERGE-IV).

Acknowledgements

Kiryluk Lab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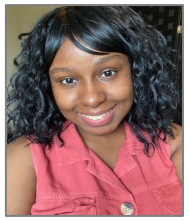
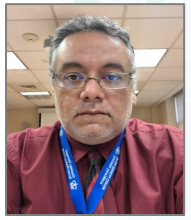
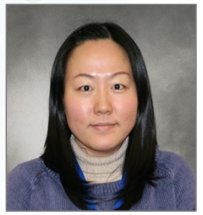

Cecilia Berrouet


German Varela


Ning 'Sunny' Shang

Columbia University

Nephrology and Center for Precision Medicine and Genomics:
Ali Gharavi, Simone Sanna-Cherchi, Maya Sabatello

Statistical Genetics:
Iuliana Ionita-Laza

Glomerular Center:
Jerry Appel, Jai Radhakrishnan, Andy Bomback, Pietro Canetta

Transplant Center:
David Cohen, Sumit Mohan

Renal Pathology:
Vivette D'Agati, Ibrahim Batal

Biomedical Informatics:
Chunhua Weng, George Hripcsak

Clinical Genetics:
Wendy Chung, Vaidehi Jobanputra

Questions?