Results of the International AAAgen GWAS meta-analysis

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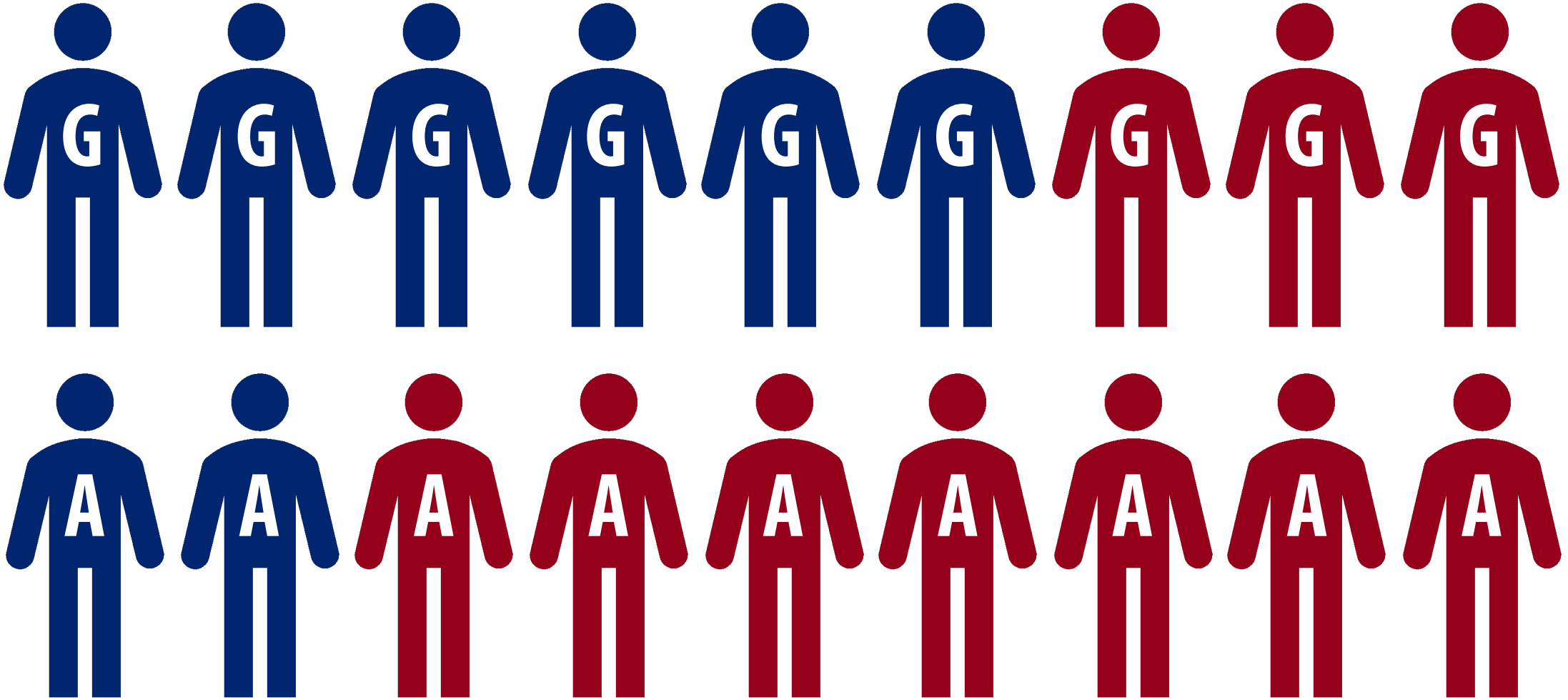
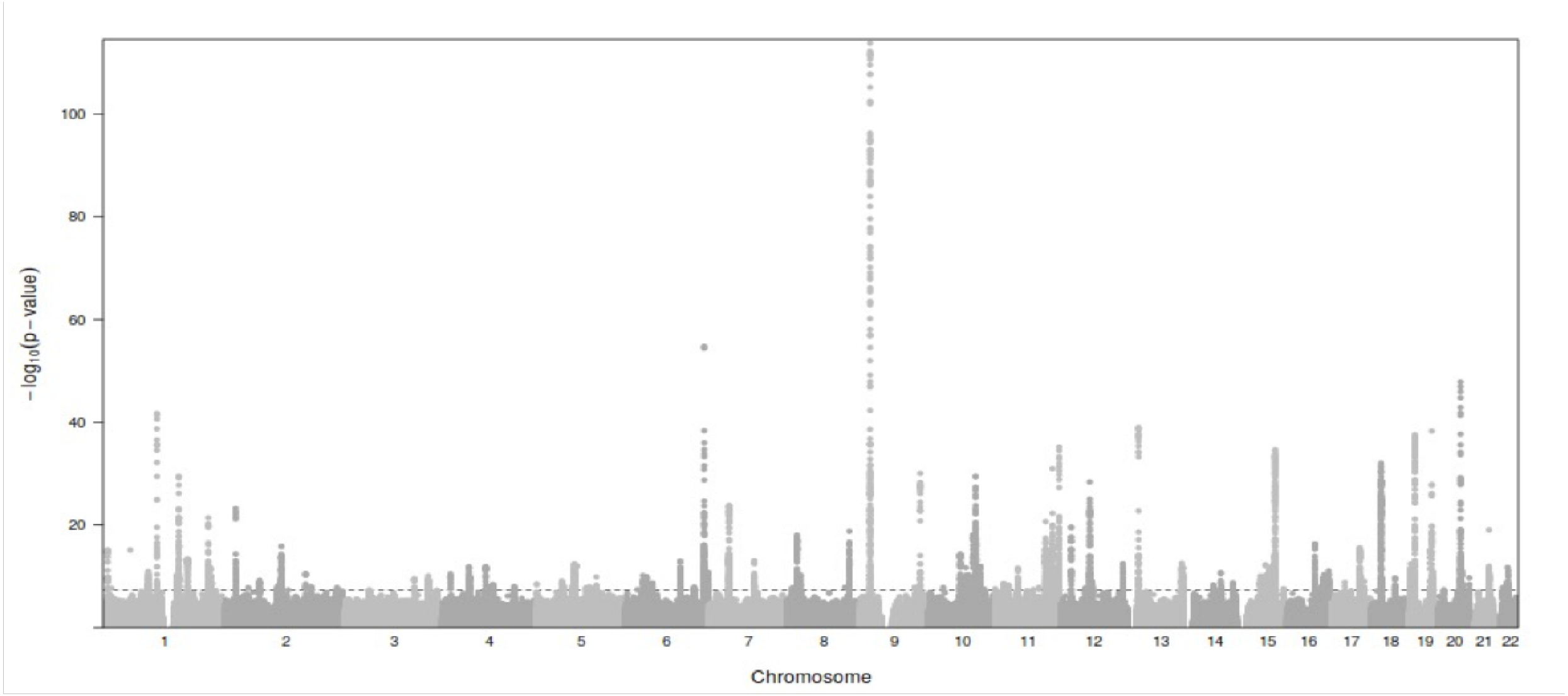
- Research support from RenalytixAI, LLC
- Personal consulting sees from Calico, Labs
- This presentation will discuss repurposing medications for off-label use in the treatment of AAA

Testing genetic association in populations



AAAgen GWAS



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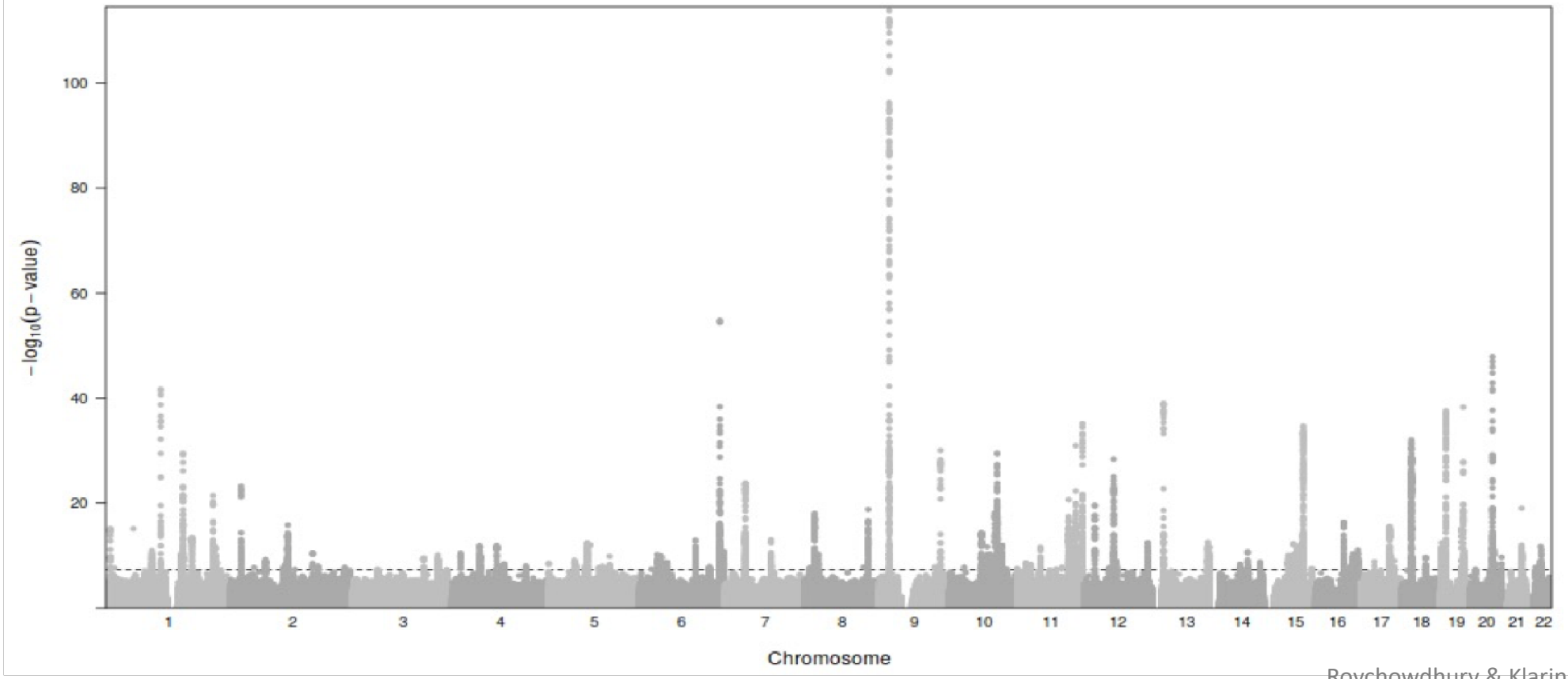
AAAgen GWAS

14 Cohorts

39,221 AAA cases

123 risk loci



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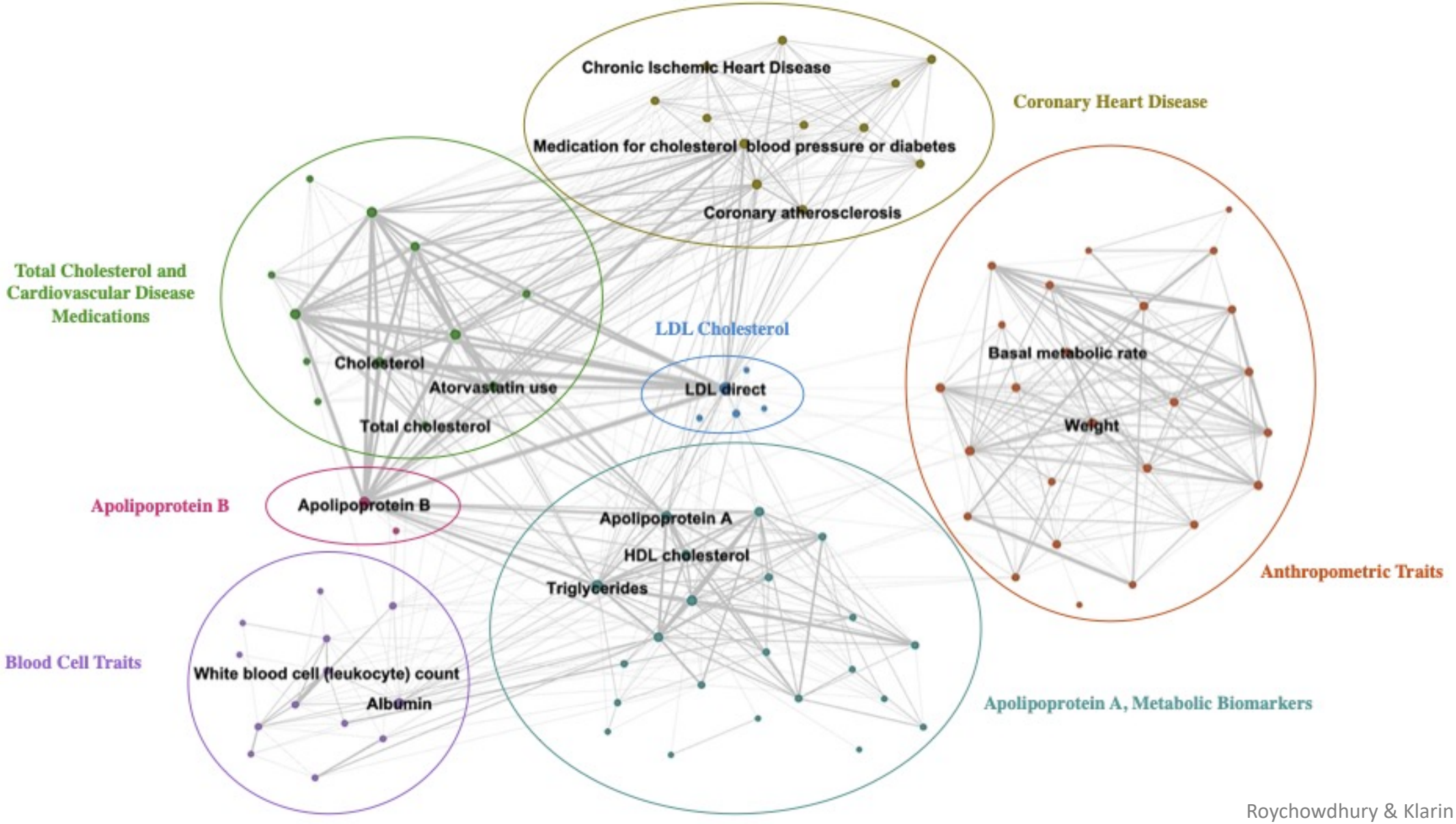
A central role for lipids and lipoproteins



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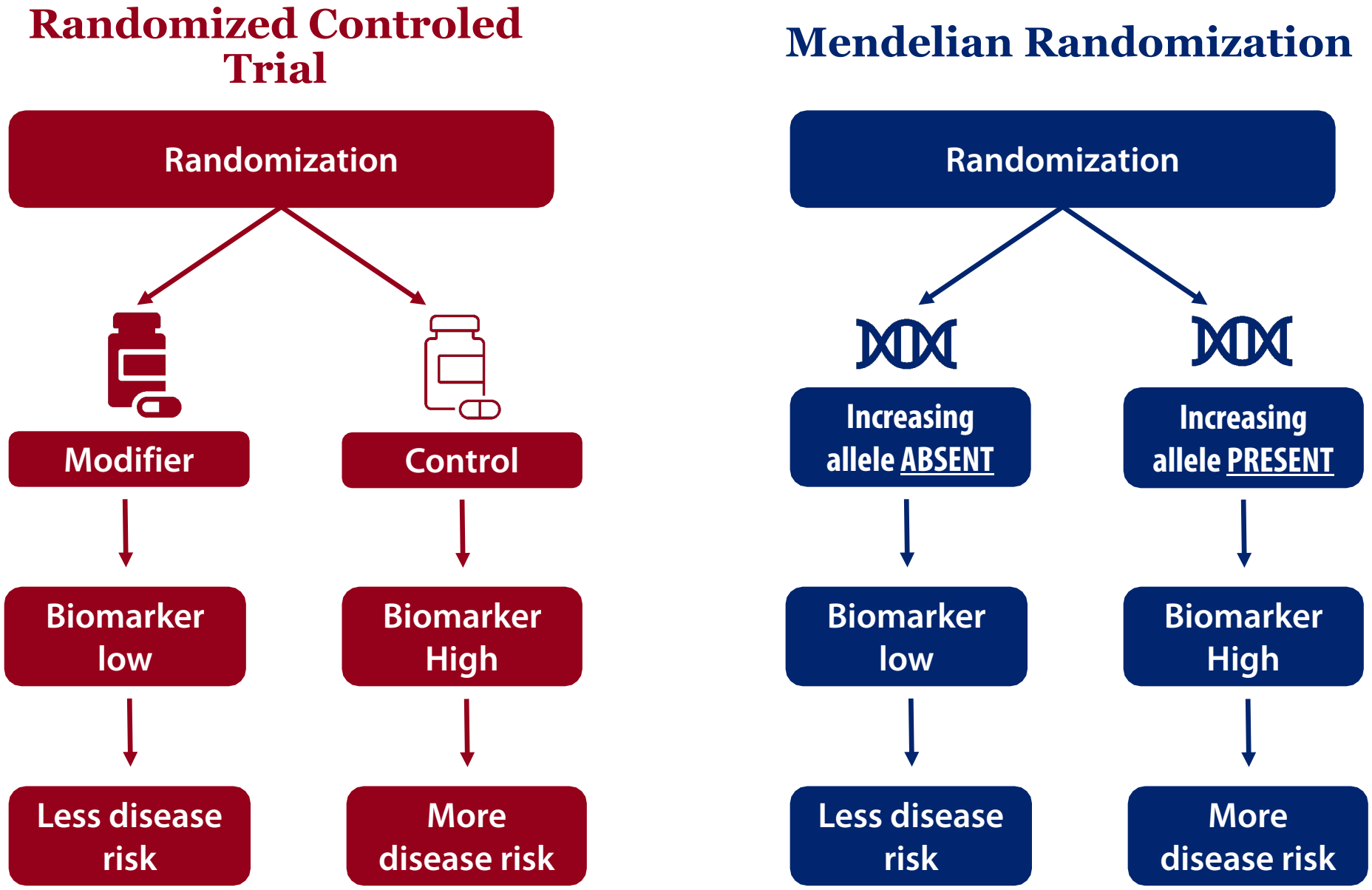
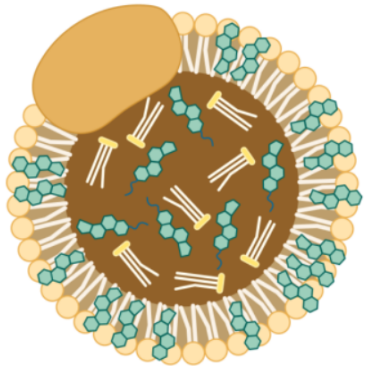
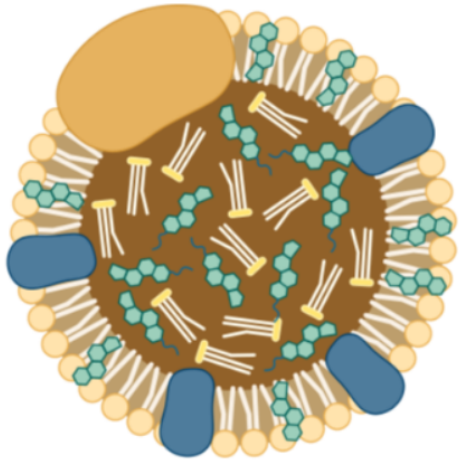

Randomized Controled Trial
Randomization
Modifier
Control
Biomarker low
Biomarker High
Less disease risk
More disease risk
Mendelian Randomization
Randomization
Increasing allele ABSENT
Increasing allele PRESENT
Biomarker low
Biomarker High
Less disease risk
More disease risk

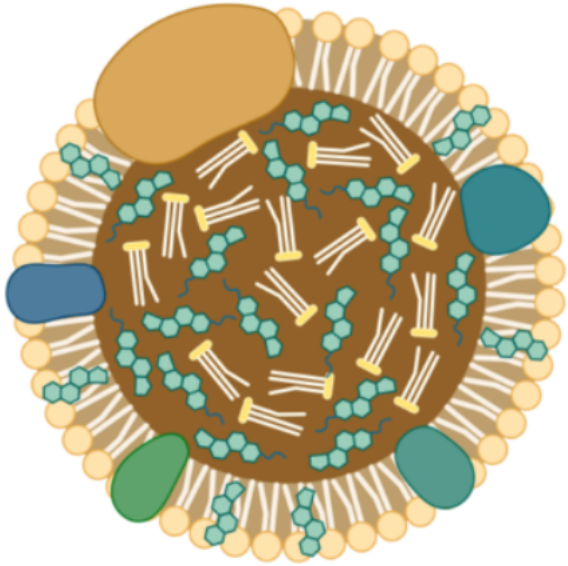
non-HDL cholesterol is causally associated with AAA



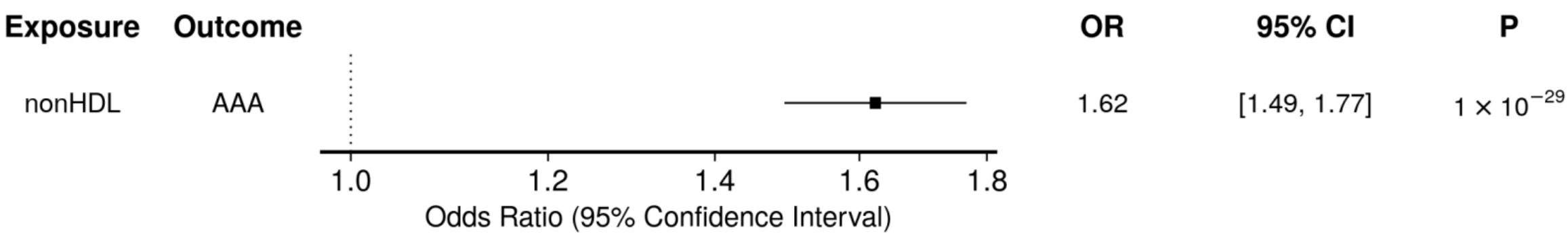
LDL-C



IDL-C



VLDL-C



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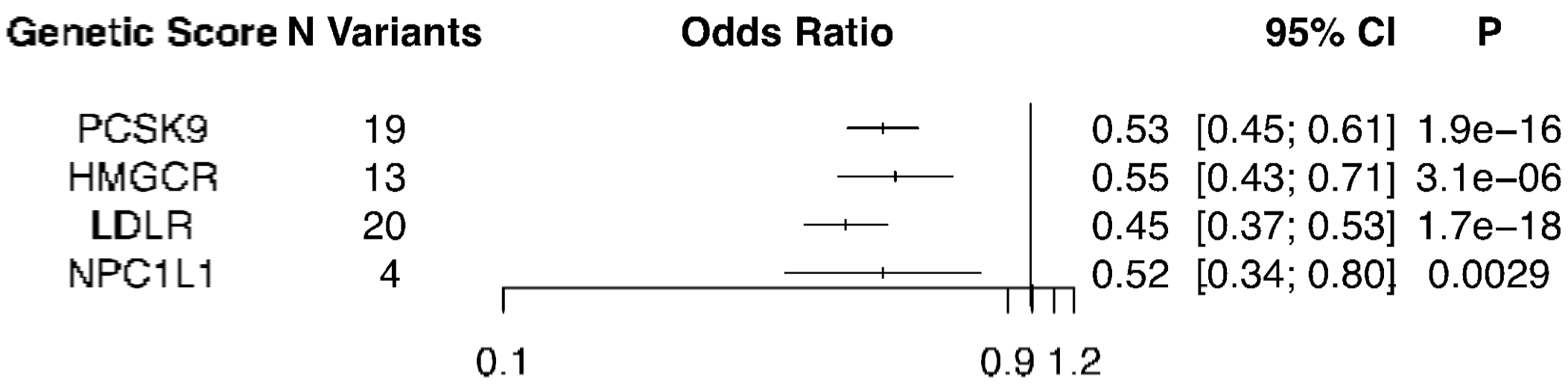
Pharmacological manipulation of lipoproteins is predicted to protect from AA



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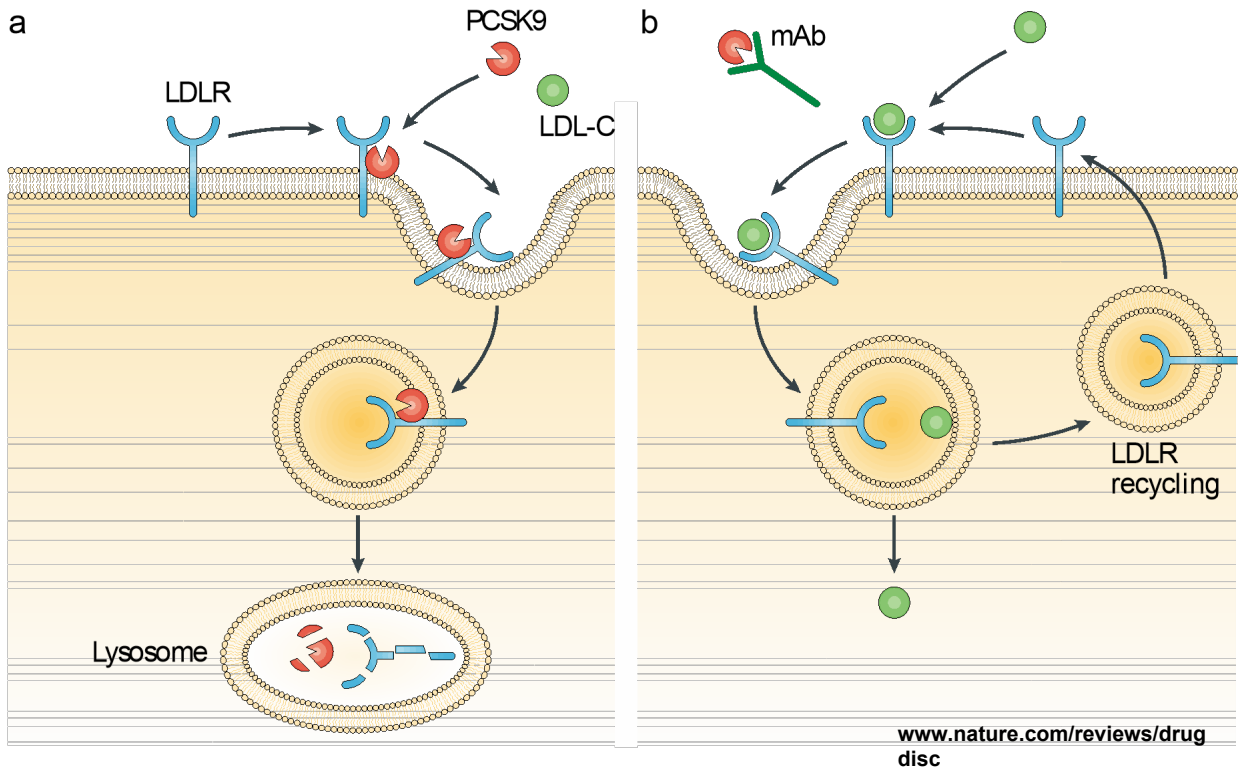
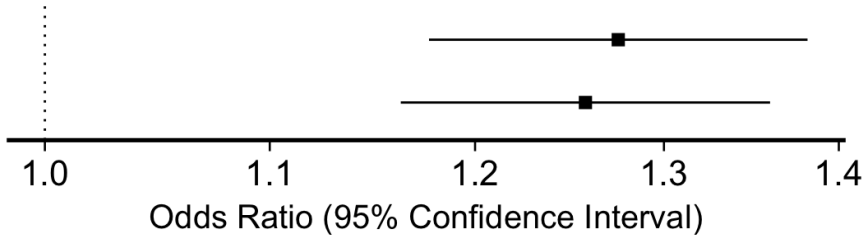
Circulating PCSK9 is a causal risk factor for AAA



Exposure	Outcome	Method	OR	95% CI	P
PCSK9	AAA	Inverse variance weighted	1.28	[1.18, 1.38]	3×10^{-9}
PCSK9	AAA	Weighted median	1.26	[1.16, 1.36]	1×10^{-8}



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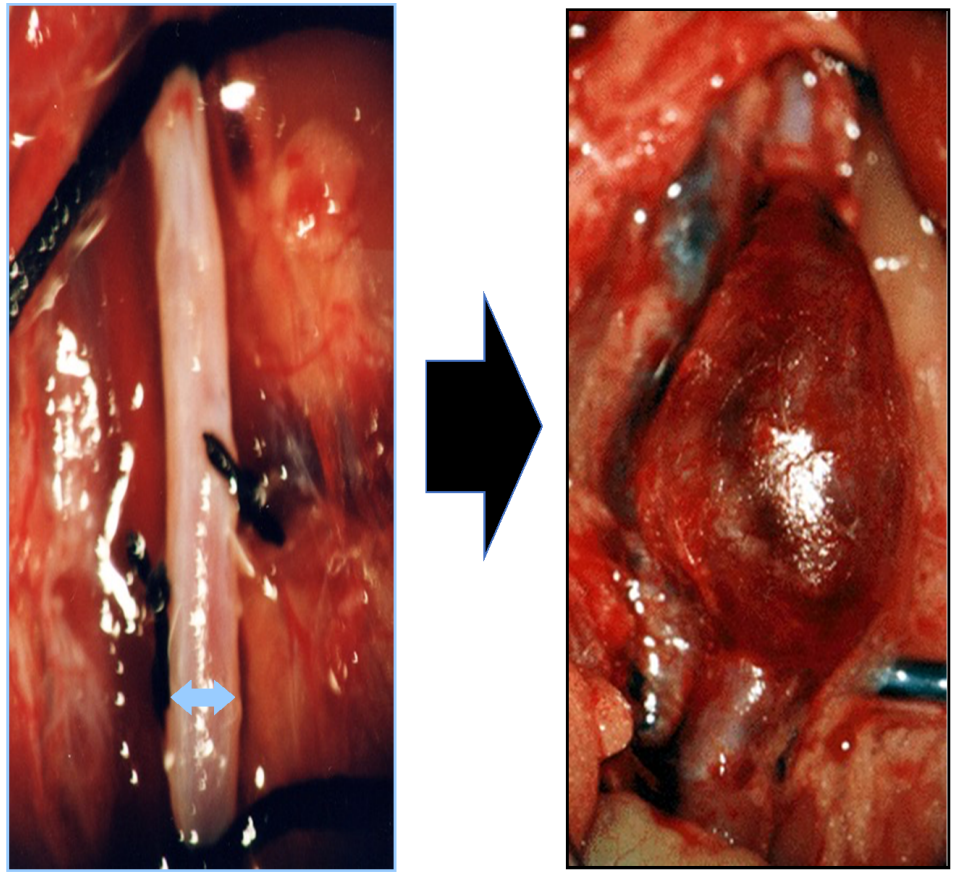
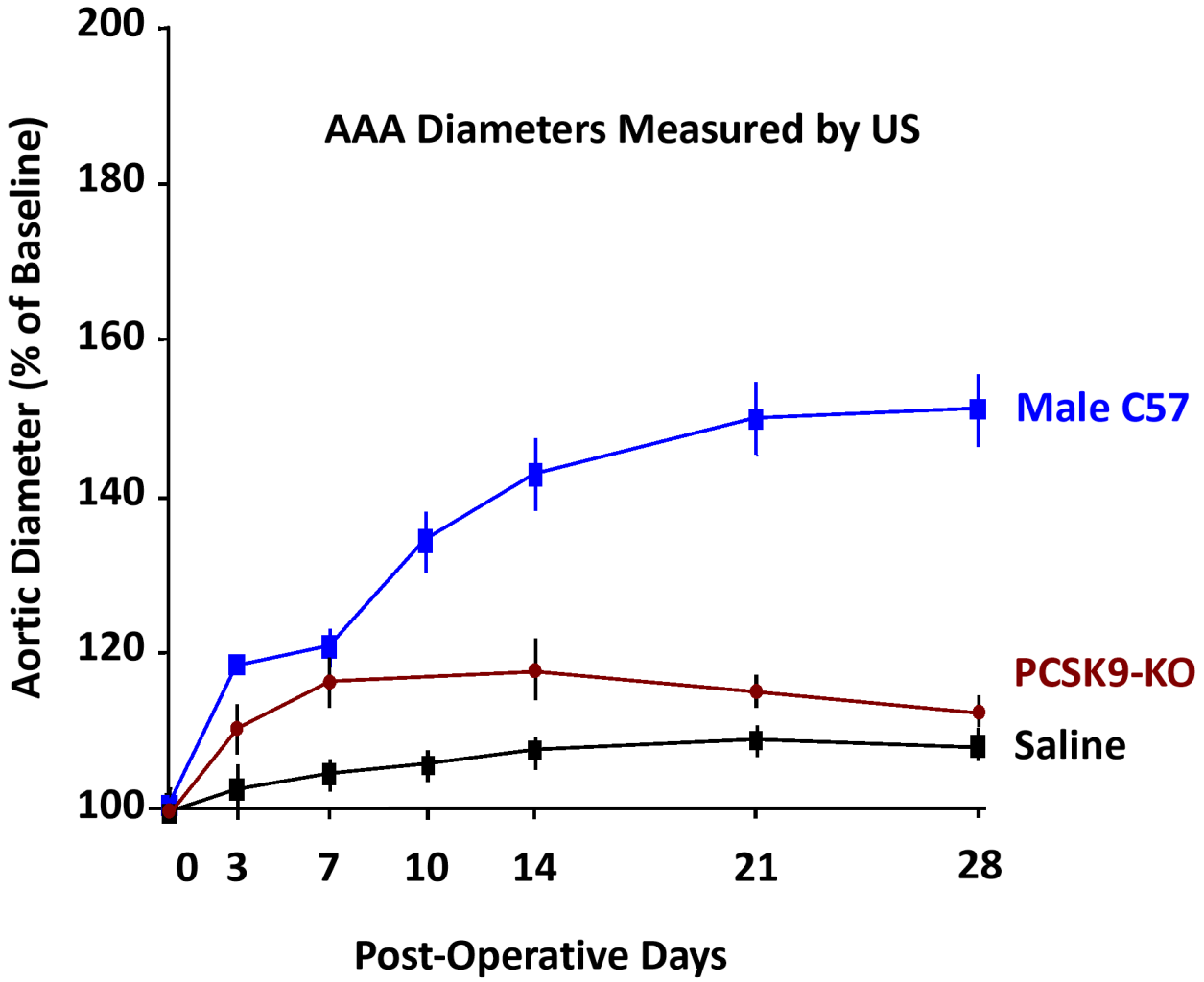
PCSK9-/- mice are resistant to elastase induced AAA





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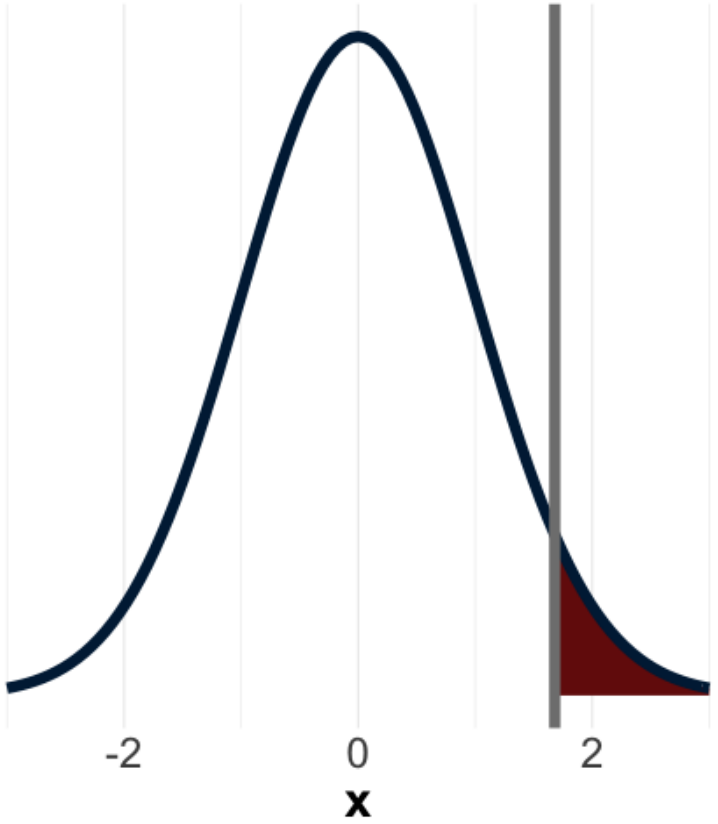
Polygenic Risk Score (PRS)

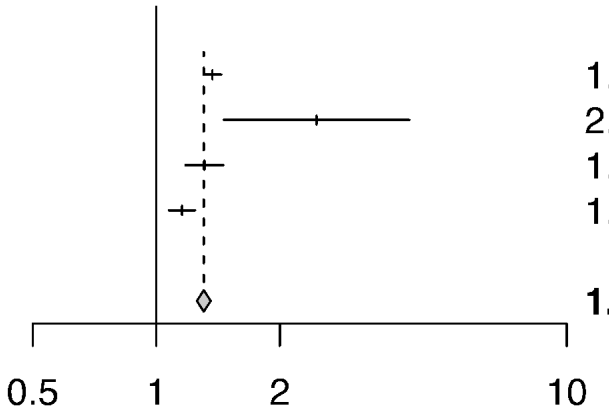
- Weighted score of multiple variants
- Weights based on GWAS data for given trait in a reference population
- Constructed to account for linkage disequilibrium
- Used to predict trait in another population
- Frequently thresholded for implementation



Polygenic risk score validates in external cohorts

B

Model	Study	Ancestry	Cases	Controls	Odds Ratio	95% CI	P Value
29 Variant PRS	MVP	European	1656	44908		1.37 [1.30; 1.44]	1.6e–34
29 Variant PRS	BioMe	European	194	9331		2.46 [1.46; 4.14]	7e–04
29 Variant PRS	PMBB	European	388	9835		1.31 [1.18; 1.46]	8.1e–07
29 Variant PRS	MVP	African	718	46380		1.15 [1.07; 1.24]	0.00015
						1.30 [1.26; 1.36]	**3.5e-41**



Klarin et al. *Circulation* 2020

Genetic informed screening for AAA

Population	Ancestry	Prevalence	95% CI	Data Source
Men aged 65-75, ever smoker	European	6-7%	NA	Randomized Control Trials
Top 5% PRS all ages/sexes	European	5.9%	5.1-6.7%	Current Study
Top 5% PRS Men > 50		8.6%	7.3-9.8%	
Top 5% PRS all ages/sexes	African	1.7%	1.3-2.2%	
Top 5% PRS Men > 50		2.5%	2.0-3.0%	

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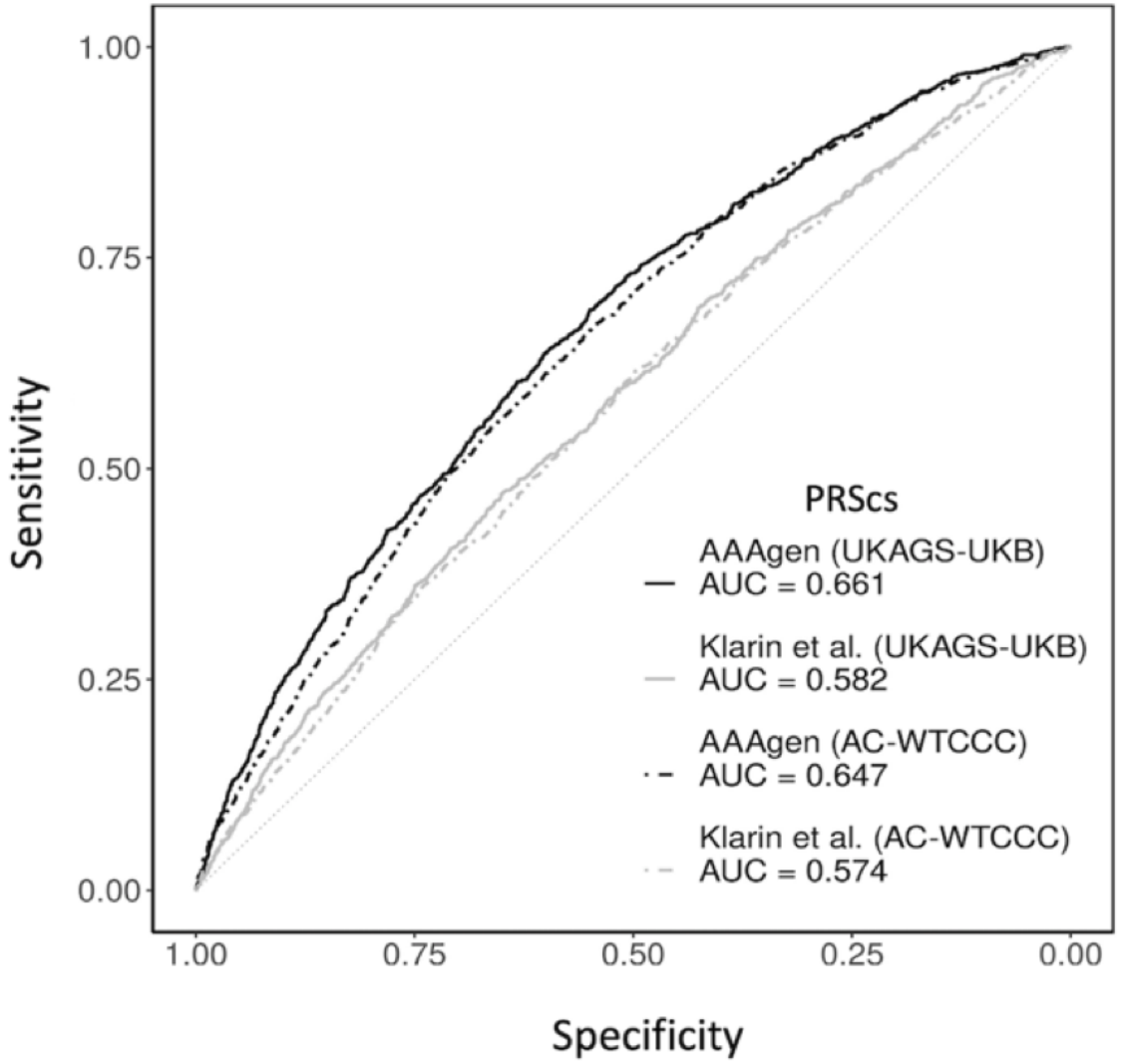
AAAgen improves polygenic AAA prediction



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Conclusions

- Large-scale genetic studies can identify DNA variants, genes, proteins, and biological pathways that lead to common vascular disease
- AAA has a large genetic component
- Blood lipids and circulating lipoproteins are causal risk factors for AAA
- LDL-C modifying therapy, and PCSK9 inhibitors in particular, may prevent AAA
- Genetics can be used to predict risk and possibly expand screening indications

AAAgen Consortium

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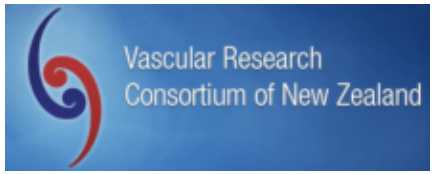

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tinyurl.com/AAAgen