

Genetic Studies of Abdominal Aortic Aneurysms

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Geisinger Clinic

Geisinger MyCode® Project

MyCode Project

CONTRIBUTE TO THE FUTURE OF HEALTHCARE

You can call us at

1.886.910.6486

to ask for more information about MyCode.

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We would like you to take part in MyCode, a project that will involve collection and storage of blood samples and health information from 200,000 patients. Researchers will use your blood to study your genes. This information will help researchers to understand how diseases develop and how we can improve detection and treatment of diseases.

WHAT WILL YOU BE ASKED TO DO?

1) Complete the MyCode consent form

2) Give us permission to collect up to two tablespoons of your blood. We will only collect the MyCode blood sample when you are already having blood drawn that your doctor ordered.

3) Choose whether your blood can be collected one time only, or whether your blood will be collected up to one time per year for as long as you allow it.

4) Allow us to get information from your electronic health record (EHR) about your health history.

WHAT WE WILL DO WITH THE INFORMATION?

If blood samples and medical information are already available, researchers can study and understand what causes diseases including ways to detect diseases earlier and to improve treatments.

WHY WERE YOU ASKED TO TAKE PART?

We are asking anyone who is 18 years of age or older and is a Geisinger Clinic patient to take part.

WHAT ARE THE BENEFITS/RISKS INVOLVED?

There are few benefits or risks to you. You will not receive money for your help. It will not cost you money to take part.

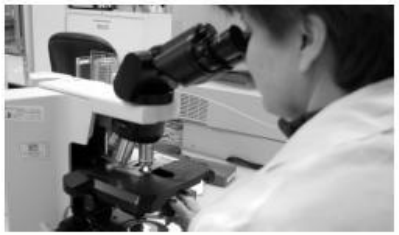
This research will not affect your health. The research may lead to discoveries to help doctors learn about diseases in general. We will take special care to protect your privacy.

WHAT IF IF YOU DON'T WANT TO BE INVOLVED?

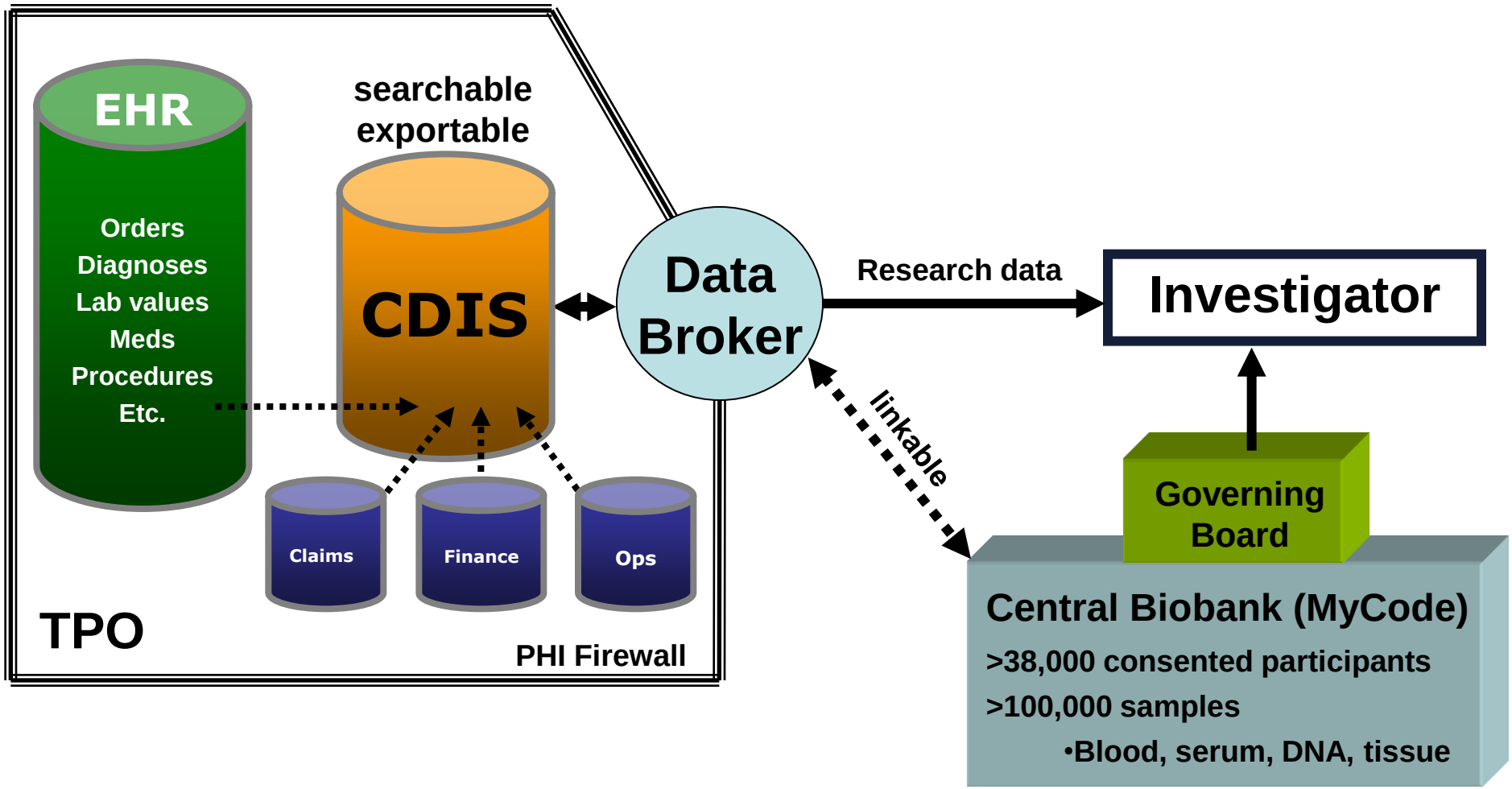
Participation is completely voluntary. Your choice to take part or not take part in the project will not affect your health care.

FOR MORE INFORMATION

You can call us at 1.866.910.6486 to ask for more information about MyCode.



Research Data Broker and Clinical Decision Intelligence System (CDIS) Data Warehouse



AAA Genome Wide Association Study

922 AAA cases

- 725 males, 197 females

1,246 population controls from Geisinger MyCode Project

- 752 males, 494 females

Genotyped on Illumina OmniExpress Arrays (655,143 SNP probes)

Imputation on 1000 Genomes data set

~1,000 AAA cases and 9,000 controls genotyped on Illumina exome arrays

Replication of *LRP1* Association with AAA

(Bown et al., AJHG 2011)

- 6,228 cases
- 49,182 controls
- Association with a SNP in *LRP1* gene:
  - -P = 4.5×10^{-10}
  - -OR 1.15 [1.10-1.21]
  - -Risk Allele [C]
  - -Allele frequency 0.62
- Increase in LRP1 expression in CC homozygotes compared to TT homozygotes

Replication of *LRP1* Association with AAA

Geisinger	AA N Freq.		GA N Freq.	GG N Freq.	MAF HWE P-value
Controls N=1591	181 0.114		714 0.449	696 0.437	[*A*]=0.34 P= 0.917
Cases N=760	59 0.078		336 0.442	365 0.480	[*A*]=0.30 P = 0.127

Cochran- Armitage Trend Test
Additive: p-value = 0.0064
Dominant: p-value = 0.0068

Logistic Regression (Additive)
p-value = 0.0065
OR 1.20 [1.12 – 1.29]

Whole exome/whole genome sequence analysis

Samples for WES

4 sib-pairs from previous linkage analysis

12 index cases from Geisinger with positive family history

- 5 females
- 7 males
- Mean age 61.6 years
- Mean AAA diameter 5.6 cm

} "extreme phenotype?"

Samples for WGS

8 related cases from 3 families

Criteria for Filtering Variants Identified by Next Generation Sequencing

- Within previously identified AAA linkage peaks
- Frequency (rare > common)
- Predicted function
  - Predicted loss-of-function
  - Probably deleterious
  - Other non-synonymous
  - UTR
  - non-coding
- Conservation (PhyloP score)
- Clustering between families
- Clustering within families
- Compatible with recessive genetic model

Summary of Whole Exome Sequencing Variants

Summary of Exome Sequence Data	
Total reads	58 x 10^6/individual
Total variants	658,287
Non-synonymous variants	22,501
Variants not in dbSNP	7,875 (35%)
Annotation score > 300	96
•in 19q13 linkage region	51 (53%)
•in other AAA linkage regions	28 (29%)
•novel variants	83 (86%)
•splice variants	30 (31%)
•conserved (PhyloP top quartile)	86 (90%)

The *eMERGE* Network

electronic Medical Records & Genomics

A consortium of biorepositories linked to electronic medical records data for conducting genomic studies

- "national consortium to develop, disseminate, and apply approaches to research that combine DNA biorepositories with electronic medical record systems for large-scale, high-throughput genetic research . . . . [use] EMR systems to investigate gene-disease relationships".
- Jointly funded by the National Human Genome Research Institute and the National Institute of General Medical Sciences of the NIH
- eMERGE – Phase 2: began July 1, 2011; increased emphasis on integrating genomic data into clinical practice

Each center participating in the consortium, organized by the National Human Genome Research Institute

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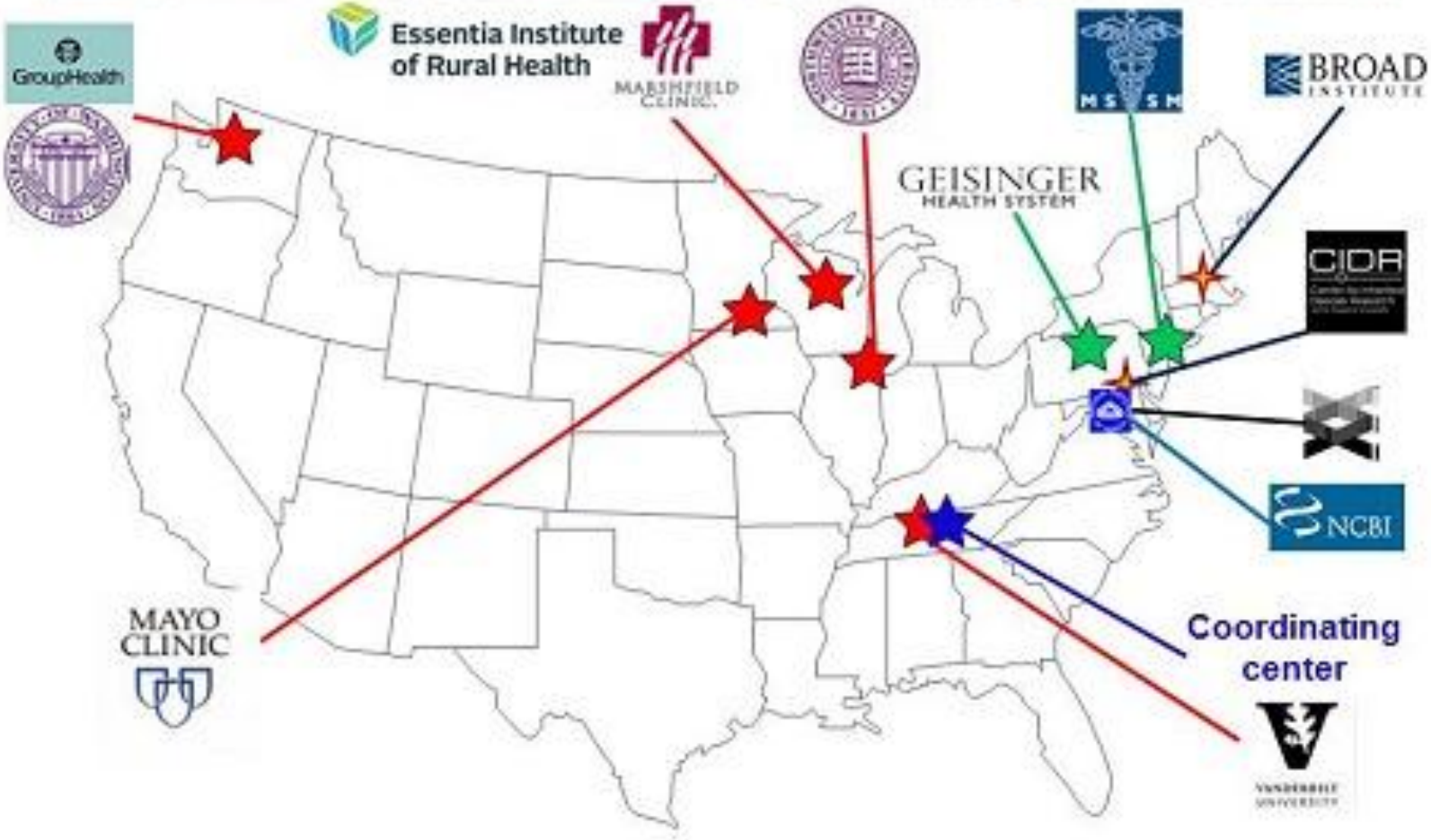
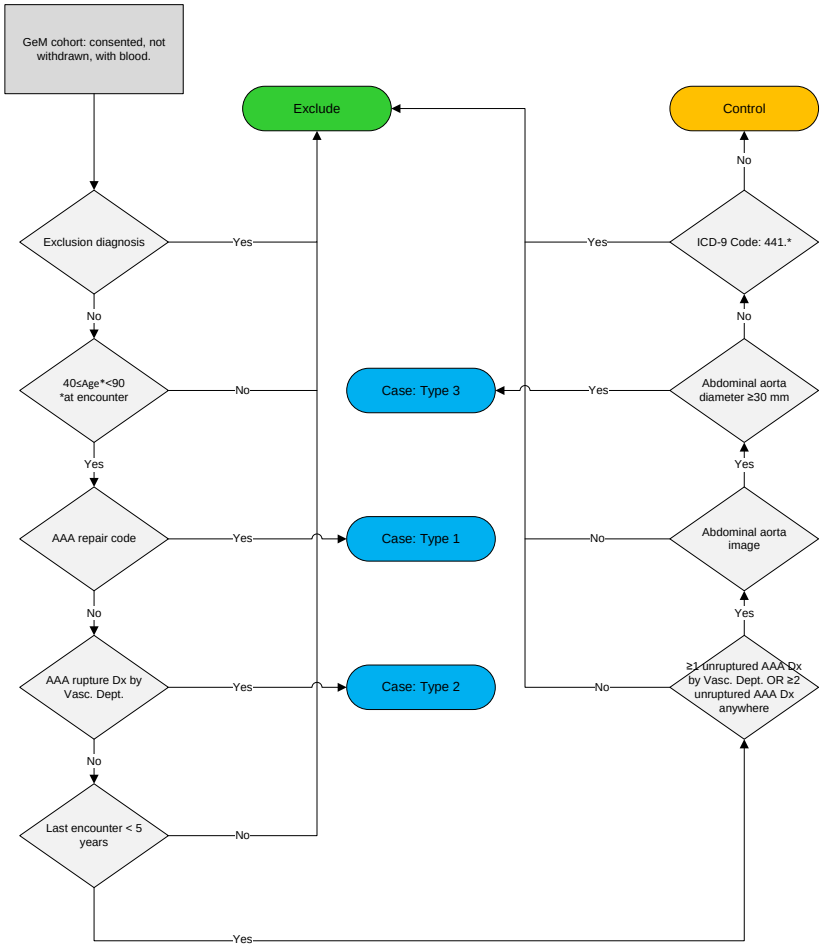


eMERGE Aims

1. Use existing biospecimens and EMR-generated phenotypes to identify new genetic variants or validate suspected variants associated with increased disease risk or treatment response for disorders with significant public health impact. (*Discovery*)
2. Develop and test approaches to incorporate genomic data into clinical care. (*Clinical Integration*)
3. Identify sociocultural concerns of patients residing in rural areas regarding genomic medicine research. Explore ethical, legal and social issues, including return of genetic findings to patients. (*ELSI*)

eMERGE AAA ePhenotyping Algorithm



- Exportable
- High predictive value
  - PPV and NPV >95%

eMERGE Samples for AAA GWAS

*Discovery**

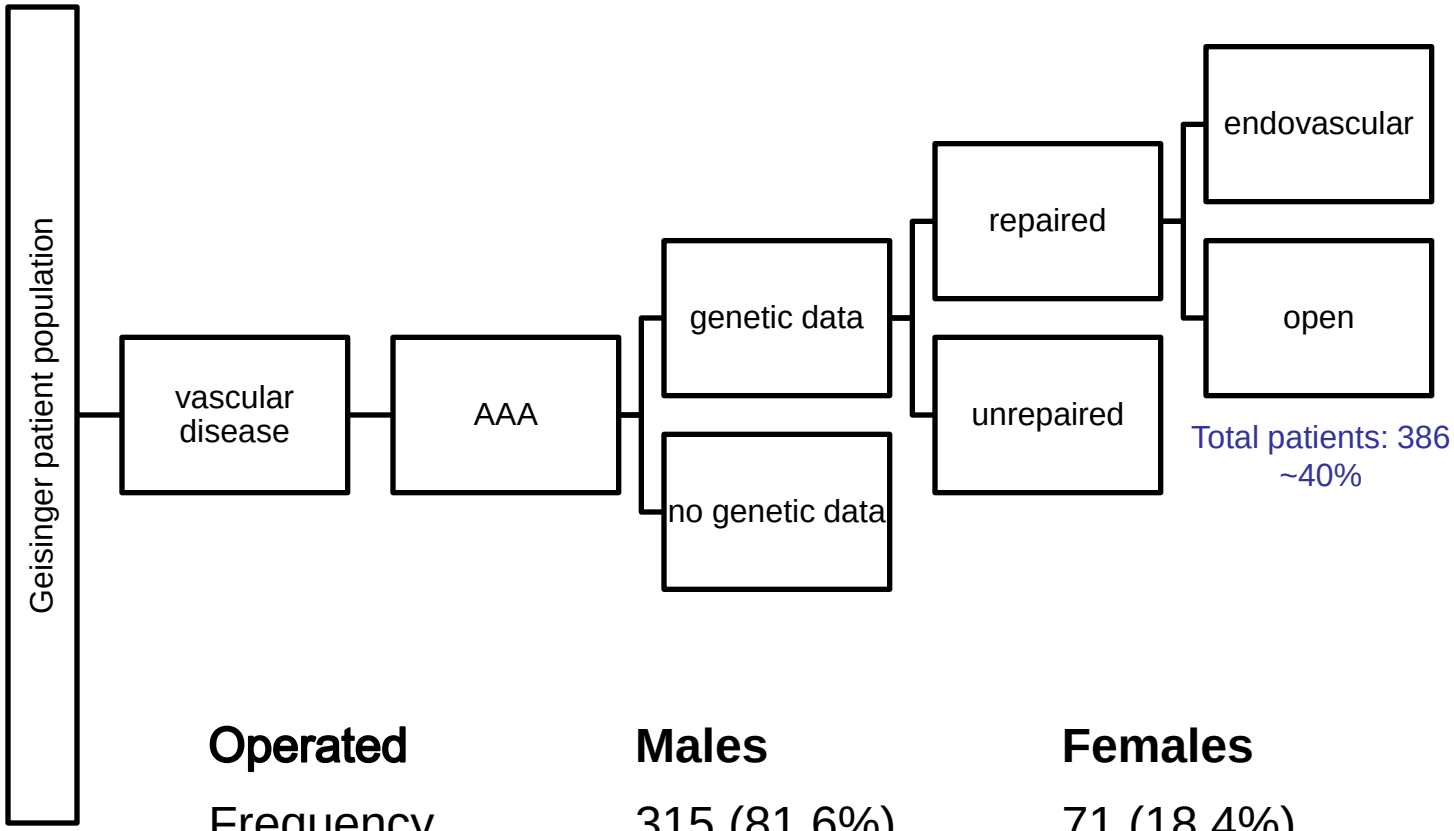
Source	cases	controls
Geisinger	724	1,231
Other sites	393	26,109

Replication

Source	cases	controls
Geisinger	100	2,000
Other sites	1,236	9,600

*all imputed to Oct 2011 1000 Genomes

Risk Model of AAA Repair Complications



Operated	Males	Females
Frequency	315 (81.6%)	71 (18.4%)
Average Age	72.8 years	73.0 years

Adverse Outcomes Following AAA Repair

- Myocardial Infarction
- Stroke
- Renal Failure
- Respiratory Failure

- Death for any reason within 0-30 days
- Death for any reason within 31-365 days

Patients with complete data = 318

Yes	47	14.8%
No	271	85.2%

Univariate Analysis for Categorical Variables

Variable	No. of patients	P Value	Odds Ratio	95% Confidence
Sex (Female)	71 (18.4)	0.76	1.12	0.53 - 2.37
Nitrate	205 (53.2)	0.30	1.37	0.75 - 2.51
Statin	155 (40.3)	0.07	1.73	0.95-3.14
Antihypertension Med	240 (62.3)	0.57	1.2	0.64-2.24
Antiplatelet Med	169 (43.9)	0.35	1.33	0.73-2.40
Ischemic Heart Disease	148 (38.4)	0.01	2.28	1.25-4.16
Congestive Heart Failure	76 (19.4)	0.23	1.52	0.76-3.02
COPD	99 (25.7)	0.03	1.95	1.05-3.64
Diabetes Mellitus	78 (20.6)	<.0001	2.58	1.36-4.90
Hypertension	247 (64.1)	0.12	1.69	0.87-3.31
Stroke	54 (14.0)	<.0001	13.4	6.78-26.4
Pacemaker	12 (3.12)	0.05	3.55	1.03-12.3
Kidney Disease	51 (13.2)	0.05	2.08	0.99-4.39
Operation Type (EVAR)	225 (58.4)	0.25	1.45	0.78- 2.70

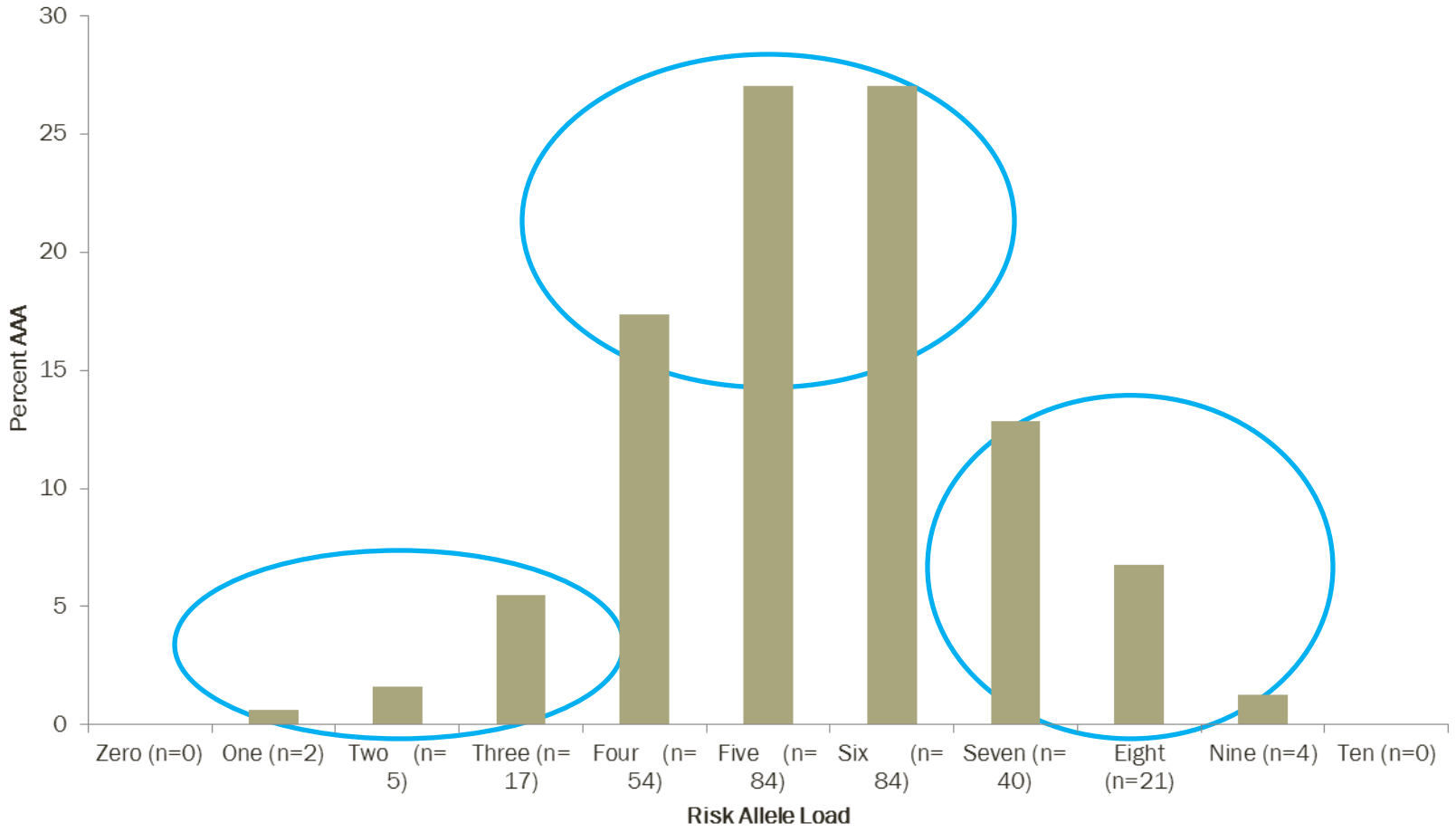
Univariate Analysis for Continuous Variables

Variable	P Value	Odds Ratio	95% Confidence
Age	0.17	1.03	0.99-1.07
Creatinine Level	0.02	1.75	1.09- 2.82
BUN Value	0.38	1.01	0.98- 1.04
Serum Sodium	0.73	0.98	0.89- 1.09
Serum Potassium	0.5	0.82	0.46-1.46
Hemoglobin	0.8	1.02	0.85- 1.22
White Blood Cell Count	0.2	0.94	0.87-1.03
BMI	0.02	1.06	1.01- 1.12
Systolic Blood Pressure	0.03	0.98	0.97- 0.99
Diastolic Blood Pressure	0.01	0.97	0.94- 0.99
Heart Rate	0.86	1.00	0.98-1.02
Respiration	0.02	1.13	1.02- 1.26

Genetic Risk Factors

Gene Symbol	SNP rs#	Location	OR (95% CI)	P	Risk Allele
DAB2IP	rs7025486	9q33	1.21 (1.14-1.28)	4.6×10^{-10}	A
CDKN2BAS	rs10757278	9p21	1.31 (1.22-1.42)	1.2×10^{-12}	G
LRP1	rs1466535	12q13	1.15 (1.10-1.21)	4.5×10^{-10}	C
CNTN3	rs7635818	3p12.3	1.33 (1.10-1.21)	0.0028	C
KCNK2	rs12039875	1q41	1.18 (1.05-1.34)	0.0072	C

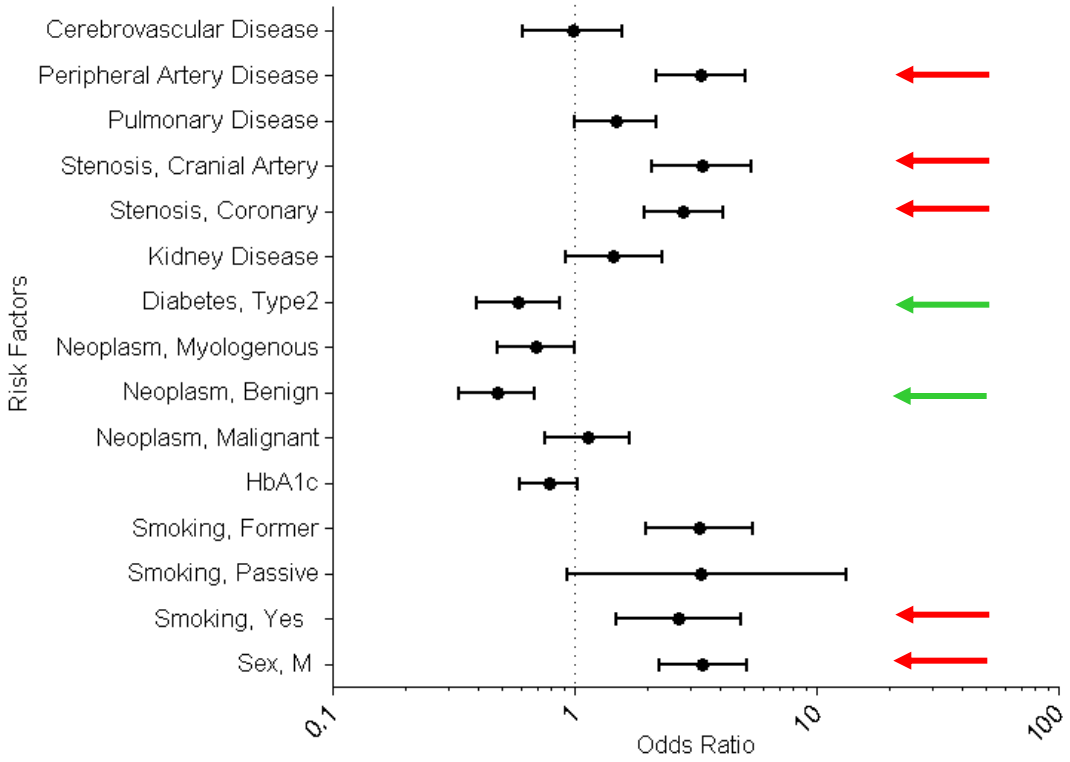
Risk Allele Frequency Distribution



Final Model

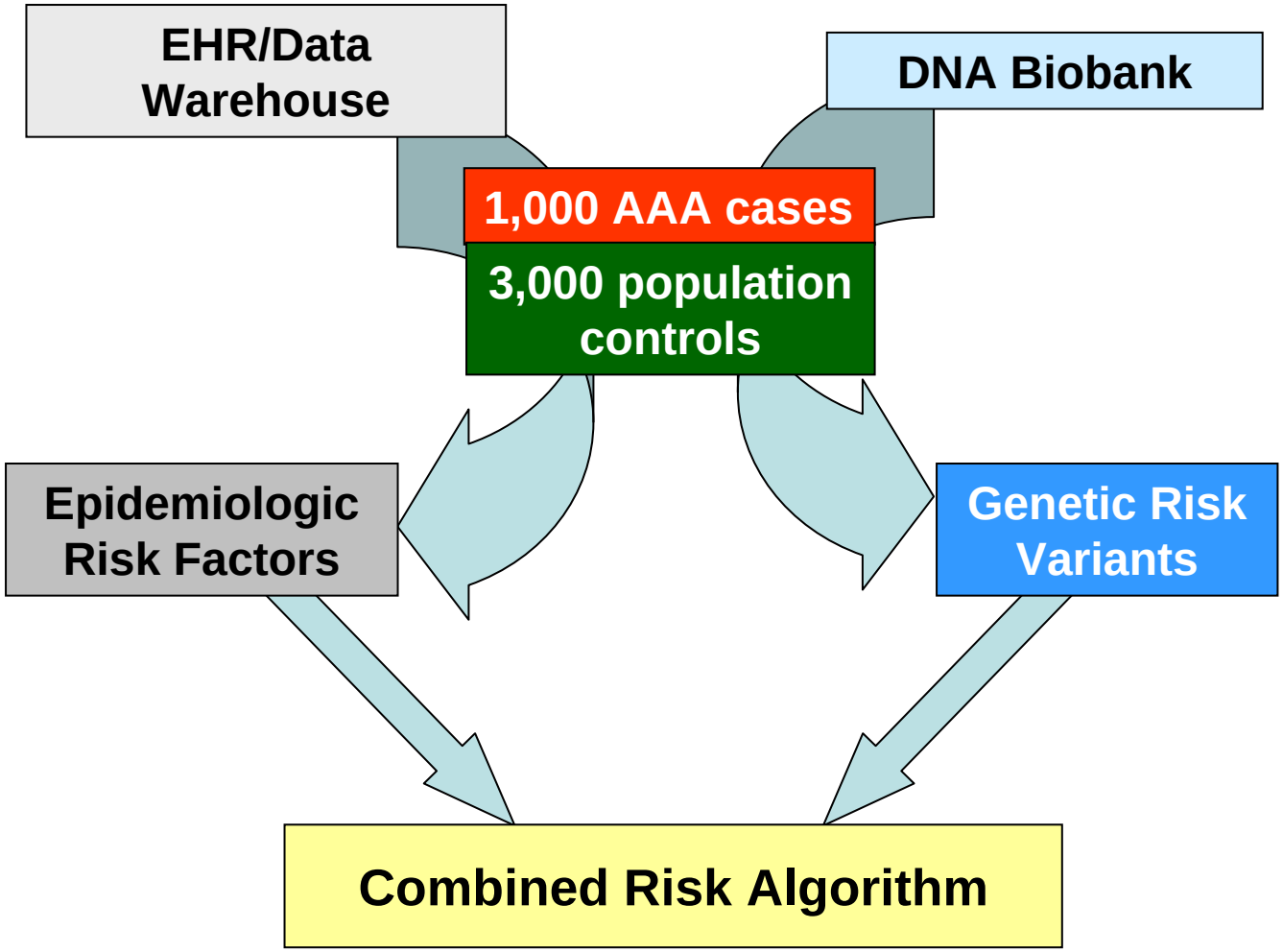
Parameter	Coefficient (β)	Odds Ratio	P Value
Sex	0.513	2.79 (1.03-7.55)	0.043
Diabetes Mellitus	0.410	2.27 (0.91-5.69)	0.081
Creatinine Value	0.618	1.86 (0.91-3.80)	0.092
Respirations	0.214	1.24 (1.07-1.44)	0.005
Genetic Risk	0.868	2.38 (1.27-4.48)	0.007
Intercept (α)	-7.957		

Risk Factors for Abdominal Aortic Aneurysm Determined by Analysis of Geisinger EMR Data

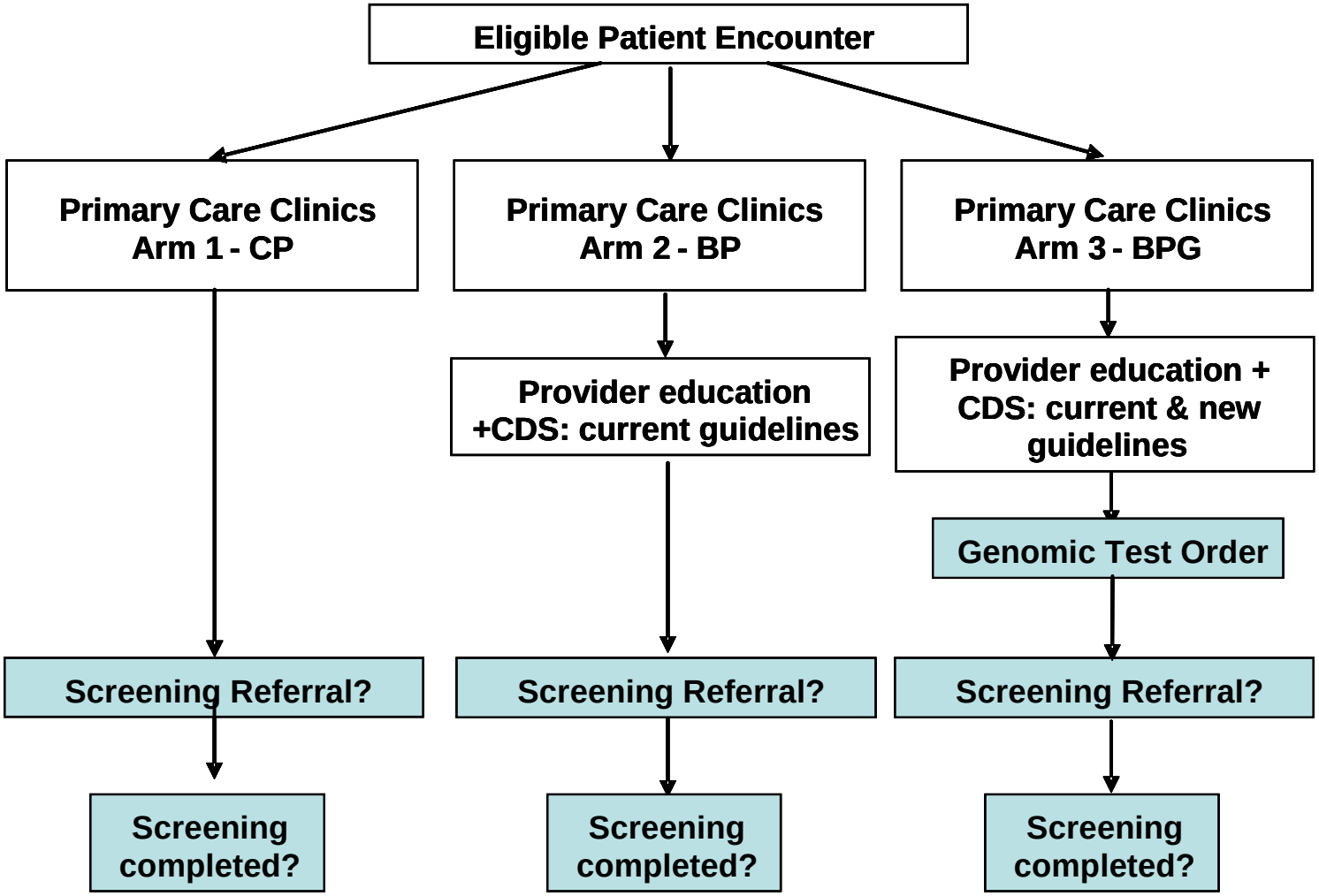


Logistic regression analysis based on ~1,000 AAA cases and ~15,000 MyCode controls

Predictive Disease Risk Modeling with EMR and Genomic Data



Implementation of a Genomically-Informed Risk Tool for AAA Screening in Outpatient Clinics



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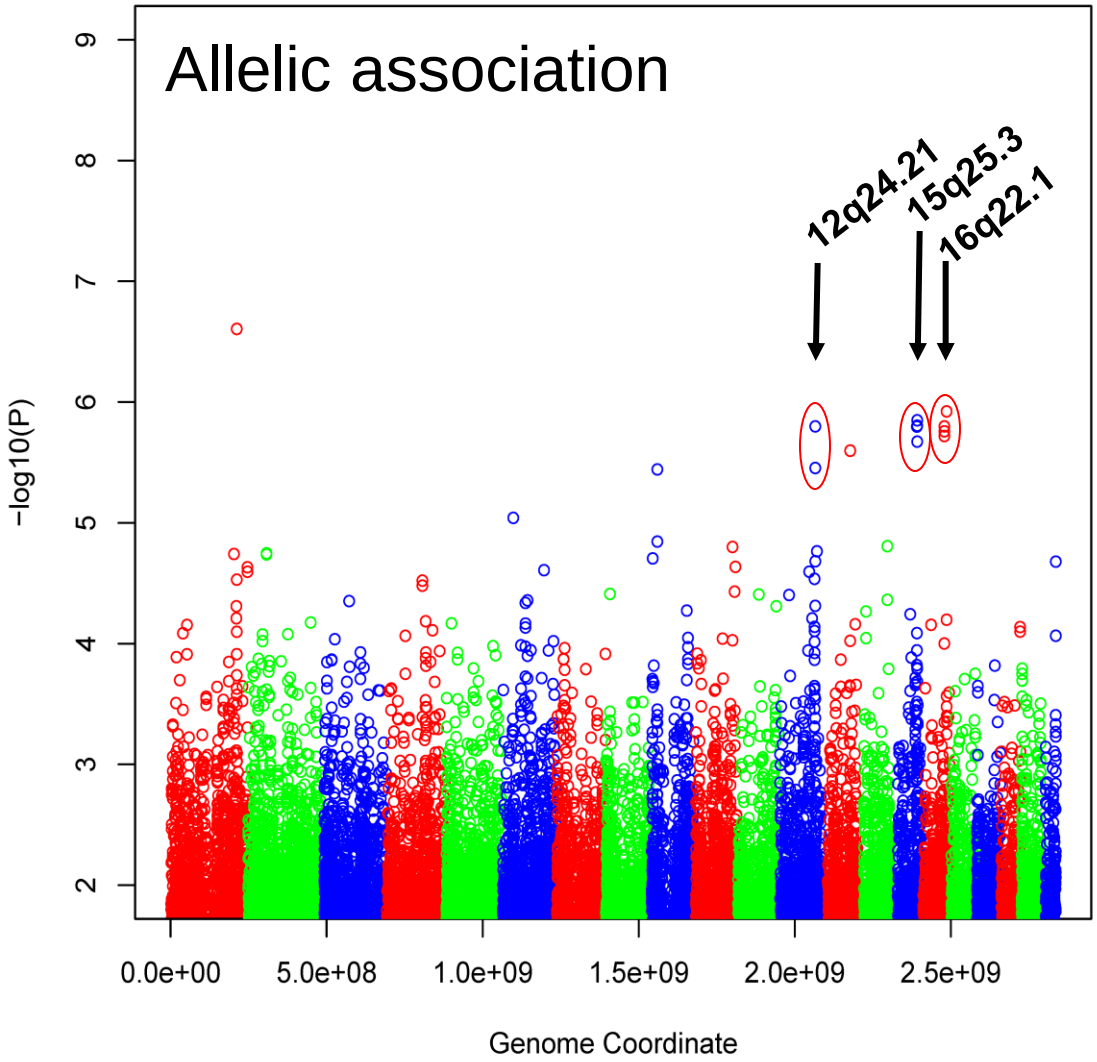
"Utility of Genomic Data to Guide Population Screening for Abdominal Aortic Aneurysms"

1. Create a novel AAA risk scoring tool that combines genetic variant and epidemiological data, using genotype and EMR-generated data from 1,000 AAA cases and 3,000 controls.

2. Prospectively validate the genomically-informed risk model in an outpatient population.

3. Develop and evaluate a clinical implementation plan for utilization of genomic data in Geisinger outpatient clinics.

AAA Genome Wide Association Study



logistic regression to control for age, sex, BMI, PAD and pulse pressure

Variables for Operative Outcomes

PRE-OP VARIABLES	LAB WORK	PAST MEDICAL HISTORY	MEDICATIONS	9p21 SNP
age	albumin	chronic renal disease	nitrates	AA
sex	aPTT	chronic respiratory disease	statins	AG
height	blood urea nitrogen	congestive heart failure	***ANTI-PLATELET***	GG
weight	creatinine	diabetes mellitus	aspirin	
BMI	hemoglobin	hypertension	Plavix	
heart rate	potassium	pacemaker	warfarin	
respiratory rate	PT/INR	peripheral vascular disease	***ANTI-HYPERTENSIVE***	
systolic BP	sodium	stroke	ACE inhibitors	
diastolic BP	white blood cell count	tobacco use	beta blockers	
ASA class		***ISCHEMIC HEART DISEASE***	calcium channel blockers	
emergent surgery		angina	diuretics	
repair year		angioplasty		
		artery bypass		
		coronary artery disease		
		heart attack		

Significant Variables for Operative Outcomes

Sex (female)	0.1082	1.242 (0.545, 2.831)	0.6068
BMI	0.0605	1.062 (1.005, 1.123)	0.0316
Creatinine	0.5735	1.774 (1.060, 2.970)	0.0291
Diastolic Blood Pressure	-0.0349	0.966 (0.939, 0.993)	0.0133
Respirations	0.1389	1.149 (1.029, 1.283)	0.0139
9p21 (rs10757278) AA genotype	-0.5864	0.490 (0.162, 1.481)	0.0713
9p21 (rs10757278) AG genotype	0.4592	1.394 (0.628, 3.093)	0.0496
Intercept (α)	-4.5253		

$$Risk\ of\ Adverse\ Outcome = e\uparrow(\alpha + [\beta\downarrow 1 \times sex] + [\beta\downarrow 2 \times BMI] + \ldots)$$