Advances in Lipoprotein(a) Physiology and *LPA* Gene Variants

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FAMILY HEART GLOBAL SUMMIT 2023

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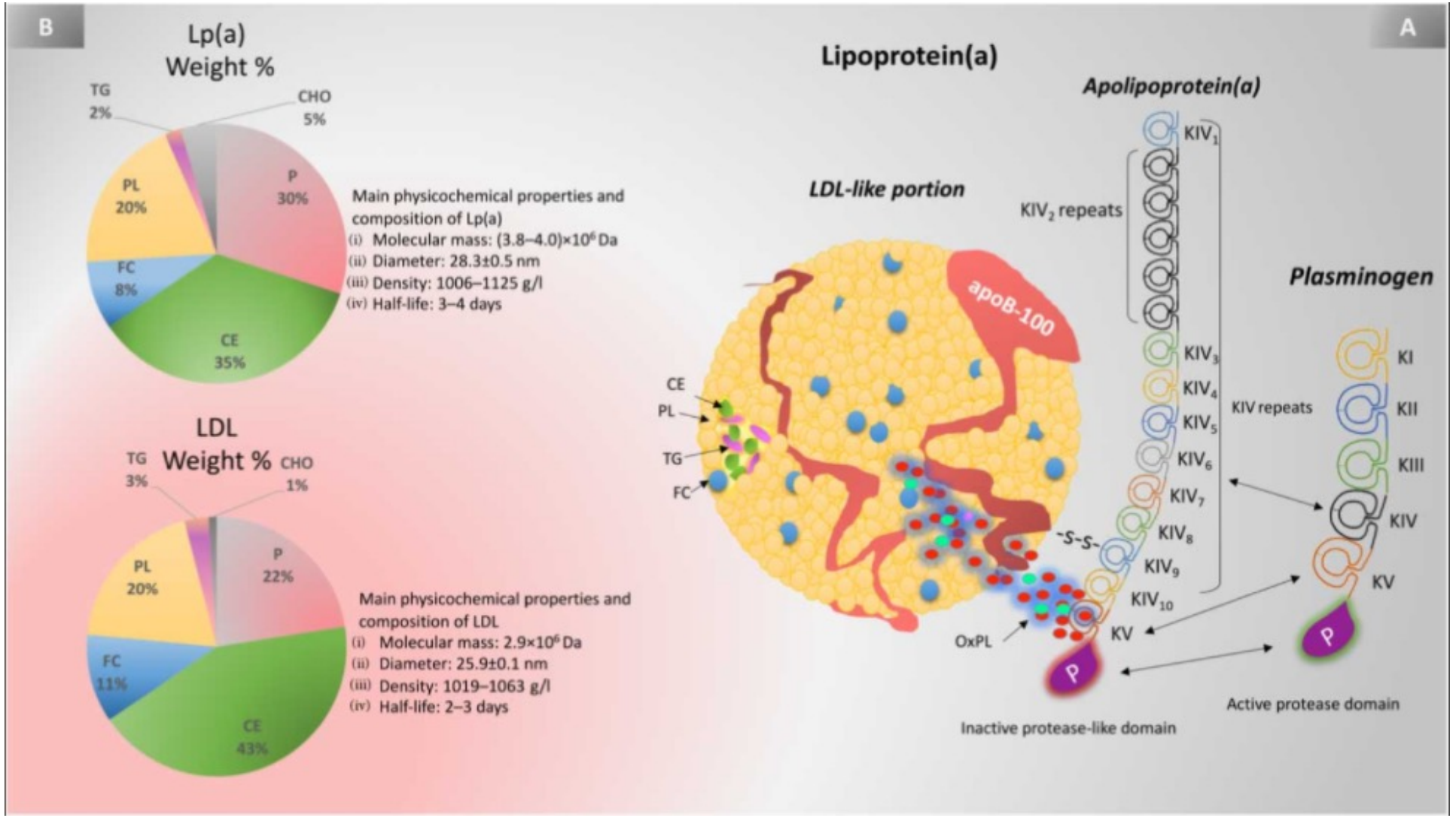
Lipoprotein(a)



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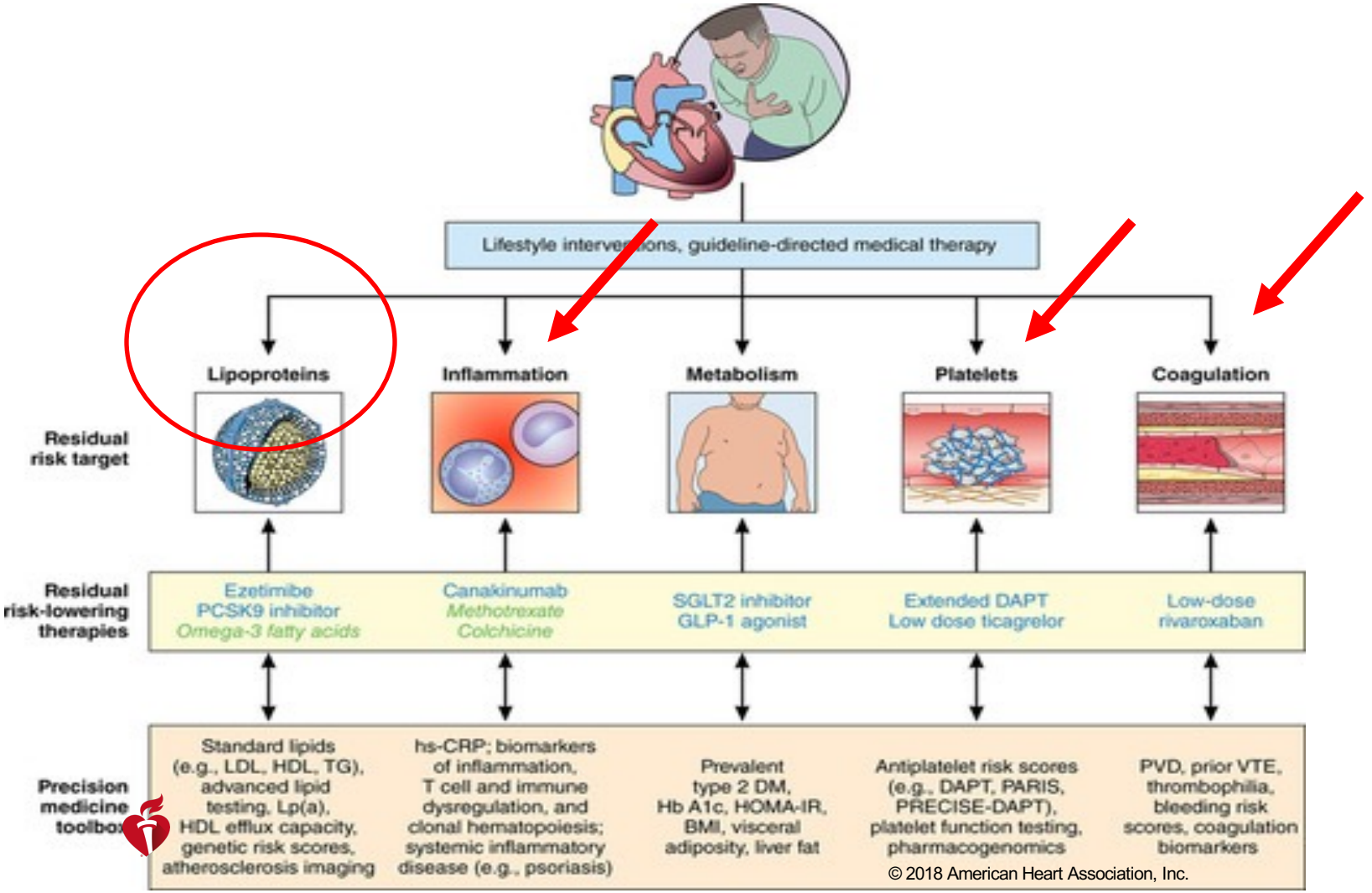
Jawi MM et al. https://www.hindawi.com/journals/jl/2020/3491764/

Why study Lp(a): Cardiovascular Residual Risk



Kershaw V. Patel. Circulation. Conceptual Framework for Addressing Residual Atherosclerotic Cardiovascular Disease Risk in the Era of Precision Medicine, Volume: 137, Issue: 24, Pages: 2551-2553, DOI: (10.1161/CIRCULATIONAHA.118.035289)

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A Heart Risk Factor Even Doctors Know Little About

Lp(a) Foundation (dissolved 2019)
(Sandra T.) Diagnosis/Billing Codes

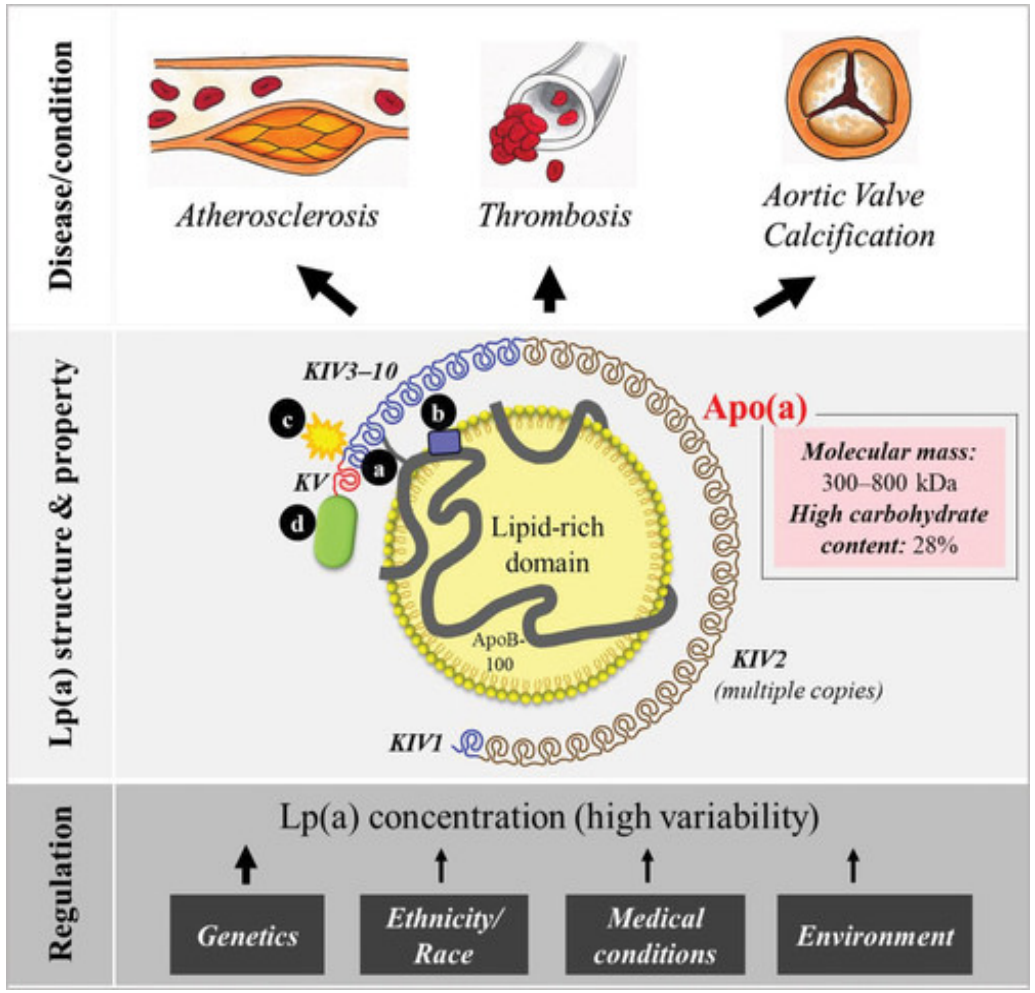
E78. 41 Elevated Lipoprotein(a)
Z83. 430 Family history of elevated Lipoprotein(a)

FH Foundation (NEW FAMILY HEART)
Lp(a) STARTS FOCUS 2020
https://thefhfoundation.org/lpa-and-familial-hypercholesterolemia

By Anahad O'Connor
Jan. 9, 2018 NY TIMES

Bob Harper, the celebrity fitness trainer from the TV show "The Biggest Loser," suffered a heart attack… He eventually found out the cause was a particle in the blood called lipoprotein(a), which few doctors test for.
Hilary Swift for The New York Times

AHA Scientific Statement on Lipoprotein(a)



Marlys L. Koschinsky, PhD (Co-Chair)
Henry N. Ginsberg, MD
Lars Berglund MD, PhD
P. Barton Duell, MD,
Donald M. Lloyd-Jones, MD, ScM
Santica M. Marcovina, PhD,

Pia R. Kamstrup, MD, PhD
Sean P. Heffron, MD, MS MSc
Calvin Yeang, MD, PhD

Gissette Reyes-Soffer. Arteriosclerosis, Thrombosis, and Vascular Biology. Lipoprotein(a): A Genetically Determined, Causal, and Prevalent Risk Factor for Atherosclerotic Cardiovascular Disease: A Scientific Statement From the American Heart Association, Volume: 42, Issue: 1, Pages: e48-e60, DOI: (10.1161/ATV.0000000000000147)

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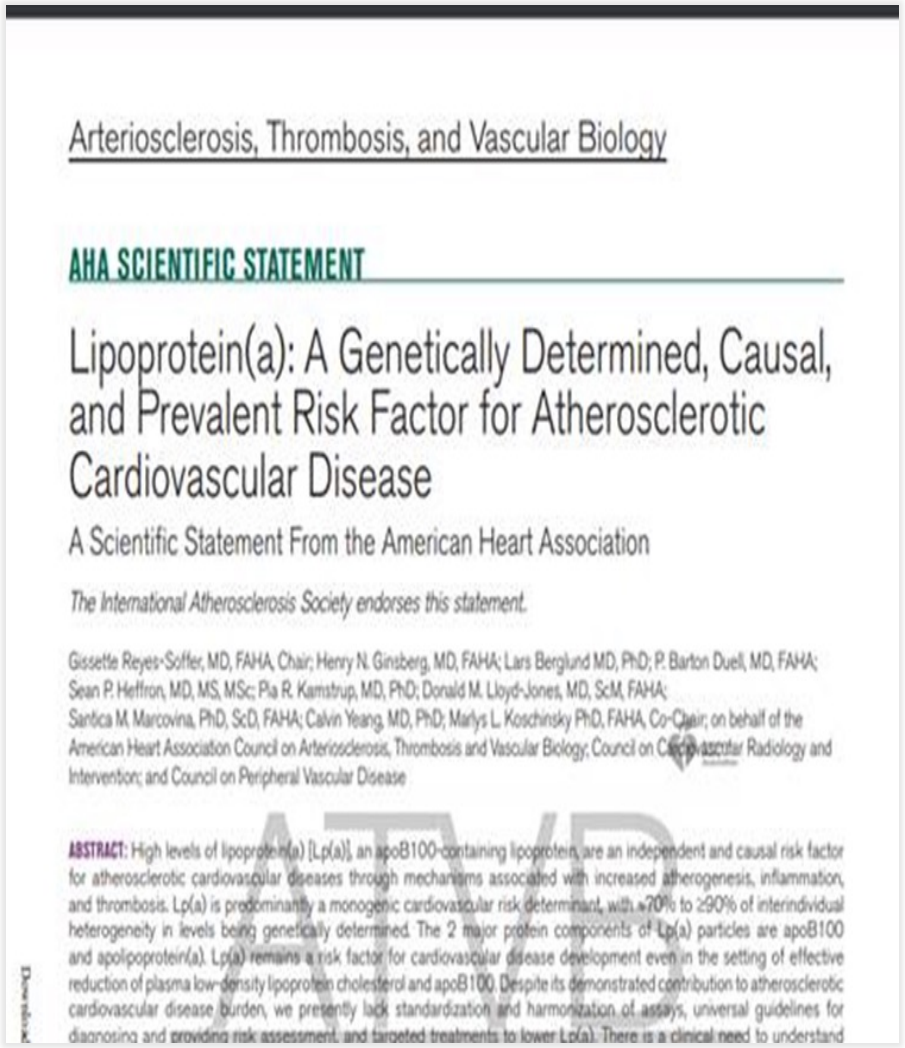
AHA Scientific Statement on Lipoprotein(a)



Arteriosclerosis, Thrombosis, and Vascular Biology

AHA SCIENTIFIC STATEMENT

Lipoprotein(a): A Genetically Determined, Causal, and Prevalent Risk Factor for Atherosclerotic Cardiovascular Disease

A Scientific Statement From the American Heart Association

The International Atherosclerosis Society endorses this statement.

Gissette Reyes-Soffer, MD, FAHA, Chair; Henry N. Ginsberg, MD, FAHA; Lars Berglund MD, PhD; P. Barton Duell, MD, FAHA; Sean P. Heffron, MD, MS, MSc; Pia R. Kamstrup, MD, PhD; Donald M. Lloyd-Jones, MD, ScM, FAHA; Santica M. Marcovina, PhD, ScD, FAHA; Calvin Yeang, MD, PhD; Marlys L. Koschinsky PhD, FAHA, Co-Chair; on behalf of the American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology and Intervention; and Council on Peripheral Vascular Disease

ABSTRACT: High levels of lipoprotein(a) [Lp(a)], an apoB100-containing lipoprotein, are an independent and causal risk factor for atherosclerotic cardiovascular diseases through mechanisms associated with increased atherogenesis, inflammation, and thrombosis. Lp(a) is predominantly a monogenic cardiovascular risk determinant, with ≈70% to ≥90% of interindividual heterogeneity in levels being genetically determined. The 2 major protein components of Lp(a) particles are apoB100 and apolipoprotein(a). Lp(a) remains a risk factor for cardiovascular disease development even in the setting of effective reduction of plasma low-density lipoprotein cholesterol and apoB100. Despite its demonstrated contribution to atherosclerotic cardiovascular disease burden, we presently lack standardization and harmonization of assays, universal guidelines for diagnosing and providing risk assessment, and targeted treatments to lower Lp(a). There is a clinical need to understand

Clinical Considerations:

1. You can measure it! If it is high, you can provide guidance to patient and family members.

2. You should measure apoB100

3. LOWER ALL OTHER RISK and apoB100

Needs in the field: Research Areas

1. **Race/ethnicity**
2. **Genetics**
3. **Disease Presentation**
4. **Conclusive Mechanisms**

Marianna Pavlyha, MD-PGY4 UCLA Vascular Surgery
NIH T32 Scholar CUIMC and Yihao Li (Data Science)

Are we measuring Lp(a)?

SRRE and Socioeconomic Determinants in Lp(a) Screening

Hispanics, Blacks, Multi-Racial and Asians significantly less likely to get tested, while Whites more likely

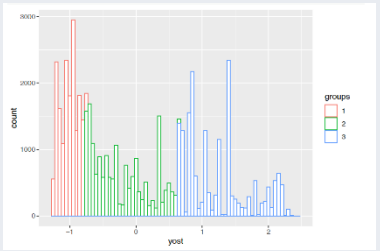
SRRE

SRRE	Estimate	P-value
Black	-1.76	<0.001***
Hispanic	-1.15	<0.001***
Multi-Racial	-4.18	<0.001***
Asian	-2.08	<0.001***
White	0.90	<0.001***

Lp(a) Measurement at CUICM
02/2020-09/2022

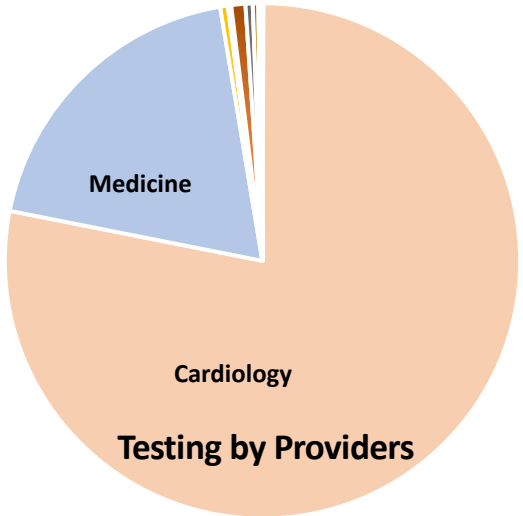
0.3% tested in general population
73% of patients compliant with test

Socioeconomic score (SES)



low SES more likely to get Lp(a) ordered than high SES

N=52,436, 4% tested for Lp(a)



Testing by Providers

Diagnosis

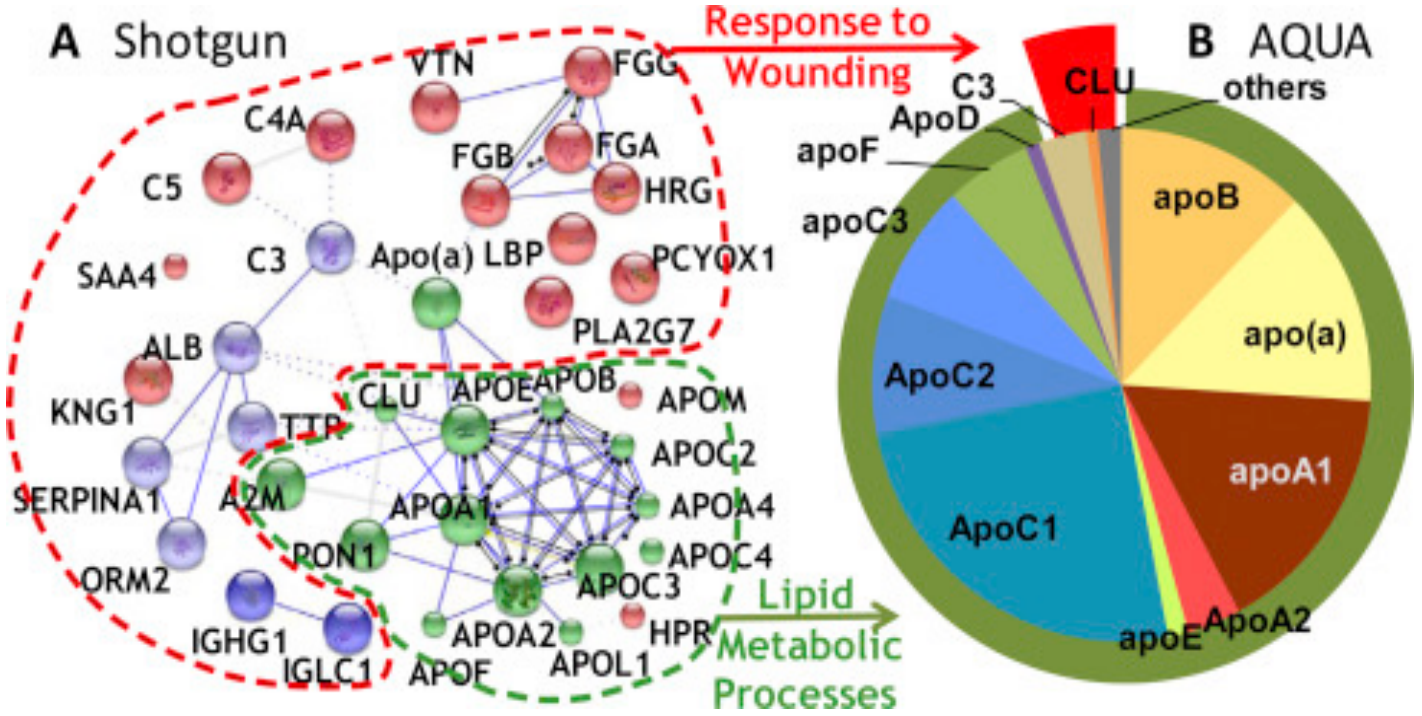
More likely to be tested

- Coronary Artery Disease
- Carotid Artery Disease
- PAD
- High LDL on statin
- FH
- Stroke
- MI

Insurance

Private vs Medicaid/Medicare

Lp(a) Particles are Mostly Involved in Lipid Metabolic Pathways



"5% of the total number of proteins molecules contributes to "response to wounding" whereas the majority of 95% of protein molecules per particle are involved in "lipid metabolic processes".

Can we use *LPA* Genetics and Link to Metabolism?

Washington Heights-Hamilton Heights-Inwood Community Aging Project

- WHICAP – community-based study
- Age 65 and older
- Seen in home at 18 – 24 month intervals
- Dx based on neuropsychological test battery, medical & functional interview
- Study cohort extended to large families from Dominican Republic and Puerto Rico
  - 6000 samples with longitudinal follow-up
  - Multi-ethnic cohort (50% Hispanics, 20% Caucasians and 30% African Americans)

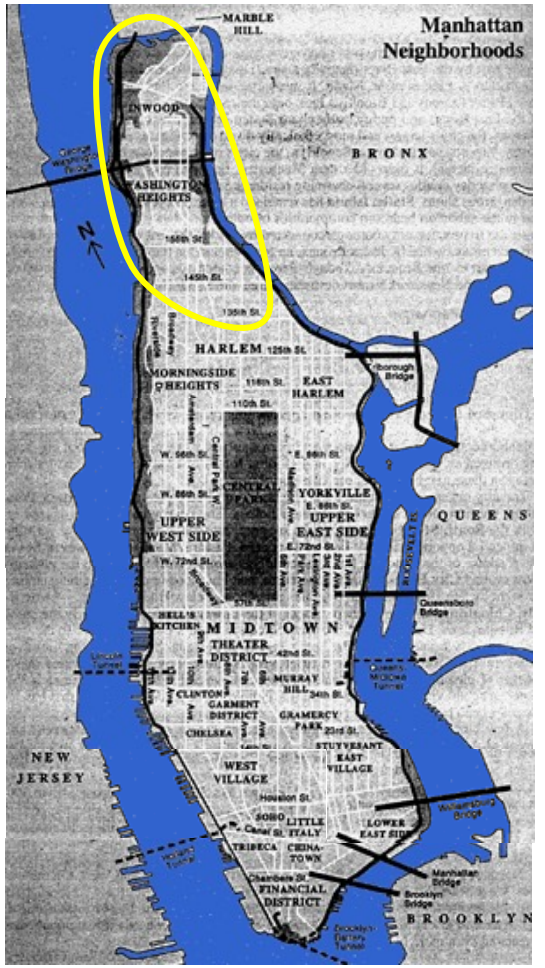
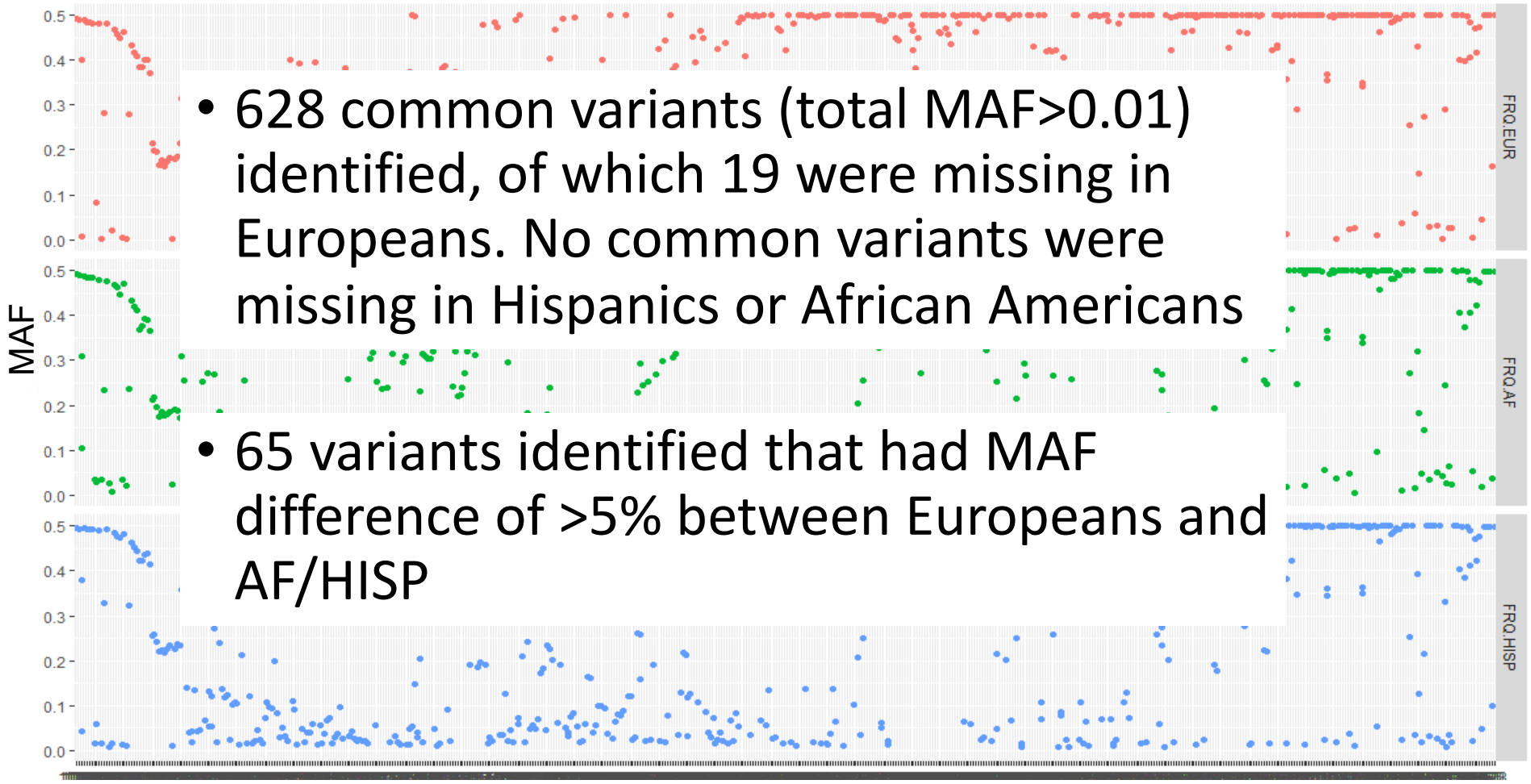


Image courtesy: Dr. Jennifer Manly

Badri N. Vardarajan, PhD, MS

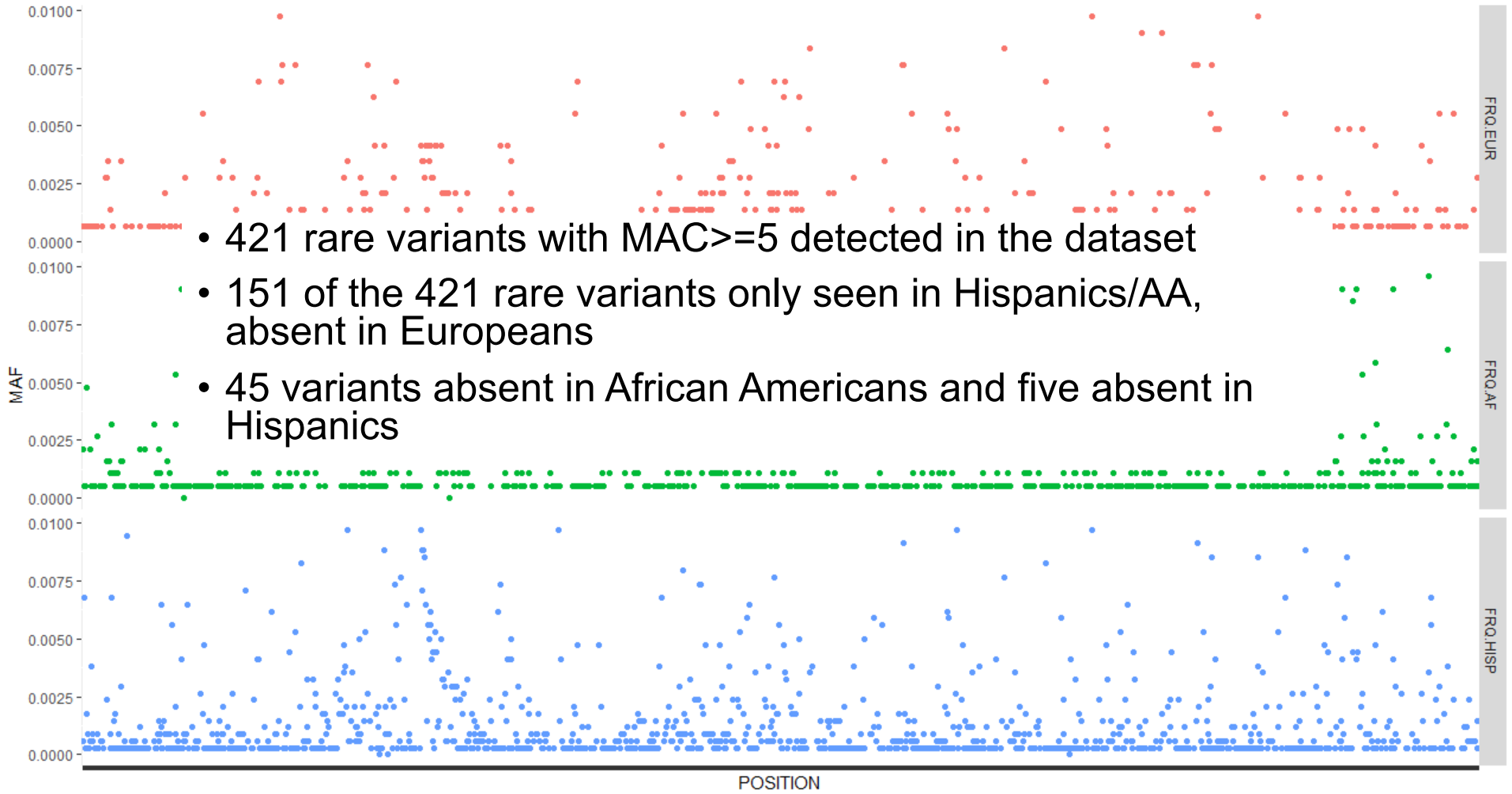
Common Variation in *LPA* KIV2 Repeat by Ethnicity



- 628 common variants (total MAF>0.01) identified, of which 19 were missing in Europeans. No common variants were missing in Hispanics or African Americans
- 65 variants identified that had MAF difference of >5% between Europeans and AF/HISP

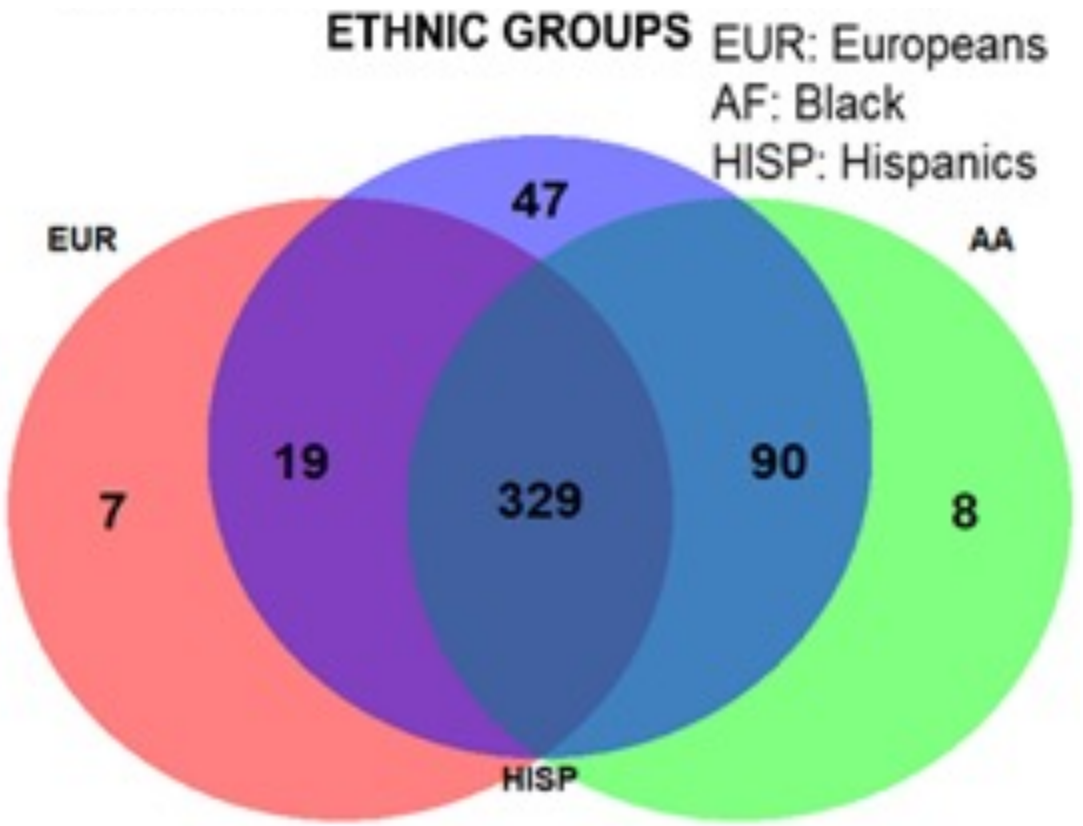
MAF: Minor Allele Frequency
EUR: Europeans
AF: Black
HISP: Hispanics

Rare Variations in *LPA* KIV2 Repeats By Ethicity



- 421 rare variants with MAC>=5 detected in the dataset
- 151 of the 421 rare variants only seen in Hispanics/AA, absent in Europeans
- 45 variants absent in African Americans and five absent in Hispanics

MAF: Minor Allele Frequency
EUR: Europeans
AF: Black
HISP: Hispanics



Overlap of All Varian
Groups

Association of *LPA* variants by Phenotype

- Tested association of variants with lipid levels, Dementia, history heart disease and Stroke
- Tested association independently in each ethnic group adjusting for age, sex and population substructure variables (PCs).
- Meta-analyzed results and included only variants observed in all three ethnic groups

Association of *LPA* variants by Phenotype

AAMarkerName	Allele1	Allele2	Effect	StdErr	P.value	Direction EUR/AA/HISP	TRAIT	NOVEL VARIANT*
4564-G/A	a	g	2.08	0.35	2.73E-09	+++	HISTORY OF HEART DISEASE	YES
5069-C/T	t	c	-36.75	6.43	1.07E-08	---	CHOLESTEROL	YES
1001-A/G	a	g	-1.68	0.30	1.47E-08	---	HISTORY OF HEART DISEASE	YES
602-G/T	t	g	2.32	0.43	5.47E-08	?++	HISTORY OF HEART DISEASE	YES
595-A/G	a	g	26.36	4.91	7.69E-08	+++	CHOLESTEROL	YES
4574-G/C	c	g	1.60	0.31	2.19E-07	+++	HISTORY OF HEART DISEASE	YES
717-G/A	a	g	2.12	0.42	3.52E-07	?++	HISTORY OF HEART DISEASE	YES
595-A/G	a	g	22.49	4.65	1.32E-06	+++	LDL	YES
943-T/G	t	g	31.33	6.49	1.39E-06	+++	CHOLESTEROL	YES
672-A/C	a	c	57.71	11.96	1.40E-06	?+?	CHOLESTEROL	YES
5092-G/T	t	g	-30.89	6.52	2.18E-06	---	CHOLESTEROL	YES

Goal:

1. Predicting Lp(a) levels (using genetic SNPs) that include Blacks and Caribbean Hispanics, historically understudied populations at increased risk for development of ASCVD and worse clinical
2. Understanding the effects of SNPS linked to Cardiovascular Disease on Lp(a) components and the production and clearance from the liver.

Collaborators and Funding

THANK YOU

- **Research Participants**
- **Lab Members (Current)**
  - Lab Tech: Nelsa Matienzo (BA)
  - Staff Scientist Anastasiya Matveyenko (BA, MS, MS)
  - T32-Post-Doc Marianna Pavlyha, MD (UCLA vascular surgery PGY-4)
  - Nurse Practitioner: Lau Y. Yung, NP (Cindy)
  - Modeling/Statistics Team: Tiffany Thomas PhD/Rajasekhar Ramakrishnan ScD
  - Data Scientist * Casual Yihao Li, BS-MS
- **CUIMC Collaborators**
  - **Henry Ginsberg Laboratory** **Neurology:** Badri Vardajeran, Jose Gutierrez
  - **IICTR CUIMC (CTSA)** **Cardiology:** Muredach Reilly, Hanrui Zhang
    - Renu Nandakumar (Mass Spec Core Director)
    - Heather Seid (Bionutrition Unit Director)
- **Other Institutions**
  - Marit Westertep- Netherlands
  - John Millar- UPENN: GCMS
  - Santica Marcovina- Medpace
  - Braxton Mitchell/Toni Pollin -University of Maryland
  - Ronald Krauss- Children's Hospital Oakland Research Institute
  - Masanori Aikawa, Sasha Singh, Brigham Women's Health
  - Calvin Yeang, Sam Tsimikas, University of California San Diego

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NIH National Heart, Lung, and Blood Institute

CUIMC NIH/NCATS– Irving Scholar Award

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American Heart Association.

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Amgen, Inc.
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