

HEART DISEASE IS PREVENTABLE

Presented by:

ROBERT ROBERTS, MD

*Cardiologist and Medical Director of Cardiovascular
Genetics and Genomics program at Dignity Health's Heart
and Vascular Institute*



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Genetics will Revolutionize Primary Prevention of Coronary Artery Disease (CAD) in Males and Females

Robert Roberts, MD, FRCPC, MACC, FAHA, FRSC, FESC, LL.D

Executive Director of Heart and Vascular Institute
Director of Cardiovascular Genomics and Genetics
St. Joseph's Hospital and Medical Center

Healthy Arizona Worksites Program
February 18, 2021



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Coronary Heart Disease is the Number One Killer in the World

**Coronary Artery Disease is pandemic,
being the number one cause of death
throughout the world.**

Mozaffarian D et al; on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics - 2015 update: a report from the American Heart Association [published correction appears in Circulation. 2015;131:e535]. Circulation. 2015;131:e29-e322. doi: 10.1161/CIR.000000000000152.

Coronary Heart Disease is Pandemic, Being the Number One Cause of Death in the World

One-third of all females and males in the world die of heart disease.



Mozaffarian D et al; on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics - 2015 update: a report from the American Heart Association [published correction appears in Circulation. 2015;131:e535]. Circulation. 2015;131:e29-e322. doi: 10.1161/CIR.000000000000152.

Premenopausal Primary Prevention of CAD

A premenopausal, asymptomatic 40 yr. old female on routine checkup has **LDL-C of 180 mg/dl (4.0 mm/l)** with no other risk factors.



Estimated 10-year Risk for CAD

The guidelines of **AHA and ACC**, using the **Pooled Cohort Equation (PCE)**, estimate the **10-year risk for this female is 2.1%**. The recommendation would be no preventative treatment is required.

Primary Prevention of CAD

Why not treat everyone with an increased plasma LDL-Cholesterol?



Plasma LDL-C in the General Population

The mean plasma LDL-C:

- **Females in their 40s** **121 mg/dl**
- **Males in their 40s** **146 mg/dl**

The guidelines recommend a plasma LDL-C of $\leq 70\text{mg/dl}$

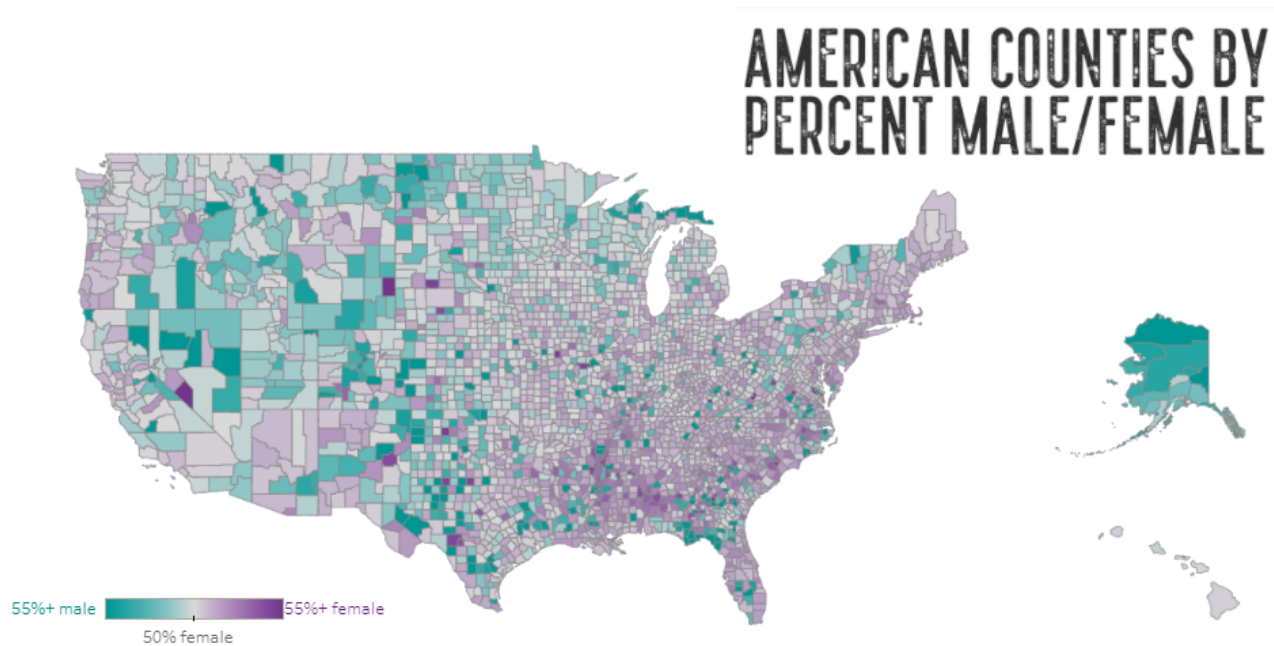
Kones R, Rumana U. Current treatment of dyslipidemia: a new paradigm for statin drug use and the need for additional therapies. *Drugs* 2015;75(11):1187–99.

Fujita H, Okada T, Inami I, Makimoto M, Hosono S, Minato M, et al. Low– density lipoprotein profile changes during the neonatal period. *J Perinatol* 2008;28(5):335–40.

Pac-Kozuchowska E. Evaluation of lipids, lipoproteins and apolipoproteins concentrations in cord blood serum of newborns from rural and urban environments. *Ann Agric Environ Med* 2007;14(1):25–9.

Primary Prevention of CAD

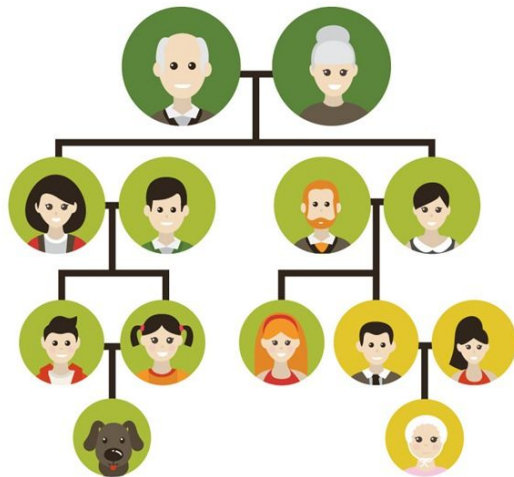
A female or male living a normal lifespan in the US has a **50% chance of experiencing at least one cardiac event.**



Murray CJ, Lopez AD. Measuring the global burden of disease. N Engl J Med 2013;369(5):448–57.

Source: <https://public.tableau.com/profile/bo.mccready8742?fbclid=IwAR3gP413-RWYI1veBp47A0B69GVc1dtf68Z211mUbx62YInhLN6fERLYJ30#!/vizhome/AmericanCountiesbyPercentMaleFemale/Dashboard1>

Traditional Risk Factors Predisposing to CAD



Hypertension

Age

Diabetes

Smoking

Lack of Exercise

Obesity

Cholesterol

Family History



BLOOD PRESSURE



Murray CJ, Lopez AD. Measuring the global burden of disease. N Engl J Med 2013;369(5):448–57.

Genetics: Predominant Risk Factor for Coronary Artery Disease

Epidemiologists have claimed for decades that 40% to 60% of risk for CAD is due to genetics.



A Common Allele on Chromosome 9 Associated with Coronary Heart Disease

**Ruth McPherson, Alexander Pertsemlidis,
Nihan Kavaslar, Alexandre Stewart,
Robert Roberts, David R. Cox, David A.
Hinds, Len A. Pennacchio, Anne Tybjaerg-
Hansen, Aaron R. Folsom, Eric Boerwinkle,
Helen H Hobbs, Jonathan C Cohen**

Science 2007:316(5830);1488 - 1491

A Common Variant On Chromosome 9p21 Affects the Risk of Myocardial Infarction.

Helgadottir A1, Thorleifsson G, Manolescu A, Gretarsdottir S, Blondal T, Jonasdottir A, Jonasdottir A, Sigurdsson A, Baker A, Palsson A, Masson G, Gudbjartsson DF, Magnusson KP, Andersen K, Levey AI, Backman VM, Matthiasdottir S, Jonsdottir T, Palsson S, Einarsdottir H, Gunnarsdottir S, Gylfason A, Vaccarino V, Hooper WC, Reilly MP, Granger CB, Austin H, Rader DJ, Shah SH, Quyyumi AA, Gulcher JR, Thorgeirsson G, Thorsteinsdottir U, Kong A, Stefansson K.

Science 2007;316(5830);1491 - 1493

9p21: First Genetic Risk Factor for CAD 2007



9p21 genetic risk variant is extremely common with one or two copies occurring in **75%** of the population

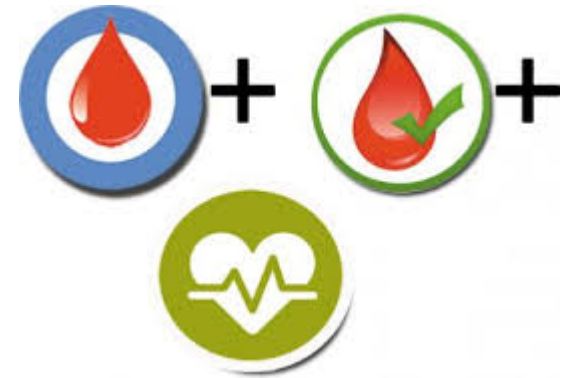
9p21 risk allele is estimated to be present in **4.5 billion people**

Homozygotes carry increased risk of **50% for CAD**
Heterozygotes carry increased risk of **25% for CAD**

McPherson R, et al. Science 2007;316(5830);1488 – 1491
Helgadottir A, et al. Science 2007;316(5846);1491-3

9p21: The First Genetic Risk Factor for CAD

**9p21 risk is independent
of known risk factors for
CAD, namely: cholesterol,
hypertension or diabetes**



Science 2007;316(5830);1488 – 1491

Helgadottir A, et al. Science 2007;316(5846);1491-3

9p21 Risk Variant for CAD Confirmed in Seven Independent Studies Involving over 60,000 Caucasians

Sample Size

Reference

23,000

McPherson R, et al. Science 2007;316;1488-1491

17,356

Helgadottir A, et al. Science 2007;316(5846);1491-3

5,000

Wellcome Trust Case Control Consortium, Nat Genet 2007;39(11);1329-37

4,864

Samani NJ, et al. N Engl J Med 2007;357;1-11

8,694

Broadbent HM, et al. Hum Mol Genet 2007;Nov 29;ddmm352

2,742

Talmud PJ, et al. Clin Chem 2008;54(3);467-474

2,362

Assimes TI, et al. Hum Mol Genet. 2008;17(15):2320-8

Total 64,018



9p21 Confirmed as a Common Risk Factor for CAD in Multiple Ethnic Groups

- **Korean**
- **Japanese**
- **Chinese**
- **East Asian**

Assimes TL, et al. Hum Mol Genet, 2008;17(15):2320-2328

Chen Z, et al. Mol Biol Rep 2008

Hinohara K, et al. J Hum Genet 2008;53(4):357-9

International Consortium for Genome-Wide Association
Studies of CAD

Coronary ARtery Disease Genome- wide Replication And Meta Analysis

CARDIoGRAM



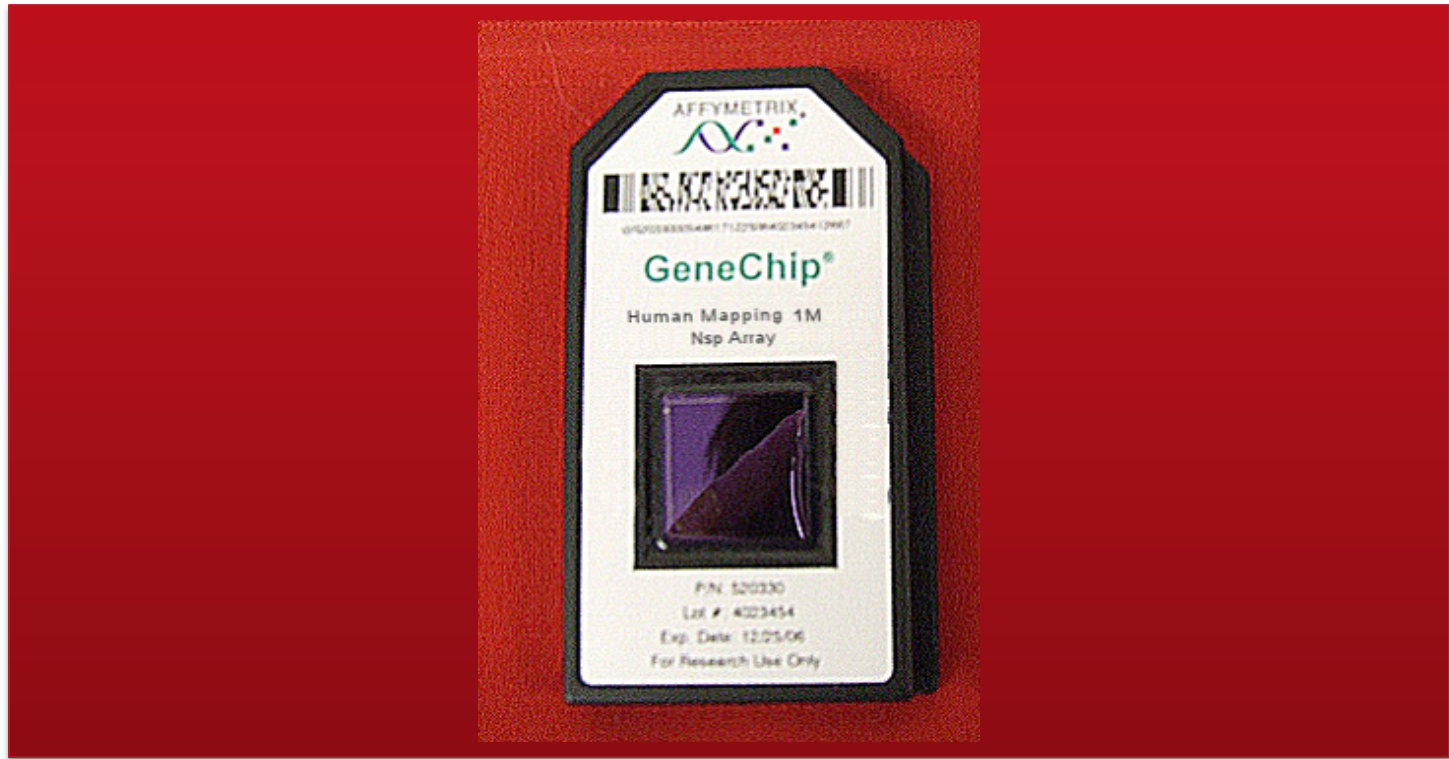
2021- 14 Years Later

Genetics of Coronary Artery Disease

- **Multiple genetic risk variants for CAD**
- **Genome wide significant**
- **Replicated in an independent population**

Assimes TL, Roberts R. *J Am Coll Cardiol.* 2016;68(25):2797-2818
Pim van der Harst, et al. *Circ Res.* 2018 Feb 2;122(3):433-443
Howson,et al. *Nat Genet.* 2017 Jul;49(7):1113-1119

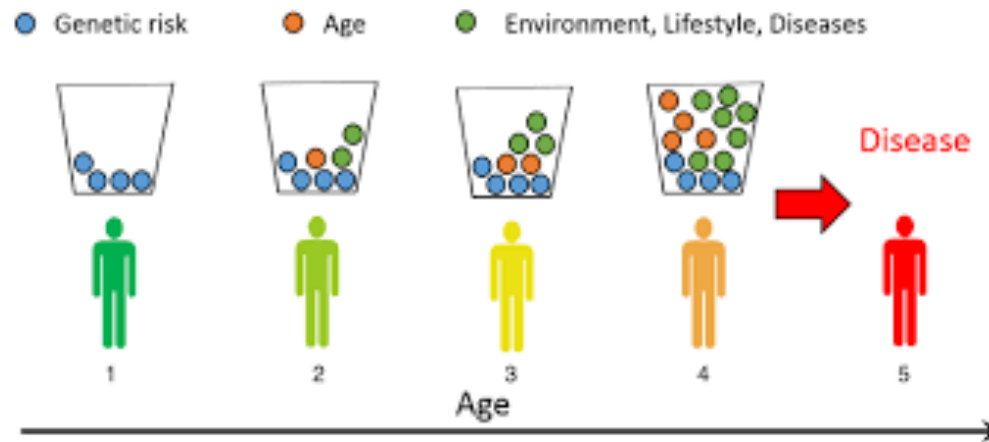
Microarray with 1.7 Million Genetic Risk Variants for CAD



Genetic Prediction of Cardiac Events

The total genetic risk burden for coronary artery disease (CAD) can be conveniently expressed in a single number referred to as the:

Genetic Risk Score (GRS)



Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials

Jessica L Mega, Nathan O Stitzel*, J Gustav Smith, Daniel I Chasman, Mark J Caulfield, James J Devlin, Francesco Nordio, Craig L Hyde, Christopher P Cannon, Frank M Sacks, Neil R Poulter, Peter S Sever, Paul M Ridker, Eugene Braunwald, Olle Melander, Sekar Kathiresan*, Marc S Sabatine**

Summary

Background Genetic variants have been associated with the risk of coronary heart disease. In this study, we tested whether or not a composite of these variants could ascertain the risk of both incident and recurrent coronary heart disease events and identify those individuals who derive greater clinical benefit from statin therapy.



DOI: [http://dx.doi.org/10.1016/S0140-6736\(14\)61730-X](http://dx.doi.org/10.1016/S0140-6736(14)61730-X)

www.thelancet.com Published online March 4, 2015 [http://dx.doi.org/10.1016/S0140-6736\(14\)61730-X](http://dx.doi.org/10.1016/S0140-6736(14)61730-X)



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Clinical Application of Genetic Variants for CAD

Population Genotyped

Primary prevention clinical trial

JUPITER

ASCOT

Secondary prevention clinical trial

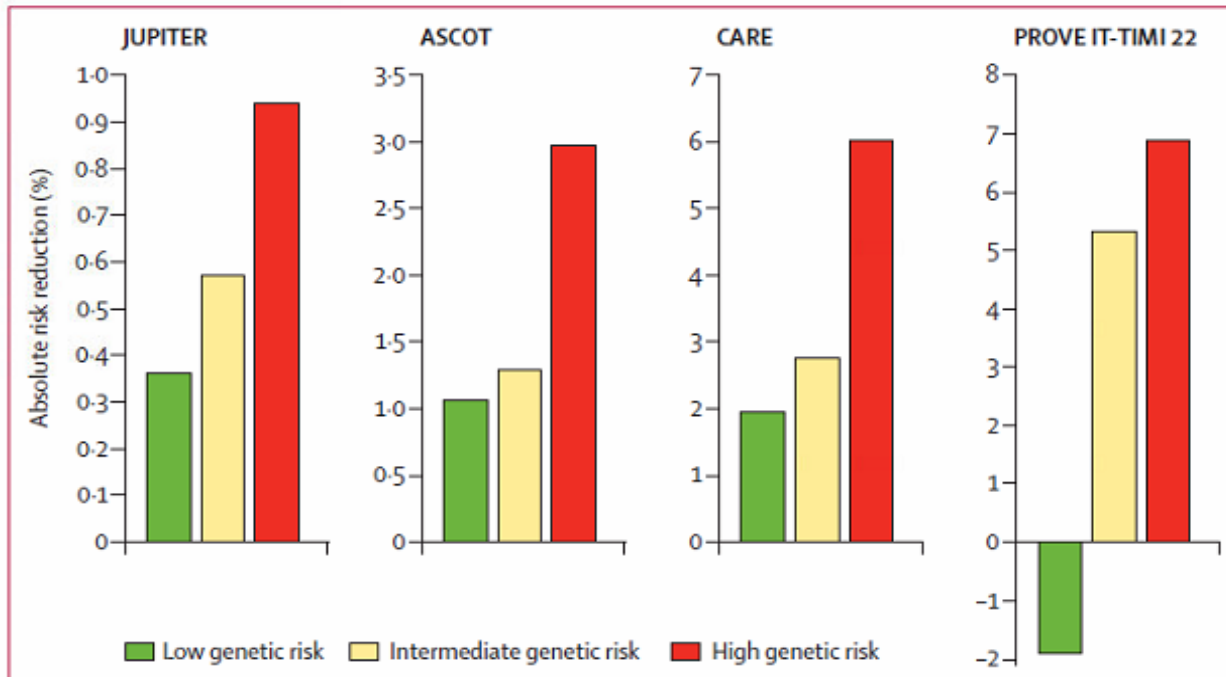
CARE

PROVE-IT-TIMI 22

Community cohort

Malmo diet and cancer study

Genetic Risk Variants Predict Response to Statin Therapy in each Risk Group



www.thelancet.com Published online March 4, 2015 [http://dx.doi.org/10.1016/S0140-6736\(14\)61730-X](http://dx.doi.org/10.1016/S0140-6736(14)61730-X)

ORIGINAL INVESTIGATIONS

Genomic Risk Prediction of CAD in Nearly 500,000 Adults



Early Screening and Primary Prevention

Michael Inouye, PhD,^{a,b,c,d,*} Gad Abraham, PhD,^{a,b,c,d,*} Christopher P. Nelson, PhD,^e Angela M. Wood, PhD,^c Michael J. Sweeting, PhD,^c Frank Dudbridge, PhD,^{c,f} Florence Y. Lai, MPHIL,^e Stephen Kaptoge, PhD,^{c,g} Marta Brozynska, PhD,^{a,b,c} Tingting Wang, PhD,^{a,b,c} Shu Ye, MD, PhD,^e Thomas R. Webb, PhD,^e Martin K. Rutter, MD,^{h,i} Ioanna Tzoulaki, PhD,^{j,k} Riyaz S. Patel, MD,^{l,m} Ruth J.F. Loos, PhD,ⁿ Bernard Keavney, MD,^{o,p} Harry Hemingway, MD,^q John Thompson, PhD,^f Hugh Watkins, MD, PhD,^{r,s} Panos Deloukas, PhD,^t Emanuele Di Angelantonio, MD, PhD,^{c,g} Adam S. Butterworth, PhD,^{c,g} John Danesh, FMedSci,^{c,g,u} Nilesh J. Samani, MD,^{e,*} for the UK Biobank CardioMetabolic Consortium CHD Working Group



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Genomic Risk Prediction of CAD in Nearly 500,000 Adults

- **Sample size of 482,629**
- **Microchip using 1.7million genetic risk variants for CAD**
- **Genetic Risk Score used to stratify for risk of CAD**

Inouye M et al.
JACC. 2018;72(16)

Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations

Amit V. Khera^{1,2,3,4,5}, Mark Chaffin ^{4,5}, Krishna G. Aragam^{1,2,3,4}, Mary E. Haas⁴, Carolina Roselli ⁴,
Seung Hoan Choi⁴, Pradeep Natarajan ^{2,3,4}, Eric S. Lander⁴, Steven A. Lubitz ^{2,3,4},
Patrick T. Ellinor ^{2,3,4} and Sekar Kathiresan ^{1,2,3,4*}

NATURE GENETICS | VOL 50 | SEPTEMBER 2018 | 1219-1224 | www.nature.com/naturegenetics



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Genetic Risk Stratification for Primary Prevention of CAD

- **Sample size of 288,978**
- **6,630,150 genetic risk variants for CAD**
- **Genetic Risk Score used to stratify for risk of CAD**

Khera, A. et al. Nature Genetics. 2018(50): 1219-1224

Genetic Risk Prediction of CAD in Nearly 500,000 Adults

- **Individuals with a GRS in the top 20% had a 3 to 4-fold increased risk for CAD.**
- **GRS is relatively independent of conventional risk factors.**



Inouye M et al.
JACC. 2018;72(16)

Genetic Risk Can be Determined Any Time from Birth Onwards

**GRS is independent of age,
remaining constant throughout
one's lifetime.**

Inouye M et al.
JACC. 2018;72(16)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease

Amit V. Khera, M.D., Connor A. Emdin, D.Phil., Isabel Drake, Ph.D., Pradeep Natarajan, M.D., Alexander G. Bick, M.D., Ph.D., Nancy R. Cook, Ph.D., Daniel I. Chasman, Ph.D., Usman Baber, M.D., Roxana Mehran, M.D., Daniel J. Rader, M.D., Valentin Fuster, M.D., Ph.D., Eric Boerwinkle, Ph.D., Olle Melander, M.D., Ph.D., Marju Orho-Melander, Ph.D., Paul M Ridker, M.D., and Sekar Kathiresan, M.D.



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Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease

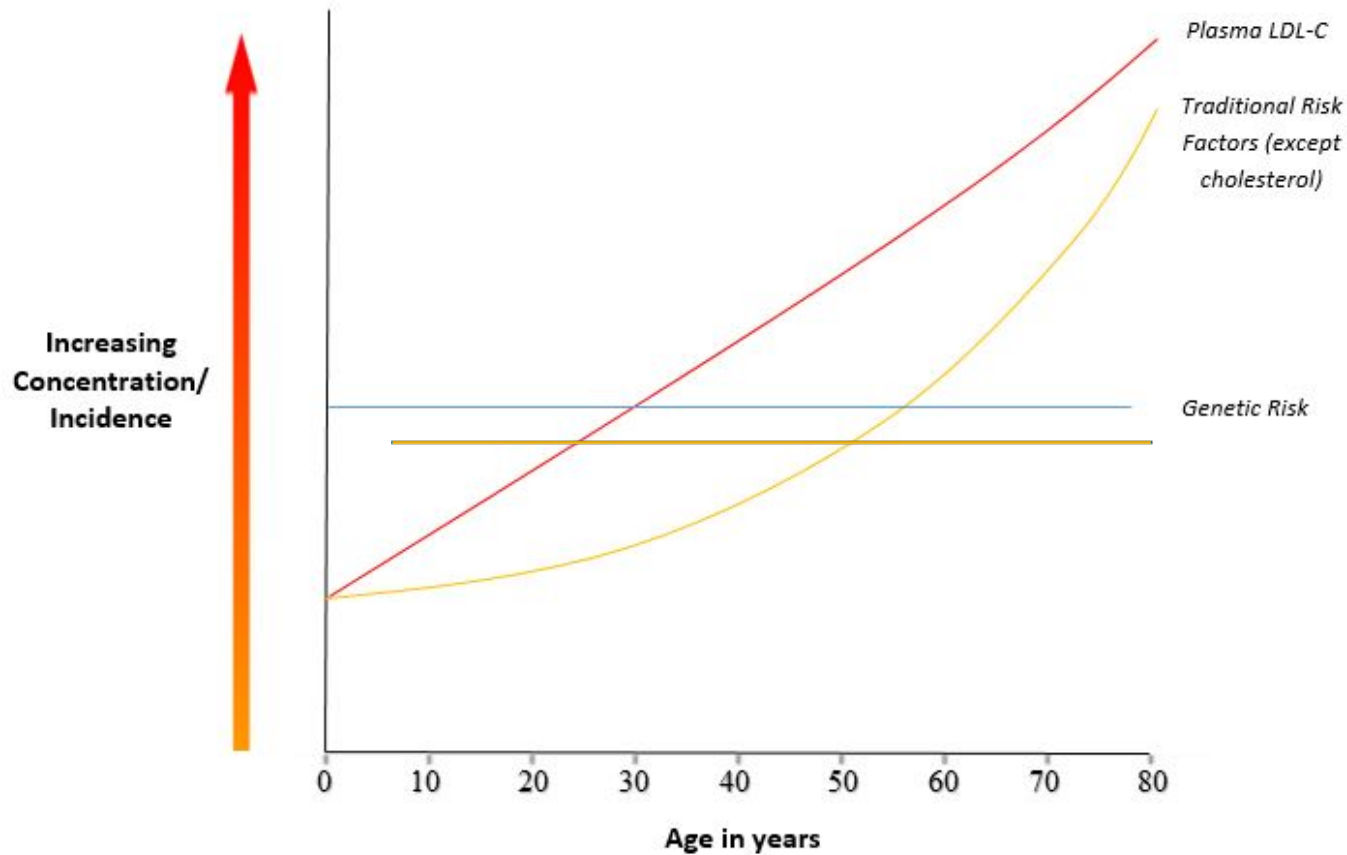
A 50% lower incidence of cardiac events was observed in those individuals with high GRS and a favorable lifestyle.

Khera AV, et al. NEJM 2016. doi:
10.1056/NEJMoa1605086

Worldwide Primary Prevention of CAD

- **Favorable lifestyle** has been shown to reduce the genetic risk for CAD.
- **Statin therapy**, a safe and inexpensive therapy, has been proven to reduce the genetic risk for CAD.

Genetic versus Traditional Risk Factors



Worldwide Primary Prevention of CAD

- **Genetic Risk Score is independent of age.**
- **Genetic risk Score is determined at conception and remains the same through one' lifetime.**

Utilizing the Genetic Risk Score to detect CAD risk will represent a **paradigm shift in primary prevention of CAD.**

Genetic Risk Screening for Coronary Artery Disease

Genetic Risk Score for CAD



Funded by SJHMC Foundation



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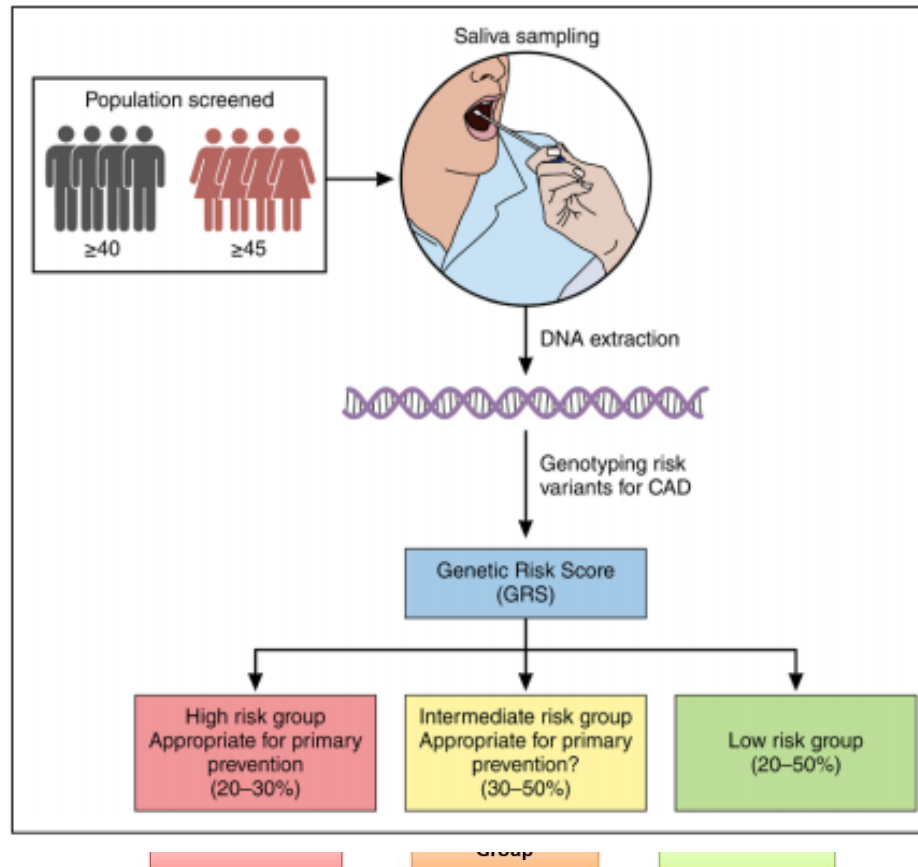
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Genetic Risk Screening for Coronary Artery Disease



A Global Map of National Genomic – Medicine Initiatives



Integration of Genomics into Healthcare

China plans to sequence the genome of 100 million Chinese by 2030 at a cost of 9.2 billion dollars.

**I would like to express
my appreciation
to all my collaborators
involved with
CARDIoGRAMplusC4D**



Thank You.

For more information about women and heart health or to request a speaker,
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Questions?



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