The Value of Genetics in Cardiovascular Risk Assesment: A Sex Specific Approach

Presented
by

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Disclosures

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Presenter	**Disclosure**
Robert Roberts, MD	None

Coronary Heart Disease is Pandemic, being the Number One Cause of Death in the world

One-third of all males and females 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.0000000000000152.

Premenopausal
Primary Prevention of CAD

A premenopausal, asymptomatic 49 yr. old female on routine checkup has LDL-C of 160 mg/dl (4.0 mm/l) with no other risk factors

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

Hunt et al, Am. J. Prev. Med. 2003;24:136

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

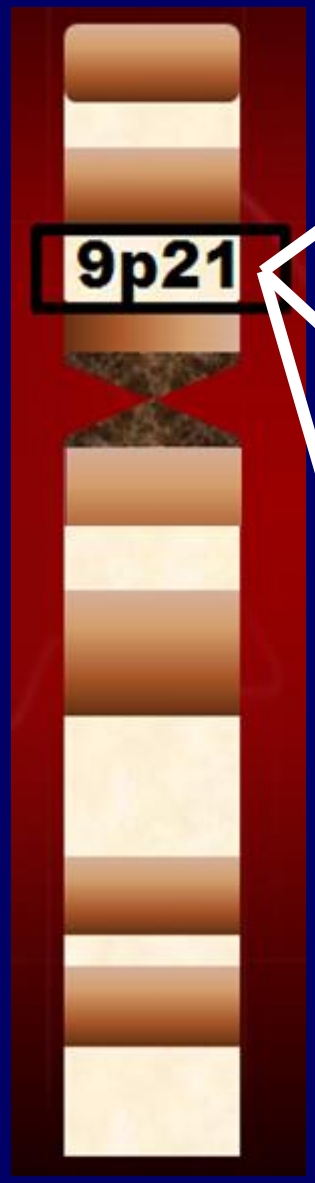
Genetics of Coronary Artery Disease

Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls

Wellcome Trust Case Control Consortium

Nature 2,007447:661-78

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

International Consortium for Genome-Wide Association Studies of CAD

Coronary ARtery DIsease Genome-wide Replication And Meta Analysis

CARDIoGRAM

2019- 12 Years Later

Genetics of Coronary Artery Disease

- 200 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

Common Genetic risk Variants for Coronary Artery Disease

1. Each genetic risk variant predisposing to CAD exerts minimal risk averaging a relative risk of only 8%
2. Risk variants are very common.
   - 50% are present in 50% of the population
   - 30% are present in 75% of the 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):1113-111

Coronary Artery Disease is Preventable

Randomized clinical trials which decreased plasma cholesterol were consistently associated with a decrease in cardiac events by 30 to 40%

Genetic Prediction of Cardiac Events

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

Genetic Risk Score (GRS).

THE LANCET

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 Stitziel*, 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.

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

Clinical Application of Genetic Risk Variants for CAD

- Sample size 48,421
- Microchip using 27 genetic risk variants for CAD
- Genetic Risk Score use to stratify risk for CAD

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

Clinical Application of Genetic Variants for CAD

Population Genotyped

Primary prevention clinical trial

JUPITER

ASCOT

Secondary prevention clinical trial

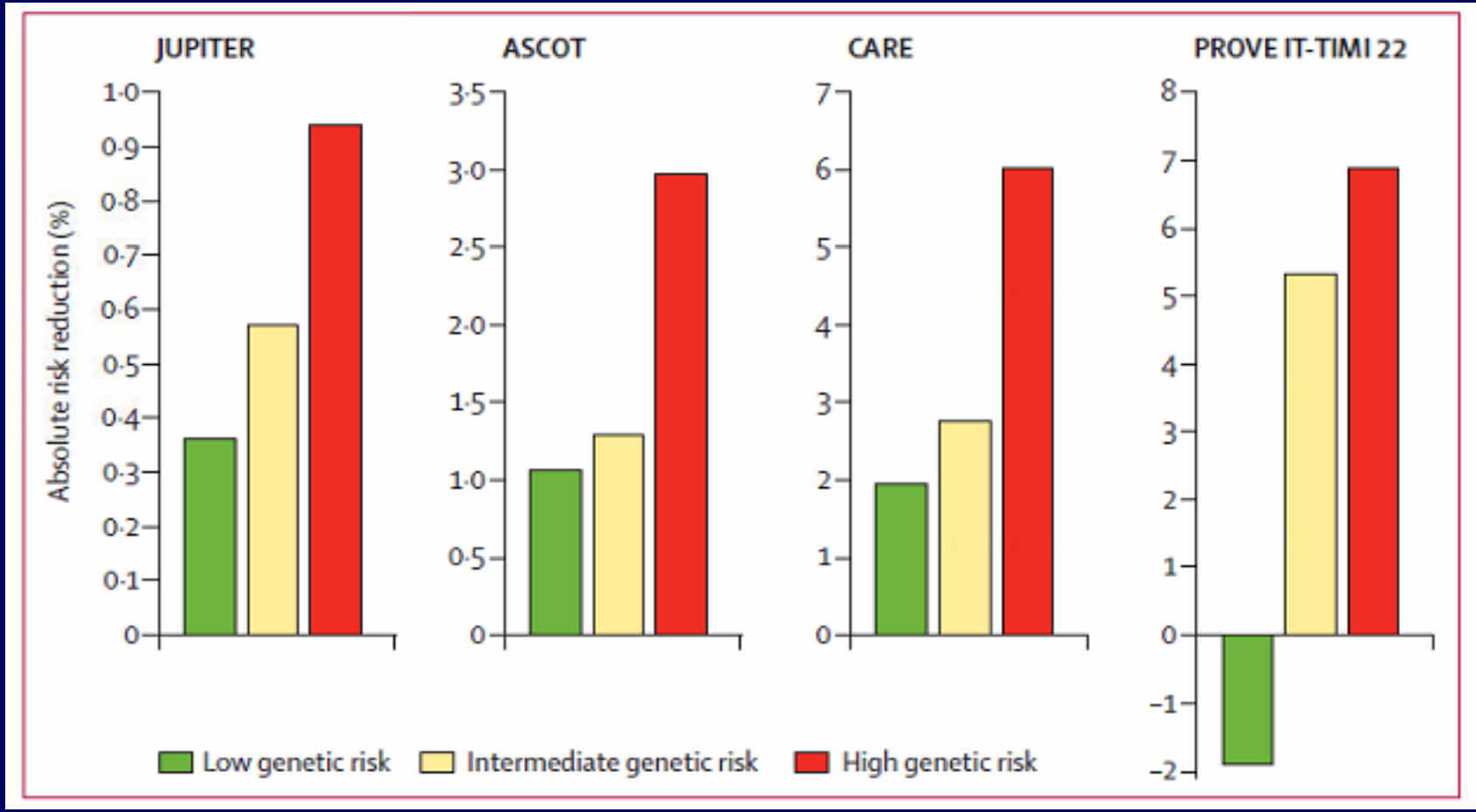
CARE

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

Genetic Risk Score Selects those Who Will Receive the Greatest Therapeutic Benefit

Genetic Score	Prevention of Cardiac Event (number to treat)
High risk	25
Intermediate risk	42
Low risk	66

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

West of Scotland Coronary Prevention Study (WOSCOPS), Cardia, BioImage

- Sample size of 10,456
- Microchip using 57 genetic risk variants for CAD
- Genetic Risk Score used to stratify for risk of CAD

Pradeep N, et al.
Circulation. 2017;135:2091-2101.

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 72, NO. 16, 2018

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

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

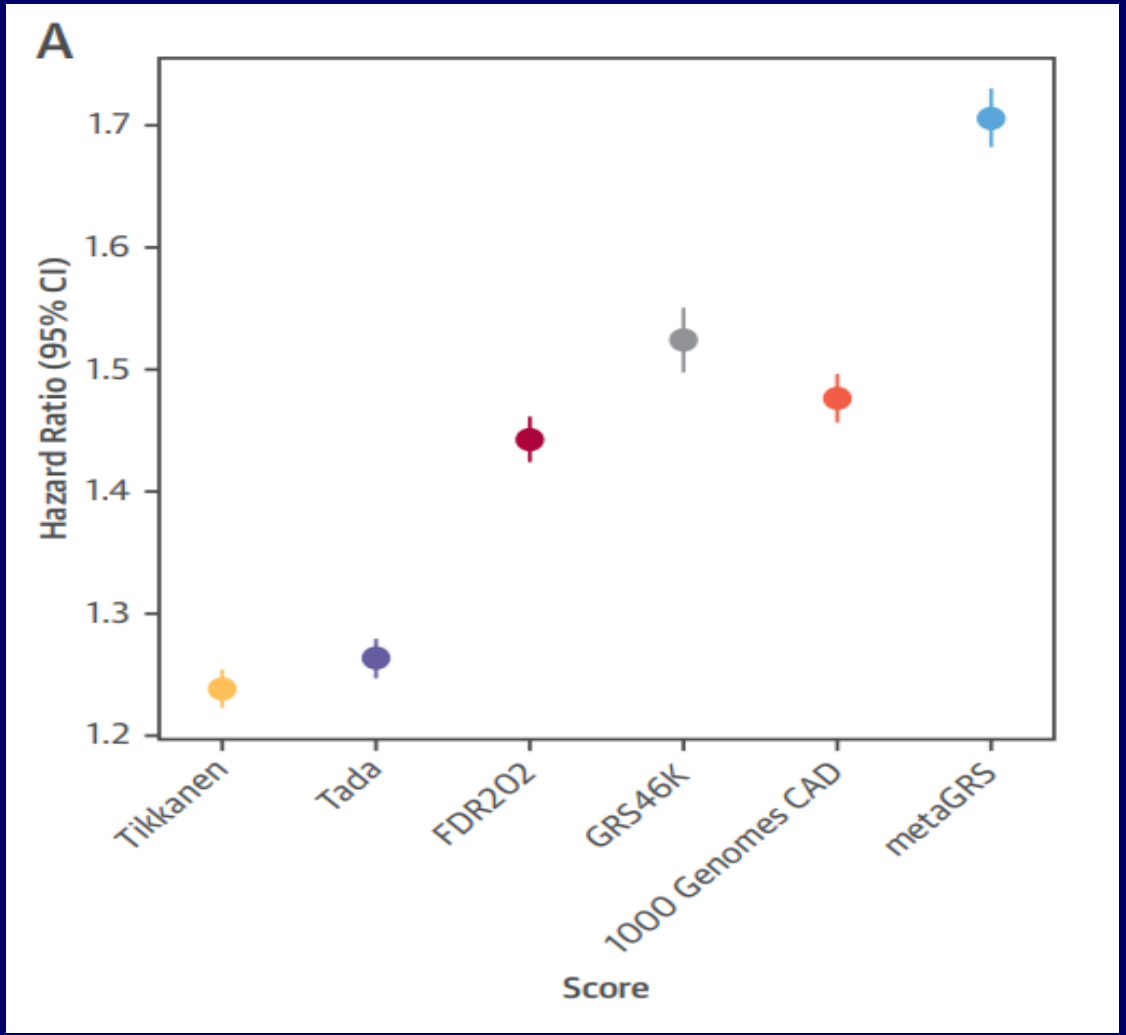
Inouye M et al. JACC. 2018:72(16)

Genomic Risk Prediction of CAD in Nearly 500,000 Adults

- **Individuals with a GRS in the top 20% had a 4-fold increased risk for CAD.**
  - **GRS is relatively independent of conventional risk factors.**
  - **GRS more potent than conventional risk factors in detecting individuals at risk for CAD.**

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

Genetic Risk Score Based on 1.7 Million Variants Superior to Previous GRS Using Less Variants



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

nature genetics

LETTERS

https://doi.org/10.1038/s41588-018-0183-z

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

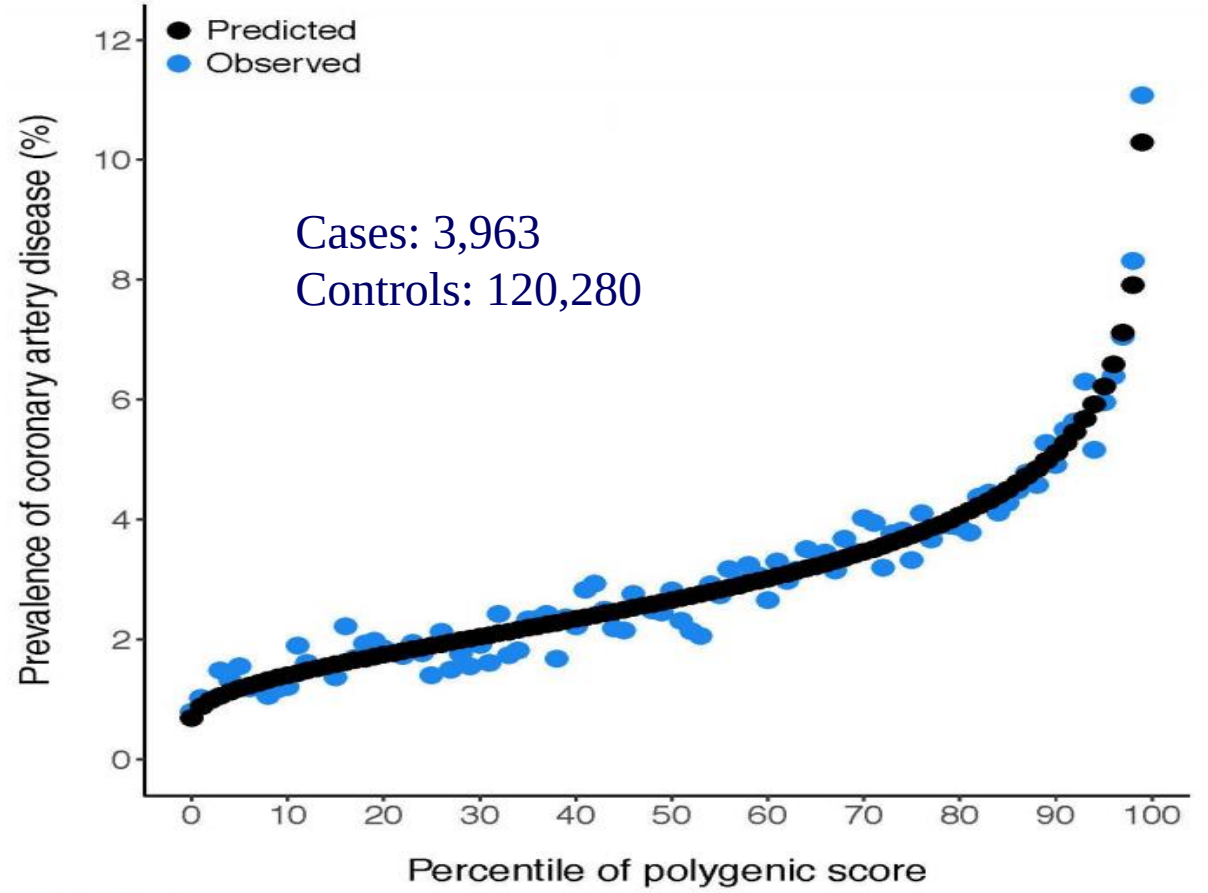
Amit V. Khera[1,2,3,4,5], Mark Chaffin[4,5], Krishna G. Aragam[1,2,3,4], Mary E. Haas[4], Carolina Roselli[4], Seung Hoan Choi[4], Pradeep Natarajan[2,3,4], Eric S. Lander[4], Steven A. Lubitz[2,3,4], Patrick T. Ellinor[2,3,4] and Sekar Kathiresan[1,2,3,4]*

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

Comparison of Predicted (GRS) vs. Observed Prevalence of CAD in Validation Dataset



Supplementary Figure 2

Predicted versus observed prevalence of coronary artery disease according to genome-wide polygenic score percentile.

For each individual within the UK Biobank testing dataset, the predicted probability of disease was calculated using a logistic regression model with only the genome-wide polygenic score (GPS) as a predictor. The predicted prevalence of disease within each percentile bin of the GPS distribution was calculated as the average predicted probability of all individuals within that bin. The shape of the predicted risk gradient was consistent with the empirically observed risk gradient, reflected by black and blue dots, respectively.

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

Genomic Risk Prediction of CAD using 6.6 Million Risk Variants

- GRS is relatively independent of conventional risk factors and much more potent in detecting individuals at risk for CAD.
- Individuals with a GRS in the top 20% had a 3-fold increased risk for CAD.

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

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.

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

Premenopausal
Primary Prevention of CAD

A premenopausal, asymptomatic 49 yr. old female on routine checkup has LDL-C of 160 mg/dl (4.0 mm/l) with no other risk factors

Impact and Cost-Effectiveness of Statin Use for Primary Prevention of Coronary Heart Disease and Stroke

Recommendations:

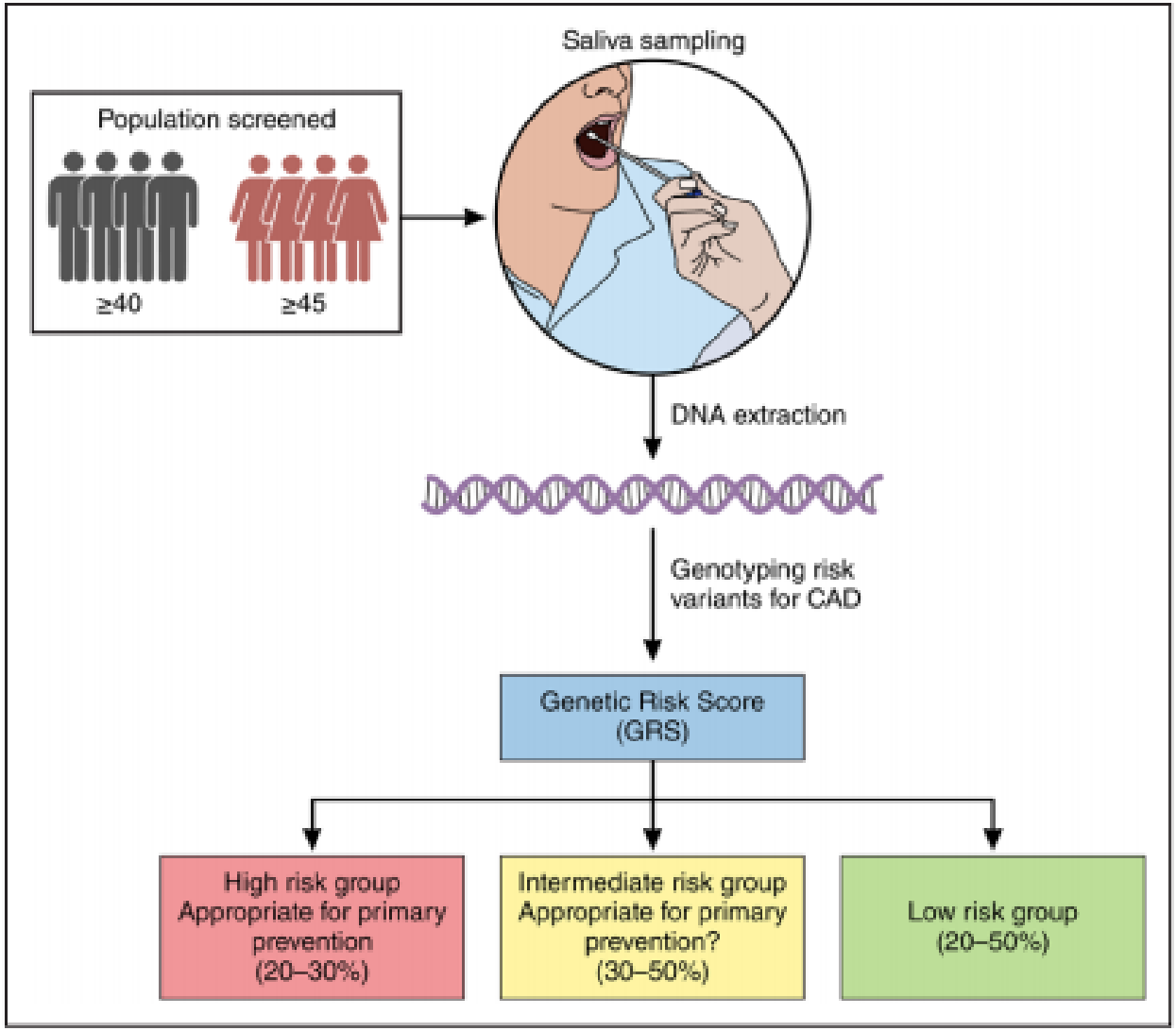
- Statins for all men 45- 74 yrs.
- Statins for all women 55-74 yrs.
- Extends statin therapy to an additional 28.8 million Americans over current guidelines
- Cost billions of dollars per year

Keller et al: Circulation, 2017 Sept 19H

Worldwide Primary Prevention of CAD

- **A Female or Male living A normal life Span in the US has a 50% chance of experiencing at least one cardiac event.**

Genetic Risk Stratification For Primary Prevention of CAD



Circulation. 2018;137:2554–2556. DOI: 10.1161/CIRCULATIONAHA.118.034732

Microarray with 1.7 million genetic risk variants for CAD

Genetic Risk Stratification For Primary Prevention of CAD

Genetic Screening and Risk Stratification for Primary Prevention of CAD in Premenopausal Women and Asymptomatic Men

Advantage of Genetic Variants over Conventional Biomarkers

One saliva or blood sample per lifetime

since one's DNA does not change over one's lifetime

Genetic Risk Score for CAD

- Risk stratification for CAD using the GRS has been confirmed in over 1 million cases and controls
- The GRS is relatively independent of conventional risk factors and has superior discriminatory power
- The GRS is independent of age and can be determined any time after birth

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**

Primary Prevention of CAD

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

Circulation

Circulation. 2018;137:2554–2556. DOI: 10.1161/CIRCULATIONAHA.118.034732

PERSPECTIVE

Genetic Risk Stratification

Tipping Point for Global Primary Prevention of Coronary Artery Disease

Robert Roberts, MD

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

CARDIoGRAMplusC4D

Acknowledgements

GRANT SUPPORT

- The Canadian Institutes of Health Research, CIHR #MOP82810, 2007, RR (PI) ($0.5 million)
- The Canada Foundation for Innovation, CFI #11966, 2007, RR (PI) ($11million)
- The Canadian Foundation for Innovation 2009, TIMEX, RR(Co-PI) ($50 million)
- National Networks of Centers of Excellence Operating Grant CANNeCTIN, CFI/CIHR #00727-000, 2007, RR (Co-IN) ($19 million)
- Agilent Technologies, RR (PI) ($50,000)
- National Heart, Lung & Blood Institute, 2004, RR (PI) ($2.5 million)

Concerns for Clinical Application of GRS for Primary Prevention

- Studies had the same population for Test and Validation- not so for clinical application.
- Studies involve primarily whites of European descent.
- Regional genetic differences.

Genetic Risk Score for CAD

Weighted Multi-Marker Genetic Risk Scores for incident CAD among Individuals of African, Latino and East-asian Ancestry

Carlos Iribarren et al. Scientific Reports : 2018, 8, 6853.