Research Highlight: The Strengths and Limitations of ASCVD Risk Prediction

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Kaiser Permanente 18th Annual COAST Conference

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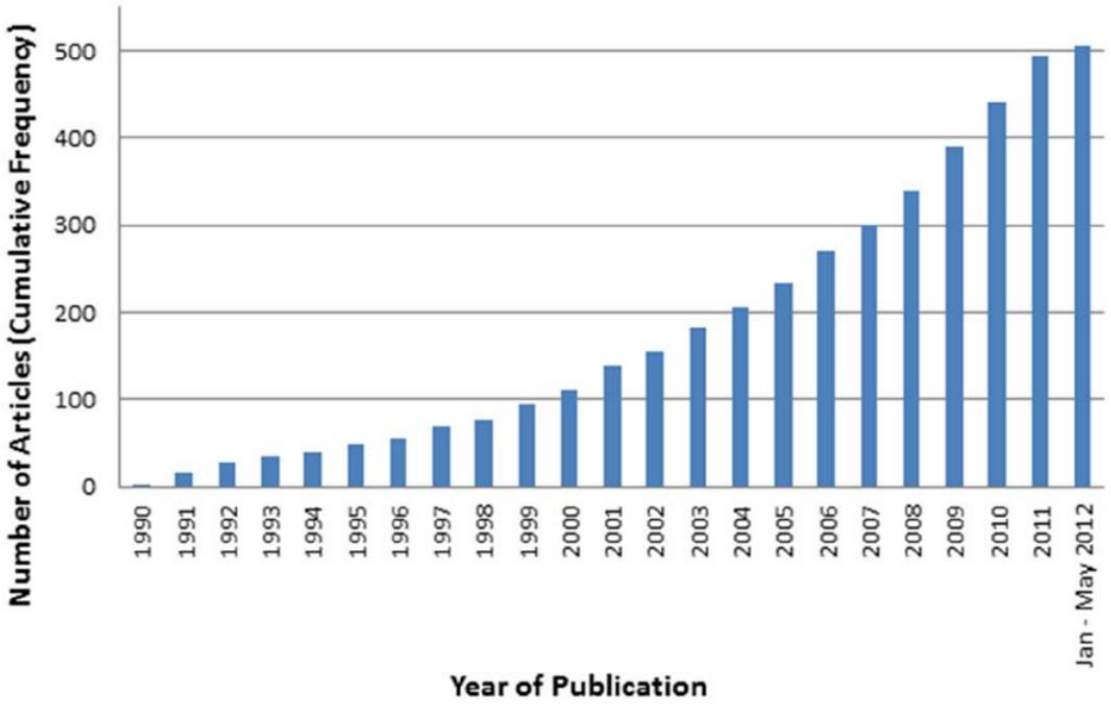
Pytha; Delphic oracle sitting atop her tripod, circa 330 BC

Outline

- Limitations of current Risk Estimator for ASCVD
- Leveraging Kaiser Permanente data and future

Clinical Prediction Models for Cardiovascular Disease



796 models have been developed that Addresses CV Disease

Circ Cardiovasc Qual Outcomes. 2015;8:368-375.

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What Makes a Good Prediction Model?

- An ideal but *probably unrealistic* model will correctly identify every patient who will develop an event vs those who will not, and will not misclassify any patients.

- The extent to which any model comes close to achieving this goal can be characterized by the 2 related properties of discrimination and calibration

JAMA October 10, 2017 Volume 318, Number 14

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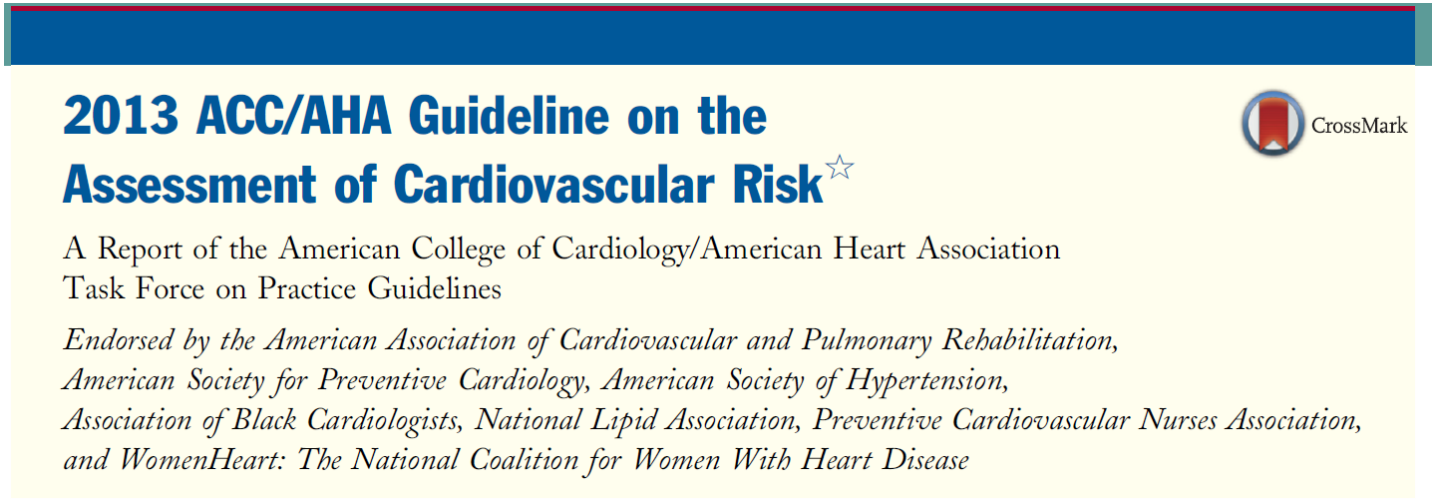

- An important step forward.
- Estimates risk for both heart disease and stroke.
- Provides estimates applicable to black/African-Americans.
- This equation was developed from several prospective U.S.-based cohorts of enrolled volunteers, primarily conducted in the 1990s, with limited ethnic diversity and age range.

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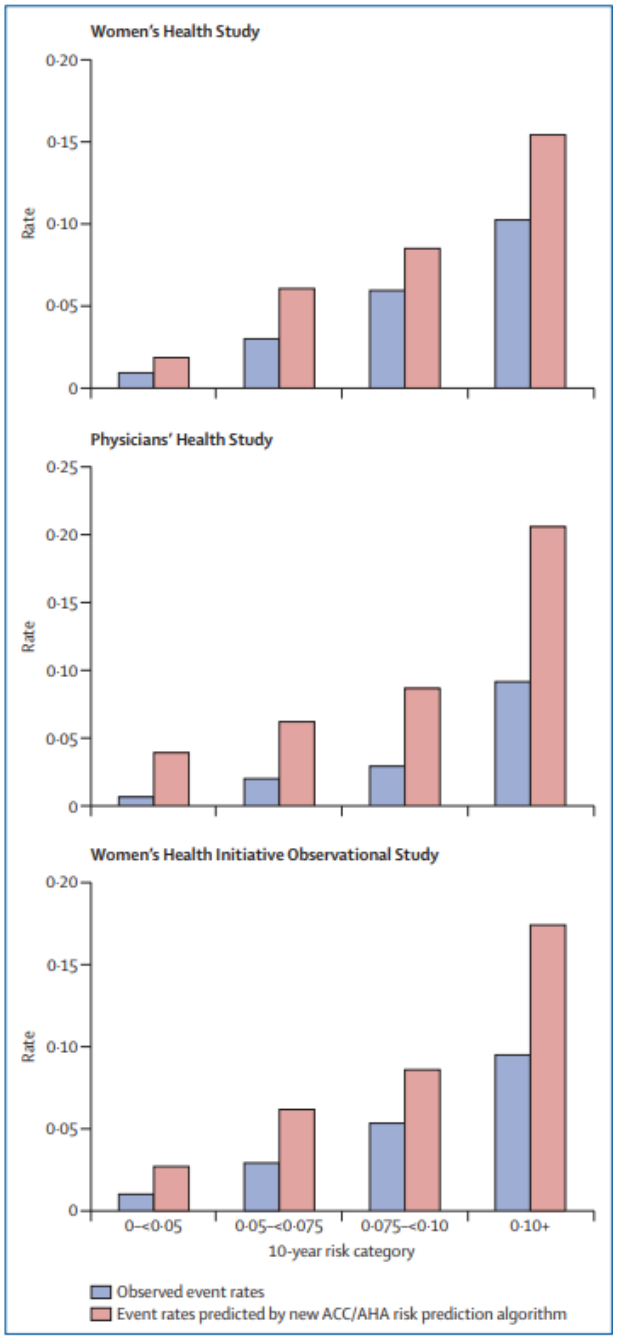
Statins: new American guidelines for prevention of cardiovascular disease

www.thelancet.com Vol 382 November 30, 2013



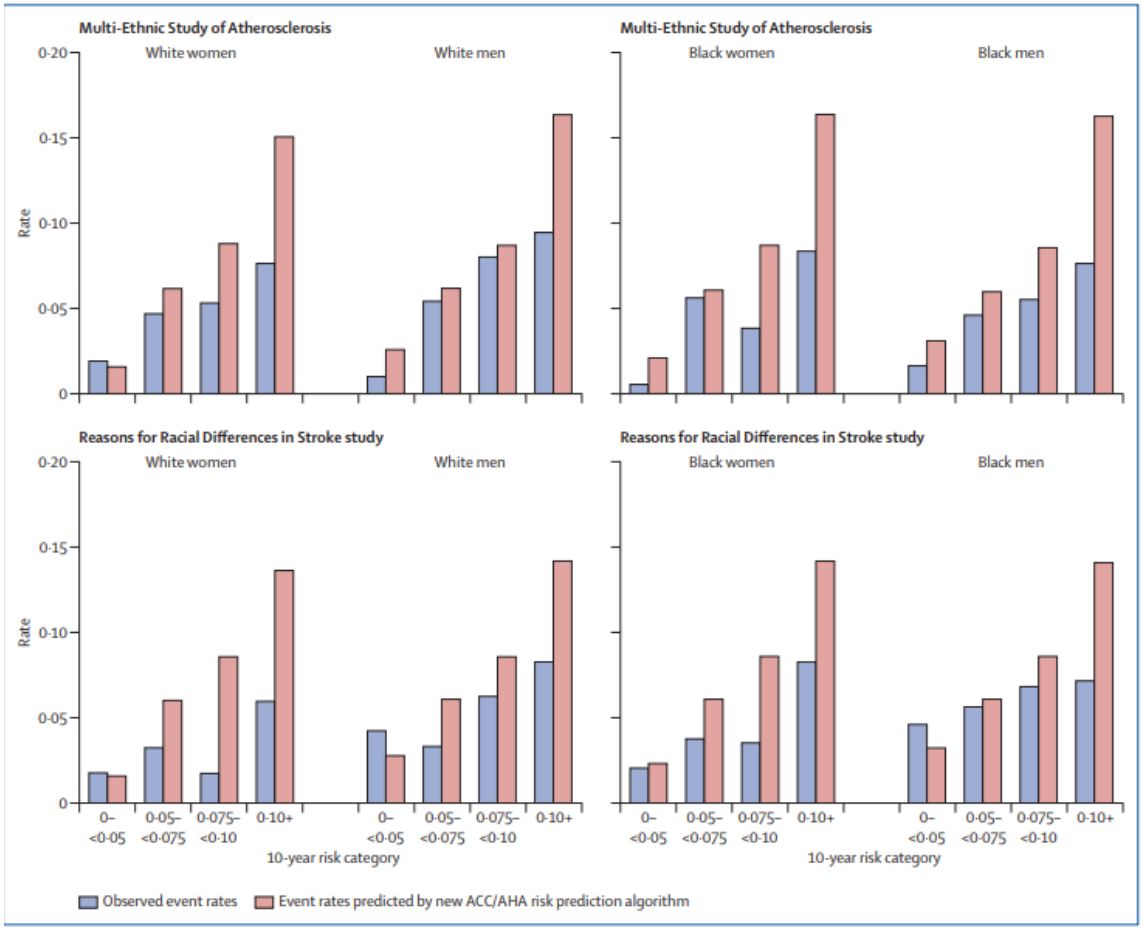


Figure 2: **Comparison of observed event rates with event rates predicted by new ACC/AHA risk prediction algorithm in two external validation cohorts described in the Full Work Group Report Supplement: the Multi-Ethnic Study of Atherosclerosis and the Reasons for Racial Differences in Stroke study**
Data are shown stratified by gender and race.

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ORIGINAL RESEARCH

Annals of Internal Medicine

An Analysis of Calibration and Discrimination Among Multiple Cardiovascular Risk Scores in a Modern Multiethnic Cohort

Andrew P. DeFilippis, MD, MSc*; Rebekah Young, PhD*; Christopher J. Carrubba, MD; John W. McEvoy, MB, BCh, BAO; Matthew J. Budoff, MD; Roger S. Blumenthal, MD; Richard A. Kronmal, PhD; Robyn L. McClelland, PhD; Khurram Nasir, MD, MPH; and Michael J. Blaha, MD, MPH

- 4227 MESA participants aged 50-74 yrs without diabetes
- AHA-ACC-ASCVD overestimated risk 86% in men and 67% in women.

Ann Intern Med. 2015;162:266-275.

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Original Investigation

Further Insight Into the Cardiovascular Risk Calculator
The Roles of Statins, Revascularizations, and Underascertainment in the Women's Health Study

Nancy R. Cook, ScD; Paul M Ridker, MD

- The pooled cohort equations have now been found to overpredict the rate of CVD in at least 7 external validation cohorts.
- Use of statins, revascularizations, or under-ascertainment could not explain the extent of overestimation in the WHS.
- Recalibration of the pooled cohort equations using available contemporary data sets might provide a solution to this problem.

JAMA Intern Med. 2014;174(12):1964-1971. (

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Critique on studies critiquing the new Risk Estimator

- Individuals in all these cohorts were either screened for participation in, or enrolled in, clinical trials, with the very real potential for healthy volunteer effects
- Some risk factor levels were self-reported in ranges, rather than directly measured, leading to concerns about imprecision.
- Cohorts might have been subject to some downstream initiation of statins.

Kaiser Permanente Northern California (KPNC)

- Large integrated healthcare delivery system currently providing comprehensive care to >4 million members in Northern and Central California

- Broad sociodemographic diversity and highly representative of local and statewide population

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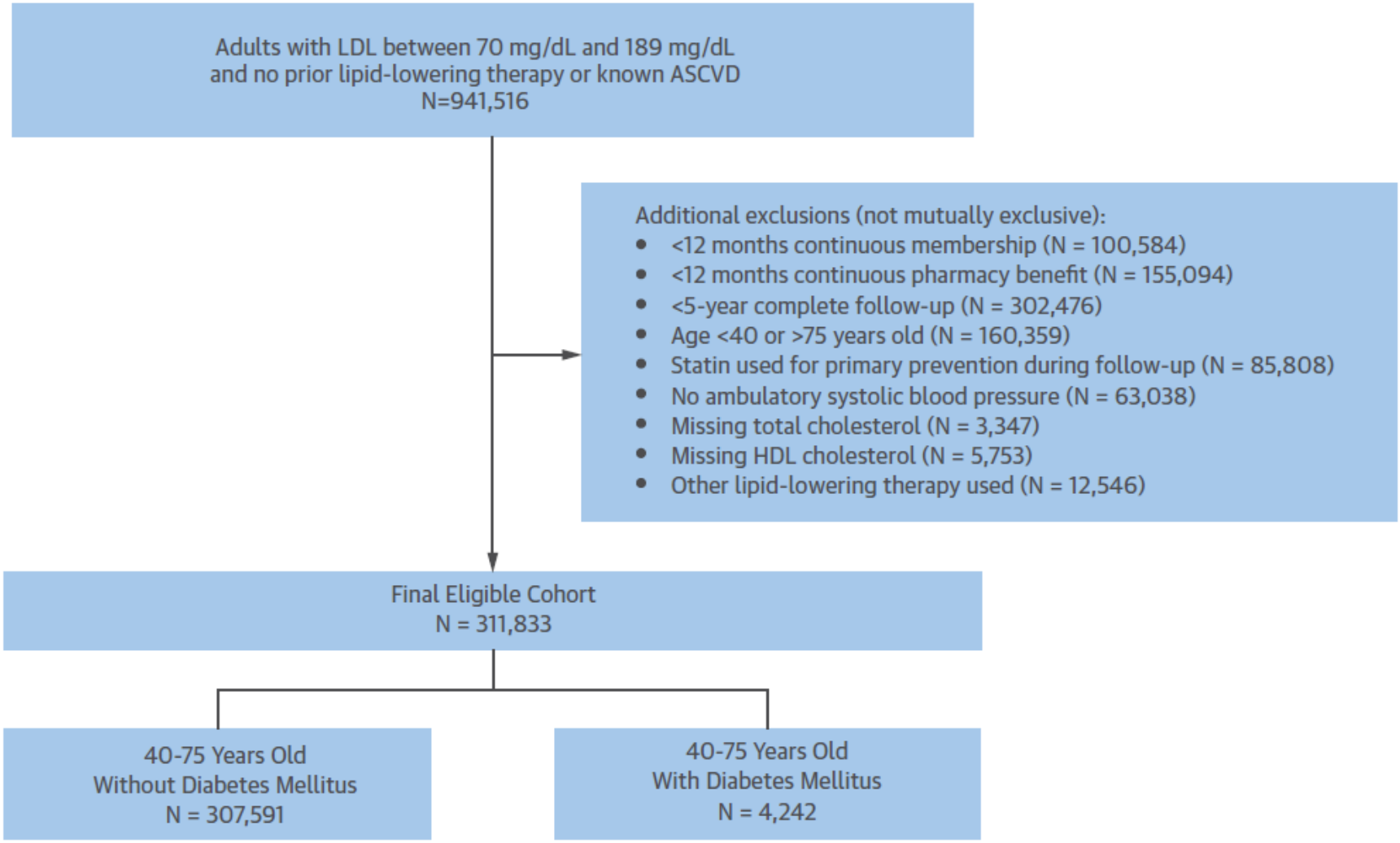
Accuracy of the Atherosclerotic Cardiovascular Risk Equation in a Large Contemporary, Multiethnic Population

Jamal S. Rana, MD, PhD,[a,b,c] Grace H. Tabada, MPH,[b] Matthew D. Solomon, MD, PhD,[a,b,d] Joan C. Lo, MD,[b,c,e] Marc G. Jaffe, MD,[c,f] Sue Hee Sung, MPH,[b] Christie M. Ballantyne, MD,[g] Alan S. Go, MD[b,c,h,i]

Eligible members in 2008 with available information to calculate ACC/AHA ASCVD risk score for primary prevention



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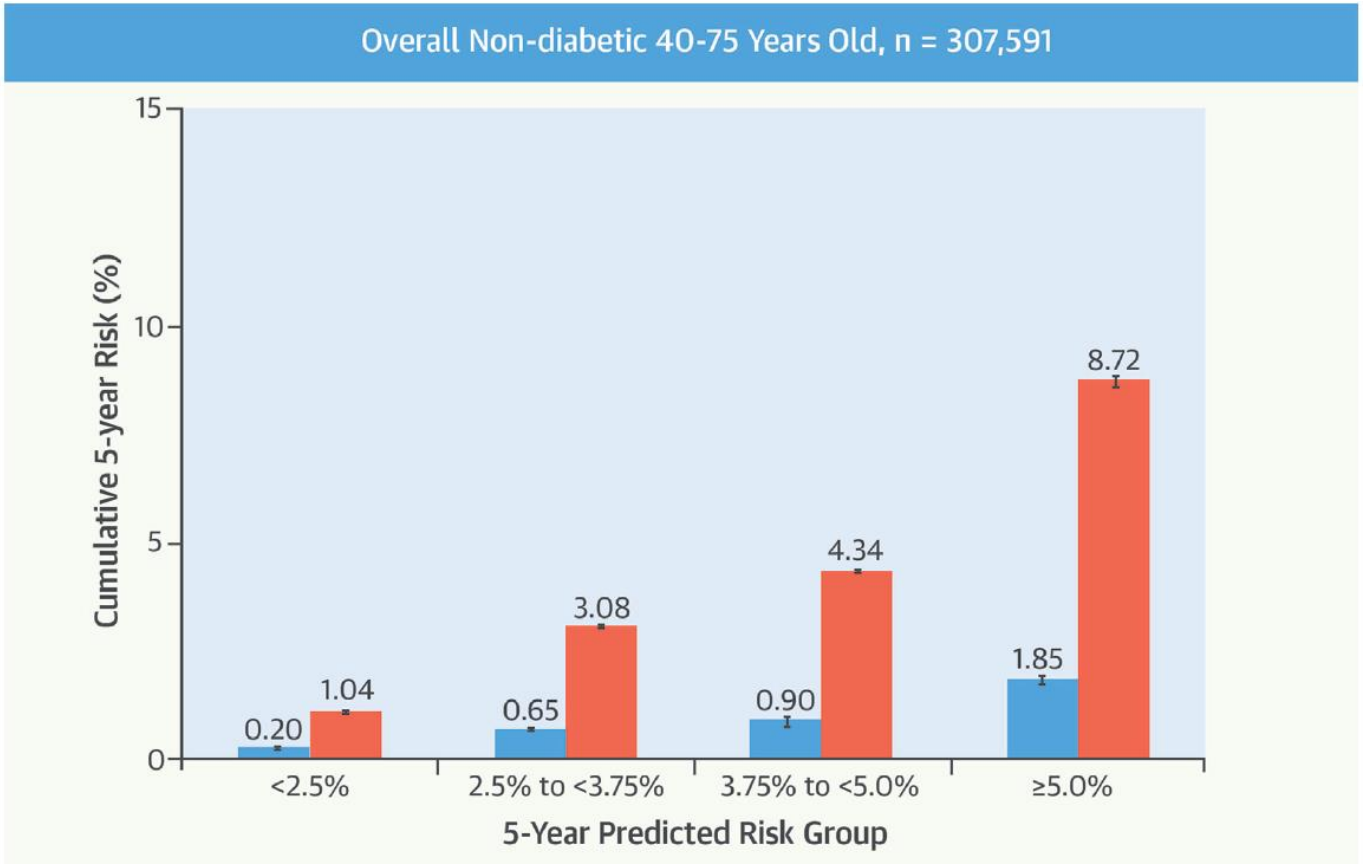
Comparison of Observed vs Expected in Subgroups



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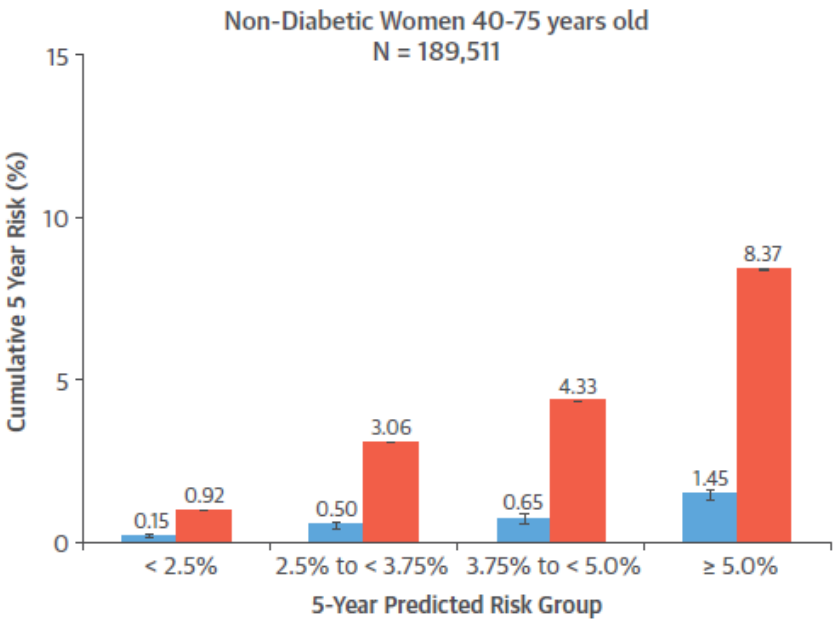
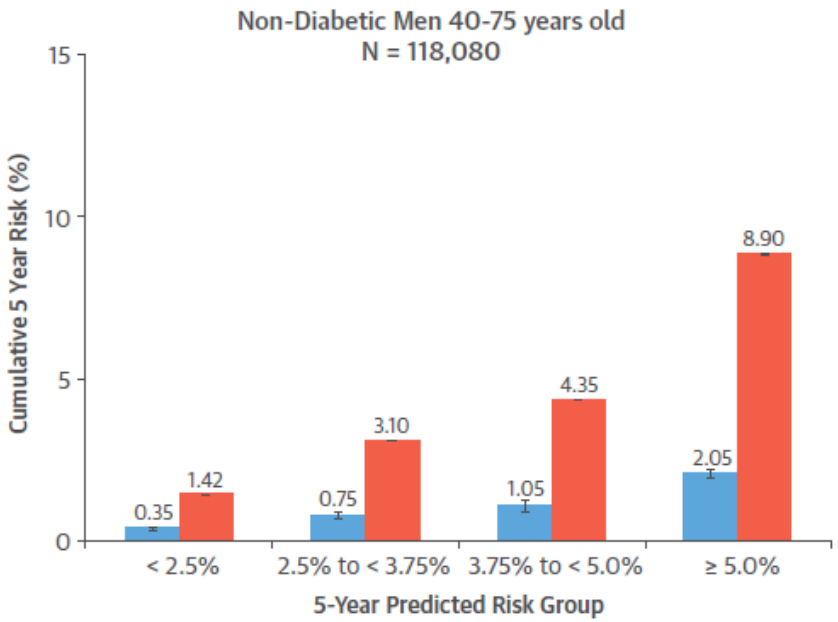
Comparison of Observed vs Expected in Subgroups by Sex





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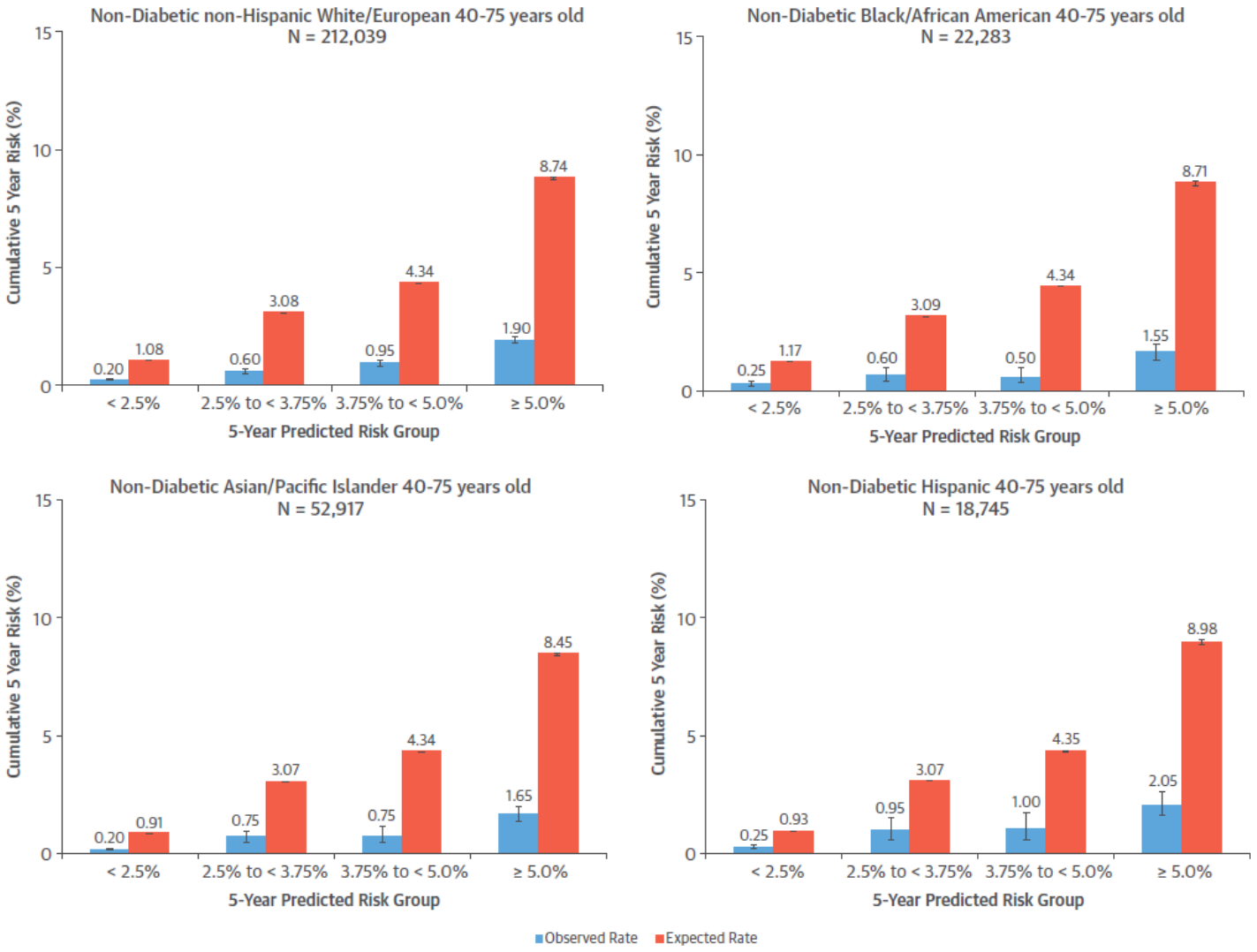
Comparison of Observed vs Expected in Subgroups by Ethnicities



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Discrimination

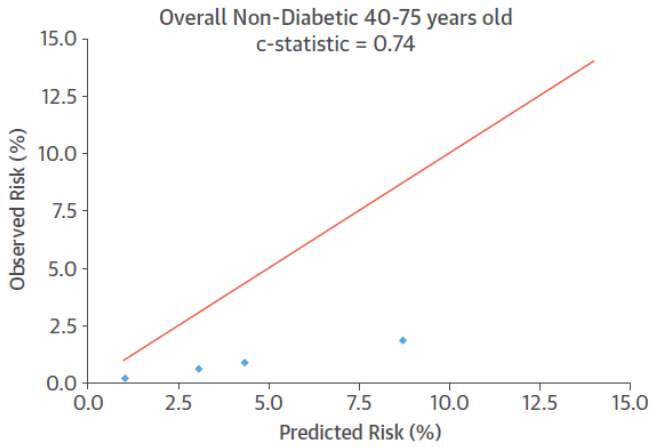
- How well the model differentiates those at higher risk of having an event from those at lower risk.

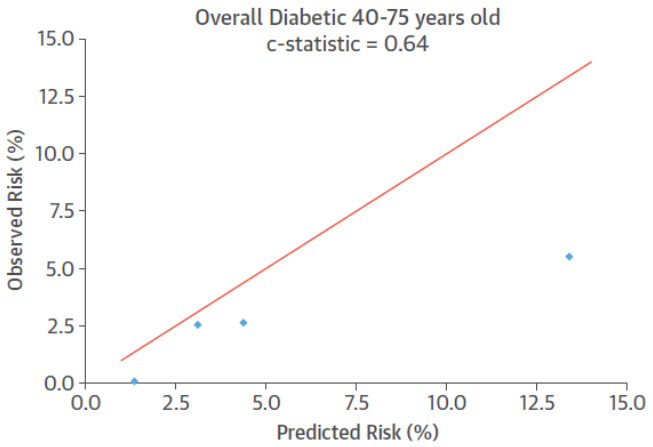
- Address the extent to which a model predicts a higher probability of having an event among patients who will vs those who will not have an event.

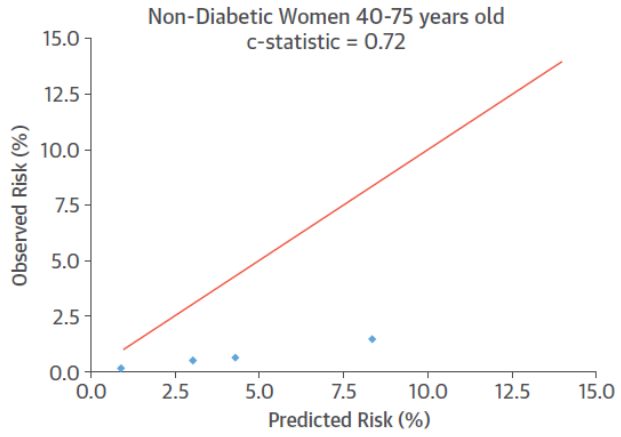
Calibration

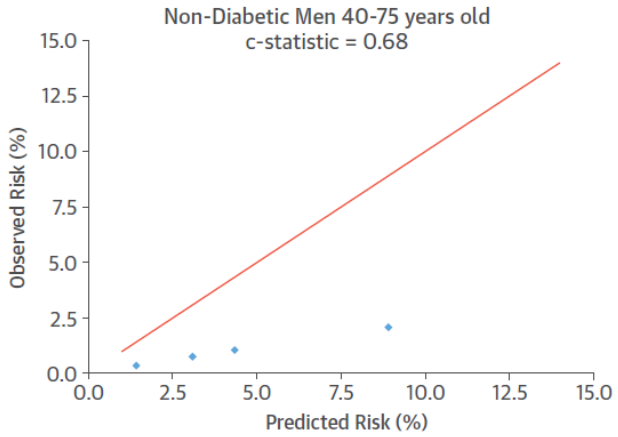
- Considered the most important property of a model
- A model informs clinicians how similar the predicted absolute risk is to the true (observed) risk in groups of patients classified in different risk strata.
- Poorly calibrated models will underestimate or overestimate the outcome of interest.
- Assessing calibration involves comparing predicted and observed risk at different levels

Calibration and Discrimination of ASCVD Risk Equation









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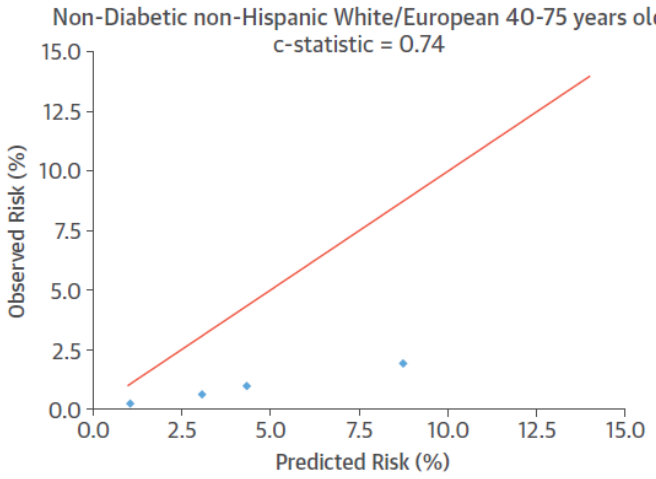
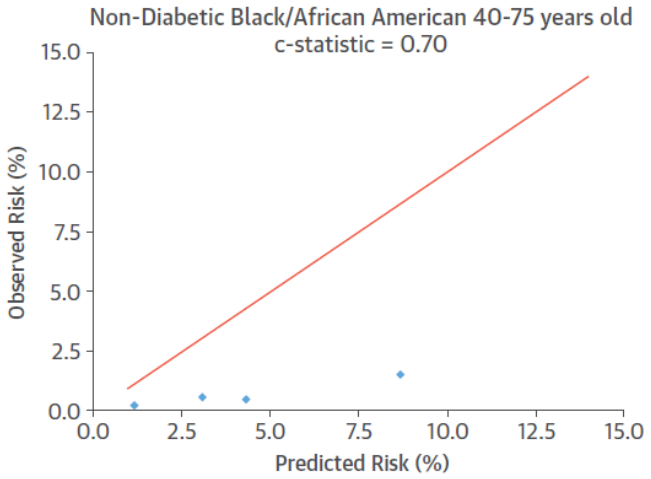
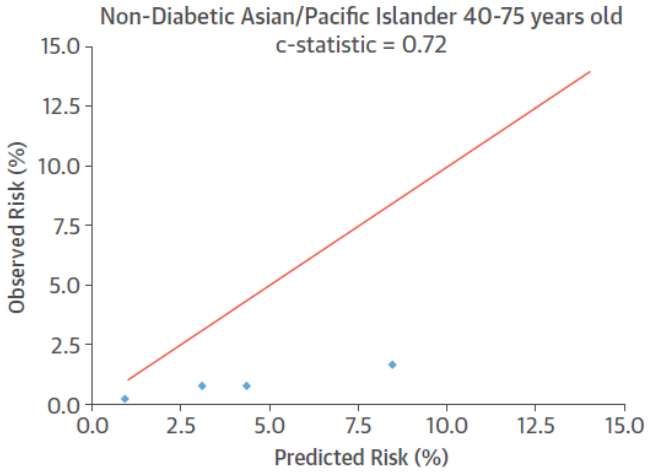
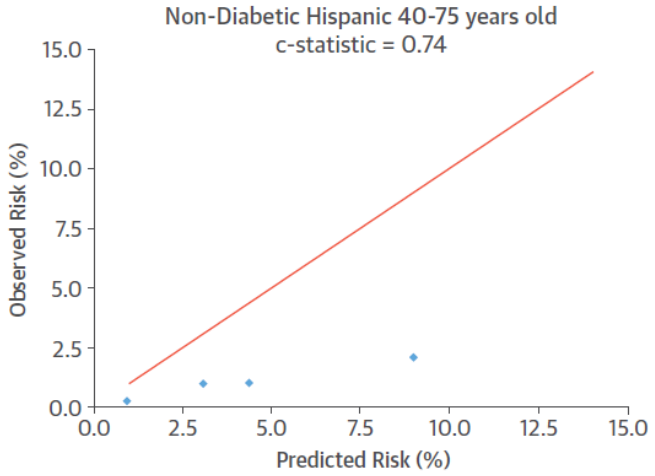
Calibration and Discrimination of ASCVD Risk Equation

Poor calibration with moderate discrimination (C statistic: 0.68 to 0.74) were observed in sex, racial/ethnic, and socioeconomic status subgroups (and in sensitivity analyses among patients receiving statins for primary prevention).









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Evidence to recalibrate the Risk Equation, especially given the individual and public health implications of wide spread application

#1 “Most Talked About Article From 2016” in the cardiovascular community per the Journal of the American College of Cardiology .

“According to metrics and qualitative data compiled by Altmetric, this research received the most media and social media attention throughout the world last year.”

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TIME

Why Your Heart Disease Risk May Not Be as High as You Think

By ALICE PARK May 2, 2016

TIME Health *For more, visit TIME Health.*

Heart disease is the leading killer of Americans, so predicting who is at highest risk of heart attack or stroke is a top priority. After decades of relying on a checklist of risk factors identified in the 1950s, which included factors like high

"It's such an enormous burden to put millions of people on statins," says Rana. "We think there is room for improvement in this."

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EDITORIAL COMMENT

The Critical Importance of Risk Score Calibration

Time for Transformative Approach to Risk Score Validation?*

Michael J. Blaha, MD, MPH

Many have called for a transformation, a challenge to the field to demonstrate that the digital revolution and “big data” analytics can be leveraged, to make risk prediction more organic, iterative, and contemporary .. Rana et al. take the first step toward such a transformation.

NEXT STEP …

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Using ACC/AHA Risk Estimator development approach, can we recalibrate and validate a more accurate ASCVD risk estimator in contemporary multiethnic population?

Recalibration of the ACC/AHA ASCVD Risk Estimator for Primary Prevention in a Large, Multiethnic Community-Based Population

Alan S. Go, MD, Grace H. Tabada, MPH, Sue Hee Sung, MPH, Marc G. Jaffe, MD, Matthew D. Solomon, MD, PhD, Jamal S. Rana, MD, PhD

American Heart Association Annual Scientific Sessions 2017

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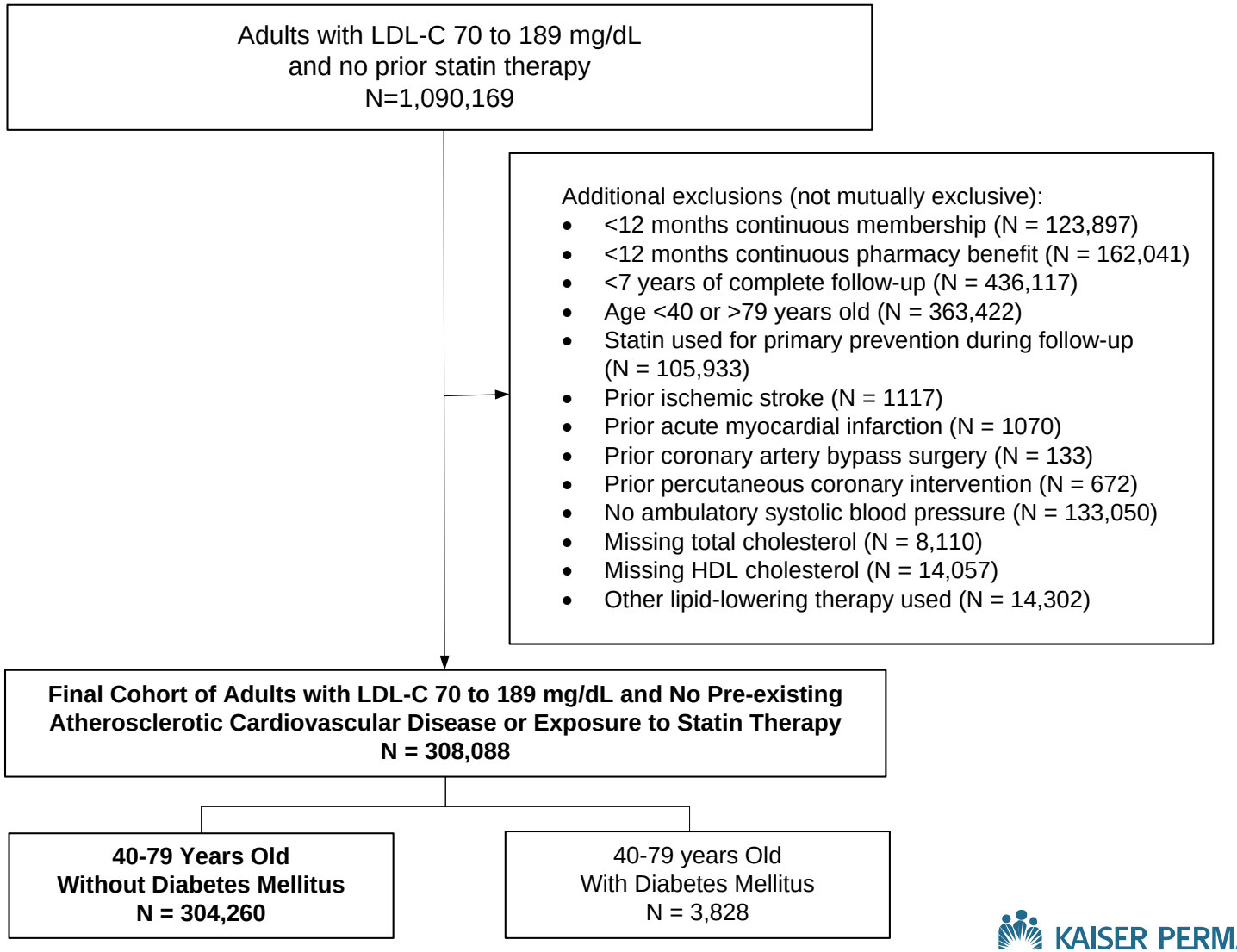
Identification of Eligible Kaiser Permanente Northern California patients



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Recalibration Approach

- Split-sample derivation and validation method. Eligible adults with 7-year complete follow-up randomly split into two equal-sized samples

    1. Derive new ASCVD risk estimator
    2. Validate new risk estimator performance

Recalibration: Analytical Steps

Same variables used in the original ACC/AHA risk estimator: age, systolic blood pressure (treated and untreated), HDL-C, total cholesterol, DM, Smoking

Tested if interactions between age and each individual variable improved prediction of outcome by running individual Cox proportional hazard models

Final regression model included all statistically significant interactions

Used coefficients of variables and interactions in final model for recalibrated KPNC ASCVD risk estimator

Evaluated recalibrated KPNC ASCVD risk estimator vs. ACC/AHA ASCVD risk estimator

- Applied new derived coefficients to original equation:

$$\boldsymbol{Risk\ score = 1 - S_7^{e^{(IndX'B - MeanX'B)}}}$$

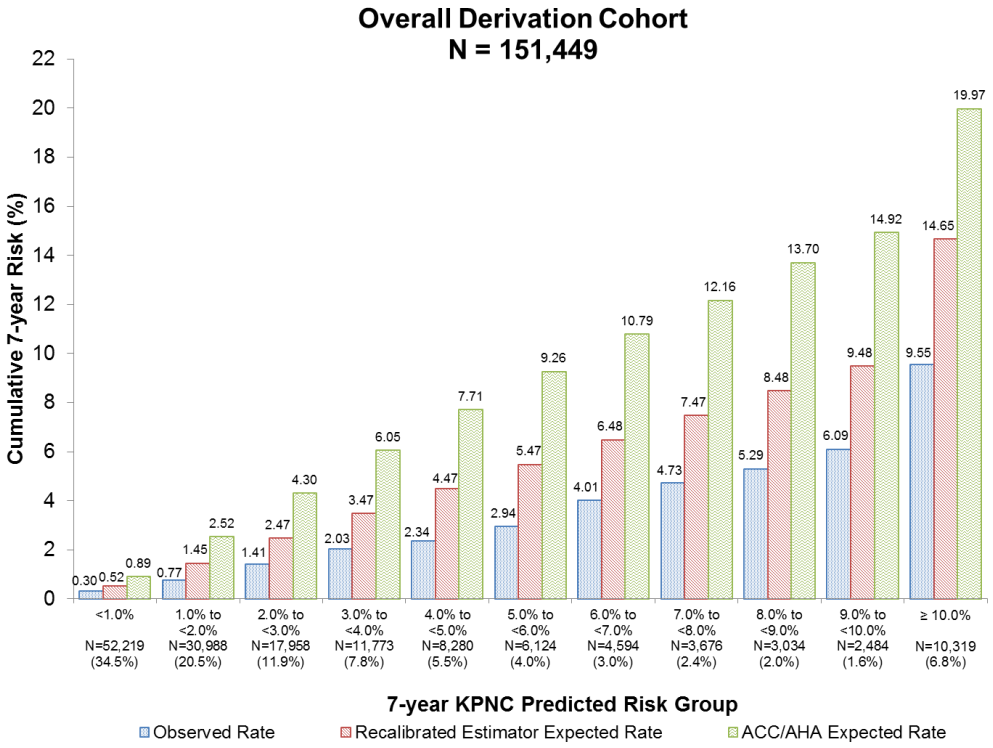
S_7 = survival free of event at 7 years

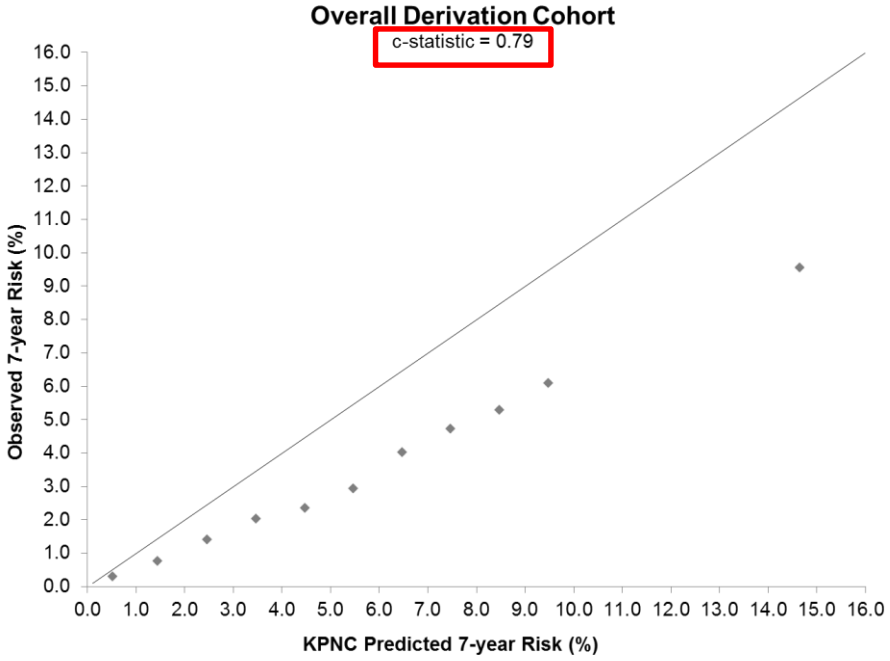
$IndX'B = \sum(Coefficient * value)$ per individual

$MeanX'B$ = race- and gender-specific overall mean

Derivation Cohort Results (N=151,449)

Improved **calibration** and **discrimination** with KPNC ASCVD Risk Estimator in 40-79 y.o. adults without diabetes and not taking statins





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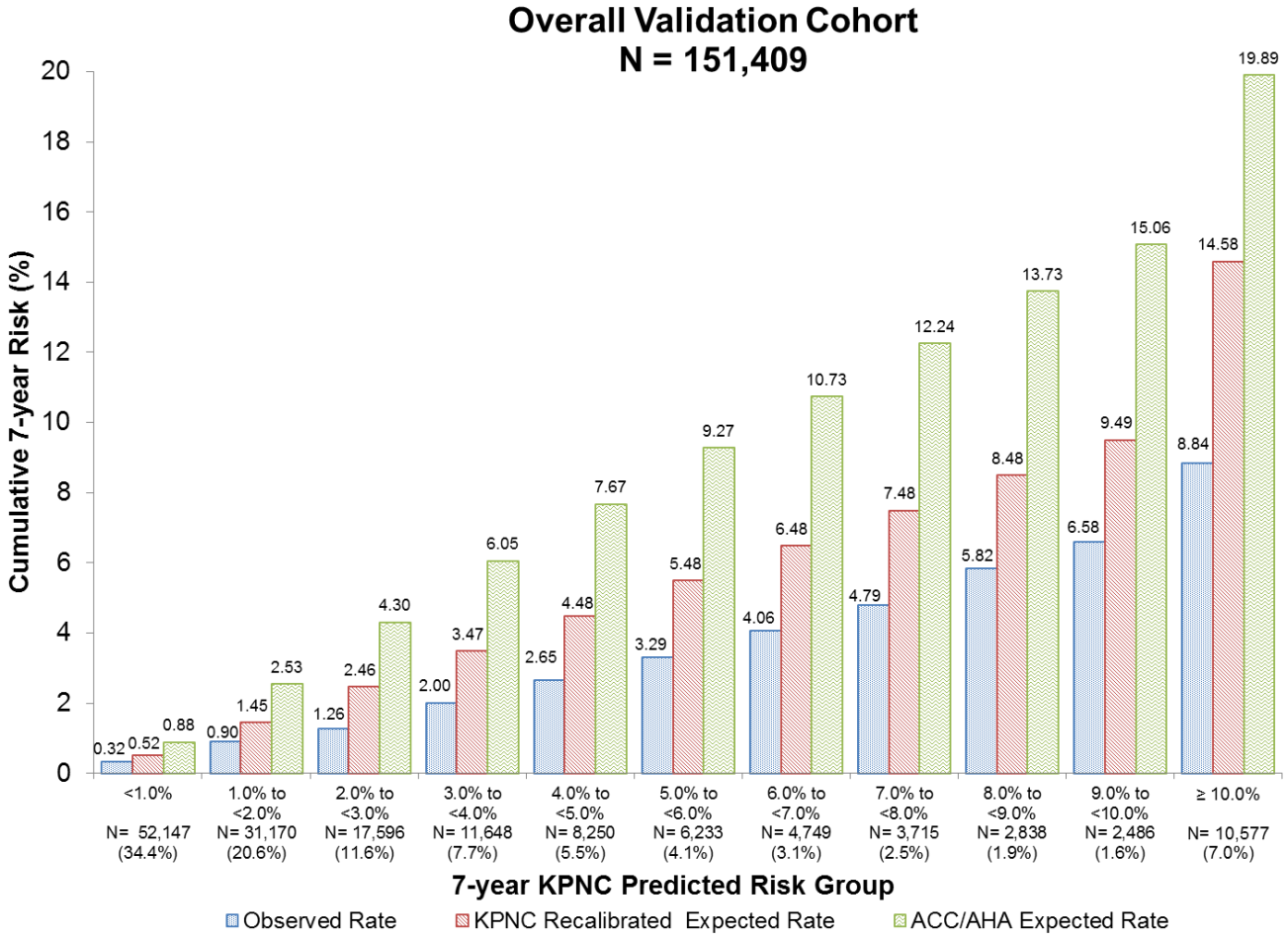
Validation Cohort Results (N=151,409)

KPNC ASCVD Risk Estimator in 40-79 year-old adults without diabetes and not taking statins



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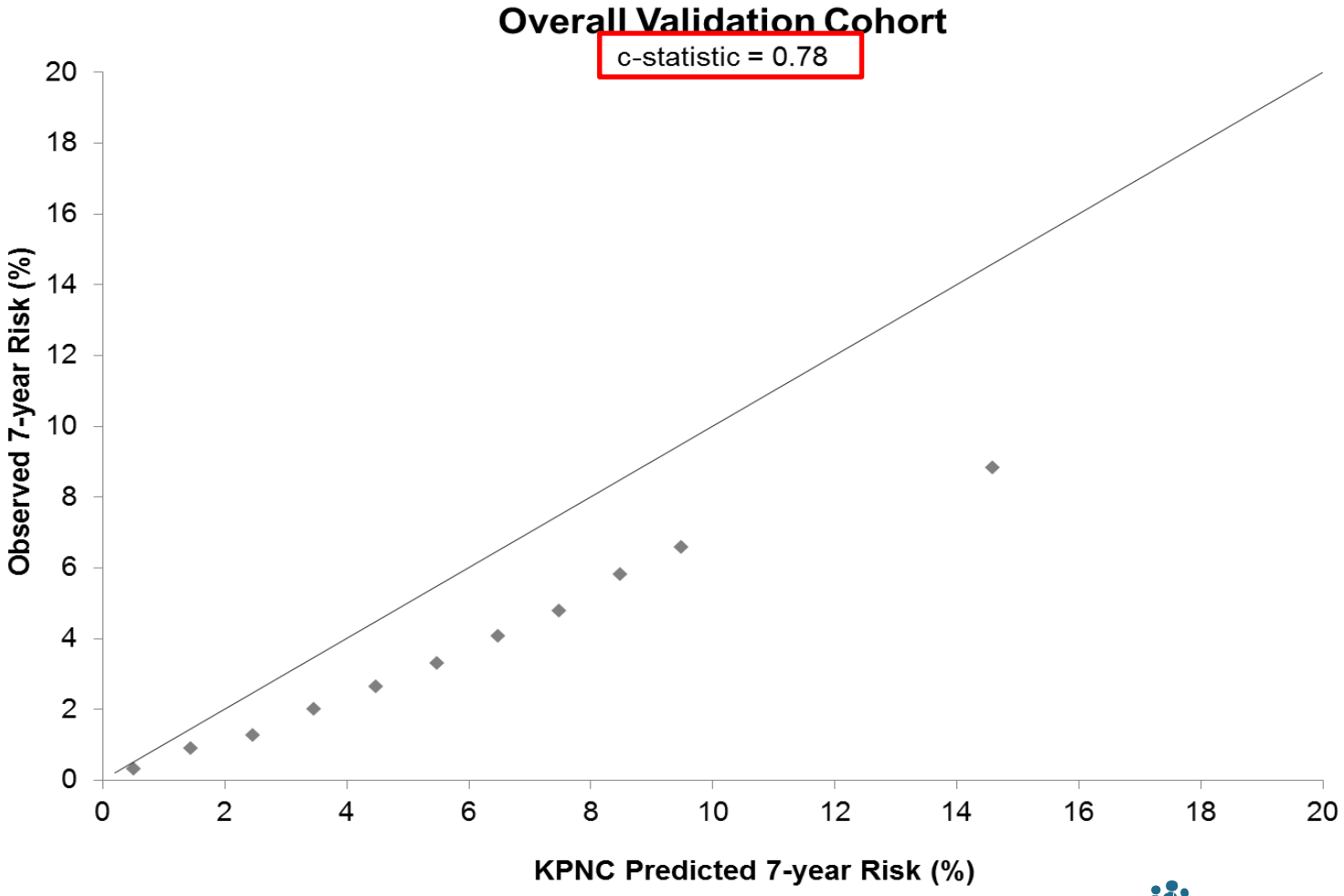
Validation Primary Prevention Cohort Results (N=151,409)

Improved **calibration and discrimination** of KPNC ASCVD Risk Estimator in 40-79 year-old adults without diabetes and not on statins



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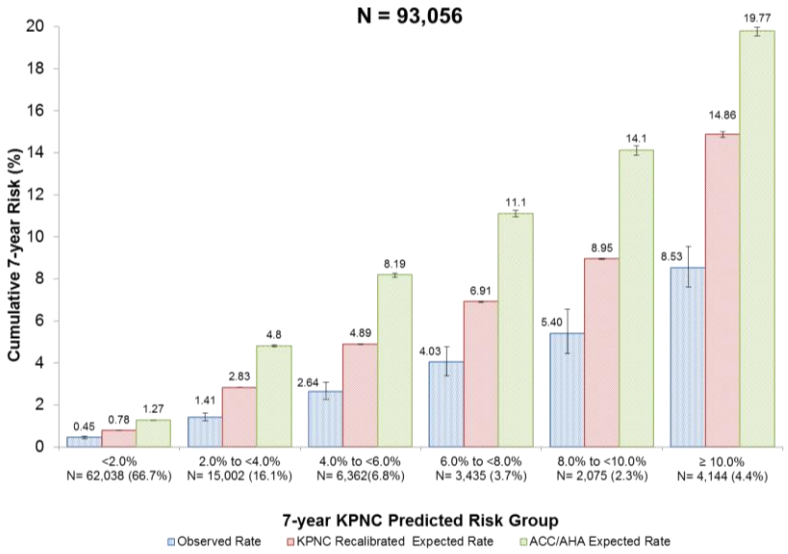
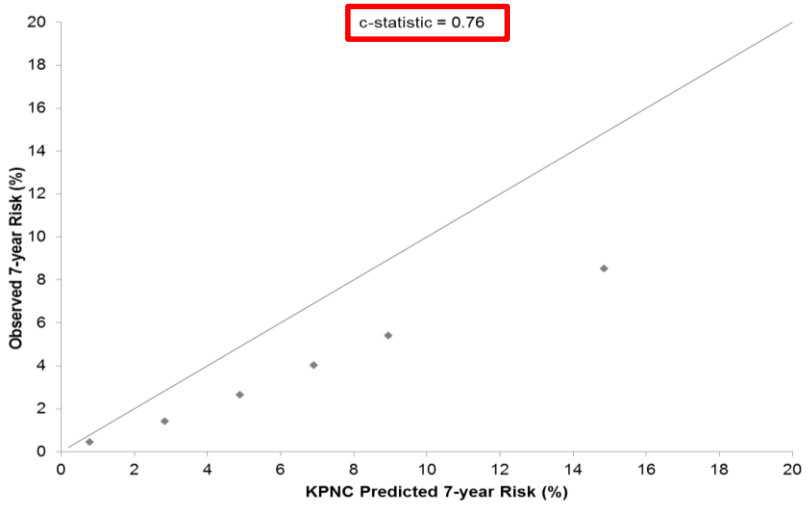
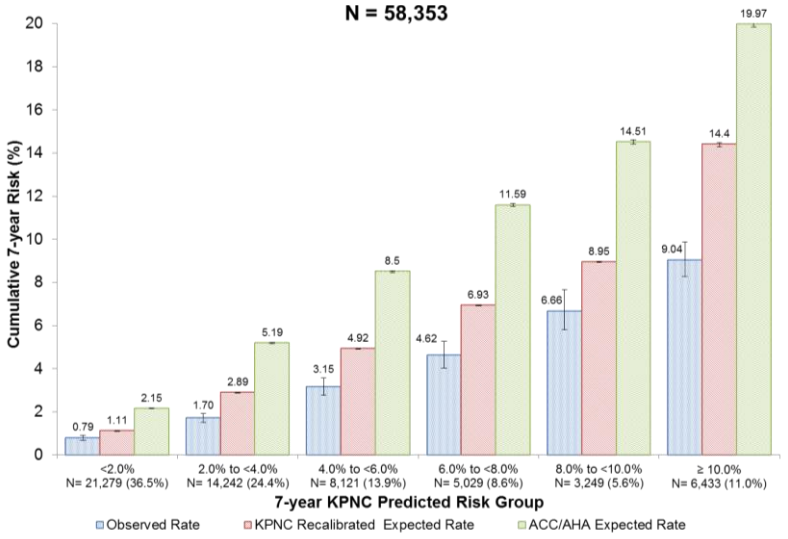
Validation Cohort Results - Gender

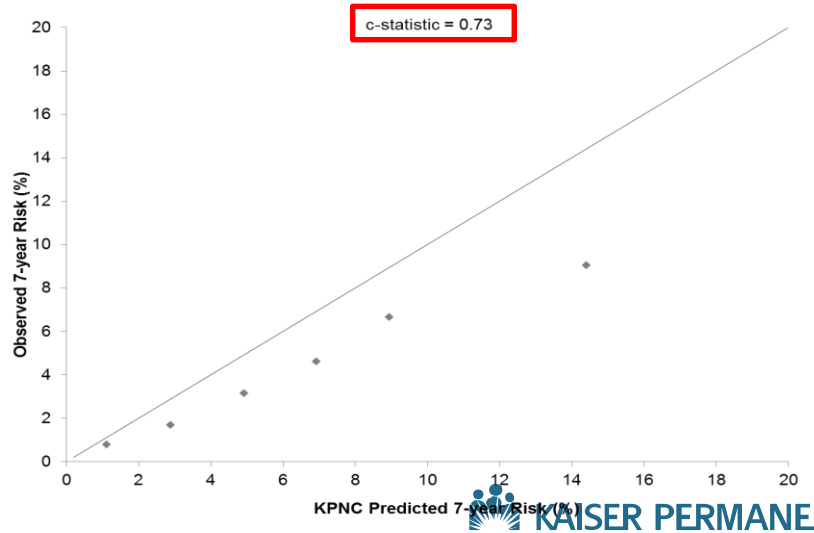
Women (N=93,056)





Men (N=58,353)





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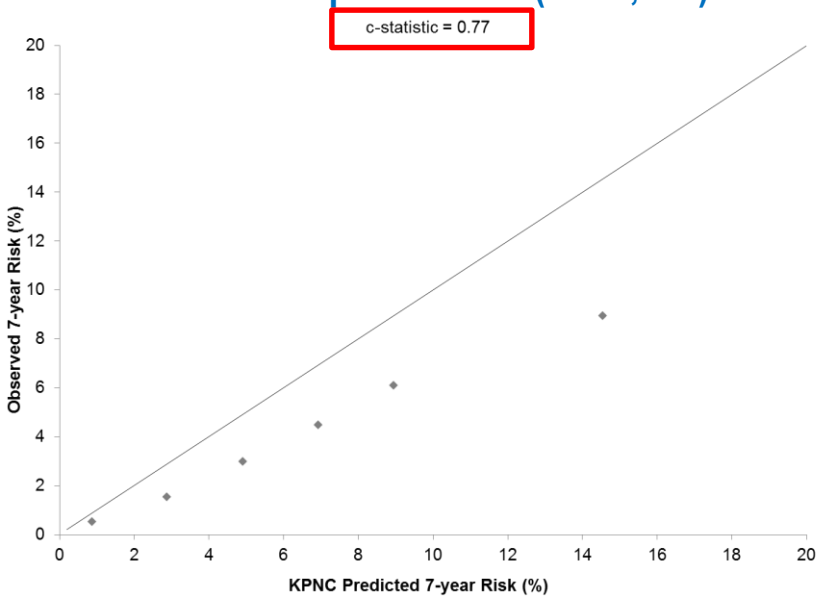
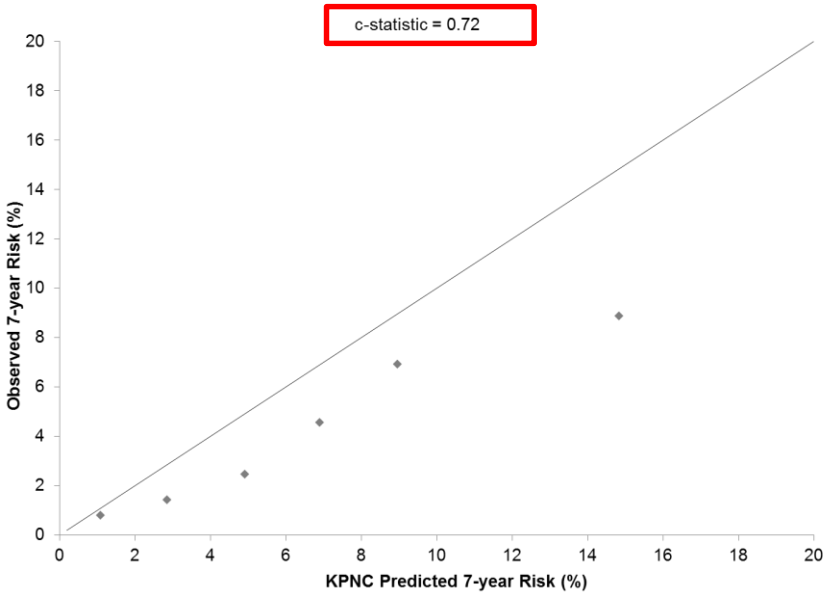
Validation Cohort Results – Race/Ethnicity

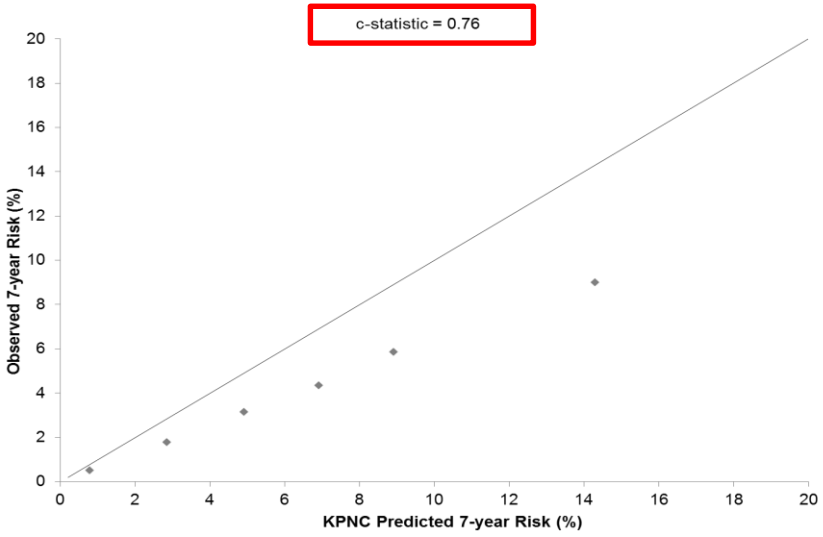
Non-Hispanic White (N=99,090)



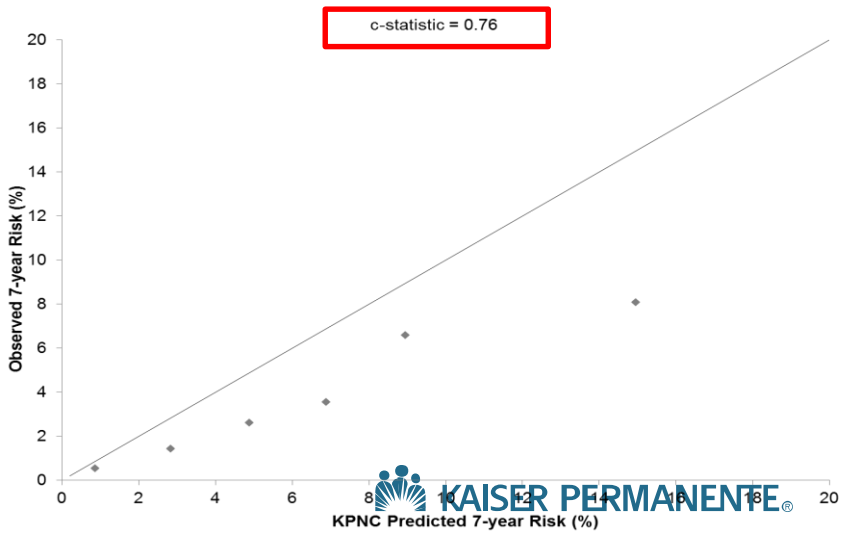
Non-Hispanic Black (N=10,173)



Asian/Pacific Islander (N=24,306)



Hispanic (N=17,840)



Summary

- Following approach used to derive ACC/AHA ASCVD Risk Estimator, our recalibrated KPNC ASCVD Risk Estimator is significantly more accurate for predicting 7-year actual risk of ASCVD event

  - ↑ calibration with only modest overestimation
  - ↑ discrimination vs. ACC/AHA risk estimator
  - Improved in all gender & race/ethnicity subgroups

FUTURE

- Additional validation underway in other contemporary, real world primary prevention populations

- Recalibrated risk estimator can better assist with shared decision-making for primary prevention strategies and serve as platform for future improvement of risk equation

CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Comparative Trends in Heart Disease, Stroke, and All-Cause Mortality in the United States and a Large Integrated Healthcare Delivery System

Stephen Sidney, MD, MPH,[a] Michael E. Sorel, MPH,[a] Charles P. Quesenberry, PhD,[a] Marc G. Jaffe, MD,[b] Matthew D. Solomon, MD, PhD,[a,c] Mai N. Nguyen-Huynh, MD,[d] Alan S. Go, MD,[a,e,f] Jamal S. Rana, MD, PhD[a,c,g]

[a]Division of Research, Kaiser Permanente Northern California, Oakland; [b]Department of Endocrinology, Kaiser Permanente Northern California, South San Francisco; [c]Department of Cardiology, Kaiser Permanente Northern California, Oakland; [d]Department of Neurology, Kaiser Permanente Northern California, Walnut Creek; [e]Departments of Epidemiology, Biostatistics, and Medicine, University of California, San Francisco; [f]Department of Health Research and Policy, Stanford University School of Medicine, Stanford, Calif; [g]Department of Medicine, University of California, San Francisco, San Francisco.

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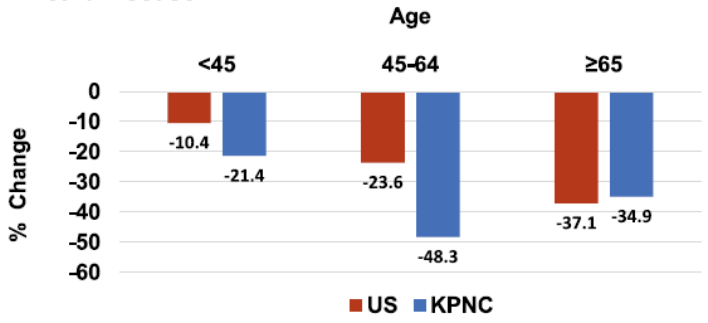
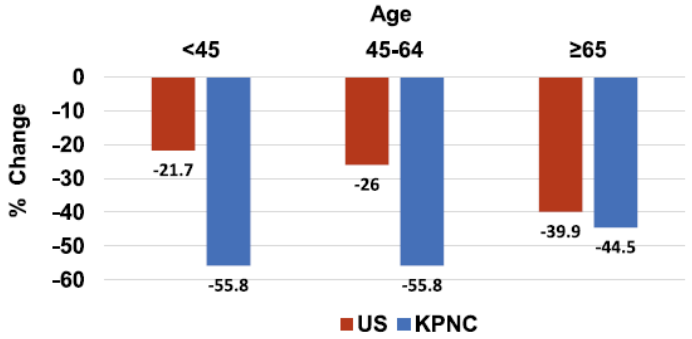
Decline in age-adjusted mortality rates (% change) from 2000 to 2015 United States vs. KPNC

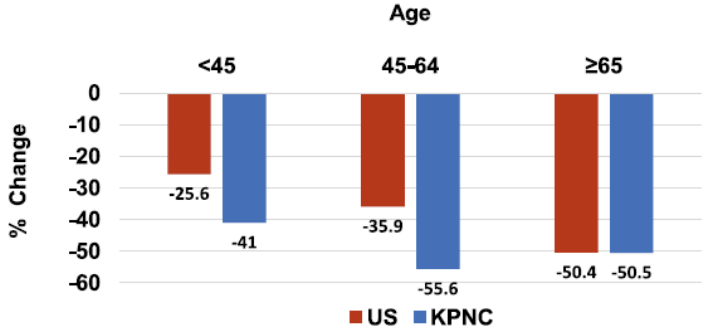
A. Heart Disease



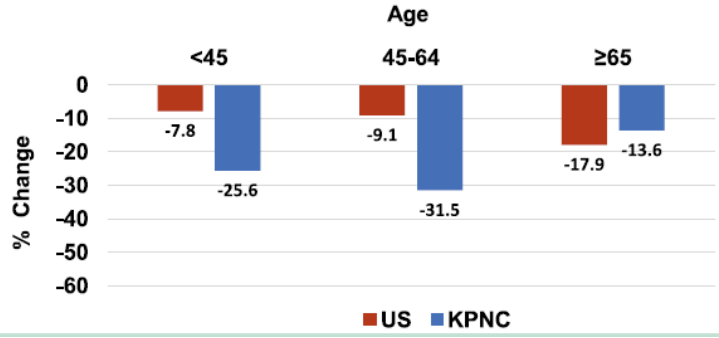
C. Stroke



B. Coronary Heart Disease



D. All-Cause



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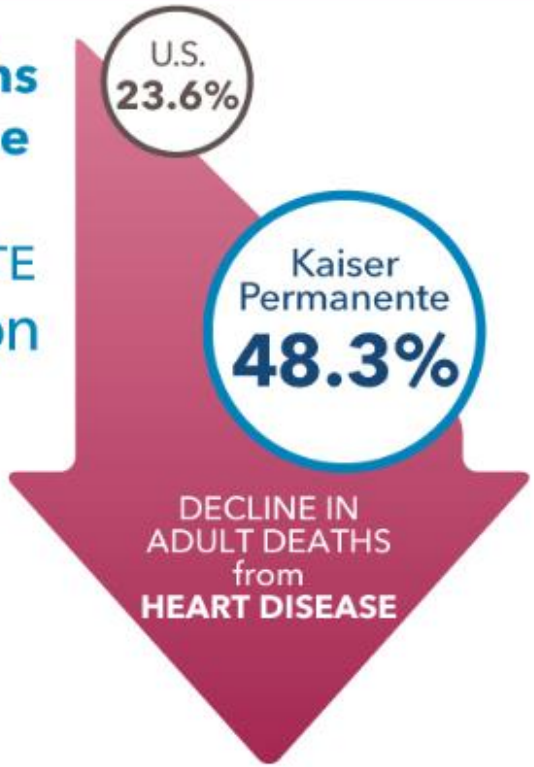
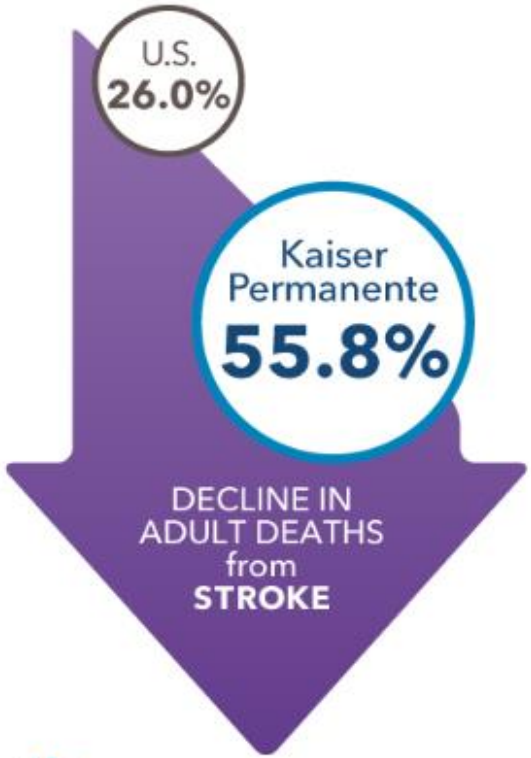
From 2000 to 2015

In **Reducing Deaths** from **Heart Disease** and **Stroke,** KAISER PERMANENTE Outpaces Nation





*NCal region, 45-64 year olds; Sidney et al., Am J Med 2018.

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Extremely large data sets that may be analyzed computationally to reveal patterns, trends, and associations

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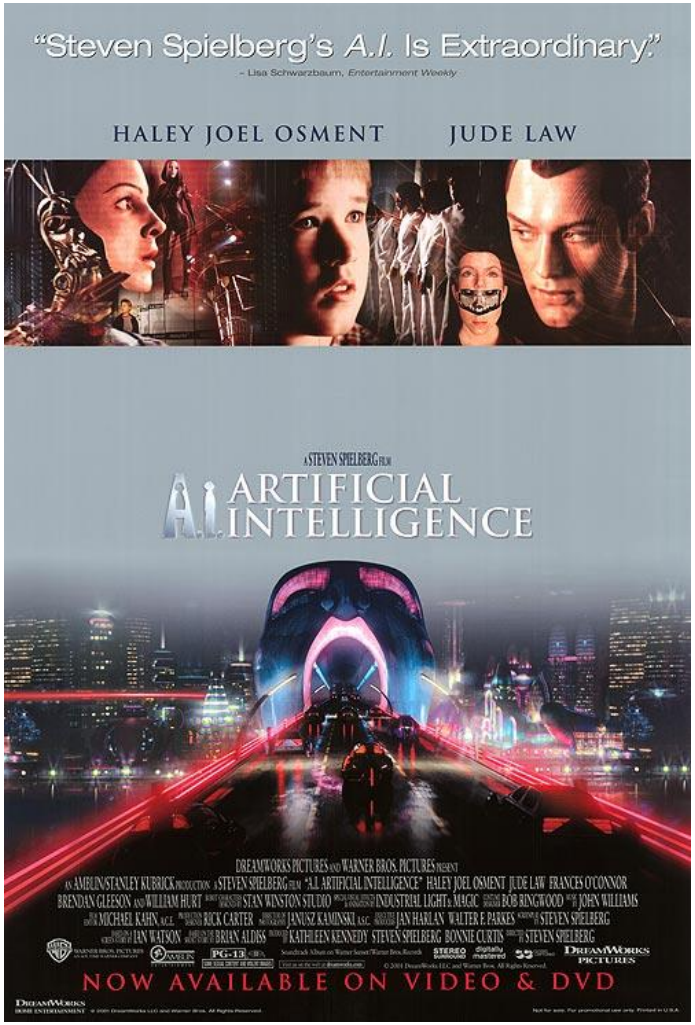

Artificial intelligence: Algorithm predicts clinical outcomes for hospital inpatients

Artificial intelligence outperforms traditional statistical models at predicting a range of clinical outcomes from a patient's entire raw electronic health record (EHR). A team led by Alvin Rajkomar and Eyal Oren from Google in Mountain View, California, USA, developed a data processing pipeline for transforming EHR files into a standardized format. They then applied deep learning models to data from 216,221 adult patients hospitalized for at least 24 h each at two academic medical centers, and showed that their algorithm could accurately predict risk of mortality, hospital readmission, prolonged hospital stay and discharge diagnosis. In all cases, the method proved more accurate than previously published models. The authors provide a case

npj Digital Medicine (2018)1:18 ; doi:10.1038/s41746-018-0029-1

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VIEWPOINT

Big Data and Predictive Analytics
Recalibrating Expectations

JAMA Published online May 29, 2018

- With the wide availability of data and predictive analytics, developing prediction models has never been easier.
- Big data and predictive analytics have substantial potential to support better, more efficient care.
- The potential of prediction to influence decision making also implies the potential for harm, through the dissemination of misinformation.

VIEWPOINT

Big Data and Predictive Analytics
Recalibrating Expectations

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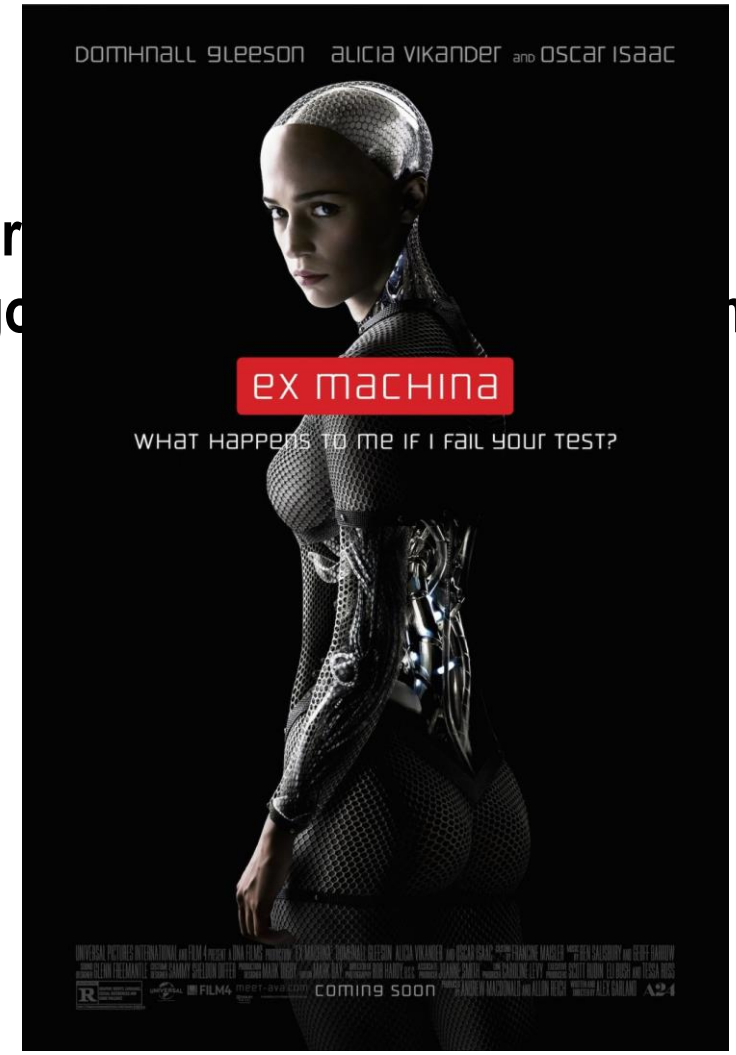

An inadequately pr mistakes one patient at a time, a faulty algo mbers of patients.

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