CONGRATULATIONS to MHIF Research Fellow Dr. Peter Tajti!

for winning the TCT Fellow Case Competition

Interviewed on KARE 11: 
Dr. Paul Sorajja
Small device shows big promise for heart patients
COAPT study using MitraClip

Interviewed on KDUZ Radio:
Dr. Jay Traverse
CONCERT and SENECA studies for stem cell therapy in HF

FEATUED MHIF STUDIES
Open for Enrollment and Referrals!

TRANSCEND for peripheral artery disease
CONTACT: JoAnne Goldman, 612-863-3973

ASAP-SVG for coronary artery disease
CONTACT: Pamela Morley, 612-863-6066

MINT for myocardial ischemia & transfusion
CONTACT: Rose Peterson, 612-863-6051

First Recipient of The Jon DeHaan Foundation Award for Innovation in Cardiology

Dr. Kelly Han is recognized for her outstanding contributions to improving both safety and quality of imaging Congenital Heart Disease in adults, children and infants.

DISSEMINATING RESEARCH

Call out to Dr. John Lesser and the IIR team, including Sue Casey, for work on the PROTECTION VI study

LateBreaker at ESC Congress in August

Published in the European Heart Journal

Study assessed the use of strategies for dose reduction during CCTA as part of a multi-center, international registry
Disclosures

• Grants from American Heart Association and NIH

• No relationships with Industry
Evolution in personalized and precision medicine

<table>
<thead>
<tr>
<th>Individualized medicine</th>
<th>Population medicine</th>
<th>Precision Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominated till ~ 1980’s</td>
<td>1980’s and onward</td>
<td>2000’s and future?</td>
</tr>
</tbody>
</table>
Cardiovascular disease prevention – and risk factors for CHD -- were known before 1950 – but largely ignored in clinical medicine

History of CHD – Henry Blackburn, MD

• “In hindsight, discussion of either the pathogenesis or treatment of coronary heart disease now seems conspicuously absent from the great classic texts on cardiology until Paul White’s in 1941. And even White, as late as his third edition in 1948, makes no mention of prevention.”

• “A heart attack after age 80 is an act of God; before 80 a failure of medicine.” “A vigorous five-mile walk will do more good for an unhappy but otherwise healthy adult than all the medicine and psychology in the world.”
Some critical observations before 1970’s

- Experimental animal work going back to 1920’s on cholesterol and atherosclerosis
- Smoking data – well known to life insurance industry as early as 1940’s
- Framingham – started 1948 – first papers appeared 1960-61

• Much skepticism and controversy about risk assessment and prevention before late 1970’s - mid 1980’s

From: What is a normal blood pressure?
Eur Heart J. 2018;39(24):2233-2240

Personalized hypertension treatment

From: What is a normal blood pressure?
Eur Heart J. 2018;39(24):2233-2240
1984: The beginning of the era of CHD prevention and continued efforts to personalize CVD prevention

Report of the National Cholesterol Education Program
Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults

1988

Personalized Lipid Treatment

Table 1. — Initial Classification and Recommended Followup Based on Total Cholesterol*

<table>
<thead>
<tr>
<th>Classification, mg/dL</th>
<th>Desirable blood cholesterol</th>
<th>Borderline-high blood cholesterol</th>
<th>High blood cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 to 239</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥240</td>
<td></td>
<td>Repeat within five years</td>
<td></td>
</tr>
</tbody>
</table>

Recommended followup:
- Total cholesterol, <200 mg/dL
- Total cholesterol, 200-239 mg/dL
- Without definite CHD or other CHD risk factors (one of which can be male sex)
- With definite CHD or other CHD risk factors (one of which can be male sex)
- Total cholesterol ≥240 mg/dL

Table 2. — Classification and Treatment Decisions Based on LDL-Cholesterol*

<table>
<thead>
<tr>
<th>Classification, mg/dL</th>
<th>Desirable LDL-cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;130</td>
<td>Borderline-high-risk LDL-cholesterol</td>
</tr>
<tr>
<td>130 to 159</td>
<td>High-risk LDL-cholesterol</td>
</tr>
<tr>
<td>≥160</td>
<td>Initiation Level, mg/dL</td>
</tr>
</tbody>
</table>

Dietary treatment:
- Without CHD or other risk factors
- With CHD or other risk factors

Drug treatment:
- Without CHD or other risk factors
- With CHD or other risk factors
2001

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults
Statin Benefit Groups

- Clinical ASCVD (1A)
- LDL-C >190 mg/dL without secondary cause (1A)
- Primary prevention – Diabetes(DM) – Age 40-75 years – LDL-C 70-189 mg/dL (1A)
- Primary prevention – No DM – Age 40-75 years – LDL-C 70-189 mg/dL; ASCVD risk ≥ 7.5%* (1A)

Validation of the Atherosclerotic Cardiovascular Disease Pooled Cohort Risk Equations

Paul Muntner, PhD; Lisandro D. Colantonio, MD; Mary Cushman, MD; David C. Goff Jr, MD, PhD; George Howard, DrPH; Virginia J. Howard, PhD; Brett Kissela, MD, MS; Emily B. Levitan, ScD; Donald M. Lloyd-Jones, MD, ScM; Monika M. Safford, MD

DESIGN, SETTING, AND PARTICIPANTS  Adults aged 45 to 79 years enrolled in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study between January 2003 and October 2007 and followed up through December 2010. We studied participants for whom atherosclerotic CVD risk may trigger a discussion of statin initiation (those without clinical atherosclerotic CVD or diabetes, low-density lipoprotein cholesterol level between 70 and 189 mg/dL, and not taking statins; n = 10 997).

"With more complete ascertainment of events in this subgroup (with Medicare data on events), there tended to be modest under-prediction of event rates by the Pooled Cohort equations."
Coronary Calcium as a Predictor of Coronary Events in Four Racial or Ethnic Groups

Robert Detrano, M.D., Ph.D., Alan D. Guerci, M.D., J. Jeffrey Carr, M.D., M.S.C.E., Diane E. Bild, M.D., M.P.H., Gregory Burke, M.D., Ph.D., Aaron R. Folsom, M.D., Kiang Liu, Ph.D., Steven Shea, M.D., Myles Szklar, M.D., Dr.P.H., David A. Bluemke, M.D., Ph.D., Daniel H. O’Leary, M.D., Russell Tracy, Ph.D., Karol Watson, M.D., Ph.D., Nathan D. Wong, Ph.D., and Richard A. Kronmal, Ph.D.

NEJM 2008, Cited Over 650 times
A Citation Classic by Thomson Reuters
Table 1. Risk of Coronary Events Associated with Increasing Coronary-Artery Calcium Score after Adjustment for Standard Risk Factors.

<table>
<thead>
<tr>
<th>Coronary-Artery Calcium Score</th>
<th>No./No. at Risk</th>
<th>Major Coronary Event‡</th>
<th>Any Coronary Event</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8/3409</td>
<td>1.00</td>
<td>15/3409</td>
<td>1.00</td>
<td>&lt;0.001</td>
<td>3.61 (1.96-6.65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1–100</td>
<td>25/1728</td>
<td>3.89 (1.72-8.79)</td>
<td>39/1728</td>
<td>7.73 (4.13-14.47)</td>
<td>&lt;0.001</td>
<td>15.97 (7.81-33.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>101–300</td>
<td>24/5250</td>
<td>7.08 (1.05-16.47)</td>
<td>41/5250</td>
<td>7.73 (4.13-14.47)</td>
<td>&lt;0.001</td>
<td>15.97 (7.81-33.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;300</td>
<td>12/833</td>
<td>6.84 (2.93–15.99)</td>
<td>67/833</td>
<td>9.67 (5.20-17.98)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LogⅢ[log(CAC+1)]§

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.20 (1.12–1.29)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.26 (1.19–1.33)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1: Distribution of coronary artery calcium by risk factor burden.
**Figure 4** Total (A) and hard (B) coronary heart disease event rates (per 1000 person-years) with increasing coronary artery calcium scores according to Framingham risk score category.

**CENTRAL ILLUSTRATION:** Proposed Decision-Making Approach to Selective Use of Coronary Artery Calcium Measurement for Risk Prediction

<table>
<thead>
<tr>
<th>Using 10-year ASCVD risk estimate plus coronary artery calcium (CAC) score to guide statin therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient's 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimate:</td>
</tr>
<tr>
<td>&lt;5%</td>
</tr>
<tr>
<td>5-7.5%</td>
</tr>
<tr>
<td>&gt;7.5-20%</td>
</tr>
<tr>
<td>&gt;20%</td>
</tr>
<tr>
<td>Consulting ASCVD risk estimate alone</td>
</tr>
<tr>
<td>Statin not recommended</td>
</tr>
<tr>
<td>Consider for statin</td>
</tr>
<tr>
<td>Recommend statin</td>
</tr>
<tr>
<td>Recommend statin</td>
</tr>
<tr>
<td>Consulting ASCVD risk estimate + CAC</td>
</tr>
<tr>
<td>If CAC score = 0</td>
</tr>
<tr>
<td>Statin not recommended</td>
</tr>
<tr>
<td>Statin not recommended</td>
</tr>
<tr>
<td>Statin not recommended</td>
</tr>
<tr>
<td>Recommend statin</td>
</tr>
<tr>
<td>If CAC score &gt; 0</td>
</tr>
<tr>
<td>Statin not recommended</td>
</tr>
<tr>
<td>Consider for statin</td>
</tr>
<tr>
<td>Recommend statin</td>
</tr>
<tr>
<td>Recommend statin</td>
</tr>
<tr>
<td>Does CAC score modify treatment plan?</td>
</tr>
<tr>
<td>CAC not effective for this population</td>
</tr>
<tr>
<td>CAC can reclassify risk up or down</td>
</tr>
<tr>
<td>CAC can reclassify risk up or down</td>
</tr>
<tr>
<td>CAC not effective for this population</td>
</tr>
</tbody>
</table>

What is the future of preventive cardiovascular medicine?

Cardiovascular Omics Compendium

Emerging Role of Precision Medicine in Cardiovascular Disease

Jane A. Leopold, Joseph Loscalzo

“Precision medicine is poised to become the next great revolution in the practice of medicine, as well as in the maintenance of cardiovascular health and the prevention and cure of cardiovascular disease. Precision medicine disrupts standard practice and draws from clinical testing, electronic health records, pan-omics profiling, big data sets, and novel analytical methods, such as systems biology and network science, to create a person-specific phenotype that can then be used to identify an optimal intervention with minimal risk.”

“The obvious benefits of this approach to patients, clinicians, and researchers are numerous and include individual phenotype specificity, identification of individuals with a similar molecular phenotype, selection of best drugs or therapies with maximal efficacy and no or limited adverse reactions, efficient selection and enrichment of clinical trial participants, potential to improve adherence and reduce costs, and creating a paradigm shift in how cardiovascular care is delivered.”
FORMULA FOR SUCCESS:
UNDER PROMISE AND
OVER DELIVER

TOM PETERS

PROMISE QUOTES.COM

Treatment Approaches

Standard-of-care

Clinical Evaluation

Standard Algorithm

Generalized Recommendation

Precision Cardiology

Therapeutic Space

Multi-Omic Information

Machine Learning

Data-Driven Recommendation

Clinician Review and Decision

Bile acid sequestrant

Coloxyl®

Non-dihydropyridine Ca²⁺ channel blocker

Verapamil

atrial

Lisinopril

ACE inhibitor

Propanolol

β-blocker

K⁺ sparing diuretic

Amiodarone

Hydralazine

Fibrate

Cholestyramine

Coloxyl®
• OR estimated at 4.4
• Lowest risk group is present in ~50%; Intermediate ~40%; Highest risk ~10%
Assessing Risk Factors as Potential Screening Tests
A Simple Assessment Tool
Nicholas J. Wald, FRS, FRCP, Joan K. Morris, PhD

Many risk factors for disease are suggested as screening tests when there is little prospect that they could be useful in predicting disease. To avoid this, it is useful to know the relationship between the relative risk of a disease or disorder in people with high and low values of a risk factor, and the equivalent screening performance in terms of the detection rate (sensitivity) for a specified false-positive rate. We describe an interactive Risk-Screening Converter, accessible from the Internet (http://www.wolfsongqmul.ac.uk/rsc/), that transforms an odds ratio into the equivalent estimates of detection and false-positive rates. The converter is intended for general clinicians, for people engaged in research into risk factors and disease, and for those who give advice on applying such research findings into medical practice. It should help to distinguish effective screening methods from ineffective ones, and so improve clinical guidelines relating to screening and the prediction and prevention of disease. Arch Intern Med. 2011;171(4):286-291.

Graph of detection rate according to false positive rate for a specified odds ratio

Enter proportion of population in lowest group
Enter proportion of population in highest group
Enter odds ratio comparing highest group with lowest group

Unaffected

Affected

50%
10%
4.4

This Risk-Screening converter is available from www.wolfsongqmul.ac.uk/rsc/

Specify the detection rate as a percentage 90.0%

False positive rate is 27.8% for a 50% detection rate
Table 3 | Prevalence and clinical impact of a high GPS

<table>
<thead>
<tr>
<th>CAD</th>
<th>Reference group</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Top 20% of distribution</td>
<td>Remaining 80%</td>
<td>2.55</td>
<td>2.43-2.67</td>
</tr>
<tr>
<td>Top 10% of distribution</td>
<td>Remaining 90%</td>
<td>2.89</td>
<td>2.74-3.05</td>
</tr>
<tr>
<td>Top 5% of distribution</td>
<td>Remaining 95%</td>
<td>3.34</td>
<td>3.12-3.58</td>
</tr>
<tr>
<td>Top 1% of distribution</td>
<td>Remaining 99%</td>
<td>4.83</td>
<td>4.25-5.46</td>
</tr>
<tr>
<td>Top 0.5% of distribution</td>
<td>Remaining 99.5%</td>
<td>5.17</td>
<td>4.34-6.12</td>
</tr>
</tbody>
</table>

Graph of detection rate according to false positive rate for a specified odds ratio

- Enter proportion of population in lowest group
- Enter proportion of population in highest group
- Enter odds ratio comparing highest group with lowest group

This ROC-Screening converter is available from www.medcalc.org.

Specify the detection rate as a percentage

False positive rate is 28.68% for a 50% detection rate

To obtain the false positive rate (FPR) for a specified detection rate (DR), enter “DR” in the box below.

To obtain the detection rate (DR) for a specified false positive rate (FPR), enter “FPR” in the box below.

Odds of being affected given a positive result (OAPR) is 1: 24

Odds ratio per 1 cd increase in value of risk factor is 1.75
From the Abstract:

An elastic net Cox regression based with 586 unimputed variables with continuous values discretised achieved a C-index of 0.801 (bootstrapped 95% CI 0.799 to 0.802), compared to 0.793 (0.791 to 0.794) for a traditional Cox model comprising 27 expert-selected variables with imputation for missing values. We also found that data-driven models allow identification of novel prognostic variables; that the absence of values for particular variables carries meaning, and can have significant implications for prognosis; and that variables often have a nonlinear association with mortality, which discretised Cox models and random forests can elucidate. This demonstrates that machine-learning approaches applied to raw EHR data can be used to build models for use in research and clinical practice, and identify novel predictive variables and their effects to inform future research.
Comparison of modelling methods

We found that random forests did not outperform Cox models despite their inherent ability to accommodate nonlinearities and interactions [48, 49]. Random forests have a number of shortcomings which may explain this. First, only a random subset of variables \( m_{	ext{sys}} \) are tried at each split, so datasets that contain a large proportion of uninformative ‘noise’ variables may cause informative variables to be overlooked by chance at many splits. Increasing \( m_{	ext{sys}} \) can improve performance, but often at a large cost in computation time. Second, when random forests are used for prediction, the predictions are a weighted average of a subset of the data, and are biased away from the extremes [50]. This may partly explain their poor calibration.

We did not find that discretisation of continuous variables improved model performance, probably because the majority of these variables had associations with prognosis that were close to linear, and the small improvement in fit was offset by the large increase in the number of model parameters.

Disadvantages of data-driven approaches

Conventional statistical modelling techniques retain advantages and disadvantages which are the converse of these: models are more readily interpretable, and may generalise better, but at the expense of requiring significant expert input to construct, potentially not making use of the richness of available data, and only being applicable to complete data.

Original Investigations

Genomic Risk Prediction of Coronary Artery Disease in 480,000 Adults

Implications for Primary Prevention
CONCLUSIONS

“The genomic score developed and evaluated in the present study strengthens the concept of using genomic information to stratify individuals for CAD risk in general populations and demonstrates the potential for genomic screening in early life to complement conventional risk prediction.”

A closer look

• METHODS: Using a meta-analytic approach to combine large-scale, genome-wide, and targeted genetic association data, we developed a new genomic risk score for CAD (metaGRS) consisting of 1.7 million genetic variants. We externally tested metaGRS, both by itself and in combination with available data on conventional risk factors, in 22,242 CAD cases and 460,387 noncases from the UK Biobank.

• RESULTS: The hazard ratio (HR) for CAD was 1.71 (95% confidence interval [CI]: 1.68 to 1.73) per SD increase in metaGRS, an association larger than any other externally tested genetic risk score previously published.

• The metaGRS stratified individuals into significantly different life course trajectories of CAD risk, with those in the top 20% of metaGRS distribution having an HR of 4.17 (95% CI: 3.97 to 4.38) compared with those in the bottom 20%.

• The metaGRS had a higher C-index (C = 0.623; 95% CI: 0.615 to 0.631) for incident CAD than any of 6 conventional factors (smoking, diabetes, hypertension, body mass index, self-reported high cholesterol, and family history).

J Am Coll Cardiol 2018;72:1883–93
False positive rate (1-specificity)
The numbers for CAC: Highest 11%;
Lowest (0) 50%; OR 10

Graph of detection rate according to false positive rate for a specified odds ratio

- Enter proportion of population in lowest group
- Enter proportion of population in highest group
- Enter odds ratio comparing highest group with lowest group
- SLR: 10

Some additional concerns about the approach
Getting to “Precision” -- Against the Odds

Detection rates for a 10% FPR by OR comparing lowest 20% to highest 20%

Assessing Risk Factors as Potential Screening Tests: A Simple Assessment Tool
Nicholas J. Wald, FRS, FRCP; Joan K. Morris, PhD.

Potential Biases in Machine Learning Algorithms Using Electronic Health Record Data

Milena A. Gianfrancesco, PhD, MPH; Suzanne Tamang, PhD, MS; Jinoos Yazdany, MD, MPH; Gabriela Schmajuk, MD, MS

JAMA Internal Medicine August 2018
Summary

• Current approaches to “precision cardiovascular prevention” are admittedly imperfect.
• But – current approaches allow considerable personalization and customization. NOT “one-size” fits all.
• Much of what is now being called “precision medicine” is not appreciably better than what already exists.
• A healthy skepticism, along with greater acceptance of, and confidence in, what we currently can do, is justified.
• George Box:

> All models are wrong, but some are useful.

— George E. P. Box —

Table. Sources of Bias in EHR Data and Their Potential to Contribute to Health Care Disparities

<table>
<thead>
<tr>
<th>Sources of Bias Entering EHR Systems</th>
<th>Potential to Differentially Affect Vulnerable Populations</th>
<th>Example of Biases With Respect to Clinical Decision Support Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing data</td>
<td>Certain patients may have more fragmented care and/or be seen at multiple institutions; patients with lower health literacy may not be able to access online patient portals and document patient-reported outcomes</td>
<td>The EHR may only contain more severe cases for certain patient populations and make erroneous inferences about the risk for such cases; conditioning on complete data may eliminate large portions of the population and result in inaccurate predictions for certain groups</td>
</tr>
<tr>
<td>Sample size</td>
<td>Certain subgroups of patients may not exist in sufficient numbers for a predictive analytic algorithm</td>
<td>Underestimation may lead to estimates of mean trends to avoid overfitting, leading to uninformative predictions for subgroups of patients; clinical decision support may be restricted to only the largest groups, spanning improvements in certain patient populations without similar support for others</td>
</tr>
<tr>
<td>Miscategorization or measurement error</td>
<td>Patients of low socioeconomic status may be more likely to be seen in teaching clinics, where data input or clinical reasoning may be less accurate or systematically different than that from patients of higher socioeconomic status; implicit bias by health care practitioners leads to disparities in care</td>
<td>Algorithm inaccurately learns to treat patients of low socioeconomic status according to less than optimal care and/or according to implicit biases</td>
</tr>
</tbody>
</table>