Cardiovascular Disease Risk Prediction: Lessons for Arthritis

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Disclosures

• Dr. Lloyd-Jones has no relationships with industry/ relevant conflicts of interest to disclose

• Grant funding:
  – NIH, AHA, CMMS
Using Clinical Decision Rules in CVD Prevention
Clinical Decision Rules

• What do we use them for?
  – Diagnosis, prognosis, treatment decisions

• Why do we need them?
  – Signs and symptoms rarely pathognomonic
  – Risk factors (almost) never deterministic
  – Need prior probability for test/treat decisions (Bayes)
    • Test or treat all? None? Some?
  – Enrich the pool for cost-effective treatment
  – Patients and clinicians are very poor at estimating risk/probability and net benefit of therapy
Treatment Thresholds
Finding net benefit

Where does your patient fall? And how do you know?

Net harm  Marginal benefit  Net benefit

Risk of adverse Event from Rx  Threshold of treatment benefit

Risk of disease
Why Do We Estimate Risk?

• Clinical/academic interest
  – Understand mechanisms of disease
  – Prognosis: assess comparative risks for different diseases or death
  – Identify risk factors/novel targets for therapy
  – Assess relative contributions of risk factors to disease incidence
  – Compare risks of disease with potential benefits and harms of therapies
Patients substantially overestimate and underestimate risk

• 1557 primary care patients asked to estimate risk on a continuous scale of 0% to 100%

<table>
<thead>
<tr>
<th>Perceived 10-year risk compared to actual 10-year risk</th>
<th>Patients (%)</th>
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<tbody>
<tr>
<td>• Mean absolute differences between perceived and actual predicted 10-year risk were:</td>
<td></td>
</tr>
<tr>
<td>• 22.9% (95% CI 21.8–24.0%) for MI</td>
<td></td>
</tr>
<tr>
<td>• 24.6% (23.4–25.8%) for stroke</td>
<td></td>
</tr>
</tbody>
</table>
Physicians overestimate and underestimate risk

- 79 physicians at all levels at 3 university hospitals
- Surveyed re: 12 primary prevention scenarios
  - Overestimation (MD estimate >1.5x actual risk)
  - Underestimation (MD estimate <0.67x actual risk)
- Only 24% of physicians' risk estimates were accurate
  - Physicians overestimated absolute risk 32% to 92% of the time
  - Physicians made larger errors in patient scenarios involving patients with high total or LDL-c levels
Why Do We Estimate **Absolute** Risk?

- Relative risk is poorly understood by clinicians and patients
  - Problem of the referent group
- Understand absolute risk for prognosis
- Improve communication and motivate lifestyle change/adherence to therapy
- Identify treatment-eligible individuals at sufficiently high risk to merit treatment and expect net cost-effective benefit
- Directly compare benefits/harms of therapy
Rationale for Absolute Risk Estimation

• Allows identification of patients at sufficient risk to merit treatment with higher likelihood of net individual and societal benefit
• Allows direct comparison of potential benefits and harms from drug therapy

CTT, Lancet 2012
BPLTTC, Lancet 2014
Lloyd-Jones et al., Circ and JACC 2019
Evidence Base for Risk Estimation

• Providing CVD risk score data had statistically significant but modest effects on:
  • Initiation/intensification of BP and cholesterol medications
  • Levels of CVD risk factors
  • Estimated 10-year CVD risk at follow-up
• Harm very unlikely
• Use of validated, quantitative risk assessment scores appears to be appropriate, safe, and moderately efficacious in helping to control risk factors … with the potential for additional value to improve decision-making.
• (Especially true if therapy is expensive - early statins, early PCSK9i)
What is Probability and How Do We Estimate It?

• Probability (likelihood) is a measure or estimation of how likely it is that something will happen or that a statement is true (Wikipedia)

• Most often, we return to \( y = mx + b \)
  
  - \( y \) = outcome or diagnosis
  - \( x \) = predictor variable(s)
  - \( m \) = weight for each predictor variable
  - \( b \) = intercept (underlying disease risk)

• Transform relative hazards/odds ratios into absolute probabilities
How Do We Know if a Risk Score “Works”? 
How Do We Measure the Performance of a Screening/Risk Prediction Test?

We should use:

- Sensitivity/specifity/predictive value
- Discrimination
  - Area under the ROC curve (AUC; C statistic)
  - Discrimination slope
- Calibration
  - Hosmer/Lemeshow and GND tests
- Informativeness criteria
  - AIC, BIC
- Likelihood ratios (LR+ and LR-)
- Brier score
- Reclassification (NRI, IDI)
Example – Risk Prediction and Clinical Decision Making in Primary Prevention of ASCVD
2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Geriatric Society, the American Society of Preventive Cardiology, and the Preventive Cardiovascular Nurses Association

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Current Paradigm for CVD Prevention

• “The intensity of prevention efforts should match the absolute risk of the patient”
  – Those at low risk should receive appropriate lifestyle counseling to remain so as long as possible
  – Those at high risk should alter lifestyle and receive early evidence-based drug therapy
  – Those at “intermediate risk” should be considered for further testing to further risk stratify for net benefit of drugs

• This latter implies sequential testing (Bayesian framework) which fits well with medical decision making
Scaling the Net Benefits

• Interventions with similar relative risk reductions across risk strata (like statins) provide the greatest absolute risk reduction in those with the highest pretreatment risk.
• Thus, determination of absolute risk and expected absolute risk reduction is necessary to adequately assess the risk-benefit ratio of an intervention for an individual patient as well as for health policy.
• And we should weigh the expected benefit against potential harms, to understand net benefit.
What About Diabetes Risk with Statins?

Moderate intensity statin assumptions
CVD 35% RRR & New onset diabetes NNH=100

High intensity statin assumptions
CVD 45% RRR & New onset diabetes NNH=33
2017 ACC/AHA Hypertension Guidelines

Blood Pressure (BP) Thresholds and Recommendations for Treatment and Follow-Up

BP Thresholds and Recommendations for Treatment and Follow-up

- **Normal BP (BP <120/80 mm Hg)**
  - Promote optimal lifestyle habits
  - Reassess in 1 y (Class IIa)

- **Elevated BP (BP 120-129/<80 mm Hg)**
  - Nonpharmacologic therapy (Class I)
  - Reassess in 3-6 mo (Class I)

- **Stage 1 Hypertension (BP 130-139/80-89 mm Hg)**
  - Clinical ASCVD or estimated 10-y CVD risk ≥10%*
    - No
      - Nonpharmacologic therapy (Class I)
    - Yes
      - Nonpharmacologic therapy and BP-lowering medication (Class I)

- **Stage 2 Hypertension (BP ≥ 140/90 mm Hg)**
  - Nonpharmacologic therapy and BP-lowering medication† (Class I)

*Note: For clinical ASCVD, refer to the American Heart Association/American College of Cardiology guidelines.
2018 AHA/ACC/Multi-Specialty Cholesterol Guidelines

Primary Prevention:
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

- **Age 0-19 y**
  - Lifestyle to prevent or reduce ASCVD risk
  - Diagnosis of Familial Hypercholesterolemia → statin

- **Age 20-39 y**
  - Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
  - Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)

- **Age 40-75 y and LDL-C ≥70-<190 mg/dL (≥1.8-<4.9 mmol/L)**
  - Without diabetes mellitus
  - 10-year ASCVD risk percent begins risk discussion

- **Age >75 y**
  - Clinical assessment, Risk discussion

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ASCVD Risk Enhancers:
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., preeclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (e.g., South Asian ancestry)
- Lipid/Biomarkers:
  - Persistently elevated triglycerides (≥175 mg/dL, ≥2.5 mmol/L)
- In selected individuals if measured:
  - hs-CRP ≥2.0 mg/L
  - Lp(a) levels >50 mg/dL or >125 nmol/L
  - apoB ≥130 mg/dL
  - Ankle-brachial index (ABI) <0.9

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Risk discussion:
**<5% “Low Risk”**
- Emphasize lifestyle to reduce risk factors (Class I)

Risk discussion:
**5% - <7.5% “Borderline Risk”**
- If risk enhancers present then risk discussion regarding moderate-intensity statin therapy (Class IIb)

Risk discussion:
**≥7.5% - <20% “Intermediate Risk”**
- If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49% (Class I)

Risk discussion:
**≥20% “High Risk”**
- Initiate statin to reduce LDL-C ≥50% (Class I)

If risk decision is uncertain:
- Consider measuring CAC in selected adults:
  - CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
  - CAC = 1-99 favors statin (especially after age 55)
  - CAC = 100+ and/or ≥75th percentile, initiate statin therapy
AHA/ACC SPECIAL REPORT

Use of Risk Assessment Tools to Guide Decision-Making in the Primary Prevention of Atherosclerotic Cardiovascular Disease

A Special Report From the American Heart Association and American College of Cardiology
Approach to Risk Assessment in 1° Prevention: CPR

- Estimate Absolute 10-year ASCVD Risk
  - Low Risk: 0 - <5%
  - Borderline Risk: 5% - <7.5%
  - Intermediate Risk: 7.5% - <20%
  - High Risk: ≥20%

- Calculate

- Personalize: Clinician-patient discussion considering risk-enhancing factors and net benefit of therapy

- Reclassify: If uncertainty or patient indecision remains, and revise decision based on results

- Lifestyle modification
- lifestyle and drug therapy
C = Calculate: Estimate 10-Year and Lifetime Risks

Estimate Absolute 10-year ASCVD Risk

- Low Risk: 0 - <5%
- Borderline Risk: 5% - <7.5%
- Intermediate Risk: 7.5% - <20%
- High Risk: ≥20%

Clinician-patient discussion considering risk-enhancing factors and net benefit of therapy

If uncertainty or patient indecision remains, consider CAC score and revise decision based on results

Lifestyle modification

Lifestyle and drug therapy
C = Calculate: Tools for Risk Estimation

• Pooled Cohort Equations – App or Online (or EHR programmable)

• ACC ASCVD Risk Estimator Plus (online/app)

• AHA ASCVD Risk Calculator (online/app)
  – http://static.heart.org/riskcalc/app/index.html#!/baseline-risk

Northwestern Medicine®
## ASCVD Risk Estimator Plus

### Form Fields
- **Current Age**: Enter age (must be between 20-79)
- **Sex**: Select Male or Female
- **Race**: Select White, African American, or Other
- **Systolic Blood Pressure**: Enter value (must be between 90-200)
- **Diastolic Blood Pressure**: Enter value (must be between 60-130)
- **Total Cholesterol**: Enter value (must be between 130 - 320)
- **HDL Cholesterol**: Enter value (must be between 20 - 100)
- **LDL Cholesterol**: Enter value (must be between 30-300)
- **History of Diabetes**: Select Yes or No
- **Smoker**: Select Current, Former, or Never
- **On Hypertension Treatment**: Select Yes or No
- **On a Statin**: Select Yes or No
- **On Aspirin Therapy**: Select Yes or No
ASCVD Risk Estimator Plus

Current Age: 55
Sex: Female
Race: African American

Systolic Blood Pressure: 145
Diastolic Blood Pressure: 84
Total Cholesterol: 210
HDL Cholesterol: 56
LDL Cholesterol: 130

History of Diabetes: No
Smoker: Current
On Hypertension Treatment: No
On a Statin: No
On Aspirin Therapy: Yes

Lifetime ASCVD Risk: 39%
Optimal ASCVD Risk: 1.8%
External Validation: REGARD$\text{S}^*$

Participants without diabetes, LDL-C of 70 to 189 mg/dL, not taking statins

Total sample

<table>
<thead>
<tr>
<th>Decile of predicted risk</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
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</thead>
<tbody>
<tr>
<td>Mean (range) predicted risk</td>
<td>1.1% [0.2-1.8]</td>
<td>2.5% [1.8-3.2]</td>
<td>3.9% [3.2-4.8]</td>
<td>5.6% [4.8-6.5]</td>
<td>7.4% [6.5-8.3]</td>
<td>9.4% [8.3-10.5]</td>
<td>11.8% [10.5-13.1]</td>
<td>14.6% [13.1-16.4]</td>
<td>18.6% [16.4-21.7]</td>
<td>26.3% [21.7-68.3]</td>
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<td>16</td>
<td>18</td>
<td>25</td>
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<td>38</td>
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*5-year follow up
Muntner et al, JAMA 2014
External Validation: REGARDS*

Participants without diabetes, LDL-C of 70 to 189 mg/dL, not taking statins

Medicare-linked sample

*5-year follow up
Muntner et al, JAMA 2014
Performance of Pooled Cohort Equations in Diverse Population Samples: Predictable

- Low risk, high SES, medicated populations
- Broad US Population (REGARDS, DHS)
  - Well Calibrated
- HIV, Inflammatory/Rheum dz
  - Under-Estimate Risk

Estimated 10-y ASCVD Risk

Patient-Clinician Discussion
P = Personalize: Refine Risk for Individual Patients

Estimate Absolute 10-year ASCVD Risk

- Low Risk: 0 - <5%
- Borderline Risk: 5% - <7.5%
- Intermediate Risk: 7.5% - <20%
- High Risk: ≥20%

Clinician-patient discussion considering risk-enhancing factors and net benefit of therapy

If uncertainty or patient indecision remains, consider CAC score and revise decision based on results

- Lifestyle modification
- Lifestyle and drug therapy
**Risk-Enhancing Factors for Clinician–Patient Risk Discussion**

- **Family history of premature ASCVD**: (males, age <55 y; females, age <65 y)
- **Primary hypercholesterolemia** (LDL-C, 160-189 mg/dL [4.1- 4.8 mmol/L]; non-HDL-C 190-219 mg/dL [4.9-5.6 mmol/L])*
- **Metabolic syndrome** (increased waist circumference, elevated triglycerides [>175 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 in women mg/dL] are factors; tally of 3 makes the diagnosis)
- **Chronic kidney disease** (eGFR 15-59 mL/min/1.73 m² with or without albuminuria, not treated with dialysis or kidney transplantation)
- **Chronic inflammatory conditions** such as psoriasis, RA, or HIV/AIDS
- **History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as pre-eclampsia**
- **High-risk race/ethnicities** (e.g. South Asian ancestry)
- **Lipid/biomarkers**: Associated with increased ASCVD risk
  - Persistently* elevated, primary hypertriglyceridemia ( ≥175mg/dL);
  - If measured:
    - **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L)
    - **Elevated Lp(a)** A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥ 50 mg/dL or ≥125 nmol/L constitutes a risk enhancing factor especially at higher levels of Lp(a)
    - **Elevated apoB ≥130 mg/dL** - A relative indication for its measurement would be triglyceride ≥ 200 mg/dL. A level ≥ 130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk enhancing factor
    - **ABI (ABI) <0.9**

*Persistent elevation of lipid/biomarkers is recommended.
R = Reclassify Risk in Selected Patients

Estimate Absolute 10-year ASCVD Risk

- Low Risk: 0 - <5%
- Borderline Risk: 5% - <7.5%
- Intermediate Risk: 7.5% - <20%
- High Risk: ≥20%

Clinician-patient discussion considering risk-enhancing factors and net benefit of therapy

If uncertainty or patient indecision remains, consider CAC score and revise decision based on results

- Lifestyle modification
- Lifestyle and drug therapy
Coronary Artery Calcification
Powerful Marker of Plaque Burden
Screening for Coronary Calcium
MESA Study (Detrano, NEJM 2008)

![Graph showing cumulative incidence of major coronary events over years to event for different coronary-artery calcium scores.](image)

- Coronary-artery calcium score:
  - >300
  - 101–300
  - 1–100
  - 0

RF-Adj HR:
- 6.84
- 7.08
- 3.89
- 1.0 (ref)
ROC Curves Showing Area Under Curve for Incident CHD: MESA

NOTE: Reasonably large increase in AUC with CAC

FRS = 0.623
+ CAC = 0.784

Yeboah J. JAMA 2012; 308:788-95.
NRI for Incident CHD with Addition of Novel Risk Marker to FRS: MESA

<table>
<thead>
<tr>
<th>Variable</th>
<th>% Reclassified</th>
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<th></th>
<th></th>
<th>% Net Correct Reclassification</th>
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<td>Low</td>
<td>Intermediate</td>
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<td>1097</td>
<td>23</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NRI for FRS + CAC = 0.659

Yeboah J. JAMA 2012;308:788-95
Reclassification of Risk by CAC

Example: MESA Study

- **CAC = 0**
- **CAC 1 - 100**
- **CAC > 100**

7.5% 10-year risk
Threshold for considering statin

Dotted line represent reference line for 10-year ASCVD risk estimate of 7.5%

Nasir et al., MESA Study, JACC 2015
**R = Reclassify Risk in Selected Patients**

- 10-year risk: 5% - <7.5% or 7.5% - <20%
  - Consider risk-enhancing factors
  - Engage patient in discussion regarding net benefit of statin therapy

**Decision**

- **Decision for No Drug Therapy**
- **Decision for Drug Therapy**

**Patient Undecided or Clinical Uncertainty Regarding Net Benefit of Statin Therapy**

- Consider CAC measurement if performed:
  - **CAC = 0**
    - Below Threshold for Statin Benefit
      - Consider avoiding or postponing drug therapy.*
  - **CAC 1 - 99 and <75th %ile for age/sex race**
    - Subclinical atherosclerosis present; risk estimate similar. Repeat clinician-patient discussion with new information. Consider statin therapy now or postpone statin and consider repeat CAC in 5 years.
  - **CAC ≥ 100 or ≥75th %ile for age/sex/race**
    - Above Threshold for Statin Benefit
      - Recommend statin therapy.

*Clinicians and patients may not wish to postpone therapy in patients with a CAC score of 0 and diabetes mellitus, heavy current cigarette smoking, or strong family history of premature ASCVD.
Approach to Risk Assessment in 1° Prevention: CPR

1. **Calculate**
   - Low Risk: 0 - <5%
   - Borderline Risk: 5% - <7.5%
   - Intermediate Risk: 7.5% - <20%
   - High Risk: ≥20%

2. **Personalize**
   - Clinician-patient discussion considering risk-enhancing factors and net benefit of therapy

3. **Reclassify**
   - If uncertainty or patient indecision remains, consider CAC score and revise decision based on results

- Lifestyle modification
- Lifestyle and drug therapy
Machine Learning
Cardiovascular Event Prediction by Machine Learning  
The Multi-Ethnic Study of Atherosclerosis

Bharath Ambale-Venkatesh, Xiaoying Yang, Colin O. Wu, Kiang Liu, W. Gregory Hundley, Robyn McClelland, Antoinette S. Gomes, Aaron R. Folsom, Steven Shea, Eliseo Guallar, 
David A. Bluemke, João A.C. Lima

<table>
<thead>
<tr>
<th>Table 1. A List of the Markers That Were Used for Prediction in This Study</th>
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</thead>
<tbody>
<tr>
<td>Traditional risk factors, demographics, anthropometry, site</td>
</tr>
<tr>
<td>Age, sex, race, body mass index, body surface area, waist/hip ratio, systolic blood pressure, diastolic blood pressure, pulse pressure, diabetes mellitus, smoking status, pack-years, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, total cholesterol, triglycerides, heart rate, creatinine, site, waist circumference, hip circumference, fasting glucose</td>
</tr>
<tr>
<td>Medication use</td>
</tr>
<tr>
<td>All hypertension, angiotensin-converting enzyme, angiotensin-II receptor blockers, lipid control, statins, β-blockers, calcium channel blockers</td>
</tr>
<tr>
<td>Atherosclerotic markers—computed tomography, carotid ultrasonography</td>
</tr>
<tr>
<td>Coronary Artery Calcium score, ankle-brachial index, common and internal carotid artery intima media thickness, maximum carotid stenosis</td>
</tr>
<tr>
<td>Questionnaire</td>
</tr>
<tr>
<td>Family history of heart attacks, alcohol use, no. of drinks per week, emphysema, asthma, arthritis, cancer, liver disease, education level, economic status/income, exercise metabolic equivalents</td>
</tr>
<tr>
<td>Magnetic resonance imaging markers</td>
</tr>
<tr>
<td>Left ventricular (LV) mass, LV end-diastolic volume, LV end-systolic volume, LV ejection fraction, LV mass/volume ratio, LV stroke volume, LV sphericity index at end diastole and end systole, LV cardiac output, LV end-diastolic wall thickness, LV end-systolic wall thickness, ascending aortic distensibility, descending aortic distensibility, pulse wave velocity, maximum ascending aortic area, maximum descending aortic area, aortic arch distance, maximum left atrial (LA) volume, minimum LA volume, maximum LA strain, total LA ejection fraction, passive LA ejection fraction, active LA ejection fraction, right ventricular (RV) mass, RV end-diastolic volume, RV end-systolic volume, RV ejection fraction, RV stroke volume</td>
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<tr>
<td>Laboratory Biomarkers</td>
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<tr>
<td>Interleukin-2 soluble receptor, plasmin-antiplasmin complex, d-dimer, Factor VIII, NT-proBNP (N-Terminal Pro-B-Type Natriuretic Peptide), cardiac troponin-T, C-reactive protein, interleukin-6, fibrinogen, homocysteine, tissue necrosis factor-α soluble receptor</td>
</tr>
<tr>
<td>Electrocardiographic main</td>
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<tr>
<td>PR duration, QRS duration, QT duration, P axis, QRS axis, T axis, Minnesota codes, ECG LV hypertrophy by cornell voltage and novacode, heart rate variability short-term and overall components, Cornell voltage</td>
</tr>
<tr>
<td>ECG all</td>
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<tr>
<td>P-, P’, Q-, R-, R’, S-, S’, T-, and T’-wave duration, amplitude, area, and intrinsicoid; middle and end of ST-segment amplitudes; amplitude at the point of 60 ms from J point; STJ amplitude; total QRS area, balance, deflection balance, intrinsicoid; for each of the leads (aVL, aVR, aVF, I, II, III, V₁, V₂, V₃, V₄, V₅, V₆)</td>
</tr>
</tbody>
</table>
Performance of ML models with shotgun phenotypes

Better than sequential testing?
• True, but...
• Fixed vs flexible treatment threshold
Polygenic Risk Scores
Polygenic Risk Scoring

- GWAS-based risk scores offered no additional utility
- Newer whole-genome genotyping techniques may allow for comprehensive polygenic risk assessment to include rare variants

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

Amit V. Khera1,2,3,4,5, Mark Chaffin4,5, Krishna G. Aragam1,2,3,4, Mary E. Haas4, Carolina Roselli4, Seung Hoan Choi4, Pradeep Natarajan4,3,4, Eric S. Lander4, Steven A. Lubitz5,2,3,4, Patrick T. Ellinor5,2,3,4 and Sekar Kathiresan1,2,3,4,*
Polygenic Risk Scoring

- Improving ability at the “high” end of risk
- But not high risk
- And not risk, but prevalence
- More work to do

a. Tada et al. (50 variants)

b. Abraham et al. (49,310 variants)

c. Genome-wide polygenic score (6,630,150 variants)
Newer Directions in Long-Term and Competing Risks for CVD
Rationale: Lifetime Risk Estimation

- Reliance **solely** on estimates of *short-term* absolute risk to *communicate risk* and *make treatment decisions* is problematic
  - Atherosclerosis is a life course disease
  - Any single risk factor can produce cumulative damage and high risk if left untreated for years
  - Almost all men <50 and women <70 are considered to be at “low” short-term risk *regardless of risk factor burden*
Rationale: Lifetime Risk Estimation

• Lifetime risk
  – The absolute cumulative risk of an individual developing a given disease before death
  – Accounts for risk of disease of interest, remaining life expectancy, and competing causes of death
  – Reflects real-life risks and population burden of disease better than Kaplan-Meier cumulative incidence
  – Allows for comparison of disease burden now and in future
  – May provide adjunctive information for individual risk assessment
KMCI vs. Lifetime Risk for CHD
Age 40

Men
Women

Cumulative Incidence
Lifetime Risk

66.5%
48.6%
31.7%
43.7%
Lifetime Risk for CHD by Age and Sex

Lifetime Risk for CHF by Age and Sex

Men

Women

Lloyd-Jones et al. Circulation 2002
Lifetime Risks for All ASCVD
Cardiovascular Lifetime Risk Pooling Project

Men, Age 45

Cumulative Risk (%) vs. Attained Age

- ≥2 Major RFs
- 1 Major RF
- ≥1 Elevated RF
- ≥1 Not Optimal RF
- Optimal RFs

Berry et al, NEJM 2012
Compression of Morbidity

Figure 2. CVD-Free Survival and Survival After CVD Events for Men and Women by Index Age and Aggregate Risk Factor Burden

A CVD-free survival and survival after CVD event for men by risk factor

Index age, 45 y

- All optimal
- ≥1 Not optimal
- ≥1 Elevated
- 1 Major
- ≥2 Major

Wilkins, JAMA 2012
BMI and Compression of Morbidity

Figure 2. Years Lived Free of and With Cardiovascular Disease (CVD) Among Middle-aged Individuals

A. Middle-aged men

B. Middle-aged women
Competing Cox Methodology

- Lets the outcomes compete to be first, rather than considering them one at a time
- Provides robust estimates of hazards and cumulative incidences for multiple endpoints simultaneously
  - And gives a total cumulative incidence for events through the end of follow up
Lifetime Risk for a Cardiovascular Event
Female, Age 45

Follow up time (y)
Cumulative Incidence (CVD Event)

4 Major Risk Factors:
- HTN 1 Major RF
- Diabetes 1 Major RF
- Smoker 1 Major RF
- Diabetes and Smoker 2 Major RFs

Ideal CV Health

All Optimals

Elevated
Summary/Take Home Points

• Risk scores can assist with more precise prognostication of patients and improved decision making for net clinical benefit
• Combinations of risk factors/markers can improve discrimination
• Discrimination, calibration, and (maybe) NRI help describe utility of risk scores
• Additional biomarkers/sequential testing strategies need to be specific and strongly and independently associated with outcomes (and are best if they are specific markers of disease or target organ damage)
• Newer risk score modeling approaches can improve discrimination and calibration at the cost of complexity/utility (?)
  – At least at present
Questions?