Allelica clinical case series
in collaboration with Dr. Elizabeth Epstein

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THE POLYGENIC RISK SCORE COMPANY

This clinical case series was developed with real-world preventive cardiology insights from Dr. Elizabeth Epstein, Scripps Health, demonstrating how the Allelica Multi-Ancestry PRS test enabled earlier, and confident preventive care decisions.

CASE 1A Coronary artery disease

Earlier treatment in a young patient with underestimated lifetime risk

Presentation

A 47 year old South Asian woman came to clinic for cardiovascular risk assessment. She had no medical history and followed a healthy lifestyle including a Mediterranean diet and regular exercise. LDL was 164 mg/dL . She had no family history of premature ASCVD and two prior pregnancies with no pregnancy-related complications. Here 10-year ASCVD risk by the AHA/ACC PREVENT calculator was 1.1%. However, she was found to have a high CAD PRS.

Additional Risk Assessment:

- **High CAD polygenic risk score (PRS)**
- No carotid plaque
- Normal BP, A1c, hsCRP, and weight
- HDL-P 41.4
- Elevated Lp(a)

Clinical Interpretation:

A high CAD PRS revealed elevated inherited susceptibility to coronary artery disease despite a low estimated 10-year ASCVD risk by the PREVENT calculator. In the context of additional risk-enhancing factors, including South Asian ancestry, LDL-C >160 mg/dL, and elevated Lp(a), this suggested that lifetime ASCVD risk was underestimated by standard risk assessment alone and supported consideration of earlier primary prevention.

Management Decision

- **Initiated lipid lowering therapy targeting LDL-C<70 mg/dL.**
  Note that having a high CAD PRS amplifies the benefit of pharmacotherapy.
- **LDL-C improved from 164 to 111 mg/dL on rosuvastatin 5mg daily.**
  Individuals with a high CAD PRS have nearly twice the benefit from statins compared to those with a low PRS [1]
- **After shared decision-making, inclisiran was initiated for further LDL lowering.**
  Individuals with a high CAD PRS have nearly three times the benefit from PCSK9 inhibitors compared to those with a low PRS [2]
- **Emphasis on continued healthy lifestyle.**
  Among people with a high CAD PRS, a healthy lifestyle is associated with a **nearly 50% reduction in risk of coronary events.** [3]

How PRS Changed Management

Without PRS, the patient may have been classified as low to intermediate risk and treated less aggressively or observed without pharmacotherapy. Incorporation of CAD PRS supported reclassification to a high risk category and prompted earlier and more intensive preventive therapy.

CASE 1B Coronary artery disease

Avoiding overtreatment in a low-risk young patient

Presentation

A 38-year-old male with no prior medical history presented for evaluation of dyslipidemia. LDL-C was 126 mg/dL and triglycerides were 217 mg/dL. He exercised regularly, followed a generally healthy diet, and had no family history of ASCVD. His 10-year risk by PREVENT was 1%, and his low CAD polygenic risk score further supported an overall low inherited risk for coronary artery disease.

Additional Risk Assessment

- **Low CAD PRS**
- Normal A1c and hsCRP
- Normal Lp(a)

Clinical Interpretation

A low CAD PRS shifted overall risk interpretation by indicating low inherited susceptibility to coronary artery disease despite mildly elevated LDL-C and triglycerides. Beyond the lipid findings alone, the patient's overall clinical profile remained consistent with low near-term and lifetime ASCVD risk. The elevated triglycerides were considered reflective of mild insulin resistance rather than underlying inherited atherosclerotic risk.

Management Decision

- **Deferred lipid-lowering pharmacotherapy**
- **Recommended Mediterranean protein and plant forward dietary modification with reduction in refined carbohydrate intake**
- **Discussed optional use of continuous glucose monitoring to guide personalized dietary optimization**

How PRS Changed Management

PRS provided reassurance that more aggressive lipid-lowering therapy was unlikely to provide substantial benefit at this stage. Instead of medicalizing a low-risk patient based on isolated LDL-C elevation, management focused on precision lifestyle intervention and longitudinal risk monitoring.

CASE 2 Alzheimer's Disease

Identifying elevated neurodegenerative risk before clinical disease onset

Presentation

A 37 year old woman with hyperlipidemia and elevated Lp(a) presents for cardiovascular risk assessment and lipid management. As part of a broader precision preention evaluation, she underwent polygenic risk testing.

CAD PRS and polygenic hypercholesterolemia scores were low; however, **she was found to have an elevated PRS for Alzheimer's disease** and carry the ApoE3/E4 genotype, which is associated with significantly increased lifetime risk for Alzheimer's disease. The patient had no cognitive symptoms and no known neurologic disease.

Clinical Interpretation

Identification of a high Alzheimer's disease PRS and EpoE3/E4 genotype highlighted elevated inherited susceptibility to future neurodegenerative disease despite the absence of cognitive symptoms or known neurologic disease. A low CAD PRS also supported low inherited cardiovascular risk. Together, these findings shifted the clinical focus toward proactive brain health optimization and aggressive management of modifiable contributors to cognitive decline, particularly vascular and metabolic risk factors.

Management Recommendations

Among APOE E4 carriers, a healthy lifestyle is associated with **a 32% lower risk of dementia** and can **cut the rate of cognitive decline in half.** [4]

Lifestyle and Risk Factor Optimization:

- Mediterranean diet, limit saturated fats [5, 6]
- Regular aerobic and resistance exercise [7, 8, 9, 10]
- Optimization of sleep quality and circadian regularity, aiming for 7 hours [12, 13] of sleep per night
- Aggressive prevention of insulin resistance and metabolic dysfunction
- Blood pressure and lipid optimization [14, 15. 16]
- Cognitive training, mindfulness, social engagement

Medications/Supplements

- Statin. While ApoE4 carriers have a smaller LDL-C reduction from statins compared to E3 carriers, they have a 67% reduction in mortality, a 40% lower risk of Alzheimer's, a significantly slower rate of cognitive decline, and less severe dementia by taking statins. [17, 18]
- Multivitamin [19]
- High-dose DHA [20, 21]

Screening and preventive monitoring

- Attention to hearing loss as a modifiable dementia risk factor
- Screening for sleep apnea if clinically indicated
- Longitudinal cognitive monitoring over time

Discussion for emerging preventive strategies

- Review of evolving evidence surrounding GLP-1 receptor agonists and neurodegenerative disease
- Discussion of future biomarker-based approaches including biologic aging (brain clock)[22] assessment and blood-based Alzheimer's biomarkers (p-tau217)[23] as evidence evolves

Counseling

The patient was counseled that ApoE4 increases susceptibility but is not deterministic, and that multidomain lifestyle intervention may meaningfully modify lifetime dementia risk.

How PRS Changed Management:

Identification of ApoE4 status expanded the clinical focus to include earlier and more personalized neurodegenerative disease prevention decades before expected disease onset.

CASE 3 Breast cancer

Earlier identification of elevated cancer risk beyond family history alone

Presentation

A 46 year old woman presented for preventive cardiovascular evaluation. She had no personal history of malignancy and no known pathogenic hereditary cancer mutation. Family history was notable only for a maternal aunt diagnosed with breast cancer in her 70s. She lived a healthy lifestyle, exercised regularly, and had a normal BMI, A1c and naturally low LDL-C. As part of a broader genomic prevention assessment, she underwent polygenic risk testing.

Work up

- **Breast cancer PRS high**
- CAD PRS not elevated
- No known monogenic hereditary cancer syndrome identified
- No prior mammogram

Clinical Interpretation:

A high breast cancer PRS identified elevated inherited susceptibility that was not fully captured by traditional clinical risk factors or family history alone, despite an estimated 5-year breast cancer risk of only approximately 1-1.5% by the BCSC v2 model. In the absence of a known monogenic hereditary cancer syndrome, this finding supported consideration of a higher-intensity screening and prevention strategy.

Management Recommendations

Among women with a high PRS, adopting a healthy lifestyle is associated with a **27-32% reduction** in risk of invasive breast cancer. [24,25]

Women with a high PRS have a greater absolute benefit from healthy lifestyle compared to those with a low PRS. [26]

Screening

- Start annual mammography
- Referral to a high-risk breast clinic for individualized assessment
- Discussion of supplemental breast MRI based on integrated lifetime risk assessment and breast density

Lifestyle and Risk Reduction[27]

- 150-300 min/week moderate intensity exercise
- BMI < 25
- Avoid alcohol
- Predominantly plant-based Mediterranean diet, incorporate whole soy foods (up to 3 servings per day); limit processed foods, red meat, refined carbohydrates; limit eggs to <5 per week
- Avoid combined estrogen-progesterone menopausal hormone therapy

Future Considerations

Attention to multicancer early detection tests for screening as evidence emerges

How PRS Changed Management:

Without PRS testing, the patient would have likely continued standard age-based screening recommendations alone. In her case, this may have resulted in delayed initiation of screening until age 50 for an average risk patient. Identification of elevated breast cancer PRS prompted earlier and more individualized cancer screening and prevention planning despite otherwise unremarkable traditional risk assessment.

General Guidance

Where PRS May Have Greatest Clinical Utility

- Young patients with low short-term but uncertain lifetime risk
- Patients with discordance between traditional risk factors and clinical suspicion
- Patients with limited family history information
- Prevention before subclinical disease develops
- Personalizing intensity of screening and intervention
- Avoiding overtreatment in low-risk patients (do no harm)

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Pre-Test Counseling

- Genes are not destiny. Polygenic risk scores reflect susceptibility , not certainty, and should be used to guide evidence-based prevention and screening strategies.
- PRS information should be empowering rather than fear-inducing. Testing may not be appropriate for patients who feel this information would provoke significant anxiety.
- PRS should be interpreted within the context of traditional risk factors, family history, lifestyle, and clinical judgment.
- Shared decision-making is essential when determining how PRS should influence management intensity.

Post-Test Counseling

- Genes are not destiny. Having a high PRS for a chronic disease is similar to having dry brush in your front yard in a high fire area: it doesn't mean that it will catch fire, but the risk is there, and steps can be taken to reduce that risk.
- Emphasize the proven power of healthy lifestyle to reduce the risk of high PRS. Healthy lifestyle is even more powerful in patients with a high PRS compared to those with a low PRS.
- Emphasize that patients with a high PRS may have a greater benefit from medications such as statins and PCSK9 inhibitors.

Contact us

for start ordering PRS testing for your patients today

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Supporting evidence

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