Case Study:

LDL and HDL Cholesterol
CHD Risk: HDL-Chol and LDL-Chol as Predictors

Men aged 50–70 y in the Framingham Heart Study
Adapted with permission from Castelli WP. Can J Cardiol. 1988;4(suppl A):5A-10A
LDL as a Biomarker

• As one of the FDA-qualified surrogate endpoints for cardiovascular disease, LDL cholesterol (LDL-C) is often viewed as the benchmark biomarker.

• The evidence supporting LDL as a biomarker rests almost entirely on the measurement of LDL-C even though LDL comprises multiple subclasses of particles with differing composition, and cholesterol is only one component of LDL particles.

• LDL particle measurements are more informative for CVD risk than LDL-C for some populations, showing that even for qualified biomarkers, developing standard measures is an ongoing process.
Because cardiovascular disease is a multifactorial chronic disease, a single risk factor for the disease (e.g., LDL-C) cannot fully account for all the variability that leads to a particular outcome.

CVD risk varies over wide range of LDL-C
At same LDL-C: increased risk if MetS, DM and/or CAD

Meta-analysis of Cholesterol Lowering CHD Trials

Proportional reduction in event rate (SE)

LDL reduction (mmol/L)

Major coronary events

CTT Collaborators, Lancet 366:12676, 3005
LDL is not a Generic Surrogate Endpoint: Lesson from Hormone Replacement Therapy

Postmenopausal hormone replacement therapy (HRT) was thought to protect women from CVD based on both observational epidemiologic data and the apparent beneficial effects of estrogen on lipoproteins and other cardiovascular disease biomarkers.

After several clinical trials, HRT was found to have no benefit on CVD incidence in healthy women, to increase mortality in the first year of therapy in women with CVD, and to increase risk for thromboembolic events.
LDL-C as a Biomarker of CVD Risk: Conclusions

• The strength of LDL-C as a surrogate endpoint is not absolute due to the heterogeneity of cardiovascular disease processes, the heterogeneity of LDL-lowering drug effects, and the heterogeneity of LDL particles themselves.

• Age, gender, and genetic factors have been shown to complicate the already complex dynamics of the LDL-CVD relationship; as a result, lowering LDL-C can never be considered a “perfect” indicator across all population groups.

• That said, there is high probability that lowering LDL-C by several interventions (e.g. statins) decreases risk of CVD, and LDL-C, although not perfect, is one of the best biomarkers for CVD.
Issues regarding HDL-C as a CVD biomarker

• There is strong epidemiologic and pathophysiologic evidence for a relation of HDL to CVD risk

• However, HDL is even more heterogeneous than LDL and includes multiple subpopulations of particles with differing functional properties and disparate effects on atherogenic mechanisms.

• Increases in HDL-C by lifestyle and drug interventions can result from multiple different metabolic effects.

• Moreover, there is as yet no conclusive evidence in humans for an independent benefit of HDL increase on CVD outcomes
Trial of Torcetrapib + Statin for HDL-Raising

[Graph showing changes in lipids (TG, HDL-C, LDL-C) over study months.]

Barter et al. NEJM 357, 2109, 2007
Primary Endpoint: Time to First Major CVD Event

Hazard Ratio 1.25
P=0.001

Event Free (%)

Atorvastatin (A) events = 373
Torcetrapib/Atorvastatin (T/A) events = 464

Days from Randomization

Major cardiovascular event: CHD death, non-fatal MI, stroke or hospitalization for unstable angina

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Barter et al. NEJM 357, 2109, 2007
HDL-C as a Biomarker of CVD Risk: Conclusion

"Current evidence does not support use as a surrogate endpoint"
“Even in the best of circumstances, it is possible for surrogate endpoints to be misleading by either overestimating or underestimating an intervention’s effect on clinical outcomes.”

Failures of Surrogate Endpoints

Biological Complexity Leads to Many Opportunities for Error

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Lessons Learned

"Interventions to address a multifactorial disease introduce potentially unforeseen effects, particularly when the causal disease pathways, the mechanisms of action of the intervention, and the characteristics of the biomarker itself are not fully understood".