# Screening of Metabolic Disorders using NMR Metabolomics and Whole Genome Sequencing

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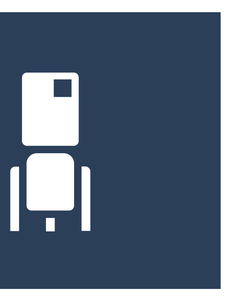
*Comprehensive metabolic profiling of blood biomarkers can provide an assessment of the molecular effects of metabolic diseases, such as lipid and amino acid disorders. This complements gene panels and sequencing efforts by quantifying the effects of rare mutations on molecular phenotypes. Through profiling of large biobanks and trials, a nuclear magnetic resonance (NMR) biomarker assay is now being used to catalogue comprehensive molecular effects of metabolic disorders. This provides a better understanding of the metabolic impact of common and rare diseases, more clear clinical interpretation of the sequencing data and novel means to track effectiveness of interventions.*

## NMR metabolomics biomarker assay

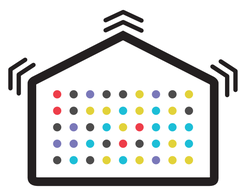


**Comprehensive panel**
*228 biomarkers*

- Routine lipids
- 14 lipoprotein subclasses
- Particle size
- Apolipoproteins
- Fatty acids
- Omega-3 and -6
- Amino Acids
- Ketones
- Glycolysis metabolites
- Chronic inflammation

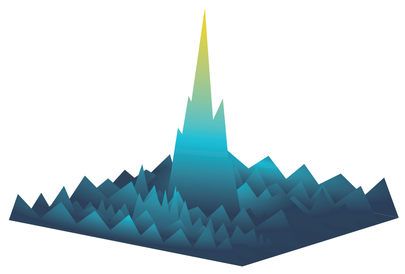
**High-throughput assay**
- *Scalable and cost-effective for population-level screening*
- *Easy sample handling*

**Molecular readout**
- *Identified metabolites*
- *Absolute concentrations*
- *Biomarkers with clinical guidelines*



**Scalable to national biobanks**
*Analyzed 500,000+ blood samples from population cohorts, randomized trials and clinical settings*

## Examples of mapping the genetic landscape of blood metabolism



**GWAS of 25,000 participants with NMR metabolomics**
Kettunen et al, *Nat Commun* 2016;7:11122

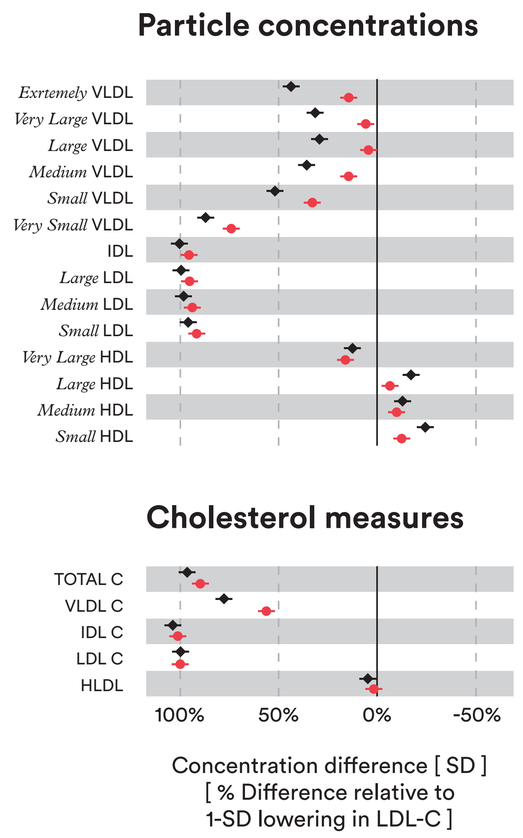
**Genome-wide single variant and gene-based analysis uncovers novel amino acid loci**
Teslovich et al, *Hum Mol Genet* 2018; 10.1093/hmg/ddy067

**CETP and HMGCR gene variants associations with lipids and CVD risk**
Ference et al, *JAMA* 2017;318:947

**CETP gene variants associated with vascular and non-vascular diseases**
Millwood et al, *JAMA Cardiol* 2018;3:34

## Combining metabolomics and lipid related mutations: Case *PCSK9* R46L

| Cohorts in the analyses with metabolomics and GWAS or sequencing data | n= |
|---|---|
| INTERVAL blood donor trial | 40,972 |
| Avon Longitudinal Study of Parents and Children, ALSPAC | 8,362 |
| FINRISK 1997 and 2007 cohorts | 10,518 |
| Northern Finland Birth Cohorts | 7,921 |
| China Kadoorie Biobank | 4,412 |
| PROSPER trial on pravastatin | 5,359 |




Effects of loss-of-function variation in *PCSK9* on select lipid measures in ~72,000 individuals from European cohort studies.

The overall metabolic effects are consistent with those of statin therapy, but discrepancies are observed for VLDL lipid measures: genetic inhibition of *PCSK9* shows weaker effects on lowering of VLDL-cholesterol compared with statin therapy (54% vs. 77% reduction).

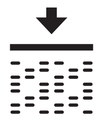
These results illustrate how molecular effects of familial hypercholesterolemia are evident in the detailed metabolic profile, and the possibility to track effects of known and novel lipid-lowering medications.

Sliz et al, BioRxiv 2018/10.1101/278861

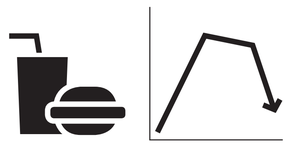
## Advantages of integrating metabolomics and whole-genome sequencing

**Interpret WGS-based findings**
*Metabolomics + adult sequencing: test molecular effects of rare mutations, including phenotype penetrance and overall burden of multiple mutations.*

**Newborn screening**
*Metabolomics +WGS for newborns: molecular readout of lipid, carbohydrate and amino acid disorders such as familial hypercholesteremia.*



**Catalogue comprehensive metabolic effects**
*Deep assessment of the molecular impact of mutations, e.g loss-of-function variants that are not fully penetrant.*



**Assess molecular response to exposures**
*Track impact of mutations in response to diet and other challenges.*

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