

# Human Metabolome as an Approach to Personalized Medicine

Amalio Telenti, MD PhD

Dep. Integrative Structural and Computational Biology

And Translational Institute

The Scripps Research Institute

- Definitions
- Human diversity in metabolome phenotypes
- Metabolome and genome biomarkers
- Pharmacogenomics and pharmacometabolomics

<b>Metabolomics</b>	<b>Genomics</b>	<b>Pharmacogenomics</b>
The study of low molecular weight molecules or metabolites found within cells and biological systems.	The study of all of a person's genes (the genome), including interactions of those genes with each other and with the person's environment.	Using an individual's genome to determine whether or not a particular therapy, or dose of therapy, will be effective.
<b>Pharmacometabolomics</b>		
Integration of the rapidly evolving science of metabolomics with molecular pharmacology and pharmacogenomics to move toward the creation of a new discipline, which aims to move to individualized drug therapy, where drugs are selected based on the metabolic status and the genetic makeup of each individual.		

<https://commonfund.nih.gov/metabolomics/overview>

<https://www.genome.gov/27552451/what-is-genomic-medicine/>

<https://www.genome.gov/19016904/faq-about-genetic-and-genomic-science/>

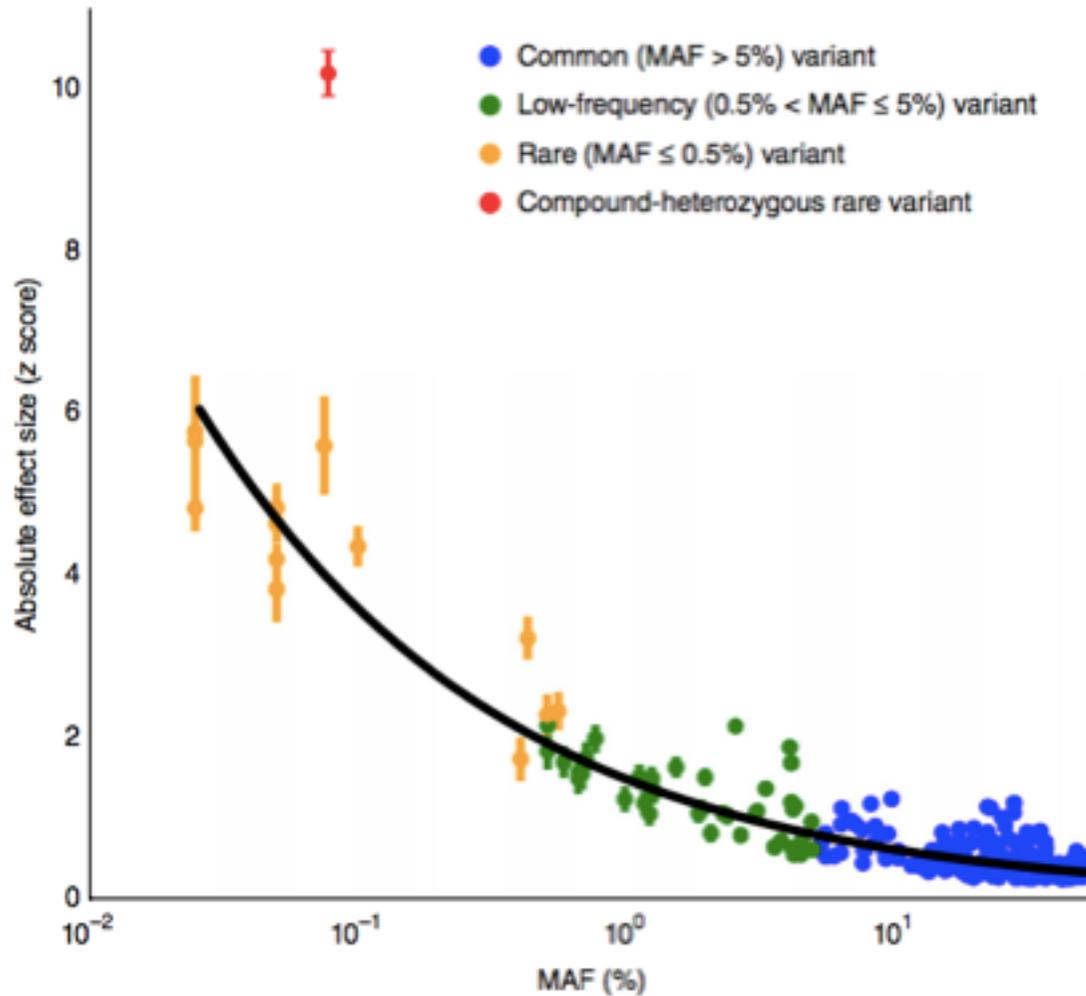
<https://pharmacometabolomics.duhs.duke.edu/home>

*Telenti A. Pharmacogenomics in press*

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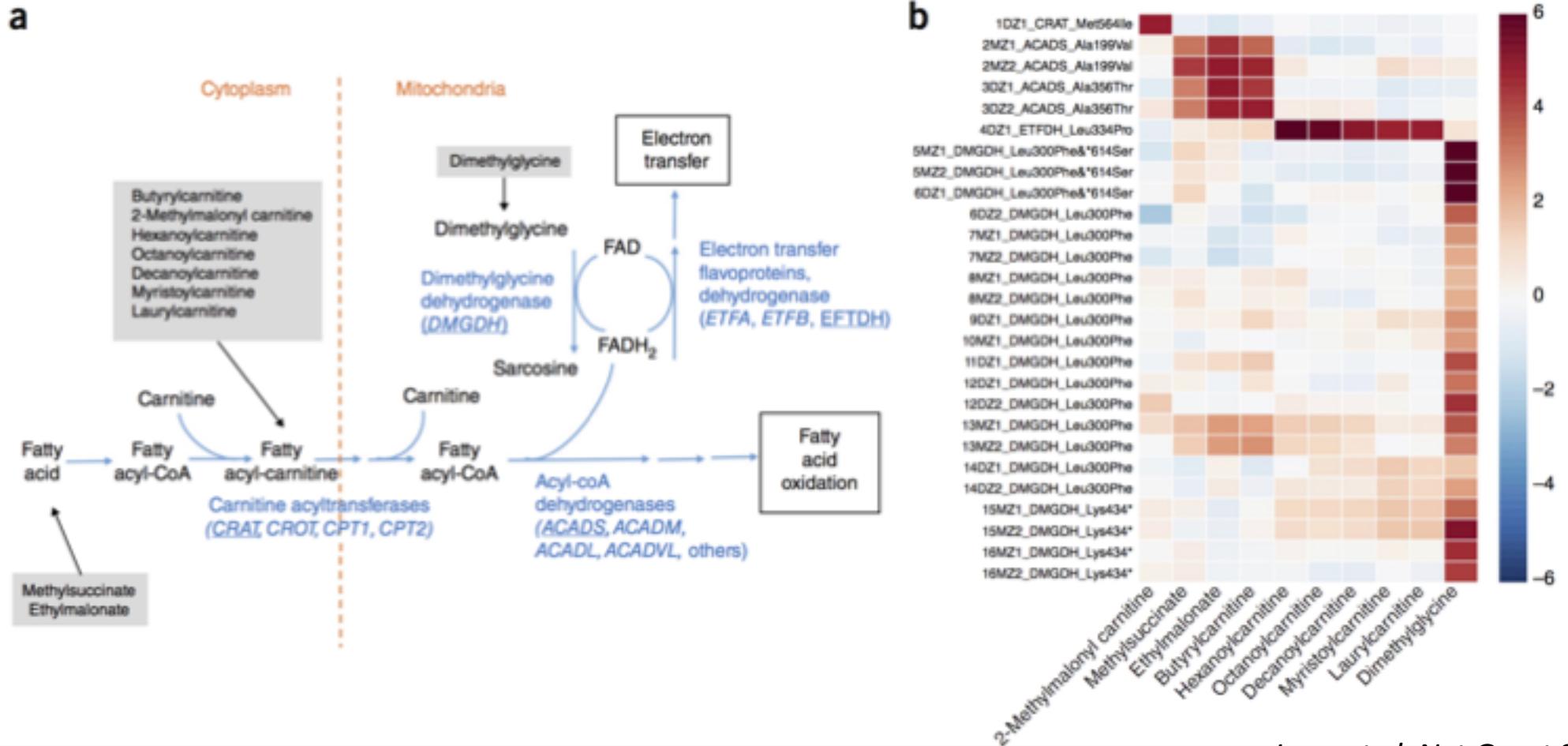


# Relationship between variant allele frequency and effect size on metabolism



- ~10% of general population carry rare variants influencing the metabolome

# Example: variants in fatty acid metabolism and beta-oxidation

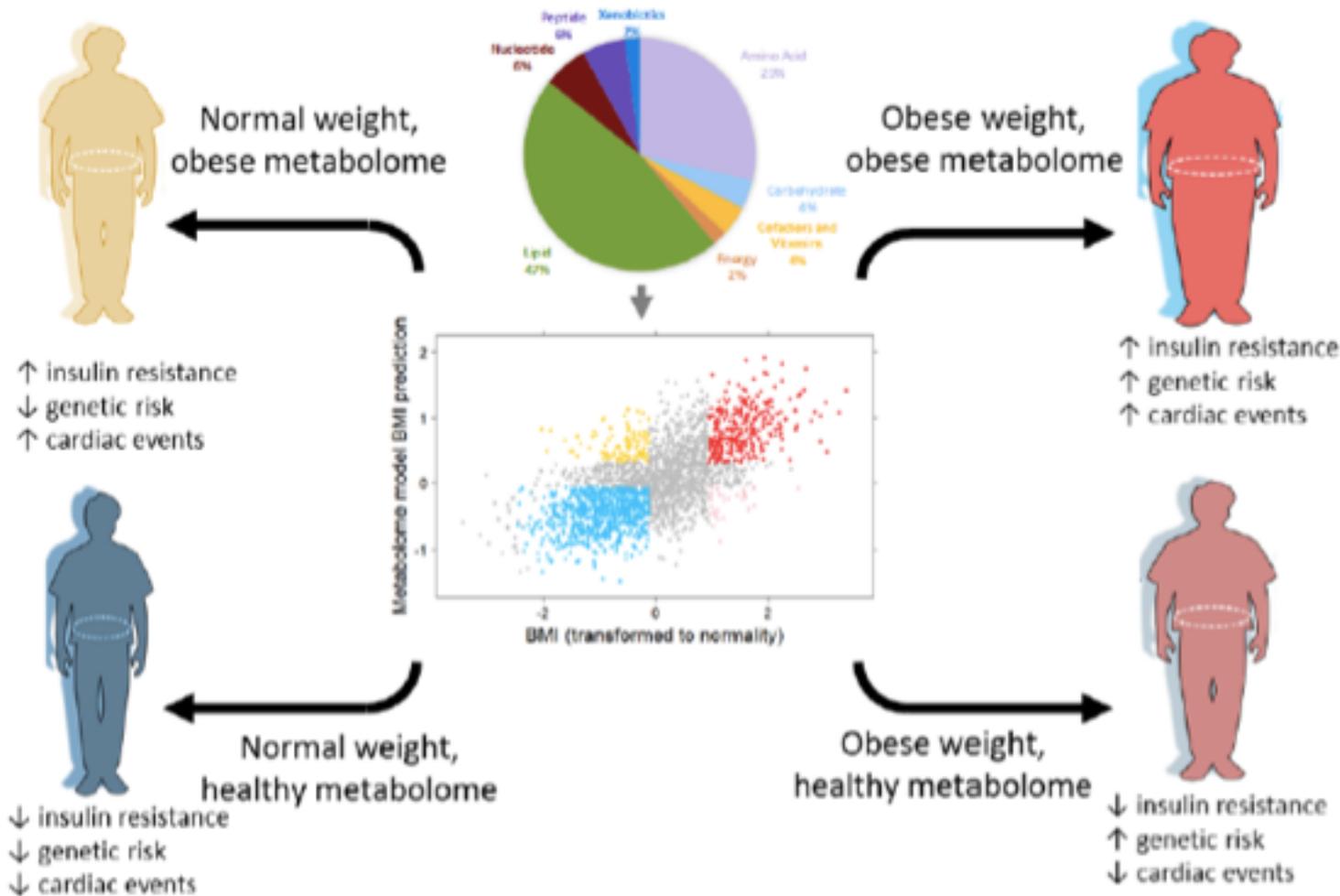


# Summary- 1

- The metabolome profile is a trait of an individual
- There is considerable common and rare variation in the general population
- Many rare variants have significant effects on unique metabolites – with unclear consequences for health
- In some ways, ***metabolomics is the “new pharmacogenetics”***

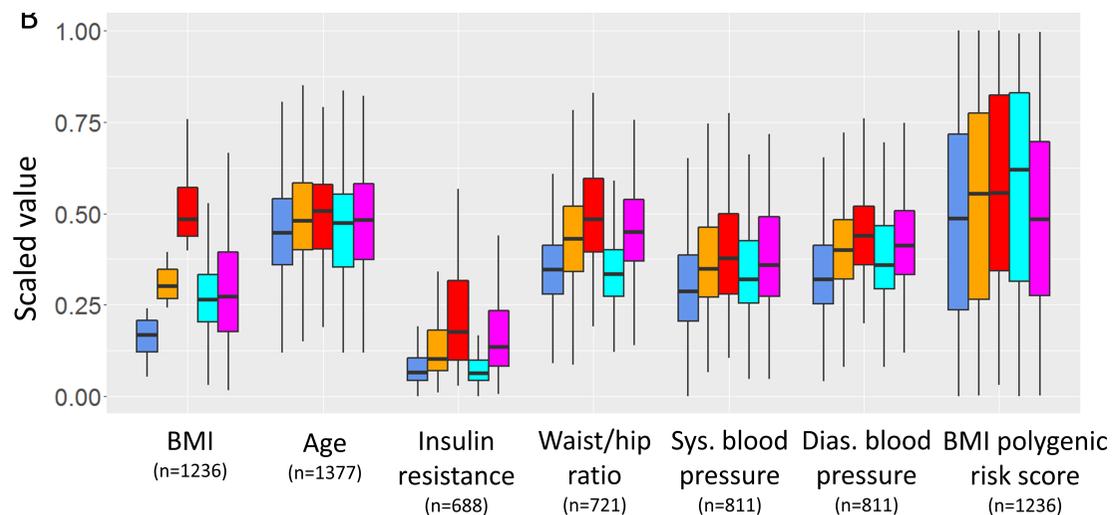
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# Profound perturbation of the metabolome in obesity

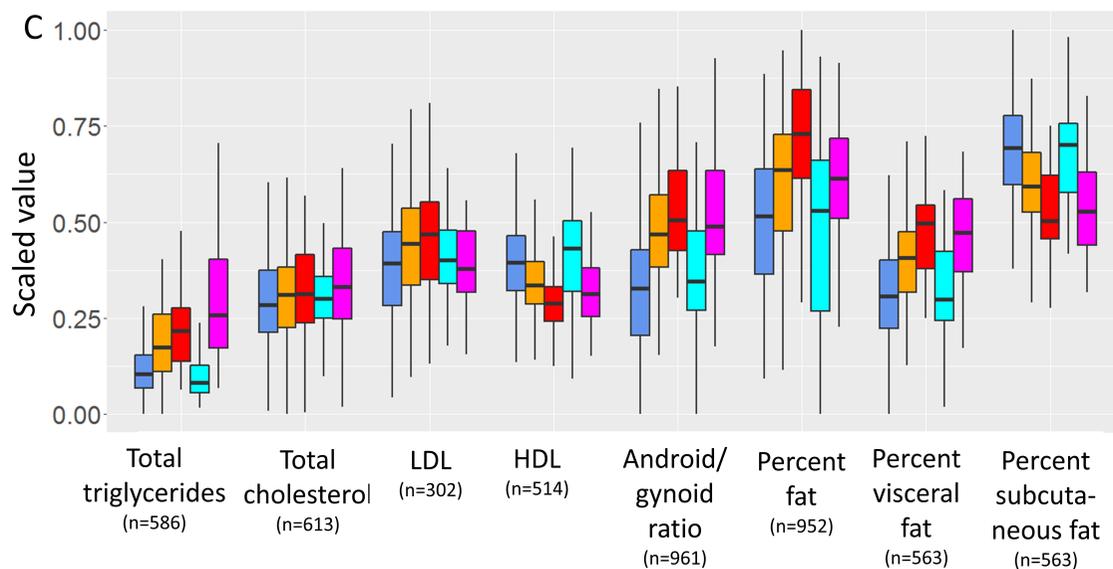


- A third of assayed metabolites are associated with changes in BMI.

# Metabolic signatures of health consequences of obesity

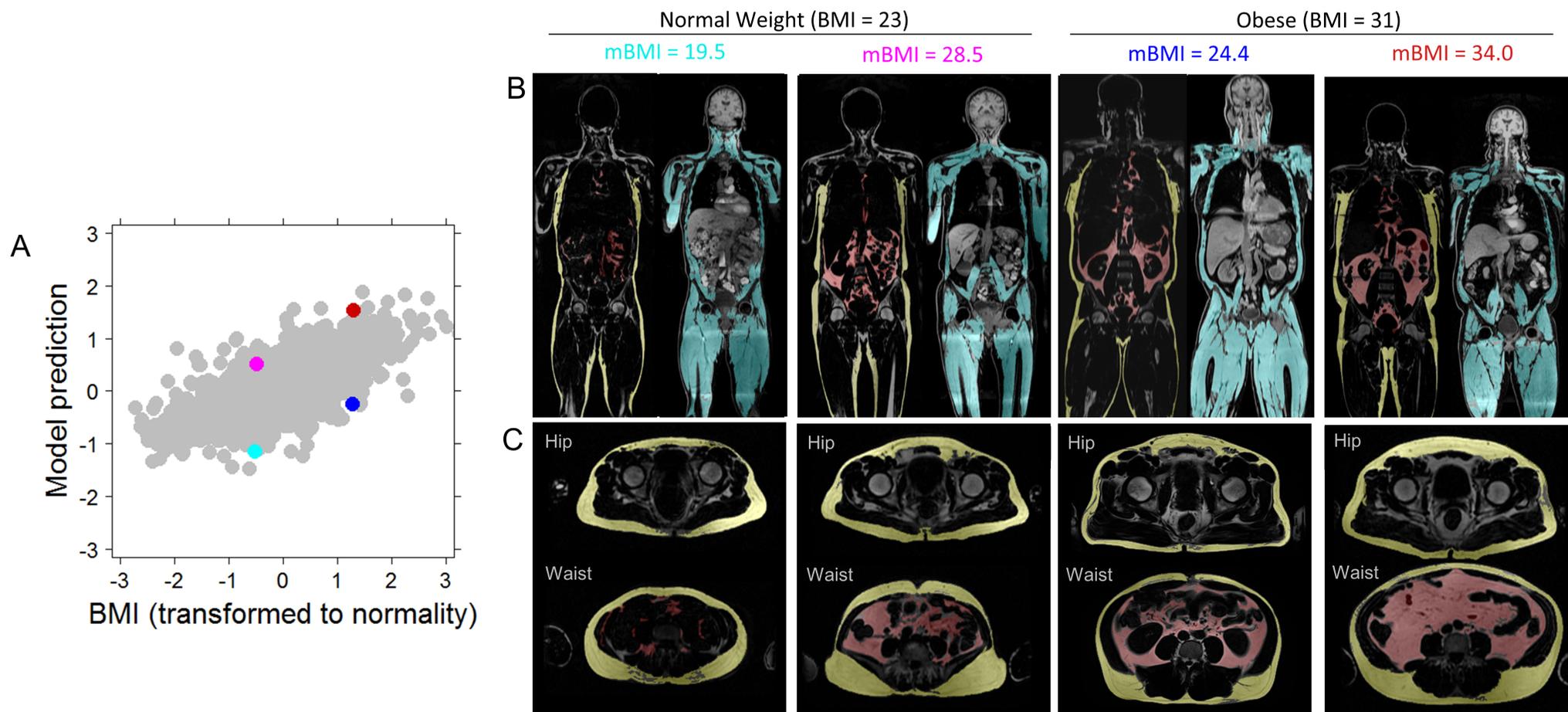


- Normal weight, metabolically healthy
- Overweight, metabolically overweight
- Obese, metabolically obese
- Outlier: Metabolic BMI << BMI
- Outlier: Metabolic BMI >> BMI

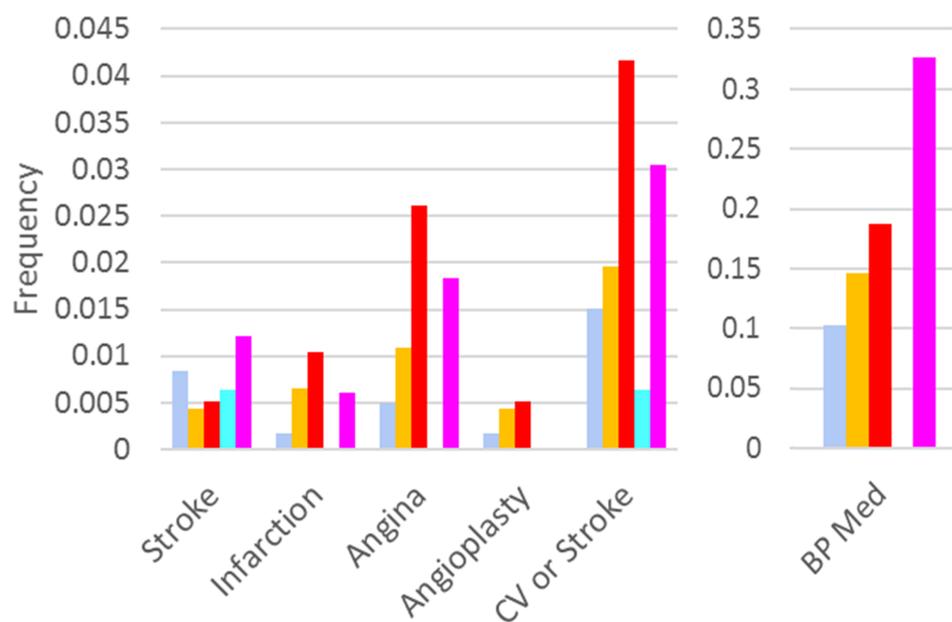


*Cirulli et al. Cell Metab. In press.*

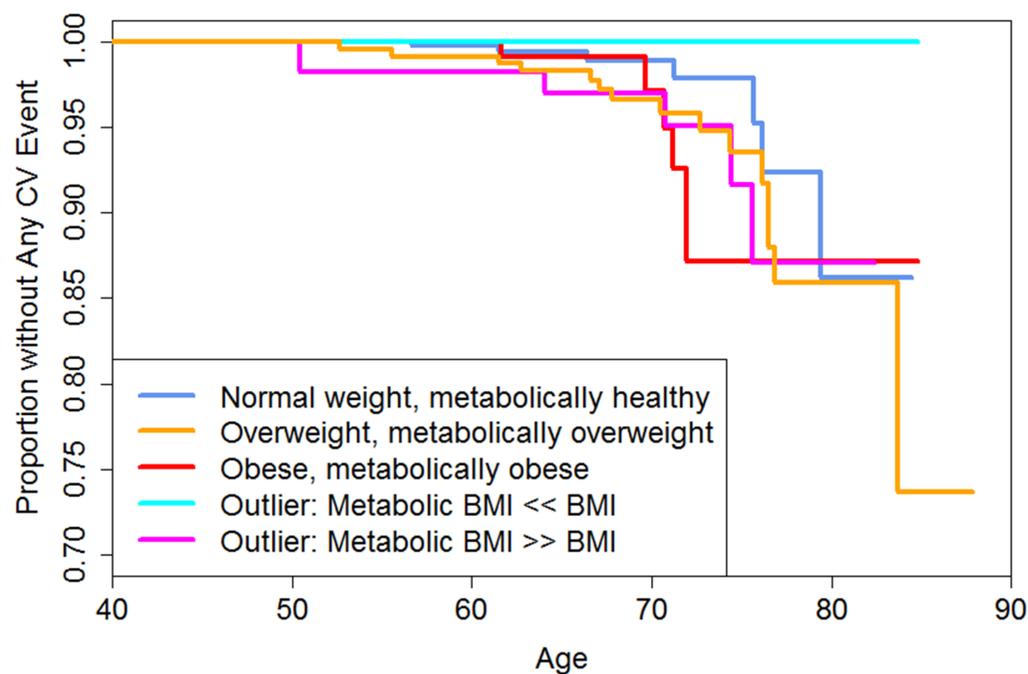
# Hallmarks of metabolic disease predicted by metabolome



# Metabolic signatures of health consequences of obesity – 13 year outcome

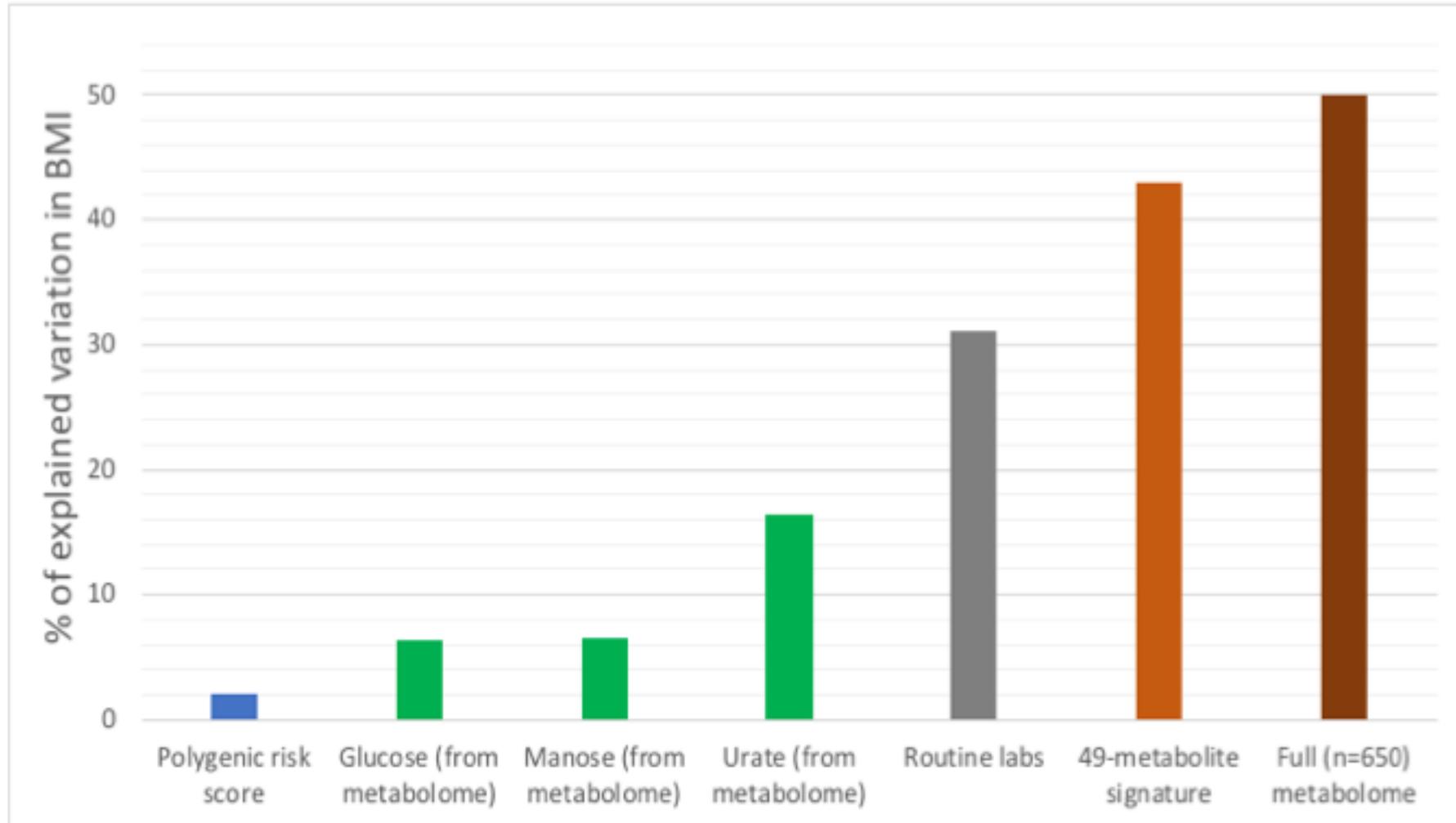


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*Cirulli et al. Cell Metab. In press.*

# Markers, signatures and Rich Biomarkers



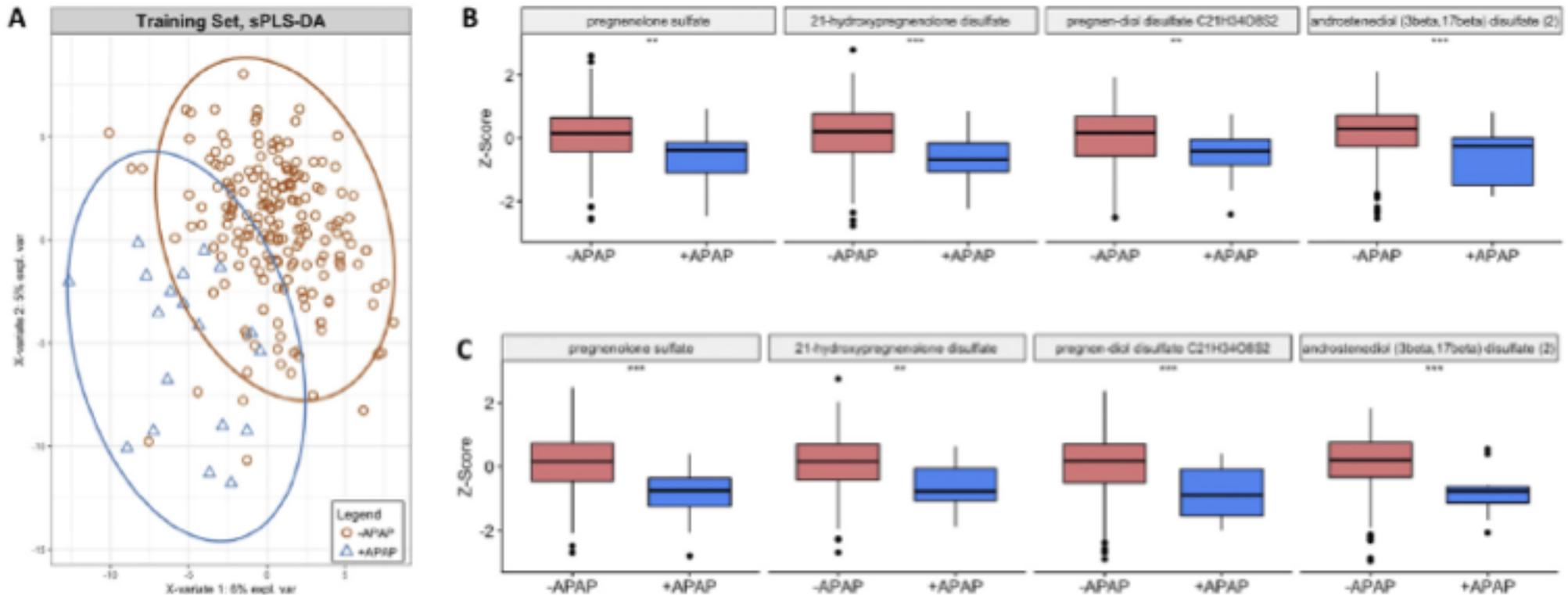
*Telenti A. Pharmacogenomics. In press.*

## Summary- 2

- Metabolome analyses generate rich biomarkers
- It is also an agile signature that can track response to intervention or treatment
- It summarizes in one single analysis multiple tests that are part of medical routine

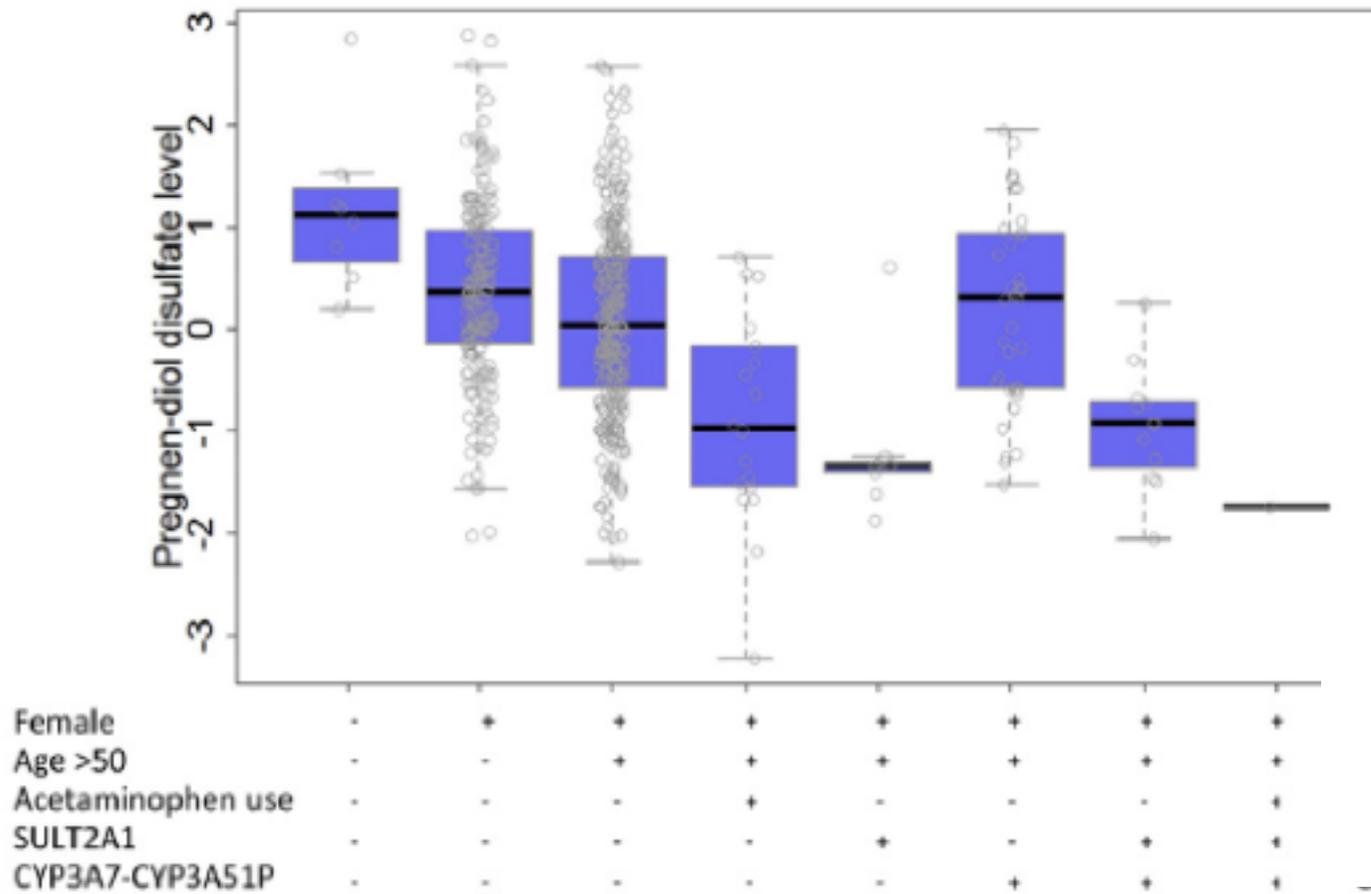
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# Drugs generate metabolome signatures



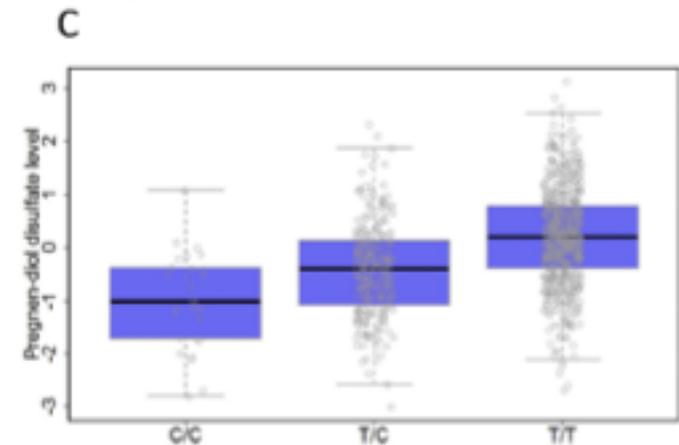
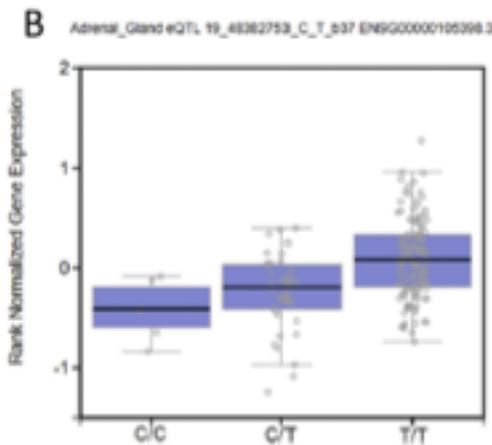
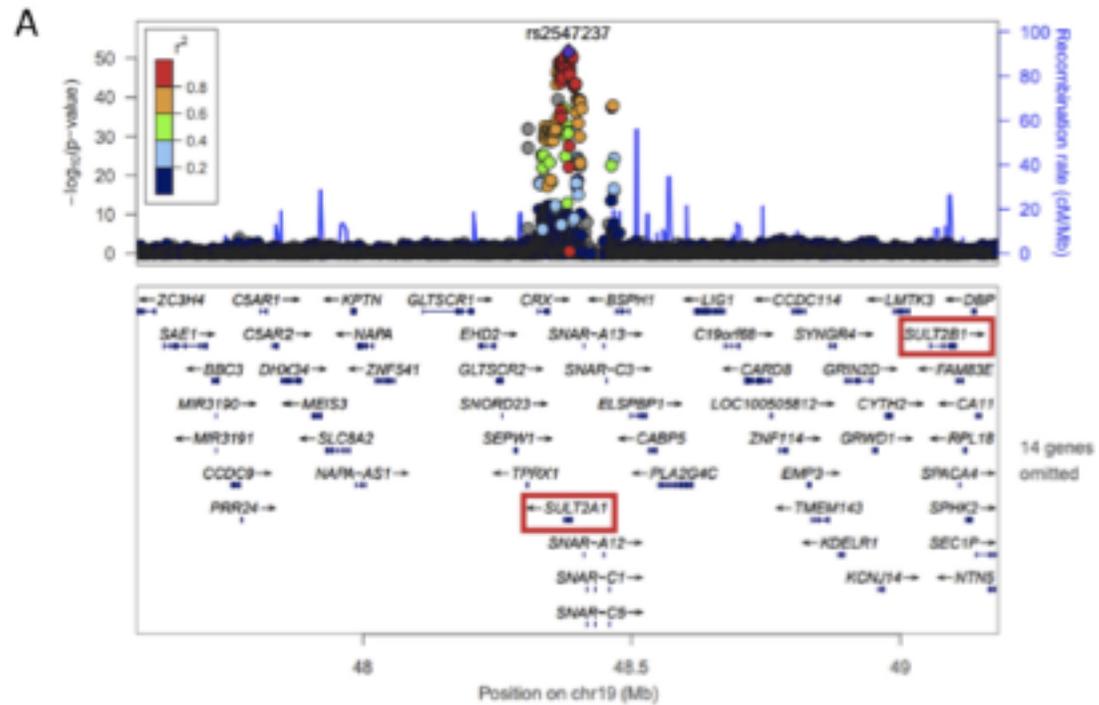
- Use of acetaminophen modifies the metabolome – with a particular impact on the sulfation of sex hormones.

# Multiple factors determine the levels of sulfated sex hormones



Cohen et al. EBioMedicine. 2018

Mendelian randomization – genes phenocopying drugs, and *vice versa*



Cohen et al. EBioMedicine. 2018

## Summary- 3

- Metabolomics is a sensitive measurement of known and unknown effects of drugs
- It may help understanding of mechanism of action and toxicity of medications
- In combination with genetics, it may help map the site of interaction (Mendelian randomization)

# Conclusions

- Metabolomics lends itself to precision medicine because:
  - It is a trait of the individual
  - It is sensitive to perturbation and disease
  - It can be integrated with other –OMICS and imaging technologies
  - Exemplifies the use of “Rich Biomarkers”

# Acknowledgments

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