National Science Challenges

HIGH-VALUE NUTRITION

Ko Ngā Kai Whai Painga

Priority Research Programme
Foods for improving gut function and comfort

Biomarkers for gut comfort

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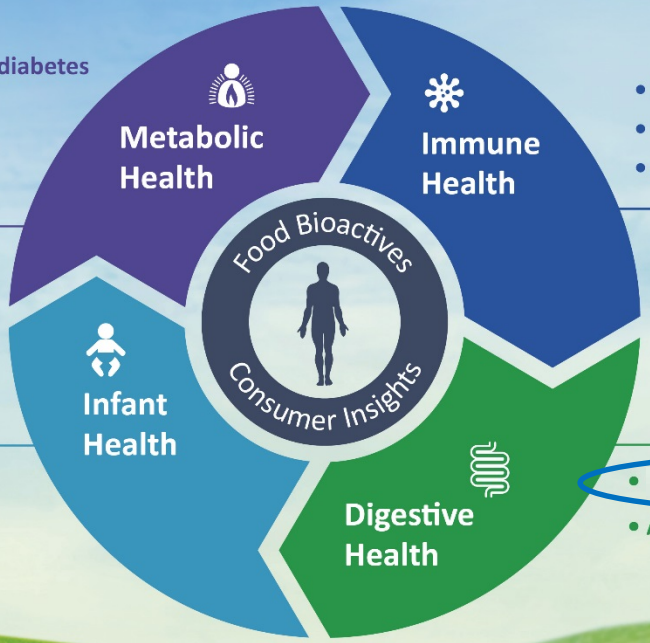
High-Value Nutrition National Science Challenge research themes and projects



- TOFI: Thin on the outside, fat inside: preventing diabetes
- Kiwifruit for glucose control
- Combined proteins for lean body mass
- Grass-fed beef for cholesterol control

- Building immune defence
- Natural milk for allergy management
- Greenshell™ mussels to manage inflamed joints

- Complementary feeding for immune protection
- Fibres for sustained energy release

- Foods for gut function and comfort
- A2 Milk for gut comfort

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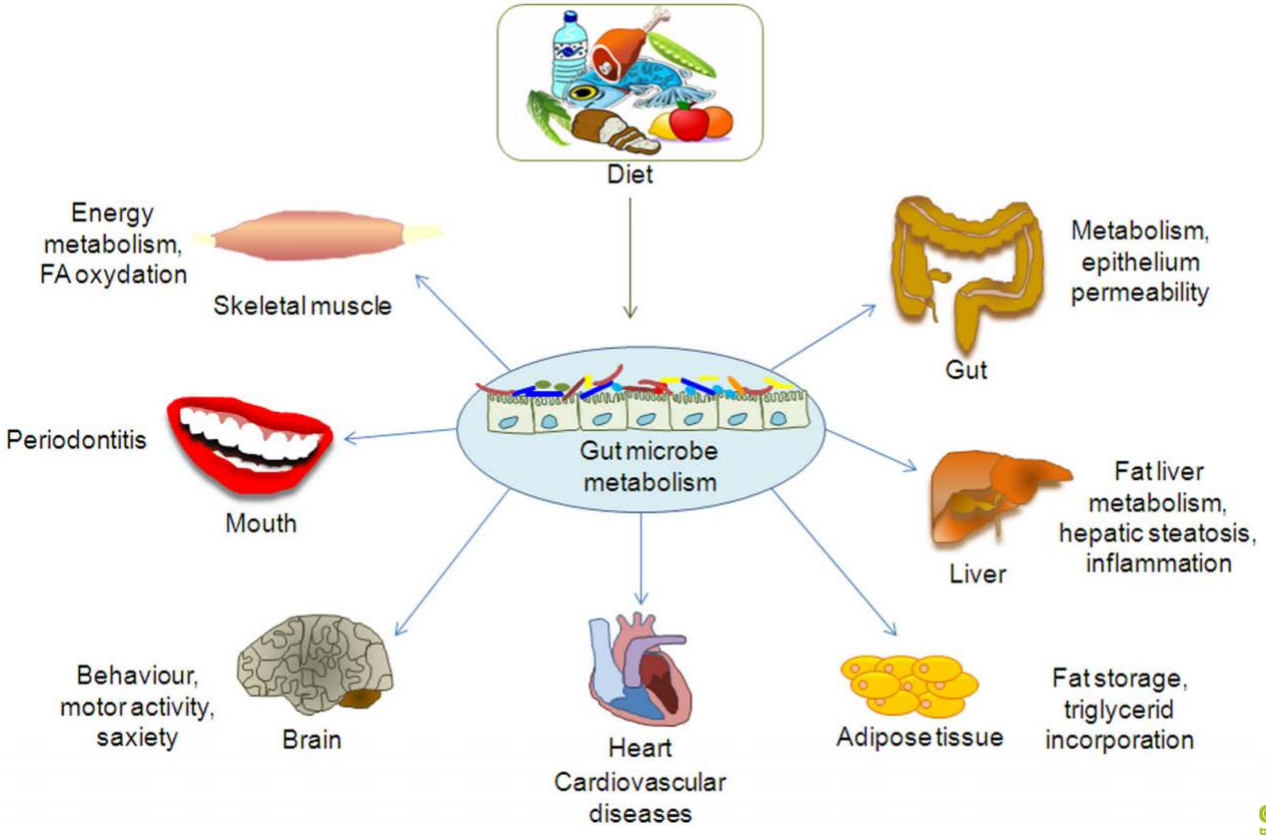
Irritable Bowel Syndrome is the ideal model for developing future foods with clinical evidence to support claims for healthy people

Heathy gut for a healthy body



- Diet impacts more than just gut health
- Gut plays a central role
- **Foods for gut function and comfort critical to health**

Vernocchi et al (2016). *Frontiers in Microbiology* 7:1144.

Biomarkers

- "A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention"[1]
- Assess digestive health[2] using models of suboptimal function and comfort such as irritable bowel syndrome (IBS)
  - Subjective assessments, e.g. questionnaires and gut symptom scores
  - Objective gut parameters such as: functionality, integrity, markers of immunity, microbiome, etc.
- Can define phenotypes
- Multiple approaches and measures enhance accuracy

[1] de Vries *et al* (2013). Markers for nutrition studies: review of criteria for the evaluation of markers. *Eur J Nutr*. 52:1685–1699
[2] Bischoff (2011). 'Gut Health': a new objective in medicine?. *BMC Med.* 9:24

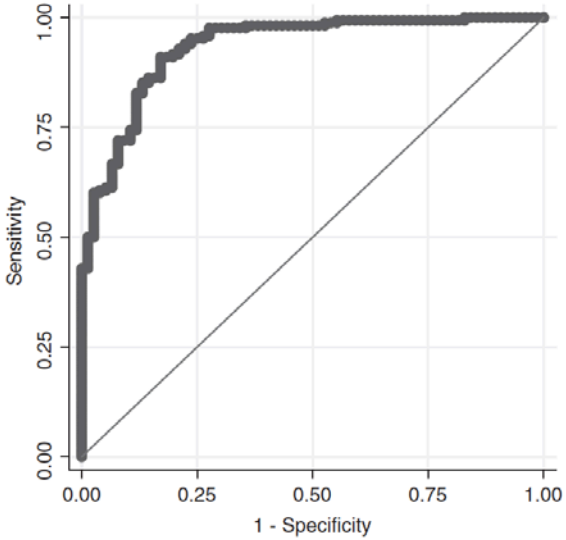
AP&T Alimentary Pharmacology and Therapeutics
(2014) 39(4):426-37.

A biomarker panel and psychological morbidity differentiates the irritable bowel syndrome from health and provides novel pathophysiological leads

M. P. Jones*, W. D. Chey†, S. Singh‡, H. Gong‡, R. Shringarpure‡, N. Hoe‡, E. Chuang‡ & N. J. Talley§

34 biomarkers and 4 psychological tools

- Inflammatory cytokines and chemokines
- Gene expression markers
- Growth factors
- Microbial antibodies
- Molecular transporters
- Markers of histamine activation
- Neurotransmitters
- Gut hormones



The full panel of biomarkers in combination with psychological measures provides strong overall differentiation of IBS cases from healthy volunteers (AUC = 0.93).

- 60 IBS constipation
- 57 IBS diarrhoea
- 51 IBS mixed
- 76 Healthy controls

→Phenotyping is not defining mechanisms

→Needs an integrated systems approach

Our whole systems approach to High-Value Nutrition science

Our biology
Organ networks
Cellular networks
Molecular networks
Genetic interaction

Our environment
Where we live
Cultural backgrounds
Social networks
Food choices

Our research focuses on understanding biological processes as complex integrated systems.
Nutrition to keep us healthy and well requires an holistic approach.

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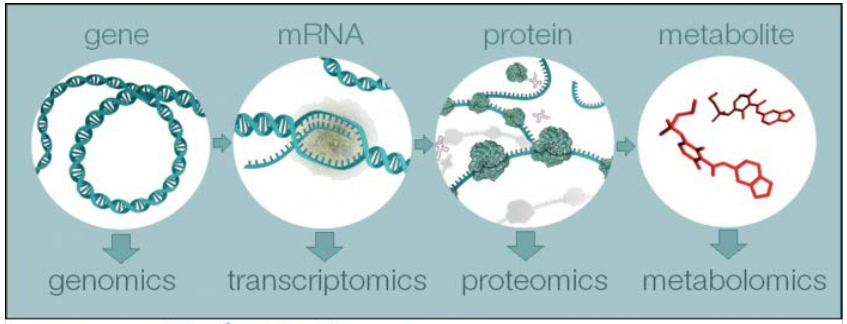
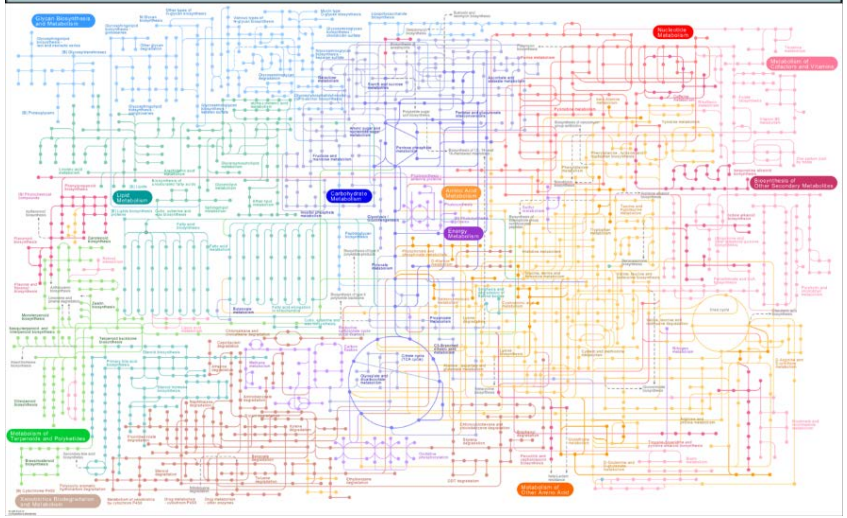
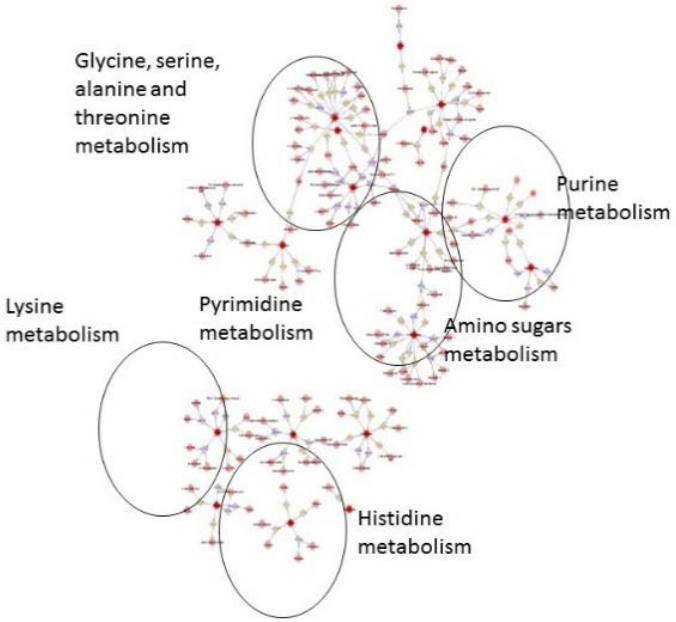
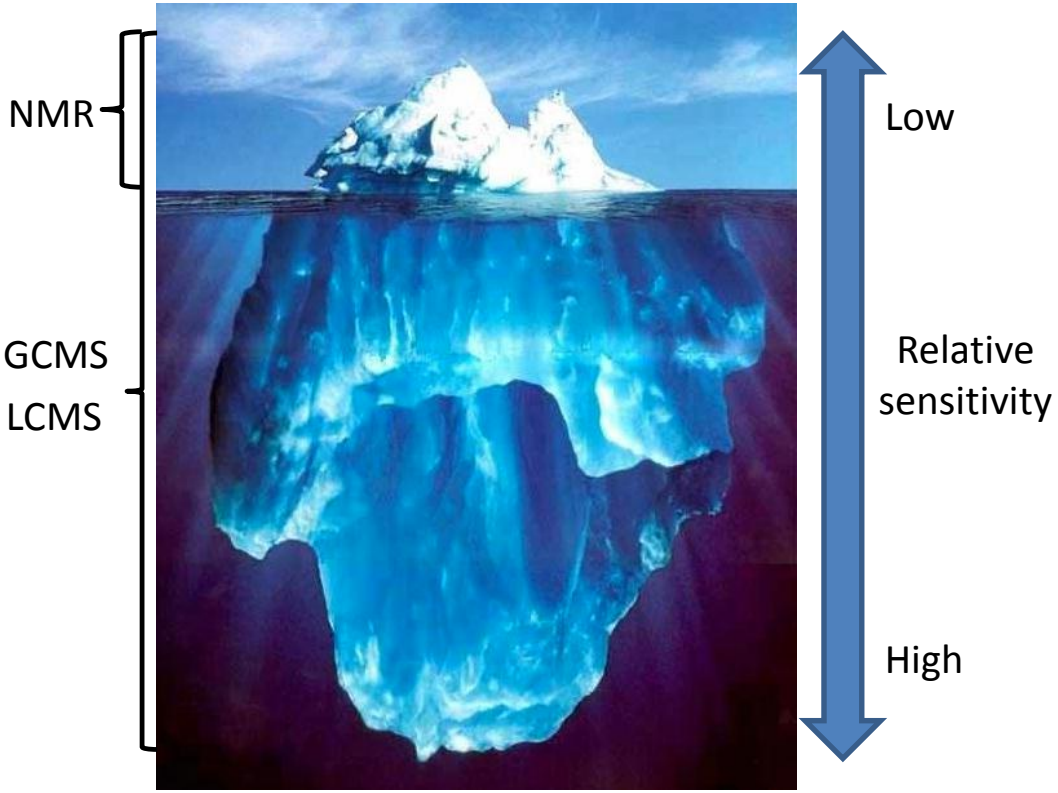
Metabolomics – biomarker discovery







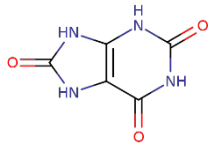
The metabolite concentration ‘iceberg’



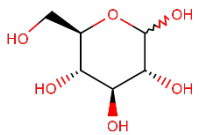
- Wide concentration range of metabolites (mM to <pM)
- Critical metabolites can occur at low concentrations e.g. hormones

✓ **Mass spectrometry gives greatest coverage of the metabolome**

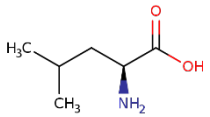
Immense molecular diversity



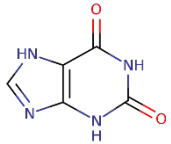
Uric acid (µM)



Glucose (mM)

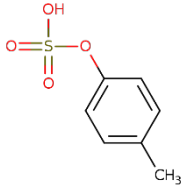


Amino acids (nM)

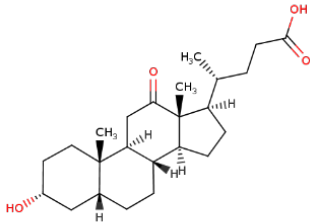


Xanthine (µM)

Polar

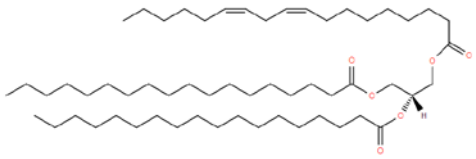


Microbial (µM)

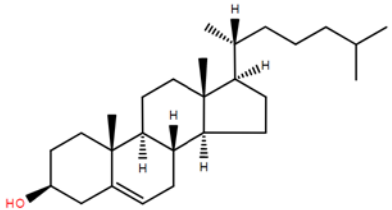


Bile acids (µM-nM)

Semi-Polar



TGs (µM-mM)



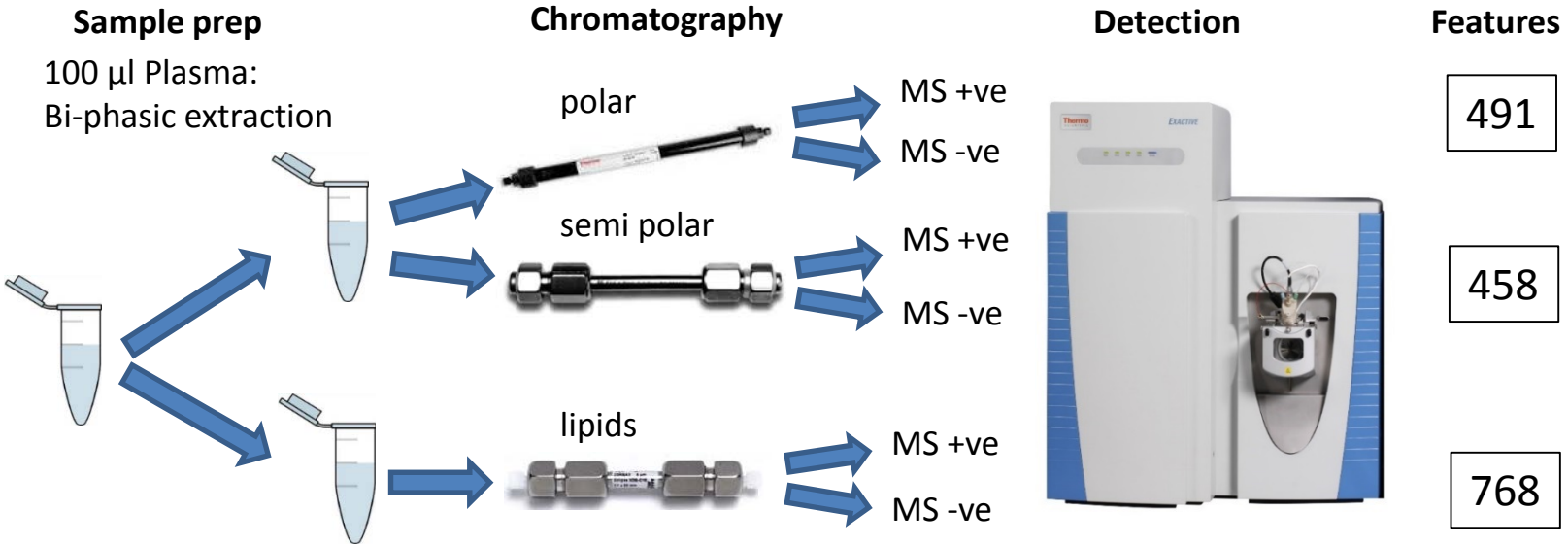
Cholesterol (µM-mM)

Non-Polar

Plasma profiling the COMFORT cohort sample set to date

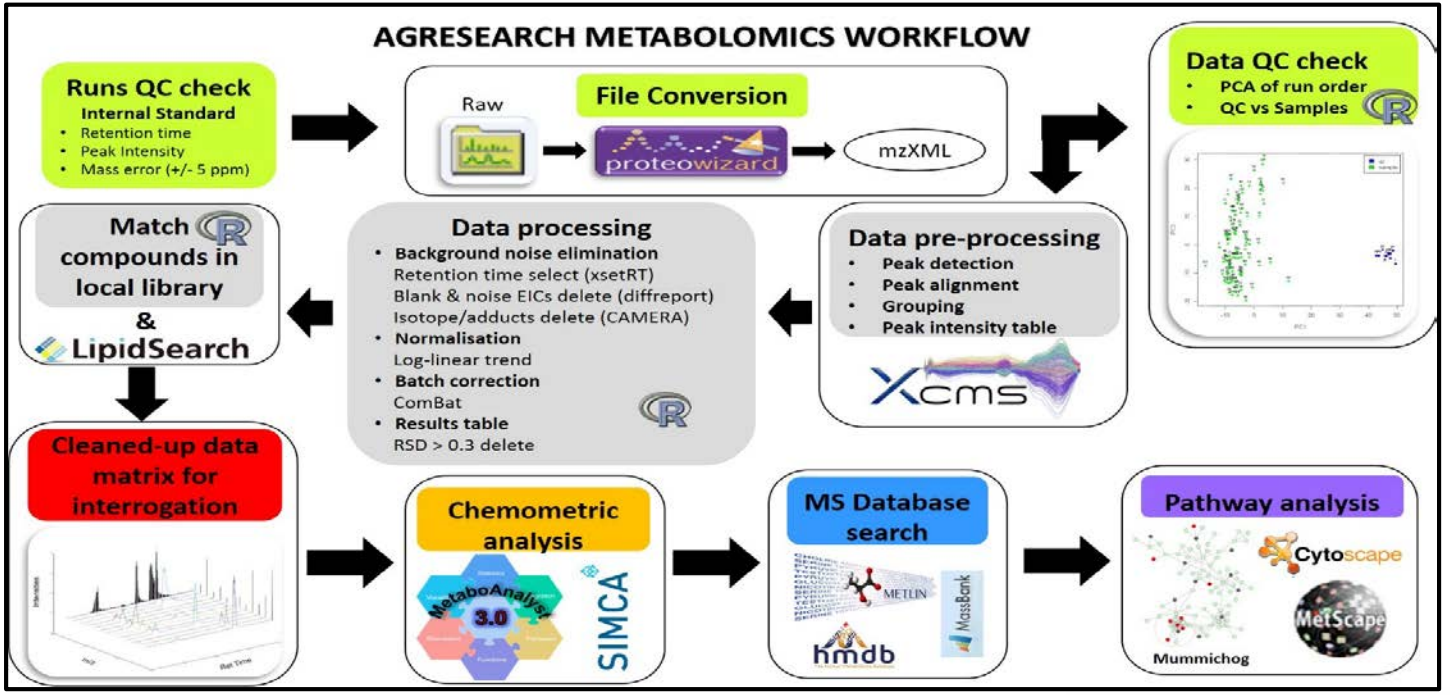
- 102 plasma samples extracted
  - 36 healthy controls
  - 24 with constipation = 17 Functional Constipation (FC) + 7 IBS-C
  - 22 with diarrhoea = 4 Functional Diarrhoea (FD) + 18 IBS-D
  - 12 with mixed symptoms (IBS-M)
  - 8 not yet diagnosed (awaiting survey data)

Multiple analytical streams

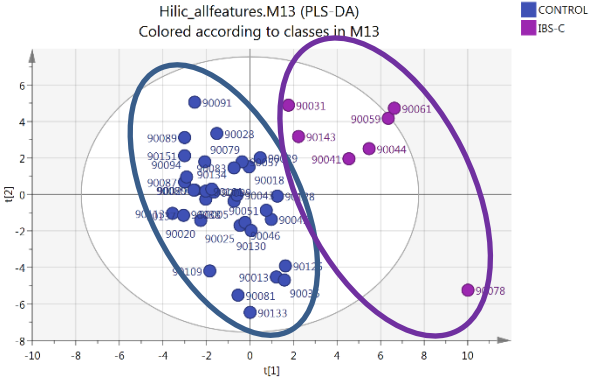


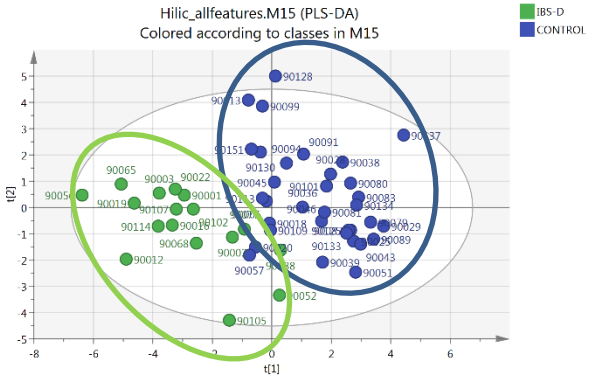
✓ **Majority of plasma metabolome measured**

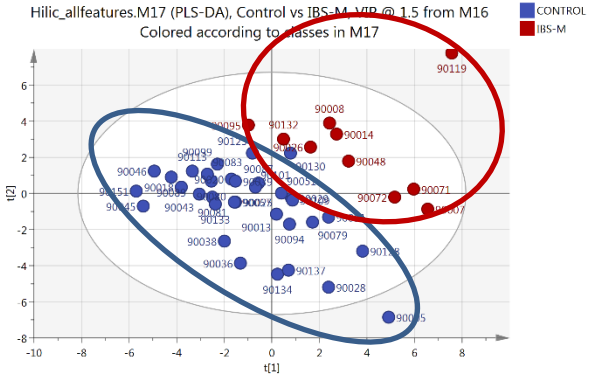
Data collection is only the beginning...

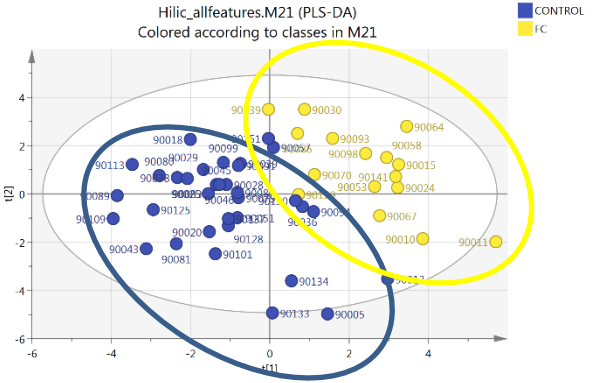


Can we differentiate IBS from a healthy gut?





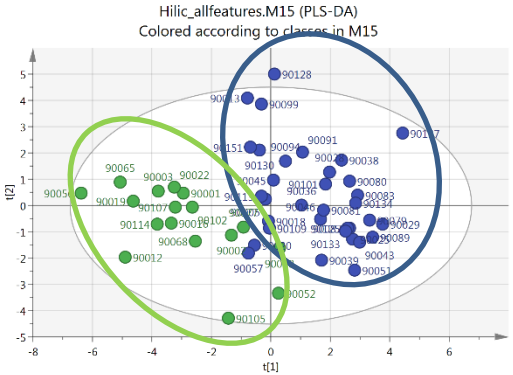




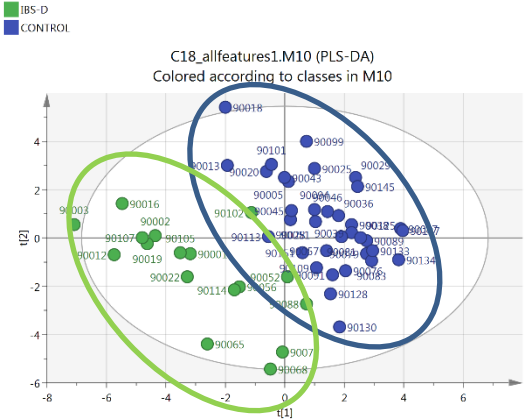
- PLS-DA of polar metabolites can (shown here)
- Similar results for semi-polar and lipid analyses
- Models show discrimination between groups

✓ **More samples will improve differentiation**

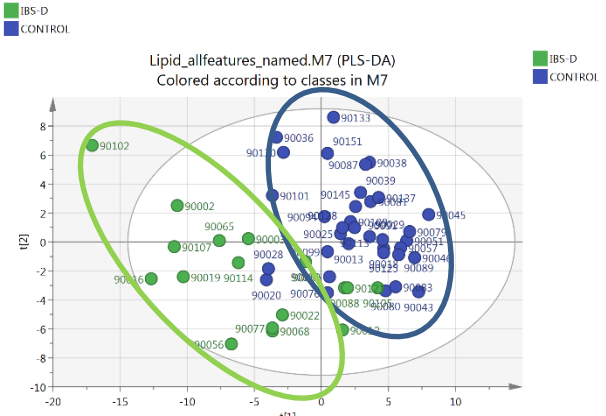
What are the metabolic drivers?
Example – Healthy gut vs IBS-D



Polar



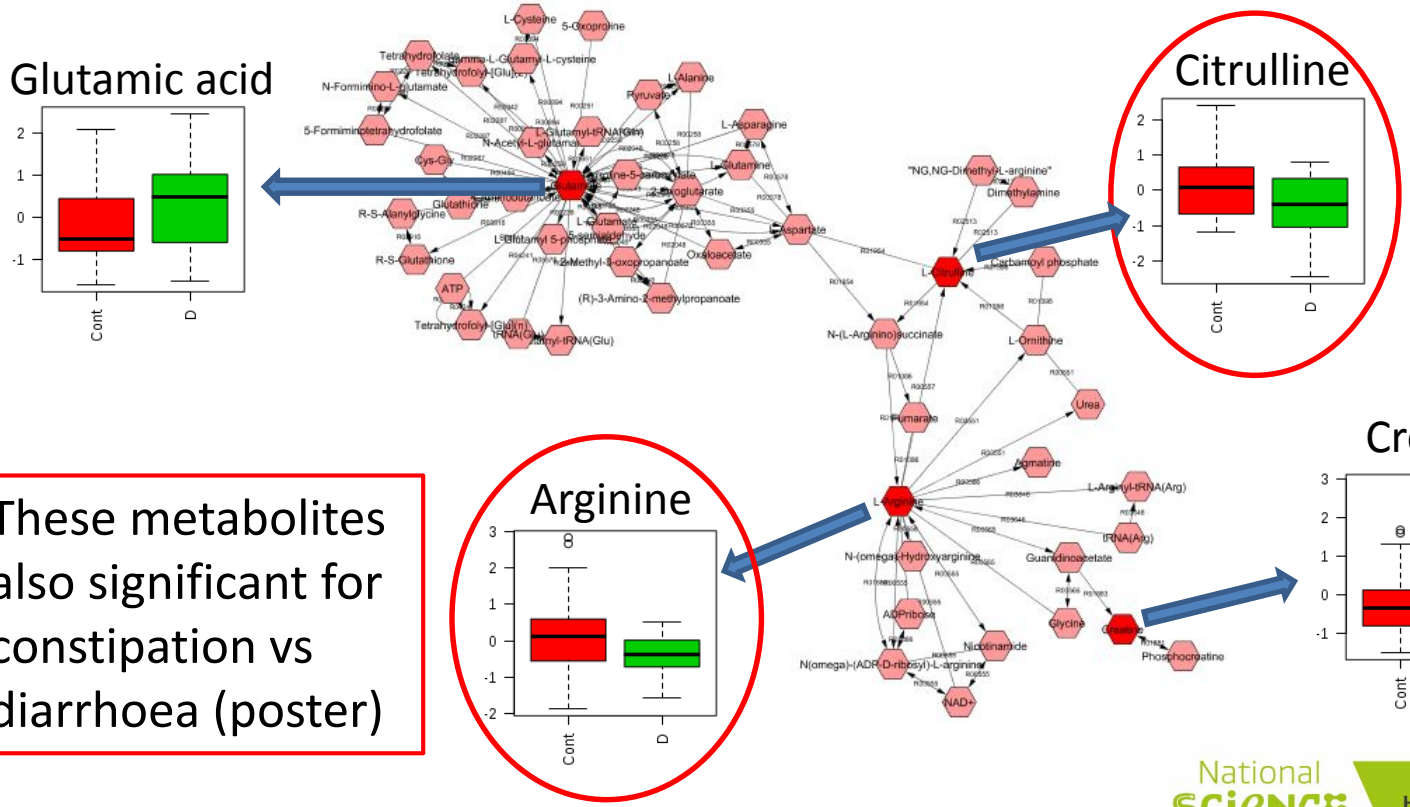
Semi-polar



Lipid

- Differentiation observed across the metabolome
- What are the key features driving separation?

Polar metabolite network: reveal key ‘hubs’



Plasma citrulline an indicator of absorptive and barrier function of the small intestine[1]

These metabolites also significant for constipation vs diarrhoea (poster)

[1] Mujagic *et al* (2016). A novel biomarker panel for IBS. *Sci Rep.* 6:26420

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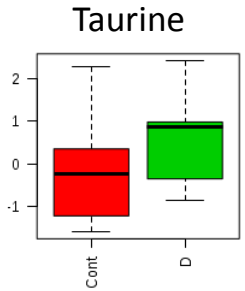
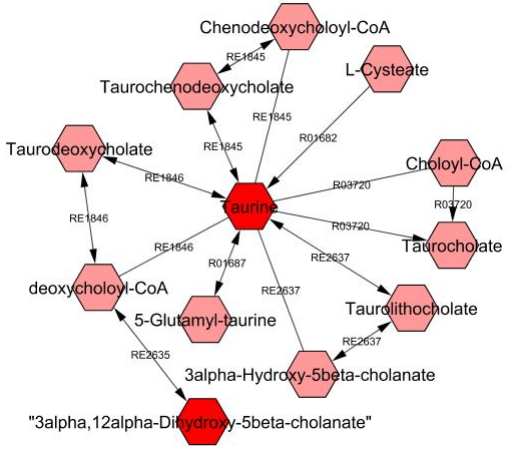
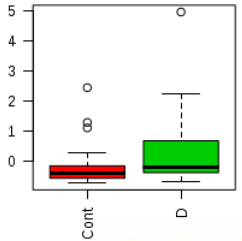
Pathway mapping can reveal new targets

- Perturbations in bile acid metabolism – elevated in IBS-D
- Pathway mapping can imply further targets for analysis (underway)



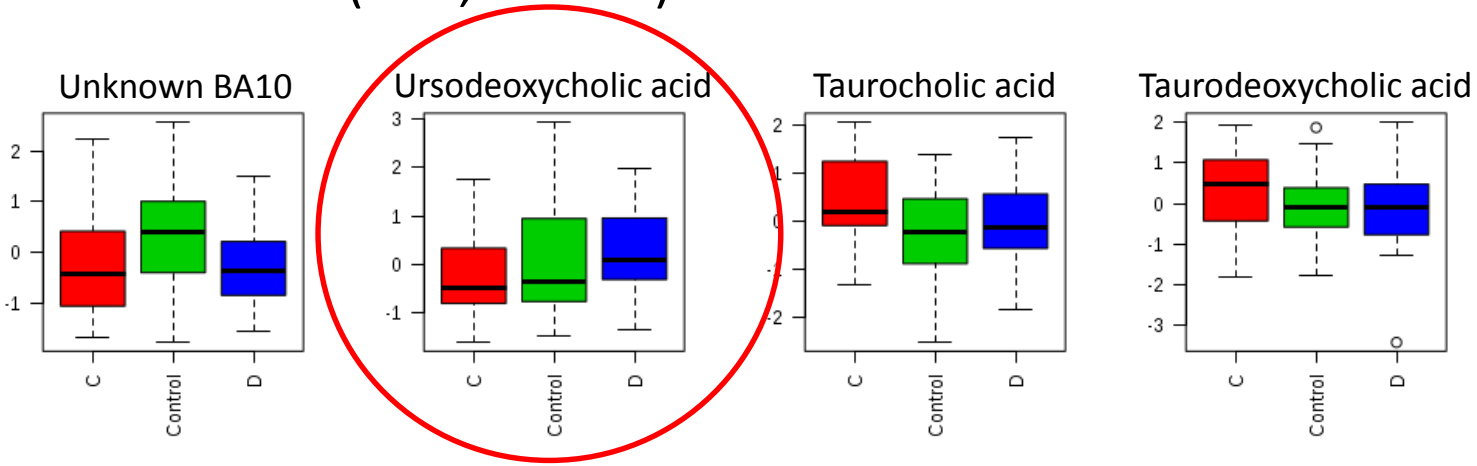


Ursodeoxycholic acid



Targeted analysis of key pathways - bile acids

- Previous studies have implicated bile acid dysbiosis[1]
- Targeted method developed and implemented at AgResearch with collaborators (APC, Ireland)



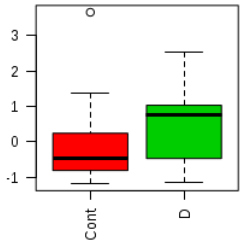
- Initial results show potential (see poster)

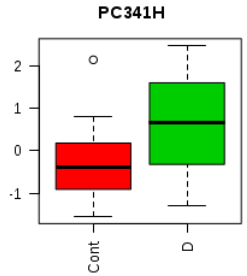
[1] Camilleri *et al* (2015). Bile acid diarrhea. *Gut and Liver* 9(3): 332–339.

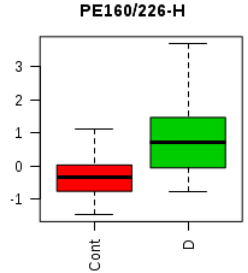
Major perturbations in lipidome

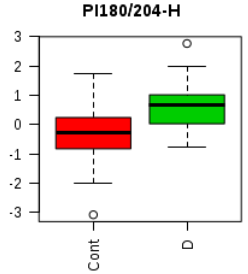
→Altered phospholipid metabolism

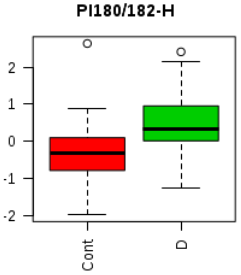
Phosphoethanolamine

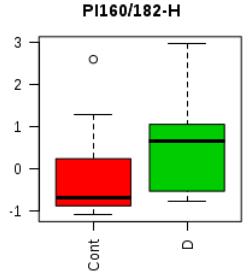


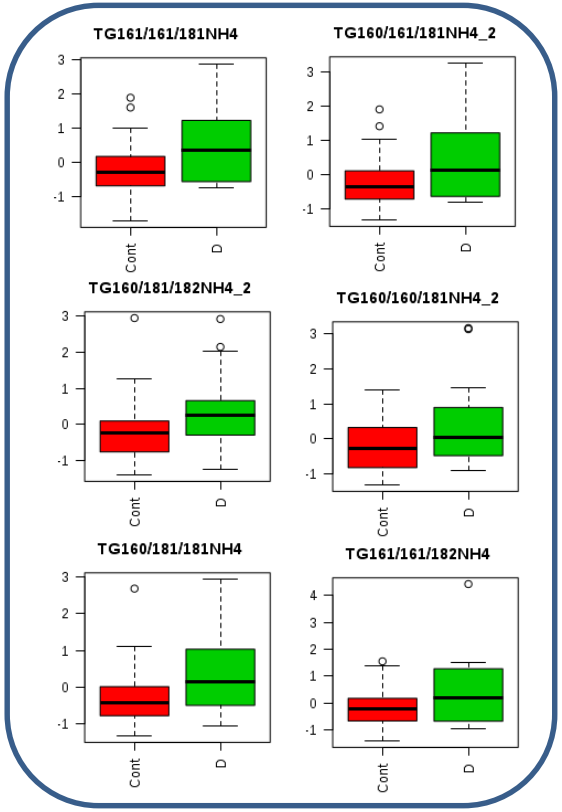












→Higher plasma triacylglycerols

Lipid metabolism: interactions within the host

- Gut microbiome can impact host lipid levels[1]:
  - Gut microbe associations with bile acid composition and plasma lipid levels
  - Short-chain fatty acid production and absorption impacts host energy metabolism
  - Bacterial intermediates further metabolised by host – possible effects on lipid levels

[1] Allayee and Hazen (2016). Contribution of Gut Bacteria to Lipid Levels. *Circ Res.* 117(9):750-754

Conclusions

- Metabolomics provides both phenotypic and mechanistic information
- Reinforces need for multi-omics approach to understand mechanisms at system level
- Increasing the COMFORT cohort size will improve predictive power to enhance the systems approach

→ *Clinical and systems approach will de-risk developing new foods with validated gut health benefits that will be highly desirable and sought after by healthy consumers*

Acknowledgements

Programme Leader/Principal Investigator

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Principal Investigator, clinical

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  - Phoebe Heenan, Shriya Sharma

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- Metabolites: Karl Fraser, AgResearch
  - Hedley Stirrat, Heike Schwendel
- Microbiota: Wayne Young, AgResearch
- Immune: Oliver Grasser, Malaghan Institute
- Proteins: Janine Cooney, Plant and Food Research

Collaborators

- Pathway Analysis: Jean-Charles Martin, INRA, BIOMET, University of Marseille, France
- Bile acids: Susan Joyce, APC Microbiome Institute, Ireland

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