

Research Leadership Award



Congratulations

Dr. David Mack
Children's Hospital of Eastern Ontario

crohn's  colitis

Crohn's and Colitis Canada 2023 Research Leadership Award

David R. Mack, MD, FRCPC
Department of Pediatrics,
CHEO and University of Ottawa

CHEO

INFLAMMATORY BOWEL DISEASE CENTRE
CENTRE DES MALADIES INFLAMMATOIRES DE L'INTESTIN



uOttawa

Faculté de médecine
Faculty of Medicine

Opportunities

- Crohn's & Colitis Canada
 - Chair, Grant-in-Aid Committee & Innovation Committee
 - Member, Scientific and Medical Advisory Committee
 - Member, COVID19 Task Force Committee
 - Member, Impact of IBD in Canada: 2018, 2023
- Co-Chair, Canadian Children's IBD (CIDsCaNN) Network
- Pediatric Representative, Clinical Affairs, CAG

Clinical Research Highlights

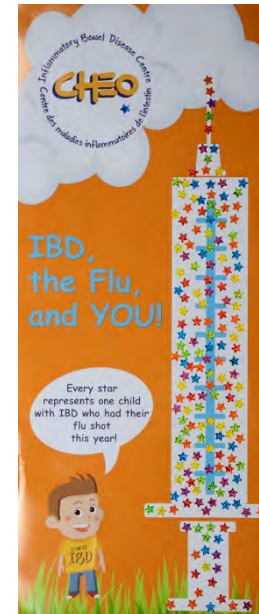
- Clinical Practice Guidelines for Pediatric CD (Gastroenterology 2019;157:320-348)

Clinical Research Highlights

- Clinical Practice Guidelines for Pediatric CD (*Gastroenterology* 2019;157:320-348)
- Collaborations: IBD Registry (USA) / GEM (Canada) / CIDsCaNN (Canada) / PROTECT Study (NIH) / CAMEO Study (NIH)

Clinical Research Highlights

- Clinical Practice Guidelines for Pediatric CD
- Collaborations: IBD Registry/GEM/CIDCaNN/PROTECT/CAMEO
- Improving Influenza Vaccination Rates (Inflamm Bowel Dis 2015;8;1761-1768)
 - Katie Huth. 26th Annual National Resident/Fellow Research Competition



Clinical Research Highlights

- Clinical Practice Guidelines for Pediatric CD
- Collaborations: IBD Registry/GEM/CIDCaNN/PROTECT/CAMEO
- Improving Influenza Vaccination Rates
- pIBD INTERMED (J Psychosomatic Res 2019;119;26-33)
 - Integrates disease complexity & psychosocial needs using objective scores to aid in clinical decision-making

**PEDIATRIC- INTERMED COMPLEXITY
ASSESSMENT GRID MANUAL**

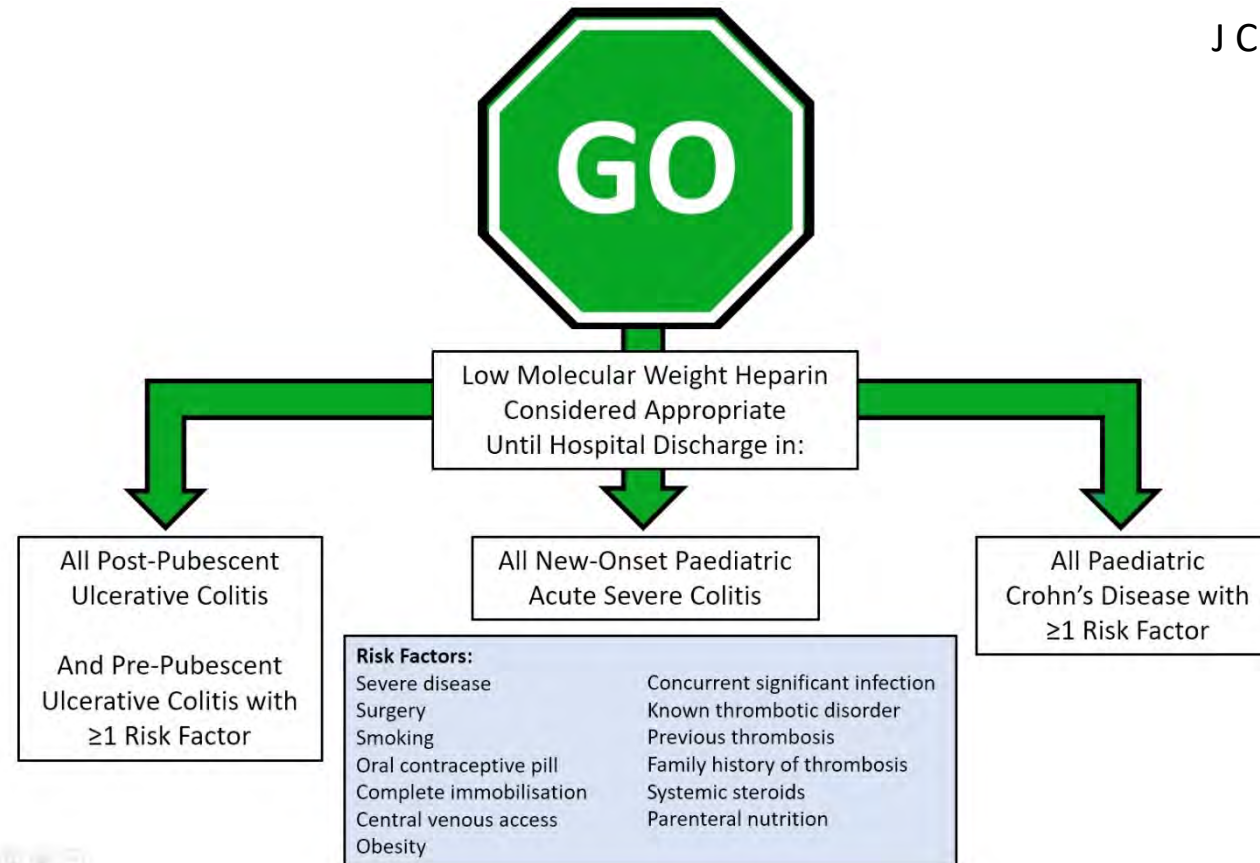


Clinical Research Highlights

- Clinical Practice Guidelines for Pediatric CD
- Collaborations: IBD Registry/GEM/CIDCaNN/PROTECT/CAMEO
- Improving Influenza Vaccination Rates
- pIBD INTERMED
- Enoxaparin safety in hospitalized children with UC (JPGN 2021;73:604-609)

Venous Thromboembolism Prophylaxis in Pediatric IBD

J Crohns Colitis 2022;16:1609-1616

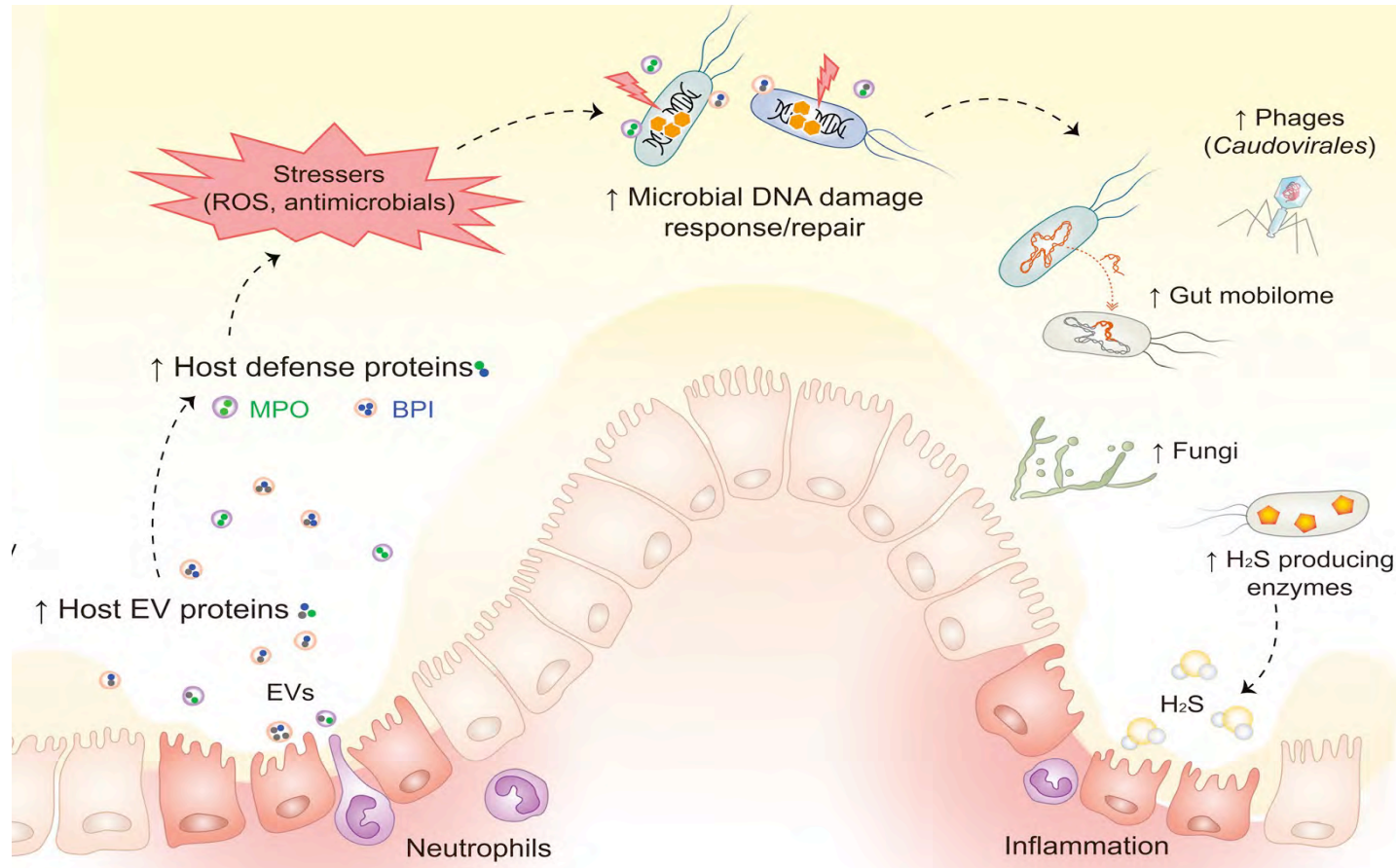


Basic/Translational Research Highlights

- Functional alteration of mucins from colitis model and preventing pathobiont intestinal cell adherence
- *Lactobacillus spp.* upregulation of intestinal epithelial cell mucin expression
 - Nathalie Godwin: 2007 Crohn's & Colitis Canada Student Research Award
- IBD pathogenesis discovery evaluating intestinal microbiome through mucosal luminal interface biospecimens analyses and integrating clinical metadata

Functional Alterations of the IBD Microbiome

Nat Comm 2018;9:2873
Gut Microbes 2023;15(1):2177488



- Extracellular vesicles carry host-defense proteins (e.g. MPO, BPI) into lumen
- Decreased crAss-like phages
 - *Caudovirales* viral contigs
- Increased presence of fungi
- Microbiota dysbiosis

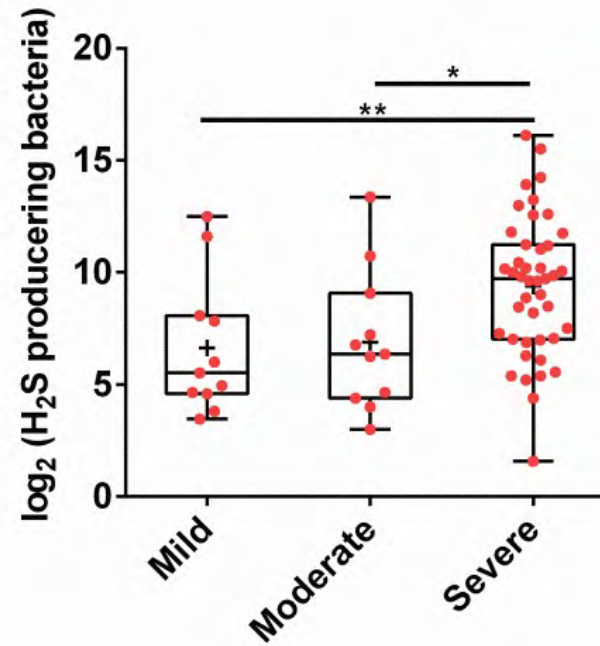
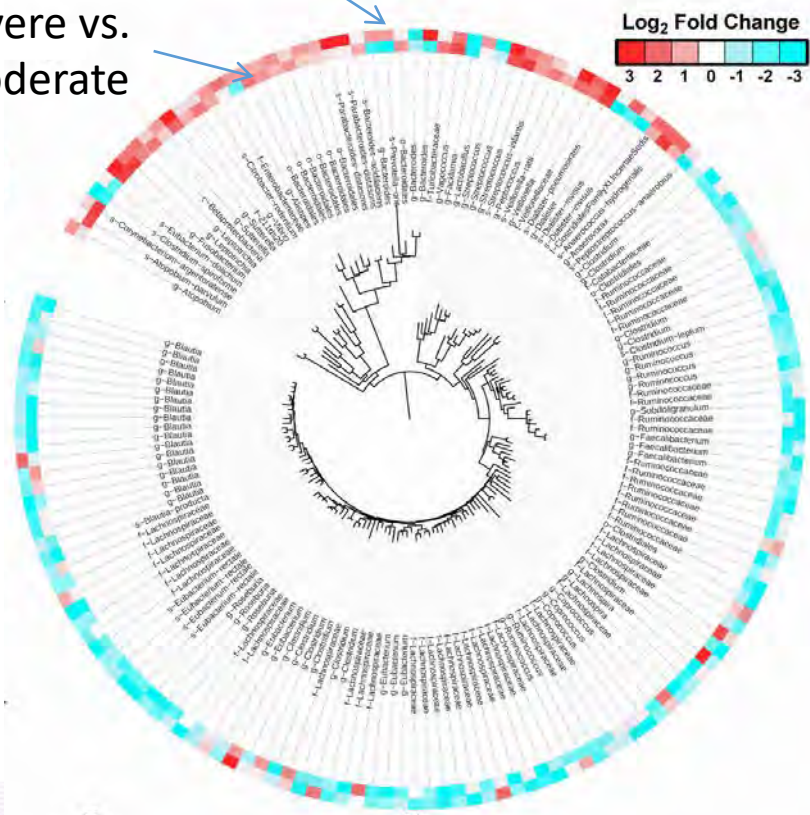
MLI Intestinal Dysbiosis in Children with CD

Who's there?/Who's not there? & Consequences

Nature Comm 2016 Nov 23;7:13419

Severe vs. Mild

Severe vs. Moderate

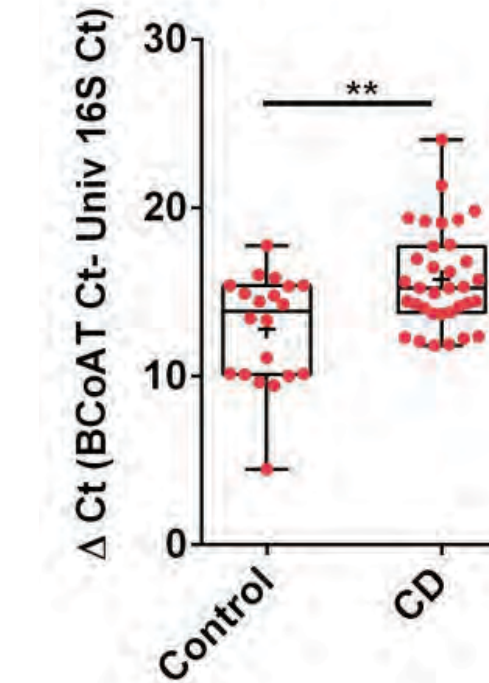
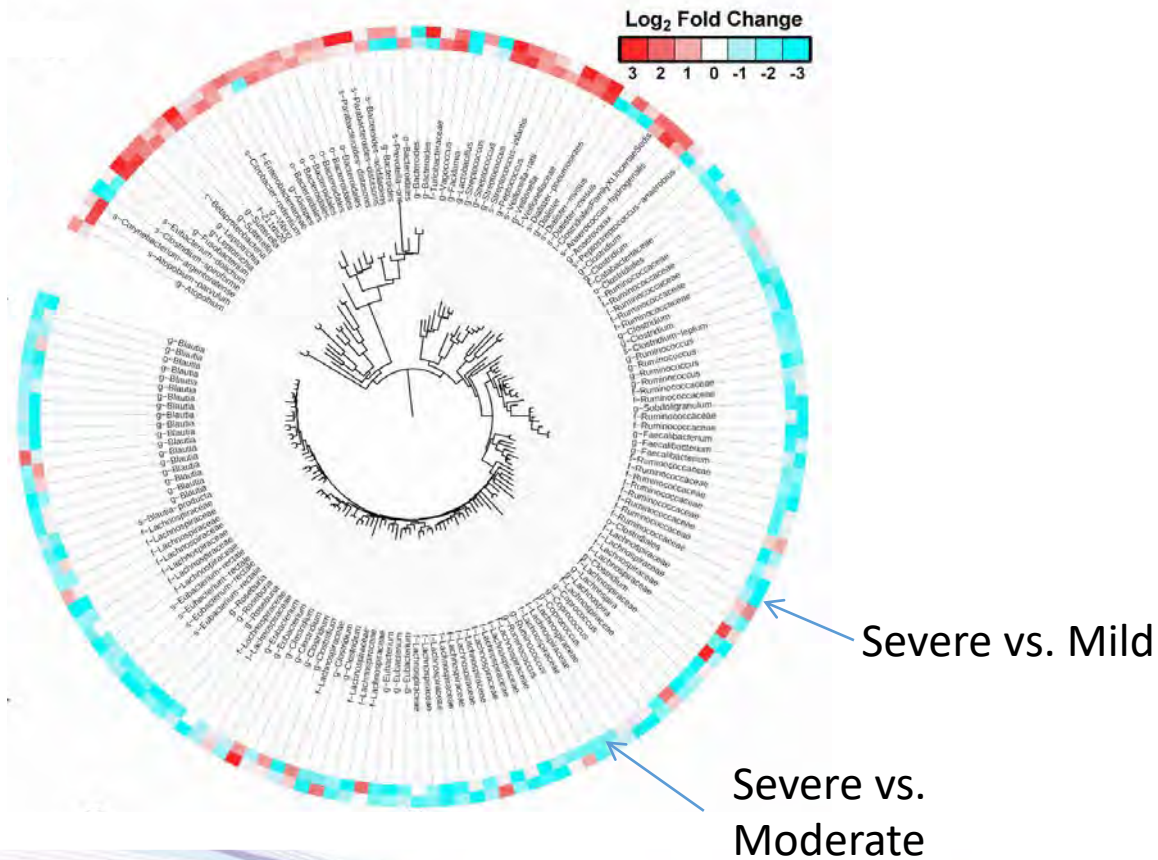


25% of all microbes (ASVs) were H₂S producers

MLI Intestinal Dysbiosis in Children with CD

Who's there?/Who's not there? & What's going on?

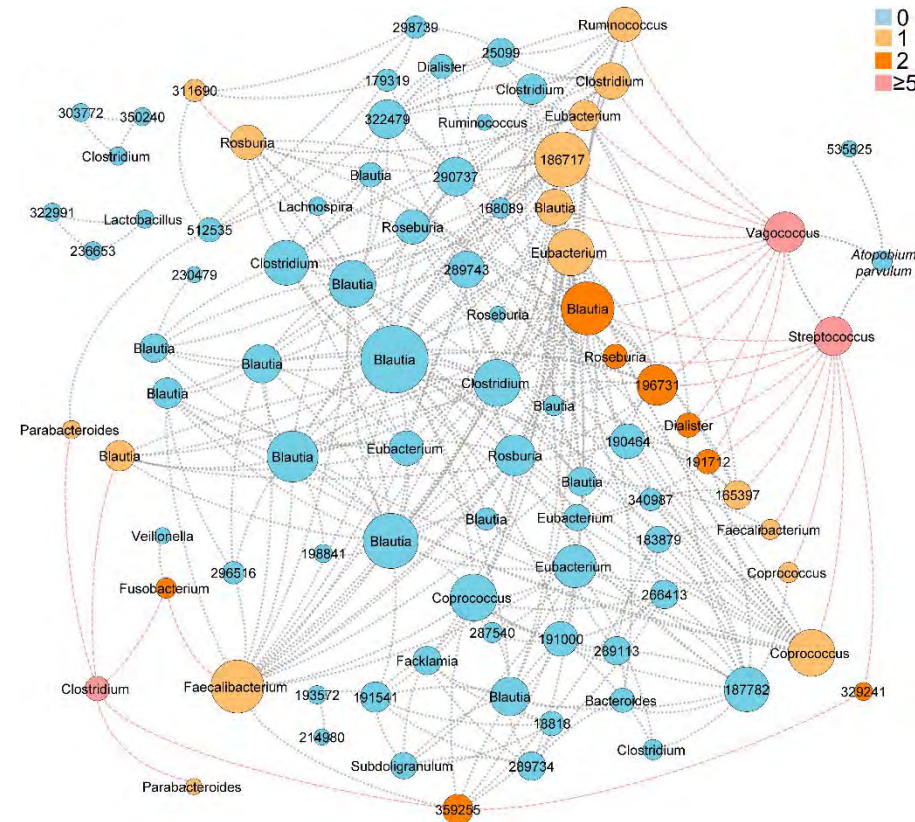
Nature Comm 2016 Nov 23;7:13419



qPCR assay targeting the butyryl-CoA:acetate CoA-transferase (BCoAT) gene

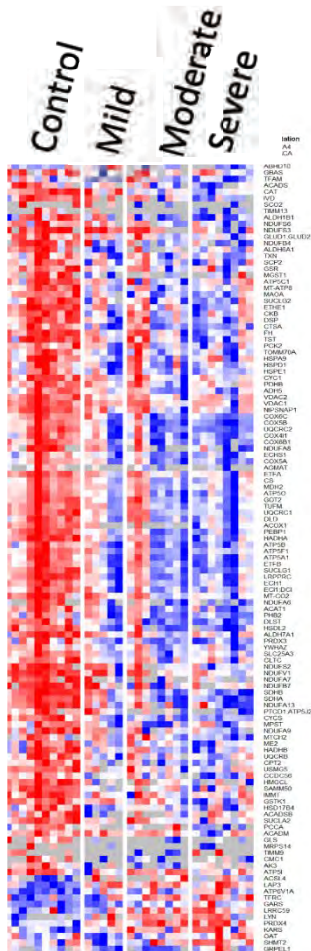
Microbial Interaction Network

Nature Comm 2016;7:13419



Differential Expression of Mitochondrial Proteins in CD

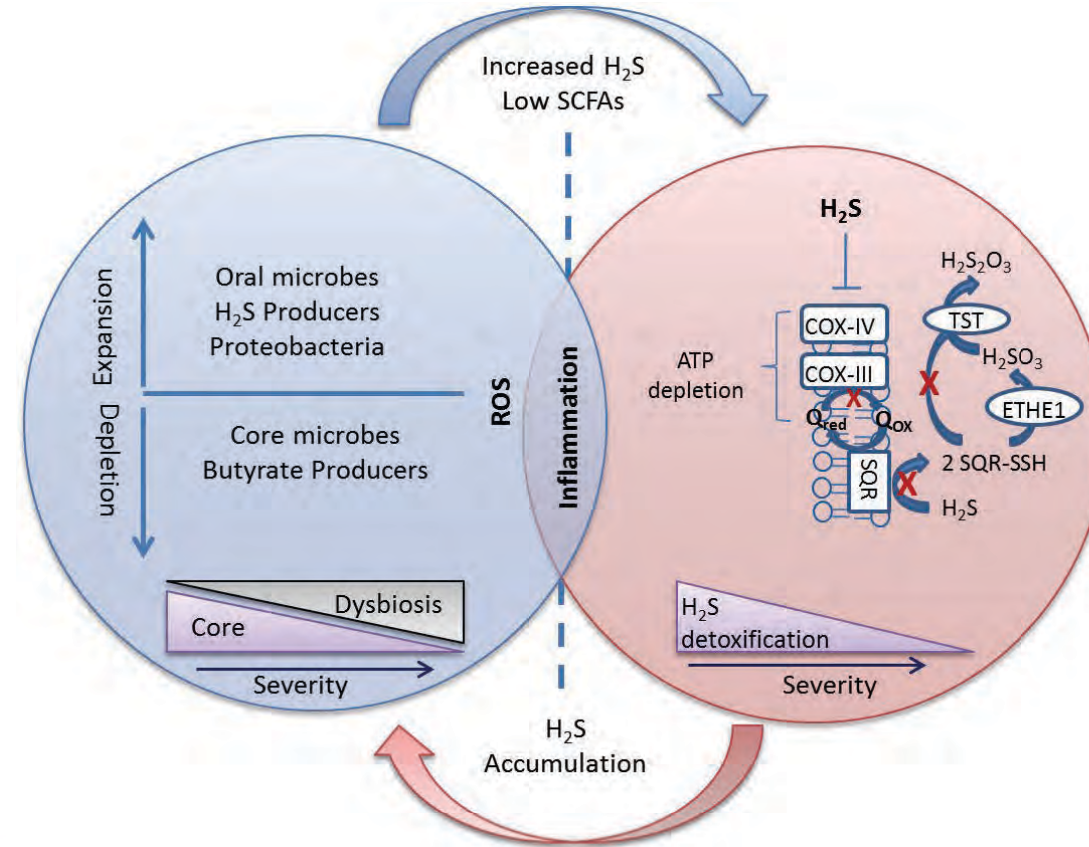
Nature Comm 2016;7:13419
Gut 2017;66(9):1573-1583



- 10% of proteins differentially expressed
- Heat map of individual mitochondrial protein expression as a function of disease severity
 - control, mild, moderate or severe Crohn's disease panels
- Red to blue colour indicates a decrease in protein expression
- Most (93.5%) were down-regulated

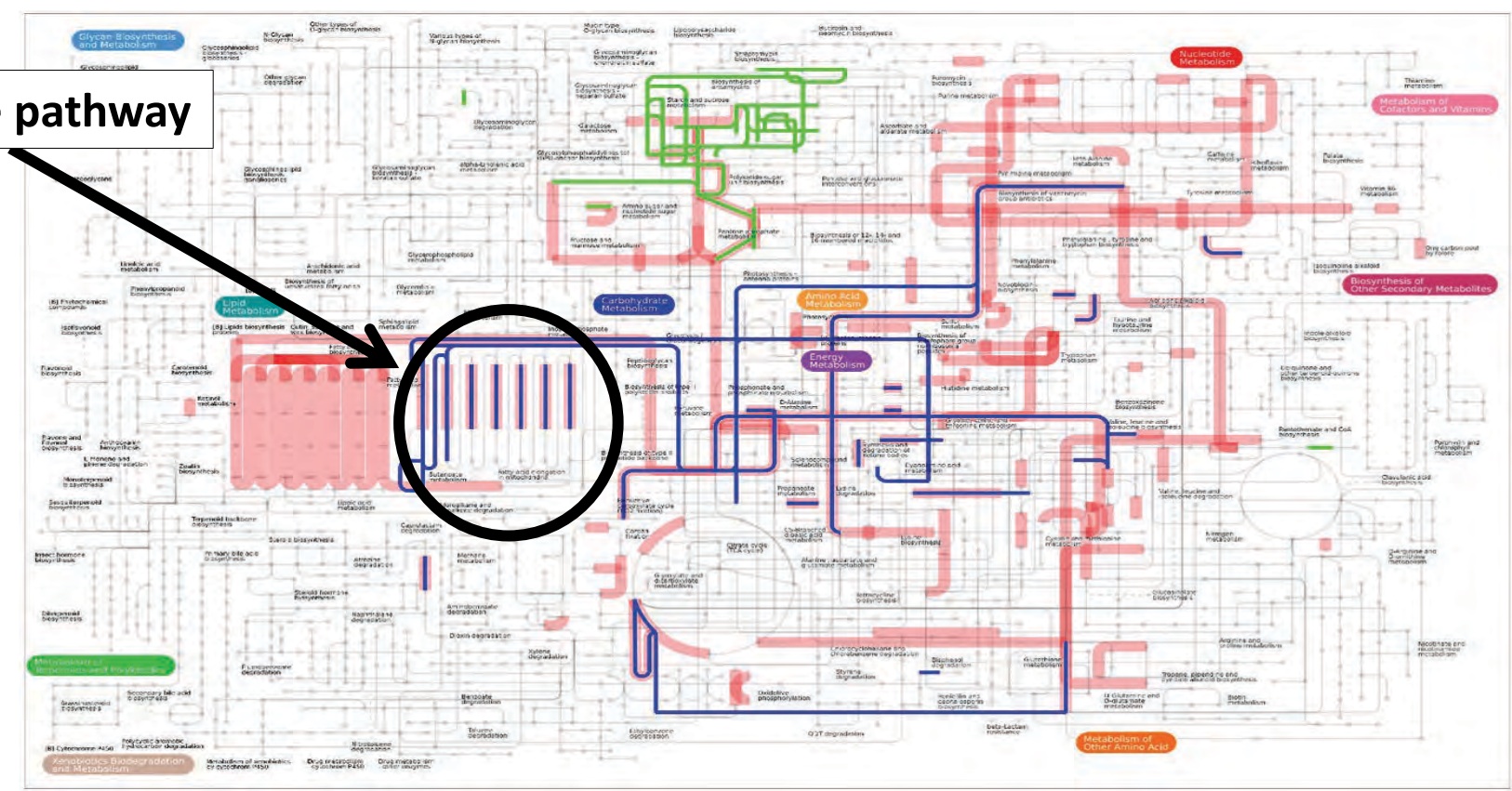
Who's there/Who's not there & What's going on: *Loss of Functional Redundancy*

Nature Comm 2016;7:13419
Nature Comm 2023;14(1):1428



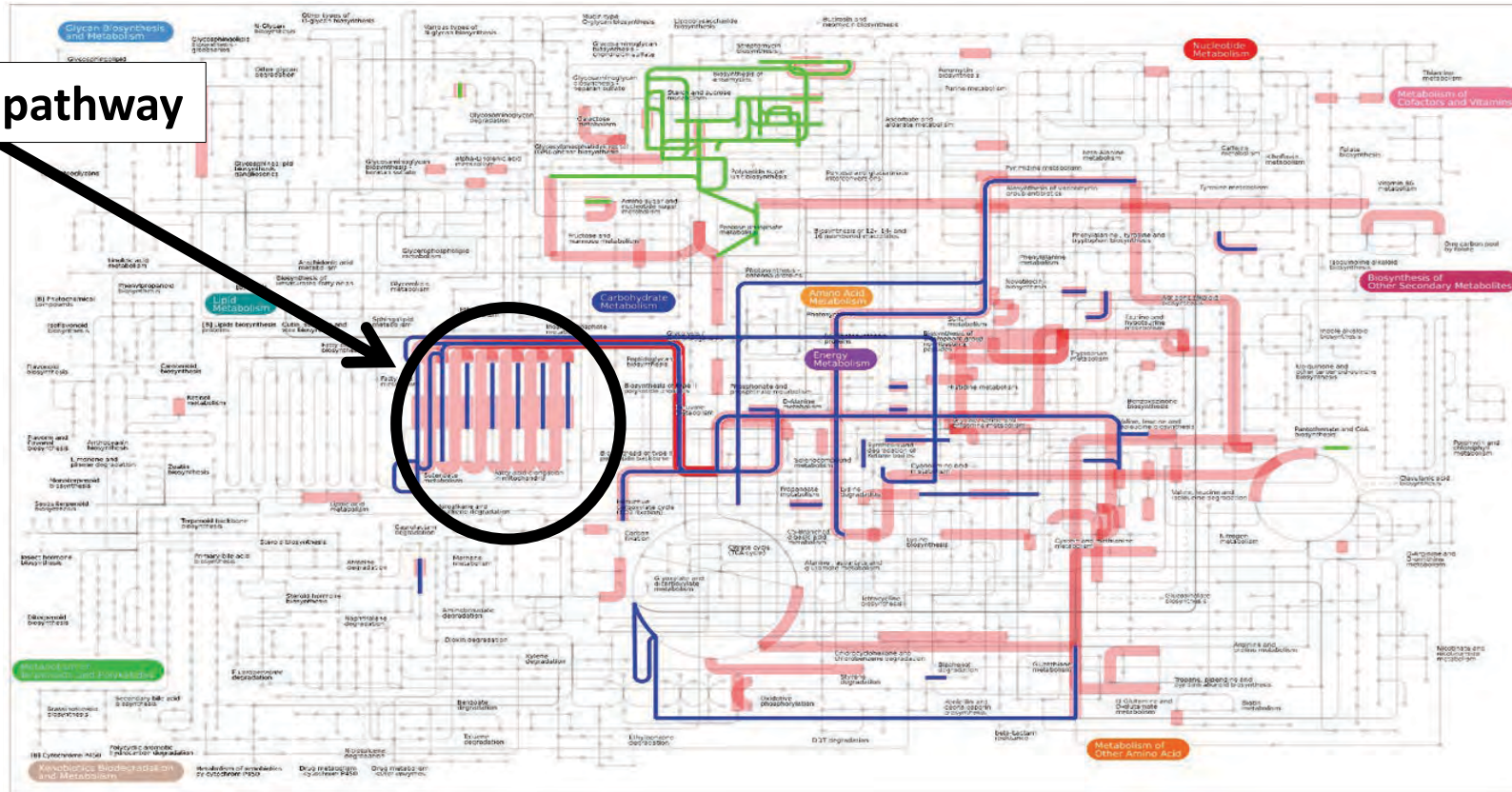
Microbiome Function: Food panel item A

Butyrate pathway



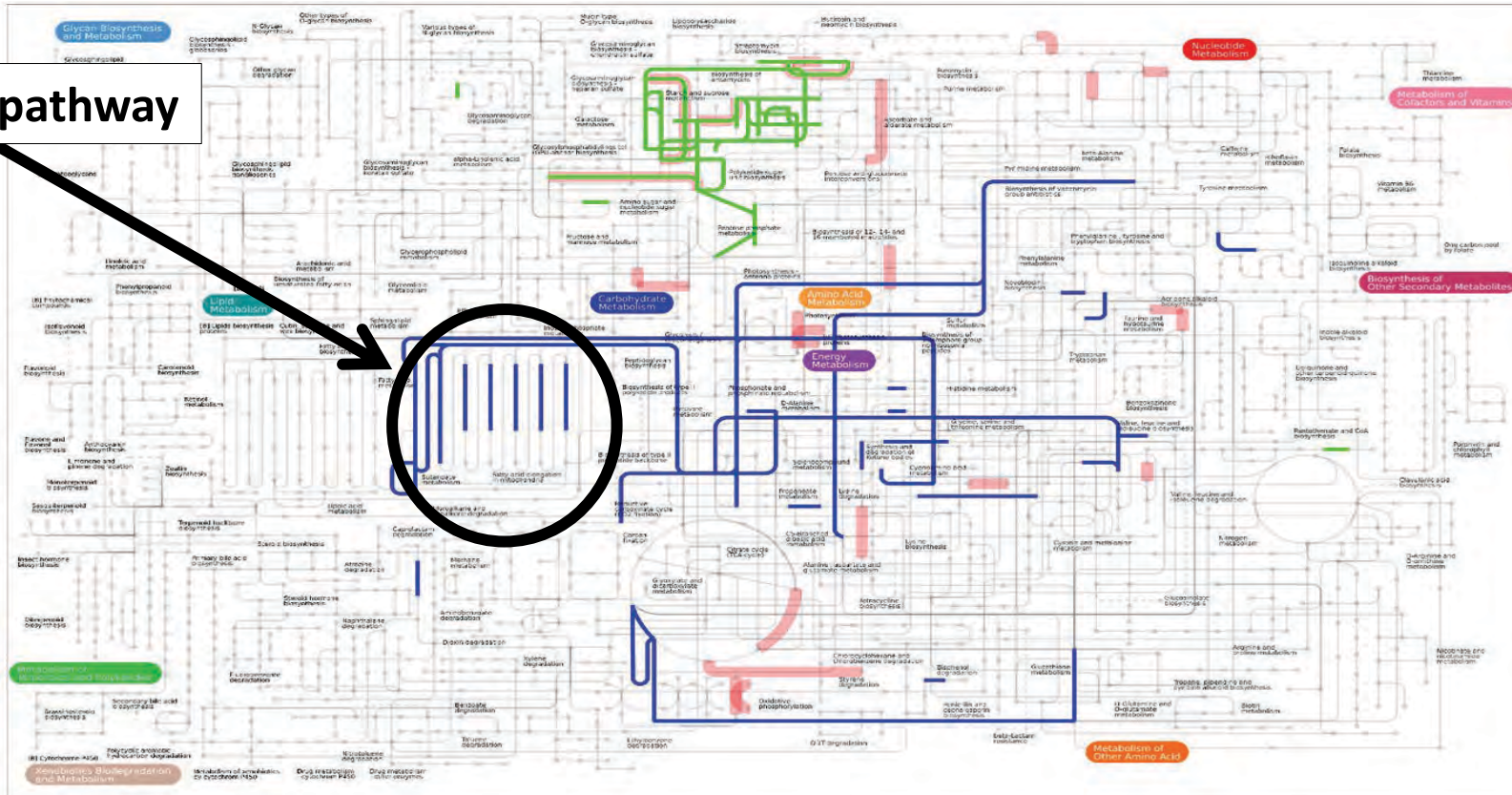
Microbiome Function: Food panel item B

Butyrate pathway



Microbiome Function: Food panel item C

Butyrate pathway

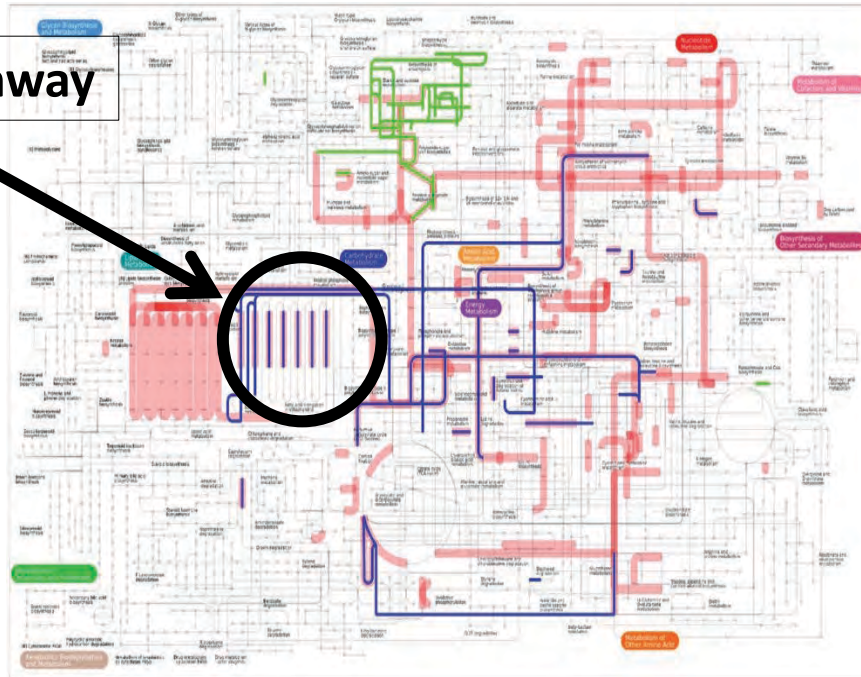


Microbiome Function: Food panel item A

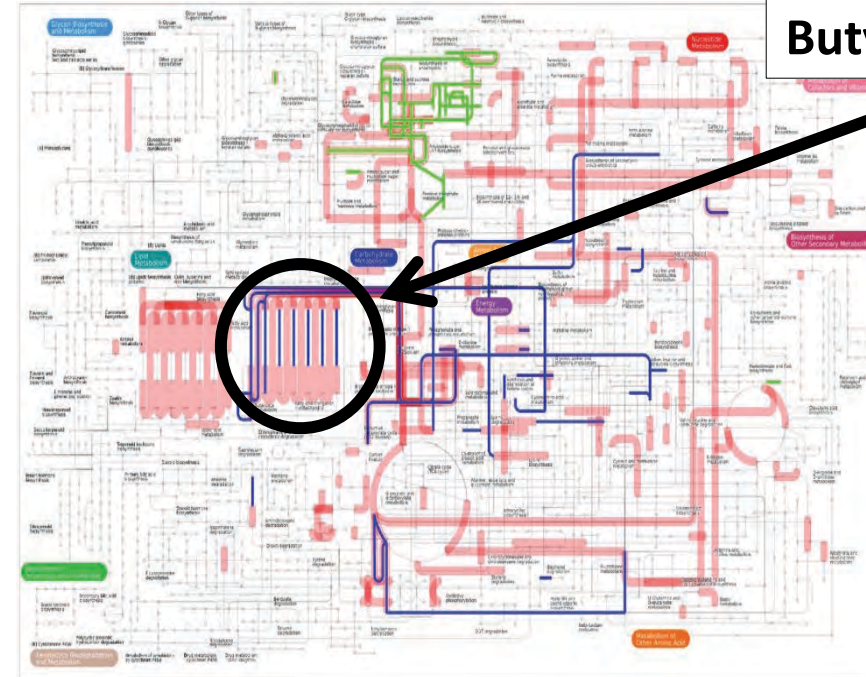
Participant 1

Participant 2

Butyrate pathway



Butyrate pathway



The microbiome functional output is individually specific

Individual variation of microbiome function

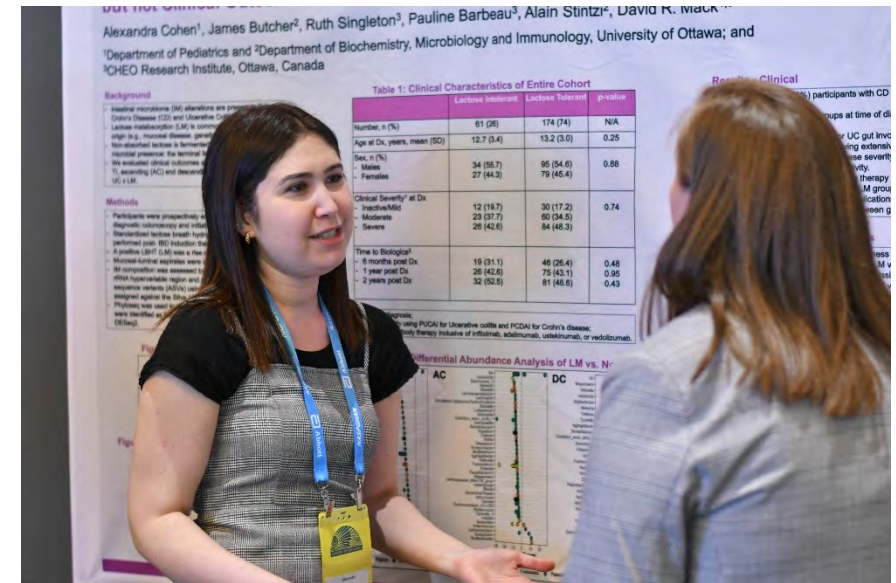
β-fructan non-fermentation
worsens IBD in some people

Lactose Malabsorption in IBD

- Pediatric IBD Microbiome database
 - N \approx 900 participants
 - N = 235 had lactose breath testing
 - CD = 149; UC = 86

Alex Cohen

2023 NASPGHAN Annual Meeting



Baseline Characterization

	Lactose Malabsorber	Lactose Absorber	P-value
Number, n (%)	61 (26.0)	174 (74.0)	
Sex, n (%)			0.88
Males/Females	34 (55.7) / 27 (44.3)	95 (54.6) / 79 (45.4)	
Age at Diagnosis, mean years \pm 1 SD	12.7 \pm 3.4	13.2 \pm 3.0	0.25
Clinical Severity at Diagnosis, n (%)			0.74
Mild	12 (19.7)	30 (17.2)	
Moderate	23 (37.7)	60 (34.5)	
Severe	26 (42.6)	84 (48.3)	

Two-year Outcome

	Lactose Malabsorber	Lactose Absorber	P-value
Monoclonal Antibody Therapy, n (%)			
6 months post diagnosis	19 (31.1)	46 (26.4)	0.48
1 year post diagnosis	26 (42.6)	75 (43.1)	0.95
2 years post diagnosis	32 (52.5)	81 (46.4)	0.43

Individual variation of microbiome function

β -fructan non-fermentation
worsens IBD in some people

Lactose non-fermentation
has no effect on IBD

Fermentation is necessary but not sufficient to host effect benefit

One size fits all = One size fits few

Individual variation of microbiome function



Fermentation is necessary but not sufficient to effect host benefit



Personalized therapy

Moving forward using knowledge from pathogenesis discovery to therapeutics discovery

- NCT04522271: RS Study
- NCT04520594: MEND Trial

Thank-you

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