ACKNOWLEDGEMENTS

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ORGANIZING COMMITTEE

SYMPOSIUM AND SCIENTIFIC PROGRAM CHAIR

L. Jane Gillis, MD, FRCPC, FCCMG
Biochemical Geneticist
BC Children's Hospital

SCIENTIFIC PROGRAM COMMITTEE AND ABSTRACT REVIEWS

Pranesh Chakraborty, MD, FRCPC, FCCMG
Director, Newborn Screening Ontario
Children's Hospital of Eastern Ontario

Chitra Prasad, MD, FRCPC, FCCMG, FACMG
Associate Professor, Genetics, Metabolism and Pediatrics
Western University and London Health Sciences Centre

Sylvia Stockler, MD, PhD, MBA, FRCPC
Division Head and Biochemical Diseases Clinic Director
BC Children's Hospital

DIETITIANS' WEBINAR
Maggie Chapman, RD
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SOCIAL EVENTS

THURSDAY, MAY 19

Welcome Reception
1830–2100
Halifax Ballroom BC, Marriott Harbourfront Hotel
Tickets: No charge for registered delegates; $40 for guests

FRIDAY, MAY 20

Garrod Symposium Gala Dinner & Entertainment
1900–2200
Pier 21 Museum
Tickets: $90.00 per person
Meet in the Marriott Harbourfront hotel lobby at 1840 to catch the bus.

Make sure you purchase a ticket for our gala evening on Friday – a lobster feast at Pier 21, Canada's Immigration Museum. Pier 21 is a National Historic Site which was the gateway to Canada for one million immigrants between 1928 and 1971. It also served as the departure point for 500,000 Canadian Military personnel during the Second World War. Today, Pier 21 hosts the Canadian Museum of Immigration at Pier 21 – Atlantic Canada's only national museum! Guests will have the opportunity to enjoy a cocktail reception in the Pier 21 Rudolph P Bratty Hall exhibition. Following the reception, dinner and presentation will be held in the Kenneth C. Rowe Hall overlooking the Halifax harbour.

SATURDAY, MAY 21

Closing Social at Garrison Brewery
1715–1815
1149 Marginal Road
Tickets: $40.00 per person
Meet in the Marriott Harbourfront hotel lobby at 1700 to catch the bus.

Unwind with us at the end of the conference at a casual social at the Garrison Brewery. Beer and snacks will be provided. Halifax has always been at the centre of a proud and vibrant Maritime brewing tradition. In 1754, William Steel was the first local brewer to quench the thirsts of early settlers and troops gathered on Citadel Hill. Many would follow, with over 20 breweries having operated by the time of prohibition.

Garrison Brewing Company is following in this tradition by producing premium ales of distinction for the local market. With an inaugural batch of "Irish Red Ale" in 1997, Garrison introduced the craft beer movement to Nova Scotians and visitors alike. Today Garrison brews a variety of full flavored, all natural, preservative free ales. Each glass represents a tribute to the art of hand-crafting ales with the finest natural ingredients.

BUSINESS MEETINGS

THURSDAY, MAY 19

1000–1200 ..... Annapolis Room
Canadian Inherited Metabolic Diseases Research Network (CIMDRN) Meeting (Invitation Only)

1400–1600 ..... Atlantic Suite
Advisory Board Meeting (Invitation Only)
Sponsored by Medunik

1800–1930 ..... Maritime Suite
Garrod Association Executive Board

SATURDAY, MAY 21

1400–1600 ..... Halifax Ballroom
Garrod Association Membership Meeting

REGISTRATION DESK HOURS

The Registration desk is located in the Nova Scotia Foyer. The desk will be open:

Thursday, May 19	1000–1900
Friday, May 20	0700–1800
Saturday, May 21	0800–1200

SCHEDULE AT A GLANCE

THURSDAY MAY 19		**ROOM**
1000–1200	Canadian Inherited Metabolic Diseases Research Network (CIMDRN) Meeting (Invitation Only)	Annapolis
1200–1300	Home Infusion Therapy for Patients living with Mucopolysaccharidosis Type I (MPSI) in Canada (lunch)	Halifax Ballroom
1300–1400	A New Paradigm for Metabolic Medicine	Nova Scotia CD
1400–1600	Advisory Board Meeting (Invitation Only)	Atlantic Suite
1400–1600	Dietitians' Webinar	Annapolis
1400–1600	Highlights and Updates on Fabry Disease: Adult and Pediatric Outcomes	Nova Scotia CD
1600–1700	Treatment Considerations for Neurodegenerative IEMs: Leukodystrophies and Epilepsies	Nova Scotia CD
1700–1800	Fatty Acid Oxidation PKU	Nova Scotia CD
1800–1930	Garrod Association Executive Board	Maritime Suite
1830–2100	Welcome Reception	Halifax Ballroom

FRIDAY MAY 20		
0730–0830	A Difficult to Identify Metabolic Disease: Late Onset Lysosomal Acid Lipase Deficiency (breakfast)	Halifax Ballroom
0830–1000	Morning Session 1: The National Working Group Experience	Nova Scotia CD
1000–1030	Refreshment Break	Nova Scotia AB
1030–1230	Morning Session 2: Development of Treatments, Evidence and Policy	Nova Scotia CD
1230–1330	New Evidence and Treatment in the Management of PKU (lunch)	Halifax Ballroom
1330–1445	Afternoon Session 1: Mitochondrial Disorders and Innovative Therapies 1	Nova Scotia CD
1445–1500	Refreshment Break and Poster Viewing	Nova Scotia AB
1500–1730	Afternoon Session 2: Innovative Therapies 2	Nova Scotia CD
1730–1830	Cocktails and Poster Viewing	Nova Scotia AB
1900–2200	Garrod Symposium Gala Dinner and Pioneer Award Presentation at Pier 21	Offsite
	Meet in the Marriot Harbourfront Hotel lobby at 1840 to catch the bus	

SATURDAY MAY 21		
0800–0900	Patient Directed Outcomes (breakfast)	Halifax Ballroom
0900–1100	Morning Session 1: High Throughput Technologies for Personalized Management of IEM	Nova Scotia CD
1100–1115	Refreshment Break	Nova Scotia AB
1115–1300	Morning Session 2: Enhancement of Established Therapies	Nova Scotia CD
1245–1300	Wrap-up and Closing Remarks	Nova Scotia CD
1300–1400	Principles in Biomarker Discover and Translational Research in Lysosomal Storage Diseases (lunch)	Halifax Ballroom
1400–1600	Garrod Association Membership Meeting	Halifax Ballroom
1715–1815	Closing Social	Offsite
	Meet in the Marriot Harbourfront Hotel lobby at 1700 to catch the bus	

POSTER PRESENTATIONS

Posters will be mounted on Thursday morning between 1000–1200. Posters are located in the exhibit area, and can viewed during all breaks. The Poster Walk will take place on Friday afternoon at 1730–1830, and presenters will be attending their posters at that time.

THURSDAY MORNING AND LUNCH | 1000–1300

1000–1200 | CIMDRN BUSINESS MEETING

Canadian Inherited Metabolic Diseases Research Network (CIMDRN) Meeting (Invitation Only)

Time 1000–1200
Room Annapolis

1200–1300 | LUNCH

Home Infusion Therapy for Patients living with Mucopolysaccharidosis Type I (MPSI) in Canada

Time 1200–1300
Room Halifax Ballroom

Speakers **Jenn and Anisa Elder**, Anisa Elder is an MPS I patient, together with her mother
Aneal Khan, University of Calgary

Objectives At the end of this session the participant will be able to:

- Identify challenges to receiving enzyme infusion therapy in Canada.
- Compare advantages versus disadvantages of home versus institutional enzyme replacement therapy.
- Determine whether there is an advantage to using home infusion as standard of care.

Sponsored by: SANOFI GENZYME

THURSDAY AFTERNOON | 1300–1800

1300–1400 | PLENARY SESSION

A New Paradigm for Metabolic Medicine

Time 1300–1400
Room Nova Scotia CD

Speaker **Mark Korson**, Genetic Metabolic Center for Education

Objectives At the end of this session, participants will be able to:

- Identify the challenges posed by a small workforce in metabolic medicine.
- Explore alternative options for clinical care.
- Discuss the potential impact of education on the advancement of metabolic medicine.
- Explain a developing world tier of metabolic medicine might look like.

1400–1600 | THREE CONCURRENT SESSIONS

Advisory Board Meeting (Invitation Only)

Time 1400–1600
Room Atlantic Suite

Sponsored by: Mēdunik Canada

Dietitians' Webinar

Time 1400–1600
Room Annapolis

1400–1510 **Dietary Practices of Inherited Metabolic Disorders in the UK**
Anita MacDonald, Consultant Dietitian in Inherited Metabolic Disorders, Birmingham Childrens Hospital, Birmingham, UK

Objectives At the end of this session, participants will be able to:

- Describe the UK dietary management of amino acid disorders.
- Discuss the UK approach to the type and dose of protein substitute used.
- Describe the UK approach to monitoring and follow up of IMD patients with dietary disorders.
- Discuss UK approaches to infant feeding of infants with amino acid disorders.

1510–1540 **Recent Clinical Data and Experience with GMP in PKU Treatment**
Debra Hook, Metabolic Dietitian, Children's Hospital Los Angeles, University of Southern California

1540–1600 **Experiencing the PKU Diet, an RD's Perspective**
Geneviève Lafrance, Metabolic Dietitian, Fleurimont Hospital, l'Université de Sherbrooke

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Highlights and Updates on Fabry Disease: Adult and Pediatric Outcomes

Time 1400–1600
Room Nova Scotia CD

Moderator **Michael L. West**, Dalhousie University

Objectives At the end of this session, participants will be able to:
- Describe the management of children and adults with Fabry disease.
- Describe the impact of antidrug antibodies on ERT in Fabry disease.
- Discuss outcomes of ERT in adults with Fabry disease.
- Describe separation of polymorphisms from pathogenic mutations in Fabry disease.
- Discuss indications for ERT and when to stop ERT.

1400–1405 **Introduction**
Michael West, Dalhousie University

1405–1425 **Fabry Disease in Children. Expectant Follow Up or ERT?**
Sarah Dyack, Dalhousie University

Objectives At the end of this session, participants will be able to:
- Describe the initiation of ERT for Pediatrics Fabry patients.
- Describe new evidence related to the controversy regarding early treatment.
- Describe CFDI Paediatric data in the context.

1425–1455 **Management and Outcomes in Adults with Fabry Disease – Lessons from the CFDI Study**
Michael West, Dalhousie University

Objectives At the end of this session, participants will be able to:
- Describe the role and limitations of ERT in Fabry disease.
- Describe the importance of non-specific therapies in the management of Fabry disease.
- Describe the newer treatments being developed for Fabry disease.

1455–1525 **Fabry Disease: Who to Treat and When to Stop. The VUS Project and the Canadian Fabry Treatment Guidelines**
Sandra Sirrs, Vancouver General Hospital

Objectives At the end of this session, participants will be able to:
- Summarize the process for ongoing evaluation of the Canadian Fabry Treatment guidelines.
- Discuss recent changes to Canadian Fabry treatment guidelines and the rationale for those changes.
- Explain risks for patients of over-interpretation of variants identified on gene panel testing.
- List 3 strategies to help further clarify diagnosis in patients with variants of unknown significance identified in the Fabry gene.

1525–1540 **When Enzyme Replacement Therapy Fails – Case Presentation**
Jill Patterson, University of Manitoba / Children's Hospital Research Institute of Manitoba

Objectives At the end of this session, participants will be able to:
- Explain the impact and challenges of antidrug antibodies on ERT in Fabry disease.
- Describe other approaches to Fabry patient treatment when ERT fails.
- Discuss the need for more research into other therapeutic options for those who develop inhibitory antibodies.

1540–1600 **Discussion**

THURSDAY AFTERNOON | 1300–1800 continued

1600–1700 | PLENARY SESSION

Treatment Considerations for Neurodegenerative IEMs: Leukodystrophies and Epilepsies

Time 1600–1700
Room Nova Scotia CD

1600–1630 **Tony Rupar**, Western University

Objectives At the end of this session, participants will be able to:

- Describe the limitations of current disease specific therapies.
- Describe the principles of new therapies.
- Identify clinical trials of new therapies.

1630–1700 **Asuri N. Prasad**, Child Health Research Institute

Objectives At the end of this session, participants will be able to:

- List different IEM's associated with epilepsy as a major manifestation.
- Summarize different seizure types and epilepsy syndromes associated with IEM's.
- Discuss different treatment interventions for epilepsy associated with IEM's.
- Summarize priorities in the management of epileptics associated with IEM.

1700–1800 | PLENARY SESSION

Fatty Acid Oxidation PKU

Time 1700–1800
Room Nova Scotia CD

Speaker **Jerry Vockley**, University of Pittsburgh/Children's Hospital of Pittsburgh

Objectives At the end of this session, participants will be able to:

- Explain the role of enzyme replacement therapy in inborn errors of metabolism.
- Explain the role of alternative metabolite therapy in inborn errors of metabolism.
- Explain the role of transcriptional activators in inborn errors of metabolism.

1800–1930 | GARROD EXECUTIVE BOARD BUSINESS MEETING

Garrod Association Executive Board

Time 1800–1930
Room Maritime Suite

WELCOME RECEPTION | 1830–2100

All attendees are welcome to attend.
Halifax Ballroom in the Marriott Harbourfront Hotel

FRIDAY BREAKFAST, MORNING, LUNCH | 0730–1330

0730–0830 | BREAKFAST SESSION

A Difficult to Identify Metabolic Disease: Late Onset Lysosomal Acid Lipase Deficiency

Time 0730–0830
Room Halifax Ballroom

Speaker **Gordon A. Francis**, University of British Columbia

Objectives To increase awareness of the clinical features and when to consider screening for LALD, the variable natural history of the disease.

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0830–1000 | PLENARY SESSION

Welcome & Introductions

Time 0830–0835
Room Nova Scotia CD

L. Jane Gillis, BC Children's Hospital

Morning Session 1: The National Working Group Experience

Time 0835–1000
Room Nova Scotia CD

Moderators **Pranesh Chakraborty**, University of Ottawa
Beth Potter, University of Ottawa

Objectives At the end of this session the participant will be able to:

- Describe the strengths and limitations of observational research methods to inform care for inherited metabolic diseases (IMD).
- Discuss the types of analyses that are or will be possible using the Canadian Inherited Metabolic Diseases Research Network (CIMDRN) data to inform care for patients in Canada.
- Identify approaches to improving patient care for IMD using patient reported outcomes.
- Describe the health system impacts of newborn screening for IMD.
- Describe an approach to using multiple data sources to better understand the management of IMD and impact on outcomes.

0835–0840 **Introduction**
Pranesh Chakraborty, University of Ottawa

0840–0850 **Synthesizing Evidence About Treatments for Rare Diseases**
Kylie Tingley, University of Ottawa

0850–0915 **A Canadian IMD Cohort: Clinical Description and Research Potential**
Pranesh Chakraborty, University of Ottawa
Kylie Tingley, University of Ottawa

0915–0930 **The Health System Impact of Newborn Screening for IMD**
Sara Khangura, University of Ottawa

0930–0950 **Patient and Family Experiences with Health Care for IMD**
Beth Potter, University of Ottawa

0950–1000 **A Comprehensive Perspective on the Canadian Experience of Modern PKU Management**
Nataliya Yuskiv, University of British Columbia

1000–1030 | REFRESHMENT BREAK AND EXHIBIT VIEWING – NOVA SCOTIA AB

1030–1230 | PLENARY SESSION

Morning Session 2: Development of Treatments, Evidence and Policy

Time 1030–1230
Room Nova Scotia CD

Moderators **Sandra Sirrs**, University of British Columbia
Sylvia Stockler, BC Children's Hospital

1030–1100 **Introduction/Overview: A 360 Degree Review on Rare Disease Drug Development**
Sylvia Stockler, BC Children's Hospital

Objectives At the end of this session the participant will be able to:
- Describe therapies for inborn errors of metabolism developed during the past centuries.
- Discuss upcoming therapies such as gene repair therapies, bioengineered enzyme replacement therapies, chaperones and the microbiome as a therapeutic vehicle.
- Describe challenges in creating evidence and demonstrating cost effectiveness of orphan drugs.
- Describe the role of patients and families in orphan drug development.

1100–1130 **Development of Treatments, Evidence and Policy**
Martin Offringa, Hospital for Sick Children

Objectives At the end of this session the participant will be able to:
- Explain what types of evidence are needed for what types of decisions.
- Compare international approaches to generation of evidence in rare diseases.
- Apply a roadmap for "evidence to decisions".

1130–1200 **Platform Presentations of selected abstracts**

1130–1145 **Outcome with Enzyme replacement therapy for lysosomal storage disorders: Triumphs and challenges in India**
Mamta N. Muranjan, MD, King Edward Memorial Hospital, Parel, Mumbai 400012, India.

1145–1200 **Lysine degradation studies and drug screens: a therapeutic approach for Pyridoxine Dependent Epilepsy**
Izabella Pena, CHEO Research Institute.

1200–1230 **Assessment of Health Technologies and Value Based Decision Making**
Devidas Menon, University of Alberta

Objectives At the end of this session the participant will be able to:
- Explain what "health technology assessment" means.
- Compare the challenges of assessing treatments for rare diseases with those associated with common diseases.
- Discuss the roles of values in resource allocation decision-making.

1230–1330 | LUNCH

New Evidence and Treatment in the Management of PKU

Time 1230–1330
Room Halifax Ballroom

Introduction and Overview
Jane Gillis, BC Children's Hospital

ACMG and European PKU Guidelines including Canadian Perspective
John Mitchell, Montreal Children's Hospital

Objective
- To provide update on ACMG guidelines, new European PKU guidelines and share current practice approach to PKU management/treatment at Montreal Children's.

New treatments including clinical trial update on Pegvaliase
Jerry Vockley, University of Pittsburgh/Children's Hospital of Pittsburgh

Objective
- To provide treatment update for managing PKU (diet, Kuvan, Kuvan Powder (in US), GMP, LNAAs), clinical trial update on Pegvaliase and any other updates.

Conclusion and Questions
Moderated by **John Mitchell**, Montreal Children's Hospital

Sponsored by: BIOMARIN

FRIDAY AFTERNOON | 1330–1830

1330–1445 | PLENARY SESSION

Afternoon Session 1: Mitochondrial Disorders and Innovative Therapies 1

Time 1330–1445
Room Nova Scotia CD

Moderators **Pranesh Chakaborty**, University of Ottawa
Annette Feiganbaum, Hospital for Sick Children

1330–1345 **MitoCanada**
Christopher Newell, University of Calgary

Objectives At the end of this session the participant will be able to:

- Describe MitoCanada – who they are, what they do.
- Describe the role patients' organizations play in not only funding research but as partners and developers of research and their potential involvement in the regulatory process.
- Discuss upcoming opportunities for clinicians, scientists and trainees to collaborate on a national agenda for mitochondrial disease.

1345–1400 **Platform Presentation of selected abstracts**

1345–1400 **Plasma cell-free mitochondrial DNA: A novel and non-invasive method to detect mutations in mitochondrial DNA**
Christopher Newell, University of Calgary

1400–1445 **Treatment of Mitochondrial Disorders**
Mark Tarnopolsky, McMaster University

Objectives At the end of this session the participant will be able to:

- Describe the cellular consequences of mitochondrial dysfunction.
- Describe the efficacy behind the "mitochondrial cocktail".
- Describe the effects of exercise upon mitochondrial function.
- Discuss the potential for exosomes as therapeutic enablers for treatment of mitochondrial disease.

1445–1500 | REFRESHMENT BREAK AND EXHIBIT VIEWING – NOVA SCOTIA AB

FRIDAY AFTERNOON | 1330–1830 continued

1500–1730 | PLENARY SESSION

Afternoon Session 2: Innovative Therapies 2

Time 1500–1730
Room Nova Scotia CD

Moderator **Annette Feiganbaum**, Hospital for Sick Children

1500–1545 **Cell Based Therapies for Metabolic Disorders**
Stephen Strom, Karolinska Institutet

Objectives At the end of this session the participant will be able to:
- Discuss how cell therapies exist for liver diseases.
- Describe how cell therapies could be either mature liver cells or stem-like cells.
- Discuss the potential problems and benefits of cellular therapies.

1545–1630 **Treatment of the Hepatic Glycogen Storage Diseases**
David Weinstein, University of Florida

Objectives At the end of this session the participant will be able to:
- Discuss treatment strategies for the glycogen storage diseases.
- Compare the differences between treatment of GSD I and the ketotic forms of GSD.
- Summarize the complications which can occur in the hepatic glycogen storage diseases.
- Discuss why high protein is critical in GSD type III.
- Explain why all types of GSD are now restricting carbohydrate.
- Discuss why fructose, sucrose, and galatose require restriction in GSD I.

1630–1730 **Updates and Evidence: Management and Treatment of Urea Cycle Disorders**
Andreas Schulze, Hospital for Sick Children

Objectives At the end of this session the participant will be able to:
- Explain the goals of management of patients with urea cycle defects.
- List specific treatments in urea cycle defects.
- Discuss limitations of current treatments.
- Summarize new trends in management and treatment of urea cycle defects.
- Discuss outcomes of Rare Disease Networks on the example of the Urea Cycle Disorder Consortium.

COCKTAILS AND POSTER WALK | 1730–1830

Nova Scotia AB

(all presenters to attend their posters)

FRIDAY EVENING | 1840–2200

Garrod Symposium Gala Dinner and Award Presentation
1900–2200
Pier 21 Museum
Tickets: $90.00 per person
Meet in the Marriott Harbourfront hotel lobby at 1840 to catch the bus.

Make sure you purchase a ticket for our gala evening on Friday – a lobster feast at Pier 21, Canada's Immigration Museum. Pier 21 is a National Historic Site which was the gateway to Canada for one million immigrants between 1928 and 1971. It also served as the departure point for 500,000 Canadian Military personnel during the Second World War. Today, Pier 21 hosts the Canadian Museum of Immigration at Pier 21 – Atlantic Canada's only national museum! Guests will have the opportunity to enjoy a cocktail reception in the Pier 21 Rudolph P Bratty Hall exhibition. Following the reception, the dinner and presentation will be held in the Kenneth C. Rowe Hall overlooking the Halifax harbour.

GARROD 2016 AWARD PRESENTATION

The Garrod 2016 Pioneer Award will be presented to
Professor Brian H. Robinson, Canada Chair in Nutrition and Metabolism, Hospital for Sick Children

SATURDAY BREAKFAST, MORNING, LUNCH | 0800–1400

0800–0900 | BREAKFAST SESSION

Patient Directed Outcomes

Time 0800–0900
Room Halifax Ballroom

0900–1100 | PLENARY SESSION

Morning Session 1: High Throughput Technologies for Personalized Management of Inborn Errors of Metabolism

Time 0900–1100
Room Nova Scotia CD

Moderators **Christiane Auray-Blais**, Université de Sherbrooke
John Mitchell, Montreal Children's Hospital

0900–0930 **Genomics to Diagnose Neurometabolic Disease: Bigger Always Better?**
Clara van Karnebeek, BC Children's Hospital/University of British Columbia

Objectives At the end of this session the participant will be able to:

- Summarize the CCMG 2015 position on clinical indications for exome sequencing.
- Discuss the framework for interpretation of variants accordng to the ACMG criteria for variant pathogenicity.
- Discuss the advanges of the metabolic phenotype for variant prioritization and subsequent validation of causality.
- Discuss the results of the TIDEX neurometabolic gene discovery study.
- Discuss the use genomics as 1st line test in the biochemical genetics clinic.

0930–1000 **Expanding Screening and Diagnostic Capacity for Amino Acidurias Through Tandem Mass Spectrometry**
Graham Sinclair, BC Children's Hospital/University of British Columbia

Objectives At the end of this session the participant will be able to:

- Summarize the capacity constraints of traditional amino acid analysis.
- Discuss the benefits and drawbacks of transitioning amino acid analysis to tandem mass spectrometry.
- Discuss the role for bloodspot amino acid analysis in routine and acute metabolic monitoring.

1000–1030 **New Twists on Old Biomarkers**
Paula Waters, Centre hospitalier universitaire de Sherbrooke (CHUS)

Objectives At the end of this session the participant will be able to:

- List three examples in which infants with elevation of a 'classic disease biomarker' were subsequently found to have a distinctly different biochemical condition.
- Contrast 'Combined malonic and methylmalonic aciduria' with other forms of methylmalonic aciduria.
- Identify a potential cause of hypersuccinylacetonemia other than tyrosinemia type 1.
- Discuss one more potential cause in the differential diagnosis of orotic aciduria.

1030–1100 **Mass Spectrometry Biomarker Analysis for the Identification, Monitoring and Follow-up of Patients**
Christiane Auray-Blais, Université de Sherbrooke

Objectives At the end of this session the participant will be able to:

- Distinguish different mass spectrometry methods for biomarker analysis.
- Interpret mass spectrometry results for detection of patients.
- Assess the importance of robust technologies for monitoring treated patients.

1100–1115 | REFRESHMENT BREAK AND EXHIBIT VIEWING – NOVA SCOTIA AB

SATURDAY MORNING & LUNCH | 0800–1345 (continued)

1115–1300 | PLENARY SESSION

Morning Session 2: Enhancement of Established Therapies

Time 1115–1300
Room Nova Scotia CD

Moderator **Maggie Chapman**, Maritime Medical Genetics Service

1115–1145 **European Dietary Guidelines of Propionic Acidaemia (PA) and Methylmalonic Aciduria (MMA)**
Anita MacDonald, Birmingham Childrens Hospital

Objectives At the end of this session the participant will be able to:
- Describe the different approaches to the nutritional support of PA and MMA across Europe.
- Describe the European energy and protein requirement guidelines for MMA/PA.
- Describe the European approach to nutritional support/enteral feeding in MMA/PA.
- Describe the application of dietary emergency regimens across Europe.

1145–1215 **Dietary Management of Tyrosinemia**
Manon Bouchard, CHU Sainte-Justine

Objectives At the end of this session the participant will be able to:
- List the main elements of nutritional treatment of tyrosinemia type 1.
- Recognize how the nutritional management must be adjusted with age.
- Identify the nutritional challenges that arise in maintaining optimal nutritional status in all age groups.

1215–1245 **Platform Presentation of selected abstracts**

1215–1230 **Comparison of high resolution respirometry and UV-Vis spectrometry for clinical mitochondrial testing – a pilot study**
Lauren MacNeil, McMaster University.

1230–1245 **Uncovering novel candidate genes in consanguineous families with pyridoxine-responsive epileptic encephalopathy**
Hilal Al Shekaili, University of British Columbia.

1245–1300 **Closing of the Garrod Symposium**
L. Jane Gillis, BC Children's Hospital

1300–1400 | LUNCH

Principles in Biomarker Discover and Translational Research in Lysosomal Storage Diseases

Time 1300–1400
Room Halifax Ballroom

Sponsored by: Shire

1400–1600 | GARROD ASSOCIATION MEMBERSHIP MEETING

Garrod Association Membership Meeting (Members Only)

Time 1400–1600
Room Halifax Ballroom

CLOSING SOCIAL | 1715–1815

Unwind with us at a casual reception.

Meet in the Marriott Harbourfront lobby at 1700 to catch the bus

ABSTRACTS

PLATFORM PRESENTATIONS

Friday May 20, 1130–1145

Outcome with Enzyme replacement therapy for lysosomal storage disorders: Triumphs and challenges in India

Mamta N. Muranjan, MD[a], Sunil C. Karande, MD[a].
[a]Genetic Clinic, Department of Pediatrics, King Edward Memorial Hospital, Parel, Mumbai 400012, India.

ERT for LSDs is not commercially available India nor is it reimbursed through insurance or government health programs. Very few patients have access to ERT through manufacturer's charitable access programs or employer reimbursement. The paper reports experience of ERT at a single center in Western India.

Objective: To study clinical characteristics of patients with LSDs and response to ERT.

Methods: Retrospective analysis for age at onset of symptoms, diagnosis and commencement of ERT. Response for Gaucher disease and Hunter syndrome was assessed in terms of published guidelines.

Results: Eleven children with Gaucher disease (four with type 3 disease) were treated with imiglucerase (average dose 23 – 53 units/kg/year) for an average duration of 55 months. Four with infantile onset Pompe disease [IOPD] and one with late onset disease were treated with alglucosidase α at an average age of 6.8 months and 25 years respectively. Idursulfase was initiated in a cognitively normal boy at 5½ years of age.

With Imiglucerase therapy, the short term outcomes in terms of hematological reconstitution was satisfactory but none of the 11 patients attained all therapeutic goals in the recommended time frame for visceral, skeletal and growth domains. Of the nine patients continuing therapy (two drop-outs due to socio-economic factors), one was enrolled in a clinical trial with Eliglustat. Four patients are adults, one employed as an accountant and two in the final year of graduation (medicine and commerce).

For Hunter syndrome, earliest response (reduction in urine GAG and liver and spleen volume) was evident by the 2nd month. Improvement in range of motion was remarkable at the shoulder joint. Late diagnosis contributed to poor outcome in IOPD with a sole survivor on ERT for 3 months.

Conclusions: Outcome for LSDs in India is determined by age at diagnosis, limited dosing and socio-economic factors.

Keywords: Enzyme replacement therapy, Gaucher disease, Hunter syndrome, Pompe disease

Friday May 20, 1145–1200

Lysine degradation studies and drug screens: a therapeutic approach for Pyridoxine Dependent Epilepsy

Izabella Pena[a], Alan Mears[a], Clara van Karnebeek[b], Sidney M. Gospe Jr.[c], Levinus A Bok[d], Paulo Arruda[e], Osama Al-Dirbashi[f], Pranesh Chakraborty[g], Kym Boycott[a], Alex Mackenzie[a].
[a]CHEO Research Institute.
[b]BC Children's Hospital.
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Pyridoxine-dependent epilepsy (PDE) is a rare autosomal recessive disorder characterized by recurrent seizures that, although resistant to conventional anticonvulsants, are alleviated by high doses of pyridoxine (vitamin B6). Mutations in the ALDH7A1 gene, which encodes the lysine-metabolizing enzyme antiquitin, cause PDE. The initial reaction of the lysine degradation pathway, catalysed by Aminoadipate-Semialdehyde Synthase (AASS), is the conversion of lysine to aminoadipate semialdehyde (AASA). AASA spontaneously cyclizes to form piperideine-6 carboxylate (P6C); both compounds are substrates for antiquitin. P6C is believed to be the primary pathogenic driver of PDE as it reacts with pyridoxal 5'-phosphate (PLP), leading to PLP depletion. Despite amelioration of seizures with pyridoxine treatment, most patients nonetheless suffer from neurodevelopmental problems. We report here for the first time increased lysine sensitivity in primary skin fibroblasts from PDE patients and the use of this novel phenotype for preclinical analysis of novel PDE therapeutic approaches. In the first case, mutations in AASS (the enzyme upstream of ALDH7A1 in the lysine catabolism pathway) results in hyperlysinemia, which is now considered a benign inborn error of metabolism. We therefore hypothesized that AASS represents a therapeutic target for PDE and have shown knock-down (KD) of AASS prevented the high P6C levels we have observed in PDE fibroblasts and also reduces their lysine sensitivity. We next used PDE cells lysine sensitivity to conduct a targeted FDA-approved drug screening which identified that fenofibrate rescues PDE cells from lysine death. The rescue is dose-dependent; moreover other fibrates confer a similar beneficial effect showing a drug class effect. Preliminary analyses suggest that fenofibrate reduces lysine degradation and thus P6C accumulation in the PDE fibroblast model. In vivo studies in wild type mice also suggest that fenofibrate reduces overall lysine degradation. We established a reliable quantification method of P6C in patient urine to be used in the future for a biomarker reduction trial using fenofibrate. An aldh7a1-/- model in zebrafish is being generated to both test the relation between P6C levels and seizure events and to assess the therapeutic value of fenofibrate and/or KD AASS therapies.

Friday May 20, 1345–1400

Plasma cell-free mitochondrial DNA: A novel and non-invasive method to detect mutations in mitochondrial DNA

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Objectives: Mitochondrial disease comprises a heterogeneous group of diseases affecting 1 in 5000 people and can be caused by gene mutations in either nuclear or mitochondrial DNA (mtDNA). Less-invasive methods to obtain mtDNA have involved collection from peripheral blood leucocytes, urine sediment and buccal swab. However, these methods are specific to the cell type collected and lack sensitivity. Research suggests that cellular apoptosis and cellular turnover release small 150-200 base pair fragments of DNA from all cell types, which can be extracted from plasma as cell-free DNA (cfDNA). Entire mtDNA has not been successfully extracted from the cell free fraction previously. As we suspect that the circular nature of mtDNA is protective, our objective was therefore to develop a methodology to extract entire cf-mtDNA from plasma.

Design & Methods: Blood samples from patients with known mitochondrial disease (n=3) and healthy controls (n=2) were collected and their cfDNA isolated. To demonstrate the presence of the mitochondrial genome within these samples, we amplified the isolated DNA using custom PCR primers specific to overlapping fragments of mtDNA. cfDNA samples were each sequenced using the Illumina MiSeq next-generation sequencing platform.

Results: We confirmed the presence of mtDNA, demonstrating that the full mitochondrial genome is in fact present within cell-free DNA isolated samples. Furthermore, sequencing yielded a positive match for mitochondrial haplogroup variability in each patient and control.

Conclusions: We report the first successful method showing positive identification of cf-mtDNA by haplotype analysis from plasma. This technique can have clinical application to identify donor mtDNA in plasma and to identify targets of mtDNA therapies.
Funding: This project was funded by MitoCanada and the Alberta Children's Hospital Research Institute. Christopher Newell was also funded by a MitoCanada PhD Scholarship.

Saturday May 21, 1215–1230

Comparison of high resolution respirometry and UV-Vis spectrometry for clinical mitochondrial testing – a pilot study

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Mitochondrial disease is predominantly an inherited condition resulting from mutations to either nuclear or mitochondrial DNA. Enzymology by UV-Vis spectrometry (UVS) measures the functional capacity of individual and paired electron transport chain complexes, often assisting in an accurate diagnosis. In vivo high resolution respirometry (HRR) is considered the gold standard of mitochondrial function testing, however degradation induced variability have prevented its use as a clinical diagnostic tool.
Objective: To compare UVS and HRR results from patients with possible mitochondrial disease.
Design & Methods: Skeletal muscle biopsies were collected from 30 patients (♀:15, ♂:15, ages: 4-73) with possible mitochondrial disease and assayed by UVS and HRR. Thresholds for abnormal activity were set at >30% or < 2 00% of reference values. Histological and/or genetic testing was completed on samples when clinically relevant.
Results: HRR and UVS results were in agreement for 10 patients determined free of mitochondrial disease. Results from 12 patients were normal by UVS but abnormal by HRR (low Complex I or II activity); 75% of whom were histologically identified with fibre atrophy or inflammation. The remaining patients (8) were abnormal by UVS and normal by HRR; 88% of whom were identified with either atrophic/necrotic fibres or genetic mutations.
Conclusion: Accurate diagnosis of mitochondrial disease is challenging and best accomplished using results from several testing methods. Although variability induced by organelle degradation remains a current limitation for its diagnostic utility, our data suggest that HRR may provide useful clinical information when performed immediately post-biopsy.
Keywords: skeletal muscle, mitochondrial respiration, spectroscopy
Funding: This research was funded in part by MitoCanada.

Saturday May 21, 1230–1245

Uncovering novel candidate genes in consanguineous families with pyridoxine-responsive epileptic encephalopathy

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Background: Pyridoxine-responsive epileptic encephalopathies (PREE) represent a clinically and genetically heterogeneous group of rare, autosomal recessive disorders[1,2]. They are characterized by recurrent seizures in the prenatal, neonatal, or postnatal period, which are typically resistant to conventional anticonvulsant treatment but show remarkable response to the administration of pyridoxine (vitamin B6)[1,3,4,5]. One such example of these disorders is pyridoxine-dependent epilepsy (PDE), a neonatal seizure disorder with reported incidence rates that range from 1:750,000 to as high as 1:20,000[6]. In most affected infants, PDE is caused by mutations in the antiquitin gene (*ALDH7A1*)[7] and subsequent inactivation of α-aminoadipic semialdehyde dehydrogenase (antiquitin, ATQ), an enzyme that functions within the cerebral lysine catabolism pathway, leading to accumulation of α-aminoadipic semialdehyde (α-AASA)[8]. Although *ALDH7A1* is the only gene for which mutations are known to cause PDE, locus heterogeneity has been demonstrated, other genes appear to be responsible in some families[9]. About 5% of infants with clinically typical PDE have no detectable mutation of *ALDH7A1*[10].
Objectives: This study was carried out to characterize the genetic defect underlying PREE in five consanguineous Omani Arab families with total of six affected children who have PDE-like clinical picture but negative ATQ biomarkers and/or negative ATQ sequencing.
Materials & Methods: Whole-genome SNP genotyping was performed using Illumina HumanOmni5-Quad/MEGA array chip. Based on the obtained high density SNP dataset, genome-wide runs of homozygosity (RoH) mapping was carried out using SNP & Variation Suite (SVS) software (Golden Helix). Whole-exome sequencing (WES) was carried out on the affected children and parents by Perkin-Elmer (Waltham, Massachusetts).
Results: After analysis of WES and RoH results, the following genes were flagged as candidates in family 1. The first candidate gene belongs to the solute carrier (SLC) family of genes. Three members of the SLC super family have been already described as vitamin transporters. To date, no transporter for vitamin B6 has been identified in humans despite multiple experimental evidence indicating the existence of an efficient and specific carrier-mediated mechanism of vitamin B6 uptake by human cells[11,12,13]. The second gene encodes a peptidase enzyme which is highly expressed in distinct regions within the brain. This enzyme was described to cleave a neuropeptide that is hypothesized to function as a neurotransmitter[14]. WES results in other families are under processing.
Acknowledgement: This study is sponsored by the OMICS2TREATID project and by a research grant from the Rare Disease Foundation, BC Children's Hospital Foundation.
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POSTER PRESENTATIONS
Friday, May 20, 1730–1830

P101 UPLC-MS/MS analysis of keratan sulfate related disaccharides as biomarkers for Morquio A Syndrome patients

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Objectives: Mucopolysaccharidosis (MPS) type IVA (Morquio A syndrome), is an autosomal recessive lysosomal storage disorder due to a defect of the enzyme N-acetylgalactosamine-6-sulfatase, which is involved in the degradation of keratan sulfate (KS), a glycosaminoglycan (GAG). The objectives of this research project were to: 1) develop and validate an efficient and robust ultra-performance liquid chromatography/tandem mass spectrometry (UPLC-MS/MS) KS method; 2) evaluate the sensitivity and specificity of this method in a cohort of untreated MPS patients; 3) determine normal reference values for KS disaccharides; 4) compare the UPLC-MS/MS method to the DMB-based spectrophotometry methodology for total GAG measurements.
Design & Methods: Keratanase II was added to urine samples for a 3 hour-digestion at 40 °C. The detection of two main disaccharides (Galb1-4GlcNAc(6S), and Gal(6S)b1-4GlcNAc(6S)) was achieved using a Xevo TQ-S mass spectrometry system (Waters Corp.) following a HILIC chromatography using an Acquity I-Class UPLC equipped with a BEH amide column.
Results: All Morquio A syndrome patients had abnormal values of KS disaccharides normalized to creatinine, while the DMB-based spectrophotometry methodology showed normal results for 4 out of 9 Morquio A patients. However, KS was also found to be slightly elevated in patients with other MPS types (I, II, and VI), where KS is not expected to be elevated considering the enzyme deficiencies involved.
Conclusion: The quantitation of urinary KS disaccharides by mass spectrometry in patients with Morquio A syndrome is a useful tool for high-risk screening studies, and for the diagnosis and monitoring of patients under enzyme replacement therapy.
Keywords: MPS IVA, Morquio A syndrome, keratan sulfate, mass spectrometry, biomarkers
Funding Acknowledgement: BioMarin Pharmaceuticals Inc.

P102 Culturally sensitive provision of rapid biochemical and molecular diagnosis at birth in children at risk for metabolic disorders

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Background: Prenatal diagnosis allows for identification of subsequent affected offspring in families who have already had a child with a severe metabolic disorder. Sometimes this is not an option, due to religious or other reasons. Children with severe metabolic disorders often present within 48 hours after birth, before newborn screening (NBS) results are available, and typically experience complicated and lengthy hospitalizations. Our centre has established rapid biochemical and DNA based testing for families who have chosen not to have prenatal diagnosis.
Methods & Results: We have identified 11 sib-pairs affected with maple syrup urine disease (Mennonite) (p.Y438N homozygous), galactosemia (Amish) (p.Q188R homozygous) Gastric intrinsic factor (GIF) deficiency (Mennonite) (c.79+IG>A and C.973delG deletion compound heterozygous) and Transcobalamin (TC) deficiency (Albanian) (R399X homozygous). In each case, cord and /or peripheral blood specimens were collected at delivery of subsequent sibs. Out of a total of 11 sibs, 5 were affected. Screen-positive Ontario newborn screening results were received between day 6 and day 8 of life.
Discussion and Conclusions: Probands with each of the 4 autosomal recessive metabolic disorders required prolonged hospitalization for hemodialysis or sepsis at <1week or developed bone marrow failure by 2 months. Subsequent affected sibs were diagnosed and managed appropriately prior to availability of NBS results, thus completely avoiding hospitalization and complications. Access to rapid biochemical and molecular technology allows for culturally sensitive delivery of diagnosis and care based on positive family history. This has made a demonstrable difference in the prognosis and outcome of patients with severe metabolic conditions.
Keywords: DNA based diagnosis, Newborn screening, maple syrup urine disease, galactosemia, transcobalamin deficiency and gastric intrinsic factor deficiency

P103 Case report of two siblings with fumarase deficiency: diagnostic odyssey solved and counselling dilemma begins

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Objectives: To appreciate the diagnostic odyssey of fumarase deficiency as well as the unique challenges associated with providing genetic counselling and clinical management for family members identified to carry a heterozygous *FH* mutation.
Design & Methods: Two siblings, age 10 years and 3 years, with developmental delay, hypotonia, strabismus, thinning of the corpus callosum and failure to thrive were thoroughly investigated for possible genetic and metabolic etiologies. Following extensive testing, whole exome sequencing was ordered.
Results: Both children were identified to be compound heterozygous in *FH* for a maternally inherited c.1431_1433dupAAA pathogenic variant and a novel, paternally inherited c.1390+1G>T variant (interpreted to be disease-causing). Previous investigations included urine organic acid analyses on two occasions for both sibs that did not demonstrate an elevation of fumaric acid. Neither parent demonstrates features of hereditary leiomyomatosis and renal cell cancer (HLRCC), an autosomal dominant tumour predisposition syndrome caused by heterozygous *FH* mutations. Further genetic testing of family members demonstrates low penetrance for an HLRCC phenotype in *FH* heterozygotes.
Conclusions: Fumarase deficiency cannot always be diagnosed by concentration of urine fumaric acid and a high index of suspicion should be maintained in the context of normal biochemical results. There appears to be low penetrance of the HLRCC phenotype in family members carrying a heterozygous *FH* mutation which allows for great uncertainty in the provision of surveillance recommendations and quoting lifetime renal cancer risk. Further studies are required to delineate HLRCC risk for family members of individuals diagnosed with fumarase deficiency.
Keywords: Fumarase deficiency, hereditary leiomyomatosis and renal cell cancer, fumarate hydratase, genetic counselling

P104 Canadian Fabry Disease Initiative Study (CFDI): 8 year outcomes of a randomized controlled trial of enzyme replacement therapy (ERT)

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Objective: To determine the long-term clinical outcomes in Fabry disease during ERT.
Methods: The CFDI is a prospective multicenter study of ERT in Fabry disease in Canada started in 2007. Patients who met national Fabry

disease treatment guidelines received ERT. Cohort b were enzyme naïve patients randomized 1:1 to agalsidase beta 1.0 mg/kg or agalsidase alfa 0.2 mg/kg both EOW. Outcomes were defined as clinical events-renal, cardiac, neurologic and death. We report the clinical outcomes during ERT at year 8 of this trial.
Results: By year 8 there are 409 enrolled, 130 M (31.8%), 242 F (59.2%), and 37 children (9%), with 117 in cohort 1b. Between May 2010 and 2012 patients in cohort 1b randomized to agalsidase beta received alfa due to shortage of agalsidase beta. Cohort 1b mean age 43.0 years had 69 (60%) patients on alfa and 46 (40%) on beta over 66.3±26.3 months. Baseline clinical parameters and concomitant drug use did not differ except for Mainz Severity Score Index 23.2±8.7 on alfa vs. 27.6±10.1 on beta (p=0.02). Outcomes of renal and cardiac parameters and Kaplan Meier analysis of time free of first clinical event (p=0.66) on different ERT do not differ. There were more clinical events on alfa (45) than beta (15), reflecting prevalence of ERT use.
Conclusions: The CFDI study remains the longest-running and largest randomized prospective trial of ERT in Fabry disease. In adults with Fabry disease, there appears to be little or no difference in clinical outcomes after 8 years of standard dose ERT.
Keywords: Fabry disease, enzyme replacement therapy, agalsidase, outcomes
Funding: The provincial governments of Canada, Genzyme, a Sanofi company, Shire Inc.

P105 Canadian Fabry Disease Initiative Study (CFDI): A prospective study of patient outcomes during switch of enzyme replacement therapy (ERT)

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Objectives: To determine the effect of switch from agalsidase beta 1.0 mg/kg EOW to agalsidase alfa 0.2mg/kg EOW in patients with Fabry disease.
Methods: The CFDI is a prospective multicenter study of ERT in Fabry disease in Canada. Due to shortage worldwide of agalsidase beta, 37 Fabry patients switched ERT. We report the outcomes (clinical events-renal, cardiac, neurologic and death) of these patients during treatment with agalsidase beta and alfa. The first six months post switch were censored because of possible carry over effect from prior agalsidase beta treatment.
Results: 37 Fabry adults (25 M, 12 F) mean age 47.8±12.6 years, Mainz Severity Score Index 32.6±11.5, ESRD 32.4%, hypertension 56.8%, pacemaker 46% and stroke/TIA 27% were included. There was no significant difference in clinical parameters pre (32.6±11.5 months) to post switch (42.5±7.8 months). There were 19 clinical events (prevalence 27%) on beta vs. 29 (prevalence 47.2%) on alfa. With censoring of the first 6 months on alfa, there were 14 events (prevalence 39%). Event free survival did not differ between beta and alfa by Kaplan Meyer analysis. Clinical event rates did not differ at 17.5 per 1000 patient months on beta or alfa after 6 months and 19.0/1000 months including the first 6 months on alfa. Cardiac events were the most common in all periods.
Conclusions: The CFDI study is the only prospective study of Fabry patient outcomes during ERT switch. Switch from agalsidase beta to alfa was associated with a transient increase in clinical events for 6 months.
Keywords: Fabry disease, enzyme replacement therapy, agalsidase, outcomes
Funding: The provincial governments of Canada, Genzyme, a Sanofi company, Shire Inc.

P106 Outcomes of infants with positive newborn screens for VLCAD deficiency in Southern Alberta

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Objectives: Very long chain fatty acyl-CoA dehydrogenase (VLCAD) deficiency is a fatty acid oxidation disorder (FAOD) with a spectrum of severity ranging from a potentially fatal, neonatal cardiomyopathic form to mild late-onset variants with minimal or no symptoms. After a positive newborn screen it can be difficult to accurately predict the phenotype with the diagnostic testing available. The aim of this study was to determine the outcomes of infants with screen positive results for VLCAD deficiency.
Methods: In this retrospective cohort study, the medical files of all patients who screened positive for VLCAD deficiency since expanded newborn screening began in Southern Alberta on April 1, 2007 were reviewed. We determined the false positive and true positive rates of screening, newborn screen results, diagnostic testing (acylcarnitines, fatty acid oxidation studies, ACADVL genotype), dietary and illness management, follow up tests, and clinical features.
Results: Seventeen (17) patients screened positive for VLCAD deficiency. Of those, one was symptomatic with severe neonatal-onset disease. Another five patients likely had mild VLCAD deficiency, and only one of these patients has been symptomatic to date. The remaining 11 patients had indeterminate results, and of these five were likely false positive due to heterozygosity for one pathogenic ACADVL variant.
Conclusions: Newborn screening for VLCAD can be lifesaving. However, the majority who screen positive will be heterozygous ACADVL mutation carriers, have mild or asymptomatic VLCAD deficiency or have an indeterminate diagnosis which may lead to family anxiety and possibly to over-medicalization of some children.

P107 Breastfeeding and breastfeeding sustainability in newborns with inborn errors of metabolism identified through expanded newborn screening

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Background: Newborn screening (NBS) facilitates early diagnosis of potentially devastating inborn errors of metabolism (IEM). Treatment of some IEM involves dietary interventions (ex: special formula/medical food). Breastfeeding is deemed best for infants, although may not be permitted exclusively for infants with an IEM. Receiving an IEM diagnosis via NBS in the first weeks of life while breastfeeding is being established may disrupt breastfeeding continuation.
Objectives: To determine the number of infants exclusively breastfed at the time of receiving a true-positive NBS result and the number of infants that receive breast milk (exclusively or not exclusively) after IEM diagnosis. Additionally, to determine factors impacting breastfeeding duration in this population.
Methods: Patient charts of eligible true-positive NBS infants (N=142) were analyzed for age, feed type, wellness at NBS retrieval, diagnosis, and interventions. Two-sample T-tests and ANOVA were used for analysis.
Results: 55% of infants were exclusively breastfed and 90% received some breast milk at NBS retrieval (mean age 9.5±4.0 days). Mean breastfeeding duration amongst all IEM diagnoses was 121±135 days. Infants receiving medical food had significantly shorter breastfeeding duration (71.5±104 days) than infants not receiving medical food (143±146 days; P=0.01). Infants unwell at retrieval breastfed less (48.0±102 days) than infants well at retrieval (132±139 days; P=0.03). 9% of mothers saw a lactation consultant/public health nurse.
Conclusions: Breastfeeding rates in positive NBS infants at time of retrieval are comparative to the Canadian population but unwell infants and those put on medical food are most likely to have breastfeeding or breast milk provision stopped.

Keywords: newborn screening, breastfeeding, nutrition, medical food

P108 Pre-analytical factors influencing blood ammonia measurement: an experimental update

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Background: Blood ammonia (NH3) is the main marker for the diagnosis and follow-up of patients affected with Urea Cycle Disorders (UCD).
Objectives: The aim of this study was to review and quantify the impact of pre-analytical factors such as phlebotomy technique, air exposure, temperature and time delay during specimen transportation and handling on ammonia concentration.
Study Design & Methods: Capillary and venous samples were collected on standard lithium heparin gel tubes from normal subjects and patients hospitalized in the intensive care unit (ICU). The samples were kept at room temperature or stored at 4 °C up to 4h before and after centrifugation, with or without air exposure.
Results: As previously described, ammonia concentration increases in capillary samples (average of 10 micromol/L compared to venous samples) and correlates with hemolytic index. No statistical and clinically significant difference in ammonia values between specimens stored at room temperature and at 4 °C up to 1 hour after blood collection (n=20, p < 0 ,147) were observed. In contrast, a statistically significant increase in ammonia concentration was seen when specimens were kept at room temperature 2 hours after centrifugation (n=20, p < 0 ,001). The same findings were also noted in specimens emanating from ICU patients. Air exposure had no impact on ammonia results in our laboratory.
Conclusions: The impact of the metabolism of blood nitrogen on ammonia concentration is minimal when samples are kept at room temperature during transportation to the laboratory. Even if gel separator tubes are used, specimens must be analyzed rapidly after centrifugation unless they are stored at 4 °C.
Keywords: ammonia, pre-analytical
Acknowledgements: the authors thank Medunik Canada for supporting laboratory technologist teaching sessions on clinical use and pre-analytical factors of blood ammonia measurement.

P109 Clinical Validation of a Point-of-care (POC) Analyzer for Whole Blood Ammonia Measurement in Patients Affected with Urea Cycle Disorders (UCD)

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Background: Blood ammonia (NH3) is the main marker for the diagnosis and follow-up of patients affected with Urea Cycle Disorders (UCD). Repetitive venous sampling is often difficult in patients less than 1 year of age. Many pre-analytical factors can cause a spurious increase in ammonia levels when samples are sent to the central laboratory for analysis.
Objectives: The aim of this study was to clinically validate a bedside testing device for whole blood ammonia measurement (PocketChem [BM] TA BA-4140, Arkay Inc.) by assessing precision, linearity, repeatability, and accuracy.
Design & Methods: Coefficients of variation (CV) were determined by repeated measurements of two control solutions. Accuracy was investigated by performing recovery experiments with ammonium sulfate. Clinical samples and ammonium sulfate spiked samples were used to do comparison studies with the enzymatic reference method on plasma (Beckman AU) and validate the linearity and limit of detection of the device. Capillary blood analysis was done on UCD patients and normal subjects.
Results: Between day CV is comparable to within day CV (5% and 8 % for concentrations of 180 micromol/Land 80 micromol/L respectively). The analytical range is comprised between 10 and 280 micromol/L. The average recovery is 100 %. There is a good correlation and concordance with the reference method. The analysis of capillary samples from finger or heel prick is subject to significant inter-users variation.
Conclusions: The PocketChem BA has acceptable precision, accuracy and satisfactory agreement with a reference method. The POC analyzer may be suitable for clinical use by well-trained staffs.
Keywords: blood ammonia, POCT
Acknowledgements: The authors thank Medunik Canada for supporting the validation of the PocketChem [BM] TA BA in patients affected with Urea Cycle Disorders.

P110 Acute and chronic management in atypical ethylmalonic encephalopathy: a case report

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Ethylmalonic encephalopathy (EE) is caused by mutations in the ETHE1 gene. ETHE1 is vital for the catabolism of hydrogen sulfide (H_2S). Patients with pathogenic mutations in ETHE1 have markedly increased thiosulfate, which is a reliable index of $H_2$2S levels. Accumulation of H_2S is thought to cause the characteristic metabolic derangement found in EE. Recently introduced treatment strategies in EE, such as combined use of metronidazole (MNZ) and N-acetylcysteine (NAC), are aimed at lowering chronic H_2S load. Experience with treatment strategies directed against acute episodes of metabolic decompensation (e.g., hemodialysis) is limited. Here we present an unusually mild, molecularly confirmed, case of EE in a 17 year old male on chronic treatment with MNZ and NAC. During a severe episode of metabolic decompensation, we employed continuous renal replacement therapy (CRRT) to regain metabolic control. On continuous treatment with NAC and MNZ during the months preceding the acute event, plasma thiosulfate levels ranged from 1.6 to 4 microg/mL (reference range 2 microg/mL) and had a mean value of 2.5 microg/mL. During the acute decompensation, thiosulfate levels were 6.7 microg/mL together with hyperlactatemia, ethylmalonic aciduria, and increased C4- and C5-acylcarnitines. CRRT decreased thiosulfate within 24 hours to 1.4 microg/mL. Following discontinuation of CRRT, mean thiosulfate levels were 3.2 microg/mL (range: 2.4 – 3.7 microg/mL) accompanied by metabolic normalization on blood gas, acylcarnitine profile, and urine organic acids. In conclusion, CRRT may help to regain metabolic control in patients with EE who have an acute metabolic decompensation on chronic treatment with NAC and MNZ.
Keywords: Ethylmalonic encephalopathy, neurometabolic disorder

P111 Therapeutic challenges in an adolescent patient with Fabry disease and high antibody titres: A case study

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The use of enzyme replacement therapy (ERT) for Fabry disease has resulted in some patients in the development of high antibody titres. We present an adolescent male patient receiving ERT over a period of three years who presented with increasing titres of IgG antibodies against α-galactosidase A with reduced ERT efficacy. At the highest, the antibody titres have been measured at 1:102,400. Measurements of urine globotriaosylceramide (GB3) concurrently showed an upward trend from 1,165 to 2,260 (microgram/mmol creatinine). Despite receiving ERT, this patient continued to have significant malaise, gastrointestinal symptoms and neuropathic pain. As well, the patient experienced frequent infusion associated reactions despite premedication. ERT was subsequently discontinued one year ago.

Unique therapeutic challenges to Fabry patient management occurred with this patient, resulting in exploration of other therapeutic options. Immunomodulation therapy to suppress the immune response to the enzyme (similar to protocols for Pompe disease) was explored as an alternative option; however the efficacy of this approach to the treatment of Fabry disease has not been published. Enzyme dose escalation as a form of immune tolerance induction was also considered as an option, as was an alternate ERT formulation. Other challenges presented by this patient include patient management strategies that consider quality of life concerns and that address psychological distress from disease progression. This case, and other similar experiences, has illustrated the need for more research into other therapeutic options for those who develop high titres of neutralizing IgG antibodies. We propose developing a unified approach to similar patients in Canada.

Keywords: Fabry disease, antibodies, therapeutic challenges

P112 Patient/caregiver online surveys on the natural history of very rare diseases: creatine deficiencies and MPS IV B/late-onset GM1 (LO-GM1) as examples

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Objectives: This study is being conducted in response to the inquiries of multiple rare disease patients who are not registered to medical or research centers. Online surveys for patient/caregivers have been created instead of physician surveys to investigate the natural history of two very rare diseases: creatine deficiencies and MPS IV B/LO-GM1.

Design & Methods: This study utilizes two REDCap based online surveys to collect cross-sectional, qualitative data from patients and their families. Patient advocates helped to evaluate the survey for its quality. A total of 67 questions for creatine deficiencies and 72 questions for Morquio B/LO-GM1 were made pertaining to patients' demographics, their health, treatments, quality of life, access to healthcare, diagnostic history, lifestyle, and participation in clinical trials. The study links are hosted on parent support group websites such as morquiob.com, the Association for Creatine Deficiencies (creatineinfo.org), and the National Organization for Rare Diseases (rarediseases.org).

Results: There has been positive feedback to the survey postings on various support groups on Facebook. As a result there have been 9 hits for the creatine survey and 5 hits for Morquio B/LO-GM1 after a week of posting, with numbers continuing to increase. Data collection will occur over a one year period.

Conclusions: Online surveys are easily accessible tools that allow for greater sampling of populations with rare diseases. The natural history data collected will contribute to the establishment of clinically meaningful outcomes for future trials, and will also help to counsel newly diagnosed patients about their health expectations.

Keywords: natural history, patient/caregiver surveys, creatine deficiency disorders, MPS IV B, late-onset GM1 gangliosidosis

P113 Biomarkers positively associated with left ventricular mass index, and Mainz Severity Score Index in a cohort of Fabry disease patients with the IVS4 + 919G >A late-onset mutation

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Objectives: Fabry disease is an X-linked panethnic lysosomal storage disorder caused by a deficiency of α-galactosidase A. The prevalence of the Fabry disease mutation IVS4 + 919G>A (IVS4) associated with the late-onset cardiac phenotype in the Taiwanese population was estimated at 1:1600 males and 1:800 females through newborn screening. The objective of this research project was to investigate the relationship between globotriaosylceramide (Gb_3), globotriaosylsphingosine (lyso-Gb_3) and related analogues and clinical manifestations of the disease.

Design & Methods: Urinary and plasma Gb_3, and lyso-Gb_3 and related analogues were analyzed using tandem mass spectrometry in a cohort of 191 adult and pediatric Fabry patients carrying the IVS4 mutation. Statistical analyses were achieved using IBM SPSS Statistics version 22. Multiple regression analyses were performed to determine the association between biomarker levels and left ventricular mass index (LVMI) and Mainz Severity Score Index (MSSI), adjusted for gender and age.

Results: Our results show that the plasma level of lyso-$Gb_3$3, and urine analogue levels of lyso-Gb_3 at (+16), (+34), and (+50) had a positive association with the LVMI, and/or the MSSI.

Conclusion: Lyso-Gb_3 and related analogues might be reliable biomarkers for patients with the IVS4 mutation, considering the observed association with LVMI and MSSI in the cohort under study. Longitudinal biomarker follow-up of children with the IVS4 mutation would be important to determine if the elevation of urinary and plasma Fabry biomarkers at a young age are predictive of the clinical outcomes of the disease, as well as its severity in adulthood.

Keywords: Fabry, mass spectrometry, globotriaosylceramide, globotriaosylsphingosine, IVS4 + 919G>A
Funding Acknowledgement: Shire

P114 Energy intake from modified low protein foods may support treatment goals for plasma phenylalanine concentrations in children with phenylalanine hydroxylase deficiency

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Introduction: Phenylalanine hydroxylase (PAH) deficiency is treated with a phenylalanine (phe)- restricted diet, to achieve recommendations for plasma phe concentrations. The diet comprises natural low protein foods (NLPF), modified low protein foods (MLPF) and medical food (MF). Research demonstrates that MF (phe-free protein supplement) is essential to the efficacy of the diet.

Objective: This study aims to show that MLPF (low in phe, high in energy) is also important to the efficacy of the diet.

Design & Methods: In a prospective observational study, plasma phe concentrations were measured and 3-day diet records analyzed for 48 children (10.7±4.6 years) with PAH deficiency. Age and intakes of protein and energy were examined in relation to plasma phe concentrations, expressed as a percentage of the upper acceptable values for age.

Results: Daily protein intake was 172±51% of dietary reference intakes and energy intake was 99±21% of estimated energy requirements (for low activity). MLPF contributed 18±12% to daily energy intake. In univariate analysis, plasma phe concentrations were positively associated with age ($p < 0.001$), but negatively associated with total protein intake ($p < 0.01$), total energy intake ($p < 0.05$) and energy intake from MLPF ($p < 0.05$). In multiple regression analysis, only age was independently significant ($p < 0.001$).

Conclusion: In this group of children with PAH deficiency, age appeared to be the only determinant of plasma phe concentrations, but dietary energy and protein contributed to the overall significance of the statistical models. These models suggest that energy intake from MLPF may be necessary in order to achieve recommended plasma phe concentrations.

Keywords: Phenylalanine hydroxylase deficiency, phenylalanine-restricted diet

P115 Sitosterolemia – a case report

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Sitosterolemia is a rare autosomal disease. It is caused by homozygous or compound heterozygous mutations in ABCG8 or ABCG5. Mutations in these genes cause excessive absorption of plant sterols and decreased hepatic excretion into bile which leads to elevated concentrations of plasma phytosterols. Clinical features of the condition include xanthomas, premature atherosclerosis, hemolytic anemia and macrothrombocytopenia.

We report a 42 year old man with a recent diagnosis of Sitosterolemia. At the age of fourteen he was diagnosed with Neiman Pick C. This was based on a history of splenomegaly requiring splenectomy, thrombocytopenia, abnormal liver biopsy with lipid abnormalities and abnormal cholesterol ester formation in cultured fibroblasts. The patient was reassessed in the metabolic clinic at the age of 36 years. He had developed additional medical concerns. He had a mitral valve replacement, dilated cardiomyopathy and he had an ICD implanted. He had no neurologic abnormalities and the diagnosis of Neiman Pick C was questioned. Molecular and biochemical investigations for Neiman Pick C were requested and were normal, refuting this diagnosis, however, an alternative diagnosis was not made. The patient was reassessed at age 41. Whole exome sequencing was requested and a pathogenic homozygous mutation was identified in ABCG8. Several variants of unknown significance in different genes were also identified that may be playing a role in the patient's clinical features including three variants in TTN and one variant in DMD. We report our patient to highlight the rare condition Sitosterolemia and describe the clinical features associated with this condition.

P116 Screening for Fabry cardiomyopathy using cardiac magnetic resonance imaging

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Objective: Fabry disease (FD) may be present in 1 to 3 percent of patients with hypertrophic cardiomyopathy (HCM). Special applications of cardiac MRI (CMR), such as late gadolinium enhancement (LGE) and non-contrast T1 mapping, show potential for identifying features of FD. The aim of this study is to evaluate the utility of CMR in identifying causes of HCM such as Fabry disease, using a genetic screening panel.

Design & Methods: This is the first prospective, case-control study to evaluate LGE and T1 mapping using a 3-Tesla CMR in patients with undifferentiated HCM. Patients with HCM at the time of CMR were enrolled for genetic testing. Patients with secondary causes of HCM (e.g. hypertension) were excluded. DNA sequencing was performed on an Illumina MiSeq™ platform using a panel of 55 genes. We anticipate enrolment of 200 subjects.

Results: So far 13 patients were recruited and 9 have undergone sequencing. CMR identified no cases of FD in agreement with DNA analysis. Five of the subjects had a putative sarcomeric protein mutation, 1 case had mitochondrial disease, and 3 were variants of uncertain significance.

Conclusions: This study utilized genetic testing to validate imaging results. Preliminary results show that CMR did not falsely identify any cases as FD. We found 55.6% of the cases had a sarcomeric protein mutation, similar to the literature. The study is currently open to recruitment and we hope to understand the role of CMR in the diagnosis of FD with further data.

Keywords: Fabry disease, Hypertrophic cardiomyopathy, screening, cardiac MRI

Funding Acknowledgement: Shire Human Genetic Therapies Center for Extramural Clinical Research and Education 10001391

P117 Hypogonadotropic hypogonadism in males with glycogen storage disease type 1

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We describe 4 patients with glycogen storage disease type 1a and 1b with hypogonadotropic hypogonadism resulting in testosterone deficiency. A possible mechanism may be recurrent elevations in cortisol in response to hypoglycemia leading to suppression of gonadotropin-releasing hormone (GnRH) release. Incorporating clinical and / or biochemical screening of the hypothalamic-pituitary-gonadal axis may be important in the management of this disease.

P118 Short-term biological variance of PHE in patients with phenylketonuria

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Control of blood phenylalanine (PHE) levels is the primary goal in managing phenylketonuria (PKU). Both the overall exposure to PHE ("area under the curve") and the variation in PHE ("standard deviation of PHE levels") are thought to contribute to long-term neurocognitive outcome.

The objective of this study was to measure the diurnal variation of PHE in patients ≥4 years of age. Four groups were studied: Patients treated with diet alone who were in poor control or good control (>1/3 or ≤1/3, respectively, of monitoring PHE levels outside the target treatment range in the 6 months preceding enrolment, n=8 "Wide PHE" and n=10 "Target PHE", respectively), patients treated with diet plus Kuvan (n=9 "Kuvan"), and patients with benign / mild hyperphenylalaninemia (not requiring diet, n=5 "Control"). Study subjects were admitted to the short-stay unit in the morning after an overnight fast and then pre-prandial and 1 and 2 hour post-prandial samples were collected for each meal over the next 24 hours. Whole blood dried blood spots (DBS) were analyzed for amino acids. The maximum, mean and standard deviation of PHE levels were calculated. Significance was calculated by two-way single factor ANOVA with post-hoc Man-Whitney U test. The mean PHE levels were 790, 288, 323, 300 uM for the Wide PHE, Target PHE, Kuvan and Control groups, respectively (p=0.0003, Wide PHE significantly higher than the other 3 groups). The maximum PHE levels showed the same pattern (p=0.0005). The standard deviation of PHE was not significantly different between the groups (68, 38, 53, 53 uM, respectively). In conclusion, PHE levels were higher in patients who historically had poor control of PHE levels, while patients who tended to be in good control on diet or who were on diet plus Kuvan had lower levels that were similar to controls.

P119 Triheptanoin (UX007) treatment in patients with long-chain fatty acid oxidation disorders (LC-FAOD) and cardiomyopathy

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Objectives: The most severe LC-FAOD phenotype may present in infancy, when energy demands are increased. Symptoms include cardiomyopathy, arrhythmia, hypoglycemia, and hepatic dysfunction. Morbidity and mortality are high despite detection by newborn screening (NBS) and early intervention with standard treatment, including supplementation with even medium chain triglycerides (MCT). Triheptanoin (UX007) is an investigational 7-carbon odd medium chain triglyceride, shown in animal studies to be both ketogenic and gluconeogenic, by providing anaplerotic substrate for the depleted TCA cycle.

Design & Methods: Triheptanoin was provided through expanded access programs for 8 infants and 2 older patients with cardiomyopathy. All were previously treated with MCT. We reviewed data provided by the treating physicians.

Results: Ten patients with LC-FAODs presented with cardiomyopathy in infancy or childhood, despite treatment with MCT. Eight were detected by NBS. Seven were treated with triheptanoin (4g/kg) on emergency treatment protocols and 3 in existing Early Access programs. Improvement occurred within 48 hours in 2 patients near death. Seven were successfully weaned from support and remain stable; a moderately severe patient with declining ventricular function did not require acute support. Two patients died: 1 developed pericardial effusion, bradycardia and cardiac arrest after treatment for almost 4 weeks; 1 died of sepsis, with normal heart function. Most common adverse events were GI related; 1 withdrew from treatment due to GI distress.

Conclusions: These data demonstrate potential therapeutic benefit of triheptanoin treatment in patients with LC-FAOD cardiomyopathy. Further studies are warranted to confirm these initial promising findings.

Funding Acknowledgment: Ultragenyx provided UX007 for emergency treatment protocols.

P120 Therapeutic challenges in two adolescent patients with Fabry disease and high antibody titres

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The use of enzyme replacement therapy (ERT) for Fabry disease has resulted in some patients in the development of high antibody titres. We present two adolescent male patients receiving ERT over a period of three years and two and a half years, respectively, who presented with increasing titres of IgG antibodies against α-galactosidase A with reduced ERT efficacy. At the highest, the antibody titres have been measured at 1:102,400 for one patient and 1:25,600 for the other. Measurements of urine globotriaosylceramide (GB3) concurrently showed an upward trend from 1,165 to 2,260, and 503 to 1,250, respectively (microgram/mmol creatinine). Despite receiving ERT, both patients continued to have significant malaise, gastrointestinal symptoms and neuropathic pain. As well, these patients experienced frequent infusion associated reactions despite premedication. ERT was subsequently discontinued for both patients one year ago.

Unique therapeutic challenges to Fabry patient management occurred with these patients, resulting in exploration of other therapeutic options. Immunomodulation therapy to suppress the immune response to the enzyme (similar to protocols for Pompe disease) was explored as an alternative option; however the efficacy of this approach to the treatment of Fabry disease has not been published. Enzyme dose escalation as a form of immune tolerance induction was also considered as an option, as was an alternate ERT formulation. Other challenges presented by these patients include patient management strategies that consider quality of life concerns and that address psychological distress from disease progression. These two patients illustrate the need for more research into other therapeutic options for those who develop high titres of neutralizing IgG antibodies. We propose developing a unified approach to similar patients in Canada.

Keywords: Fabry disease, antibodies, therapeutic challenges

P121 Proposed study of possible unmet clinical care needs of PKU adults diagnosed via newborn screening

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Objectives: To inform clinicians of proposed study of potential unmet needs for clinical care of PKU adults early diagnosed through newborn screening (NBS) programs. The objectives of this study are to document: (a) history of confirmed diagnoses of PKU via NBS programs in each jurisdiction, (b) the status of long-term follow-up of NBS confirmed diagnosed cases and (c) possible unmet needs for clinical care of this population.

Design & Methods: The hypothesis of this study is that likely the majority of PKU adults diagnosed via NBS programs in Canada are not in active clinical case notwithstanding the recommendation in 2000 of the international scientific consensus conference that PKU requires treatment for life.[1] This hypothesis is based on the observations and estimates of a similar study in the United States published in 2013 that an estimated 71 percent of early-diagnosed PKU adults were not in active clinical care.[2]

This study will start by ascertaining the numbers of cases of confirmed diagnoses of PKU by each provincial and territorial NBS program annually since the start of each program. This work will likely involve extensive archival research for some programs. This work will provide the denominator. The study will continue with a survey of treating clinics across Canada to ascertain the number of PKU adults who are in active clinical care currently. This survey will provide the numerator. The study will include follow-up with clinics to refine the available data. The CIMDRN study project cannot address this hypothesis as it is focused on pediatric patients.

Results: Data will be analyzed to confirm or otherwise the hypothesis. Results will be shared with treating clinics and governments to help address the extent of unmet needs for clinical care focused on PKU adults.

Conclusions: To be determined.

References:

[1]Phenylketonuria: Screening and Management. NIH Consensus Statement online 2000 October 16-18: 17(3): 1-27
[2]Newborn screening 50 years later: access issues faced by adults with PKU. Genetics in Medicine (2013) 15, 591-599

P122 Cytosolic phosphoenolpyruvate carboxykinase deficiency presenting with acute liver failure following gastroenteritis

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Background: We report a patient from a consanguineous family who presented with transient acute liver failure and biochemical patterns suggestive of disturbed urea cycle and mitochondrial function, for whom conventional genetic/metabolic investigations for acute liver failure failed to yield a diagnosis.

Methods: Trio whole exome sequencing was performed (42X) with bio-informatics analysis via our TIDEX customized pipeline, and subsequent Sanger sequencing of candidates. PEPCK activity was measured in transfected mutant vs wildtype COS-1 cells in the direction of oxaloacetate formation (published methods).

Results: Of the 14 genes harbouring recessive / hemizgous (n=9) and *de novo* (n=5) mutations, the homozygous 12-bp deletion (p.GVPLV123V) in *PCK1* encoding cytosolic phosphoenolpyruvate carboxykinase (PEPCK) was the most compelling based on function and (likely) pathogenic nature of the variants. Compared to wildtype transfected COS-1cells, mutant PEPCK activity was significantly reduced, similar to the empty vector, confirming the deleterious nature of the homozygous *PCK1* mutant.

Discussion: We propose that PEPCK deficiency should be considered in the young child with unexplained liver failure, especially with TCA cycle metabolite accumulation on urine organic acid/amino acid profiles with hyperammonemia suggestive of a proximal urea cycle defect during the acute episode. If suspected, intravenous administration of dextrose should be initiated. Long-term management comprising avoidance of fasting with the provision of a glucose polymer emergency regimen for illness management may be sufficient to prevent future episodes of liver failure.

Conclusion: This case report provides further insights into the (patho-)physiology of energy metabolism, confirming the power of genomic analysis of unexplained biochemical phenotypes.

Keywords: PEPCK, hyperammonemia, hepatopathy, lactic acidosis, treatment

Funding Acknowledgment: BC Children's Hospital Foundation, Genome BC (SOF-195), Michael Smith Foundation for Health Research (Scholar Award for CvK), Canadian Institutes for Health Research (#301221 grant).

P123 Delineating the patient population with Medium chain acyl-CoA dehydrogenase deficiency (MCADD): British Columbia Children's Hospital (BCCH) clinic experience

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Background: Medium chain acyl-CoA dehydrogenase deficiency (MCADD) is a rare genetic disorder, and the most common fatty acid oxidation disorder occurring 1 in 12000 births in British Columbia (BC). MCADD has been part of the new born screening (NBS) program in BC since 2002. Following confirmation of the newborn screening for MCADD, targeted genetic testing for the common two mutations in the *ACADM* gene is performed. Full gene sequencing is undertaken for patients where one or no common mutation is detected. We currently follow 50 patients with MCADD, age 4 weeks to 14 years. While initially all MCADD patients were started on L-Carnitine at birth, the practice was changed in 2013 supplementing only patients with below the normal free carnitine levels.

Methods: Chart review was performed and information on several parameters was obtained: molecular results, patients started on L-carnitine at birth, carnitine supplementation including dosage and free carnitine levels.

Results: The clinic follows 50 patients; 28 are homozygous for the common c.985A>G variant, and 4 patients are compound heterozygous for the c.985A>G and c.199T>G variant. Currently 37 patients are supplemented with L-Carnitine; dose ranging from 13 to 105 milligram/kilogram/day (mean of 43 milligram/kilogram/day). 7 patients were not started on L-carnitine at birth and maintained normal free carnitine level on follow up. With the change in practice 18 patients stopped L-carnitine, 11 of which required restarting supplementation.

Summary: The MCADD patients differ in their need for carnitine supplementation. Further delineation of factors influencing this, including genotype correlation will be performed.

Keywords: Medium chain acyl-CoA dehydrogenase deficiency, l-carnitine, free carnitine, new born screening, variants

P124 Neuropsychological and quality of life outcomes in untreated adults with mild hyperphenylalaninemia with phenylalanine levels between 360 and 600 µmol/L

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Background: Thresholds to treat hyperphenylalaninemia have been historically discrepant, with the majority of clinics treating phenylalanine (PHE) levels >360 µmol/L. There is no consensus about the neuropsychological function and quality of life of untreated patients with mild hyperphenylalaninemia (MHP), with PHE levels 360-600 µmol/L. Further well designed studies of functioning in untreated individuals with MHP are needed to clarify findings of the limited studies that show variable outcomes in this population.

Objectives: To determine whether neurocognitive, psychological, and quality of life outcomes for adults with MHP, as defined by untreated PHE levels between 360-600 µmol/L, are within the normal population values.

Methods: Eligible subjects were administered a comprehensive neuropsychological battery measuring IQ, executive function, and quality of life. Statistical analysis was performed using z-tests and interclass correlation coefficients.

Results: 10 subjects were studied. No difference was found in full-scale IQ scores using the Wechsler Adult Intelligence Scale when compared to Canadian normative data. On the Beck Depression and Anxiety Inventories, 10% of patients reported moderate depression, and 40% reported mild-moderate anxiety. CANTAB cognitive testing showed deficits in executive functioning, working memory, and reaction time when compared to age and gender normative data.

Conclusion: The sample size was limited but these results warrant further research into the potential adverse effects of untreated MHP with PHE levels >360 µmol/L on executive function and emotional regulation. Improved treatment options, including better nutritional products to aid with diet adherence and pharmaceutical options, may make management of patients with MHP more feasible.

Keywords:

Funding Disclosure: Investigator initiated study funded by BioMarin Pharmaceuticals Inc.

P125 Characterization of the biochemical, molecular and clinical phenotype of patients with a diagnosis of VLCADD, including those identified via NBS in the Maritime region of Canada, as well as British Columbia

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Objective: Very long-chain acyl-CoA dehydrogenase deficiency (VLCADD) is a rare genetic disorder of fatty acid metabolism. Accurate diagnosis and early detection are crucial for favourable clinical outcomes for these patients and for this reason VLCADD is now part of most expanded newborn screening (NBS) programs including the Canadian Maritime provinces of Nova Scotia, New Brunswick and Prince Edward Island, as well as British Columbia. Little is known about the clinical course of this heterogeneous condition and, while there are consensus protocols based on case studies and expert opinion, there are currently no evidence-based guidelines for diagnosis and treatment. Our aim was to review and summarize patient NBS and clinical data with our primary objective to characterize the biochemical, molecular and clinical phenotype of patients with a diagnosis of VLCADD, including those identified via NBS in the Maritime region of Canada, as well as British Columbia.

Design & Methods: Data was collected using a chart review and included genotypes, clinical phenotype, and VLCAD residual enzyme activity (REA).

Results: In the Maritime provinces, we have identified 18 patients ranging in age from birth to 25 years of age. We have identified previously reported mutations as well as a novel splice-site variant in patients of Acadian ancestry in those ascertained via NBS, as well as in those born prior to the availability of NBS for VLCADD. Ten of these patients are asymptomatic, while the remainder show a wide range of clinical phenotypes. Four patients have been identified via NBS in British Columbia, with different genotypes than those on the east coast, including four novel mutations. Three of these patients have been asymptomatic, while the fourth has presented with elevated creatine kinase with mild illnesses, and left ventricular hypertrophy.

Conclusions: Review of clinical data showed that ≤10% REA correlates with development of symptoms in the Maritime patients including significant hypoglycemia, myopathy, cardiomyopathy and death. Moreover our data also suggest that individuals with REA within 10-15% are also at risk to develop symptoms. Genotype and REA are closely correlated, and even in cases where REA is unknown, the genotype can provide valuable prognostic information.

P126 Cardiac Outcomes in Very-Long-Chain Acyl-CoA Dehydrogenase Deficiency in the Maritimes: The Role of ECG and ECHO in Long Term Follow-Up

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Background and Aims: Very long-chain acyl-coenzyme A dehydrogenase deficiency (VLCADD) is a rare disorder of fatty acid metabolism associated with multi-organ failure, cardiomyopathy and metabolic decompensation. With early diagnosis now achieved through newborn screening (NBS), treatment can be initiated before the onset of symptoms to prevent or reverse clinical deterioration. We sought to characterize cardiomyopathy and arrhythmias in patients with VLCADD in the Maritime Provinces and any association with residual enzyme activity.

Methods: All patients in the Maritime Provinces diagnosed with VLCADD were included (N=18). Mutation type and residual enzyme activity was identified using functional enzyme assay. Previous echocardiogram (ECHO; N=42), electrocardiogram (ECG; N=43) and clinic reports were analyzed to document the presence or absence of cardiomyopathy and any documented arrhythmias or symptomatic events.

Results: Residual enzyme activity ranged from 0-19%. Seventeen of 18 patients had an ECHO and ECG soon after diagnosis, with no significant findings. Five patients experienced transient symptoms (hypoglycemia and/or myopathy) with no cardiac sequelae. One patient (with 0% enzyme activity) was diagnosed with VLCADD and cardiomyopathy on autopsy before VLCADD screening was added to NBS.

Conclusions: With early diagnosis by NBS and necessary treatment, patients with VLCADD in the Maritime provinces did not develop cardiomyopathy or symptomatic arrhythmias. Patients with residual enzyme activity as low as 4% experienced no cardiac involvement identified through repeat ECHO and ECG studies.