Topic: Newborn Screening for MCAD (medium chain acyl-CoA dehydrogenase) Deficiency.

Summary: MCAD deficiency is an autosomal recessive disorder of fatty acid oxidation with an incidence of up to 1/12,000. Early diagnosis and treatment may prevent sudden death or long-term disability.

Bottom line: Parents-to-be should be informed of newborn screening for MCAD deficiency and other disorders, preferably in the prenatal period. The panel of disorders screened for varies by province; physicians should familiarize themselves with their local newborn screening program.

The Disease
- MCAD deficiency is a disorder of fatty acid oxidation.
- Breakdown of fatty acids in mitochondria is an essential part of the body’s ability to produce energy.
- Disorder: inability to break down fatty acids leading to accumulation of “medium chain” fatty acids.

The Gene
- MCAD is one of the enzymes involved in mitochondrial fatty acid β-oxidation.
- The gene that causes MCAD deficiency is ACADM.
- It has an autosomal recessive pattern of inheritance.
- Mutations of the ACADM gene result in a deficient amount of enzyme or a defective enzyme.
- Highest frequency of MCAD deficiency is found in people of Northern European ancestry, in whom the incidence is approximately 1/12,000.

Consequences of having a faulty gene
- Children with MCAD deficiency usually appear normal at birth.
- Usually presents during first 3 years (average age 12 months), but can occur in neonatal period.
- Symptoms triggered by catabolic stress such as fever, illness, or fasting.
- Symptoms:
  - Hypoglycemia, vomiting, lethargy, encephalopathy, hepatomegaly, seizures, apnea, cardiac arrest.
  - Can progress quickly: lethargy → coma → death.
  - Long-term outcomes: developmental & behavioural disabilities, chronic muscle weakness, seizures, failure to thrive, cerebral palsy, attention deficit disorder.
  - 25% of untreated infants die with first episode; of remainder, half will have neurologic impairment.
- MCAD deficiency is a preventable cause of some cases of Sudden Infant Death Syndrome (SIDS).
  - MCAD deficiency thought to be responsible for ~1% of SIDS cases.
  - Early diagnosis and treatment can prevent sudden death.

Role of family physician with expecting parents and parents of all newborns
- Discuss newborn screening.
- Discuss benefits (see below).
- Discuss how testing is done, timing, and that repeat sample is sometimes required.
- Discuss difference between screening and diagnostic (confirmatory) test.
- Discuss possible results.
- Answer questions/give information.
**Testing**
- Positive result detects elevated level of medium chain acylcarnitines as measured by Tandem Mass Spectrometry analysis of blood spot.
- Heel prick blood samples are taken between 1 (24 hours) and 7 days after birth.
- If tested before 24 hours (i.e. if early discharge) – should be retested within 5 days.
- If infant <37 weeks gestation or sick – collect specimen at 5-7 days of age and indicate on NBS card.
- Indicate if infant is receiving total parenteral nutrition, antibiotics or has had blood transfusion as these may affect results.
- Results
  - Screen positive means:
    - further testing is required to confirm the diagnosis
    - does NOT mean that the infant is affected
  - If diagnosis confirmed, it is recommended that the infant be referred to a metabolic genetics centre to provide counseling, management and follow up.

**Benefits of genetic testing**
- Good prognosis with treatment
  - Infants with MCAD deficiency require frequent feedings, avoidance of fasting or hypoglycemia.
  - Need to prevent metabolic crises and their sequelae.
  - Acute episodes are managed with IV fluids (10% dextrose) until hypoglycemia reversed to normal.
  - High carbohydrate, low fat diet – formulas containing medium chain triglycerides as primary source of fat should be avoided.
  - Toddlers: 2g/kg of uncooked cornstarch at bedtime to ensure sufficient glucose overnight.
  - Carnitine supplementation can be considered.
  - Pediatric and nutrition consultations are recommended.
- Parents of child with MCAD deficiency are likely carriers of the disorder and have 25% chance of another child with this disorder – prenatal testing is available and genetic counselling is recommended.

**Harms/limitations of newborn screening**
- Parental anxiety awaiting confirmatory testing for screen positive, ongoing anxiety for those diagnosed.
- False positive and false negative results.
- Exposure of non-paternity.

**Web Resources:** [www.newbornscreening.on.ca](http://www.newbornscreening.on.ca), [www.marchofdimes.com](http://www.marchofdimes.com), [www.genetests.org](http://www.genetests.org), [http://genes-r-us.uthscsa.edu/](http://genes-r-us.uthscsa.edu/)


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Dr Carroll is Principal Investigator of the GenetiKit Project and is the Sydney G Frankfort Chair in Family Medicine at Mount Sinai Hospital and an Associate Professor in the Department of Family Medicine at the University of Toronto.

In alphabetical order, other members of the GenetiKit Team are as follows: Dr Allanson is Chief of the Department of Genetics at the Children's Hospital of Eastern Ontario (CHEO) in Ottawa, Ontario and Full Professor in the Department of Pediatrics at the University of Ottawa. Dr Blaine is an Assistant Professor in the Department of Family and Community Medicine at the University of Toronto in Ontario and Lead Physician of the STAR Family Health Team in Stratford, Ontario. Ms Cremin is a Genetic Counselor in the Hereditary Cancer Program at the BC Cancer Agency in Vancouver. Ms Dorman is a Genetic Counselor at the Sudbury Regional Hospital in Ontario. Ms Gibbons is a Genetic Counselor at the North York General Hospital in Ontario. Dr Graham is Vice-President of Knowledge Translation, Canadian Institutes of Health Research. Dr Grimshaw is a Professor in the Department of Medicine and Director of the Clinical Epidemiology Program at the Ottawa Health Research Institute. Ms Honeywell is an Assistant Professor in the Department of Pediatrics at the University of Ottawa and in the CHEO Departments of Genetics and Cardiology. Dr Meschino is a Clinical Geneticist at North York General Hospital and Assistant Professor in the Department of Paediatrics at the University of Toronto. Ms Permaul is a Research Associate in the Granovsky Gluskin Family Medicine Centre at Mount Sinai Hospital. Dr Wilson is an Associate Professor in the Department of Epidemiology and Community Medicine at the University of Ottawa.