NEWBORN SCREENING **ONTARIO**
DÉPISTAGE NÉONATAL **ONTARIO**

# MOLECULAR REQUISITION

SHIP SAMPLES TO: **NSO SPECIMEN HUB**
**415 Smyth Road Ottawa, ON K1H 8M8**

Lab Use Only

**PATIENT INFORMATION**

Health Card Number

Sex
○ Male ○ Female
○ Ambiguous ○ Unknown

Date of Birth
yyyy mm dd

Patient's Telephone Contact Number

MRN/Hospital Number

Patient's Last Name

Patient's First Name ☐ Fetus of:

Patient's Address

Ethnicity: _____

**For STAT requests please indicate how a shorter TAT will change patient management:**
○ Ongoing pregnancy; result needed for decision making within 6wks (i.e. termination or birth)
Estimated due date:
○ Positive newborn screens where molecular results are essential for treatment decisions
○ Expedited results will directly impact management decisions
For inquiries please contact nsomolecular@cheo.on.ca

**ORDERING PROVIDER**
Name
Email
Phone Fax
Institution

**Copy results to clinician/practitioner:**
Name
Phone Fax

**Copy results to clinician/practitioner:**
Phone Fax

## TEST REQUESTED *see FAQ section on NSO website for more information*

- ☐ Targets of Newborn Screening – targeted panel (complete Section 1)
- ☐ Primary Immune Deficiencies – augmented exome slice (complete Section 2; whole blood or DNA)
- ☐ Mitochondrial Diseases – augmented exome slice (complete Section 3; whole blood or DNA)
- ☐ TREC (DBS only) ☐ *check here if purines also required*
- ☐ SMA - ddPCR/MLPA
- ☐ *CFTR* common mutation panel (for carrier testing and CF newborn screen positive only)
- ☐ Familial Variant Testing (complete table below)
- ☐ Maternal Cell Contamination (MCC) studies (for prenatal and umbilical cord blood testing)

## SPECIMEN TYPE

- ☐ Whole Blood (room temp, EDTA tubes)
  Adult 2x5mL, Children 2x4mL, Infant ≤2yo 1x3mL
- ☐ Umbilical Cord blood (maternal sample for MCC studies required) ☐ EDTA blood ☐ DBS
- ☐ DNA (>10 µg with at least [50ng/ µL])
  Source: _____
- ☐ DBS (Dried bloodspot - Whatman 903)
- ☐ Other:_____
  Contact NSO prior to sending

☐ Variant reinterpretation (must attach NSO report issued >=1 year ago)

## SPECIMEN COLLECTION

| | | | |
|---|---|---|---|
| Date of collection (YYYY/MM/DD) | | Time of Collection (24HR) | |
| # Tubes (if applicable) | | Specimen ID | |

*Please contact us if this is a precious sample.* For more information on precious samples and our sample retention policy, please visit our website.

## AUTHORISATION

I certify that the patient and/or legal guardian has been informed of the nature of the genetic test requested, including benefits, risks, possible results, limitations and possible implications for himself/herself and his/her family. I have answered this person's questions and have obtained informed consent for this testing.

Signature of the ordering healthcare provider:

## TESTING FOR KNOWN FAMILIAL VARIANT(S) ☐ Please provide proband's report or NSO report number and family history

| | | | |
|---|---|---|---|
| Proband's Name / DOB: | | Relationship to Proband: | |
| Gene and Variant(s):<br>*Transcript (NM number) required if report not attached* | | | |

Personal History: ☐ Asymptomatic ☐ Symptomatic:

Family History:

Name(s) and DOB of other submitted family members:

Complete NSO's billing form if patient is not covered by OHIP; attach subsequent pages/sections as needed



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## SECTION 1: MOLECULAR TESTING FOR DISEASES TARGETED BY NEWBORN SCREENING ONTARIO

| Disease Targeted: | |
|---|---|

Gene (or choose from list below); *If a multi-gene panel is being requested, please indicate if you are suspicious of a specific gene(s):*

Clinical Indication:

Family History (please attach all relevant documents related to previous test results and clinical diagnosis):

### AMINO ACID DISORDERS *(requesting a panel is equivalent to requesting all related subpanels)*

| x | PANEL | x | SUBPANEL | GENES |
|---|---|---|---|---|
| ☐ | Homocystinuria | ☐ | Hypermethioninemia | *ADK, AHCY, CBS, GNMT, MAT1A, SLC25A13* |
| | | ☐ | Hypomethioninemia | *MTHFR, MTR, MTRR* |
| ☐ | Phenylketonuria | ☐ | PAH Deficiency | *PAH* (sequencing + reflex MLPA as needed) |
| | | ☐ | Biopterin Deficiencies | *DNAJC12, GCH1, PCBD1, PTS, QDPR, SPR* (for PKU panel, *PAH* will be done with reflex to these genes) |
| ☐ | Tyrosinemia | ☐ | Elevated Succinylacetone | *FAH, GSTZ1* |
| | | ☐ | Elevated Tyrosine | *HPD, TAT* |
| ☐ | Urea Cycle Diseases | ☐ | High citrulline | *ASS1, SLC25A13* |
| | | ☐ | High ASA | *ASL* |
| | | ☐ | Low citrulline | *CPS1, NAGS, OTC* |
| | | ☐ | Other | *ARG1, CA5A, GLUL, GLUD1, OAT, SLC7A7, SLC25A2, SLC25A15* |
| ☐ | Maple Syrup Urine Disease | | | *BCKDHA, BCKDHB, DBT, DLD* |

### ORGANIC ACID DISORDERS *(requesting a panel is equivalent to requesting all related subpanels)*

| x | PANEL | x | SUBPANEL | GENES |
|---|---|---|---|---|
| ☐ | Multiple carboxylase Deficiency | ☐ | Biotinidase Deficiency | *BTD* |
| | | ☐ | Other | *CA5A, HLCS* |
| ☐ | Propionic / Methylmalonic acidemias | ☐ | PA | *PCCA, PCCB* |
| | | ☐ | MMA | *ACSF3, ALDH6A1, MCEE, MLYCD, MMAA, MMAB, MMUT, SUCLA2, SUCLG1* |
| | | ☐ | MMA + Homocysteinemia | *ABCD4, AMN, CBLIF, CD320, CUBN, HCFC1, LMBRD1, MMACHC, MMADHC, TCN1, TCN2* |
| ☐ | Isovaleric acidemia | | | *ACADSB, FLAD1, IVD* |
| ☐ | Glutaric aciduria Type 1 | | | *GCDH* |
| ☐ | Isobutyryl-CoA dehydrogenase deficiency | | | *ACAD8* |
| ☐ | Succinic semialdehyde dehydrogenase deficiency | | | *ALDH5A1* |
| ☐ | b-ketothiolase deficiency | | | *ACAT1* |
| ☐ | Guanidinoacetate Methyltransferase Deficiency | | | *GAMT* |

### FATTY ACID OXIDATION DISORDERS ☐ Check here to request ALL genes noted below

| x | PANEL | GENES | |
|---|---|---|---|
| ☐ | Carnitine Uptake Deficiency | *SLC22A5* | |
| ☐ | MCAD Deficiency | *ACADM* (c.985A>G common mutation and del/dup +/- reflex sequencing) | ☐ **Check here for direct to sequencing** |
| ☐ | LCHAD/MTP Deficiency | *HADHA, HADHB* (*HADHA* c.1528G>C + reflex sequencing) | ☐ **Check here for direct to sequencing** |
| ☐ | VLCAD Deficiency | *ACADVL* | |
| ☐ | MADD/Glutaric Aciduria Type2 | *ETFA, ETFB, ETFDH, FLAD1, SLC52A2, SLC52A3, SLC52A1* | |
| ☐ | CPT2 Deficiency | *CPT2* | |
| ☐ | CACT Deficiency | *SLC25A20* | |
| ☐ | CPT1 Deficiency | *CPT1A* (p.Pro479Leu common mutation + reflex sequencing) | ☐ **Check here for direct to sequencing** |
| ☐ | Other FAOD | *ACAA2, ACAD9, ACADL, ACADS, ECHS1, HADH* | |

### CONGENITAL ADRENAL HYPERPLASIA (if both requested, *CYP21A2* will be performed first and reflex to panel)

| | | |
|---|---|---|
| ☐ | 21-Hydroxylase Deficiency | *CYP21A2* (includes MLPA and long-range PCR analyses for CNVs and common rearrangements) |
| ☐ | Other | *ARMC5, CYP11B1, CYP11B2, CYP17A1, HSD3B2, POR, PRKAR1A, STAR* |

### GALACTOSEMIA

| | | |
|---|---|---|
| ☐ | GALT Deficiency | *GALT* |
| ☐ | Other | *GALK1, GALE, GALM, GLUT2 (SLC2A2)* |



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## SECTION 2: MOLECULAR TESTING FOR INBORN ERRORS OF IMMUNITY

### PANEL SELECTION

☐ Severe Combined/Primary Immune Deficiency (251 gene augmented exome slice), please visit our website for full list of genes

**SUBPANELS**

☐ ADA Deficiency (*ADA*)

☐ Chronic Granulomatous Disease (*CYBA, CYBB, CYBC1, G6PD, NCF1*, NCF2, NCF4*) [*limited coverage due to high homology with duplicated regions in genome; please note that this gene is not included in the full severe combined/primary immune deficiency panel]

**Additional testing to ensure full coverage of NCF1 can only be requested if patient has had an abnormal neutrophil oxidative burst index*

☐ Aicardi-Goutières syndrome (*ADAR, IFIH1, RNASEH2A, RNASEH2B, RNASEH2C, SAMHD1, TREX1*)

### CLINICAL DETAILS

Please provide detailed information regarding patient's phenotype, age of onset of symptoms, previous tests completed, and family history:

- Age of onset:
- Family history:
- Other:

**CLASSIC PRESENTATIONS**

☐ ADA deficiency
☐ Aicardi-Goutières syndrome
☐ Autoimmune lymphoproliferative syndrome
☐ Chronic granulomatous disease
☐ Common variable immunodeficiency
☐ Familial cold autoinflammatory syndrome
☐ G6PD deficiency
☐ Hyper IgE syndrome – Autosomal Dominant
☐ Hyper IgE syndrome – Autosomal Recessive
☐ Mendelian susceptibility to mycobacterial disease
☐ Severe combined immunodeficiency
☐ Wiskott-Aldrich syndrome
☐ **Other (indicate if you are suspicious of a specific gene):**

**LABORATORY FEATURES**

☐ Elevated inflammatory markers
☐ Anemia
☐ Neutropenia
☐ Lymphopenia
☐ Thrombocytopenia
☐ Eosinophilia
☐ Abnormal Neutrophil Oxidative Burst Index
☐ Abnormal TREC assay
☐ Low or absent CD4+ T cell number
☐ Low or absent CD8+ T cell number
☐ Abnormal T cell function
☐ Low or absent NK function
☐ Low or absent B cell number
☐ Agammaglobulinemia
☐ Increased immunoglobulins: ☐ IgG ☐ IgA ☐ IgM ☐ IgE
☐ Decreased immunoglobulins: ☐ IgG ☐ IgA ☐ IgM ☐ IgE
☐ Poor specific antibody response to vaccine

**CLINICAL FEATURES**

**RHEUMATOLOGICAL/IMMUNE DYSREGULATION**

☐ Arthritis
☐ Granulomas
☐ Hepato/splenomegaly
☐ Lymphadenopathy
☐ Recurrent fevers
☐ Systemic lupus erythematosus
☐ Vasculitis

**HEMATOLOGICAL**

☐ Autoimmune cytopenia
☐ Bone marrow failure
☐ Evan's syndrome
☐ Hemophagocytic lymphohistiocytosis
☐ Lymphoma

**GASTROINTESTINAL**

☐ Chronic diarrhea
☐ Celiac disease
☐ Enteropathy
☐ Inflammatory bowel disease
☐ Perianal abscess/fistula
☐ Liver/biliary disease

**INFECTIONS**

☐ Abscesses
☐ Candidiasis
☐ Epstein-Barr virus
☐ Mycobacterium tuberculosis
☐ Non-tuberculous mycobacteria
☐ Recurrent infections: ☐ bacterial ☐ fungal ☐ viral
☐ Recurrent pneumonia
☐ Skin and/or connective tissue infections

**DERMATOLOGICAL**

☐ Alopecia
☐ Bullous pemphigoid
☐ Dermatitis/eczema
☐ Psoriasis
☐ Urticaria
☐ Vitiligo
☐ Warts

**PULMONARY**

☐ Asthma
☐ Bronchiectasis
☐ Chronic obstructive pulmonary disease
☐ Interstitial lung disease

**OTHER**

☐ Developmental delay
☐ Endocrinopathy
☐ Facial dysmorphisms
☐ Failure to thrive
☐ Hearing loss
☐ Microcephaly
☐ Short stature
☐ Unexplained weight loss



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## SECTION 3: MOLECULAR TESTING FOR MITOCHONDRIAL DISEASES

Criteria for testing requires selections from at least one classic presentation OR at least one pathologic/lab feature OR at least one biochemical feature OR (at least one sign in CNS/heart/eyes/muscles AND one "other")

### PANEL SELECTION

☐ Full Mitochondrial Nuclear Gene Panel (425 gene augmented exome slice), please visit our website for full list of genes

**SUBPANELS**

- ☐ Mitochondrial Encephalopathy / Leigh Disease (117 genes)
- ☐ mtDNA Depletion and Deletion (19 genes)
- ☐ Progressive External Ophthalmoplegia (PEO) / Optic Atrophy (77 genes)
- ☐ Pyruvate Dehydrogenase Complex Deficiency (16 genes)

*Please contact laboratory to request another subset of the full nuclear gene panel*

### CLINICAL DETAILS

Please provide detailed information regarding patient's phenotype, age of onset of symptoms, previous tests completed, and family history:

- Age of onset:
- Family history:
- Other:

**CLASSIC PRESENTATIONS**

- ☐ Alpers disease
- ☐ Chronic progressive external ophthalmoplegia (CPEO)
- ☐ Gentamicin-related sensorineural hearing loss
- ☐ Kearns-Sayre syndrome
- ☐ Leber's hereditary optic neuropathy (LHON)
- ☐ Leigh disease
- ☐ Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)
- ☐ Mitochondrial neuro-gastro-intestinal encephalopmyopathy (MNGIE)
- ☐ Multiple symmetric lipomatosis
- ☐ Myoclonic epilepsy with ragged-red fibers (MERRF)
- ☐ Neuropathy, ataxia, and retinitis pigmentosa (NARP)
- ☐ Pearson syndrome
- ☐ Primary lactic acidosis
- ☐ Sensory-ataxia, neuropathy, dysarthria and ophthalmoparesis (SANDO)
- ☐ **Other (indicate if you are suspicious of a specific gene):**

**PATHOLOGIC/LABORATORY FEATURES**

- ☐ Ragged red fibers: _____ %
- ☐ COX-negative fibers: _____%
- ☐ Ultrastructurally abnormal mitochondria by electron microscopy
- ☐ Muscle biopsy consistent with mitochondriopathy (affix report)

**BIOCHEMICAL FEATURES**

- ☐ Persistent hyperalaninemia
- ☐ Persistent abnormal excretion of lactate, pyruvate of TCA intermediates in urine
- ☐ Evidence of mtDNA depletion or multiple mtDNA deletions (affix results)
- ☐ <30% activity of any RC complex in tissue or cell line
- ☐ Increased lactate pyruvate ratio (>25) in skin fibroblasts

**CLINICAL FEATURES**

**CENTRAL NERVOUS SYSTEM (CNS)**

- ☐ Developmental delay
- ☐ Regression
- ☐ Movement disorder
- ☐ Seizures
- ☐ Hemiplegic or complicated migraine
- ☐ Peripheral neuropathy
- ☐ Sensorineural hearing loss

**HEART**

- ☐ Arrhythmias
- ☐ Cardiomyopathy
- ☐ Conduction block

**EYES**

- ☐ Optic atrophy
- ☐ Pigmentary retinopathy

**MUSCLES**

- ☐ Hypotonia
- ☐ Rhabdomyolysis
- ☐ Fixed weakness of skeletal muscle
- ☐ Ataxia

**OTHER**

- ☐ Clinical progression with stepwise exacerbation of symptoms
- ☐ Elevated alanine (PAA)
- ☐ Elevated 3-methylglutaconic acid (UOA)
- ☐ GI tract: pseudoobstruction
- ☐ GI tract: hepatopathy
- ☐ Lactic acidosis (in non-acute illness setting)
- ☐ Proximal renal tubulopathy (Fanconi syndrome)
- ☐ Sideroblastic anemia
- ☐ Short stature (<2 SD below normal)
- ☐ Type 2 diabetes mellitus
- ☐ Unexplained failure to thrive



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