Criteria for Genetic Testing Related to Epilepsy

Genetic Testing Advisory Committee (GTAC) Recommendation to the Ministry of Health and Long-Term Care

- GTAC recommends that genetics tests for epilepsy be publicly funded, under the conditions and per the criteria outlined in this report, including the patriation of all genetic testing for epilepsy to Ontario laboratories.

October 2016

Note: This publication is technical in nature and is available in English only due to its limited targeted audience. This publication has been exempted from translation under the French Language Services Act.

Remarque: Cette publication est de nature technique et est disponible en anglais uniquement en raison de son public cible limité. Cette publication a été exemptée de la traduction en vertu de la Loi sur les services en français.
About The Genetic Testing Advisory Committee

New genetic tests are being rapidly developed and promoted as high tech tools to improve diagnostic medicine and facilitate patient treatment. A formal evaluation process is required to assess the validity and effectiveness of new and existing genetic tests to better manage health care spending.

The Genetic Testing Advisory Committee (“GTAC”) was established in April 2014 with a three year mandate to review the clinical utility and validity of genetic tests and provide advice to the Ministry of Health and Long-Term Care (“ministry”) on the provision of genetic tests in Ontario. The creation of GTAC is in keeping with the direction of the Excellent Care for All Act and the Ontario Action Plan for Health Care to promote the delivery of high-quality health care based on the best available scientific and clinical evidence.

The purpose of GTAC is to review and provide reports on existing and new genetic tests. These reports, in addition to other factors (e.g. implementation feasibility, available funding and resources, system level impacts, and social and ethical factors) will guide the ministry’s decision-making on public funding of genetic tests in Ontario.

Review Process

The evaluation process for a genetic test is determined by whether the test is to be provided in Ontario or through the Out-of-Country (OOC) Program Exceptional Access process.

General Stream Process: Ontario Genetic Tests

1. Genetic test selection
2. Evidence-based analysis
   a. Literature review of clinical and academic publications on the genetic test
   b. Referral to an expert sub-committee
   c. GTAC deliberation of the available evidence
3. Draft GTAC report and recommendation prepared
4. Posting draft in Open for Comment
5. Assessment of stakeholder/public comments
6. Posting of finalized GTAC report and recommendations

Exceptional Access Process: OOC Genetic Test

1. OOC genetic test application/submission
2. Assign to appropriate GTAC member for evaluation and recommendation
3. OOC Response to requesting physician.

Website
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Appendix A: Epilepsy Genetic Testing Criteria Working Group ........................................................................ 18
1. Background

Epilepsy is a chronic disease that is characterized by recurrent unprovoked seizures. With a prevalence of 4-5 per 1000 persons, epilepsy is the second most common neurological condition, with approximately 75,000 adults and 15,000 children living with epilepsy in Ontario. The Ontario Brain Institute estimates there are approximately 6,100 new physician-diagnosed cases in Ontario each year (Ng R, et al. Brain Disorders in Ontario: Prevalence, Incidence, and Costs from Health Administrative Data. Toronto, ON: Institute for Clinic Eval Sci. 2015). While the exact proportion of epilepsies occurring secondary to monogenic and polygenic mutations is currently unknown, it is speculated that up to 75% of epilepsies have a genetic underpinning. In certain epileptic conditions, the likelihood of a genetic etiology may be even higher, particularly the epileptic encephalopathies. Given that genetic testing is indicated in patients with medically refractory epilepsy and that this group represents 30% of those with epilepsy, about 30% of cases, i.e. a potential ~ 1830 patients per year, could proceed to genetic testing.

The impact of a genetic diagnosis in a person with epilepsy can be quite significant. Accurate genetic diagnosis may direct treatment towards disease modifying therapies and/or medications known to be effective in certain epilepsy syndromes. Genetic diagnosis may also elucidate a prognosis and limit further investigations that have associated risks and cost. Similarly, a genetic diagnosis may spare patients the morbidity and society the costs, of unnecessary epilepsy surgery. Further, genetic diagnoses often help identify potential co-morbidities allowing for optimization of treatment and the avoidance of unnecessary morbidity. As well, with appropriate genetic diagnosis, genetic counseling for future pregnancies is often possible. Finally, a genetic diagnosis brings closure and peace of mind to the families of those with a genetic disease whether treatable or not.

A negative genetic result in the diagnostic evaluation of epilepsy also carries benefit. A negative test may allow the patient to proceed without delay towards critical therapies (such as epilepsy surgery) that would not be indicated in most genetic epilepsies. A negative genetic result therefore may avoid long delays to appropriate treatments, delays that result in poor outcomes.

Though a significant and growing body of literature implicates specific genes and mutations in particular epileptic conditions, there is little general guidance available on the circumstances in which genetic testing is indicated and test selection in order to guide optimal test appropriateness and benefit.

The following criteria have been developed to aid clinicians in determining the indications for genetic testing (focused gene panels, or comprehensive epilepsy gene panels) in adults and children with epilepsy.

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2 http://www.ices.on.ca/Publications/Atlases-and-Reports/2015/Brain-Disorders-in-Ontario


2. Expert Panel Objective

Given the above, GTAC convened an Expert Panel to document criteria that would aid clinicians in determining the indications for genetic testing in order to guide optimal test appropriateness and benefit.

This would include inclusion and exclusion criteria as well as recommendations for the use of different types of panel tests, guided by several factors:

- Diagnostic precision
- Cost
- Test Sensitivity
- Test Specificity and avoiding detection of variants of unknown significance (VUS)

The committee would like to thank the Expert Panel (see Appendix A) for their diligence and hard work in creating this report. The Committee endorses the Expert Panel’s full report, which is captured in the remainder of this document.

To ensure an open and transparent approach, the review process included extensive stakeholder consultation including:

- Input from academic centres in Ontario
- Input from broader neurology sector
- Public posting through the Committee’s website
3. Recommendation Summary

GTAC supports the Expert Panel recommendations, as follows:

1. Mandatory prerequisites for:
   a. referral to a District or Regional Epilepsy Centre for an epileptology consultation,
   b. genetics consultation if there are dysmorphic features, and
   c. consultation with a clinical biochemical geneticist or a physician with training in metabolic disorders if clinical features suggest an inborn error of metabolism.

2. Prerequisite diagnostic procedures for all patients as well as diagnostic procedures that are dependent upon clinical circumstance

3. Circumstances in which genetic testing is indicated

4. Conditions under which genetic testing is not indicated

5. Criteria and examples for:
   • single gene testing or focused gene panels that may be utilized when the genetic heterogeneity is considered low
   • focused gene panels to be used for potentially treatable conditions
   • gene panels to be used when the genetic heterogeneity is considered “high” and the diagnosis is “clear”
   • comprehensive epilepsy gene panels, or whole exome sequencing that are indicated when genetic heterogeneity is considered “high” and the clinical diagnosis is “unclear”

6. General limitations and considerations with NGS-based panel tests. These guidelines provide clarity to guide the reader as to which types of panels should be used depending upon the clinical circumstance coupled with the degree of genetic heterogeneity as outlined above. Rather than specifying which panels to use, options are provided for the clinician (epileptologist or geneticist) faced with a variety of clinical circumstances and genetic history.

Additionally GTAC supports the Expert Panel’s recommendations for future steps in order to maximize appropriate testing:

• Through the Epilepsy Implementation Task Force the working group could explore a role for epilepsy centres to act as a network promoting consultation between and amongst epileptologists to support optimal test selection for patients, regardless of geographic location.

• Patriotism of all genetic testing (including biochemical genetic tests) for epilepsy to Ontario laboratories. The working group would work with the ministry and Ontario laboratories on the development of smaller set of panels to cover circumstances in which genetic testing is indicated. Patriotism would also nurture important dialogue between clinicians and laboratory directors and personnel in test selection, analysis and interpretation.
4. **Circumstances that would indicate the need for genetic testing**

1. *When the clinical features (age of onset, seizure semiology, and EEG features) are consistent with a distinct electroclinical syndrome as defined by the International League Against Epilepsy (ILAE), with the exception of benign epilepsy syndromes (See 7 below).*
   
   For example:
   
   - Epileptic encephalopathies (Includes conditions such as Ohtahara syndrome, early onset myoclonic encephalopathy, West syndrome, malignant migrating partial seizures, etc.)
   - Seizures associated with a fever as major trigger (excluding patients meeting clinical criteria for simple febrile seizures). For example:
     - Dravet syndrome
     - Generalized epilepsy with febrile seizures plus
   - Idiopathic (genetic) generalized epilepsy (IGE) refractory to treatment. For example:
     - Early onset absence epilepsy
     - Myoclonic epilepsy where progressive, associated with neurocognitive regression, and/or is medically refractory

2. *When the prognosis based on clinical and EEG findings is poor or the likelihood of lethal outcome is high. For example:*

   - Increased frequency and/or severity of seizures, risk for sudden unexpected death of epilepsy (SUDEP)
   - Myoclonic epilepsy where progressive, associated with neurocognitive regression, and/or is medically refractory
   - Epileptic encephalopathies (poorly characterized on clinical and semiological grounds and a lack of distinctive features on the EEG)

3. *When epileptic seizures are refractory to medical treatment as defined by the ILAE.*

   - Any other form of IGE refractory to treatment (especially important when the differential includes IGE or a frontal lobe epilepsy with rapid, secondarily generalization)
   - Sporadic focal onset pharmaco-resistant epilepsy

4. *When epilepsy is associated with features suggestive of treatable inborn errors of metabolism.*

   - Clinical features strongly suggestive of an inborn error of metabolism, for example:
     - Family history of known condition
     - Parental consanguinity
     - Newborn or metabolic screening identifies a biochemical marker associated with “metabolic” epilepsy
Examples of important treatable conditions include (List is not complete):
  o Pyridoxine dependent epilepsy
  o Pyridoxal phosphate dependent epilepsy
  o Creatine deficiency syndromes
  o Glucose transporter (GLUT1) deficiency
  o Cerebral Folate deficiency

**Note:** Biochemical biomarkers are generally more sensitive than genomic approaches to ascertain these conditions; genomic testing should not be relied on in isolation to RULE OUT such conditions.

5. *When epilepsy is associated with distinctive patterns of malformations of cortical development identified on neuroimaging studies. For example:*

   - Hemimegalencephaly
   - Lissencephaly
   - Schizencephaly
   - Sub cortical band heterotopia (double cortex)
   - Cortical dysplasia with focal epilepsy
   - Opercular dysplasia/asymmetric, unilateral or bilateral
   - Holoprosencephaly
   - Agenesis of corpus callosum
   - Polymicrogyria
   - Periventricular heterotopia
   - Tuberous Sclerosis

6. *When epilepsy is associated with clinical signs of neurodegeneration. Neurodegeneration may manifest as:*

   - Developmental regression in children
   - Variable but progressive neurological symptoms of cognitive impairment, motor disability and/or other neurological signs and symptoms
   - Examples include:
     o Acquired Epileptic Aphasia (Landau Kleffner syndrome)
     o Epileptic encephalopathy with continuous spike wave activity in sleep
     o MECP2 duplication syndrome and Rett syndrome
     o Atypical Rolandic epilepsy with language deficits+/- cognitive disability
     o Progressive myoclonic epilepsies ((Unverricht-Lundborg, NCL, Lafora body, sialidosis)
7. *When epilepsy is associated with paroxysmal neurological features. For example:*

- Paroxysmal dyskinesias
- Episodic ataxias
- Hemiplegic migraine

8. *When epilepsy is associated with additional syndromic features such as developmental delay/ intellectual disability, multiple congenital anomalies, dysmorphic features. For example:*

- Angelman and Angelman-like syndromes
- Pitt-Hopkins syndrome
- Rett syndrome, and syndromes with Rett-like features
- Mowat Wilson
- X-linked Epilepsy with Mental Retardation
- Syndromic Mental Retardation associated with epilepsy
- Tuberous sclerosis
- Epilepsy with global developmental delays or autistic traits unspecified/or not classified

9. *When familial epilepsy is present, defined as at least 2 first-degree family members with related epilepsy syndromes, unless the epilepsy syndrome is benign as listed under 7 below.*
5. Requirements to proceed to focused gene panels or comprehensive epilepsy gene panels pursuant to the determination of a genetic diagnosis in adults and children with epilepsy.

- **Mandatory prerequisites**
  - If the epilepsy is uncontrolled, referral to, or consultation with, a District or Regional Epilepsy Centre for an epileptology consultation (consistent with Provincial Guidelines for the Management of Epilepsy in Adults and Children\(^5\)) is required.
  - If epilepsy is well controlled or if there are dysmorphic features, referral to a clinical geneticist is required.
  - If there is developmental regression or other clinical features suggestive of an inborn error of metabolism, consultation with a biochemical geneticist or a physician with training in inherited metabolic disorders is strongly recommended.

- **Diagnostic procedures that are always indicated before proceeding to focused gene panels, comprehensive epilepsy gene panels**
  - EEG +/- EEG video
  - Consult with epileptologist
  - MRI +/- MRS

- **Diagnostic procedures that are dependent upon clinical circumstance, but not required for progression to focused gene panels or comprehensive epilepsy gene panels**
  - Metabolic: These investigations should be tailored to the specific clinical presentation (consider consultation); commonly employed tests may include: MR spectroscopy, lactate, gas and lytes, glucose, ammonia, plasma and/or CSF amino acids, total homocysteine, urine organic acids, acylcarnitine profile, sulfite screen, urine S-sulfocysteine, uric acid, biotinidase, and/or urine alpha-aminoacidipic semialdehyde, other tests as clinically indicated.
  - Neonatal/infantile seizures: Consider trial of pyridoxine (B6), pyridoxal phosphate, and folinic acid.
  - Cerebrospinal fluid studies: routine cytology, glucose, lactate, amino acids, consider neurotransmitters.
  - Chromosomal microarray in presence of developmental delay/intellectual disabilities and/or dysmorphic features.
  - Any of these investigations may suggest a single gene test or a specific gene panel, for example, specific inborn error of metabolism gene, cortical malformation gene panel, or mitochondrial gene panel.
  - Note that if any of these tests are under consideration, or if the results will require additional expertise for interpretation, this may indicate a need for consultation with a clinical and/or biochemical geneticist.

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\(^5\)Epilepsy Implementation Task Force, Provincial Guidelines for the Management of Epilepsy in Adults and Children, Version 1.0, January 2015, Critical Care Services Ontario (accessed Feb 10, 2016) [https://www.criticalcareontario.ca/Provincial_Guidelines_for_the_Management_of_Epilepsy_in_Adults_and_Children](https://www.criticalcareontario.ca/Provincial_Guidelines_for_the_Management_of_Epilepsy_in_Adults_and_Children)
6. Criteria for focused gene panels or comprehensive epilepsy gene panels in adults and children with epilepsy pursuant to the determination of a genetic diagnosis.

- **If clinical diagnosis is clear and genetic heterogeneity is low, focused gene panels are indicated. For example:**
  - Dravet
  - Progressive myoclonic epilepsy
  - Cortical Malformation panel
  - Angelman-like syndrome
  - Rett-like syndrome

Examples of Panels are provided in Table 1

- **If a treatable epilepsy is under consideration, a STAT epilepsy panel focused on treatable conditions should be considered (e.g.: early onset epilepsy, in conjunction with or after biochemical markers have been tested). Examples of important treatable conditions include (List is not complete):**
  - Pyridoxine dependent epilepsy
  - Pyridoxal phosphate dependent epilepsy
  - Creatine deficiency syndromes
  - Glucose transporter (GLUT1) deficiency
  - Cerebral Folate deficiency
  - Serine biosynthesis disorders

Examples of available Panels are given in Table 2

- **Where the clinical diagnosis is clear and genetic heterogeneity is high (e.g. Lennox Gastaut, Infantile spasms, epileptic encephalopathies), but the clinical diagnosis is not indicative of a treatable condition either a focused gene panel or comprehensive epilepsy panel should be done. For example:**
  - Epileptic encephalopathies- (Ohtahara syndrome, Infantile spasms, malignant migrating partial seizures, Lennox Gastaut syndrome, Dravet syndrome)
Examples of available panels are provided in Table 3

- **If the clinical diagnosis is not clear and genetic heterogeneity is unknown, either a focused gene panel or comprehensive epilepsy panel should be done. For example:**
  
  o Seizures associated with a fever as major trigger—Febrile Seizures plus (Excluding patients meeting clinical criteria for simple febrile seizures)
    
    o Generalized epilepsy with febrile seizures plus
    o Epilepsy in females with mental retardation
  
  o Epilepsy syndromes associated with focal and multifocal seizures
    
    o Autosomal dominant nocturnal frontal lobe epilepsy
    o Familial temporal lobe epilepsy with auditory features
    o Familial focal epilepsy with variable foci
    o Sporadic Focal onset pharmacoresistant epilepsy
  
  o Epilepsy associated with regression/dysfunction in language/communication +/- development
    
    o Acquired Epileptic Aphasia (Landau Kleffner syndrome)
    o Epileptic encephalopathy with continuous spike wave activity in sleep
    o Atypical Rolandic epilepsy with language deficits +/- cognitive disability
    o Early onset progressive myoclonic epilepsy
  
  o Idiopathic (genetic) generalized epilepsy (IGE) refractory to treatment
    
    o Early onset absence epilepsy
    o Juvenile Myoclonic epilepsy where progressive, associated with neurocognitive regression, and/or medically refractory
    o Any other form of IGE refractory to treatment (especially important when the differential includes IGE or a frontal lobe epilepsy with rapid, secondarily generalization).

  Examples of Available Panels are given in Table 4

- **Epilepsies suggestive of mitochondrial diseases or in the context of mitochondrial diseases: please refer to the mitochondrial testing document [see http://www.newbornscreening.on.ca/sites/default/files/ontario_mitochondrial_disease_testing_requisition.pdf].**
7. Conditions that do not indicate a need for genetic testing

- Recognizable seizure syndrome with benign course
- Benign childhood epilepsy with central temporal spikes (previously termed benign rolandic epilepsy)
- Mesial temporal lobe epilepsy with hippocampal sclerosis
- Typical Childhood Absence epilepsy *(although if early onset or medically refractory should consider and test for GLUT1 deficiency)*
- Juvenile myoclonic epilepsy well controlled on medications and without intellectual disability or any signs of neurodegeneration
- Acquired Epilepsy (In these conditions, epilepsy is often associated with a primary neurological condition, which may or may not have a genetic basis, but the epilepsy is usually acquired.) Such conditions include:
  - Post traumatic epilepsy
  - Epilepsy secondary to neonatal-perinatal HIE and sequelae
  - Epilepsy associated with cerebral palsy related to periventricular leukomalacia (PVL)
  - Epilepsy secondary to brain tumors or systemic malignancy
  - Epilepsy associated with complications of chemotherapy, post-transplant immunosuppression
  - Epilepsy related to radiation therapy
  - Epilepsy related to infections of the central nervous system (CNS) (viral, bacterial, TB, fungal) and complications thereof
  - Epilepsy associated with CNS inflammation (autoimmune, vasculitis)
8. **General limitations and considerations with NGS-based panel tests**

- Coding regions +10-20 base pairs flanking exonic sequence are typically covered
- Coverage may not be 100% (though typically >97%)
- Depending on capture method, exon 1 is often poorly covered.
- Repeat sequence(s) present within exonic sequence may be difficult to call
- Copy number variants are also not reliably called
- Limited ability to detect mosaicism
- For many (most) panels the molecular diagnosis rate is not known
- Pre-test counselling regarding possible test outcomes is required before ordering genetic testing. This should include discussion of variants of uncertain significance, risk of incidental and/or secondary findings, and, as applicable, consent for return of incidental and/or secondary findings.
### Table 1. Examples of Panel Testing available when the genetic heterogeneity is considered low

<table>
<thead>
<tr>
<th>Company</th>
<th>Name of Test</th>
<th>No. Genes</th>
<th>ROI Coverage</th>
<th>Depth of Coverage</th>
<th>Variants of interest confirmed by sanger</th>
<th>Cost</th>
<th>Turn-around time</th>
<th>University Services</th>
<th>URL to information</th>
</tr>
</thead>
<tbody>
<tr>
<td>GeneDx</td>
<td>Progressive Myoclonic Epilepsy</td>
<td>17</td>
<td>100%</td>
<td>15x</td>
<td>yes</td>
<td>3340</td>
<td>4 week</td>
<td><a href="http://www.genedx.com/wp-content/uploads/crm_docs/info_sheet_epilepsy_prog.pdf">http://www.genedx.com/wp-content/uploads/crm_docs/info_sheet_epilepsy_prog.pdf</a></td>
<td></td>
</tr>
<tr>
<td>MNG</td>
<td>Comprehensive Neuronal Migration Disorders</td>
<td>111</td>
<td>97%</td>
<td>30x</td>
<td>as needed</td>
<td>1850</td>
<td>8 weeks</td>
<td><a href="http://www.medicalneurogenetics.com/OpenTestSearch/TestDetail.asp?Show=NGS387">http://www.medicalneurogenetics.com/OpenTestSearch/TestDetail.asp?Show=NGS387</a></td>
<td></td>
</tr>
<tr>
<td>Transgenomics</td>
<td>Rett/Atypical Rett/Angelman</td>
<td>16</td>
<td>&gt;99%</td>
<td>20x</td>
<td>yes</td>
<td>3920</td>
<td>12-16 weeks</td>
<td><a href="http://www.transgenomic.com/product/rettatypical%E2%80%90rettangelman%E2%80%90ngs%E2%80%90panel/">http://www.transgenomic.com/product/rettatypical‐rettangelman‐ngs‐panel/</a></td>
<td></td>
</tr>
<tr>
<td>Transgenomics</td>
<td>Tuberous Sclerosis Complex Panel</td>
<td>2</td>
<td>100%</td>
<td>na</td>
<td>na</td>
<td>3396</td>
<td>2-4 weeks</td>
<td><a href="http://www.transgenomic.com/product/tsc-tuberous-sclerosis-complex/">http://www.transgenomic.com/product/tsc-tuberous-sclerosis-complex/</a></td>
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</tr>
<tr>
<td>Fulgent</td>
<td>Rett/Angelman NGS Panel</td>
<td>18</td>
<td>98-99%</td>
<td>10x</td>
<td>as needed</td>
<td>1950</td>
<td>4-6 weeks</td>
<td><a href="http://fulgentdiagnostics.com/test/rett%E2%80%90angelman%E2%80%90ngs%E2%80%90panel/">http://fulgentdiagnostics.com/test/rett‐angelman‐ngs‐panel/</a></td>
<td></td>
</tr>
<tr>
<td>Athena Diagnostics</td>
<td>Epilepsy Advanced Sequencing Evaluation - Neuronal Migration disorders</td>
<td>29</td>
<td>100%</td>
<td>20x</td>
<td>as needed</td>
<td>2995</td>
<td>4-6 weeks</td>
<td><a href="http://athenadiagnostics.com/ViewFullCatalog/epilepsy-advanced-sequencing-evaluation-neuronal-m">http://athenadiagnostics.com/ViewFullCatalog/epilepsy-advanced-sequencing-evaluation-neuronal-m</a></td>
<td></td>
</tr>
<tr>
<td>Athena Diagnostics</td>
<td>Complete Tuberous Sclerosis Evaluation</td>
<td>2</td>
<td>100%</td>
<td>20x</td>
<td>as needed</td>
<td>2995</td>
<td>4-6 weeks</td>
<td><a href="http://athenadiagnostics.com/ViewFullCatalog/complete-tuberous-sclerosis-evaluation">http://athenadiagnostics.com/ViewFullCatalog/complete-tuberous-sclerosis-evaluation</a></td>
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<tr>
<td>University of Chicago Genetic services</td>
<td>Angelman syndrome Testing (Tier2)</td>
<td>4</td>
<td>100%</td>
<td>15x</td>
<td>na</td>
<td>4400</td>
<td>4 weeks</td>
<td><a href="http://dnatesting.uchicago.edu/sites/default/files/01AS_67.pdf">http://dnatesting.uchicago.edu/sites/default/files/01AS_67.pdf</a></td>
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<tr>
<td>University of Chicago Genetic services</td>
<td>Rett/Angelman</td>
<td>21</td>
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<td>15x</td>
<td>yes</td>
<td>4400</td>
<td>6-8 weeks</td>
<td><a href="http://dnatesting.uchicago.edu/sites/default/files/01%20NGS%20Rett%20Angelman_10.pdf">http://dnatesting.uchicago.edu/sites/default/files/01%20NGS%20Rett%20Angelman_10.pdf</a></td>
<td></td>
</tr>
<tr>
<td>University of Chicago Genetic services</td>
<td>Brain Malformation - Cerebral Cortical Malformation</td>
<td>46</td>
<td>100%</td>
<td>15x</td>
<td>yes</td>
<td>3900</td>
<td>8 weeks</td>
<td><a href="http://dnatesting.uchicago.edu/sites/default/files/01%20NGS%20Brain_Malformation_1.pdf">http://dnatesting.uchicago.edu/sites/default/files/01%20NGS%20Brain_Malformation_1.pdf</a></td>
<td></td>
</tr>
<tr>
<td>University of Chicago Genetic services</td>
<td>Brain Malformation - Holoproencephal y</td>
<td>9</td>
<td>100%</td>
<td>15x</td>
<td>yes</td>
<td>3500</td>
<td>8 weeks</td>
<td><a href="http://dnatesting.uchicago.edu/sites/default/files/01%20NGS%20Holoproencephal">http://dnatesting.uchicago.edu/sites/default/files/01%20NGS%20Holoproencephal</a> y_1.pdf</td>
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<tr>
<td>University of Chicago Genetic services</td>
<td>Brain Malformation - Lissencephaly</td>
<td>26</td>
<td>100%</td>
<td>15x</td>
<td>yes</td>
<td>6000</td>
<td>8 weeks</td>
<td><a href="http://dnatesting.uchicago.edu/sites/default/files/01%20NGS%20Lissencephal">http://dnatesting.uchicago.edu/sites/default/files/01%20NGS%20Lissencephal</a> y_13.pdf</td>
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<tr>
<td>University of Chicago Genetic services</td>
<td>Brain Malformation - Polymicrogyria</td>
<td>15</td>
<td>100%</td>
<td>15x</td>
<td>yes</td>
<td>3700</td>
<td>8 weeks</td>
<td><a href="http://dnatesting.uchicago.edu/sites/default/files/01%20NGS%20Polymicrogyria_66.pdf">http://dnatesting.uchicago.edu/sites/default/files/01%20NGS%20Polymicrogyria_66.pdf</a></td>
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<td>na</td>
<td>na</td>
<td>4400</td>
<td>4 weeks</td>
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<td>Centogene</td>
<td>Dravet syndrome</td>
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<td>100%</td>
<td>30x</td>
<td>yes</td>
<td>1676</td>
<td>3 weeks</td>
<td><a href="https://www.centogene.com/centogene/inc/testCatalogueDetail/factsheet/5100_Dravet_syndrome_panel_V1.pdf">https://www.centogene.com/centogene/inc/testCatalogueDetail/factsheet/5100_Dravet_syndrome_panel_V1.pdf</a></td>
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<td>Neuronal Migration disorder Panel</td>
<td>43</td>
<td>100%</td>
<td>30x</td>
<td>yes</td>
<td>4400</td>
<td>5 weeks</td>
<td><a href="https://www.centogene.com/centogene/inc/centogene-test-catalogue-detail.php?test=NGS&amp;Id=20122&amp;search=Neuronal_migration_disorders_panel">https://www.centogene.com/centogene/inc/centogene-test-catalogue-detail.php?test=NGS&amp;Id=20122&amp;search=Neuronal_migration_disorders_panel</a></td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Example of Panel Testing available for potentially treatable conditions (for example, GLUT1 testing)

<table>
<thead>
<tr>
<th>Company</th>
<th>Name of Test</th>
<th>No. Genes</th>
<th>ROI Coverage</th>
<th>Depth of Coverage</th>
<th>Variants of interest confirmed by Sanger</th>
<th>Cost</th>
<th>Turn-around-time</th>
<th>Sanger sequencing available</th>
<th>URL to information</th>
</tr>
</thead>
<tbody>
<tr>
<td>GeneDx</td>
<td>STAT Epilepsy Panel</td>
<td>18</td>
<td>100%</td>
<td>15x</td>
<td>yes</td>
<td>3824</td>
<td>2 weeks</td>
<td>Yes</td>
<td><a href="http://www.genedx.com/wp-content/uploads/2014/10/info_sheet_STAT_Epilepsy1.pdf">http://www.genedx.com/wp-content/uploads/2014/10/info_sheet_STAT_Epilepsy1.pdf</a></td>
</tr>
</tbody>
</table>

Table 3. Examples of Panel Testing when the genetic heterogeneity is considered “high” and the diagnosis “clear” (for example, early infantile epilepsy encephalopathy)

<table>
<thead>
<tr>
<th>Company</th>
<th>Name of Test</th>
<th>No. Genes</th>
<th>Pick-up rate</th>
<th>ROI Coverage</th>
<th>Depth of Coverage</th>
<th>Variants of interest confirmed by Sanger</th>
<th>Cost</th>
<th>Turn-around-time</th>
<th>Sanger sequencing available</th>
<th>URL to information</th>
</tr>
</thead>
<tbody>
<tr>
<td>GeneDx</td>
<td>Infantile Epilepsy Panel</td>
<td>53</td>
<td>22%</td>
<td>100%</td>
<td>15x</td>
<td>yes</td>
<td>3824</td>
<td>4 weeks</td>
<td>Yes</td>
<td><a href="http://www.genedx.com/wp-content/uploads/crm_docs/info_sheet_epilepsy_info.pdf">http://www.genedx.com/wp-content/uploads/crm_docs/info_sheet_epilepsy_info.pdf</a></td>
</tr>
<tr>
<td>MNG</td>
<td>Epileptic Encephalopathy</td>
<td>80</td>
<td>--</td>
<td>97%</td>
<td>30x</td>
<td>as needed</td>
<td>1200</td>
<td>8 weeks</td>
<td>yes</td>
<td><a href="http://www.medicalneurogenetics.com/OpenTestSearch/TestDetail.aspx?code=NGS386">http://www.medicalneurogenetics.com/OpenTestSearch/TestDetail.aspx?code=NGS386</a></td>
</tr>
<tr>
<td>Athena Diagnostics</td>
<td>Epilepsy Advanced Sequencing Evaluation - Epileptic encephalopathies</td>
<td>31</td>
<td>--</td>
<td>100%</td>
<td>20x</td>
<td>as needed</td>
<td>2995</td>
<td>4-6 weeks</td>
<td>yes</td>
<td><a href="http://athenadiagnostics.com/view-full-catalog/e/epilepsy-advanced-sequencing-evaluation-epileptic">http://athenadiagnostics.com/view-full-catalog/e/epilepsy-advanced-sequencing-evaluation-epileptic</a></td>
</tr>
<tr>
<td>Prevention</td>
<td>Early Epileptic Encephalopathy Nextgen sequencing</td>
<td>66</td>
<td>--</td>
<td>100%</td>
<td>20x</td>
<td>yes</td>
<td>2327.5</td>
<td>3-4 weeks (up to 45 days)</td>
<td>yes</td>
<td><a href="https://www.preventiongenetics.com/clinical-dna-testing/test/early-infantile-epileptic-encephalopathy-nextgen-sequencing-NGS-panel/2891/">https://www.preventiongenetics.com/clinical-dna-testing/test/early-infantile-epileptic-encephalopathy-nextgen-sequencing-NGS-panel/2891/</a></td>
</tr>
<tr>
<td>University of Chicago Genetic services</td>
<td>Early Infantile Epileptic Encephalopathy</td>
<td>30</td>
<td>--</td>
<td>100%</td>
<td>15x</td>
<td>yes</td>
<td>4500</td>
<td>8 weeks</td>
<td>yes</td>
<td><a href="http://dhating.uchicago.edu/sites/default/files/01%20NS%20IEE_20.pdf">http://dhating.uchicago.edu/sites/default/files/01%20NS%20IEE_20.pdf</a></td>
</tr>
<tr>
<td>Centogene</td>
<td>Early Infantile Epileptic Encephalopathy</td>
<td>14</td>
<td>--</td>
<td>100%</td>
<td>30x</td>
<td>yes</td>
<td>4,087</td>
<td>3 weeks</td>
<td>yes</td>
<td><a href="https://www.centogene.com/centogene/inc/testCatalogDetail/factsheet/5026_IEE_panel_V1.pdf">https://www.centogene.com/centogene/inc/testCatalogDetail/factsheet/5026_IEE_panel_V1.pdf</a></td>
</tr>
</tbody>
</table>

ROI Coverage: when 100%, implies a Sanger sequencing panel or that Sanger sequencing was used to cover regions of poor coverage in an NGS panel
Table 4. Examples of Panel Testing when genetic heterogeneity is considered “high” and the clinical diagnosis is “unclear”

<table>
<thead>
<tr>
<th>Company</th>
<th>Name of Test</th>
<th>No. Genes</th>
<th>Pick-up rate</th>
<th>ROI Coverage</th>
<th>Depth of Coverage</th>
<th>Variants of interest confirmed by sanger</th>
<th>Cost</th>
<th>Turn-around time</th>
<th>Sanger sequencing available</th>
<th>URL to information</th>
</tr>
</thead>
<tbody>
<tr>
<td>GeneDx</td>
<td>Comprehensive Epilepsy Panel</td>
<td>70</td>
<td>16%</td>
<td>100%</td>
<td>15x</td>
<td>yes</td>
<td>4600</td>
<td>4 weeks</td>
<td>Yes</td>
<td><a href="http://www.genedx.com/wp-content/uploads/crm_docs/info_sheet_epilepsy_comp.pdf">http://www.genedx.com/wp-content/uploads/crm_docs/info_sheet_epilepsy_comp.pdf</a></td>
</tr>
<tr>
<td>GeneDx</td>
<td>Childhood Onset Epilepsy</td>
<td>50</td>
<td>--</td>
<td>100%</td>
<td>15x</td>
<td>yes</td>
<td>3924</td>
<td>4 weeks</td>
<td>Yes</td>
<td><a href="http://www.genedx.com/wp-content/uploads/crm_docs/info_sheet_epilepsy_child.pdf">http://www.genedx.com/wp-content/uploads/crm_docs/info_sheet_epilepsy_child.pdf</a></td>
</tr>
<tr>
<td>MNG</td>
<td>Comprehensive Epilepsy</td>
<td>168</td>
<td>--</td>
<td>&gt;97%</td>
<td>30x</td>
<td>as needed</td>
<td>1850</td>
<td>8 weeks</td>
<td>Yes</td>
<td><a href="http://www.medicalneurogenetics.com/topics/what/NGS/NGS3560">http://www.medicalneurogenetics.com/topics/what/NGS/NGS3560</a></td>
</tr>
<tr>
<td>Transgenomics</td>
<td>Comprehensive Epilepsy Evaluation</td>
<td>377</td>
<td>--</td>
<td>&gt;97%</td>
<td>20x</td>
<td>yes</td>
<td>4130</td>
<td>16 weeks</td>
<td>Yes</td>
<td><a href="http://www.transgenomic.com/product/comprehensive-epilepsy-evaluation-panels/">http://www.transgenomic.com/product/comprehensive-epilepsy-evaluation-panels/</a></td>
</tr>
<tr>
<td>Transgenomics</td>
<td>Febrile seizure panel</td>
<td>6</td>
<td>--</td>
<td>100%</td>
<td>na</td>
<td>n/a</td>
<td>4,200</td>
<td>2-4 weeks</td>
<td>Yes</td>
<td><a href="http://www.transgenomic.com/product/febrile-seizure-panel/">http://www.transgenomic.com/product/febrile-seizure-panel/</a></td>
</tr>
<tr>
<td>Transgenomics</td>
<td>Female febrile panel</td>
<td>7</td>
<td>--</td>
<td>100%</td>
<td>na</td>
<td>n/a</td>
<td>4,725</td>
<td>2-4 weeks</td>
<td>Yes</td>
<td><a href="http://www.transgenomic.com/product/female-febrile-seizure-panel/">http://www.transgenomic.com/product/female-febrile-seizure-panel/</a></td>
</tr>
<tr>
<td>Fulgent</td>
<td>Epilepsy NGS Panel</td>
<td>343</td>
<td>--</td>
<td>90-99%</td>
<td>10x</td>
<td>as needed</td>
<td>1950</td>
<td>4-6 weeks</td>
<td>Yes</td>
<td><a href="http://fulgentdiagnostics.com/test/epilepsy-agnostic-panel/">http://fulgentdiagnostics.com/test/epilepsy-agnostic-panel/</a></td>
</tr>
<tr>
<td>Athena Diagnostics</td>
<td>Epilepsy Advanced Sequencing Evaluation</td>
<td>141</td>
<td>--</td>
<td>100%</td>
<td>20x</td>
<td>as needed</td>
<td>3495</td>
<td>4-6 weeks</td>
<td>Yes</td>
<td><a href="http://athenadiagnostics.com/view-full-catalog/epilepsy-advanced-sequencing-evaluation#section1">http://athenadiagnostics.com/view-full-catalog/epilepsy-advanced-sequencing-evaluation#section1</a></td>
</tr>
<tr>
<td>Athena Diagnostics</td>
<td>Epilepsy Advanced Sequencing Evaluation - Generalized, absence, focal, myoclonic</td>
<td>36</td>
<td>--</td>
<td>100%</td>
<td>20x</td>
<td>as needed</td>
<td>2995</td>
<td>4-6 weeks</td>
<td>Yes</td>
<td><a href="http://athenadiagnostics.com/view-full-catalog/epilepsy-advanced-sequencing-evaluation-generalizing">http://athenadiagnostics.com/view-full-catalog/epilepsy-advanced-sequencing-evaluation-generalizing</a></td>
</tr>
<tr>
<td>Athena Diagnostics</td>
<td>Epilepsy Advanced Sequencing Evaluation - Syndromic</td>
<td>26</td>
<td>--</td>
<td>100%</td>
<td>20x</td>
<td>as needed</td>
<td>2995</td>
<td>4-6 weeks</td>
<td>Yes</td>
<td><a href="http://athenadiagnostics.com/view-full-catalog/epilepsy-advanced-sequencing-evaluation-syndromic">http://athenadiagnostics.com/view-full-catalog/epilepsy-advanced-sequencing-evaluation-syndromic</a></td>
</tr>
<tr>
<td>Athena Diagnostics</td>
<td>Epilepsy Advanced Sequencing Evaluation - Infantile spasms</td>
<td>10</td>
<td>--</td>
<td>100%</td>
<td>20x</td>
<td>as needed</td>
<td>2495</td>
<td>4-6 weeks</td>
<td>Yes</td>
<td><a href="http://athenadiagnostics.com/view-full-catalog/epilepsy-advanced-sequencing-evaluation-infantilespasms">http://athenadiagnostics.com/view-full-catalog/epilepsy-advanced-sequencing-evaluation-infantilespasms</a></td>
</tr>
<tr>
<td>Athena Diagnostics</td>
<td>Epilepsy Advanced Sequencing Evaluation - XL Intellectual disability</td>
<td>27</td>
<td>--</td>
<td>100%</td>
<td>20x</td>
<td>as needed</td>
<td>2495</td>
<td>4-6 weeks</td>
<td>Yes</td>
<td><a href="http://athenadiagnostics.com/view-full-catalog/epilepsy-advanced-sequencing-evaluation-xlintellecaldisability">http://athenadiagnostics.com/view-full-catalog/epilepsy-advanced-sequencing-evaluation-xlintellecaldisability</a></td>
</tr>
<tr>
<td>Prevention</td>
<td>Early Epileptic Encephalopathy, Reccessive Nextgen sequencing</td>
<td>40</td>
<td>--</td>
<td>100%</td>
<td>20x</td>
<td>yes</td>
<td>1,653</td>
<td>3-4 weeks</td>
<td>yes</td>
<td><a href="https://www.preventiongenetics.com/clinical-dna-testing/test/early-infantinepileptic-encephalopathy-recessive-nextgen-sequencing-ngs-panel/2747">https://www.preventiongenetics.com/clinical-dna-testing/test/early-infantinepileptic-encephalopathy-recessive-nextgen-sequencing-ngs-panel/2747</a></td>
</tr>
<tr>
<td>University of Chicago Genetic services</td>
<td>Infantile and Childhood Epilepsy sequencing</td>
<td>94</td>
<td>--</td>
<td>100%</td>
<td>15x</td>
<td>yes</td>
<td>5000</td>
<td>8 weeks</td>
<td>yes</td>
<td><a href="http://dnatesting.uchicago.edu/sites/default/files/01520.NGS%20Epilepsy_B.pdf">http://dnatesting.uchicago.edu/sites/default/files/01520.NGS%20Epilepsy_B.pdf</a></td>
</tr>
<tr>
<td>Centogene</td>
<td>Epilepsy (absence) in childhood panel</td>
<td>6</td>
<td>--</td>
<td>100%</td>
<td>30x</td>
<td>yes</td>
<td>1,261</td>
<td>3 weeks</td>
<td>Yes</td>
<td><a href="https://www.centogene.com/centogene-centogene-test-catalogue-detail.php?test=NGS&amp;ID=20065&amp;disease=Epilepsy_(absence)_in_childhood_panel">https://www.centogene.com/centogene-centogene-test-catalogue-detail.php?test=NGS&amp;ID=20065&amp;disease=Epilepsy_(absence)_in_childhood_panel</a></td>
</tr>
<tr>
<td>Centogene</td>
<td>Epilepsy (generalized) with febrile seizures</td>
<td>6</td>
<td>--</td>
<td>100%</td>
<td>30x</td>
<td>yes</td>
<td>1,857</td>
<td>3 weeks</td>
<td>Yes</td>
<td><a href="https://www.centogene.com/centogene-centogene-test-catalogue-detail.php?test=NGS&amp;ID=20067&amp;disease=Epilepsy_(generalized)_with_febrele_seizures_panel">https://www.centogene.com/centogene-centogene-test-catalogue-detail.php?test=NGS&amp;ID=20067&amp;disease=Epilepsy_(generalized)_with_febrele_seizures_panel</a></td>
</tr>
<tr>
<td>Centogene</td>
<td>Epilepsy (partial) hereditary panel</td>
<td>27</td>
<td>--</td>
<td>100%</td>
<td>30x</td>
<td>yes</td>
<td>4,400</td>
<td>3 weeks</td>
<td>Yes</td>
<td><a href="https://www.centogene.com/centogene-centogene-test-catalogue-detail.php?test=NGS&amp;ID=20069&amp;disease=Epilepsy_(partial)_hereditary_panel">https://www.centogene.com/centogene-centogene-test-catalogue-detail.php?test=NGS&amp;ID=20069&amp;disease=Epilepsy_(partial)_hereditary_panel</a></td>
</tr>
<tr>
<td>Courtagen</td>
<td>epISEEK Comprehensive</td>
<td>447</td>
<td>--</td>
<td>98.40%</td>
<td>20x</td>
<td>as needed</td>
<td>4,110</td>
<td>4-6 weeks</td>
<td>Yes</td>
<td><a href="http://www.courtagen.com/test-menu-genetic-test-episeek.htm">http://www.courtagen.com/test-menu-genetic-test-episeek.htm</a></td>
</tr>
<tr>
<td>Courtagen</td>
<td>epISEEK Focus</td>
<td>76</td>
<td>--</td>
<td>96%</td>
<td>20x</td>
<td>as needed</td>
<td>3,375</td>
<td>4-6 weeks</td>
<td>Yes</td>
<td><a href="http://www.courtagen.com/test-menu-episeek-focus.htm">http://www.courtagen.com/test-menu-episeek-focus.htm</a></td>
</tr>
</tbody>
</table>
### Appendix A: Epilepsy Genetic Testing Criteria Working Group

<table>
<thead>
<tr>
<th>Name</th>
<th>Role</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Carter Snead III</td>
<td>Paediatric Neurologist</td>
<td>The Hospital for Sick Children, University of Toronto</td>
</tr>
<tr>
<td>Dr. Danielle Andrade</td>
<td>Neurologist</td>
<td>University Health Network (Toronto Western Hospital), The Hospital for Sick Children, University of Toronto.</td>
</tr>
<tr>
<td>Dr. Elizabeth Donner</td>
<td>Pediatric Neurologist</td>
<td>Hospital for Sick Children, University of Toronto.</td>
</tr>
<tr>
<td>Dr. David Dyment</td>
<td>Medical Geneticist</td>
<td>Children’s Hospital of Eastern Ontario, University of Ottawa</td>
</tr>
<tr>
<td>Dr. Asuri Narayan Prasad</td>
<td>Pediatric Neurologist</td>
<td>Children’s Hospital, London Health Sciences Centre, University of Western Ontario</td>
</tr>
<tr>
<td>Dr. Sharan Goobie</td>
<td>Medical Geneticist</td>
<td>Children’s Hospital, London Health Sciences Centre, University of Western Ontario</td>
</tr>
<tr>
<td>Dr. Kym Boycott</td>
<td>Medical Geneticist</td>
<td>Children’s Hospital of Eastern Ontario, University of Ottawa</td>
</tr>
<tr>
<td>Dr. Matthew Lines</td>
<td>Medical Geneticist</td>
<td>Children’s Hospital of Eastern Ontario, University of Ottawa</td>
</tr>
</tbody>
</table>