**Letter of Medical Necessity for Rett/Angelman Syndrome Panel**

**Patient Information**

**Date:**

**Patient Name:**

**Patient DOB:**

**Insurance Company Name, Address, City, State:**

**Policy Number:**

**Group Number:**

**ICD10 Codes:**

**Test Information**

**Test Name:** Rett/Angelman Syndrome Panel

**CPT Codes:** 81302x1, 81304x1, 81404x1, 81405x2, 81406x2

**Laboratory:**

GeneDx, Inc.

(NPI#1487632998 / TAXID#205446298 / CLIA#21D0969951)

207 Perry Parkway

Gaithersburg, MD 20877

Telephone: (301) 519-2100

Fax: (201) 421-2010

This letter is in regards to my patient, [FIRST NAME LAST NAME], to request full coverage for the Rett/Angelman Syndrome Panel to be performed by GeneDx. It is my professional determination that testing is medically necessary and will have a direct impact on this patient’s treatment and management.

**Patient Clinical and Family History**

This testing is requested due to this patient’s personal medical history, which includes the following clinical findings:

* Add Phenotype
* Add Phenotype
* Add Phenotype

The patient’s family history is negative for related conditions / unknown / remarkable for the following related clinical features:

The patient has previously had the following uninformative genetic and other testing:

* Add test
* Add test
* Add test

**Clinical Evidence and Guidelines for Testing**

The Rett/Angelman Syndrome Panel includes germline analysis of genes causing neurodevelopmental disorders with overlapping clinical presentations. Panel testing includes sequencing and deletion/duplication analysis of multiple genes as well as simultaneous methylation-sensitive MLPA testing to evaluate for methylation abnormalities causing Angelman syndrome.

The Rett/Angelman Syndrome Panel targets genes causing Rett syndrome, Angelman syndrome, and several other disorders with overlapping clinical features, including Pitt-Hopkins syndrome. Although the clinical features of these disorders may overlap, the prognosis and medical management depend on the specific diagnosis, and these some of these disorders are progressive. Therefore, early diagnosis is essential to allow optimal direct and supportive care, including allowing indicated monitoring that can ameliorate morbidity and prevent early mortality.1

These disorders are inherited in an autosomal dominant, autosomal recessive, or X-linked manner and have overlapping presentations. Genetic testing is useful to help confirm a diagnosis of a specific syndrome and can elucidate the specific genetic cause for the disorder, which has important implications for medical management. Additionally, genetic testing can help individuals avoid other expensive, invasive, and potentially risky diagnostic testing, such as lumbar puncture, muscle biopsy, video EEG, and multiple imaging studies.1,2 Due to the heterogeneous nature of these conditions and the significant overlap in clinical symptoms among individuals with different types of movements and seizures, multi-gene panels result in a higher diagnostic yield than traditional diagnostic methods and single gene testing.1,2

**Patient Clinical Utility and Medical Management Implications**

Knowing the specific genetic etiology can provide essential information about prognosis and can assist with decisions about treatment and management. For example, individuals with variants in *TCF4, NRXN1*, or *CNTNAP2* respond optimally to sodium valproate to improve abnormal respiratory patterns including frequent apneic episodes associated with hypoxemia.3 Additionally, daily treatment with acetazolamide can decrease frequency and duration of hyperventilatory and apneic episodes and improved oxygen saturation.4 Molecular genetic testing is also critical for determining appropriate treatment for individuals with Rett and Rett-like syndrome since patients with pathogenic variants in *MECP2* should consider the use of beta-blockers or cardiac pacing due to their risk for prolonged QTc.1 Surveillance for urogenital anomalies, congenital heart defects, eye anomalies, and Hirschsprung disease is recommended for individuals with pathogenic variants in the *ZEB2* gene causing Mowat-Wilson syndrome so that appropriate medical and/or surgical care can be instituted in order to avoid significant morbidity and mortality.5 Individuals with Angelman syndrome should avoid anticonvulsants that increase GABA levels in the brain, including vigabatrin, tigabine, and carbamazepine, which can induce non-convulsive status epilepticus or onset of new seizure types.6

Specifically for this patient, the results of this test will also {ADD ADDITIONAL INFORMATION}

**Summary**

The Rett/Angelman Syndrome Panel at GeneDx is a highly sensitive and cost-effective genetic test. I am requesting coverage for this medically necessary test in order to establish appropriate medical management for this patient. Without testing, treatment would be suboptimal, subjecting this patient to increased morbidity and potentially early mortality.

Thank you for your review and consideration. If you have questions, or if I can be of further assistance, please do not hesitate to call me at (XXX) XXX-XXXX.

Sincerely,

Signature

Ordering Provider’s Name

References:

1. Christodoulou J, Ho G. MECP2-Related Disorders. 2001 Oct 3 [Updated 2012 Jun 28]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1497/>
2. Van Buggenhout and Frynes (2009) Angelman syndrome (AS, MIM 105830). *Eur J Hum Genet* 17:1367-1373 (PMID: 19455185)
3. Maini et al., (2012) Clinical and polygraphic improvement of breathing abnormalities after valproate in a case of Pitt-Hopkins syndrome. J Child Neuro 27:1585-1588. (PMID: 22378662)
4. Verhulst et al., (2012) Acetazolamide for severe apnea in Pitt-Hopkins syndrome. Am J Med Genet 158A:932-934. (PMID: 22407847)
5. Adam MP, Conta J, Bean LJH. Mowat-Wilson Syndrome. 2007 Mar 28 [Updated 2019 Jul 25]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1412/>
6. Dagli AI, Mueller J, Williams CA. Angelman Syndrome. 1998 Sep 15 [Updated 2017 Dec 21]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1144/>