**Letter of Medical Necessity for Exome Sequencing**

**Instructions for Health Care Practitioner:**

1. This letter template is being provided as a tool to clinicians to assist in communication with payers.
2. The template is to be printed on the physician’s letterhead.
3. Specific patient information must be included in the following letter in order for this to be effective.
4. The areas that must be edited/deleted are indicated in grey on the template.

Exome Sequencing/Whole Exome Sequencing

(Test Codes: 36935 Proband, 36936 Trio, 36938 Reanalysis)

<Date>

ATTN: <Medical Director/ Physician Name>, M.D.

 <Institution/Insurance Company>

 <Street Address>

 <City>**,** <State> <Zip>

RE: <Patient Name>

DOB: <MM/DD/YYYY>

Member ID: <Insurance ID Number>

Group #: <Enter Group #>

Dear Doctor <Medical Director/ Physician Name>:

I am writing this letter on behalf of my patient <Patient Name> to request that you approve whole exome testing as part of his/her care. I strongly suspect the cause of his/her condition is genetic and, if so, knowing which gene(s) are involved is likely to impact the management of his/her care in ways described below. I am choosing exome testing at this juncture over targeted genetic testing because <**CHOOSE ONE**: no targeted genetic test is well suited for this phenotype – **OR** –targeted gene testing was done and found to be negative>.

<Patient Name> is a <age>-year-old <gender > with <list symptoms and clinical findings>.

1. <Symptom #1 with ICD-10 code>

2. <Symptom #2 with ICD-10 code>

…

<Add family history if relevant –

* Family history is negative suggesting either a de novo genetic variant or an autosomal recessive disease. **OR**
* Family history is significant for (insert information), which provides further evidence that this condition has genetic underpinnings.>

This patient has received genetic counseling regarding the benefits and risks of whole exome sequencing.

**Rationale for Testing**

Exome testing has been shown to be successful at identifying the genetic cause of conditions when patients have multiple congenital anomalies and/or neurodevelopmental disorders, as is the case with this patient. Detection rates range from about 28.8% to as high as 57.5% for this patient population.1-7 Furthermore, in those with a genetic cause identified by exome testing, 20.9% to 49% of patients had a change in their management based on the exome results.1,8,9 Additionally, a molecular diagnosis often obviates the need for future medical procedures and/or testing that otherwise would have been ordered such as <insert examples of prior and potential future procedures and testing such as exploratory or corrective surgeries, imaging studies, specialty referrals, laboratory studies, pharmaceutical trial and error, psychoeducational evaluations>. Furthermore, in some instances, this utility includes an end to the costly diagnostic odyssey <and/or switch to palliative care>.

In addition to clinical impact, this exome testing may also reduce the overall health care costs for this patient. Cost savings are supported by multiple domestic and international studies. One study indicated that savings were independent of a positive exome result, suggesting that a definitive exome result ends the diagnostic odyssey even when results are negative.10 Another study comparing panel testing to exome found that almost 23% of patients would not have received a genetic diagnosis without exome analysis.11

I anticipate one or more of the following benefits from this test for this patient:

1. obtain a diagnosis for phenotype,
2. avoid additional unnecessary and costly procedures,
3. end the diagnostic odyssey, and/or
4. inform best treatment therapy.

In conclusion, I am requesting that <Patient Name> be approved for the exome testing Test Code 36935 Proband, or 36936 Trio, or 36938 Reanalysis offered by Quest Diagnostics. Quest Diagnostics is particularly well suited to perform this exome for this patient for the following reasons:

1. Their test has the ability to detect both sequence variations and copy number variants in the same test, which increases the likelihood of determining the genetic underpinnings of this disorder. Not all laboratories offer this ability to detect copy number variations as part of this test. Studies have demonstrated about 2% positive detection rate for copy number variations.12,13
2. Quest includes mitochondrial genome testing as part of their exome test.
3. Genetic counselors and other medical and genetic staff are involved in collecting and reviewing the phenotype type data, which is crucial for interpretation.
4. Peer-reviewed standardized DNA Variant Scoring system for pathogenicity assessments in Mendelian disorders that aligns with ACMG and AMP guidelines.14
5. <If family members are available and you plan to order a trio, include this sentence>. Lastly, both family members of this patient are available to aid in the interpretation and Quest’s exome test allows me to order this test as a trio, which increases the likelihood of a meaningful genetic interpretation.3

I hope you will support this letter of medical necessity for <Patient Name>. Please feel free to contact me at <Physician Phone> if you have additional questions.

Sincerely,

<Physician Name>, MD

NPI #: <Physician NPI#>

Contact information:

< Address>

<City>**,** <State>, <Zip>

Contact Phone No.: <phone number>

Test codes/CPT codes: Proband 36935/81415, Trio 36936/81415 and 81416x2, Reanalysis 36938/81417

The CPT codes provided are based on AMA guidelines and are for informational purposes only. CPT coding is the sole responsibility of the billing party. Please direct any questions regarding coding to the payer being billed.

**References:**

**1.** Iglesias A, Anyane-Yeboa K, Wynn J, et al. The usefulness of whole-exome sequencing in routine clinical practice. *Genet Med.* 2014;16:922-931. doi: 10.1038/gim.2014.58.

**2.** Valencia CA, Husami A, Holle J, et al. Clinical impact and cost-effectiveness of whole exome sequencing as a diagnostic tool: a pediatric center's experience. *Front Pediatr.* 2015;3:67. doi:

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**3.** Retterer K, Scuffins J, Schmidt D, et al. Assessing copy number from exome sequencing and exome array CGH based on CNV spectrum in a large clinical cohort. *Genet Med.* 2015;17:623-629. doi: 10.1038/gim.2014.160

**4.** Stark Z, Tan TY, Chong B, et al. A prospective evaluation of whole-exome sequencing as a first-tier molecular test in infants with suspected monogenic disorders. *Genet Med.* 2016;18:1090-1096. doi: 10.1038/gim.2016.1

**5.** Meng L, Pammi M, Saronwala A, et al. Use of exome sequencing for infants in intensive care units: ascertainment of severe single-gene disorders and effect on medical management. *JAMA Pediatr.* 2017;171:e173438. doi: 10.1001/jamapediatrics.2017.3438

**6.** Vissers L, van Nimwegen KJM, Schieving JH, et al. A clinical utility study of exome sequencing versus conventional genetic testing in pediatric neurology. *Genet Med.* 2017;19:1055-1063. doi: 10.1038/gim.2017.1 doi: 10.1038/ejhg.2016.146

**7.** Trujillano D, Bertoli-Avella AM, Kumar Kandaswamy K, et al. Clinical exome sequencing: results from 2819 samples reflecting 1000 families. *Eur J Hum Genet.* 2017;25:176-182. doi: 10.1126/scitranslmed.3010076

**8.** Soden SE, Saunders CJ, Willig LK, et al. Effectiveness of exome and genome sequencing guided by acuity of illness for diagnosis of neurodevelopmental disorders. *Sci Transl Med.* 2014;6:265ra168.

**9.** Tan TY, Dillon OJ, Stark Z, et al. Diagnostic Impact and Cost-effectiveness of Whole-Exome Sequencing for Ambulant Children With Suspected Monogenic Conditions. *JAMA Pediatr.* 2017;171:855-862. doi: 10.1001/jamapediatrics.2017.1755

**10.** Vrijenhoek T, Middelburg EM, Monroe GR, et al. Whole-exome sequencing in intellectual disability; cost before and after a diagnosis. *Eur J Hum Genet.* 2018;26:1566-1571. doi: 10.1038/s41431-018-0203- 6

**11.** Dillon OJ, Lunke S, Stark Z, et al. Exome sequencing has higher diagnostic yield compared to simulated disease-specific panels in children with suspected monogenic disorders. *Eur J Hum Genet.* 2018;26:644-651. doi: 10.1038/s41431-018-0099-1

**12.** Retterer K, Juusola J, Cho MT, et al. Clinical application of whole-exome sequencing across clinical indications. *Genet Med.* 2016;18:696-704. doi: 10.1038/gim.2015.148

**13.** Pfundt R, Del Rosario M, Vissers L, et al. Detection of clinically relevant copy-number variants by exome sequencing in a large cohort of genetic disorders. *Genet Med.* 2017;19:667-675. doi: 10.1038/gim.2016.163

**14.** Karbassi I, Maston GA, Love A, et al. A standardized DNA variant scoring system for pathogenicity assessments in Mendelian disorders. *Hum Mutat.* 2016;37:127-134. doi: 10.1002/humu.22918