Date

Dear Medical Director,

I am writing this letter of medical necessity on behalf of the patient

[PATIENT\_FIRST\_NAME] [PATIENT\_LAST\_ NAME] [DOB]

to request coverage for genetic testing for Whole Genome Sequencing (also known as WGS) to be performed at Rady Children’s Institute for Genomic Medicine, a high complexity CLIA-certified, California Licensed, CAP-accredited laboratory located in San Diego, California.

The purpose of this test is to rapidly identify the underlying molecular basis of a genetic disorder in an affected individual by performing a comprehensive analysis of the patient’s entire genome to enable real time changes in inpatient management. This test has the potential to change management, improve clinical outcomes and reduce cost of total care for this patient.

1. This case has been evaluated by [DR.\_FIRST\_LAST NAME], a clinician with expertise in clinical genetics, who believes there is a high likelihood of a genetic etiology.
   1. At the present time we cannot recognize a specific clinical diagnosis. Due to the heterogeneous nature of rare genetic disorders. The most efficient and cost-effective way to confirm a genetic diagnosis in this patient is to perform whole genome sequencing as recommended by the American College of Medical Genetics and Genomics.
   2. Rather than sequencing the many potential candidate individual genes, WGS is the fastest (*Petrikin* et.al.) and most cost-effective way (*Farnaes* et. al) to search for a mutation among the large number of potential genes that could be causing this condition.
2. The family has been counseled about the potential risks of genetic testing.
3. There is potential for a change in management and clinical outcome for this case. Specifically, WGS in neonates has been demonstrated to improve clinical outcomes and reduce the total cost of care.

In this case, specific changes that may be anticipated include*:* [fill in]

Without a specific genetic etiology, this child is at risk for [give example e.g. ineffective or inappropriate medication, is faced with invasive procedures/testing as the next diagnostic/therapeutic step, such as muscle biopsy, other.]

Due to these benefits, and consistent with specialty guidelines, genome sequencing is medically warranted in my patient. As such, I am ordering this medically necessary test and affirm that my patient has provided informed consent for genetic testing.

[*If ordering familial trio testing, add following through “biological parents.]*

Comparing this individual’s sequence to additional family member’s data will signifi-cantly increase the utility of the test results and increase the likelihood of identifying a disease-causing gene while decreasing the chance of obtaining variants of unknown clinical significance (*Clark, 2018*).

This method of evaluation is especially important for individuals with apparently sporadic disease, when no one else in the family is similarly affected. By analyzing parents and unaffected sibs in cases of sporadic disease, it is frequently possible to identify de novo or new mutations in the child not present in either parent or to identify recessive diseases with one mutation inherited from each parent.

Therefore, we are requesting “trio” testing of the affected child and both biological parents.

The clinical applications of Whole Genome Sequencing (WGS) have now been well supported by the following lines of evidence:

1. **The Policy Statement by The American College of Medical Genetics and Genomics** published in 2012 on the clinical application of genomic sequencing recommends genome sequencing in four clinical scenarios (ACMG Board). Most relevant to our patient:

*“WGS should be considered in the clinical diagnostic assessment of a phenotypically affected individual when: A patient presents with a defined genetic disorder that demonstrates a high degree of genetic heterogeneity, making WGS analysis of multiple genes simultaneously a more practical approach.”*

1. **The clinical utility of WGS has been well established** and therefore should not be considered experimental.
   1. WGS has the advantage of speed and efficiency relative to WES and Sanger sequencing of multiple genes. WGS has greater ability to detect large deletions or duplications in protein-coding regions compared to WES and is superior to chromosome microarray testing in detecting copy number variants in the chromosomes.
   2. WES shares some limitations with Sanger sequencing, for example, it will not identify the mutations in intronic sequences or gene regulatory regions; chromosomal changes; large deletions; duplications or rearrangements within genes or nucleotide repeats.
   3. Whole genome sequencing in a randomized control trial has demonstrated increased diagnostic yield and reduced time to diagnosis compared with standard care that includes panel and whole exome testing (*Petrikin*).
   4. Whole genome sequencing has been shown to have a superior diagnostic utility to chromosome microarray. Among studies published in 2017, the diagnostic utility of WGS was significantly greater than CMA (P < 0.0001, I2 = 13% and I2 = 40%, respectively). The clinical utility of WGS (0.27, 95% CI 0.17–0.40, I2 = 54%) has been shown on meta-analysis to be superior to WES (0.17, 95% CI 0.12–0.24, I2 = 76%) and higher than CMA (0.06, 95% CI 0.05–0.07, I2 = 42%) (*Clark*).
   5. Rapid whole genome sequencing in neonates has demonstrated both improved clinical outcomes and a reduction in the total cost of care (*Farnaes*) compared with standard workup

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NAME & TITLE DATE

**References**

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ACMG Board of Directors.

**ACMG Policy Statement: Points to consider in the clinical application of genomic sequencing.**

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