Letter of Medical Necessity for Genetic Testing

To whom it may concern:

I am writing this letter of medical necessity on behalf of our patient {PATIENT NAME}, to request coverage for genetic testing for very early onset inflammatory bowel disease (VEO-IBD). Inflammatory bowel disease is a chronic disease of the intestinal tract, for which there is no cure. VEO-IBD is unique in that it can be caused by a genetic defect that can be identified by the VEO-IBD genetic panel offered through the Children's Hospital of Philadelphia. This letter documents the medical necessity for genetic testing in light of the patient's medical history.

{PATIENT NAME} is a {AGE} year-old F/M who presents with the following:

Patient Active Problem List

Diagnosis	Code

I have determined that this test is medically necessary because of the following aspects of this patient's presentation: ***

{PATIENT'S NAME} course over the past several months/years *** has indicated a primary genetic disorder as the cause for his/her *** very early onset inflammatory bowel disease.

Information on VEO-IBD:

Inflammatory bowel disease is a chronic inflammatory disorder of the intestinal tract that results in high morbidity. IBD diagnosed in children less than 6 years old is a distinct, rare, yet growing entity known as very early onset inflammatory bowel disease (VEO-IBD). These patients often have a more severe disease course compared to older children and adults with IBD, and frequently fail conventional therapy requiring intestinal surgery at a young age. Furthermore, while IBD is a common disease in the general population, VEO-IBD is a rare disease and often misdiagnosed. Although there has been a dramatic rise in the incidence, is rising over time, VEO-IBD still encompasses less than 1 percent of all patients with IBD.

Mounting evidence in the literature has shown that some children with VEO-IBD have single gene defects in immune pathway and enterocyte-related genes that are causative for the disease; and therefore, genetic testing is an important part of the evaluation of VEO-IBD. (Uhlig et al 2013, Peterson et al 2017, Suzuki et al 2017, Kammermeier et al 2014). Because many of the genes that cause VEO-IBD are involved in primary immunodeficiency, these children can have immune dysregulation and suffer catastrophic sequale of their disease without appropriate targeted therapy. By identifying the genetic defect that causes VEO-IBD in some patients, we may be able to target future therapy and avoid complications including hospitalization, surgery and potentially even life-threatening complications such as severe infection, malignant transformation and death.

The CHOP VEO-IBD gene panel contains 98 genes that have been shown to be causative for VEO-IBD:

ADA, *ADAM17*, *AICDA*, *AIRE, ARPC1B*, *BTK*, *CD19*, *CD40*, *CD40LG*, *CD81*, *CHD7*, *CIITA*, *COL7A1*, *CR2*, *CTLA4*, *CYBA*, *CYBB*, *DCLRE1C*, *DKC1*, *DOCK8*, *FERMT1*, *FOXP3*, *FUT2*, *G6PC3*, *HPS1*, *HPS4*, *HPS6*, *ICOS*, *IKBKB*, *IKBKG**, *IKZF1*, *IL10*, *IL10RA*, *IL10RB*, *IL21*, *IL23R*, *IL2RA*, *IL2RG*, *IL7R*, *ITCH*, *ITGB2*, *ITK*, *LCK*, *LIG4*, *LRBA*, *LYST*, *MALT1*, *MEFV*, *MVK*, *MYO5A*, *NCF2*, *NCF4*, *NFAT5*, *NFKB1*, *NFKB2*, *NLRC4*, *NLRP12*, *NOP10*, *PIK3R1*, *PLCG2*, *PRF1*, *PTEN*, *RAB27A*, *RAC1*, *RAC2*, *RAG1*, *RAG2*, *RET*, *RFX5*, *RFXANK*, *RFXAP*, *RTEL1*, *SH2D1A*, *SKIV2L*, *SLC37A4*, *STAT1*, *STAT3*, *STAT5A*, *STAT5B*, *STX3*, *STXBP2*, *STXBP3*, *TAP1*, *TAP2*, *TERC*, *TERT*, *TINF2*, *TNFAIP3*, *TNFAIP6*, *TNFRSF13B*, *TRAF3*, *TTC37*, *TTC7A*, *UNC13D*, *UNG*, *WAS*, *XIAP*, *ZAP70*.

Rationale for Testing:

The purpose of this test is to identify a pathogenic mutation(s). The methodology used by the CHOP Lab is able to find these mutations with a very high degree of sensitivity. Results of this test will have a direct impact on defining the patient's diagnosis, treatment and management and will provide prognostic information that will assist in the clinical management of the patient. Some genetic findings require targeted therapies. In addition, it will allow for proper genetic counseling and family planning.

Based on the above findings, it is medically necessary to proceed with further genetic/diagnostic testing to identify the underlying etiology for the following medical management reasons:

Medication use - Based on the underlying diagnosis there may be treatments that would cure the disease process, including hematopoietic stem cell transplant. Likewise, there are medications that are contraindicated.

Treatment of other organ systems possibly involved - Patients with genetic disorders can have multi-system involvement and knowing the underlying etiology will allow for targeted and specific monitoring and treatment.

Prognosis - Knowing the underlying etiology, is absolutely necessary for long-term prognostication and for his overall future medical management.

Avoiding - Unnecessary interventions and possibly invasive diagnostic testing

Family planning - Identification of other at-risk relatives in the family since the underlying etiology is genetic.

In summary, I am requesting that {PATIENT NAME} be approved for the Very Early Onset Inflammatory Bowel Disease Gene Panel through the Children's Hospital of Philadelphia with the following CPT codes: 81404, 81405, 81406, 81407, 81479.

Sincerely,

***

Billing Information:
Patient's insurance:
***

Testing will be completed at the following lab:
Children's Hospital of Philadelphia - NPI: 1215921457
Children's Hospital of Philadelphia - Tax ID: 231352166

This testing is not available at Quest Diagnostics or LabCorp but is only offered at the Children's Hospital of Philadelphia. Therefore, we ask that you issue a prior authorization as an in-network benefit.

Laboratory: The Children's Hospital of Philadelphia
Test Name: Very Early Onset Inflammatory Bowel Disease Gene Pane
CPT codes: 81404, 81405, 81406, 81407, 81479

References:
Uhlig HH, Schwerd T, Koletzko S, et al. The diagnostic approach to monogenic very early onset inflammatory bowel disease. *Gastroenterology*. 2014a;147:990-1007 e3.

Kammermeier J, Drury S, James CT, et al. Targeted gene panel sequencing in children with very early onset inflammatory bowel disease–evaluation and prospective analysis. *J Med Genet*. 2014;51:748-755.

Kelsen et al, NASPGHAN position paper on the evaluation and management for patients with very early onset inflammatory bowel disease. *J Pediatric Gastroenterol Nutr* 2019. PMID 31899730

Sullivan KE et al. Very early onset inflammatory bowel disease: an integrated approach *Curr Opion Allergy Clin Immuol* 2018 PMID 30299395

Ouhed, et al. Very Early Onset Inflammatory Bowel Disease: A Clinical Approach With a Focus on the Role of Genetics and Underlying Immune Deficiencies. Inflamm Bowel Dis. 2020 May 12;26(6):820-842 PMID 31833544

Suzuki et al. Targeted sequencing and immunological analysis reveal the involvement of primary immunodeficiency genes in pediatric IBD: a Japanese multicenter study. *J. Clin. Immunol.* 2017; 37: 67-79

Petersen BS et al. Opportunities and challenges of whole-genome and -exome sequencing. *BMC Genet* 2017;18(1):14

Benchimol et al. Trends in epidemiology of pediatric inflammatory bowel disease in Canada: Distributed network analysis of multiple population-based provincial health administrative databases. *Am J Gastroenterol* 2017; 112:1120-34.

CHOP VEO-IBD Website: https://www.chop.edu/centers-programs/very-early-onset-inflammatory-bowel-disease-veo-ibd-program/about