Patient consent form for postnatal whole exome sequencing (short-read WES) 5th EDITION

Postnatal sequencing of all gene exons (short-read Whole Exome Sequencing) is a complex genetic test that detects pathogenic mutations in regions (exons) of genes associated with known genetic diseases and syndromes according to the OMIM® database.I understand that this is a test based on specific clinical indications and/or specific family medical history and is performed in order to explain specific clinical indications as far as possible or to investigate the causes related to family medical history. The test is not generally performed without relevant indications.

I understand that the above test may:

- Reveal one or more findings that constitute the complete or partial cause of the condition and/or specific family medical history for which I was referred.

- Reveal one or more findings that constitute the possible cause of the condition and/or specific family medical history for which I was referred, i.e., likely pathogenic findings (class 4) in genes that are potentially related to the condition and/or specific family medical history for which I was referred.

- Reveal one or more findings whose clinical significance cannot be assessed with current literature and other data – findings of uncertain/unknown clinical significance (Variants of Uncertain/Unknown Significance - VUS)

- Fail to reveal findings that constitute the cause of the condition and/or the specific family medical history for which I was referred. The absence of findings during the above test does not rule out that the condition and/or specific family medical history for which I was referred have a genetic cause that was not detected in the above test, nor does it rule out the existence of a genetic disease in general, as although it is estimated that >85% of variants in monogenic diseases are located within exons or at the boundaries of exons/introns, there may also be "deep" intronic variants (findings located in the introns of genes), as well as variants in non-coding regions, such as promoters, enhancers, etc., which short-read WES testing typically cannot detect. Furthermore, short-read WES testing does not detect large deletions/duplications (large INDELS), copy number variants (CNVs), trinucleotide repeat expansions (e.g., Fragile X syndrome), methylation disorders and uniparental disomy (UPDs, such as Silver-Russell, Beckwith-Wiedemann, Angelman, Prader-Willi syndromes, etc.) and nucleotide changes in the mitochondrial genome. Furthermore, short-read WES cannot reliably detect variants located in regions with pseudogenes or duplicate genes (e.g., spinal muscular atrophy, Gaucher disease, CAH, etc.), regions with a high percentage of G/C bases (G/C rich regions), and regions with repeated identical nucleotides (homopolymer regions). It should also be noted that, for technical reasons, 100% coverage of the entire exome is not achieved, as approximately (~3-5%) of the total genetic regions tested are not represented by a sufficient number of copies during analysis and therefore escape testing, or other quality parameters are not met, such as regions with an unbalanced distribution of nucleotides between alleles or strands (strand bias) or constitute nucleotide changes that are likely to affect mRNA splicing but are not recognized as such by the bioinformatics analysis tools used by our laboratory for data interpretation and therefore they cannot be assessed and they are ignored as findings.

I understand that variant classification is based on international literature and the guidelines of the American College of Medical Genetics and Genomics (ACMG). During the evaluation process, clinical information and personal and family history provided by me and/or the referring physician to Access to Genome - ATG are used.

I understand that in order to complete the evaluation of the findings, it may be recommended that other members of my family (parents, siblings, etc.) also be examined.I understand that the assessment of the significance of findings may change in the future based on newer scientific data, resulting, for example, in a pathogenic or likely pathogenic finding being classified as benign or likely benign, and vice versa.

I understand that the final report of the test will report findings that constitute the complete or partial cause of the condition and/or the specific family medical history for which I was referred, i.e., pathogenic findings (class 5 variants) in genes potentially related to the condition and/or specific family medical history for which I was referred, or findings that constitute the probable cause of the condition and/or specific family medical history for which I was referred, i.e. likely pathogenic findings (class 4 variants) in genes potentially related to the condition and/or specific family medical history for which I was referred.

I understand that I will not be informed about benign (class 1 variants) or likely benign (class 2 variants) findings or findings of uncertain/unknown clinical significance. Exceptionally and only in special cases, findings of uncertain/unknown clinical significance may be reported, taking into account the reason for referral, family history, and clinical indications, and always in consultation with the referring physician.

I understand that findings of uncertain/unknown clinical significance not reported in the Whole Exome Sequencing analysis may be reported or re-evaluated as likely pathogenic or pathogenic in a subsequent analysis, if new clinical, phenotypic, bibliographic, or other data and new technical capabilities emerge.

I understand that findings of uncertain/unknown clinical significance reported in the analysis may be reported or re-evaluated as likely pathogenic or pathogenic or as likely benign or benign in a subsequent analysis, provided that new clinical, phenotypic, bibliographic, or other data and new technical capabilities emerge.Based on the testing methodology, there is a possibility of secondary findings, such as pathogenic mutations in genes unrelated to the condition for which I was referred. The ACMG has recommended a list of genes* whose mutations lead to serious conditions that require special management. Due to the above characteristics of the conditions, I am given the opportunity to be informed about any pathogenic mutations I carry in these specific genes. I wish to be informed about any pathogenic mutations I carry in the genes on the ACMG list:

□ YES

□ NO

I understand that I will not be informed of any other incidental or non-incidental findings (other than those mentioned in the previous paragraph), e.g. mutations in genes not related to the condition for which I was referred and not included in the above ACMG list, or mutations in single heterozygotes (single mutations) in genes related to recessive inheritance according to the OMIM database, etc. Furthermore, I will not be informed of any inaccuracies in the family relationships reported (e.g., non-paternity or non-maternity), except in cases where this is necessary in order to determine the inheritance of any findings.

I understand that ATG reserves the right to inform the referring physician of any other incidental findings in my test.I understand that ATG will store the results of the genetic analysis for as long as required by law (medical records must be kept for ten (10) years from the patient's last visit, Article 14 of Law 3418/2005).

I understand that ATG will store any available processed biological sample for a maximum period of up to two (2) years, and the raw or intermediate test data (e.g., BCL, BAM, VCF, FASTQ files, etc.) for a maximum period of up to four (4) weeks from the issuance of the test result, depending on the storage capacity for biological samples and digital data.

It is strongly recommended that the analysis includes simultaneous analysis of the child and parents (trio analysis), as this helps to interpret the findings more accurately and increases diagnostic yield.

In the case of Trio analysis, the parents' samples are sequenced, and the sequences are checked only to determine the inheritance of any findings detected in the child. No sequence analysis is performed and no other findings are sought in the parents that are not inherited by the child.

Please fill in your name in capital letters and sign your name.The Patient / Parent / Guardian

Full Name:

ID Number:

Signature:

* ABCD1 ACTA2 ACTC1 ACVRL1 APC APOB ATP7B BAG3 BMPR1A BRCA1 BRCA2 BTD CACNA1S CALM1 CALM2 CALM3 CASQ2 COL3A1 CYP27A1 DES DSC2 DSG2 DSP ENG FBN1 FLNC GAA GLA HFE HNF1A KCNH2 KCNQ1 LDLR LMNA MAX MEN1 MLH1 MSH2 MSH6 MUTYH MYBPC3 MYH11 MYH7 MYL2 MYL3 NF2 OTC PALB2 PCSK9 PKP2 PLN PMS2 PRKAG2 PTEN RB1 RBM20 RET RPE65 RYR1 RYR2 SCN5A SDHAF2 SDHB SDHC SDHD SMAD3 SMAD4 STK11 TGFBR1 TGFBR2 TMEM127 TMEM43 TNNC1 TNNI3 TNNT2 TP53 TPM1 TRDN TSC1 TSC2 TTN TTR VHL WT1