Hadassah Medical Organization
Human Genetics Department

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Consent Forms for Clinical Whole Exome

A. *General explanation*:

1. Exome analysis is a method for determining the sequence of coding regions in the DNA and for identifying clinically relevant variants in these regions.
2. The purpose of the analysis is to provide a molecular diagnosis for serious medical conditions in a patient.
3. The DNA consists of genes and regulatory regions between the genes. The genes themselves consist of exons, which are the code for protein synthesis, and introns, which include regulatory regions. The exons comprise only 1-2% of the DNA but it appears that about 80% of the disease-causing variants reside within them.
4. For the purpose of the analysis, a DNA sample is obtained from the patient, most often by extraction from blood. The sequencing is performed either at the Hadassah genetic laboratory on a local sequencer or shipped to a CLIA-accredited lab in the USA. The bioinformatics interpretation is performed in-house at Hadassah (EMQN certified). Turnaround time is approximately one month.
5. In addition to bioinformatics tools, interpretation is based on the detailed report of the health state of family members, including biologic relationship among them.
6. In order to clarify the significance of the findings, it may be needed to segregate specific variants in DNA of family members. These additional tests may extend the analysis time.
7. In general, trio analysis (patient and parents) is recommended, as it enables comparison of the exonic sequence of the patient to that of the parents. Trio analysis increases diagnostic yield and shortens analysis time.
8. Mitochondrial DNA sequencing is routinely included in the exome analysis, as of June 2020.

B. *Analysis and Limitations:*

1. In contrast to most medical tests, where interpretation of the data yields either a positive or negative result, exome analysis reveals multiple changes (variants), some of uncertain significance. Determining the clinical relevance of a particular variant is limited by the literature available at the time of analysis. The analysis identifies variants (usually involving single or few nucleotides) in exons and their flanking regions (splice sites). However, about 6% of the exons are not captured by exome analysis; thus, variants in these exons are neither covered nor reported.
2. Copy number variations (CNV) analysis: Copy number variations (deletions and duplications) are detected by analysis of the depth of coverage at each genomic point in an individual exome, as compared to other samples. CNV analysis utilizes two tools to identify potential CNVs: CNV-finder (an in-house script) and CNV KIT (PMID: 27100738). Suspected CNVs covering two or more exome will be reported, with the limitations of the capture design. Notably, the sensitivity of CNV detection

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from exome read depth analysis is inferior to the sensitivity of single nucleotide variant detection, and CNV analysis fails in a small percentage of samples. In such cases, chromosomal microarray analysis is recommended. Uniparental disomy (UPD) analysis: This is done using the UPDio tool (PMID: 24356988), and is possible only in trio exome analysis (proband and both parents).

3. mtDNA analysis: Mitochondrial DNA changes are analyzed, and data are compared to the Mitomap and ClinVar databases. Variants with heteroplasmy under 10% are not reported.
4. Given the above limitations, it is clear that failure to identify a disease-causing variant by this analysis does not exclude a genetic disorder in the patient.

D. *Reporting of results:*

1. Following bioinformatics analysis, a final report will be sent to the referring physician. The referring physician is responsible for reporting the results to the patient and for ensuring that the family receives appropriate genetic counselling.
2. Similarly, results of family members will be communicated to them through their physician, if specifically requested, and should be accompanied by genetic counselling.
3. The raw material generated during the analysis (FASTQ files) is available for transfer at no extra charge.
4. The lab will determine which variants may be relevant to the patient's phenotype, based on the genetic literature available at the time of the analysis. In general, variants which indicate an existing disease, and which are compatible with the clinical findings for which the test was requested, will be reported.

E. *Secondary findings:*

1. Medically actionable findings: The Exome results might include findings that are medically actionable according to the list of recommendations of the American College of Medical Genetics (ACMG SF V3.2, PubMed: 37347242). These include variants in genes that increase the risk for different types of cancer, heart disease, and miscellaneous phenotypes. Some of these conditions may manifest in childhood, and others manifest in adulthood. Identification of individuals at risk for these diseases allows for specific surveillance regimens and/or early treatment. A more detailed explanation regarding these genes and their associated-conditions can be given within the framework of a genetic counseling session.

   Adult examinees may choose to opt-out of this analysis. For minors, only findings that are relevant to childhood will be reported. It is recommended that minors re-contact the genetic clinic after the age of 18, in order to receive adult-onset findings.

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2. Carrier status for recessive diseases: Trio exome sequencing provides the opportunity to report on genes which cause rare monogenic diseases inherited in an autosomal recessive and X-linked patterns, for which both members of a couple carry a known pathogenic variant. This test will only report changes that are known to be pathogenic or expected to be pathogenic in the relevant medical literature and databases. This test is not meant to replace the available tests offered for carrier screening, since it does not include critical tests such as fragile X, deep intronic known pathogenic mutations, or known pathogenic copy number variants such as intragenic deletions.

F. *Details:*

1. Requested Exome: ☐ single ☐ duo ☐ trio ☐ quatro
2. Proband:
   Name_____ I.D._____ Gender: M / F
3. Other examinees:
   Relation to proband _____ Name_____I.D._____ Gender: M / F
   Relation to proband _____ Name_____I.D._____ Gender: M / F
   Relation to proband _____ Name_____I.D._____ Gender: M / F
4. Sample type (if not blood in EDTA)_____
5. Ethnic origin and relationship between parents:
   Mother's ethnic origin _____
   Father's ethnic origin _____
   Parental relatedness _____
6. Reason for referral (phenotype in HPO terms)
   _____
   _____
   _____

G. *Consent:*

1. I understand that the raw data of this analysis will be stored anonymized at the Hadassah exome database, and agree that de-identified data can be shared with other clinicians or researchers. Furthermore, cumulative data from exome analyses may be published in the medical literature, provided that it is de-identified.
2. I understand that the analysis result is valid to our contemporary clinical knowledge, and it is likely that our knowledge regarding the genetic basis of disease will improve in the future. Consequently,

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I may ask the referring physician/counselor in the future whether a revision of the exome data can be performed. In addition, the lab reserves the right to re-contact the patient/family if new relevant findings arise.

3. With my signature I confirm that I have read this consent form, that I received genetic counselling specific for exome analysis, and that I was granted the opportunity to ask questions. I understand the analysis and its limitations and request to perform the analysis.
4. I understand that a report of the results will be sent to the referring physician and that I should return to him/her in order to receive the results and their clinical interpretation, in the form of genetic counselling.
5. I understand that it is possible that the analysis will not identify a disease-causing variant in the exons and that this does not exclude a genetic disorder.
6. Secondary findings:
   I understand that secondary findings may be reported to me, as described in clause D. If one wishes to opt-out, he shall state it here (with full name, I.D, relation to proband and signature)
   _____
   _____
   _____
   I understand that one cannot refuse to receive reports of secondary findings (of childhood relevance) for a minor.
   7. I [agree / disagree] to use my de-identified specimen for research to improve genetic testing for all patients and contribute to scientific research, including sharing the data anonymously.

H. *Signature:*

Date _____

Relation to proband _____ Name _____ signature _____

Relation to proband _____ Name _____ signature _____

- **The signature from all adult examinees is mandatory.**

Referring physician/counselor _____

Medical organization _____

His/her e-mail address _____

His/her signature _____

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