INFORMED CONSENT

3billion requires a copy of a signed consent form from the patient to be legally able to conduct a genetic analysis. Please send this signed consent form with the sample(s).

A general description of whole exome sequencing

Whole exome sequencing (WES) refers to reading only the exome region of the human genome using next-generation sequencing technology. Although exomes account for less than 2% of the entire human genome, 85% of the variants associated with diseases are located in this region. Therefore, WES is being effectively used to identify genetic changes related to the Mendelian disorders reported to date.

The purpose of WES test

3billion provides rare diseases genetic testing based on whole exome sequencing to detect genetic changes associated with the diseases. Unlike the limited scope of conventional genetic testing, whole exome sequencing can search tens of thousands of genes at once to identify disease-causing pathogenic variants, dramatically reducing the time and cost it takes to diagnose genetic diseases. Thus, clinical diagnosis based on WES data enables timely treatment of disease and prediction of possible complications, as well as advanced family planning through genetic counseling.

Results reported from WES test

1. Genetic variants that may have caused the patient's symptoms will be included.
2. Genetic variants found in genes relevant to the patient's condition and may majorly impact health will be included, unless you decide that you do not want this information. Please see the section on optional consent on the next page.
3. Genetic variants identified in family members and relevant to the patient's symptoms will be included in the patient's report. Family members will not receive separate written reports.

Limitation of WES test

1. Not all exons in the genome are targeted.
2. Certain types of a genetic variant may not be detectable (eg. large copy number variants, methylation defects, variants in genes with highly homologous pseudogenes, variants in mitochondrial genome, and trinucleotide repeats expansion).
3. WES is limited in the detection of alterations confounded by various non-Mendelian factors (penetrance, variable expressivity, multifactorial disease, epigenetic factors, phenocopies, and uniparental disomy).
4. The entire experimental process in which exome sequencing is performed cannot be guaranteed as 100% free of the following errors: Rarely occurring trace contamination, rare technical errors in the laboratory, DNA damage affecting data analysis, inconsistent scientific classification systems, inaccurate reports of family relationships or clinical outcomes, and/or inaccurate/incomplete explanation of clinical findings.
5. This test result might be inconclusive. While some genetic variants are known to be benign and others disease-causing, a portion of genetic variants found could be of uncertain significance. Depending on the results of this test, a physician or health care provider may recommend genetic counseling or further testing.

Family member discrepancies

The results of this test can tell the patient and their family that they have a genetic disease or are at an increased risk for such a condition. If multiple family members are tested, the precise interpretation of the results depends on the exact relationships between family members. If the provided relationship does not reflect genetic analysis outcome (due to adoption or other family circumstances that produce lack of direct biological correlation), 3billion will not inform you of this inconsistency, unless this information is necessary for the completion and accurate medical interpretation of the requested analysis.

De-identification and use of WES data

De-identification refers to the process of rendering the patient's data anonymous, which protects the patient's privacy; the patient data will be stored anonymously and only be accessible to 3billion, not to any other institutions. The results of this test may be summarized anonymously in case studies at meetings, scientific journals, or DNA variation databases to improve understanding, diagnosis, and treatment of similar clinical conditions. In addition, de-identified data will be used for internal research, validation of analysis procedures, and product development for profit and non-profit purposes.

Sample storage

3billion discards the sample after the patient was diagnosed or the procedure of genetic testing was completed. Accordingly, for patients with no pathogenic variant, 3billion is not obliged to perform Sanger sequencing even if a causal variant(s) is identified in the subsequent reanalysis.

Confidentiality

3billion will report results to the physician or healthcare provider who ordered the test. 3billion will not give results to other individuals without your written permission. The written report is expected to become part of the patient's medical record. The patient's health insurance provider or other parties may have legal access to this information.

Optional consent

Secondary finding

A secondary finding will be included in the final report according to the American College of Medical Genetics recommendations for reporting of secondary finding once your physician placed an order.

*Secondary finding: as whole exome sequencing reads tens of thousands of genes at a time, a much greater number of genetic variations are detected than traditional tests. Secondary finding can occur when it is identified that genes that are not directly related to the disease may cause other serious health problems to the patient. We report such secondary finding along with the disease-causing genes and recommend appropriate clinical management and treatment.

- ☐ Yes, I agree to include secondary finding in the final report.
- ☐ No, I do not agree.

PATIENT SIGNATURE

By signing this form, I acknowledge that I have read this Informed consent for genetic rare disease diagnosis and understand its content. I have had the opportunity to ask questions about this form and my questions have been adequately answered. Also I understand that I can withdraw my consent with effect for the future in full or in part at any time, and I have the right not to know the results of the genetic analyses as mentioned in the preceding description.

If the undersigning is the legal guardian of the patient, he/she herewith confirms to provide the above consent declarations not for himself/herself but on behalf of the respective patient.

Name: _____ **Date of birth:** _____

Signature: _____ **Date:** _____

Name and relationship of legal guardians, if patient is a minor: _____

Signature of legal guardians, if patient is a minor: _____

MEDICAL PROFESSIONAL SIGNATURE

By signing this form, I acknowledge that I am the referring physician or certified healthcare professional. I have explained the purpose of the test described above. The patient has had the opportunity to ask questions regarding this test and/or receive genetic counseling. The patient has voluntarily decided to carry out this test performed by 3billion.

Medical professional signature: _____ **Date:** _____