Physician's Guide for Informed Consent

This guide covers a range of information which ought to be provided to the patient (or the authorized representative), in order to inform and obtain his/her consent for sample analysis for a neuromuscular disorder and sample preservation and research use at the National Center of Neurology and Psychiatry (hereinafter referred to as NCNP). Please go through this handbook carefully before providing any information to the patient. Should you have any questions or concerns, please do not hesitate to contact us. Please also inform the patient, that NCNP wishes to preserve samples at our center as long as possible for post-analytical research use. The samples will be utilized for the development of new treatments and such. If the patient consents to Sample Preservation and Research Use, please have the appropriate box checked. Please inform the patient that the consent to Sample Preservation and Research Use is voluntary. Refusal of the consent will involve no penalty or loss of benefits to which the patient is entitled for diagnostic analysis. The patient or the authorized representative can revoke the consent for Sample Preservation and Research Use at any time.

Prior to providing any information to the patient who wishes to receive our diagnostic service, please ensure that the patient is provided with "Patient's Guide for Informed Consent" as well. However, please note that this handbook as well as its accompanying consent form only covers the consent to Sample analysis for Diagnosis, and Sample Preservation and Research Use. If you need to obtain other consent regarding the collection of a sample (such as which tissue, how and who collects it), you may need to obtain such a consent separately.

Who to Explain to and to Obtain Consent from

Please provide the following information to the patient and/or his/her authorized representative. If the patient decides to give consent, please obtain his/her or his/her authorized representative signature in the signature column in the consent form. Please note that an authorized representative is required in case the patient is not in a condition to give a valid consent (e.g. the patient is a minor, or an adult with diminished decision-making capacity for example, as a result of trauma, intellectual disability, some forms of mental illness, or dementia.). In this case, a voluntary guardian, a person with parental authority, a guardian or a curator can be designated as a representative. The patient's spouse, adult child, parent, adult brother or sister, grandchild, grandparent, relative living together or someone who is considered equivalent to a relative may become a representative. If the patient's muscle condition makes it impossible to sign their own signature, the patient may grant permission to their representative to sign on their behalf. In this case, please indicate that it was signed on behalf of the patient.

Pathological / Biochemical Analysis

Please cover the followings information.

① The content of the analysis such as the purpose of analysis and its limitations, interpretation of the analysis.

② The patient can cancel the analysis at any time by submitting such a request through their attending physician, as long as the cancellation is notified to us prior to the release of the final report.

③ Personal information is strictly protected. A received sample is immediately given a number, and during the analysis process the sample is handled without personal identifiers, which is called anonymization. Also, the access to the received clinical information, which is important upon interpreting the analytical findings and making a diagnosis, is granted only to the physicians in charge of diagnosis. Likewise, the access to any patient identifiable information such as name and hospital ID is granted only to the diagnostic physicians as well as the administrators who take care of the consent form. The personnel responsible for the

administration of personal information (Privacy Officer) is the Director-General of the TMC (Translational Medical Center)

④ The sample will be preserved for at least one year, considering the possible need of second analysis. However, in the situation that a preserved sample has become unsuitable for analysis due an unexpected accident such as a breakdown of freezer and natural disaster, we are exempt from responsibility. Also, if the patient (or their authorized representative) wishes, this preservation may be cancelled at any time through the attending physician.

⑤ Explanation of the result
The analysis result will be released to the attending physician from the Analysis Conductor in writing. The patient (or their representative) may receive explanation about the analysis result from the attending physician.

⑥ Other specialized analyses
In case we have identified the need of a more special analysis which is not available at NCNP, we will send the sample to collaborative research facilities for further detailed analysis. Even in this case, the analysis result will also be released to the attending physician from NCNP. The following is the list of collaborative research facilities as of today.

- Biochemical analysis of metabolic myopathy, conducted by Dr. Hideo Sugie at Tokoha University and Dr. Tokiko Fukuda at Hamamatsu Medical University.
- Analysis of myositis-associated autoantibodies, conducted by Dr. Shigeaki Suzuki at Keio University.

⑦ Other necessary information to cover
Please cover other necessary information such as postal fee and analysis fee. (Analysis fee is free of charge as of today, however it is subject to change.) There is a possibility that the patient will be asked to pay the actual cost of the analysis. In this case, we will provide additional documents for explanation.

Genetic Analysis

Through the progress in genetic researches, genetic analysis is increasingly becoming a crucial method for diagnosing many disorders. However, unlike general analyses, a genetic analysis can reveal information not only about the patient but also about their family members. Likewise, such an analysis can serve the purpose of presymptomatic and carrier diagnosis. It is important for the patient to fully understand the special nature of such an analysis. Because of the above reason, the privacy of the patient and their family members must be kept in strict confidence. While keeping the special nature of genetic analysis in mind, please ensure the patient is provided with genetic counselling prior to the analysis. Also, the counselling should mention that depending on its pathogenesis and the method used for variant detection, there is a possibility that the analysis result does not lead to a confirmation of a diagnosis. Upon explaining the analysis result to the patient, please provide genetic counselling service as much as possible. Such a counselling should take into consideration factors such as patterns of inheritance and age of onset. If necessary, please contact our Genetic Counselling Unit of the National Center Hospital. (Telephone: +81-(0)42-341-2711, extension 5824)

If you have ordered a genetic analysis at the same time as a pathological/biochemical analysis, and if the patient has chosen the option “Genetic Analysis for Any Possible Disorder”, we will conduct a necessary genetic analysis in accordance with our pathological/biochemical analysis result. There is also a possibility that a genetic analysis could be conducted in the future when it became available. In case the patient selects the aforesaid option, they have to be informed about the possibility that an analysis to identify a disorder that is out of the initial assumption could be conducted. Also, in case the genetic analysis has revealed a result different from the initially suspected disorder, please provide the patient with appropriate genetic counselling, taking into account factors such as the differences in patterns of inheritance.

If the patient wishes only for the analysis of a specific disorder, please check the appropriate box and specify the name of the disorder. Please contact our personnel responsible for the

analysis to find out which disorders are covered by our analysis. The list of personnel is found at the end of this handbook.

The advances in genetic sequencing technologies have enabled us to widely analyze the whole exon of an entire gene which is known as whole-exome sequencing, as well as analyzing the whole genome which is known as whole genome sequencing. In particular, if the patient has chosen the option “Genetic analysis for any possible disorder”, it is highly likely that such a large-scale analysis could be conducted. Please explain about this possibility to the patient.

Since the large-scale genome sequencing costs lower when it is performed in mass bulk, there are cases where economic efficiency can be achieved by outsourcing the analysis to external companies. In these cases, part of the analysis is likely to be performed by external companies which have been selected and contracted in conformity with the rules of NCNP. Please explain about this possibility to the patient. The sample information is fully anonymized, hence the patient’s personal information will never be disclosed to these external companies.

Although there is still a number of genomic information without associated interpretation, theoretically our analysis result could unexpectedly reveal an incidental finding which could cause a significant harm to the patient’s health. Please confirm with the patient whether they wish to be informed in case such a finding is revealed, and check the appropriate box if they do wish to be informed. However, even when a large genome sequencing is performed, the subsequent analysis to interpret the raw sequencing data is limited to targeted regions/targeted genes aiming to elucidate disease causation and pathogenesis, therefore it is not certain that all kinds of health-harming information can be obtained. Also, information such as a patient’s vulnerability to various disorders is usually not detected, as our analysis does not intend to serve such a purpose. Please mention the above to the patient.

In recent years, as a way to overcome intractable disorders, the necessity of sharing genetic sequencing data associated with disease information is increasingly recognized. In particular, the deposition of genetic sequencing data into a public database has become an essential requirement for any public funded analyses, as well as for paper publication in international journals. This is because, overcoming a disorder requires the promotion of researches by a number of researches using genetic sequencing information that contains accurate clinical information. Please explain to the patient that, in principle, any genetic data obtained through sequencing is to be deposited in a public database, since various large-scale genetic analyses performed at NCNP are in most cases supported by various public research funding such as AMED funding (Japan Agency for Medical Research and Development).The type of data which does not reveal an individual’s identity, such as variant frequency information, is deposited into open databases, such as the database specified by AMED and others so that the data is utilized by an unspecified number of researchers. On the other hand, an individual’s comprehensive genetic sequencing data is, together with disease information, deposited into a closed database specified by AMED and others. Any personal identifiers such as name, address, contact number and hospital ID are completely removed prior to such data registration. Please also explain to the patient that, even when their consent is withdrawn, removing their data from such databases might not be possible anymore since the research has been proceeded through the shared information.

Please fully explain to the patient that various technical limitations exist in genetic analysis, and especially a large-scale genetic sequencing technology is still under a developmental stage, hence as a consequence our analysis result might fail to identify a decisive pathological variant. Similarly, please understand that it could take quite a long time till the release of analysis report due to the limitation in funding and manpower.

Please explain to the patient that they hold the right to amend their consent at any time, such as cancelling the genetic analysis and changing the scope of the analysis to a specific disorder. Such a change and cancellation request has to be submitted to us through the attending physician. Please explain the above to the patient (or their authorized representative). If the patient consents, please obtain their signature in the signature column of our consent form.

Some of the genetic analysis fees are covered by health insurance; the others bill the actual cost. Please provide any necessary explanation to the patient and obtain their consent about the cost. If you have any questions, please contact our personnel in charge at the MGC (Medical Genome Center).

Preservation and Research Use

The cause of many neuromuscular disorders is still unknown and the whole picture of their disease causation and pathogenesis is yet to be elucidated. Meanwhile, a number of patients are waiting for the development of new medicines and effective cure. It is indispensable for the achievement of such a goal to promote researches with your patient's sample and clinical information (including clinical history and findings). We sincerely ask for your patient's cooperation.

Please explain the followings to your patient, and if they consent, please obtain their signature in the signature column of our consent form.

The explanation should cover the following elements of information.

① The consent to Research Use is a voluntary choice of the patient (or their authorized representative). Researches will contribute to the development of new treatments and such.

③ The use of resources and clinical information is limited to researches conducted at domestic and foreign research institutes with the aim of elucidating pathomechanism and developing therapy for neuromuscular disorders. The research approach varies; some researches use a large number of patients' resources with a specific disorder or with a variety of disorders, while others focus on using a smaller number of patients' resources. In any case, when a research requires a patient's resource after the completion of its diagnosis, such a research plan must be submitted to and approved by the Ethics Committee of NCNP.

④ Genome sequencing is likely to be conducted to identify genes that are associated with disease causation and pathogenesis. With the progress in genetic sequencing technologies, the whole-exome sequencing as well as the whole-genome sequencing is becoming more acknowledged. When necessary, such a large-scale analysis is likely to be conducted.

⑤ In principle, any genetic data obtained through sequencing is to be deposited in a public database specified by AMED (Japan Agency for Medical Research and Development) and others. An individual's detailed genetic sequencing data is deposited into a closed database specified by AMED and others together with disease information. Any personal identifiers such as name, address, contact number and hospital ID are completely removed prior to such a data registration.

⑥ When a resource is used for research purpose, the patient's identifiable information will never be provided to NCNP researchers as well as joint researchers at external facilities. However, the complete anonymization would not be achieved in case such a research is conducted by the physician or those who were involved in diagnosis.

⑦ For diagnostic purpose, samples will be preserved at least for one year considering the case where an additional analysis might be required. On the other hand, for research purpose the samples will be preserved for as many years as possible. Additionally, although resources have already been anonymized through a substitution by numbers, we also keep a comparison list that matches patients with their numbers so that we can revisit their clinical information at a later day. The access to such a list is only granted to the Privacy Officer and a limited number of Subofficers.

⑧ If the patient consents to the use of their information by foreign research institutes in addition to domestic institutes, please check the appropriate box. This enables international joint researches to be conducted.

⑨ When a resource is offered to public biobanks to serve as a research resource, a strict anonymization will be implemented with no generation of comparison list. Please ask the patient if she consents to offering their resource to such public biobanks as well as commercial enterprises. If the patient consents, please have the appropriate box checked.

⑩ Various types of data could be presented for an academic and educational purpose. In this case,

data will be completely kept anonymized so the data is unable to be tracked back to the patient. If an associated comparison list is available, we can provide the details of such a presentation individually as well as directly to the patient (or their authorized representative). However, please ensure the patient is provided with a genetic counselling before and after the disclosure. Our genetic counselling unit is also available (with consulting fee). Moreover, as researches progress further, there is a possibility that new diagnostic information would become available in the future. In this case, we will report the diagnosis result to the attending physician. However, we might withhold the report in these circumstances: 1) when the patient's contact address is not available due to reasons such as too much time has passed since the collection of data, or 2) when disclosure of diagnosis result is likely to harm the patient's or a third party's life, body, property and other rights and interests. Also, with regard to the disclosure of genetic information to a minor, we will discuss with the patient and/or his or their authorized representative, as well as refer to the advice by our Ethics Committee, in order to decide whether or not to disclose, and ways to disclose such information.

⑪ Researches can unexpectedly reveal an incidental finding that can cause a serious harm to a patient's health. Please confirm with the patient if she wishes to be informed about such a finding, and check the appropriate box if the patient do wish to be informed. However, especially in case of a genetic analysis, even when a large-scale analysis is performed, the subsequent analysis to interpret the raw sequencing data is limited to targeted regions/targeted genes aiming to elucidate disease causation and pathogenesis, therefore it is not certain that all kinds of health-harming information can be obtained. Also, information such as a patient's vulnerability to various disorders is usually not detected, as our analysis does not intend to serve such a purpose.

⑫ The patient (or their authorized representative) does not have a right to file a patent based on the achievement of the research.

Revocation of Consent

The patient may withdraw or make changes to any part that she has acknowledged in the "Consent Form for Diagnosis, Preservation and Research Use" at any time. The attending physician shall provide the patient (or their representative) with the form "Request Form to Amend Consent" which is found at the end of this handbook. The patient (or their authorized representative) shall fill out and return the form to us so we can take necessary procedures. In particular, if the request accompanies the need to destroy their samples, we will issue a proof of disposition to the patient (or their representative) in writing.

Protection and Archiving of Personal Information

Any personal identifiable documents which contain patient information will be stored in a lockable storage room, and will also be recorded in a database. This database is accessible only from the specified four units of computers in NCNP; one unit at the Sample Reception Desk of the MGC, two units in the Pathology Conference Room of the Department of Genomic Medicine Development which is located on the 1st floor of the TMC building, one unit in the Department of Neuromuscular Research of the National Institute of Neuroscience. These computers are connected via a private network and are completely disconnected from other network. Only the Analysis Conductor (who also holds the role of the Sample Administrator) and the personnel who conduct operations under his instruction are allowed to access the database.

The original copy of the complete consent form with signature is kept by the Analysis Conductor, therefore the original copy shall be submitted to us. The attending physician shall keep a physician's copy in the patient's medical record, and the patient (or their authorized representative) shall keep a patient's copy.

List of Analysis Conductors (also the Administrators of Samples and Bioresources) and Privacy Officers

Analysis Conductors and Administrators of Samples and Bioresources：

Ichizo Nishino (Director of the Department of Genomic Medicine Development of the MGC, Director of the Department of Neuromuscular Research, Clinical fellow at the Genetic Diagnosis Unit of the National Center Hospital)

Narihiro Minami (Researcher of the Department of Genomic Medicine Development and the Department of Neuromuscular Research, Medical Technician at the Genetic Diagnosis Unit)

Yuichi Goto (Director-General of the MGC, Director of the Department of Mental Retardation and Birth Defect Research, Head Physician at the Genetic Diagnosis Unit of the National Center Hospital)

Privacy Officer：Keiji Wada (Director-General of the Translational Medical Center)

Subofficer ：Toshiaki Hirata (Head of the General Affairs Section)

Advisors ：

Ichizo Nishino (Director of the Department of Genomic Medicine Development of the MGC, Director of the Department of Neuromuscular Research, Clinical fellow at the Genetic Diagnosis Unit of the National Center Hospital)

Narihiro Minami (Researcher of the Department of Genomic Medicine Development and the Department of Neuromuscular Research, Medical Technician at the Genetic Diagnosis Unit)

Yuichi Goto (Director-General of the MGC, Director of the Department of Mental Retardation and Birth Defect Research, Head Physician at the Genetic Diagnosis Unit of the National Center Hospital)

The above list of personnel is subject to change without notice due to organization and personnel change.

Contact:
National Center of Neurology and Psychiatry
MGC Sample Reception Desk
Address: 4-1-1 Ogawahigashi-Cho, Kodaira-Shi, Tokyo, JAPAN
Telephone: +81-(0)42-341-2711 (Operator), +81-(0)42-346-1770 (Direct)

Approved by Ethics Committee on 24 February, 2017

Modified in conformity with the revised ethical policy, on 30 May, 2017