'Muscle Disease Diagnostic Support (Normal) and Preservation and Research Use (Muscle Repository)'

Explanatory Documents

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A. 'Muscle Disease diagnostic support'

1. Name of this research project

Project name: 'Muscle Disease Diagnostic Support and Preservation and Research Use (Muscle Repository)'
This project is conducted with the approval of the Center's Ethics Committee and the President.

2. Support for the diagnosis of muscle diseases

The project consists of 'Muscle Disease Diagnostic Support' and 'Preservation and Research Use (Muscle Repository)'.
The 'Muscle Disease Diagnostic Support' provides a more detailed analysis for cases where the diagnosis cannot be made in the usual practice or is difficult to make; and, therefore, is performed as a broadly defined practice. This document has been prepared to ensure that the participants (or their parents if the participants are children) understand the contents of the explanation regarding the 'Muscle Disease Diagnostic Support (Normal)', which addresses the diagnosis of muscle diseases for affected or suspected affected persons (participants). The doctor in charge will assist and support the participant to properly understand the contents of the project. If you agree to participate in this project, please complete the consent document for participation in the project. The following is a detailed explanation of the tests and research and the National Center of Neurology and Psychiatry will not conduct any tests or research using specimens taken from the participants (or their parents if the participants are children) without the consent of the participants. Please also understand that the results of this project may generate materials participant to intellectual property rights in the future, such as conference presentations, thesis publications, and patent rights. The abovementioned rights do not belong to the participants.
The doctor in charge hold the responsibility of deciding that it is necessary to examine blood, muscle, nerve, skin, and other tissues to diagnose the disease in participants suspected of having

a neuromuscular disease. Tissue samples taken from the participant undergo examination at the Medical Genome Center (MGC) in the TMC building of the National Center of Neurology and Psychiatry, where pathological tests (looking at form), biochemical tests (looking at function) and genetic tests (looking at DNA and RNA) are conducted. Some tests are also performed at cooperating diagnostic centers. Diagnosis by tissue examination can be broadly divided into pathology, biochemistry, and genetic testing. The doctor in charge certifies that participation in the project is in accordance with the laws and regulations of their country, and that samples can only be sent if they are in compliance.

(1) Matters relating to pathology, biochemistry and autoantibody testing

Pathology is the method of examination that involves stabilizing the tissues in a special way such that slides can be made and stained to highlight the different properties of the tissues and the appearance or ‘shape’ can observed under a microscope. Biochemical tests examine the 'function' of the muscle tissues, for example, to see their ability to produce energy. Autoantibody tests look for antibodies that recognize and damage the body's own cells and tissues. Pathology, biochemistry, and autoantibody tests require special techniques and equipment that need trained specialists to interpret the results. These tests are carried out at the MGC Genomic Medicine Development Department (in the TMC building) of the National Center of Neurology and Psychiatry, in collaboration with the Hospital Genetic Testing and Diagnostic Laboratory, the First Department of Disease Research and the Second Department of Disease Research of the Institute of Neurology. If more specialized tests are deemed necessary for diagnosis, the specimen is sent to a collaborating research center for further detailed testing. For all cases, the National Center of Neurology and Psychiatry reports the test results to the doctor in charge. The joint research centers that carry out these specialized analyses are as follows:

- Kazuma Sugie, Tokiwa University, Biochemical analysis of metabolic muscle diseases
- Fuyuko Fukuda, Hamamatsu University School of Medicine, Biochemical analysis of metabolic muscle diseases
- Shigeaki Suzuki, Keio University, Myositis-specific autoantibody analysis
- Nahoko Okiyama, Tokyo Medical and Dental University, Myositis-specific autoantibody analysis
- Yoshiki Sekijima, Shinshu University, Amyloid myopathy pathomorphology
- Tomoyuki Awaya, Kyoto University, AI-based splicing site prediction
- Masakazu Mimaki, Teikyo University, Mitochondrial respiratory chain complex analysis

(2) Matters related to genetic testing.

Genetic testing 'looks at DNA and RNA' and advances in medical science have made it an essential test for making a definitive diagnosis of a specific disease. Some diseases are covered by insurance and the number is expected to increase in the future.

(2)-1 Exhaustive screening of diagnosed muscle pathology cases for mutations in known causative genes of muscle diseases

The First Department of Disease Research of the National Institute of Neurological Research, National Center of Neurology and Psychiatry has performed disease categorization of inherited muscle diseases based on the pathological features of muscle biopsy findings and analyzed them using four gene analysis panels. However, genetic analyses were not performed if a hereditary

muscle disease was not suspected pathologically. Nevertheless, as there are cases that may present as acquired muscle diseases that may eventually be categorized as hereditary, a means to ensure how such cases could not be missed was developed. Therefore, if the patient agrees to participate in the 'Exhaustive screening of muscle pathology cases for mutations in known causative genes of muscle diseases' (Ethics Committee approval number: A2021-083, date of approval: 10 November 2021), for muscle pathology cases requested from January 2022 onwards, the patient's DNA that has been extracted from the patient's blood, regardless of the results of muscle pathology, will be used and the said DNA will be used to perform the necessary genetic testing in all cases. (However, the 'Exhaustive screening of muscle pathology cases for mutations in known causative genes of muscle diseases' is not applicable to cases where a muscle pathological diagnosis was requested before 2021 or where a muscle pathology diagnosis was not performed, and is invalid even if the 'Participation in exhaustive screening of muscle pathology cases for mutations in known causative genes of muscle diseases' is ticked in the consent document. The abovementioned limits preclude the use of the samples indicated.)
*Please see Appendix 1 (p18-20) for a description of A2021-083: Screening for mutations in known causative genes of muscle diseases for all diagnosed cases of muscle pathology.

(2)-2 Other genetic analyses

The technology for analyzing genes has advanced dramatically and it is now possible to examine all DNA and RNA (called whole-genome analysis) and all protein-coding parts of all genes (called exons and the process is called whole-exome analysis). The analysis of intronic and untranslated regions obtained by whole-genome analysis is evolving at a rapidly increasing rate and whole-genome data, as well as RNA sequencing data are accessed and studied in the cloud from a specific IP address in an environment where only specific parties with a unique identification and password are allowed to enter. Indeed, it is not uncommon for causative abnormalities to be found only after such large-scale analysis.
Such large-scale analyses could, theoretically, reveal susceptibility and trends in various diseases. In some cases, the findings that had been discovered unexpectedly could have important health consequences (called incidental findings). Please tick the appropriate box if you would like to be informed when such findings are obtained. However, even if a large-scale analysis is performed, the analysis to make sense of the raw data does not necessarily provide information on various health effects, as the analysis is usually performed only on regions of interest and related genes for the purpose of elucidating the cause and pathology of specific muscle diseases. In addition, information such as susceptibility to various diseases other than the disease of interest is usually not revealed, as this is not the purpose of the analysis.

The specimens are stored for at least one year, as are pathology, biochemistry, and antibody testing-related materials, with the possibility of retesting.

(3) Future confirmation of diagnosis.

If no diagnosis of the participant's disease can be made during the first evaluation, a diagnosis may be confirmed in the future using the participant's specimens, if the participant has **agreed to the clause 'storage and research' of the material (specimens and various clinical information).** In such cases, the diagnosis will be reported to the doctor in-charge. However, it may not be possible to report the results if the contact details are unknown for reasons such as a long period of time having passed, or if disclosure could harm the life, body, property or other

rights and interests of the participant or a third party. In addition, when disclosing genetic information on minors in the event that a diagnosis is confirmed in the future, we will discuss the matter with the participant and his or her surrogate and decide whether and how to disclose the information based on the opinion of the Ethics Committee. If the new diagnosis is based on a genetic test, the doctor in-charge will be contacted so that genetic counselling can take place before or after the diagnosis is made. The genetic counsellor at the hospital will be available for consultation.

(4) Provision of materials (specimens and various clinical information) to other facilities for diagnostic purposes.

If the participant (or parents if the participant is a child) agrees to 'storage and research' of materials (specimens and various clinical information) at our center and the specimens are stored at our center, in the event that it becomes necessary to carry out diagnostic tests that are not performed in our center at a later date with another institution, please submit a 'Diagnostic Sample Request Form' and we will respond appropriately. In such cases, if necessary, we will also share our diagnostic data with the facility where the test was carried out. If the hospital you go to for consult has changed and you wish to re-obtain the previous diagnostic results, you will be asked to submit a 'Request for Provision of Diagnostic Information'. In both cases, this is to confirm the consent of the participant or the surrogate, so please contact your doctor or the MGC specimen reception desk (mbx@ncnp.go.jp).

(5) Attribution of analysis data.

Data, such as the data naturally obtained from the accumulation of specimens, and information, such as the clinical information from participants and the frequency of diseases obtained from the compilation of such data, belong to the National Center of Neurology and Psychiatry.

3. Purpose and significance of the 'Muscle Disease Diagnostic Support'.

The aim of muscle disease diagnostic support is to provide a more detailed analysis in cases that cannot be diagnosed or are difficult to diagnose in the usual clinical practice. These are performed as part of the broader medical practice.

4. Method of implementation and duration of the 'Muscle Disease Diagnostic Support' project.

1) Specimens and clinical information handled by the 'Muscle Disease Diagnostic Support'.

As part of the broader medical treatment, the doctor in-charge sends specimens, which may include frozen skeletal muscle, cultured cells (muscle and/or skin), genomic DNA, and clinical information on the participant (examination findings, laboratory data, images, etc.) to the center to support the logistical limitations of the diagnosis of muscle diseases. The specimens derived from prenatal and pre-onset diagnoses are also handled.

2) Use of diagnostic data and various clinical information for academic and educational purposes

Diagnostic data and various clinical information that have been anonymized as part of the project may be used for academic presentations or educational purposes, such as conference presentations and research papers.

3) Information disclosure

The 'Muscle Disease Diagnostic Support' will only take place once the center has explained its contents in writing and the participant has explicitly stated that he or she understood and consented to it. New information about the project will be published on the 'Portal for participants' (https://www.ncnp.go.jp/nin/guide/r1/patients.html) from time to time.

4) Registration of genetic analysis data in public databases.

In recent years, it has become increasingly recognized that in order to overcome intractable diseases, it is necessary for many researchers to share genetic analysis data linked to disease information. Among other things, the registration of genetic analysis data in public databases is becoming a prerequisite for analyses using public research funds and for publication in international journals. This is because it is important for the understanding of the diseases that genetic analysis information with accurate clinical information is used by many researchers to promote research. The various large-scale genetic tests carried out by the National Center of Neurology and Psychiatry are often supported by public research funds from the Japan Agency for Medical Research and Development (AMED) and other public research funds. The genetic data obtained from the analysis is required, in principle, be registered in a public database. Data on frequencies, such as the frequency of genetic changes found in the general population or in participants with the same disease, that cannot be used to identify individuals, are registered in a public database set up by the AMED and made available to an unspecified number of researchers. This data is made available to an unspecified number of researchers. On the other hand, the detailed genetic analysis data of an individual, with all general personal information (name, address, contact details, hospital ID, etc.) removed, will be registered together with disease information in a public database with restricted sharing and restricted publication, as defined by the AMED and others. Please note that it may be difficult to delete information upon withdrawal of consent if the data for research use has been shared in this manner.

(5) Information on genetic counselling available.

Genetic analysis may be used in the support of muscle disease diagnosis. Genetic testing differs from routine testing in that it can provide information about the participant as well as the participant's family members and may also be used for pre-onset or prenatal diagnosis. You will, therefore, receive a full explanation from your doctor to ensure that you fully understand the characteristics of such genetic tests. If possible, we recommend that you get the information about specialized genetics from a genetic counselling professional. If you do not have a genetic counsellor, please contact our outpatient genetic counselling service and a member of staff will be happy to help you. (Telephone number: +81+42-341-2711, internal line 5824)

The test results are sent to your doctor, who will explain the results to you. However, if the request is made by the doctor in-charge of genetic counselling, the results will be reported to that doctor. If you have any questions or concerns about the explanation of the results after the test, please do not hesitate to ask your doctor or contact the MGC specimen reception desk.

5. Burdens, risks and benefits that may arise from 'assisted diagnosis of muscle diseases'.

(1) Adverse events.

There are no specific new adverse events arising from 'Muscle Disease Diagnostic Assistance'.

(2) Other burdens and disadvantages.
Similar to above, no particular burdens or disadvantages are apparent.

6. Financial burden associated with the 'Muscle Disease Diagnostic Support'.
With regard to the diagnostic material (specimens and various clinical information), there are no new financial burdens or rewards arising from the implementation of the project for post-diagnostic storage purposes.

7. Withdrawal of consent after provision of materials (specimens and various clinical information)
Participation in 'Muscle Disease Diagnostic Support (Normal)' is freely decided upon by the participant (or parents if the participant is a child). Even if you have already given your consent, you can withdraw your consent at a later date. In such cases, we will do our best to comply with the withdrawal request, but please note that it may be difficult to take action even if you wish to withdraw your consent for 'Muscle Disease Diagnostic Support', for example if the material (specimens and various clinical information) cannot be identified because the material you have provided has already been anonymized.

8. Handling of personal information, etc.
1) Methods for anonymization
In principle, when carrying out tests, the specimens should be numbered and work on without any personally identifiable information. This is called anonymization. However, anonymization by leaving which number corresponds to which person is called linkable anonymization. This type of anonymizations is performed because a corresponding identifier between the individual who has been tested and the specimen number is necessary in order to return the test results. The person who manages such a correspondence list is called a personal information manager, and this duty is performed by the Director of the First Department of Disease Research, National Institute of Neurological Research, National Center of Neurology and Psychiatry, and the Director of the MGC Genome Clinical Development Department (dual appointment). When diagnostic tests are requested from other facilities, personal information is naturally not provided.

2) Methods of safe management of personal data, e.g.
Personal data are stored in a database in the computer at the MGC specimen reception desk/genetic testing and diagnosis room, which is managed by medical technicians. The personal information can also be accessed on one PC (in the photon microscopy room of the First Department of Disease Research at the Institute of Neurology) and two PCs (in the organizational discussion room of the MGC Genome Clinical Development Department on the first floor of the TMC building) connected to that PC via a dedicated line (intranet), but access to the personal information is limited to the MGC specimen reception desk/gene testing and diagnostic room clerks who assist in registration, as well as the only people with access to personal information are the clerks of the MGC Specimen Reception Desk/Gene Testing and

Diagnostic Laboratory and qualified researchers/research students of the MGC Genome Clinical Development Department. Of course, they are not allowed to disclose information obtained in the course of their work. In addition, most of the actual persons in charge are doctors, clinical laboratory technicians, etc. and are obliged to maintain confidentiality. Access to materials (specimens and various clinical) and diagnostic data is restricted to the building itself, to the departments and to the rooms by card key, and only authorized personnel are allowed in and out. In addition, the original consent forms and documents containing medical information necessary for diagnosis (e.g., referral letters from attending physicians) are stored in a locked archive in the Organizational Discussion Room of the MGC Genomic Medicine and Clinical Development Department.
The PCs containing the information database are connected by a dedicated line (intranet) and are isolated from the external network; both PC login and database access are password-controlled and only authorized personnel can view them.

9. Conflicts of interest regarding funding sources, researchers and other research projects
The project is mainly funded by grants from the Research and Development Fund for Psychiatric and Neurological Diseases and the First Department of Disease Research of the MGC and the Institute of Neurology. However, some research funds may be used from the Japan Research and Development Medical Agency Research Fund and the Health and Labour Sciences Research Grant. The conflicts of interest of the Center's researchers in this project are reviewed by the Center's Conflict of Interest Management Committee and managed appropriately. The conflict-of-interest status of researchers from joint research organizations has also been verified to ensure that there are no issues.

10. To obtain or view the project plan and documents relating to the research project
You may view the project plan and the documents regarding the research methodology, to the extent that they do not interfere with the protection of personal data and other information of other participants in the project and with the operation of the project concerned.

11. About the ethics committee that reviewed the support for the diagnosis of muscle diseases
When the Ethics Committee (hereinafter referred to as the 'Committee') is requested by the head of the research organization to give its opinion on the appropriateness of conducting research, etc., the Committee will review the research from an ethical and scientific perspective, including information on conflicts of interest of the research organization and researchers, in a neutral and fair manner. If you have any enquiries about the committee's procedures, list of members, deliberations and other information on this research, you can find them at the URL below.

《Ethics Committee》
Ethics committee of National Center of Neurology and Psychiatry
Establisher: National Center of Neurology and Psychiatry, President
Location: 4-1-1 Ogawa-higashi machi, Kodaira, Tokyo
Document viewing is available at the following URL

[URL]: https://www.ncnp.go.jp/hospital/partnership/ethics/index.html

12. Implementation system for diagnostic support for muscle diseases, name of the research organization, and name of the principal investigator.

Persons responsible for conducting tests and managing materials (specimens and various clinical information) and personal information managers

- Ichizo Nishino, Director of Medical Genome Center; Director of Neuromuscular Research, National Institute of Neuroscience; Medical staff, Hospital Genetic Testing and Diagnostics Laboratory

Principal investigators in joint research organizations

- Kazuma Sugie, Tokiwa University, Biochemical analysis of metabolic muscle diseases
- Fuyuko Fukuda, Hamamatsu University School of Medicine, Biochemical analysis of metabolic muscle diseases
- Shigeaki Suzuki, Keio University, Myositis-specific autoantibody analysis
- Nahoko Okiyama, Tokyo Medical and Dental University, Myositis-specific autoantibody analysis
- Yoshiki Sekijima, Shinshu University, Amyloid myopathy pathomorphology
- Tomoyuki Awaya, Kyoto University AI-based splicing site prediction
- Masakazu Mimaki, Teikyo University, Mitochondrial respiratory chain complex analysis

13. Contact details for consultations and other enquiries regarding support for diagnosis of muscle diseases

If the participant or the participant's family members have any questions or concerns about this research project, please do not hesitate to contact the enquiry desk at the end of this explanatory document. Please note that we may not be able to respond or answer your questions due to reasons such as the protection of the personal information of the providers of other materials (specimens and various clinical information) and the intellectual property rights of the researchers.

If you wish to make a complaint, for example, if you have been inconvenienced in the implementation of the project, please contact the Project Manager.

○ Contact person for enquiries about the project :
4-1-1, Ogawa-higashi-machi, Kodaira, Tokyo 187-8552, Japan
Specimen Reception Desk, Medical Genome Center, National Center of Neurology and Psychiatry.
Telephone number: +81+42-341-2711 (main line)
E-mail: mbx@ncnp.go.jp (E-mail preferred)

○ Project Manager:
4-1-1, Ogawa-higashi-machi, Kodaira, Tokyo 187-8502, Japan
National Institute of Neuroscience, National Center of Neurology and Psychiatry
Ichizo Nishino
E-mail: nishino@ncnp.go.jp

B. 'Preservation and Research Use (Muscle Repository)'

If you agree to the conditions in 'Preservation and research use (muscle repository)', the materials from the participant (specimens and various clinical information from the patient) will be carefully stored as a 'muscle repository' and used when re-examination is necessary. This will also be used for research aimed at clarifying the etiology and pathology of the disease, as well as developing treatment methods. The doctor in charge certifies that participation in the project is in accordance with the laws and regulations of their country, and that samples can only be sent if they are in compliance.

1. Purpose and significance of preservation and research use

(1) Purpose and significance of 'preservation of materials (specimens and various clinical information)'.

- Possibility of re-inspection

The purpose of preservation of materials to allow availability for the possibility of re-inspection for better understanding of the condition and more appropriate management to the patient. Tests such as muscle pathology and genetic analysis may need to be repeated for technical reasons such as when new discoveries related to a disease have been developed. To do so, it is necessary to 'preserve the materials and documentation (specimens and various clinical information)'. This is because of the possibility that a diagnosis may be made in the future due to scientific breakthrough, even if it was not made at the time of initial testing.

Tests such as muscle pathology and genetic analysis may not be able to make a diagnosis at present. However, new testing methods and a more detailed analytical methods may be developed that will allow a diagnosis to be made in the future. Such a diagnosis can be made in the future if the 'Preservation of documentation (specimens and various clinical information)' is agreed upon by the participants or the participants' representative and the specimens are stored in the 'Muscle Repository'.

- Possibility of a diagnosis in the future, even if it is not available at present

It is also possible that a detailed analysis may be required in the future, even for cases when a diagnosis has already been made upon first submission. If specimens are stored, such diagnoses can be made in the future.

- Possibility of even if a diagnosis is made at present, a detailed analysis may be required in the future

Certain diagnoses made at present may no longer be relevant in the future due to changes in the concept of a disease or changes and subdivisions in disease classifications as a result of advances in medical science. New therapies are also constantly being developed for various diseases based on detailed and exhaustive pathological evaluation. If specimens are stored in the Muscle Repository, it will be possible to make a diagnosis in line with the latest disease nomenclature, concepts, and taxonomy and, more importantly, carry out further detailed analysis to see if the patient is eligible for the latest treatment protocols, without having to collect the specimens again. If a specimen is taken again in the future, it can be compared with the existing specimen, and the progression or changes in disease-status based on the new testing that will be performed can be determined.

- Use for research

The importance of preservation for research use for future treatment cannot be emphasized enough. The causes of many neuromuscular diseases remain unknown and there are no standard

treatments. In order to elucidate the causes of the diseases and develop new drugs and therapies as quickly as possible, research using the participants' materials (specimens and various types of clinical information) are essential. This requires the long-term preservation of specimens from test participants.

(2) Purpose and significance of 'research use of materials (specimens and various clinical information)'.
The National Center of Neurology and Psychiatry and many national and international research institutes carry out research to clarify the causes and pathology of diseases and to develop treatments. There, individual specimens and clinical information, including those of the participants, are valuable research resources for solving the treatment of neuromuscular diseases as quickly as possible. Even for undiagnosed cases, the discovery of a promising treatment candidate is often the catalyst for further research. On the other hand, for existing diseases, studies using multiple specimens from the same disease group can be extremely useful for research into the pathogenesis and development of treatment common to all diseases, even in the presence of individual differences.

2. Method of implementation and duration of the project with regard to preservation and research access

1) Participants of preservation and research use

All materials (specimens and various clinical information) and diagnostic data sent for the purpose of participating in the 'Muscle Disease Diagnostic Support' project are participant to storage in the 'Muscle Repository'. If specimens are collected at the center's hospital, formalin-fixed specimens stored in the clinical laboratory of the center's hospital are also included.

2) Methods of storing materials (specimens and various clinical information).

The materials (specimens and various clinical information) and diagnostic data will be kept under strict control in the Medical Genome Center, located at the restricted admission area on the first floor of the TMC building. Specimens will be stored for at least one year and will continue to be stored as part of a 'muscle repository' for as long as possible thereafter for the duration of the project.

(3) Provision (sharing) of materials (specimens and various clinical information) and diagnostic data and their use in research.

(1) Provision of materials (specimens and various clinical information) and diagnostic data for research use involve certain considerations.

Anonymized material (specimens and various clinical information) is provided for research approved by the Ethics Committee. If you wish to use materials from other institutions, you can apply for details via the MGC Specimen Reception Desk (mbx@ncnp.go.jp) or the NCNP Biobank Research Desk (biobank@ncnp.go.jp) and a contract will be signed with the National Center of Neurology and Psychiatry before the materials are provided.

(2) Institutions to be served.

(i) National and international research institutions.

Materials (specimens and various clinical information) and diagnostic data from the Muscle

Repository may be provided for research conducted by national and international academic research institutions. The Ethics Committee of the National Center of Neurology and Psychiatry will review the scientific and ethical validity of the need for the data, providing it only if deemed appropriate.

(ii) Domestic and foreign commercial enterprises.
Materials (specimens and various clinical information) and diagnostic data may be provided by the 'Muscle Repositories' for research conducted by national and international commercial companies for a fee. In particular, the majority of the development of new therapeutic drugs is carried out by commercial pharmaceutical companies. Research and development conducted by such commercial companies, including pharmaceutical companies, could also benefit from the use of specimens from test participants, which would help to elucidate the pathology of neuromuscular diseases and develop treatments as soon as possible. The scientific and ethical appropriateness of the use of materials (specimens and various clinical information) and diagnostic data will be reviewed by the Utilization Committee of the National Center of Neurology and Psychiatry when such materials (specimens and various clinical information) and data are provided, and by the Ethics Committee of the National Center of Neurology and Psychiatry when such materials (specimens and various clinical information) and data are used in joint research. The data (specimens and various clinical information) and diagnostic data will only be provided if the Ethics Committee of the National Center of Neurology and Psychiatry conducts a review of their scientific and ethical appropriateness and deems them appropriate. Information such as epidemiological data obtained from the accumulation of materials (specimens and various clinical information) and diagnostic data in the Muscle Repository belongs to the National Center of Neurology and Psychiatry, but if undisclosed information is to be provided to individual commercial companies, among others, it must be provided in accordance with the separately specified agreement with the National Center of Neurology and Psychiatry. If undisclosed information is provided to individual commercial companies and similar institutions, it may be provided if the scientific and ethical considerations surrounding the use of information has been reviewed and judged to be appropriate by the Center's Muscle Repository Information Provision Review Committee, a review committee that has been established separately for this purpose.

(iii) Public organization banks.
The Muscle Repository may provide materials (specimens and various clinical information) and diagnostic data to public tissue banks. Public tissue banks are public institutions that secure the resources necessary for research and provide them to research institutes. In Japan, the best-known examples are those operated by RIKEN, the Human Science Foundation, and the National Institute of Biomedical Innovation (NIBIO). When materials are provided there, they are widely used for scientific research. In the provision of such materials, once anonymized, the clinical information of the participant can never be traced back again (this is called unlinkable anonymizations), which ensures that privacy is protected. However, in this case, it is not possible to inform the participants of the research results.

(iv) Registration of genetic analysis data in public databases.
The various large-scale genetic analyses carried out at the National Center of Neurology and

Psychiatry and its collaborating research facilities are often supported by public research funds from the AMED and other public research funds. The genetic data obtained from the analysis will, in principle, be registered in a public database. Data on the frequency of genetic changes found in the general population or in participants with the same disease, which cannot be identified by individuals, are registered in a public database set up by the AMED and made available to an unspecified number of researchers. On the other hand, detailed genetic analysis data on an individual, with all general personal information (name, address, contact details, hospital ID, etc.) removed, will be registered together with disease information in a public database with restricted sharing and restricted publication, as defined by the AMED and other regulatory institutions. Please note that as this type of research through sharing data progresses, it may be difficult to delete information upon withdrawal of consent.

(3) Research use of materials (specimens and various clinical information).
If materials (specimens and various clinical information) are provided by the Muscle Repository for research purposes, they may be used for secondary research purposes, including

The types of research that may be carried out include:
(i) Biochemical, molecular biological, and molecular genetic research; such as extracting DNA, RNA, and proteins and their analysis at the molecular level or at various levels in a multilayered manner (omics analysis) to clarify the causes and pathology of diseases and to develop therapeutic modalities in, primarily, a research setting.

(ii) Histological and pathological studies: studies in which specimens are cut into thin sections and histochemical or immunostaining is performed or electron microscopy is used to observe minute morphological changes.

(iii) Cell biological research: research to analyze the functions of genes and molecules or to evaluate the efficacy of candidate drugs, etc., by using cultured cells such as from the muscle or skin (cells immortalized by iPS or other technologies may be used).

(iv) Epidemiological studies: studies that investigate what diseases are common and what characteristics are found in those who show certain findings, followed by conducting statistical analyses to show real-world applicability.

(v) Other: materials may also be used for research purposes other than those mentioned above, aimed at elucidating the etiology/pathology or developing treatments. In any case, the research will only be carried out if it has been reviewed and approved by a separate ethics committee, which deemed that the research is appropriate.

Procedures for research use require regulatory entities. Research using materials (specimens and various clinical information) and diagnostic data is carried out after a separate review and approval by an ethics committee in accordance with the Ethical Guidelines for Life Sciences and Medical Research Involving Human Participants.

3. Burdens, risks and benefits that may arise from preservation and research use

(1) Adverse events

As the project involves the storage of materials (specimens and various clinical information) in the 'Muscle Repository' after diagnosis, and no new specimens are collected for the primary purpose of registration in the 'Muscle Repository'. No undesirable events (adverse events) of any kind will occur to the participants due to registration in the said repository.

(2) Other burdens and disadvantages

As above, no particular situation is applicable.

(3) Anticipated benefits

The preservation of materials (specimens and various clinical information) is beneficial to participants in that it enables responses to cases in which retests are necessary, as described in 1.(1) Purpose and significance of "Preservation of materials (specimens and various clinical information)"; it may enable a diagnosis to be made in the future even if no diagnosis is made at present; and it may enable responses to cases in which detailed analysis is required in the future due to changes in disease concepts or classifications, among others. The benefits to the participant include the possibility of responding to cases where re-testing is required, where a diagnosis can be made in the future even if it is not currently available, and where detailed analysis may be required in the future due to changes in disease concepts and classifications. Although there is almost no direct benefit from research use, it is expected that research results will lead to the elucidation of the etiology and pathology of diseases and the development of new diagnostic methods, medicines, and medical treatment protocols in the future.

(4) The risk that preservation becomes impossible

The project aims to maintain the 'Muscle Repository', which has accumulated materials (specimens and various clinical information), for as long as possible, but it may be discontinued if it becomes difficult to continue the project due to lack of budget or if the project is no longer necessary due to the consolidation of biobanks. In such cases, we will work with other national centers to ensure that valuable materials (specimens and various clinical information) are used as effectively as possible. Please note that although we have taken all possible countermeasures and mitigation strategies against disasters, there is a risk of damage and loss or dispersal of materials (specimens and various clinical information) in the event of a disaster of a larger or unpredictable scale.

4. Financial burden or responsibility associated with the storage of materials (specimens and various clinical information)

There are no new financial burdens or rewards for storing materials (specimens and various clinical information) as 'muscle repositories'.

5. Withdrawal of consent for 'storage and research use' of materials (specimens and various clinical information).

Participation in the 'storage and research use' project of materials (specimens and various clinical information) is a decision that is made by the participant (or parents if the participant is a child) freely and without any form of coercion, direct or otherwise. Even if you have already given

your consent to 'storage and use', you can withdraw your consent at a later date. In such cases, we will do our best to comply with the withdrawal request, but please note that it may be difficult to do so, for example, if the material (specimens and various clinical information) cannot be identified because it has already been anonymized.

6. Handling of personal and other information in storage and research use

1) Methods of anonymization and safe management of personal data, e.g.
As this project covers materials (specimens and various clinical information) and diagnostic data sent for the purpose of participating in the 'Muscle Disease Diagnosis Support', 'Prenatal Diagnosis' or 'Pre-Onset Diagnosis' projects, anonymization methods and safety management methods for personal information and related matters, are based on the methods prescribed by the 'Muscle Disease Diagnosis Support', 'Prenatal Diagnosis' and 'Pre-Onset Diagnosis' projects.

2) Information sharing of the National Center of Psychiatry and Neurology Hospital case study.
Information on participant materials (specimens and various clinical information) for which specimens are collected at the National Center of Neurology and Psychiatry Hospital will be shared as specified in 'A2015-151: Establishment of an inter-study collaboration system using Super ID' (see the relevant public notice for details).
https://www.ncnp.go.jp/hospital/partnership/docs/2015-761.pdf).

7. Methods of storage and disposal of materials (specimens and various clinical information)

- Methods of storage and quality control of specimens and information.

Documents related to the implementation of the project (copies of various applications and reports, consent documents, submitted consent withdrawal forms, common medical questionnaires, symptom assessments, etc.) and personal information are stored in a database on a PC in the MGC specimen reception counter/genetic testing and diagnosis room, while the original consent documents and documents containing medical information necessary for diagnosis (e.g. referral letter from the attending physician) are The original consent documents and documents containing medical information necessary for diagnosis (e.g. referral letter from the attending physician) are stored in a locked archive in the Organizational Discussion Room of the MGC. In addition, as specimens derived from prenatal and pre-onset diagnoses are also handled, the residual specimens are also stored in the muscle repository.

- Handling of specimens and information after the end of the project

The project is intended to continue over a long period of time. If the project has to be terminated for some reason, we aim to continue only the provision of materials (specimens and various clinical information) for about three to five years after the decision has been made. The Steering Committee will also discuss the fate of the materials after the termination of the project and consider depositing them in other banks as much as possible, as mentioned above.

8. Conflicts of interest regarding funding sources, researchers and other research projects in 'Preservation and Research Use'

The project is mainly funded by grants from the Research and Development Fund for Psychiatric

and Neurological Diseases and grants for Department of Neuromuscular Research and MGC, although some research funds may be used from AMED and the Health and Labour Sciences Research Grant. The conflicts of interest of the Center's researchers in this project are reviewed by the Center's Conflict of Interest Management Committee and managed appropriately. The conflict-of-interest status of researchers from joint research organizations has also been checked to ensure that there are no problems.

9. Handling of research results for those who have provided materials (specimens and various clinical information)

If, at the time of obtaining consent, the participant of the research is informed or wishes to be informed of the results when results are incidentally obtained that are considered important for the protection of the health of the research participant and his/her family, the participant of the research will, in principle, be informed. At that time, if necessary, we will consult with the specialist and the doctor in-charge of the participant and recommend that he or she receive medical attention at an appropriate medical institution. In addition, as this project is not about testing itself, measurement errors cannot be ruled out, there is a risk of mix-ups due to anonymizations and, therefore, retesting is usually necessary, and it is the participant's choice and responsibility whether or not to receive medical treatment afterwards. No responsibility is assumed for the results of any subsequent tests or other results. No compensation can be provided for the costs of subsequent treatment provided by specialists.

10. Compensation for damage to health caused by 'preservation and research use'.

No new health hazards will arise as a result of the implementation of this project, in which materials (specimens and various clinical information) are stored in the 'Muscle Repository'.

11. Public access to information on preservation and research use

The institutions to which you have provided the materials (specimens and various clinical information) and diagnostic data registered and stored in the Muscle Repository may inform you about the start of the research by posting a public notice when the research is conducted. The center will post such notices below for your information.

National Center of Psychiatry and Neurology website.
https://www.ncnp.go.jp/hospital/partnership/ethics_result.html

Homepage of the First Department of Disease Research.
https://www.ncnp.go.jp/nin/guide/r1/koukokubun.html

12. To obtain or view the project plan and documents relating to the research project

You may view the project plan and documents relating to the research methodology to the extent that this does not hinder the protection of personal data and other information of other participants in the research and the originality of the research concerned.

13. Ethics committee that reviewed the study

When the Ethics Committee (hereinafter referred to as the 'Committee') is requested by the head of the research organization to give its official evaluation on the appropriateness of conducting research and related matters, the Committee will review the research from an ethical and scientific perspective, including information on the conflicts of interest of the research

organization and researchers, in a neutral and fair manner. If you have any enquiries about the committee's procedures, list of members, deliberations, and other information on the research review, you can find them at the URL below.

《Ethics Committee》
Ethics committee of National Center of Neurology and Psychiatry
Establisher: National Center of Neurology and Psychiatry, President.
Location: 4-1-1 Ogawa-higashimachi, Kodaira, Tokyo
Document viewing is available at the following URL
［URL]: https://www.ncnp.go.jp/hospital/partnership/ethics/index.html

14. Implementation system for preservation and research use, name of the research organization, and name of the responsible person
The person responsible for conducting tests and managing materials (specimens and various clinical information) and personal information managers
Ichizo Nishino, Director of Medical Genome Center (concurrent post), Director of the Department of Neuromuscular Research, National Institute of Neuroscience, and Medical Officer (concurrent post) at the Hospital Genetic Testing and Diagnostic Laboratory

15.Contact for consultations and other enquiries on preservation and research use.
If the participant or the participant's family members have any questions or concerns about this research project, please do not hesitate to contact the enquiry desk at the end of this explanatory document. Please note that we may not be able to respond or answer your questions as extensively as you may require due to reasons such as the protection of the personal information of the providers of other materials (specimens and various clinical information) and the intellectual property rights of the researchers.
If you wish to make a complaint, for example in the unfortunate event of being inconvenienced during the implementation of the project, please contact the Project Manager.

○ Contact person for enquiries about the project:
4-1-1, Ogawa-higashi-machi, Kodaira, Tokyo 187-8552, Japan
Specimen Reception Desk, Medical Genome Center, National Center of Neurology and Psychiatry, National Center of Neurology and Psychiatry.
Telephone number: +81+42-341-2711 (main line)
E-mail: mbx@ncnp.go.jp (E-mail preferred)

○ Project Manager:
4-1-1, Ogawa-higashi-machi, Kodaira, Tokyo 187-8502, Japan
National Institute of Neuroscience, National Center of Neurology and Psychiatry
Ichizo Nishino
E-mail: nishino@ncnp.go.jp

(Appendix 1)

[Project Name]
Comprehensive genetic screening of muscle diagnosed pathology cases for known causative genes of muscle disease (Ethics Committee approval number: A2021-083, date of approval: 10 November 2021)

[Principal investigator]
Ichizo Nishino, Department of Neuromuscular Research, Institute of Neuroscience, National Center of Neurology and Psychiatry

[Purpose and significance of the project]
The aim of this study is to build on the muscle repositories conducted in the Muscle Disease Diagnostic Support Project. This is done by performing genetic analysis in all cases for which blood samples were received from the patient with simultaneous muscle pathology diagnosis at our centre during the study period, ensuring not to miss the diagnosis of all the hereditary muscle diseases including cases which seem to be acquired muscle diseases. A genetic analysis is performed in all cases using a gene panel. The objective is to offer a comprehensive understanding of hereditary muscle diseases with unidentified causes, serving as the foundation for the development of potential treatments. All analyses will be carried out at the Medical Genome Center, Department of Neuromuscular Research, National Institute of Neuroscience, National Centre of Neurology and Psychiatry.

[Method and duration of the project]
Subjects: All cases registered in the Muscle Repository in the 'Muscle Disease Diagnostic Support and Preservation and Research Use (Muscle Repository) ' (PI: Ichizo Nishino) from January 2022 onwards are eligible.
Samples: Samples: patient genomic DNA, serum, information, etc.: age, sex, clinical pathology information, genetic mutation information.
Study period: 2021.11.10 – 2027.3. 31

[Criteria for participation in the study: reasons for selection as a research subject]
The study invites participants who meet all of the following criteria to participate
● Main selection criteria
Blood sample meeting the following conditions
1. Cases in which skeletal muscle was collected for diagnostic purposes by a method approved in the " Muscle Disease Diagnostic Support and Preservation and Research Use (Muscle Repository) " (Ethics Committee approval number: A2019-123, date of approval: 02/03/2020) and sent to our center for diagnostic purposes, with blood also being sent at the same time
2. Consent to the use of specimens for the 'elucidation of the aetiology and pathogenesis of neuromuscular diseases and the development of therapeutic methods' which approved in the ethics committee obtained
● Main exclusion criteria
Subjects who do not wish to be informed of the results of the genome analysis

[Testings to be carried out]

Hereditary Muscle Disease panel (HM panel) analysis for known muscle disease causative genes. The HM panel covers 99.78% of all exonic and exon-intron boundary regions of 115 genes with mutations identified in at least two Japanese patients by March 2021.
(When necessary, transcriptomic, proteomic and metabolomic analyses are also performed in parallel).

[Burden and anticipated risks and benefits to the research subjects]

1) Burdens and risks that may arise.
(1) Adverse events.
No new specimens will be collected for this study, so there are no specific new adverse events.
(2) Other burdens and disadvantages.
As above, none in particular.
2) Anticipated benefits.
*See p14 of the explanatory document 'Muscle Disease Diagnostic Support and Preservation and Research Use (Muscle Repository)'.
3) If the research is discontinued
*See p14 of the explanatory document ' Muscle Disease Diagnostic Support and Preservation and Research Use (Muscle Repository) '.

[Withdrawal of consent after participation in research: consent to research being carried out or continued can be withdrawn at any time]

Participation or continuation in this research is entirely volunatry for the consenting individual. If the consenting person refuses to participate in this research, they will not be disadvantaged in any way. Even after initially consenting and the commencement of the study, participants retain the right to discontinue their involvement at any time without facing any disadvantages. However, if genetic analysis data are already registered in public databases, erasing the information upon withdrawal of consent may pose challenges.

[Methods of disclosing information on research].

Research subjects have the right to request and examine the research protocol and materials on research methods, provided that such access does not compromise the protection of personal information for other research subjects or jeopardize the originality of the research. The procedures for obtaining or inspecting these materials are also outlined.

[Handling of personal information]

*See ' Muscle Disease Diagnostic Support and Preservation and Research Use (Muscle Repository) ', Explanatory document, p7.

[When providing samples/information to a person in a foreign country]

*Not applicable.

[Methods of storage and disposal of samples and information, secondary use]

*See ' Muscle Disease Diagnostic Support and Preservation and Research Use (Muscle

Repository) ' Explanatory document, p 15.

[Conflicts of interest regarding research, including sources of funding and researchers]
This research is funded by an open research grant from Sanofi Inc. However, this research is planned and carried out independently by the researcher and the research results will not be distorted in favour of Sanofi Ltd. by this. Therefore, Sanofi Inc. has no influence on the research results, etc.
https://www.sanofi.com/en/science-and-innovation/clinical-trials-and-results/investigator-sponsored-studies/
The Center's Conflict of Interest Management Committee has reviewed and appropriately addressed any conflicts of interest among the researchers involved in this study. The conflict of interest status of researchers from joint research organizations has also been checked and verified as satisfactory.

[Handling of research results by participants]
*See p. 16 of the explanatory document ' Muscle Disease Diagnostic Support and Preservation and Research Use (Muscle Repository) '.

[Name of the research organisation and the name of the principal investigator]
National Institute of Neurology and Psychiatry
Ichizo Nishino, Department of Neuromuscular Research, Institute of Neuroscience

[For any queries regarding this project]
If you or a family member of a consenting individual have any questions or concerns about this research, please do not hesitate to contact the enquiry desk at the end of this briefing document. Please note that we may not be able to respond or answer your questions due to reasons such as the protection of the personal information of other research participants or the intellectual property rights of the researcher.
If you have any complaints, such as if you have been inconvenienced in the conduct of this research, please contact the Project Manager.

♦ Contact person for enquiries about the study (Progect Manager)
Ichizo Nishino, Department of Neuromuscular Research, Institute of Neuroscience
National Institute of Neurology and Psychiatry
187-8502. 4-1-1 Ogawa-higashimachi, Kodaira, Tokyo
Telephone number 042-341-2711 (main line)
e-mail: mbx@ncnp.go.jp