Molecular Medicine Laboratory
Clinical Sciences Building
Concord Hospital CONCORD NSW 2139
Tel: +61-2-9767 7009 Fax: +61-2-9767 6194

Request Form for Exome Sequencing*

► Patient information

Surname
Given names
Date of birth
Sex ☐ male ☐ female
Ethnic background ☐ Caucasian ☐ Asian ☐ Indigenous Australian ☐ Other:
Address
State
Postcode
City
Telephone
Email

► Payment details

Invoice will be sent to the referring clinician/hospital (or attach details if different)

Clinician
Provider No
Department
Hospital/Institution
Address
State
Postcode
City
Telephone
Email

► Disease gene panel

☐ Charcot Marie Tooth ☐ Hereditary Spastic Paraplegia ☐ Familial Motor Neuron Disease
☐ Ataxia ☐ Congenital Myasthenic Syndrome

► Type of exome analysis

☐ One disease gene panel analysis only (Limited to genes known to cause the condition)
☐ Exome wide analysis (extensive neuropathy gene panel)
Exome wide analysis *only available after the disease gene panel analysis does not reveal the genetic cause of the disorder*

► Expected inheritance

☐ Autosomal dominant ☐ Autosomal recessive ☐ X-linked ☐ Unknown

► Material (blood is strongly preferred)

☐ Blood (EDTA) ☐ DNA (only in agreement)
extracted from:

► Informed consent exome sequencing

☐ Yes, I have informed the patient or the legal guardian of the patient.
(for your signature and further details, see end of page 3)

► Informed consent scientific medical research

The patient or his/her legal guardian agrees to further use of the material for medical research in line with the current diagnostic question: ☐ Yes ☐ No

* N.B: Intronic sequences and large sequence deletions/duplications/re-arrangements are not detectable.

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► Clinical information

General

Age of diagnosis: □ infancy □ childhood □ young adult □ later life

□ Intellectual disability: mild/moderate/severe

□ Developmental delay

□ motor delay □ speech/language □ other:

Nervous system

□ ataxia (cerebellar)
□ chorea
□ dystonia
□ epilepsy
□ behavioral problems:
ADHD/autism/….....
□ hypertonia
□ hypotonia
□ lethargy
□ migraine
□ nystagmus
□ polyneuropathy
□ pyramidal features
□ spasticity
□ stroke-like episodes
□ MRI/CT abnormality:….....
□ sensory loss
□ pupils non-reactive
□ scoliosis

Muscle

□ atrophy
□ exercise intolerance
□ muscle anomalies, please specify:
□ (electrically silent) cramps
□ muscle stiffness
□ myalgia
□ myotonia
□ myo-edema
□ rippling
□ muscular dystrophy
□ ocular muscle weakness
(ptosis, diplopia, eye movement disorder)
□ facio-bulbar muscle weakness
(swallowing feeding, dysarthria, facial myopathy)
□ limb-girdle muscle weakness
□ distal muscle weakness
□ rhabdomyolysis
□ hyperCK-emia
□ cardiac symptoms
(cardiomyopathy, arhythmia)
□ Respiratory symptoms:…….

Other:

□	□ .....
□	□ .....
□	□ .....
□	□ .....
□	□ .....
□	□ .....
□	□ .....
□	□ .....
□	□ .....

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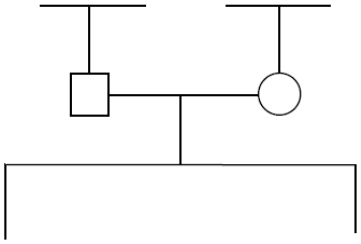
► Family history

□ consanguinity



Please mark individual of the present request with arrow (→)
Designate affected family members as ■ /●.
Indicate previous sent family samples with name and date of birth.

► Previous DNA testing done?

□ Yes* □ No
*Please specify type of analysis/genes:

► Informed consent for exome sequencing (continued from page 1)

I have explained to the patient or the legal guardian of the patient that genes known to play a role in the condition in question will be analyzed in the first step of the process. The test results of this will be discussed with the patient or the legal guardian of the patient.

If this initial testing does not identify a cause and further analysis is required (by selection of exome analysis type above), the remaining part of the exome will subsequently be analyzed. Relevant findings to the condition in question will be reported.

I have also explained to the patient or the legal guardian of the patient that there is a small chance that unsolicited findings not related to the condition in question may be identified. If this is the case, this will be reviewed by an independent committee of experts, who will decide whether or not this incidental finding will be reported back to the clinical geneticist involved.

Signature of the clinician *Date*

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Additional information for requesting molecular diagnostic testing at the Molecular Medicine Laboratory at Concord Hospital

1. Requests
   - 1.1. In order to prevent delays and errors, requests for molecular diagnostics should be clear and comprehensive. By filling out the request form completely, all necessary details are provided.
   - 1.2. By accepting a request for molecular diagnostics, the Molecular Medicine Laboratory commits itself to conduct the requested research with care and expertise, in accordance with the quality guidelines specified for our laboratory.
   - 1.3. Requests may be rejected in case insufficient information is provided to guarantee a result which is in accordance with our quality guidelines. The requesting party is contacted immediately when this applies.
   - 1.4. The Molecular Medicine Laboratory must be able to contact the referring clinician in case of queries regarding the patient or the requested tests.
   - 1.5. The invoice will be sent to the referring physician/hospital. In case a different billing address should be used, this needs to be indicated clearly on the request form.

2. Samples
   - 2.1. The requesting party should make sure that the sample tubes are properly labelled with name, gender and date of birth of the patient, and are accompanied by a completed request form.
   - 2.2. A volume of 6-9 ml EDTA blood is required per patient (for neonates this is at least 1 ml), which should be shipped by regular mail at room temperature, in plastic (no glass) tubes. Other materials/tissues only after consultation.
   - 2.3. When requirements 2.1 and 2.2 are not met, the Molecular Medicine Laboratory is not obliged to accept the samples.
   - 2.4. When no other arrangements have been made at the time of the request, Molecular Medicine Laboratory will store or dispose of the samples and/or remaining material according to the rules and regulations of the Division. Additional information under 6.

3. Testing
   - 3.1. The Molecular Medicine Laboratory determines which procedures, methods and equipment are employed to conduct the requested analysis.
   - 3.2. All procedures are carried out according to all applicable standards, rules and regulations. Details can be sent on request.
   - 3.3. In case a particular request involves procedures which are outside the scope of expertise and experience of the Department, Molecular Medicine Laboratory will contact the requesting party about outsourcing these activities.
   - 3.4. Molecular Medicine Laboratory is not responsible for all activities and storage which occur prior to the acceptance of a sample.

4. Results
   - 4.1. Results (test results, advise, information etc.) are provided in writing.

5. Patient confidentiality
   - 5.1. The privacy of all patients is guaranteed as stated in the NSW Pathology rules and regulations on patient confidentiality.

6. Use of patient material
   - 6.1. Please note that DNA will be stored from this patient's sample at the Molecular Medicine Laboratory. The sample will be kept indefinitely unless a written request for its disposal is received from the patient or his lawful representatives.
   - 6.2. Molecular Medicine Laboratory uses coded patient material for research purposes. Only testing in line with the original request will be carried out. The referring physician will be informed in case this leads to results that are relevant for the patient.
   - 6.3. For the development and improvement of new and existing techniques, Molecular Medicine Laboratory uses coded patient material, for control and validation among others. In case the patient objects to the use of the material for this purpose the patient or his lawful representative can contact Prof Garth Nicholson (Head of Department).

Disclaimer of exome sequencing test

The aim of this test is to reveal the cause of the disorder in the counselee, not to reveal the putative carrier status of recessive disorders.
This exome sequencing test produces data that covers the majority of the exome. Nevertheless, some areas of the exome are poorly covered or absent from the data. Thus, mutations in those regions may remain unidentified. Furthermore, some types of mutations (such as repeat expansions, copy-number variants, mitochondrial-DNA mutations and areas beyond the exome, including introns and promoters) will not have been detected by this test. The gene panels are updated regularly, but may be incomplete due to the continuous identification of novel genes in human disease. Specific information about the coverage, gene panels, etc. is available on request.

Consent Form for Exome Sequencing

Patient		**Parent or Guardian**	
Surname	Given Name(s)	Surname	Given Name(s)
Address		Address	
	Postcode		Postcode
Date of Birth	Telephone	Date of Birth	Telephone

To be completed by the Health Professional

I, _____have informed this patient/parent/guardian regarding results and limitations of exome sequencing. We have discussed the consequences and procedures involved in testing and the storage of patient data.

To be completed by the Patient/Guardian

1. I wish that DNA from **me/my child/person under my legal guardianship** will be stored and tested by exome sequencing for the following condition and type of analysis:

   Condition:_____
   Type of analysis:
   - ☐ Only genes known to cause the condition (gene panel)
   - ☐ Genes known to cause the condition followed by exome wide analysis

2. I understand that only genes known to cause the condition in question will be analyzed initially. The test results will be discussed with me on completion of the analysis. If this initial testing does not identify a cause, and I have opt for further exome analysis, all genes will then be analyzed (exome wide analysis, in specific cases analysis of *de novo* variants). In this case I will also be informed if findings relevant to the condition in question are identified by exome sequencing.

3. If I have opted for further/complete exome analysis I understand that there is a small chance that incidental findings not related to the specific condition in question may be identified.

   I understand that any incidental findings will be assessed. Only if the mutation identified is considered to have a significant impact on my health/the health of my child, the laboratory in consultation with my doctor may inform me of these incidental findings.

4. I understand that the knowledge of genetic conditions is likely to improve in the future. I can ask my doctor if further information becomes available about the exome sequencing results relating to the genetic condition in my family.

5. I understand that the information from the exome sequencing will be stored at the Molecular Medicine Laboratory at Concord Hospital and that it may be shared with researchers in other departments after it is de-identified.

6. I understand that I have the ability to withdraw my consent at any time without influencing **my management/the management of my child/my person under my legal guardianship.**

7. I have had the opportunity to ask additional questions I and am satisfied with the explanations.

_____ _____
Signature of Patient/Guardian Print name of Patient

_____ _____
Signature of Health Professional Date

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Consent for Payment for Exome Sequencing

This is to advise that Medicare does not cover you for the exome sequencing analysis performed by this laboratory. The full cost of this testing must therefore be paid by the patient.

We require your consent before proceeding with this testing with the understanding that you will accept responsibility for payment.

After the Molecular Medicine Laboratory performs this test, you will be issued an invoice for the cost by NSW Health.

TEST REQUESTED	COST
☐ Limited to genes known to cause the condition (gene panel)	$1,800
☐ Exome wide analysis (extensive neuropathy gene panel)	$2,400

I, _____ DOB _____ understand that exome sequencing is not covered by Medicare. I hereby agree to accept responsibility for full payment of the DNA test listed above, as requested by my medical practitioner on _____ (date).

Patient Signature_____ Date_____

Updated: January 2015

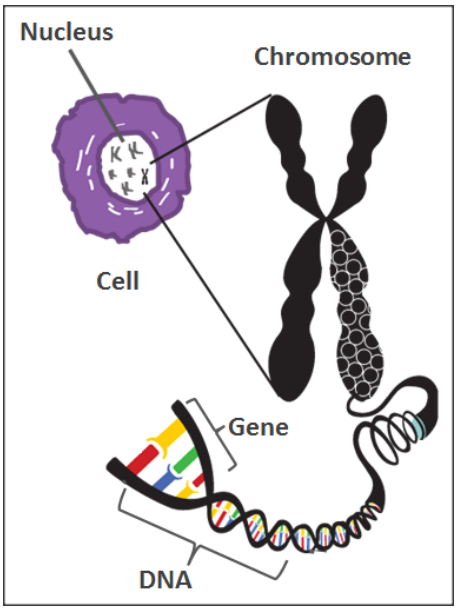
Information sheet: Genetic Testing – Exome Sequencing

Exome sequencing is a new approach of genetic testing. This information sheet explains essential facts about exome sequencing:

- What is 'genetic information'?
- Why exome sequencing?
- Which genes will be analysed?
- How many patients get a diagnosis from exome sequencing?
- What are the limitations of exome sequencing?
- What are possible results of exome sequencing?
- What impact does future research have on exome sequencing?
- What is required for exome sequencing?
- How are exome sequencing results used in research?

What is 'genetic information'?

Each cell of the human body stores the heritable biological information in chromosomes. These genetic instructions determine our appearance and initiate the development of all organs, such as brain, lungs and heart. Body cells usually contain 46 chromosomes, arranged as 23 pairs. One of each of these pairs is inherited from our father and the other from our mother. 22 pairs of chromosomes are similar in men and women. The 23rd pair is called the sex chromosomes. These are called XX in women and XY in men. The image shows a cell containing chromosomes. One chromosome is enlarged and shows that it consists of DNA from which genes are made.



The chromosomes contain genetic instructions which are packaged in form of genes. There are about 20,000 genes in each cell. All genes have specific functions, however the function of all genes is not yet known. These genes usually come in pairs, one from each parent. A genetic condition may occur if one or more genes don't function. This may be due to missing parts of a gene or an alteration to the information within the gene. It can be important to identify the DNA alteration responsible for the disease in question for both diagnosis in you and other family members. A non-functioning gene may either be inherited from one of both parents or occur for the first time in a person. Such gene alterations are also called gene mutations and are present in all people. They are sometimes associated with disease.

Why exome sequencing?

Previously, only one gene at a time could be tested. It could therefore take many years to identify the cause of a disease caused by one of many genes. It is now possible to test all 20,000 genes at once by exome sequencing. This means that the cause of a hereditary disease may be detected within a shorter time period.

Which genes will be analysed?

For most conditions, only genes known to cause a disorder, rather than all 20,000 genes, will be tested in the first instance. If no gene alteration is identified, the remaining genes will then be screened. In this situation we can't predict whether (or when) a cause will be identified as the specific gene causing the condition will not be known.

How many patients get a diagnosis from exome sequencing?

Exome sequencing determines a genetic diagnosis in about one in every three patients (33%) who have the test.

What are the limitations of exome sequencing?

It is possible that this test will not find a reason for your signs and symptoms. About 50% of patients tested do not receive a diagnosis from exome sequencing.

Exome sequencing is not a perfect test and this technology is new. Our current understanding of the human exome is limited and we do not know the function of many genes. Each person has hundreds of variations throughout their genes that appear to cause no harm at all. These are called polymorphisms. If we saw a change in a gene that was not known to cause the disease in question, the change might be found on testing but we may not realise its significance. Sometimes this requires studying many family members, to identify changes that are not known to cause disease but nonetheless segregate with the affected members of a family. In a single affected person this is not possible.

In addition some parts of the exome are not examined. Furthermore, exome sequencing does not detect certain types of mutations, nor if parts of the genome are missing or duplicated, nor does it detect changes outside of the exome that nonetheless cause disease. For any of these reasons, it is possible that exome sequencing will not find some mutations that are actually present in the DNA.

What are possible results of exome sequencing?

There are 4 possible outcomes after exome sequencing:

1. One or more gene alterations are identified that are assessed as explaining the condition in you.
2. One or more gene alterations are identified where the significance is not immediately clear. In this case additional testing in other family members may be required to determine if the result is relevant to the condition. It is your choice whether you will inform your family and/or request that other family members participate in genetic testing. Your family will not be approached by your health care providers.
3. No gene alterations are identified that could explain your condition. In this situation, testing would continue for possible causes of the condition in question as more information regarding associated genes is identified in the future.
4. When all genes are tested, there is a small chance that gene alterations could be identified by chance that are not related to the disorder being investigated. These are called co-incidental findings. An example of this could be a gene alteration associated with an increased risk of cancer in you or your child. This could have important consequences for you and/or other family members. Any co-incidental findings will be assessed to determine if they are to be reported. Please note we do not specifically examine any or all of the genes known to cause other diseases, including cancer. The absence of any comment on genes known to cause other diseases including cancer does not imply that we have checked the sequence of these genes nor that we have excluded possible mutations or other changes in these genes in you.

In all situations you will be informed of the results of exome sequencing by your doctor.

What impact does future research have on exome sequencing?

Knowledge of the function of genes and diseases is increasing rapidly. It is possible that should the cause of the condition tested in you is not identified now, that it could still be identified in the future as knowledge increases.

What is required for exome sequencing?

A blood sample will be required from you (6-9ml) from which DNA will be extracted. The DNA sample will be stored at the Molecular Medicine Laboratory as per legal requirements.

Your written consent for exome sequencing will be needed prior to any testing being done.

How are exome sequencing results used in research?

The information obtained by exome sequencing is also important to assist in the understanding of the causes of hereditary conditions. Your test results will be de-identified and stored at the Molecular Medicine Laboratory. Your results may be shared anonymously with accredited research groups. Should there be anything of potential importance to you identified through this research; it will be reported to your doctor.