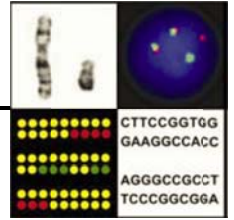


University of Wisconsin Collaborative Genomics Core

Clinical Exome Sequencing Information Form for Medical Providers



Exome Sequencing Analysis

Exome Sequencing is used to detect variants in protein-coding DNA. The exome will be sequenced to an average read depth of 85-100X. Over 97% of the exome will be fully covered at $\geq 10X$ read depth.

Turn-around Time: 4-6 weeks

How to order:

SLH test codes

- 895M64: Proband Analysis Only
- 895M65: Duo Analysis (Proband+Parent)
- 895M66: Trio Analysis (Proband+Parents)

Specimen Requirements

Blood: 5-10 ml EDTA

Isohelix™ Saliva Collection kit used according to manufacturer instructions

- Complete the attached CGC Genetic Diagnosis Request Form 131
- Complete the attached CGC Medical and Family History Form, including a three generation pedigree. Please describe all findings using HPO terms. An online tool is available at: <http://compbio.charite.de/phenomizer/>
- Consent patient for testing. See attached consent form. Please include the following in your discussions with the patient:
 - The possible test results, including the option of receiving secondary findings
 - Potential implications for other blood relatives
 - Test limitations. This test does not sequence the entire genome. This test will not identify certain types of sequence variation, including large insertions, deletions, copy number variations, triplet repeat expansions and structural chromosome rearrangements.

Please feel free to contact our laboratory's genetic counselor with any questions. Phone: 608-262-0402



(PLEASE PRINT USING CAPITALS- FIELDS IN RED ARE REQUIRED)

(1) Patient Last Name		First Name		Middle Name	
(2) Name Change- Former Last Name					
(3) Patient Address					
(4) City		State		Zip	
				County of Residence	
(5) Date of Birth		(6) Age		(7) Sex <input type="checkbox"/> Male <input type="checkbox"/> Female	
(13) ADDITIONAL REPORT COPIES NEEDED?					
Please check this box <input type="checkbox"/> AND Enter the clinician's name and address on the back of this form					
(8) Ethnicity <input type="checkbox"/> Hispanic/Latino <input type="checkbox"/> Non-Hispanic/ Latin		(9) <input type="checkbox"/> Amer Indian <input type="checkbox"/> Asian <input type="checkbox"/> Other _____		<input type="checkbox"/> Black/African Amer <input type="checkbox"/> Pacific Islander <input type="checkbox"/> White	
(10) Chart #/ Patient ID Number		(11) Submitter Specimen ID Number		(15) NPI # _____	
(16) Attached copies of front and back of insurance card(s)? <input type="checkbox"/>					

(18) <input type="checkbox"/> MEDICAID# _____		<input type="checkbox"/> MEDICARE# _____	
<input type="checkbox"/> PRIVATE INSURANCE# _____		<input type="checkbox"/> Bill to Submitter	

(20) Please write the letter corresponding to the appropriate ICD-10 Code to the left of the test name below (where applicable)

(A) ICD-10 Code _____ (B) ICD-10 Code _____ (C) ICD-10 Code _____ (D) ICD-10 Code _____ (E) ICD-10 Code _____

(21) Date of collection	(22) Time of collection
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Specimen Source <input type="checkbox"/> Amniotic Fluid <input type="checkbox"/> Blood <input type="checkbox"/> Chorionic Villus Sample <input type="checkbox"/> Paraffin Section (tissue type _____)	Gestational Age: _____
<input type="checkbox"/> Products of Conception (tissue type _____) <input type="checkbox"/> Tissue Biopsy (tissue type _____)	Ultrasound Age: _____
	Estimated Date of Delivery: ___ / ___ / ___

Reason for Referral (please provide in addition to ICD-10 code above):

<p>CHROMOSOME ANALYSIS</p> <ul style="list-style-type: none"> <input type="checkbox"/> 801 Chromosome Analysis, Blood <input type="checkbox"/> 803 Chromosome Analysis, Blood, Abridged Examination for Familial Chromosome Rearrangements <input type="checkbox"/> 850 Chromosome Analysis, Amniotic Fluid <input type="checkbox"/> 852 Chromosome Analysis, Amniotic Fluid, Abridged (must also order 890) <input type="checkbox"/> 855 Chromosome Analysis, Chorionic Villus Sample <input type="checkbox"/> 857 Chromosome Analysis, CVS, Abridged (must also order 890) <input type="checkbox"/> 831 Chromosome Analysis, Products of Conception/ Tissue Biopsy <input type="checkbox"/> 860 Tissue culture and shipment for additional testing 	<p>MOLECULAR ANALYSIS</p> <ul style="list-style-type: none"> <input type="checkbox"/> 828 Molecular Analysis, Fragile-X, Genetic Diagnosis <input type="checkbox"/> 889 Methylation-Specific PCR, SNRPN gene, 15q11.2 <input type="checkbox"/> 890 Chromosomal Microarray Analysis (CMA), SNP-based <ul style="list-style-type: none"> <input type="checkbox"/> Tiered (Hold array pending chromosome analysis) <input type="checkbox"/> Concurrent (with chromosome analysis) <input type="checkbox"/> 890 FAM Targeted Microarray Analysis (Family Studies) <input type="checkbox"/> 895M64 Exome Sequencing- Proband Analysis Only <input type="checkbox"/> 895M65 Exome Sequencing- Duo Analysis <input type="checkbox"/> 895M66 Exome Sequencing- Trio Analysis <input type="checkbox"/> 895M41 Cardiomyopathy/Arrhythmia NGS <input type="checkbox"/> 895M50 Targeted Variant Analysis via Sanger DNA Sequencing (variant nomenclature: _____) 	<ul style="list-style-type: none"> <input type="checkbox"/> 842C91 Hereditary Hemochromatosis [HHPCR] <input type="checkbox"/> 842C92 Factor II Genotyping [PTPCR] <input type="checkbox"/> 842C90 Factor V Genotyping [FVPCR] <p>FISH ANALYSIS</p> <ul style="list-style-type: none"> <input type="checkbox"/> 873 Prenatal Aneuploidy Panel, Amniotic Fluid <input type="checkbox"/> 875 Stillbirth Aneuploidy Panel, Paraffin Embedded <input type="checkbox"/> 871F28 DiGeorge /Velo-cardio-facial / Schpritzen /Conotruncal anomaly Syndrome, Deletion 22q11.2, TUPLE1 <input type="checkbox"/> 871F34 SRY (Sex determining Region of Y), Yp11.3 <input type="checkbox"/> 870F52 X and Y sex chromosomes
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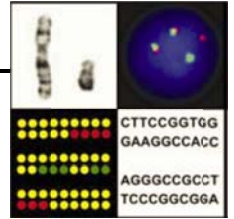
A sample processing fee is charged for blood samples that have only FISH analysis

WSLH contributes submitted clinical information and test results for molecular cytogenetic tests to a HIPAA-compliant, de-identified public database a part of the National Institutes of Health's effort to improve diagnostic testing and our understanding of the relationships between genetic changes and clinical symptoms. For information about the ClinVar database, visit their website at <http://www.ncbi.nlm.nih.gov/clinvar/>. Confidentiality of each sample is maintained. Patients may request to withdraw consent for the storage of their sample and/or use of the data by: 1) checking the box below, 2) calling the laboratory at (608) 262-0402 and asking to speak with a genetic counselor, or by 3) visiting our website at www.slh.wisc.edu/cytogenetics.

Refusal for inclusion in these efforts may be indicated by checking this box. (If the box is not checked, the data will be anonymized and used.)

University of Wisconsin Collaborative Genomics Core

Informed Consent Form – Clinical Exome Sequencing



This form should be read by you and your doctor and/or genetic counselor. It explains the test that he or she would like you to think about having done. The form includes the types of results the test can give you and what they might mean for you and/or your family. For more detailed information on genetics, genetic disease, inheritance, or genetic testing, please consult with a genetic counselor. You may contact our laboratory's genetic counselor by calling 608-262-0402.

PURPOSE

1. The purpose of this test is to find any changes (variants) that might be in your DNA. DNA is the molecule that makes up your genes.
2. This looks at thousands of genes at the same time.
3. This test is used when medical/family history and/or physical exam strongly suggest a genetic cause for the features seen in you or your family.
4. The decision to have this testing should be made by you and your doctor. If you wish to speak to a genetic counselor about this testing, you can call 608-262-0402 and ask for a genetic counselor.

TEST PROCEDURE

1. You will give a blood sample (5-10cc or about 2 teaspoons). The blood sample will be sent to the UW Collaborative Genomics Core.
2. Your DNA will be separated from the blood sample and tested ("sequenced").
3. The DNA sequence will be studied to look for changes in your DNA that could explain the features seen in you or your family.
4. Other members of your family may be asked to have testing done to help us understand your test results. The UW Collaborative Genomics Core will recommend who in your family should be asked to have testing. Their participation is voluntary.
5. This test will not find all changes in your DNA. Not all areas of your DNA are being tested. This test will sequence most of the areas that contain our genes, but not all. Some types of changes (large rearrangements, copy number variation (CNV), trinucleotide repeat expansions, epigenetic effects) may not be found.
6. Many gene changes are expected to be found in your DNA sequence. Some changes are normal and do not cause health problems. Only medically important changes related to the request provided by your doctor will be reported.
7. DNA changes that might be important will be confirmed by a second test before being reported.

RESULTS

1. Test results will be reported to your doctor and/or genetic counselor assisting you with this testing.
2. Possible reported test results include:
 - Pathogenic (or likely pathogenic)- A clinically significant DNA change IS detected. We might find one or more changes in your genes that explain the features seen in you or your family.
 - A clinically significant change IS NOT detected. We might not find any specific change in your genes that would explain the features seen in you or your family. This result does not rule out a genetic cause for the features seen in you or your family.
 - Variant of uncertain significance- A result of uncertain clinical significance is detected. We might find changes in your genes, but may not know if they explain the features seen in you or your family.
3. Secondary findings might be detected. We might find changes in your genes that are not related to the features seen in you or your family, but might put you or your family at risk for a *different* genetic disease. The features of this different disease might or might not be visible at this time. You may choose whether or not to have secondary findings reported to you. The types of secondary findings that we will report include:
 - a. Pathogenic and likely pathogenic findings in known autosomal recessive disease genes and X-linked disease genes in females. This is a form of pan-ethnic carrier screening. Two variants are required to cause autosomal recessive disease. If a single variant is found, the health of the carrier is not typically affected, but there may be a risk to the carrier's children and may impact reproductive decision making.
 - Pathogenic and likely pathogenic finding in genes that have been outlined by the American College of Medical Genetics and Genomics (ACMG) Secondary Findings Committee. These disorders are mostly treatable autosomal dominant disorders that are associated with predisposition to increased cancer risk (ex. hereditary colon cancer, hereditary breast cancer), connective tissue disorders (ex. Marfan syndrome, Loeys-Dietz syndrome), and inherited cardiac diseases (ex. hypertrophic cardiomyopathy, long QT syndrome).

4. Not all DNA changes (variants) will be reported. DNA changes that will not be reported include:
 - a. Variants commonly seen in healthy people (benign variants)
 - b. Variants that might slightly increase your risk for common disease (ex. diabetes, asthma, high blood pressure).
5. Only DNA changes (variants) found in the nuclear genome will be reported. Findings associated with mitochondrial disease due to mitochondrial DNA variants will not be reported at this time.
6. Test results may show that the true blood relationships of the family members being tested are reported incorrectly (for example: non-paternity – the stated father of a child is not the biological father). If discovered, this information will be verbally reported to the ordering healthcare provider, but will not be written in the final report.
7. Test results will be reported for the patient only. If other members of your family (mother and/or father of the patient) have testing done, information about the inheritance of any reported variant will be included on the patient's test report. Other family members who have testing to help us understand your results will not get a test result for themselves.

IMPLICATIONS OF RESULTS

1. Even if this testing finds a DNA change that may be causing the features seen in you or your family, it might not change your healthcare or treatment.
2. Results may have health and/or reproductive implications for other blood relatives. If you are found to have a clinically significant DNA change, your blood relatives (i.e. mother, father, siblings, children, etc.) may also carry that change.
3. The UW Collaborative Genomics Core will use your DNA sequence and medical/clinical information to provide the most accurate data and interpretation currently possible. However, at any time new scientific information could significantly alter the interpretation or significance of any DNA change (variant). It is your responsibility to re-contact your doctor for updated information regarding variants.

POTENTIAL BENEFITS OF TESTING

1. Your results may help your doctor make more informed decisions about your healthcare and management.
2. You may receive no benefit from testing.

POTENTIAL RISKS OF TESTING

1. There are very few physical risks associated with this testing.
2. Genetic testing may cause emotional stress. Some people may feel anxious or depressed after learning genetic information about themselves and/or their children.
3. Genetic testing results can sometimes seem confusing. A person might make an important decision that cannot be undone based on confusion about the results (i.e. reproductive decisions).
4. In rare cases, people with genetic diagnoses had problems with insurance coverage. Talk to your doctor or genetic counselor if you have concerns about genetic discrimination prior to any testing.
5. Test results may show that the true blood relationships of the family members being tested are reported incorrectly (ex. non-paternity – the stated father of a child is not the biological father).

Please contact our laboratory's genetic counselor by calling 608-262-0402 if you have any questions or concerns regarding this testing and/or its potential risks.

Please demonstrate your understanding of this testing by indicating whether the following statements are true or false

- | | |
|--|---------------|
| a. This testing is voluntary. | TRUE or FALSE |
| b. You may receive no benefit from this testing. | TRUE or FALSE |
| c. All DNA changes found will be included in the final report. | TRUE or FALSE |
| d. It could be important for other blood relatives to know the results of this test. | TRUE or FALSE |
| e. Why are you having this testing? _____ | |

Please indicate whether you want possible secondary findings reported to you/your doctor:

Secondary findings are limited to pathogenic and likely pathogenic findings in known autosomal recessive or X-linked disease genes and additional genes that have been outlined by the ACMG Secondary Findings Committee. Secondary findings will only be reported if you OPT-IN. Please initial next to the following statements if you OPT-IN.

_____ Yes, if found, I want secondary findings associated with autosomal recessive and X-linked disease included in the final results.

_____ Yes, if found, I want secondary findings associated with the ACMG Secondary Findings Committee included in the final report.

By signing below I acknowledge the following:

1. This testing is voluntary.
2. The sensitivity of this test is not 100% and that the cause of the features seen in me or my family may not be identified by this testing.
3. I have been informed of the risks and benefits of this testing and have been given a chance to have my questions answered by a genetics professional.
4. I am aware of what test results will and will not be disclosed to me.
5. I am aware that this testing could reveal true blood relationships.
6. I have read this consent form and will receive a copy for my records.
7. I give permission to have the UW Collaborative Genomics Core perform DNA sequencing of myself/my child.

Name of patient being tested (please print)

Date of Birth (MM/DD/YYYY)

Signature of patient
(see below if patient is a minor or decisionally-impaired adult)

Date (MM/DD/YYYY)

Provider Statement

I have explained the genetic testing to this individual. I have reviewed the possible outcomes and limitations outlined above and have answered all questions.

Signature of provider

Date (MM/DD/YYYY)

If patient is a minor or decisionally-impaired adult the following is required:

Signature of parent or legal guardian

Date (MM/DD/YYYY)

Printed name

Specify relationship to patient: _____

***** **OPTIONAL** *****

Please indicate whether you want your/your child’s leftover (residual) DNA saved. This is a form of DNA banking and is provided free of charge for exome sequencing patients.

I authorize banking of residual DNA for future diagnostic testing or research studies authorized by me or the current Specimen Owner (policy below).

Authorized Specimen Owner

Name (Last, First)	
Street Address	
City	
State	
Zip Code	
Signature and Date	

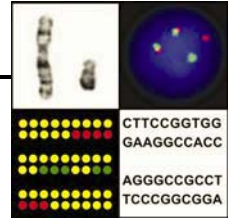
UW Cytogenetics Services DNA Bank Policy

The purpose of this DNA Bank is to isolate and store purified human DNA for future diagnostic testing or research studies authorized by the Specimen Owner.

1. This Bank will adhere to the guidelines proposed by the American Society of Human Genetics (Am. J. Hum. Gen. 42:781 (1988)) and the current recommendations of the American College of Medical Genetics Storage of Genetic Materials Committee.
2. Because of the complexity and implications of DNA banking, blood samples will be processed and stored only after receiving a complete informed consent for DNA banking form signed by both the depositor and his/her healthcare provider, knowledgeable in the area of human genetics.
3. DNA will be extracted from 10-20cc sample of blood. The amount of purified DNA recovered and the integrity of the sample will be ascertained prior to storage, and successful storage will be reported to the depositor.
4. A very small percentage of blood samples from which the DNA is to be extracted may be lost in shipping or inadvertently destroyed. This Bank and the University of Wisconsin are not responsible for such loss. In the event that no DNA is obtained from the specimen submitted, the depositor will be notified immediately and requested to provide an additional specimen at no additional charge for processing and storage of the sample.
5. The DNA sample will be divided and stored at in two separate locations equipped with temperature control alarms. The samples shall then be stored indefinitely, except as further described in this policy.
6. It is the responsibility of the depositor or sample owner to inform the DNA Bank of address changes or if they choose to have their sample removed from the bank and destroyed.
7. Banked DNA is the property of the depositor, the person from whom the sample was taken, or their designee. In the event the DNA is obtained from a child, the sample is in control of the legal guardian until which time the depositor is no longer a minor under current law. In the event the depositor dies before transferring ownership to another individual, the sample will be destroyed. Ownership can be transferred to another individual at any time by writing to this laboratory.
8. Release for clinical testing of any portion of the DNA deposited requires the written request and authorization of the depositor, specifying the testing facility or medical professional and address where the specimen(s) will be analyzed (any paperwork needing to be sent with the sample should be included with your request.) The University of Wisconsin Cytogenetics Laboratory DNA Bank will not be held responsible for diagnostic testing of these specimens in other facilities. The DNA will be released only to the designated medical professionals or diagnostic laboratories. Because of the complexity and implications of DNA testing, the DNA sample will be released for testing only through a physician or genetic counselor designated by the depositor.
9. The DNA Bank will obtain written informed consent of the depositor or subsequent owner of the DNA before using any part of the sample for research unless such consent is not required by law. The DNA Bank retains the right to contact the depositor regarding permission for this use.
10. The bank reserves the right to destroy a sample at any time after making reasonable attempts without success to contact the depositor using the last known address or if the Bank determines that the sample is not the depositor's.
11. The depositor may contact the DNA Bank at any time. Current contact phone: 608-262-0402.
12. The DNA sample and all information received shall be held in strict confidence.
13. The depositor may request to have the sample destroyed or transferred to another medical laboratory at any time. Written directions from the depositor are required. No refund of any part of the processing and storage fee will be made in the event the sample is destroyed or transferred.

University of Wisconsin Collaborative Genomics Core

Phenotype and Family History Form – Whole Exome Sequencing



Patient Name: _____ DOB: _____ Gender: [] M [] F

Genetics Professional: _____ Contact Number: _____

Medical History

*Please describe all findings using HPO terms if available. An online tool is available at: <http://compbio.charite.de/phenomizer/>
Include clinical diagnosis and previous genetic testing results if known.*

Clinical Diagnosis:

Perinatal history:

Cardiac:

Growth:

Gastrointestinal:

Cognitive/Developmental:

Musculoskeletal:

Behavioral/Psychiatric:

Genitourinary:

Cutaneous:

Immunologic:

Neurological:

Metabolic:

Hearing/vision:

Hematologic:

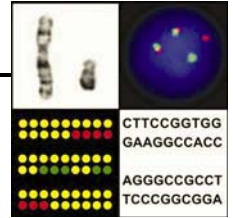
Craniofacial:

Other:

Please list all previous genetic testing undergone by patient, including results:

University of Wisconsin Collaborative Genomics Core

Phenotype and Family History Form – Whole Exome Sequencing



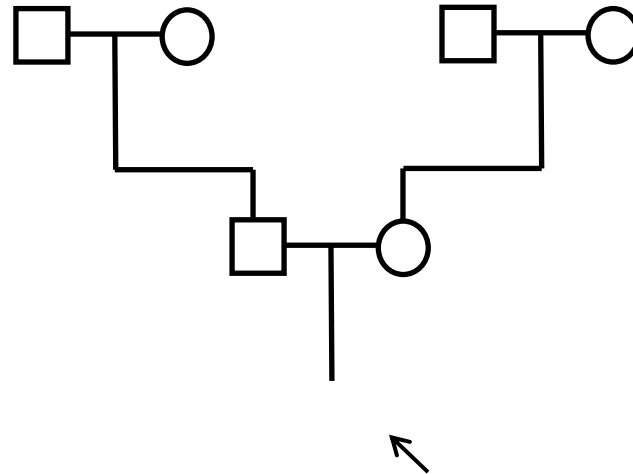
Patient Name: _____ DOB: _____

Family History

Please draw a 3 generation family pedigree. Include detailed medical history as well as cause and age of deaths and any consanguinity if known.

Ethnicity on paternal side:

Ethnicity on maternal side:



Grandparents

Parents, aunts,
and uncles

Proband and siblings