CGT Test Requisition Form

The fields marked with * are required to carry out the test

*TEST TYPE:

NEW ANALYSIS (requires a biological sample)

- ☐ **CGT Bank/Donor** (includes genetic information data upgrade)
- ☐ **CGT Plus** (includes genetic information data upgrade)
- ☐ **CGT Exome**
- ☐ **CGT Personalised/Mirror** *Indicate relevant test _____
- ☐ **CGT SYNC/Sequential**

Include analysis of X-linked conditions (*biologically female patients only)? ☐ **YES** ☐ **NO**

	Reproductive Partner/Donor Name/Medical Record Number/Patient ID	*Relevant gene(s)
1		
2		
3		
4		

RE-ANALYSIS (for patients who have previously had CGT)

- ☐ **CGT SYNC/Sequential re-analysis**

	Reproductive Partner/Donor Name/Medical Record Number/Patient ID	*Relevant gene(s)
1		
2		
3		
4		

DETAILS OF REFERRING CLINICIAN

*Clinic: _____

*Referring Clinician: _____

*Email (for results delivery): _____

PATIENT 1 - DEMOGRAPHIC DETAILS

Medical Record Number/Patient ID: _____

*First name: _____ *Surname: _____

*Date of birth: _____ Email: _____

*Biological sex: ☐ Male ☐ Female

Ethnic group (if the patient belongs to more than one ethnic group, please indicate below):

☐ Caucasian ☐ East Asian ☐ South Asian ☐ Arab ☐ Other _____

☐ Ashkenazi ☐ Hispanic ☐ GRT ☐ African/Caribbean ☐ Unknown

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PATIENT 1 - CLINICAL DETAILS

*Sample collection date: _____ Extraction performed by (full name): _____

*Type of sample: ☐ Blood ☐ Saliva ☐ DNA

Tube label: _____

*Is this testing for a donor? ☐ Yes ☐ No

*Relevant clinical information (if applicable):

☐ Bone marrow transplant ☐ Recent blood transfusion (<60 days) ☐ Congenital or acquired chimera

*Family/patient history:

☐ No family history ☐ Family history (1) ☐ Patient is a known carrier (1)

(1) Specify gene(s) (if applicable): _____

(Please include report(s) if available)

PATIENT 2 - DEMOGRAPHIC DETAILS

Medical Record Number/Patient ID: _____

*First name: _____ *Surname: _____

*Date of birth: _____ Email: _____

*Biological sex: ☐ Male ☐ Female

Ethnic group (if the patient belongs to more than one ethnic group, please indicate below):

☐ Caucasian ☐ East Asian ☐ South Asian ☐ Arab ☐ Other _____

☐ Ashkenazi ☐ Hispanic ☐ GRT ☐ African/Caribbean ☐ Unknown

PATIENT 2 - CLINICAL DETAILS

*Sample collection date: _____ Extraction performed by (full name): _____

*Type of sample: ☐ Blood ☐ Saliva ☐ DNA

Tube label: _____

*Is this testing for a donor? ☐ Yes ☐ No

*Relevant clinical information (if applicable):

☐ Bone marrow transplant ☐ Recent blood transfusion (<60 days) ☐ Congenital or acquired chimera

*Family/patient history:

☐ No family history ☐ Family history (1) ☐ Patient is a known carrier (1)

(1) Specify gene(s) (if applicable): _____

(Please include report(s) if available)

CONSANGUINITY

Are Patient 1 and Patient 2 related by blood? ☐ Yes (relationship: _____) ☐ No

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PATIENT SIGNATURE(S) AND DONOR RESULTS PREFERENCE(S) (IF APPLICABLE)

By signing this test requisition form, I voluntarily ask Igenomix to perform the test indicated above. I have read and received a copy of the Informed Consent for Carrier Genetic Testing. I have been adequately informed of the risks, benefits and limitations of this test.

*Patient 1's signature: _____ *Date: _____

For donors only - Patient 1 results preference: ☐ I would like to receive my CGT results. ☐ I would not like to receive my CGT results.

*Patient 2's signature: _____ *Date: _____

For donors only - Patient 2 results preference: ☐ I would like to receive my CGT results. ☐ I would not like to receive my CGT results.

REFERRING CLINICIAN SIGNATURE

I certify that the referring clinician and patient(s) details given in this test requisition form are accurate to the best of my knowledge and that I have requested the test indicated above based on my professional judgment. I have explained the limitations of this test and have answered any questions to the best of my ability. I understand that Igenomix may require further information, and I agree to provide this information if necessary.

*Referring clinician's signature: _____ *Date: _____

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Informed Consent for Carrier Genetic Testing

CGT
Carrier Genetic Test
by Igenomix

PURPOSE

The purpose of carrier screening, or the Carrier Genetic Test (CGT), is to identify individuals who are at an increased risk of having a child with a genetic condition. This provides the opportunity for informed reproductive decisions that can reduce the chance of passing on autosomal recessive and X-linked conditions included in the test. The ideal time to consider carrier screening is prior to conception to provide for the broadest range of reproductive options. Carrier screening can also be considered during pregnancy.

Most healthy individuals are carriers of one or more genetic variants that can lead to severe conditions in offspring. Carriers usually have no symptoms and often have no known family history of the condition. Most genes come in pairs; one copy is inherited from each biological parent. For recessive conditions, both copies of a gene pair must contain disease-causing variants for a person to be affected. For X-linked conditions, since females have two copies of the X chromosome and males have only one, females can be carriers and still be healthy but pass on the variant to male offspring who would be affected.

Carrier screening assesses the presence of disease-causing (pathogenic or likely pathogenic) variants in genes associated with autosomal recessive conditions in a reproductive couple, as well as variants in genes linked to the X chromosome in females. If both reproductive partners (the egg provider and the sperm provider) are carriers of variants in the same gene associated with an autosomal recessive condition, there will be an increased chance of 1 in 4 (or 25%) of having a child affected with that specific condition. If a female is a carrier of an X-linked condition, there is a chance of 1 in 2 (or 50%) of having a male child affected with that condition. Some female carriers may also exhibit symptoms, generally milder than those seen in males.

Reproductive matching may be performed to assess the reproductive risk for a specific pairing of an egg source (e.g., patient or egg donor) and sperm source (e.g., partner or sperm donor). Expanded carrier screening panels do not always include the same genes. Exome sequencing technology enables data upgrades of the CGT panel to include additional genes if necessary to match genes analysed by a different carrier screening test and reported as positive for the reproductive partner.

GENETIC COUNSELLING

It is recommended that you have counselling with a genetic counsellor who specialises in carrier screening prior to signing this consent form. The genetic counsellor will describe the benefits and limitations of carrier screening as well as answer any additional questions about this test. You may also request a consultation to review the results after the testing has been completed. Counselling can be arranged by emailing support.uk@igenomix.com or by speaking with your fertility clinic.

PROCEDURE

A blood sample is collected and shipped to Igenomix along with a completed Test Requisition Form. If the Test Requisition Form is not correctly completed, analysis may be put on hold until the correct information is obtained. DNA is isolated from the sample. Next generation sequencing (NGS) is performed for exonic regions where gene coding regions are located. Complementary analysis to detect common variants not amenable to detection with NGS technology may be performed for some genes. Bioinformatic filtering and analysis is performed on the sequencing results based on the test panel selected and any additional gene(s) requested by the ordering clinician. Clinical interpretation of the variants is performed based on the standards and recommendations of professional bodies (Richards et al., 2015). A results report is generated and sent to the ordering clinician within 25 working days. A small percentage of samples may be delayed due to unforeseeable circumstances. Should this occur, the ordering clinic will be notified.

Genetic matching compares the carrier screening results of the reproductive couple, as defined by the ordering clinician. Full reports for any carrier screening test performed outside of Igenomix must be submitted for matching with an Igenomix report. A match report will be generated indicating "low reproductive risk" or "increased reproductive risk" for the reproductive couple. Separate match reports will be generated for each pairing of an egg and sperm source, for example, if a patient's test results are being compared to those of more than one gamete donor. Exome sequencing data may be upgraded to include additional genes as necessary to match genes reported as positive on the reproductive partner's carrier screening test, if any. Data upgrading generally does not require additional sequencing or the collection of a new sample. Occasionally, additional analysis is necessary, and a new sample may be required.

BENEFITS

The primary benefit of carrier screening is to provide individuals who are considering family planning, or who are currently pregnant, with information about their potential carrier status in order to estimate the reproductive risk for autosomal recessive and X-linked conditions. If an increased reproductive risk is identified, patients have the opportunity to consider reproductive testing options that can reduce the chance of having affected offspring.

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ALTERNATIVES

Carrier screening is an optional test. You may choose to decline it if you do not wish to pursue it, even if it was recommended to you by a healthcare professional. Considering natural conception or assisted reproduction without the use of carrier screening may be an alternative option. It is recommended to discuss the benefits, risks, limitations, and alternatives to carrier screening with your ordering clinician or with a genetic counsellor before having this test.

RISKS AND LIMITATIONS

1. **Sample collection:** The risks of sample collection are expected to be minimal. There is a small chance of infection for any blood draw.
2. **Clinical utility:** Carrier screening is not intended to be used for the purpose of diagnostic testing for clinically affected individuals. The clinical sensitivity of a screening test may be lower than that of a diagnostic test.
3. **Genes analysed:** The test only includes the analysis of the specific genes included in the test requested. Lists of the genes analysed for each test are available at https://www.igenomix.eu/genetic-solutions/cgt-carrier-genetic-test/. Not all conditions with known X-linked or recessive inheritance are screened. X-linked genes will not be analysed for male individuals.
4. **Variant detection:** Next generation sequencing technology cannot detect large deletions or duplications (copy number variants or CNVs), gene rearrangements, or trinucleotide repeat expansions. Complementary testing with gene-specific technology will be performed for some common variants not amenable to detection by sequencing. Variants not included in the complementary testing and not amenable to sequencing will not be detected. Some variants may not be detected in areas of low sequence coverage. Additional gene-specific limitations and considerations are available to the ordering clinician.
5. **Phase:** Variant phase cannot be determined by NGS testing. If two variants in the same gene are detected, they may both be on the same gene copy (in cis), which would be associated with carrier status, or be on opposite gene copies (in trans), which could be associated with symptoms of the condition. Therefore, the individual would be *at least* a carrier of the condition. If two SMN1 copies are detected, the possibility that both copies are on the same gene copy and the patient is a "silent carrier" of SMA cannot be ruled out.
6. **Variant classification:** Only variants classified as pathogenic or likely pathogenic will be reported. Variants of unknown significance (VUSs) will not be reported. Variant classification can change over time.do Igenomix is not obligated to recontact patients or ordering clinicians if a VUS is reclassified. Patients and/or ordering clinicians may contact Igenomix should an updated report be desired.
7. **Non-informative results:** There is a chance of non-informative results for one or more variants. Some variants in some samples may not pass our quality control parameters due to low coverage of the genomic region of interest. If this happens, these variants will be reported as non-informative. A redraw and retesting may be considered. There is a chance that the sample may be of insufficient quality for testing and a new sample collection will be requested.
8. **Incidental findings:** The results of carrier screening may uncover an undiagnosed condition or a carrier status that is associated with an increased risk of clinical symptoms. Such situations might arise when a female is found to be carrier of an X-linked condition, when an individual is found to carry two variants in the same autosomal recessive gene, or when a variant is detected in a recessive gene that also has dominant manifestations. This type of result requires personalised genetic counselling.
9. **Reproductive matching:** The validity of reproductive matching depends on the accuracy of the individual test reports being compared. Igenomix is not responsible for any error in reproductive risk assessment if matching to an external report is inaccurate in any way. The validity of the reproductive matching is also subject to the limitations of each individual test, one of which may have been performed by an external genetic testing laboratory. Reproductive matching ensures that any gene reported as positive on one carrier screening report was appropriately included in the other carrier screening test. However, it is possible that the variants analysed for each gene may be different, especially if the tests utilised different technology. These differences can occur when comparing two reports from Igenomix, for example, if different test versions with different methodology are compared, or when comparing an Igenomix report to a report issued by an external laboratory. Such differences may have particular clinical relevance in cases of consanguinity or high variant frequency.
10. **Ethnicity:** Expanded carrier screening is considered a pan-ethnic test. However, additional carrier screening may be indicated for individuals with certain ethnic backgrounds, such as haemoglobin electrophoresis and complete blood count (CBC) for individuals of Hispanic, Southeast Asian, Middle Eastern, and African descent. Additionally, some ethnic populations (e.g., Ashkenazi Jewish) have a high carrier frequency of CNVs in some genes that may not be detected. Enzyme studies for HEXA may be considered for individuals of Ashkenazi Jewish descent.
11. **Misdiagnosis:** There is a chance of misdiagnosis either through a false positive or a false negative result. There is a small chance that the result is inaccurate for a procedural reason, such as an error during the collection and labelling of the sample, processing, data collection and/or interpretation. The presence of homopolymers, rare DNA changes, and/or non-functional, duplicated gene sequences (pseudogenes) may confound the analysis. Other biological circumstances could invalidate the test results, such as the presence of congenital or acquired chimerism. Chimerism is the coexistence

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of the patient's own cells with others from a donor, including the possibility of an exclusive donor cell colonization. Congenital chimerism is very rare and develops when two twin embryos become one early in development. Acquired chimerism can occur temporarily through a blood transfusion, or permanently through a bone marrow transplant. Any history of transfusion and/or transplant should be indicated on the test requisition form. A saliva sample is preferred in cases of transfusion or transplant, to reduce the chance of discrepant results.

12. **Residual risk:** A negative carrier screening result reduces but does not eliminate the chance of being a carrier of the genes included in the analysis. There remains a residual carrier risk for each condition tested due to the limitations of the technology. A reduced reproductive risk does not eliminate the possibility of having affected offspring. The possibility of new (*de novo*) variants in a child cannot be ruled out. Additionally, some variants may be present in only some parts of the body (mosaic). Such a mosaic variant, if present in the egg or sperm lineage cells, may be passed on to offspring and be associated with increased reproductive risk. However, if the variant is not present in the sample submitted for carrier screening, it cannot be detected.
13. **Other genetic and non-genetic conditions not analysed:** Carrier screening cannot assess the carrier risk for all known genetic conditions. For many genetic conditions, the exact cause and associated genetic factors are still unknown. Conditions with mitochondrial inheritance, autosomal dominant conditions, multifactorial conditions, and most conditions with digenic inheritance are not included, unless otherwise indicated. Carrier screening does not assess the risk to have a pregnancy or child with a chromosomal abnormality, such as Down syndrome. Carrier screening cannot guarantee the birth of a healthy child. There is a 3-5% risk of birth defects in the general population. These may be caused by genetic and/or non-genetic factors.

RECOMMENDED FOLLOW-UP TESTING & REPRODUCTIVE OPTIONS

Carrier screening for the reproductive couple can be performed simultaneously or sequentially. Carrier screening for both members of the reproductive couple provides the most accurate reproductive risk assessment. If one person is tested first and is identified to be a carrier for one or more recessive conditions, carrier screening for the reproductive partner is recommended for at least the same gene(s) in which a variant was identified. If a female individual is tested first and found to be a carrier for an X-linked condition, carrier screening for the male reproductive partner for the condition may not be indicated. If a male individual is the first to test and tests negative, carrier screening for the female reproductive partner is recommended for X-linked conditions.

If there is an increased reproductive risk and/or personal health risk identified on carrier screening, referral to a genetic counsellor or a medical specialist familiar with carrier screening is recommended. You may also request a consultation with a genetic counsellor from Igenomix. If both the egg and sperm provider are identified as carriers of the same autosomal recessive condition, there is a 1 in 4 (or 25%) chance for each offspring to inherit both variants. If the egg provider is identified as a carrier of an X-linked condition, there is a 1 in 2 (or 50%) chance for each offspring to inherit the variant. If there is increased reproductive risk for a condition, several reproductive options may be considered, including:

1. Gamete donor selection. The use of an egg donor or sperm donor may be considered, or a different egg or sperm donor may be selected if there is an adverse match with the currently selected donor.
2. Pre-implantation genetic testing for monogenic diseases (PGT-M) using in vitro fertilization (IVF) and testing embryos prior to transfer.
3. Prenatal testing, including chorionic villus sampling (CVS) or amniocentesis.
4. Not becoming pregnant or family building through adoption.

Identifying an increased reproductive risk also enables diagnostic testing in the newborn period to be planned, especially if treatment options exist for the condition. Because of the limitations of carrier screening, additional preimplantation and/or prenatal testing options to assess for chromosomal abnormalities or to screen for birth defects should be discussed with your clinician. The carrier screening test may identify variants that may be carried by other family members. You are encouraged to share your carrier status with other family members, especially those in their reproductive years.

CANCELLATION

Testing may be cancelled at any time by the referring clinician prior to receiving samples at Igenomix. If the test has been paid for but not performed (for any reason including cancellation or transportation delay), the payment will be refunded. Once samples have been received at the laboratory and the testing process has begun, it may not be possible to cancel testing nor refund payment. Please contact your referring clinician as soon as possible should you decide you no longer wish to proceed with testing.

SAMPLE RETENTION

Unless required by law, Igenomix is not obligated to store DNA samples, and any samples (blood and/or saliva) and DNA obtained during sample processing may be discarded after results are reported or the test is discontinued for any reason. Untested samples may be discarded after cancellation or if received without a signed consent and/or test requisition form.

Potential future clinical testing on stored samples as ordered by a clinician or for quality control may be possible upon request if samples remain in storage. Sample quality may decline over time, and future testing may not yield informative results.

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DATA PRIVACY

Your privacy is a priority for the Igenomix Group ("Igenomix"). Your identity and all data referring to your personal information will be confidential and only Igenomix personnel will be permitted access to this information, along with the relevant authorities when required by the laws of the applicable jurisdiction.

Your personal data will be processed on behalf of your clinician/healthcare provider for the purpose of carrying out the genetic test. Your clinician/healthcare provider is the data controller and Igenomix is the data processor. Igenomix will process your personal data following the instructions and directions of your clinician/healthcare provider. We therefore recommend that you contact your clinician/healthcare provider directly if you would like to know more about the processing of your personal data. If you need to contact Igenomix, you can get in touch with our Data Protection Officer by email (privacy@igenomix.com) or by postal mail to the following address: Igenomix Spain Lab S.L Edificios Europark, Parque Tecnológico, Ronda de Narcís Monturiol, nº11, B, 46980 Paterna, Valencia.

Your sample will be analysed by Igenomix or an associated group selected by Igenomix. Igenomix reserves the right to carry out part of or all the analyses included in the test through third party laboratories certified with recognised international quality standards, and with the same level of data protection security measures. Any results obtained in this way will be inspected by Igenomix and this approach will be indicated in the issued report.

Pursuant to the laws on the Protection of Personal Data, your referring clinician/healthcare provider must have your consent to perform the test(s) requested and to process your data. You may, at any time, exercise your rights regarding access, rectification, opposition, erasure, automated decisions, limitation, and/or portability by sending an email to privacy@igenomix.com, providing proof of the requesting party's identity.

FOR DONORS ONLY: RESULTS OPTIONS AND DATA UPGRADE AUTHORISATION

In accordance with your clinic's and/or referring clinician's policies, you may be asked to indicate your results preference on the CGT Test Requisition Form. Your options include:

- To receive the CGT results: You would like the referring clinician to inform you about your test results, accepting that such results might indicate an increased risk of transmitting hereditary conditions to your offspring, even though you may not show any symptoms of such conditions.
- Not to receive the CGT results: You do not want to have access to or to receive any information about the results of this test. You understand that the results may have implications for current or future offspring and your biological relatives. However, if necessary to avoid serious damage to your health and/or that of your biological relative(s), this information may be brought to your attention by the referring clinician, depending on the required local legislation.

Your DNA may be sequenced for a greater gene content than initially included in the requested Carrier Genetic Test, given that this may be necessary for gene matching purposes (see Procedure section for information regarding data upgrading). The matching test can establish that there is an increased genetic risk of having affected offspring; in this case, the relevant clinician(s) will take the appropriate steps to manage this result, and you will not be informed of the matching outcome. If you require further information about the results of a data upgrade, you or your referring clinician/healthcare provider must contact Igenomix (support.uk@igenomix.com) directly.

PATIENT CONSENT

Having read and understood the information above:

- I have decided to proceed with CGT. I request that Igenomix performs CGT on the sample(s) sent by my clinician or submitted by me. This consent applies to all subsequent matching reports, data upgrades, and/or any sequential reanalysis ordered by the referring clinician. However, Igenomix may require a new consent due to changes in technology, process, interpretation, etc.
- I acknowledge the indications, procedure, risks, limitations, and potential implications of the proposed test, as well as the financial cost of said test(s).
- I have been given the opportunity to talk with an Igenomix genetic counsellor to ask questions about CGT and the information contained in this consent form. I understand that an Igenomix genetic counsellor is available to answer any additional questions I may have. If genetic counselling is not requested, I agree to have testing performed without first speaking with an Igenomix genetic counsellor.

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