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Igenomix® PART OF VITROLIFE GROUP

Test Requisition Form **CGT SYNC**

Fields marked with * are required to perform the test.

1) ANALYSIS REQUESTED

CGT SYNC provides analysis of all GENES OF INTEREST that you include in SECTION 4

***Include analysis of 66 X-linked genes?** ☐ **YES** ☐ **NO**
(Female patients only)

2) CLINICIAN INFORMATION

***Referring clinician** _____ ***Clinic/Centre:** _____

***Email of clinic/clinician:** _____ Tel: _____

3) PATIENT INFORMATION

***Full name:** _____ ***Date of birth:** _____

***Unique patient ID (if available):** _____ ***Sample collection date:** _____

***Sex:** ☐ Male ☐ Female ***Sample type:** ☐ Blood ☐ Saliva

Ethnic group **(we strongly recommend including this)**. Please select all that apply.

☐ Caucasian ☐ East Asian ☐ South Asian ☐ Arab / ME ☐ Other _____
☐ Ashkenazi J. ☐ Hispanic ☐ Romani ☐ Afro-_____ ☐ Unknown

If the patient has previously had CGT from Igenomix, please tick here: ☐

CGT SYNC reanalysis for previous CGT patients can generally be performed without a new sample.

4) DETAILS OF INDIVIDUAL(S) OF INTEREST

CGT SYNC provides targeted screening of a **patient** (named above) against one or more **individual(s) of interest** who are known carriers of/suspected carriers of/affected by a recessive condition, such as a partner or gamete donor candidate. CGT SYNC screens the patient for these **genes of interest** to significantly reduce the risk that the patient carries a likely pathogenic/pathogenic variant in the same gene(s) as an individual(s) of interest.
Please provide the details of the individual(s) of interest below. Space for additional entries is available in the APPENDIX at the end of this form.
In some circumstances, Igenomix may request a genetics report for an individual(s) of interest.

		GENES OF INTEREST	
#	DETAILS OF INDIVIDUAL(S) OF INTEREST (IF AVAILABLE)	*GENES CARRIED/AFFECTED IN INDIVIDUAL OF INTEREST	RELEVANT CLINICAL & FAMILY HISTORY
1	Name: _____ DoB: _____ Unique ID: _____ Relation to patient: ☐ Partner ☐ Donor ☐ Other _____		
2	Name: _____ DoB: _____ Unique ID: _____ Relation to patient: ☐ Partner ☐ Donor ☐ Other _____		
3	Name: _____ DoB: _____ Unique ID: _____ Relation to patient: ☐ Partner ☐ Donor ☐ Other _____		

If you have included extra entries in the APPENDIX, please tick here: ☐

HEALTHCARE SPECIALIST AUTHORISATION

I certify that the patient and prescribing clinician's details given in this request form are accurate to the best of my knowledge and that I have requested the test indicated above based on my professional judgement. I have explained the limitations of this test and have answered any questions based on medical judgement. I understand that Igenomix may require further information and I agree to provide this information if necessary.

*Healthcare Specialist's signature _____ Date: ____/____/____

PATIENT CONSENT

By signing this request form, I voluntarily ask Igenomix to perform the test indicated above. I have read and received a copy of the informed consent included in these pages. I have also been adequately informed of the risks, benefits and limitations of this test.

*Patient's signature _____ Date: ____/____/____

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Studies of our genes — DNA — estimate that **most healthy people are carriers of one or more recessive mutations** which, if passed on to offspring, can cause severe disorders in certain circumstances(1). These studies also show that, **without genetic testing, it is not possible to know who carries these mutations**, since, in most cases, carriers of recessive mutations have no symptoms and no family history of the disorder. Genetic tests to identify carriers, targeted at healthy individuals, are known as **genetic screening tests, or carrier screening tests.** Therefore, the aim of carrier testing is to identify which individuals, including potential gamete donors, or couples, have this type of mutation. Using the results, based on the type of disorder(1), it can be established whether there is a high risk of transmitting hereditary diseases to offspring. If a high risk is detected (25% or higher), different reproduction options may be considered ; regarding donors, the suitability of the potential gamete donor is assessed. The ultimate purpose is to provide intended parents with information that will help them consider various clinical options and procedures to reduce the incidence of genetic disorders in newborns.

(1) **Autosomal recessive inheritance and X-linked disorders.** For **autosomal recessive disorders**, two altered copies of the same gene must be inherited, one from each biological parent, for symptoms to appear. If both biological parents are carriers of a recessive disorder, the risk of having a child affected by the disorder is 25%, (1 in 4).
For **X-linked gene mutations**, a female carrier is at risk of having an affected male offspring, with a 50% (1 in 2) chance that any male offspring will be affected. In some instances, female carriers of X-linked conditions may display some mild symptoms.

CGT SYNC: DESCRIPTION, PURPOSE AND ADVANTAGES OF ANALYSIS

The CGT SYNC test aims to identify carriers of pathogenic or likely pathogenic variant(s) associated with specific monogenic diseases (Mendelian diseases). Usually, CGT SYNC is indicated when a member of a couple or a gamete donor candidate(s) (an '**individual(s) of interest**') is a known carrier in one or more specific genes, referred to as the **genes of interest**. CGT SYNC screens the patient for the genes of interest to detect variants in these genes which, when combined with the individual of interest, means that there is an increased risk of having an affected child. Genes of interest are sequenced (using next generation sequencing - NGS) for all coding nucleotides and some selected adjacent gene regions. CGT SYNC focuses on the detection of single nucleotide variants (SNV) and small insertions/deletions (indels). In certain cases, the NGS analysis may include the detection of gene copy number variation (CNV). Unless otherwise indicated, the CGT SYNC analysis does not include complementary methods (MLPA, qPCR, etc.) for analysing CNVs.

The process for conducting the **CGT SYNC** test is as follows:

1. Blood/saliva sample collection.
2. DNA extraction.
3. Sequencing (NGS) of the genes of interest, as per section 4 of the Test Requisition Form. Testing for all coding nucleotides and some selected adjacent gene regions (splice sites, etc.). In female patients, if requested in section 1, 66 additional X-linked genes (Listed in **Table 1** below) will also be analysed.
4. Occasionally, the analysis of certain genes may require a different (non-NGS) method that will be specified in the CGT SYNC report methodology section.
5. Bioinformatic analysis of sequencing raw data related to the genes of interest listed in section 4 of the Test Requisition Form (also including, if requested, the 66 additional X-linked genes listed in **Table 1**).
6. Variant(s) clinical interpretation following professional guidelines (ACMG, Richards et al., 2015).
7. A results report is issued, including pathogenic and likely pathogenic variants in the gene(s) of interest and, if selected, the analysed X-linked genes. Variants of unknown significance (VUS) are not included. Variant classification is based on current scientific and medical understanding. Future queries to understand whether any reported variants have been reclassified since the report was issued should be sent to info.uk@igenomix.com.

If a patient has previously performed CGT with Igenomix and this is indicated in section 3, then it may be possible to perform retrospective analysis of the genes of interest without a new sample. In this case, steps 1-4 above do not apply.

To perform any of these analyses, the test requisition form must be correctly completed. Otherwise, analysis may be suspended until the required information has been provided to the laboratory.

Given the complexity of the genetic tests and the significant implications of the test results, the results obtained must be interpreted in conjunction with other clinical and family data, within the general context of a medical practice run by health professionals. The result reports are strictly confidential. CGT SYNC results will be available within up to 25 working days of sample receipt at the laboratory. Where CGT SYNC is being performed without a new sample (because the patient has had a previous CGT test), the results will be available within 7 working days of receipt of the test requisition form. A small percentage of samples may be delayed due to unforeseeable causes. Should this occur, the corresponding clinician in charge will be notified.

The CGT SYNC analysis will be performed by the Igenomix Group ("Igenomix"). However, Igenomix reserves the right to carry out part or all the analyses that make up the test through third-party laboratories, accredited to recognized international quality standards, and /or periodically evaluated by Igenomix. The results obtained in this way will be reviewed by Igenomix and such circumstances will be indicated in the final report issued.

While there are considerable benefits to the CGT test, limitations exist that are described below:

a. The CGT SYNC test analyses only the specified gene(s) of interest and not others (as per test request), aiming to identify pathogenic and/or likely pathogenic variants. However, it does not guarantee the detection and identification of all the pathogenic/likely pathogenic variants that may exist.

   i. Some recessive genes also have dominant alleles associated with dominant phenotypes; however, since this is not a diagnostic test, the CGT SYNC-associated interpretation will only be provided for recessive phenotypes. Also, digenic inheritance is not assessed, unless otherwise indicated.

   ii. Even when the genetic or molecular basis of a potential mutation is known, it is not possible to guarantee the detection of 100% of variants since some may be located in regions of low sequencing coverage, outside the gene regions under study, such as regulatory regions of gene expression or in deep intronic regions (from position +3 and -3).

b. Optionally, for female patients, the CGT SYNC test can analyse variants in genes inherited in an X-linked inheritance pattern. However, it does not include all X-linked disorders whose genetic basis is already known. The analysis will include specific genes, as listed in **Table 1** below. When requested, Igenomix will review these X-linked genes to detect and report any mutations that are included in Igenomix's carefully curated mutations master list for these X-linked genes. For details about specific variants included in the mutations master list, please contact info.uk@igenomix.com.

c. The Next Generation Sequencing (NGS) technique has the following technical limitations:

   i. DNA changes caused by large rearrangements (deletions and duplications) cannot be detected, unless otherwise indicated.

   ii. Trinucleotide expansions are not detected; a complementary method (non-NGS) may be applied if needed and will be described in the methodology section.

   iii. After sequencing, areas without coverage or very low coverage may prevent the detection of possible pathogenic variants.

d. The CGT SYNC test is highly accurate, but as with all genetic tests, there are, in addition to the above limitations, other factors that can affect the results. Therefore, a negative test result reduces but does not totally rule out the possibility of having affected offspring, due, among others, to the following reasons (non-exhaustive):

   i. *De novo* mutations in one of the biological parents' gamete cells (including cells from gamete donors) cannot be assessed.

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ii. Presence of somatic or germline mosaicism that creates differences in the DNA between tissues cannot be ruled out. These types of mosaicism are created after the fusion of parental gametes and can affect some but not all parts of the body. This mosaicism cannot be detected if the tissue where it was created is not studied and if it is not present in a significant portion of its cells. In any case, the incidence of this happening is relatively low.

iii. Presence of rare polymorphisms and/or pseudogenes and/or homopolymers may lead to false negative and positive results.

iv. In a specific sample, some of the variants may not pass our quality control parameters due to low coverage of the genomic region in question. In this case, that variant position will be reported as non-informative.

v. Other medical reasons may coexist that invalidate the test result and, therefore, should be investigated by the medical team before proposing the test. This is the case for individuals identified as congenital chimeras or acquired chimeras; patients who have had a recent blood transfusion, or who have ever had a bone marrow transplant. Congenital chimerism occurs when there is a partial or total fusion of two embryos; this possibility is low or very low. Allogeneic bone marrow transplants generate chimerism or coexistence of the patient's own cells with others from the donor, including the possibility of exclusive colonization of the donor cells. All these circumstances will generate discrepant results if the analysed DNA comes from a peripheral blood sample. In the case of bone marrow transplantation, the scientific literature describes cases solved by working with a saliva sample; this may avoid possible genetic discrepancies (relating to germ cells).

vi. As in any laboratory test, there is a small chance that the result is inaccurate for a procedural reason, an error during the collection and labelling of the sample, an error in processing, data collection or interpretation.

Table 1 – Additional X-linked genes analysed if requested in section 1 of the Test Requisition Form. Available for female patients only. When requested, Igenomix will review these X-linked genes to detect and report any mutations that are included in Igenomix's carefully curated mutations master list for these X-linked genes. For details about specific variants included in the mutations master list, please contact info.uk@igenomix.com.

ABCD1, AP1S2, AR, ARSL, ARX, ATP7A, ATRX, BRWD3, BTK, CD40LG, CHM, COL4A5, CUL4B, CYBB, DCX, DKC1, DLG3, DMD, EDA, EMD, F8, F9, FGD1, FMR1, FTSJ1, G6PD, GJB1, GLA, GPR143, HCFC1, HPRT1, HSD17B10, IDS, IL1RAPL1, IL2RG, KDM5C, L1CAM, MECP2, MTM1, NDP, NR0B1, OCRL, OPHN1, OTC, PAK3, PDHA1, PGK1, PHF8, PLP1, POU3F4, PQBP1, PRPS1, RP2, RPGR, RS1, SH2D1A, SLC16A2, SLC6A8, SYN1, THOC2, UPF3B, WAS, ZDHHC9, ZNF711.

DATA PRIVACY, STORAGE AND RESEARCH USE OF SAMPLES

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. You will find further information on the Igenomix Privacy Policy, along with all your rights at www.igenomix.com, or this information may be provided to you upon request by sending an email to privacy@igenomix.com.

We would like to inform you that your personal data will only be processed to: (1) Fulfil the obligations arising from the provision of the services contracted by you; (2) Check and guarantee the quality of the services provided (internal audits, quality controls, laboratory validation studies); (3) For educational purposes, provided that it remains anonymous throughout and you cannot be identified during the analysis of the data, which will not be linked to your personal data; (4) For research purposes, scientific publications and presentations, provided that it remains anonymous throughout and you cannot be identified during the analysis of the data, which will not be linked to your personal data; and (5) Personally address any doubts or suggestions made by the patient during the process and monitor the proper performance and resolution of the test, including the indefinite retention of your data, except where local laws of the applicable jurisdiction state otherwise.

You also declare that you understand and accept that you will not obtain, either now or in the future, any economic benefit for any research carried out, and that there is no intention to compensate you for the products developed from any research.

The sample will be analysed by Igenomix or an associated group selected by Igenomix on an international level. Igenomix reserves the right to carry out part or all of the analyses included in the test through third party laboratories accredited to recognised international quality standards, or failing this, they will be periodically assessed by Igenomix. Any results obtained in this way will be inspected by Igenomix and this circumstance will be indicated in the final report issued.

The samples and data associated with the same shall be held by the laboratory in accordance with Igenomix's sample retention policy which meets all legal requirements.

Pursuant to the laws on the Protection of Personal Data[1], the requesting party must have the patient's consent to perform the diagnostic tests requested and to process their data. You may, at any time, exercise your rights regarding access, rectification, opposition, erasure, automated decisions, limitation, portability, by sending an email to privacy@igenomix.com, providing proof of the requesting party's identity.

RESULTS PREFERENCES FOR DONORS ONLY: (INDICATE AN OPTION OF YOUR CHOICE)

☐ Not to receive any information at all: I don't want to have access to or to receive any information about the results of the test. However, if the information is necessary to avoid serious damage to my health or that of my biological relative(s), I understand that this information will be brought to the attention of my referring clinician, who will adhere to the required local legislation when considering the delivery of these results to me.

☐ To receive the CGT results: I would like Igenomix to inform the ordering healthcare provider about my CGT test results, accepting that such results might indicate the risk of transmitting hereditary conditions to my offspring, even though I may not show any symptoms of such conditions.

I have been informed that this consent may be withdrawn at any time. However, if such withdrawal takes place once the **CGT** test has been done, **IGENOMIX** may not continue using my genetic data in the computer system, unless it is disassociated from my identity and used for research purposes.

HAVING READ AND UNDERSTOOD THE FOREGOING, I AM ARE AWARE OF:

The indications, procedure, success rate, risks and complications of the proposed treatment, as well as the financial cost of said test(s).

The fact that medical staff are at my disposal to expand on any aspect of the information that is not sufficiently clear to me.

I confirm that I have understood the explanations given to me in clear and simple language, and that my referring clinician allowed me to make comments, clarifying any issues I raised and informing me that I may freely withdraw my consent at any time.

The result of the CGT SYNC test is limited to the test design and scientific understanding at the time the test is performed. Only mutations that can be identified with our current platform and methodology will be detected.

I declare that I have received adequate explanations and counselling from a clinician who has offered me information about the importance of the test, including possible alternatives that may be available to me; and the clinician is available to me for any questions or additional counselling that I may require once the results of the test are known. I also accept that the results of the test(s) may be passed on to my clinician, so that he or she can advise me correspondingly on the suitable treatment to follow.

[1]**For patients residing outside of the United States:** under certain jurisdictions, clients residing outside the United States may at any time request to have their personal information deleted from our active databases, subject to the applicable laws and regulations in each jurisdiction. Although we can delete your personal information from our active databases, part or all of your personal information shall remain stored in back-up files for the purpose of complying with legal, regulatory or other requirements. Information that has already been coded and/or anonymised may not be recoverable or traceable for destruction, deletion or modification. If you wish to have your personal information removed from our active databases, please contact us at privacy@igenomix.com.

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APPENDIX FOR ADDITIONAL ENTRIES TO SECTION 4

IF YOU INCLUDE ADDITIONAL ENTRIES HERE, PLEASE ENSURE THAT YOU HAVE TICKED THE BOX IN SECTION 4.

		GENES OF INTEREST	
#	DETAILS OF INDIVIDUAL(S) OF INTEREST (IF AVAILABLE)	*GENES CARRIED/AFFECTED IN INDIVIDUAL OF INTEREST	RELEVANT CLINICAL & FAMILY HISTORY
4	Name: _____ DoB: _____ Unique ID: _____ Relation to patient: ☐ Partner ☐ Donor ☐ Other _____		
5	Name: _____ DoB: _____ Unique ID: _____ Relation to patient: ☐ Partner ☐ Donor ☐ Other _____		
6	Name: _____ DoB: _____ Unique ID: _____ Relation to patient: ☐ Partner ☐ Donor ☐ Other _____		
7	Name: _____ DoB: _____ Unique ID: _____ Relation to patient: ☐ Partner ☐ Donor ☐ Other _____		
8	Name: _____ DoB: _____ Unique ID: _____ Relation to patient: ☐ Partner ☐ Donor ☐ Other _____		
9	Name: _____ DoB: _____ Unique ID: _____ Relation to patient: ☐ Partner ☐ Donor ☐ Other _____		

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