NEWBORN SCREENING TEST REQUEST FORM

The fields indicated with (*) are mandatory to proceed with the test.

Type of Test

Newborn Screening Test

Referring clinician/healthcare provider: *	Clinic/Hospital/Centre: *

Patient (newborn) information *

Full name / ID _____

DOB: _____ MRN: _____

Biological sex at birth: Male ☐ Female ☐

Parental consanguinity Yes ☐ No ☐

Sample information *

Type of sample:

☐ Venous Blood

☐ 2 X Buccal Swabs

Date of collection: _____

Sample collection performed by (full name):

_____

Ethnic group: Arab ☐ Caucasian ☐ South Asian ☐ East Asian ☐ Ashkenazi ☐ Hispanic ☐ Romani ☐ Afro-_____ ☐

Other (indicate): _____ *Please indicate all appropriate ethnicities if belonging to more than one ethnic group

Parent / Legal Guardian (P1) information: *

Full name: _____ DOB: _____ MRN: _____ Biological sex at birth: _____

Relationship to patient: _____ Ethnic group: _____

Parent / Legal Guardian (P2) information: *

Full name: _____ DOB: _____ MRN: _____ Biological sex at birth: _____

Relationship to patient: _____ Ethnic group: _____

Parents/Legal Guardian signature *

By signing this form, I voluntarily request that Igenomix perform the indicated newborn screening test and I authorise them to contact me if required. I have read and received a copy of the consent document from my provider. I have been adequately informed of the risks, benefits, and limitations of this test.

The signatories declare under their own responsibility that they hold the parental authority or legal representation of the minor whose sample and data are objects of the test.

Signature (P1) Signature (P2)

Date: Date:

Email:

☐ I do not consent to the processing of my newborn's/my information for research purposes.

☐ I would also like to be informed if the newborn is a carrier of a pathogenic or likely pathogenic variant in the genes analysed.

Clinician/Healthcare provider details *

I confirm that the information in this form is complete and accurate to the best of my knowledge, that I have ordered the indicated test based on my professional judgement and that the patient has signed either the Igenomix consent form, or an internal one, provided and stored as required by national guidelines and/or legislations. Any non-Igenomix, internal consent form will include the limitations and risks of analysis as stated in the Igenomix consent form, and any other relevant information that could impact patients' decision-making in performing the test, and/or potentially impact the result of the test. I have addressed the limitations of this test and have answered any questions the parents/legal guardians had to the best of my ability. I understand that Igenomix or its affiliated companies, agents or subcontractors may need additional information and I agree to provide it as needed for the purposes of reimbursement or test completion.
I authorise the genetic test for this patient.

Clinician/Healthcare provider signature	
Date:	
Clinician´s email to receive the report	Email ID 1:
	Email ID 2:

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INFORMED CONSENT FOR THE NEWBORN SCREENING TEST

TEST PURPOSE AND POTENTIAL RESULTS

Igenomix NBS is a genetic screening test aimed at healthy newborns – it is not a diagnostic test. Any newborn who shows symptoms of a disorder or has a family history of any of the diseases tested should be referred for diagnostic testing rather than a screening test.

The aim of the Igenomix NBS test is to facilitate the early detection of more than 200 potentially actionable and treatable genetic diseases, based on the analysis of known disease-causing variants in the 237 genes included in the test.

The genes analysed are associated with developmental and metabolic disorders, which can cause serious health conditions that may manifest at an early age. For many of these disorders, in the absence of treatment, the severity of the condition increases significantly with time, with the symptoms in many cases being irreversible.

Pathogenic or likely pathogenic variants are gene alterations of clinical relevance that are predicted to cause disease. Autosomal dominant diseases are caused by a single disease-causing variant in one of the two alleles of a gene on an autosome, whereas autosomal recessive diseases are caused by the presence of a disease-causing variant in both alleles of a gene on an autosome. X-linked diseases are caused by disease-causing variant(s) in a gene on the X chromosome; inheritance can be X-linked dominant or X-linked recessive. Males only have one copy of the X chromosome (and one Y chromosome), whereas females have two copies of the X chromosome, and therefore the consequences of carrying disease-causing variant(s) in a gene on the X chromosome differs in males and females.

In the case of a positive result, the information obtained may instigate a clinical assessment, subsequent diagnostic confirmation of a disorder and the establishment of a treatment, if necessary. This may avoid the appearance of symptoms, or mitigate their effects, to improve the long-term health outcomes of the newborn.

Before undergoing the genetic test, you should be made aware of the implications of the possible results. There are four possible outcomes of this test:

A. **Positive result:** In the case of a dominant disease, a positive result would indicate that one pathogenic or likely pathogenic variant has been identified in a gene that causes a dominant disease. In the case of a recessive disease, a positive result would indicate that at least two pathogenic or likely pathogenic variants have been identified in a gene that causes a recessive disease. For X-linked diseases, the clinical implications of carrying one or more pathogenic or likely pathogenic variant(s) may differ in males and females.

B. **Negative result:** No pathogenic or likely pathogenic variants have been identified in any of the genes studied. A negative result reduces, but does not eliminate, the genetic predisposition to the diseases studied. This is due to the constraints of current scientific knowledge, as well as the limitations of the test and the techniques used.

C. **Carrier result:** A pathogenic or likely pathogenic variant has been identified in a gene involved in the development of an autosomal recessive disease, or in an X-linked recessive disease if the newborn is female. Typically, the presence of a disease-causing variant in the other allele of the gene would be necessary for the patient to develop symptoms compatible with the disease. The carrier result will be reported only if it has been explicitly requested in the TRF (by checking the box on page 1).

D. **Non-informative result:** A result can be considered non-informative if the sample does not pass our quality control checks for DNA concentration/quality. The most frequent cause of this is low DNA concentration due to inadequate sampling or degradation of the sample due to poor handling, storage, or transport to the laboratory.

GENETIC COUNSELLING

Approximately 3-5% of babies are born with a birth defect due to many different causes. A child with a negative NBS test is still at risk of having or developing a genetic condition.

Performing genetic testing on an individual may lead to results that have clinical and reproductive implications for both the individual tested and their family members. Participation in genetic testing is voluntary.

This test will only report information regarding the conditions included in the Igenomix NBS test. Due to limitations of the test, not all variants within these genes may be detected. Additional testing may be ordered by your clinician if necessary.

The referring clinician should ensure the provision of appropriate pre- and post-test genetic counselling, aimed at providing information on the requested test, the objective, the possible results, and the implications of each possible result.
Igenomix professionals are at the disposal of the patient and the providers for the clarification of any questions that may arise.
In the event of a positive result, or a carrier result if this information has been requested, Igenomix offers post-test genetic counselling free of charge, as well as patient support and follow-up as needed.

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PROCEDURES, RISKS, AND LIMITATIONS

The process of conducting the test will be as follows:

1. Collection of one venous blood sample or two buccal swab samples (using a specialised oral collection kit). If the sample is collected with a swab or extraction kit that is not validated by Igenomix and the protocol is not approved by Igenomix, the sample may not be accepted, since these kits may have a decreased/different sensitivity and would impact the quality of DNA and interpretation of the results.
2. Extraction of DNA from the biological sample and quality control review.
3. Next generation sequencing (NGS) of 237 gene regions where known variants are located. The list of genes analysed in the newborn screening test is available via this link (https://www.igenomix.co.uk/genomics-precision-diagnostic/newborn-screening). The list of variants analysed within each gene is available upon request from Igenomix.
4. Additional testing to analyse frequent disease-causing variants not detected using NGS technology will be conducted by alternative methods:
   - Deletions / duplications in the *SMN1* gene and deletions in the *CYP21A2* gene using quantitative polymerase chain reaction (qPCR).
   - Frequent disease-causing variants in the *CYP21A2* gene by mini-sequencing.
   - Large deletions / duplications of the *DMD* gene by multiplex ligation dependent probe amplification (MLPA).
5. Bioinformatic analysis of the NGS results.
6. Preparation of the screening report.

The test request form must be correctly completed in order to process the sample. Analysis may be suspended until the required information is received by the laboratory.

If the extracted DNA does not pass the quality control checks another sample will be requested. In the case of a non-informative result, the Igenomix team or the referring healthcare provider will be in contact regarding next steps.

Given the complexity of the genetic tests, and the potentially significant implications of the test results, the results obtained must be interpreted in conjunction with family and clinical data, within the general context of a medical practice run by healthcare professionals. The result reports are strictly confidential.

The report will be generated within the turnaround time (TAT) of 25 calendar days. A small percentage of samples may be delayed due to unforeseen circumstances. Should this occur, Igenomix will inform the corresponding clinician of the delay. Igenomix will not be liable, under any circumstances, for any delay beyond the TAT.

The report will only include variants present in the analysed genes that have been previously classified as pathogenic or likely pathogenic. Variants of uncertain significance will not be reported. Carrier results will only be included in the report when specifically requested (by checking the box on page 1).

The database may be updated, and clinical classifications may vary over time. Thus, the variants may be reclassified in the future. In the event of the newborn showing any symptoms, a diagnostic investigation is recommended. To determine whether there have been any changes to the classifications of the variants, please contact info.uk@igenomix.com.

While there are considerable benefits of the Igenomix NBS test, some limitations exist. These are described below:

a) The newborn screening test exclusively analyses variants included in the list, and not others.
   - It does not include all existing genetic disorders, as analysis is restricted to known disease-causing variants that cause early-onset, actionable disorders.
   - Mitochondrial, digenic, and multifactorial diseases are not included.

b) Next generation sequencing technology may not be able to detect all types of disease-causing variants due to the following limitations:
   - The technology cannot detect large deletions and duplications greater than 15 base pairs, homopolymer extensions, variants in pseudogene regions, gene fusions, balanced translocations, chromosomal rearrangements, inversions, aneuploidies, uniparental disomies, expansions of repeated regions and variants in regulatory regions or intronic regions beyond ± 3 base pairs.
   - Some variants may not be detected in areas of low sequencing coverage.
   - Copy number variations (CNVs - the number of copies of a specific region in the genome of an individual) included in the test will not be analysed using NGS.

c) The complementary tests included in the newborn screening test allow the analysis of relevant variants that are not detectable by NGS technology, although in turn, they present, in addition to general limitations, the following specific limitation:
   - The sensitivity for the *SMN1* gene is approximately 96%, since point mutations and small insertions / deletions are not analysed. If the qPCR result is normal, it is not possible to discern whether the two copies are located in opposite alleles of the gene (in trans; non-carrier), or if they are in the same allele and, therefore, there are no copies in the other allele (in cis; carrier).

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d) General limitations:
- As with any laboratory test, there is a very small chance that the result will be inaccurate for a procedural reason, such as an error during sample collection and labelling, or an error in processing, data collection, or interpretation.
- The presence of low frequency polymorphisms and/or pseudogenes and/or homopolymers could lead to false negative and/or false positive test results.
- In a specific sample, some of the variants may not meet our quality criteria due to low sequencing coverage of a specific genomic region. In this case, the variant will be reported as non-informative.

DATA PRIVACY, STORAGE AND RESEARCH USE OF SAMPLES

Your newborn's privacy is a priority for the Igenomix Group ("**Igenomix**"). Your newborn's identity and all the data referring to your newborn's personal information will be confidential. You can find more detailed information in connection with the data controller, the data needed to be processed, the purposes and legitimate grounds and the information regarding the retentions of the samples, the guarantees implemented for international transfers and the existence of an internal policy by reaching out to our Data Protection Officer through the following email address privacy@igenomix.com or with postal mail to the address Igenomix, S.L.U., Edificios Europark, Parque Tecnológico, Ronda de Narcís Monturiol, nº11, B, 46980 Paterna, Valencia.

Purpose

Igenomix would like to inform you that your newborn's personal data will be processed only to: (1) fulfil the obligations derived from the delivery of services hired by you, including the collection and processing by your clinician and Igenomix of your newborn's "Personal (Health) Data" (meaning in particular and in each case insofar as provided: personal details including name and address, family relations, age/date of birth, gender, ethnicity, nationality, insurance information, symptoms and other medical information, disease, the study material/sample with identifiable genetic data, and the genetic analysis results and findings) as far as required to conduct the genetic analysis including any necessary transfers of your newborn's Personal (Health) Data between clinician and Igenomix; (2) review and provide the quality of the services provided (internal audit, quality control, laboratory validation studies); (3) be used for educational purposes, scientific publications and presentations, as long as the individual remains anonymous and he/she is not identified during data analysis; the results of these investigations may benefit the future health of the participant; (4) inform you or your clinician or – if Igenomix has been instructed by a laboratory acting on behalf of your clinician to inform such laboratory – about the results of the genetic analysis; (5) provide upon request to you, your clinician or – as the case may be – the requesting laboratory, the raw data of the genetic analysis; (6) personally answer any questions and suggestions raised by you during the process and to monitor the correct execution and resolution of the test, including the indefinite retention of personal data, unless the applicable local laws of jurisdiction establish otherwise; and (7) contact you in the future to request your evaluation regarding the services received, perform commercial communications (including "cross-selling" and "up-selling") of associated companies regarding healthcare and scientific research activities, as well as for participation in market studies, specific research projects and the development of new products.

Research Purposes

I understand that my newborn's Personal (Health) Data and (remaining) sample may help in further research, development and improvement of diagnostic methods and possibly therapeutic solutions. Such measures may in the future also enable and support medical advice and guidance to my newborn and family members, e.g., if related to the diagnosis and treatment of a potential genetic disease.

I agree that Igenomix stores, once pseudonymised, (1) the Personal (Health) Data I provided and information on (affected) family members – if they expressly consented – and the results of the genetic analysis and; (2) my newborn's sample (including original and processed sample) for a period of 30 years and uses this data and the remaining samples, once pseudonymised, for the purpose of scientific (internal or external) and commercial research in the field of Human Genetics in order to contribute to the diagnosis and treatment of genetic diseases and to understand the implications of genetics in the health and wellbeing of individuals, their susceptibility to diseases and their potential response to treatments. Consent can be revoked at any time as explained below.

Access to such pseudonymised data might be granted to public and private healthcare institutions and pharmaceutical or bio-medical companies world-wide for the referred purposes. The relevant guarantees will be adopted to ensure the legitimacy of the research and the legitimacy of the data transfer (especially if the recipient is in a non-EEA country).

Please visit http://www.igenomix.com or contact privacy@igenomix.com for updated information on the research projects in which your newborn's pseudonymised data may be used.

Retention period

Genetic data of a personal nature shall be kept for a minimum period of five years from the date on which they were obtained, after which time you may request their cancellation. Except if you have granted your consent for your newborn's Personal Data to be used for Research Purposes, in the absence of a request by you (i) the data shall be kept for such period as is necessary to preserve the health of the person from whom the data were obtained or of third parties related to him/her; or (ii) the data can be anonymised and used by Igenomix or third parties for any legitimate purpose. The samples and associated data will be saved in the laboratory according to the Igenomix sample retention policy which meets the legal requirements.

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Data protection rights

According to the law on the Protection of Personal Data, the laboratory should have informed consent to carry out the requested screening tests as well as for data processing. At any time, you can exercise your right of access, rectification, opposition, suppression, automated decisions, limitation, portability, and/or revoke your consent by contacting privacy@igenomix.com, providing the documentation demonstrating your identity. You understand that data in Igenomix databases – once anonymised – cannot be destroyed upon request as it is unidentifiable and untraceable.

Data protection claims can be submitted to the competent data protection authority.

The sample will be analysed by Igenomix or an associated group selected by Igenomix (in such cases, the relevant guarantees will be adopted to ensure data protection standards are equivalent to European standards). Igenomix reserves the right to carry out all or part of the analyses included in the test through Third-party Laboratories certified with recognised international quality standards, or failing this, they will be periodically evaluated by Igenomix. Any results obtained this way will be inspected by Igenomix and this circumstance will be indicated in the final report.

HAVING READ AND UNDERSTOOD THE INFORMATION ABOVE, THE NEWBORN'S PARENTS/LEGAL GUARDIANS CONFIRM THAT:

1) I have been informed of the indication, purpose, characteristics, scope, procedure, success rate, risks, complications, limitations and economic cost of this genetic test, and my questions have been answered successfully. The explanations have been facilitated in a clear and simple language, and my attending clinician clarified all observations and questions. I declare that I have received appropriate genetic counselling from qualified personnel such a physician, clinician, or a genetic counsellor. They have offered information regarding the implications of the analysis, including the possible follow-up support and, where appropriate, further testing that may be available according to the results. I understand that they will be at my disposal for any questions or additional genetic counselling that I may require once the results of the test are known.
2) I understand the fact that the medical staff are at my disposal to expand on any aspect of the information that is not sufficiently clear.
3) I understand that the results of this test do not substitute a medical diagnosis performed in a clinical setting, or genetic counselling provided by a healthcare professional. I accept that Igenomix does not take responsibility for the use, by me or my clinician, of the results obtained and any consequences of such use.
4) I understand that it is possible that I may be asked for a new sample if the screening complexity requires the use of other genetic tests or if the sample obtained is not optimal in quality or quantity. I also understand that there is a possibility that a DNA sample from the biological parents or other family members may be needed for the purpose of completing the study or aiding in a better interpretation of the tests performed. I will be informed if this is required. Igenomix assumes that, in the tests used to identify the origin of the genetic alterations of interest, the clinician has confirmed that the samples of the referred parents correspond to the biological parents.
5) The personal and medical information that I have provided is truthful and reliable. I also understand that the clinical team may contact me to ask for additional clinical data, including information needed for research purposes.
6) I understand that the information obtained may have implications for future pregnancies and other family members, and I assume the responsibility of sharing such information with them.
7) Due to the complexity of the genetic tests, and the important implications of their results, these must be interpreted together with other clinical and family data by healthcare professionals. Thus, I accept that the report of the results is sent to the ordering clinician, so that they can best advise me.
8) I understand that a negative result does not guarantee the absence of a disease due to a genetic cause, as the result is dependent on the test requested and the test limitations described in this document, as well as in the report of the results.
9) I accept that I will not obtain, either now or in the future, any economic benefit for any research project carried out, nor do I expect to benefit from the development of products that result from any research.
10) I have been informed that that this informed consent can be withdrawn at any time.
11) I agree to the extraction of my newborn's biological sample, as well as to the shipping of the sample to Igenomix facilities to perform the genetic testing and analysis.

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