Igenomix®

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IGENOMIX DUBAI LABORATORY
USER MANUAL

1 IGENOMIX LABORATORY

1.1 INTRODUCTION

Igenomix FZ-LLC is a medical testing laboratory (Permit No. CL-LB-0010-15) specializing in reproductive genetic services and is part of a multinational company with headquarters in Valencia, Spain.

Igenomix currently performs different tests in-house that can summarized as the following: Preimplantation Genetic Testing for monogenic Diseases (PGT-M), Preimplantation Genetic Testing for Aneuploidy (PGT-A), Preimplantation Genetic Testing for Structural Rearrangements (PGT-SR), Non-invasive prenatal tests (NACE®/NACE®24). Additional, specialised tests are also offered (see section 3.1).

Additionally, Igenomix offers different tests that are currently outsourced including: Endometrial Receptivity Analysis (ERA), Endometrial Microbiome Metagenomic Analysis (EMMA), Analysis of Infectious Chronic Endometritis (ALICE), Preimplantation Genetic Testing for Monogenic Disorders (PGT-M), Preimplantation Genetic Testing for Aneuploidy (PGT-A), and Preimplantation Genetic Testing for Structural Rearrangements (PGT-SR); Genetic Testing for Products of Conception (POC); Carrier Genetic Test (CGT), Sperm Aneuploidy Testing (SAT) and ONCODONA and Non-invasive prenatal tests (NACE® extended 24)

1.2 OPENING TIMES

The laboratory facilities for sample reception are open:

+ from Sunday to Thursday 9:00am to 6:00 pm

Customer Support service is available:

+ From Sunday to Thursday 9:00am – 6:00pm

1.3 CONTACT DETAILS

General Enquiries contact details:

+ by Email to info.me@Igenomix.com

+ by Tel: +971 4 551 9465 (ext 1)

Specific NACE®; NACE®24 y NACE® Extended 24 Extended test info:

+ by Email to nace.me@igenomix.com

+ by Tel: +971 4 551 9465 alternatively +971 55 515 7021

1.4 LAB ADDRESS

Unit 501-502, Building 40
Dubai Health Care City

P.O. Box 66566 Dubai UAE

General enquiries:
Email: info.me@igenomix.com
Tel: **+971 4 551 9465**

Website: www.igenomix.net

2 MAIN ACTIVITIES

2.1 General Information

All genetic tests are carried out as clinically appropriate. Additional information regarding the different tests offered is available to users on the IGENOMIX's Middle East Website and can also be requested by email to: info.me@Igenomix.com or nace.me@igenomix.com , specifically for NACE® products. If you prefer to contact us by phone you can use **+971 4 551 9465** for all the products, or for NACE® products you can contact us directly on mobile **+971 55 515 7021**.

Further interpretation of reports is available to users by calling the laboratory **(+971 4 551 9465**) and requesting to speak with our Genetic counselor / Lab Director.

Further information about the offered tests can be found on the IGENOMIX's Middle East webpage

2.2 COMPLAINT PROCEDURE

The laboratory is committed to delivering service of the highest quality at all times to ensure patient safety and customer satisfaction. For your convenience, any complaints about the service can be addressed through different channels. After receipt, complaints will be passed to the relevant members of staff.

+ by Email write us to info.me@Igenomix.com

+ by phone: call us in **+971 4 551 9465** (ext 1)

+ through our "request information" section or

+ through the complaint form included in the Quality section, both accessible on our website.

All complaints will be answered in less than 2 working days

2.3 LABORATORY POLICY ON PROTECTION OF PERSONAL INFORMATION

The laboratory follows strict policies on Information Governance and maintains a data protection infrastructure in line with Local REGULATION

Further information about Igenomix Dubai Privacy Policy can be found on the IGENOMIX's Middle East Website

2.4 REQUIREMENTS PRIOR TO SENDING A SAMPLE

Given the complexity of the genetic tests and the significant implications of the test results, the tests must be prescribed by competent healthcare professionals (usually doctors) and the results obtained must be interpreted in conjunction with other clinical data, within the general context of a medical practice run by healthcare professionals.

Before referrals can be made, users need to complete the "Clinic Enrollment Form" (for healthcare professionals), or the "Customer Enrollment Form" (for patients) which can be requested by email from info.me@Igenomix.com. Once the form is completed it should be returned by email to info.me@Igenomix.com.

The Test Requisition Form and the Informed Consent Form (if applicable) need to be completed, placed into the provided return courier envelope, and included in the kit box along with the sample to be sent to the laboratory.

Any Test Requisition Form or Test Informed Consent can be requested by email from info.me@Igenomix.com.

Igenomix highly recommends that the test instructions, which can be found on the Igenomix webpage or requested from our Customer Support Service by email or phone (see section 1.3), are carefully read prior to sending samples These documents provide relevant information about sample requirements, patient preparation, test documentation, sample collection and sample shipping for the different offered tests

2.5 LABORATORY CRITERIA FOR ACCEPTING AND REJECTING SAMPLES

The following cases may lead to sample rejection:

- Samples not accompanied with their documentation (Test Requisition Form and Informed Consent)
- Sample documentation (Test Requisition Form and Informed Consent) has not been correctly completed
- Mandatory fields in sample documentation, identified on the forms with an asterisk (*), have not been completed
- Missing patient and/or clinician signature on the Test Requisition and Informed Consent
- Incorrectly labelled, unlabeled or damaged sample containers (usually tubes)
- Using an outdated version of the Test requisition Form and/or Informed Consent form may delay the report or lead to sample rejection
- Failure to meet the specific test requirements indicated in the test instructions (for example, specific timings of sample collection, minimum amounts of sample, specific biological status of patient, etc.)

2.6 INSTRUCTIONS FOR COMPLETION OF REQUEST DOCUMENTATION

All the forms clearly state the mandatory fields to be completed. The Test Requisition Form must be signed by the referring clinician. The Informed Consent form must be signed by the patient.

In most of the Igenomix tests, the Test Requisition Form and the Informed Consent are combined within the same document. In those cases, you can find the signature boxes for both the clinician and the patient at the end of the combined form. For PGT family tests (PGT-A, PGT-SR and PGT-M) and some other tests the signature box for patients can be found at the end of the informed consent form.

Please review carefully the documents associated to each test. Feel free to contact Igenomix Customer Support if you have any concerns about the appropriate completion of these forms.

3 TESTS OFFERED

3.1 Tests performed in-house

The laboratory currently performs the following major tests in-house: Preimplantation Genetic Testing for monogenic Diseases (PGT-M), Preimplantation Genetic Testing for Aneuploidy (PGT-A), Preimplantation Genetic Testing for Structural Rearrangements (PGT-SR), Non-invasive prenatal tests (NACE®/NACE®24).

In addition to the above tests, the laboratory offers different tests that are currently outsourced including: Endometrial Receptivity Analysis (ERA), Endometrial Microbiome Metagenomic Analysis (EMMA), Analysis of Infectious Chronic Endometritis (ALICE), Genetic Testing for Products of Conception (POC); Carrier Genetic Test (CGT), Sperm Aneuploidy Testing (SAT) and ONCODONA and Non-invasive prenatal tests (NACE® extended 24), Cytogenetic tests: Fast Prenatal (QF-PCR), Molecular studies: Fragile-X syndrome (CCG expansion), Cystic fibrosis (study 50 frequent mutations); Y Chromosome Microdeletions; G20210A Prothrombin (FII) Analysis ; G1691A Factor V Leiden Analysis; C677T and A1298C MTHFR Analysis; Hemochromatosis (mutations C282Y, H63D, S65C); Spinal muscular atrophy (deletion exons 7/8)

If you require additional information about our test portfolio, please contact our Customer Support service.

3.2 Preimplantation Genetic Testing for Monogenic Diseases (PGT-M)

PGT-M test description:

PGT-M may be performed on embryos during in vitro fertilisation (IVF) treatment to test for single gene diseases or to perform HLA matching. PGT-M, requiring only a small number of cells, identifies which embryos are not at an increased risk of developing the tested disease. The goal of PGT-M is to help couples start a “healthy” family and avoid the difficult choice of having to terminate a pregnancy if a “positive” result is obtained through prenatal diagnosis. PGT- M is performed by using PCR.

Pre-requirements for accepting a PGT-M case:

Prior to offering PGT-M, the genetic reports for the affected partner and for certain family members with known disease status must be available and sent to the laboratory of Igenomix. The report must clearly identify the gene and the mutation responsible for the disease/disorder to be tested by PGT-M. Family history information relating to the disease is also necessary to assess the case properly. With this information, Igenomix will give an answer about the technical viability of PGT-M and will require the samples needed for the PGT-M workup (pre-PGT-M) test. A case discussion with a senior member of laboratory staff will be required in certain instances. The scenarios where PGT-M can be considered include autosomal dominant disorders, autosomal recessive disorders, X-liked disorders and HLA matching.

NOTE: Embryo sex will be revealed when reporting PGT-M for X-linked disorders.

PGT-M test sample requirements:

For pre-PGT-M, a minimum of 1x3 ml of peripheral blood (in EDTA tubes) and/or a buccal swab (less recommended) from the prospective parents and other relevant family members is needed. Based on the outcome of pre-PGT-M, the laboratory will inform the IVF clinic by email whether PGT-M can be offered or not. The patients can then start their treatment towards PGT-M or seek alternative treatment which can be further discussed with a senior member of laboratory staff

For PGT-M, 1 embryo cell is required for day three biopsy. 5-6 cells are required for a day five biopsy.

The solution used for "washing/tubing" the biopsied cells is provided by Igenomix. The biopsied cells must be "tubed" in sterile 0.2ml microcentrifuge tubes provided by Igenomix. The lid of these tubes must be labelled with the female patient initials followed by the embryo number. The "plate/rack" in turn is placed in a sterile plastic bag in a cooler with "ice packs" also provided by the laboratory.

Further information on how to prepare a sample can be found and downloaded from the Igenomix website or requested by email from our Customer Support service, see section 1.3. The "Embryo Biopsy Worksheet" and the "Test Requisition Form" (included within the provided kit and additionally available either from the Igenomix website or requested by email) must be completed and placed in a plastic sleeve inside the cooler prior to transport.

Professional user validation for PGT tests ('DRY RUN'):

Following the enrolment of a new clinic (see section 2.4), we recommend performing a "validation" or "dry run" for every embryologist involved in the embryo biopsy/tubing for PGT-M. This process aims to provide reduce the likelihood of difficulties with clinical cases that could lead to a failure to determine a result(s) for the sampled embryo(s). Instructions on how to complete a "validation run" can be requested by email. A validation/dry run report is issued after the analysis and signed by a senior member of laboratory staff or the Laboratory Director.

PGT-M sample transportation to the laboratory:

For PGT-M workup (pre-PGT-M), blood samples and/or buccal swabs should be sent to the laboratory by either first class mail or a similar secure service (DHL, UPS etc.) and must be packed according to a set of ADR guidelines known as P650, or "Packaging Instructions P650" and clearly labelled 'Exempt Human Specimen UN3373' when the sample is not delivered from Spain (this courier service is not offered by Igenomix but outsourced to a third-party logistics company). Carriage is at Room Temperature. We recommend shipping the samples with a cold gel pack if outside temperatures exceed 35ºC. Avoid freezing the sample when introducing the cold gel pack.

For PGT-M, the clinic needs to notify the laboratory before a sample is ready and the laboratory will offer to arrange for sample collection. The PGT kit provided by Igenomix must be used for the shipment, including the cooler box. **Freeze the ice packs, cool-rack and biopsied samples before the shipment.** The sample should be sent to the laboratory by either first class mail or a similar secure service (DHL, UPS etc.) and must be packed according to a set of ADR guidelines known as P650, or "Packaging Instructions P650" and clearly labelled as 'Exempt Human Specimen UN3373' when the sample is not delivered from Spain (this courier service is not offered by the laboratory but outsourced to a third-party logistics company).

For further details on how to send the samples, please review the test instructions included on the Igenomix website or contact Igenomix Customer Support service (see section 1.3).

PGT-M test turnaround time (TAT):

The clinician that has requested the test will receive the results.

Pre-PGT-M results will be available **within 3 weeks** for common mutations and **6 weeks** for the non-frequent mutations, from receipt of samples by Igenomix.

PGT-M results will be available **within 10 working days** from receipt of samples by Igenomix.

PGT-M Reporting:

For pre-PGT-M the following results can be obtained:

- **Fully Informative (FI)**: Each of the wild-type and mutant alleles in both members of the couple are unique.
- **Semi Informative (SI)**: The wild-type and mutant alleles have unique polymorphic marker, but one of the values is equivalent between both members of the reproductive couple.
- **Non-Informative (NI)**: The wild-type and mutant alleles have the same polymorphic marker in the individual carrying the mutation.
- **Not Applicable (NA)**: The individual does not carry a mutation or is carrying a mutation/variant in homozygous state and so informativity is not applicable.

For PGT-M the following results can be obtained, for each embryo, as a result of performing this test:

- **Normal:** Embryo found not to inherit the "at risk haplotype". This embryo is expected to be unaffected by the indicated genetic mutation.
- **Carrier:** Embryo found to inherit one parental "at risk haplotype". This embryo is expected to be a carrier for the tested genetic mutation, in the same way as the carrier parent(s).
- **Abnormal:** Embryo found to inherit the parental "at risk haplotype". This embryo is expected to be affected by the indicated disorder.
- **At risk:** This embryo has inherited the haplotype linked to the tested indication and is at risk of being affected.
- **Seek genetic counseling:** Genetic counseling is recommended to discuss the risks of transferring this embryo.
- **No DNA detected:** DNA was not detected, due to the absence of, or degraded DNA.
- **Non-informative:** A reliable result could not be achieved due to factors such as Allele Drop Out (ADO), parental/external contamination, recombination and others.

3.3 Preimplantation Genetic Testing for Aneuploidy (PGT-A)

PGT-A test description:

PGT-A is a genetic test that may be performed on embryos during IVF treatment to screen for numerical chromosomal abnormalities. Chromosomally normal embryos are most likely to implant and develop to term. PGT-A helps clinicians and patients undergoing IVF decide which embryos to transfer. The method, requiring only a small number of cells, is comprehensive as it analyses all 24 chromosomes for chromosomal copy number using Next Generation Sequencing (NGS).

Pre-requirements for accepting a PGT-A case:

No specific pre-requirements are needed in order accept a case. Specific test indications and relevant clinical information can be reported in the test requisition form.

PGT-A sample requirements:

For PGT-A, one cell from day 3 of embryonic development (blastomere biopsy) or 4-8 cells from day 5, 6 or 7 of embryonic development (trophectoderm biopsy) are required. The biopsied cell/s must be cleaned using the "washing/loading buffer" supplied by the laboratory to eliminate any potential source of contamination and transferred to a small sterile 0.2ml tube supplied by the laboratory. The lids of these tubes must be labelled with the female patient initials followed by the embryo number. The 0.2ml tubes must be placed in the "plate/rack" provided by the laboratory, the "plate/rack" placed in a sterile plastic bag and inside the cooler shipping box with the "ice packs" also provided by the laboratory. Further information on how to prepare a sample can be found and downloaded from the website or requested by email to the Igenomix Customer Support service (see section 1.3).

The "Embryo Biopsy Worksheet" and the "Test Requisition Form" (included within the provided kit and additionally available either from the Igenomix website or requested by email) must be completed and sent with the samples inside the shipping box or by e-mail to the laboratory.

Professional user validation for PGT tests (DRY RUN):

Following the enrolment of a new clinic (see section 2.4), we recommend performing a "validation" or "dry run" for every embryologist involved in the embryo biopsy/tubing for PGT-A. This process aims to provide reduce the likelihood of difficulties with clinical cases that could lead to a failure to determine a result(s) for the sampled embryo(s). Instructions on how to complete a "validation run" can be requested by email. A validation/dry run report is issued after the analysis and signed by a senior member of laboratory staff or the Laboratory Director.

PGT-A sample transportation to the laboratory:

The clinic must notify the laboratory before a sample is ready and the laboratory will offer to arrange for sample collection. The PGT kit provided by Igenomix must be used for the shipment, including the cooler box: freeze the ice packs, cool-rack and biopsied samples before the shipment.

The sample should be sent to the laboratory by either first class mail or a similar secure service (DHL, UPS etc.) and must be packed according to a set of IATA guidelines for "Packaging Instructions" and clearly labelled as 'Exempt Human Specimen UN3373' when the sample is not delivered from UAE (this courier service is not offered by the laboratory but outsourced to a third-party logistics company).

For further details on how to send the samples please review the test instructions included on the Igenomix website or contact to Igenomix Customer Support service (see section 1.3).

PGT-A test turnaround time:

The clinician that has requested the test will receive the results.

For PGT-A samples with **deferred transfer** results will be available **within 7 working days** from receipt of samples by Igenomix.

For PGT-A samples with **fresh transfer** results will be available **on the morning of the day following the receipt of samples** by Igenomix.

PGT-A reporting:

Igenomix uses an internal validated algorithm for whole chromosome aneuploidies, partial deletion/duplications and mosaicism calling. The following results can be obtained, for each embryo, as a result of performing this test:

- **Normal/euploid**: when mosaic aneuploidy levels are <30%, and no partial deletion/duplications ≥10Mb in size are detected.
- **Abnormal/aneuploid:** when mosaic aneuploid levels are ≥30% and/or partial deletion/duplications ≥10Mb in size are detected. If mosaicism information is requested by the clinic/user, "Mosaic samples" are reported as either "low mosaic aneuploid" when having 30%-<50% aneuploid cells, or "High mosaic aneuploid" when having ≥50%-<70% aneuploid cells.

  Embryos that have another uniform aneuploid chromosome are never reported as mosaic but as abnormal/aneuploid.
- **No DNA detected:** when insufficient DNA is detected in the sample.
- **Non informative:** when the quality of the sample is suboptimal and leads to an NGS result below the required quality thresholds.

3.4 Preimplantation Genetic Testing for structural rearrangements (PGT-SR)

PGT-SR test description:

PGT-SR is a genetic test to detect specific chromosomal imbalances in embryos arising from parental chromosomal rearrangements. The test will also detect numerical chromosomal abnormalities not associated with the parental chromosomal rearrangement. This method uses NGS to analyse all 24 chromosomes and requires multiple trophectoderm cells from a blastocyst biopsy. Currently, PGT-SR at Igenomix has been validated to detect chromosomal abnormalities that are ≥ 6Mb.

Pre-requirements for accepting a PGT-SR case:

Before planning a PGT-SR cycle, the couple must provide the karyotype report of the structural anomaly to their prescribing physician for Igenomix staff review, who will request, if required, a pre-PGT-SR study. Pre-PGT-SR consists of a genetic study prior to the commencement of a PGT-SR cycle. This study is performed on a DNA sample of the carrier of a structural chromosomal abnormality, to confirm whether it is possible to address the case through PGT-SR and establish the diagnostic strategy to be applied in the PGT-SR cycle.

PGT-SR test sample requirements:

For pre-PGT-SR (if required), 4 mL of peripheral blood (in EDTA or Heparin-Lithium tubes, as requested by the Igenomix staff to the prescribing physician) from the carrier of the structural chromosomal abnormality (and/or other family members if required) are needed. Based on the outcome of the pre-PGT-SR, the laboratory will inform the IVF clinic by email whether PGT-SR can be offered.

For PGT-SR, 4-8 cells from day 5, 6 or 7 of embryonic development (trophectoderm biopsy) are required. The biopsied cell/s must be cleaned using the "washing/loading buffer" supplied by the laboratory to eliminate any potential source of contamination and, transferred to a small sterile 0.2ml tube supplied by the laboratory. The lid of these tubes must be labelled with the female patient initials followed by the embryo number. The 0.2ml tubes must be placed in the "plate/rack" provided by the laboratory, the "plate/rack" placed in a sterile plastic bag and inside the cooler shipping box with the "ice packs" also provided by the laboratory.

Further information on how to prepare a sample is found in the "Washing_Tubing Instructions" that can be downloaded from the Igenomix website or requested by email. The "Embryo Biopsy Worksheet" and the "Test Requisition Form" (included within the provided kit and additionally available either from the Igenomix website or requested by email) must be completed and sent with the samples inside the shipping box or by e-mail to the laboratory.

Professional user validation for PGT-SR tests (DRY RUN):

Following the enrolment of a new clinic (see section 2.4), we recommend performing a "validation" or "dry run" for every embryologist involved in the embryo biopsy/tubing for PGT-SR. This process aims to provide reduce the likelihood of difficulties with clinical cases that could lead to a failure to determine a result(s) for the sampled embryo(s). Instructions on how to complete a "validation run" can be requested by email. A validation/dry run report is issued after the analysis and signed by a senior member of laboratory staff or the Laboratory Director.

PGT-SR sample transportation to the laboratory:

For pre-PGT-SR, blood samples should be sent to the laboratory by either first class mail or a similar secure service (DHL, UPS etc.) and must be packed according to a set of IATA guidelines for "Packaging Instructions and clearly labelled "Exempt Human Specimen UN3373" when the sample is not delivered from UAE (this courier service is not offered by the laboratory but outsourced to a third-party logistics company). Carriage is at Room Temperature. We recommend shipping the samples with a cold gel pack if outside temperatures exceed 35ºC. Avoid freezing the sample when introducing the cold gel pack.

For PGT-SR The clinic must notify the laboratory before a sample is ready and the laboratory will offer to arrange for sample collection. The PGT kit provided by Igenomix must be used for the shipment, including the cooler box: **freeze the ice packs, cool-rack and biopsied samples before the shipment.**

The sample should be sent to the laboratory by either first class mail or a similar secure service (DHL, UPS etc.) and must be packed according to a set of IATA guidelines for "Packaging Instructions and clearly labelled 'Exempt Human Specimen UN3373' when the sample is not delivered from UAE (this courier service is not offered by the laboratory but outsourced to a third-party logistics company).

For further details on how to send the samples please review the test instructions included on the Igenomix website or contact to Igenomix Customer Support service (see section 1.3).

PGT-SR test turnaround time:

The clinician that has requested the test will receive the results.

For pre-PGT-SR, results will be available **within 4 weeks** from receipt of samples by Igenomix.

For PGT-SR samples with **deferred transfer** results will be available **within 7 working days** from receipt of samples by Igenomix.

For PGT-SR (Robertsonian translocation only) samples with **fresh transfer** results will be available **on the morning of the day following the receipt of samples** by Igenomix.

PGT-SR reporting:

For **pre-PGT-SR** there are two possible results:

- the structural alteration that is the subject of study for pre-PGT-SR **can be detected,** therefore, PGT-SR can be offered.
- the structural alteration that is the subject of study for the pre-PGT-SR **cannot be detected**, therefore, The PGT-SR cannot be offered.

For PGT-SR, Igenomix uses an internal validated algorithm for whole chromosome aneuploidies, partial deletion/duplications and mosaicism calling. The following results can be obtained as a result of performing this test:

- **Normal-euploid/balanced:** when mosaic aneuploidy levels are <30%, and no partial deletion/duplications ≥6Mb in size are detected.
- **Abnormal-aneuploid/unbalanced:** when mosaic aneuploid levels are ≥30% and/or partial deletion/duplications ≥6Mb in size are detected. Specific unbalances arising from the parental chromosomal rearrangement are reported as aneuploid/unbalanced. If mosaicism information is requested by the clinic/user, "Mosaic samples" are reported as either "low mosaic aneuploid" when having 30%-<50% aneuploid cells, or "High mosaic aneuploid" when having ≥50%-<70% aneuploid cells. Embryos that have another uniform aneuploid chromosome are never reported as mosaic but as abnormal/aneuploid.
- **No DNA detected:** when insufficient DNA is detected in the sample.
- **Non informative:** when the quality of the sample is suboptimal and leads to an NGS result below the required quality thresholds.

3.5 NACE® & NACE®24

NACE® and NACE®24 test description:

Unlike invasive prenatal diagnosis, which can pose a risk to an ongoing pregnancy, NACE® is a non-invasive prenatal genetic screening test. NACE® uses the latest sequencing technology (NGS) to analyse placental DNA compared to maternal DNA in order to detect certain fetal anomalies with high precision and reliability. Two in-house versions of the test exist: NACE® and NACE®24. NACE® is designed to detect fetal Trisomy 21, 18, 13 and sex chromosome aneuploidies and NACE® 24 is designed to detect fetal chromosome aneuploidies in all 24 chromosomes.

NACE® and NACE®24 Pre-requirements for accepting a case:

Specific pre-requirements are needed in order accept a case.

- This test is recommended for cases from week 10 of pregnancy onwards. Any case that does not fulfil this requirement will be rejected.

Other specific test indications and relevant clinical information can be reported in the test requisition form.

NACE® and NACE®24 Sample requirements:

Collect between 1x7ml (minimum) and 1x10 ml (maximum) of maternal peripheral blood in a Streck tube, using only the collection materials provided by the laboratory in the provided NACE kit.

Instructions on how to prepare a sample are available and can be downloaded from the Igenomix website or requested by email. The “Test Requisition Form” (provided within the provided kit and additionally available either from the Igenomix website or requested by email) must be completed and placed in the NACE kit.

NACE® and NACE®24 sample transportation to the laboratory:

The clinic needs to notify to Igenomix when a sample will be ready, and the laboratory will offer to arrange for sample collection. Transportation will be conducted in custom-made kits provided by the laboratory. Carriage is at Room Temperature. We recommend shipping the samples with a cold gel pack if outside temperatures exceed 35ºC or if sent from outside UAE (international deliveries). Avoid freezing the sample when introducing the cold gel pack.

We do not recommend storage of samples, after collection, for more than 5 days at room temperature or 7 days when refrigerated. Samples that exceeded these times when they reach Igenomix may be rejected.

The sample should be sent to the laboratory by either first class mail or a similar secure service (DHL, UPS etc.) and must be packed according to a set of IATA guidelines for “Packaging Instructions and clearly labelled 'Exempt Human Specimen UN3373’ when the sample is not delivered from UAE (this courier service is not offered by the laboratory but outsourced to a third-party logistics company).

For further details on how to send the samples please review the test instructions included on the Igenomix website or contact to Igenomix Customer Support service (see section 1.3).

NACE® tests turnaround time:

The clinician that has requested the test will receive the results within **7 working days** for NACE® and NACE24® of sample reception at Igenomix.

Results will also be sent to patients (if the email address was provided within the Test Requisition Form)

NACE® test reporting:

The following results can be obtained as a result of performing this test

+ No alteration detected: The patient is considered to be at low risk for the studied condition(s).

+ Alteration detected: The patient is considered to be at high risk for the reported condition(s) with a very high Positive Predictive Value (PPV).

+ Suspected alteration detected: The patient is considered to be at high risk for the reported condition (s) with a low PPV.

+ Non-informative: It is not possible to offer information on the chromosomal state of the pregnancy from maternal blood due to inadequate quality and/or quantity of derived foetal DNA.

+ Sex of the foetus (sexual chromosomes)

- **I**n single pregnancies, male or female sex is reported
- In the case of twin pregnancies, the presence or absence of Y chromosome is reported. This option is not available for NACE® 24

4 Outsourced tests

The laboratory currently offers outsourced tests, including a non-invasive prenatal test (NACE® Extended 24) and the ONCODONA® test (breast and ovarian cancer screening test)

4.1 Endometrial Receptivity Analysis (ERA)

ERA test description:

The lack of synchronisation between the embryo, which must be ready to be implanted and endometrial receptivity is believed to be one of the causes of recurring implantation failure. ERA is a test that was developed and patented in 2009 by Igenomix after more than 10 years of research and development.

The ERA test helps to evaluate the woman's endometrial receptivity and thus identify a 'window of implantation' from a molecular perspective. The test analyses the expression levels of 248 genes linked to the status of endometrial receptivity, using RNA sequencing (through NGS) on material biopsied from the endometrium. Following the analysis, a specific computational predictor classifies the samples according to their expression profile in the corresponding endometrial stage (proliferative, pre-receptive, early receptive, receptive, late receptive or post-receptive). This data will enable a personalised embryo transfer (pET), synchronising endometrial receptivity with an embryo prepared for implantation.

Pre-requirements for accepting an ERA case:

No specific pre-requirements are needed in order accept an ERA case. We strongly encourage you to carefully read the "ERA-EMMA-ALICE Manual" for further information in addition to the specific ERA-EMMA-ALICE test instructions. You can download these documents from the Igenomix website and from the specific website https://www.igenomix.net/genetic-solutions/endometrio-clinics/com/

ERA test sample requirements:

Endometrial tissue (~70mg by mass or ~7mm by size) placed in a cryotube containing RNA stabilizing solution (1,5 ml) provided by the laboratory. The ERA test requires an endometrial biopsy that should be carried out on day LH+7/HCG+7 (natural cycle) or day P+5 (Hormone Replacement Therapy cycle). The cryotube containing the sample must be refrigerated (4-8°C) for a minimum of 4 hours before shipping. For shipment, the cryotube containing the endometrial biopsy must be placed inside a blister as secondary container.

In order to obtain a fully confident test result, the ERA-EMMA-ALICE Manual details must be strictly followed. This document can be downloaded either from the ERA-EMMA-ALICE website (https://www.igenomix.net/genetic-solutions/endometrio-clinics/com), the Igenomix website or requested by email.

The "Test Requisition Form" (provided within the provided kit and additionally available either from the ERA-EMMA-ALICE website (https://www.igenomix.net/genetic-solutions/endometrio-clinics/com) or requested by email) must be completed and sent with the sample inside the shipping box.

ERA sample transportation to the laboratory:

The clinic needs to notify to Igenomix when a sample will be ready, and the laboratory will offer to arrange for sample collection. Transportation will be conducted in custom-made kits provided by the laboratory. Carriage is at Room Temperature. We recommend shipping the samples with a cold gel pack if outside temperatures exceed 35ºC. Avoid freezing the sample when introducing the cold gel pack. To maintain sample stability, transit at room temperature should not exceed 5 days in order to ensure the preservative action of the liquid in the cryotube.

The sample should be sent to the laboratory by either first class mail or a similar secure service (DHL, UPS etc.) and must be packed according to IATA guidelines for "Packaging Instructions and clearly labelled 'Exempt Human Specimen UN3373' when the sample is not delivered from UAE (this courier service is not offered by the laboratory but outsourced to a third-party logistics company).

For further details on how to send the samples please review the test instructions included on the Igenomix website or contact to Igenomix Customer Support service (see section 1.3).

ERA test turnaround time:

The clinician that has requested the test will receive the results **within 15 natural days** from sample reception by Igenomix.

ERA test reporting:

The result of the test can be:

+ Receptive (R): This gene expression profile is compatible with a normal, receptive endometrium. In this case, we recommended performing a blastocyst(s) transfer following the same protocol utilized during this Endometrial Receptivity Analysis (ERA) test.

+ Early Receptive (PREt): This gene expression profile means that the endometrium is at the beginning of the receptive stage. In this case, we recommend the administration of progesterone (HRT cycle) or rest (natural cycle) for 12 hours more relative to when the biopsy was taken, before performing a blastocyst(s) transfer.

+ Late Receptive (eT): This gene expression profile means that the endometrium is at the end of the receptive stage. In this case, we recommend the administration of progesterone (HRT cycle) or rest (natural cycle) for 12 hours less relative to when the biopsy was taken, before performing a blastocyst(s) transfer.

+ Proliferative (F): This gene expression profile is concordant with an endometrium at a proliferative stage. We recommend that you contact the ERA laboratory to evaluate the protocol in which this endometrial biopsy was performed.

+ Pre-receptive (PREd1/PREd2): This gene expression profile is concordant with an endometrium at a pre-receptive stage due to the potential displacement of the window of implantation. For some results, we may require analysis of a second biopsy on the recommended day to be able to provide a transfer timing recommendation.

+ Post-receptive (T): This gene expression profile is concordant with an endometrium at a post-receptive stage due to the potential displacement of the window of implantation. To confirm this result, analysis of a second biopsy on the recommended day is required.

+ Non-informative: The profile analysed does not match the control gene expression profiles present in the ERA predictor. We recommend that you contact the ERA laboratory to evaluate the protocol in which this endometrial biopsy was performed.

+ Insufficient RNA: It was not possible to determine the gene expression profile of the sample because there was not enough genetic material. This occurs in approximately 2.5% of samples received. A new endometrial biopsy is required.

+ Invalid RNA: It was not possible to determine the gene expression profile of the sample due to the poor quality of genetic material obtained. This occurs in approximately 3% of samples received. A new endometrial biopsy is required.

The ERA report for most samples includes a recommendation for performing a personalized embryo transfer (pET). For some patients, as indicated above, another biopsy may be required.

4.2 Endometrial Microbiome Metagenomic Analysis (EMMA)

EMMA test description:

An "endometrial microbiome" is composed of various microorganisms co- existing in balanced proportions in the endometrium/uterine cavity. Of these microorganisms, the bacterial genus *Lactobacillus*, when present at certain levels, indicates a "healthy" uterine cavity. Recent studies have demonstrated that dysbiosis of the uterine cavity is associated with poor reproductive outcomes in assisted reproduction patients. This evidence suggests that altered endometrial *Lactobacillus* levels (and the presence of other bacteria) could play a role in infertility.

EMMA can be used for by patient wishing to conceive, being especially useful for patients with Recurrent Implantation Failure (RIF) or Recurrent Miscarriage (RM).

EMMA can be performed between days 15 and 25 of the natural cycle (only for patient with regular cycles 26- to 32-day duration), or during the progesterone intake days (preferably P+5) in an HRT cycle. The EMMA test can be performed on the same biopsy used for an ERA test, another sample is not necessary. The EMMA test includes ALICE test.

EMMA uses NGS (Next Generations Sequencing) to analyse the complete microbiome profile for an endometrial tissue sample. The test is based on DNA extraction followed by amplification and sequencing of the bacterial 16S ribosomal RNA gene.

Pre-requirements for accepting an EMMA case:

No specific pre-requirements are needed in order accept an EMMA case. We strongly encourage you to carefully read the "ERA-EMMA-ALICE Manual" for further information in addition to the specific ERA-EMMA-ALICE test instructions. You can download these documents from the Igenomix website https://www.igenomix.net/genetic-solutions/endometrio-clinics/com/

EMMA test sample requirements:

Endometrial tissue (~70mg/~7mm) placed in a cryotube containing RNA stabilizing solution provided by the laboratory. If the EMMA test will be performed together with ERA test, then the biopsy has to be taken following the ERA instructions - i.e. on day LH+7/HCG+7 (natural cycle) or day P+5 (HRT cycle).

If the EMMA test is going to be performed alone (without ERA), the sample must always be taken in the secretory phase: between days 15 to 25 of the natural cycle (only for patient with regular cycles 26- to 32-day duration), or during the progesterone intake days (preferably P+5) in an HRT cycle. Any other situation (cycle with contraceptives, amenorrhea, etc...) should be consulted with Igenomix specialists before taking the sample.

The cryotube containing the sample must be adequately closed, shaken and refrigerated (4-8º C) for a minimum of 4 hours before shipment. For shipping, the cryotube containing the endometrial biopsy must be placed in a blister pack as a secondary container.

In order to obtain a fully confident test result, the ERA-EMMA-ALICE Manual details must be strictly followed. This document can be downloaded either from the ERA-EMMA-ALICE website (https://www.igenomix.net/genetic-solutions/endometrio-clinics/com), the Igenomix website or requested by email.

The "Test Requisition Form"for ERA-EMMA-ALICE are requested by email and must be completed and sent with the sample inside the shipping box.

EMMA sample transportation to the laboratory:

The clinic needs to notify to Igenomix when a sample will be ready, and the laboratory will offer to arrange for sample collection. Transportation will be conducted in custom-made kits provided by the laboratory. Carriage is at Room Temperature. We recommend shipping the samples with a cold gel pack if outside temperatures exceed 35ºC. To maintainsample stability, transit at room temperature should not exceed 5 days in order to ensure the preservative action of the liquid in the cryotube.

The sample should be sent to the laboratory by either first class mail or a similar secure service (DHL, UPS etc.) and must be packed according to a set IATA guidelines for "Packaging Instructions and clearly labelled 'Exempt Human Specimen UN3373 when the sample is not delivered from UAE (this courier service is not offered by the laboratory but outsourced to a third-party logistics company).

For further details on how to send the samples please review the test instructions included on the Igenomix website or contact to Igenomix Customer Support service (see section 1.3).

EMMA test turnaround time:

The clinician that has requested the test will receive the results **within 15 calendar days** from sample reception by Igenomix.

EMMA test reporting:

The result of the test can be:

+ Normal endometrial microbiome: The most abundant bacterial genus in the sample is *Lactobacillus*, which indicates a physiologically healthy endometrial microbiome. No microbiological intervention is required.

+ Microbiome with ultralow biomass: A low amount of bacterial DNA has been detected in the endometrial sample. Increasing the level of *Lactobacilli* in the reproductive tract would be advisable to achieve a physiologically healthy microbiota.

+ Dysbiotic profile: The percentage of *Lactobacilli* is below the standard recommended for endometrial health. Increasing the level of *Lactobacilli* in the reproductive tract would be advisable to achieve a physiologically healthy microbiota.

+ Abnormal endometrial microbiome: DNA from pathogenic bacteria of the reproductive tract have been detected in a significant amount in the endometrial sample. The removal of pathogens and an increase in the level of *Lactobacilli* in the endometrium would be advisable to achieve a physiologically healthy microbiota.

+ Non-informative: The sample presents a chaotic microbiological profile, impossible to represent in a result. This could be due to contamination of the sample with skin bacteria during collection or preservation. We recommend the analysis of a new sample.

+ Invalid sample: The sample does not meet the minimum quality requirements to be processed. This can be due to insufficient starting material to perform the amplification and sequencing. The most likely cause of this is sample degradation or a very small biopsy size. Excessively large endometrial biopsy size could also result in suboptimal preservation of the tissue and degradation. We recommend the analysis of a new sample.

The EMMA report includes a suggested therapy, where appropriate. For some patients, another biopsy may be required.

4.3 Analysis of Infectious Chromic Endometritis (ALICE)

ALICE test description:

The best example of a pathology caused by an altered “endometrial microbiome” is chronic endometritis (CE). CE is a persistent inflammation of the endometrial lining caused by infection of the uterine cavity, mainly by bacterial pathogens.

ALICE detects the most frequent bacteria that cause CE. It is a subset test of EMMA that can be ordered as a stand-alone test.

ALICE can be used for by patient wishing to conceive, being especially useful for patients with Recurrent Implantation Failure (RIF) or Recurrent Miscarriage (RM).

ALICE can be performed between days 15 and 25 of the natural cycle (only for patient with regular cycles 26- to 32-day duration), or during the progesterone intake days (preferably P+5) in an HRT cycle. The ALICE test can be performed on the same biopsy used for an ERA test; another sample is not necessary.

ALICE uses NGS to analyse the complete endometrial microbiome profile for an endometrial tissue sample and reports the presence and percentage of specific pathogenic bacteria. The test is based on DNA extraction followed by amplification and sequencing of the bacterial 16S ribosomal RNA gene.

Pre-requirements for accepting an ALICE case:

No specific pre-requirements are needed in order accept an ALICE case. We strongly encourage you to carefully read the "ERA-EMMA-ALICE Manual" for further information in addition to the specific ERA-EMMA-ALICE test instructions. You can download these documents from the Igenomix website https://www.igenomix.net/genetic-solutions/endometrio-clinics/com/

ALICE sample requirements:

Endometrial tissue (~70mg/~7mm) placed in a cryotube containing RNA stabilizing solution provided by the laboratory. If the ALICE test will be performed together with the ERA test, then the biopsy has to be taken following the ERA instructions - i.e. on day LH+7/HCG+7 (natural cycle) or day P+5 (HRT cycle).

If the ALICE test is going to be performed alone (without ERA), the sample must always be taken in the secretory phase: between days 15 to 25 of the natural cycle (only for patient with regular cycles 26- to 32-day duration), or during the progesterone intake days (preferably P+5) in an HRT cycle. Any other situation (cycle with contraceptives, amenorrhea, etc...) should be consulted with Igenomix specialists before taking the sample.

The cryotube containing the sample must be adequately closed, shaken and refrigerated (4-8º C) for a minimum of 4 hours before shipment. For shipping, the cryotube containing the endometrial biopsy must be placed in a blister pack as a secondary container.

In order to obtain a fully confident test result, the ERA-EMMA-ALICE Manual details must be strictly followed. This document can be downloaded either from the ERA-EMMA-ALICE website (https://www.igenomix.net/genetic-solutions/endometrio-clinics/com), the Igenomix website or requested by email.

The "Test Requisition Form" for ERA-EMMA-ALICE are requested by email and must be completed and sent with the sample inside the shipping box. If the mandatory fields in the ERA-EMMA-ALICE Test Requisition Form are not properly completed, samples may be rejected.

ALICE sample transportation to the laboratory:

The clinic needs to notify to Igenomix when a sample will be ready, and the laboratory will offer to arrange for sample collection. Transportation will be conducted in custom-made kits provided by the laboratory. Carriage is at Room Temperature. We recommend shipping the samples with a cold gel pack if outside temperatures exceed 35ºC. To maintain sample stability, transit at room temperature should not exceed 5 days in order to ensure the preservative action of the liquid in the cryotube.

The sample should be sent to the laboratory by either first class mail or a similar secure service (DHL, UPS etc.) and must be packed according to a set of IATA guidelines for "Packaging Instructions and clearly labelled 'Exempt Human Specimen UN3373' when the sample is not delivered from UAE (this courier service is not offered by the laboratory but outsourced to a third-party logistics company).

For further details on how to send the samples please review the test instructions included on the Igenomix website or contact to Igenomix Customer Support service (see section 1.3).

ALICE test turnaround time:

The clinician that has requested the test will receive the results **within 15 calendar days** from sample reception by Igenomix.

ALICE test reporting:

The result of the test can be:

+Negative for chronic endometritis: The amount of DNA from chronic endometritis-causing bacteria is not significant. No microbiological intervention is required.

+Positive for chronic endometritis: DNA from chronic endometritis causing bacteria has been detected in a significant amount in the endometrial sample. Chronic endometritis is associated with adverse reproductive outcomes, specifically repeated implantation failure and recurrent miscarriage. The removal of pathogens and an increase in the level of Lactobacilli in the reproductive tract would be advisable to achieve a physiologically healthy microbiota.

+ Non-informative: The sample presents a chaotic microbiological profile, impossible to represent in a result. This could be due to contamination of the sample with skin bacteria during collection or preservation. We recommend the analysis of a new sample.

+ Invalid sample: The sample does not meet the minimum quality requirements to be processed. This can be due to insufficient starting material to perform the amplification and sequencing. The most likely cause of this is sample degradation or a very small biopsy size. Excessively large endometrial biopsy size could also result in suboptimal preservation of the tissue and degradation. We recommend the analysis of a new sample.

The ALICE report includes a suggested therapy, where appropriate. For some patients, another biopsy may be required.

4.4 Sperm Aneuploidy Testing (SAT)

SAT test description:

The Sperm Aneuploidy Test (SAT) is a diagnostic test that helps to assess male infertility by measuring the percentage of spermatozoa with chromosomal abnormalities in a semen sample. The SAT result provides an estimation of the transmission risk of chromosomal abnormalities to the embryo and potential offspring. The test specifically analyses the chromosomes most commonly observed in spontaneous miscarriages and affected offspring with chromosomal abnormalities (chromosomes 13, 18, 21, X and Y). The test uses Fluorescence In Situ Hybridization (FISH).

Pre-requirements for accepting a SAT case:

Prior to offering a SAT analysis due to an abnormal karyotype in the patient, a “genetics report” that clearly identifies the karyotype is required, and if appropriate, a case-discussion with a senior member of staff.

Prior to offering a SAT analysis for ejaculate, testis and epididymis frozen samples, a case-discussion with a senior member of staff will be needed to clarify the sample pre-processing protocol at the referring lab.

SAT sample requirements:

Ejaculate, epididymis and testicle sperm samples washed and suspended in sperm culture medium inside a conical tube (the culture medium is not provided by Igenomix).

Instructions on how to prepare a sample are available and can be downloaded from the Igenomix website or requested by email. The "Test Requisition Form" (provided within the provided kit and additionally available either from the Igenomix website or requested by email) must be completed and sent with the sample inside the shipping box

SAT sample transportation to the laboratory:

The clinic needs to notify to Igenomix when a sample will be ready, and the laboratory will offer to arrange for sample collection. Transportation will be conducted in custom-made kits provided by the laboratory. Carriage is at Room Temperature. We recommend shipping the samples with a cold gel pack if outside temperatures exceed 35ºC. Avoid freezing the sample when introducing the cold gel pack.

To ensure sample quality, we strongly recommend sending SAT samples to Igenomix within 3 days of collection

The sample should be sent to the laboratory by either first class mail or a similar secure service (DHL, UPS etc.) and must be packed according to a set of IATA guidelines for "Packaging Instructions and clearly labelled 'Exempt Human Specimen UN3373' when the sample is not delivered from UAE (this courier service is not offered by the laboratory but outsourced to a third-party logistics company).

For further details on how to send the samples please review the test instructions included on the Igenomix website or contact to Igenomix Customer Support service (see section 1.3).

SAT test turnaround time:

The clinician that has requested the test will receive the results **within 10 working days** from sample reception by Igenomix.

SAT test reporting:

The following results can be obtained as a result of performing this test:

+ **Normal:** the sample shows a similar percentage of abnormal sperm compared to an internal control dataset.

+ **Abnormal:** the sample shows a statistically significant increase in the percentage of abnormal sperm compared to the internal control dataset.

4.5 Testing for Products of Conception (POC)

POC test description:

POC is a genetic test that can provide information to help determine if pregnancy loss was caused by a chromosomal abnormality. POC testing, performed on tissue retrieved from the lost pregnancy, is comprehensive as it analyses all 24 chromosomes for gross chromosomal abnormalities using NGS.

Pre-requirements for accepting a POC case:

No specific pre-requirements are needed in order accept a case. Specific test indications and relevant clinical information can be reported in the test requisition form.

POC test sample requirements:

Tissue from the lost pregnancy is required. A tissue sample with a minimum size of 3x3 mm, preferably without blood, must be placed in a specimen pot (usually provided by the laboratory) and covered with saline solution.

In addition, and as a control to test for maternal contamination and polyploidy (when appropriate) by STR analysis, 1x4ml of peripheral blood from the mother in EDTA tubes (provided by the laboratory) is required.

Instructions on how to prepare a sample are available (POC Instructions) and can be downloaded from the Igenomix website or requested by email. The "Test Requisition Form" (provided within the provided kit and additionally available either from the Igenomix website or requested by email) must be completed and sent with the sample inside the provided shipping box.

POC sample transportation to the laboratory:

The clinic needs to notify to Igenomix when a sample will be ready, and the laboratory will offer to arrange for sample collection. Transportation will be conducted in custom-made kits provided by the laboratory. Carriage is at Room Temperature. We recommend shipping the samples with a cold gel pack if outside temperatures exceed 35ºC. Avoid freezing the sample when introducing the cold gel pack.

The sample should be sent to the laboratory by either first class mail or a similar secure service (DHL, UPS etc.) and must be packed according to a set of IATA guidelines for "Packaging Instructions and clearly labelled 'Exempt Human Specimen UN3373' when the sample is not delivered from UAE (this courier service is not offered by the laboratory but outsourced to a third-party logistics company).

For further details on how to send the samples please review the test instructions included in the Igenomix website or contact to Igenomix Customer Support service (see section 1.3).

POC tests turnaround time:

The clinician that has requested the test will receive the results **within 10 working days** from sample reception by Igenomix.

POC test reporting:

The following results can be obtained as a result of performing this test:

- **Normal:** when no aneuploidy or partial deletion/duplication has been detected, and the additional STR analysis does not identify maternal cell contamination or polyploidy.

- **Abnormal:** when aneuploidy or partial deletion/duplication ≥10Mb in size has been detected. Information about the detected abnormality is provided.
- **Maternal cell contamination:** when a normal female result has been obtained but the additional STR analysis only detects maternal origin of the sample.
- **Non informative:** when the quality of the sample is suboptimal and leads to an NGS result below the required quality thresholds.

4.6 Carrier Genetic Test (CGT)

CGT test description:

CGT is a family of genetic tests designed to detect carriers of known pathogenic mutations that pose risks for future progeny of having a serious genetic disorder. A "positive" result indicates the presence of one or more mutations in the individual. In these cases, we strongly recommend similar testing of the individual's partner if the couple wishes to have a child. Alternatively, both partners can be tested simultaneously.

If both reproductive partners are carriers of a mutation in the same single gene, there is high risk (25%) of having a child affected by a genetic disease. In these cases, there are options to significantly reduce the risk of having affected children, such as PGT-M, gamete donation, and other options. It is also possible to conceive naturally and resort to prenatal diagnosis. A negative result indicates that the person does not carry any of the mutations studied by the test. The test uses mainly NGS technology for detecting mutations, but additional studies to detect frequent mutations not detected through NGS are used for some genes.

Lists of genes and mutations analysed for each test are available on the webpage https://cgt.igenomix.com

CGT test pre-requirements for accepting a case:

No specific pre-requirements are needed in order accept a case. Specific test indications and relevant clinical information can be reported in the test requisition form.

CGT test sample requirements:

A minimum of 1x 4ml of peripheral BLOOD in an EDTA tube, usually provided by Igenomix.

Instructions on how to prepare a sample are available (see CGT Instructions) and can be downloaded from the Igenomix website or requested by email. The "Test Requisition Form" (provided within the provided kit and additionally available either from the Igenomix website or requested by email) must be completed and placed in the CGT kit.

CGT sample transportation to the laboratory:

The clinic needs to notify to Igenomix when a sample will be ready, and the laboratory will offer to arrange for sample collection. Transportation will be conducted in custom-made kits provided by the laboratory. Carriage is at Room Temperature. We recommend shipping the samples with a cold gel pack if outside temperatures exceed 35ºC. Avoid freezing the sample when introducing the cold gel pack.

The sample should be sent to the laboratory by either first class mail or a similar secure service (DHL, UPS etc.) and must be packed according to a set of IATA guidelines for "Packaging Instructions and clearly labelled 'Exempt Human Specimen UN3373' when the sample is not delivered from UAE (this courier service is not offered by the laboratory but outsourced to a third-party logistics company).

For further details on how to send the samples please review the test instructions included on the Igenomix website or contact to Igenomix Customer Support service (see section 1.3).

CGT test turnaround time:

The clinician that has requested the test will receive the results within 25 working days from sample reception by Igenomix. For some CGT Matching cases 3 additional working days may be required.

CGT test reporting:

The following results can be obtained as a result of performing this test:

- **A positive test result** indicates the detection of a mutation(s) in a tested gene(s). If a patient and partner are both carriers of mutations in the same gene associated with AR inheritance, there is a 25% chance that any child they have together would be affected. If a woman is a carrier of a mutation in a gene associated with X-linked inheritance, there is a 50% chance that male children the patient has may be affected; any female children have a 50% chance of being a carrier.
- **A negative test result** indicates that mutations have not been detected in the analyzed genes. For genes with a negative test result, the risk of having affected children for the corresponding disorders is decreased significantly compared to the general population

4.7 NACE® Extended 24

NACE® Extended 24 test description:

Unlike invasive prenatal diagnosis, which can pose a risk to an ongoing pregnancy, NACE® is a non-invasive prenatal genetic screening test. NACE® uses the latest sequencing technology (NGS) to analyse placental DNA compared to maternal DNA in order to detect certain fetal anomalies with high precision and reliability. NACE® Extended 24 is designed to detect fetal chromosome aneuploidies in all 24 chromosomes and six additional microdeletions

NACE® Extended 24 pre-requirements for accepting a case:

Specific pre-requirements are needed in order accept a case.

- This test is recommended for cases from week 10 of pregnancy onwards. Any case that does not fulfil this requirement will be rejected.

Other specific test indications and relevant clinical information can be reported in the test requisition form.

NACE® Extended 24 sample requirements:

Collect between 1x7ml (minimum) and 1x10 ml (maximum) of maternal peripheral blood in a Streck tube, using only the collection materials provided by Igenomix in the provided NACE® kit.

Instructions on how to prepare a sample are available (see NACE® Instructions) and can be downloaded from the Igenomix website or requested by email. The "Test Requisition Form" (provided within the provided kit and additionally available either from the Igenomix website or requested by email) must be completed and placed in the NACE kit.

NACE® Extended 24 sample transportation to the laboratory:

The clinic needs to notify to Igenomix when a sample will be ready, and the laboratory will offer to arrange for sample collection. Transportation will be conducted in custom-made kits provided by the laboratory. Carriage is at Room Temperature. We recommend shipping the samples with a cold gel pack if outside temperatures exceed 35ºC or if sent from outside UAE (international deliveries). Avoid freezing the sample when introducing the cold gel pack.

We do not recommend storage of samples, after collection, for more than 5 days at room temperature or 7 days when refrigerated. Samples that have exceeded these times when they reach Igenomix may be rejected.

The sample should be sent to the laboratory by either first class mail or a similar secure service (DHL, UPS etc.) and must be packed according to a set of IATA guidelines for "Packaging Instructions and clearly labelled 'Exempt Human Specimen UN3373' when the sample is not delivered from UAE (this courier service is not offered by the laboratory but outsourced to a third-party logistics company).

For further details on how to send the samples please review the test instructions included on the Igenomix website or contact to Igenomix Customer Support service (see section 1.3).

NACE® Extended 24 test turnaround time:

The clinician that has requested the test will receive the results within **10 working days** (NACE24 Extended) of sample reception at Igenomix.

Results will also be sent to patients if the email address was provided within the Test Requisition Form

NACE® Extended 24 test reporting:

The following results can be obtained as a result of performing this test

+ No alteration detected: The patient is considered to be at low risk for the studied condition(s).

+ Alteration detected: The patient is considered to be at high risk for the reported condition(s) with a very high Positive Predictive Value (PPV).

+ Suspected alteration detected: The patient is considered to be at high risk for the reported condition (s) with a low PPV.

+ Non-informative: It is not possible to offer information on the chromosomal state of the pregnancy from maternal blood due to inadequate quality and/or quantity of derived foetal DNA.

+ Sex of the foetus (sexual chromosomes):

- **I**n single pregnancies, male or female sex is reported

4.8 ONCODONA®

ONCODONA® test description:

The ONCODONA® genetic test analyses 21 genes to identify mutations that are associated with a high risk of inherited breast and ovarian cancer. The test is based on next generation sequencing (NGS) and is designed to identify most changes or mutations in the 21 genes analysed in this test (BRCA1, BRCA2, CDH1, PTEN, TP53, PALB2, STK11, ATM, BARD1, BRIP1, CHEK2, MLH1, MSH2, MSH6, MRE11A, MUTYH, NBN, PMS2, PMS1, RAD51C, RAD50).

ONCODONA test. Sample requirements:

Two sample collection alternatives are offered for this test: either SALIVA or peripheral BLOOD

The SALIVA sample must be collected using the supplied ORAGENE-DNA Tube, included into the ORAGENE-DNA box provided by the laboratory. Alternatively a minimum of 1x 3ml of peripheral BLOOD in an EDTA tube, usually provided by the laboratory, is required.

Instructions on how to prepare a sample are available and can be downloaded from the Igenomix website or requested by email. The "Test Requisition Form" (provided within the provided kit and additionally available either from the Igenomix website or requested by email) must be completed and placed in the ONCODONA kit.

ONCODONA test sample. Transportation to the laboratory:

The clinic needs to notify to Igenomix when a sample will be ready, and the laboratory will offer to arrange for sample collection. Transportation will be conducted in custom-made kits provided by the laboratory. Carriage is at Room Temperature. If you are sending a BLOOD sample, we recommend shipping the samples with a cold gel pack if outside temperatures exceed 35ºC. Avoid freezing the sample when introducing the cold gel pack. To maintainsample stability, transit at room temperature should not exceed 5 days in order to ensure the preservative action of the liquid in the cryotube.

The sample should be sent to the laboratory by either first class mail or a similar secure service (DHL, UPS etc.) and must be packed according to a set of IATA guidelines for "Packaging Instructions and clearly labelled 'Exempt Human Specimen UN3373' when the sample is not delivered from UAE (this courier service is not offered by the laboratory but outsourced to a third-party logistics company).

For further details on how to send the samples please review the test instructions included on the Igenomix website or contact to Igenomix Customer Support service (see section 1.3).

ONCODONA test. turnaround time:

The clinician that has requested the test will receive the results **within 30 working days** of sample reception by Igenomix

ONCODONA test reporting:

The following results can be obtained as a result of performing this test

+ **A positive test result** indicates the detection of a mutation in the tested genes.

+ **A negative test result** indicates that no mutations have been identified in the tested genes.

4.9 WHOLE EXOME SEQUENCING (WES)

Whole Exome Sequencing (WES) test description:

Determining the order of nucleotides, building blocks of the DNA, in an individual's genetic code is called sequencing. Next-generation sequencing (NGS) is the new sequencing technique that can allow rapid sequencing of large amounts of DNA at the same time. Whereas, the older forms of sequencing could only analyze one section of DNA at once. NGS has advanced the study of genetics and is used at wide range to test for genetic disorders.

The complete set of DNA (genetic information material) including all of its genes that a human being possesses is referred to as the human genome. The exome is composed of all the exons (coding parts of a gene) within the genome and it comprises about only 2% of the human genome. Although the exome is a small part of the genome, about 85% of all known disease-causing genetic variations (mutations) located in the exome. Whole exome sequencing has proven to be an efficient method to determine the genetic basis of many Mendelian or single gene disorders.

Until recently, WES testing had been considered the genetic test of last resort. However, thanks to technology advances in genetic testing, WES is now being considered as a first-line genetic test in complex cases. It took scientists 10 years to sequence the first genome, however today we can do it in less than 48 hours. WES is increasingly used in healthcare and research to identify genetic variations that cause a disease and confirming the diagnosis at a molecular level. While WES is used to detect exonic variations, DNA variations outside the exons that affect gene activity and protein production leading to genetic disorders are detected using whole genome sequencing (WGS), which pans the entire genome of an individual.

Utility of WES:

WES is used in diagnosing or evaluating a genetic disorder where the results are expected to influence medical management and clinical outcomes of a patient or a family directly or indirectly. With the advent of technology, sequencing has become a routine process in clinical diagnosis which aids a great number of genetic variations to the existing databases. There has been an incredible growth to the known diseasing causing genes and list is increasing intermittently. In this scenario, sequencing and analyzing a small number of genes at a time is costly and time-consuming process. This may further delay the diagnosis, having an impact on patient's quality of life.

WES is a cost-effective diagnostic solution which permits sequencing data from ~24,000 genes (almost all coding genes) from a simple blood draw. It is more effective and examines a much wider range of targets, which is especially worthwhile diagnosing most of the genetic disorders.

Pre-requirements for accepting WES:

Currently, Igenomix offers WES for a screening (healthy family study) and diagnostic (based on a history of the disease in the family) purposes. The diagnostic WES can be offered for an individual (with abnormal clinical findings), couple (with a family history of a genetic disease) or trio (testing an index patient along with the parents).

The screening test can be performed on a healthy family/couple who wants to know about the genetic makeup of their own and there are no other specific pre-requirements from the clinician. For the diagnostic clinician but if it is for the proband or trio diagnostic tests, the clinician needs to provide the clinical information like

1. Physical observations any abnormality of the patient
2. Previous/ancillary test information
3. Consanguinity, Ethnicity, Comorbidities, Genetic predisposition
4. Age at onset of symptoms (Early onset monogenic disorders)
5. Family history of genetic disease(s)

WES sample requirements:

For genetic testing through WES, following sample types are accepted. A thorough labelling of the tube with unique identifying information is suggested, incorrect labeling can lead to rejection of the sample. The minimum required information to identify and accept a sample is - Patient's full name, Date of birth, Gender and Medical Record Number.

Sample type	Container	Volume	Transportation temperature
Peripheral blood	EDTA vacutainer	3 - 4 ml	20-25°C
Purified genomic DNA	In a sealed eppendorf tube	A minimum 1 microgram of DNA at a concentration of 50-100 ng/microliters	20-25°C
Product of Conception	Tissue in sterile container in saline Cardiac or cord blood in Vacutainer	3-4 mm POC specimen or 50-100 mg of each tissue	20-25°C

Further information on how to prepare a sample can be found and downloaded from the website or requested by email to the Igenomix Customer Support service (see section 1.3).

The 'informed consent' form and the 'test requisition from' (included within the provided kit) must be properly filled-in and signed by the patient and sent with the samples inside the shipping box or by e-mail to the laboratory.

WES sample transportation to the laboratory:

The clinic needs to notify to Igenomix when a sample will be ready, and the laboratory will offer to arrange for sample collection. Transportation will be conducted in custom-made kits provided by the laboratory.

Carriage is at Room Temperature. As you are sending a BLOOD sample, we recommend shipping the samples with a cold gel pack if outside temperatures exceed 35ºC. Avoid freezing the sample when introducing the cold gel pack. To maintainsample stability, transit at room temperature should not exceed 5 days in order to ensure the preservative action of the liquid in the cryotube.

The sample should be sent to the laboratory by either first class mail or a similar secure service (DHL, UPS etc.) and must be packed according to a set of IATA guidelines for "Packaging Instructions and clearly labelled 'Exempt Human Specimen UN3373' when the sample is not delivered from UAE (this courier service is not offered by the laboratory but outsourced to a third-party logistics company).

For further details on how to send the samples please review the test instructions included on the Igenomix website or contact to Igenomix Customer Support service (see section 1.3).

WES test turnaround time (TAT):

The clinician that has requested the test will receive the results in a TAT of 28-32 working days for all WES related tests.

WES reporting:

WES allows for the identification of patient's genetic variations located in entire protein coding (exome), reported intronic and untranslated regions of the genome. Igenomix uses an internal validated algorithm for whole exome sequencing analysis and interpretation of the results. Genetic test results are classified and reported based on the recommendations of American College of Medical Genetics and Genomics (Richards *et al.,* 2015). According to the guidelines of ACMG 2015, a genetic variant is classified either Pathogenic, Likely pathogenic or Benign, Likely benign; any genetic variant which is not fulfilling the criteria of pathogenic or benign is classified as a 'variant of uncertain significance'.

Positive result (Pathogenic & Likely pathogenic) – identification of a causative genetic change in a gene that has been linked to patient's symptoms/ disease. A positive result enables the doctor to make a clear diagnosis and help decide on any treatment or other steps to safeguard patient's health and family management.

Unclear result (Variant of uncertain significance) – a genetic variation has been identified and the gene concerned is known to be associated with disorder, but it is not certain if the specific variation that has been identified causes the disorder. Additional genetic testing in the other family members and/or physical examination of the patient and/or ancillary tests (if required) can be considered which could help to prove the causative nature of the genetic results obtained.

Negative result (**no genetic variations are identified**) - either there is no genetic cause for the disorder in question, or no mutation exists in the covered regions of the exome. Additional analysis, such as whole genome sequencing or alternate test (in some cases), may be recommended.

Incidental findings - sometimes, an identified variant is associated with a different genetic disorder that has not yet been diagnosed in the proband (these are called incidental or secondary findings).

5 CERTIFICATION, ACCREDITATION AND EXTERNAL ASSESSMENT SCHEMES

IGENOMIX LABORATORY is CAP certificated (College Of American Pathology), since 2016 (CAP NUMBER 9051461, AU-ID : 1753304) , for the PGT tests

The laboratory annually participates in External Quality Assessments (EQA) (also known as Proficiency Testing, PT) with internationally recognized schemes accredited to ISO 17025 or offered by CAP organizations.

For some tests, no EQA scheme is available. For these tests, the lab performs an internal Alternative Assessment (AA) twice a year to provide objective evidence for the acceptability of examination results.

All tests that are included in certification/accreditation schemes participate in any assessment program (either PT or AA) that may further assist in the continued assessment of the reliability of the offered tests by Igenomix.

Igenomix Dubai works with referral labs that meet certain criteria to ensure the maximum quality in the services is provided.