User Manual

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Table of Contents

1. Igenomix UK

1.1 Introduction

Igenomix UK Ltd is a medical testing laboratory specialising in reproductive genetic services and is part of a multinational company with headquarters in Valencia, Spain. The laboratory currently performs two tests in-house: Preimplantation Genetic Screening (PGS) and testing for Products of Conception (POC). The laboratory offers other services that are currently outsourced to the headquarters in Spain including Preimplantation Genetic Diagnosis (PGD), Endometrial Receptivity Analysis (ERA), a Carrier Genetic Test (CGT), Sperm Aneuploidy Testing (SAT) and a non-invasive prenatal test (NACE/NACE extended 24).

1.2 Laboratory opening times

The laboratory is open Monday – Friday 9:00am to 5:00pm

1.3 Contact details

Key members of staff:

Prof. Alan Thornhill, PhD. State Registered Clinical Scientist (Clinical Embryology). Country Manager UK & Senior Scientific Advisor, Igenomix International.

Dr Roy Pascal Naja, MSc, PhD. State Registered Clinical Scientist (Genetics). Laboratory Director UK.

Ms Aylin Mutlu, MSc. Laboratory Specialist.

Ms Seema Dhanjal, MSc, MPhil. State registered Clinical Scientist (Genetics). Local Quality Manager.

Ms Belen Arnau. Global Quality Manager.

General Enquiries:

Email: info.uk@igenomix.com, support.uk@igenomix.com

Tel: +44(0)2080688176

Laboratory enquiries:

Email: lab.uk@igenomix.com

Tel: +44(0)2080689410/+44(0)1483685245

1.4 Address

Igenomix UK Ltd

Surrey Technology Centre

40 Occam Road

Guildford, Surrey, GU2 7YG

2 Main activities

2.1 General information

Genetic tests are carried out as clinically appropriate. Additional information regarding the different tests offered is available to users on the Igenomix UK website and can also be requested by emailing: info.uk@igenomix.com, support.uk@igenomix.com. Further interpretation of the report is available to users by calling the laboratory and requesting to speak with a senior member of staff. The laboratory is committed to delivering service of the highest quality at all times to ensure patient safety and customer satisfaction. Any comments, suggestions or complaints about the laboratory service should be emailed to the laboratory email address lab.uk@igenomix.com, after which they will be passed to the relevant members of staff or Quality Manager. The laboratory follows strict policies on Information Governance, including the protection of personal information as detailed in the "Data Protection Act 2004".

2.2 Tests offered

2.2.1 Tests performed in-house

The laboratory currently performs two tests: Preimplantation Genetic Screening (PGS) and testing for Products of Conception (POC).

Preimplantation Genetic Screening (PGS)

Description: PGS is a genetic test that may be performed on embryos during in vitro fertilisation (IVF) treatment to screen for numerical chromosomal abnormalities. Chromosomally normal embryos are most likely to implant and develop to term. PGS 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).

Sample requirements: One cell is required for a day three embryo biopsy and 5-6 cells are required for a day five embryo biopsy. The solution used for "washing/tubing" the biopsied cells is provided by the laboratory. The biopsied cells must be placed in sterile 0.2ml microfuge tubes provided by the laboratory. In turn, the 0.2ml tubes must be placed in a "plate/rack" inside a plastic bag placed in a cooler with "ice packs" also provided by the laboratory.

User validation: Following the successful enrolment of a new clinic (see section 3), a validation or "dry run" should be performed for every embryologist involved in embryo biopsy. A "dry run" manual is provided to the clinic detailing the steps that need to be followed and a "dry run" report is issued after the run is analysed and signed by a competent member of the laboratory team and the Laboratory Director. Clinical samples taken by an embryologist will only be processed after his/her successful completion of a "dry run".

Transportation to the laboratory: The clinic must notify the laboratory before a sample is ready and the laboratory will offer to arrange for sample pickup. The transportation will be conducted in custom-made kits provided by the laboratory. Carriage is at Room Temperature.
Note: Please remove the "ice packs" from the kit once received and store at -20^{0}C until sending them along with the samples back to the laboratory.
Turnaround time: Report turnaround time (TAT) is 10 working days following sample reception.

Testing for Products of Conception (POC)
Description: POC is a genetic test that can provide information to help determine the reason for a miscarriage. Most miscarriages are caused by chromosome abnormalities. POC testing, performed on tissue retrieved from the lost pregnancy, is comprehensive as it analyses all 24 chromosomes for gross chromosomal abnormalities using NGS.
Sample requirements: Biopsied tissue from the lost pregnancy is required. The tissue must be placed in a specimen pot (provided by the laboratory) containing saline solution. In addition, and as a control to test for maternal contamination (when appropriate), 1x10ml of peripheral blood in EDTA tubes (provided by the laboratory) is required.
Transportation to the laboratory: The clinic must notify the laboratory before a sample is ready and the laboratory will offer to arrange for sample pickup. The transportation will be conducted in custom-made kits provided by the laboratory. Carriage is at Room Temperature.
Turnaround time: Report TAT is 14 working days following sample reception.

Important notes:
Unlabelled, mislabelled or damaged samples will not be accepted.
Samples not accompanied by the relevant "Test Requisition Form" will not be processed.
The report for samples accompanied by an incomplete "Test Requisition Form" will not be released until the form is completed (see section 3).
When the outside ambient temperature exceeds 35°C please contact the laboratory for further instructions on how to send the samples.

2.2.2 Outsourced tests

The laboratory currently offers other tests that are outsourced to the headquarters in Spain including Preimplantation Genetic Diagnosis (PGD), Endometrial Receptivity Analysis (ERA), a non-invasive prenatal test (NACE), a Carrier Genetic Test (CGT) and Sperm Aneuploidy Testing (SAT).

Preimplantation Genetic Diagnosis (PGD)

Description: PGD may be performed on embryos during IVF treatment to test for single gene diseases and certain chromosomal abnormalities. PGD, requiring only a small number of cells, identifies which embryos are not at an increased risk of developing the disease. The goal of PGD 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. The method uses linkage analysis combined with "minisequencing" for mutation detection.

Sample requirements:

For the pre-PGD protocol, peripheral blood and/or a buccal swab from the prospective parents and other relevant family members is needed and is case-dependent and should be discussed with senior members of staff. Once the pre-PGD protocol is completed the laboratory will inform the IVF clinic and the patients can start their treatment towards PGD.

For PGD, one cell is required for a day three biopsy and 5-6 cells are required for a day five biopsy. The solution used for "washing/tubing" the biopsied cells is provided by the laboratory. The biopsied cells must be placed in sterile 0.2ml microfuge tubes provided by the laboratory. In turn, the 0.2ml tubes must be placed in a "plate/rack" inside a plastic bag placed in a cooler with "ice packs" also provided by the laboratory.

Transportation to the laboratory:

For pre-PGD, blood samples and/or buccal swabs should be sent to the laboratory by either first class mail or a similar secure service (DHL, UPS…) and packed according to UN packing requirement PI 650 and clearly labelled 'diagnostic specimen UN3373' (this service is not offered by the laboratory but outsourced to a third-party logistics company).

For PGD, the clinic needs to notify the laboratory before a sample is ready and the laboratory will offer to arrange for sample pickup. The transportation will be conducted in custom-made kits provided by the laboratory. Carriage is at Room Temperature.

Note: Please remove the "ice packs" from the kit once received and store at -20°C until sending them along with the samples back to the laboratory.

Turnaround time: The setup of a protocol (Pre-PGD) is case-dependent and varies between seven days (panel of frequent diseases) to six weeks ('new" disease). Once the samples arrive at the laboratory, the report TAT is 24-48 hrs for a "fresh" embryo transfer cycle and 7-10 working days for a "frozen" embryo transfer cycle.

Endometrial Receptivity Analysis (ERA)

Description: The lack of synchronisation between the embryo ready to be implanted and endometrial receptivity is believed to be one of the causes of recurring implantation failure. ERA is a test that has been 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 236 genes linked to the status of endometrial receptivity, using RNA sequencing (NGS) on material biopsied from the endometrium. Following the analysis, a specific computational predictor classifies the samples according to their expression profile as "Receptive" or "Non-Receptive". This data will enable a personalised embryo transfer (pET), synchronising endometrial receptivity with an embryo prepared for implantation.

Sample requirements: Endometrial tissue (~50mg) placed in a cryotube containing RNA stabilizing solution provided by the laboratory. The cryotube containing the sample must be refrigerated (4-8°C) for a minimum of 4 hours before shipping.

Transportation to the laboratory: The clinic needs to notify the laboratory before a sample is ready and the laboratory will offer to arrange for sample pickup. The transportation will be conducted in custom-made kits provided by the laboratory. Carriage is at Room Temperature.

Turnaround time: Report TAT is 10 working days.

NACE & NACE extended 24

Description: Unlike invasive prenatal diagnosis that 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 fetal DNA compared to maternal DNA in order to detect certain fetal anomalies with high precision and reliability. Two versions of the test exist: NACE and NACE Extended 24. NACE is designed to detect fetal Trisomy 21, 18, 13 and sex chromosome aneuploidies and NACE Extended 24 is designed to detect fetal chromosome aneuploidies in all 24 chromosomes and 10 additional microdeletions.

Sample requirements: 1x 10ml of peripheral blood in a Streck tube provided by the laboratory.

Transportation to the laboratory: The clinic needs to notify the laboratory before a sample is ready and the laboratory will offer to arrange for sample pickup. The transportation will be conducted in custom-made kits provided by the laboratory. Carriage is at Room Temperature.

Turnaround time: Report TAT is 10 working days.

Carrier Genetic Test (CGT)

Description: CGT is a genetic test 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 that case, the test is highly recommended to the individual's partner if the couple wishes to have a child. Alternatively, both partners can be tested simultaneously.

If both are carriers of a mutation in the same single gene, there is high risk of having a child affected by a genetic disease. In these cases, there are options to conceive healthy children, such as PGD or gamete donation. 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. The test uses NGS.

Sample requirements: 2x 4ml of peripheral blood in EDTA tubes provided by the laboratory.
Transportation to the laboratory: The clinic needs to notify the laboratory before a sample is ready and the laboratory will offer to arrange for sample pickup. The transportation will be conducted in custom-made kits provided by the laboratory. Carriage is at Room Temperature.
Turnaround time: Report TAT is 20 working days.

Sperm Aneuploidy Testing (SAT)

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 offspring. The test specifically analyzes 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).

Sample requirements: 1x 10 ml of semen in culture media in a conical tube placed inside a padded envelope (not provided by the laboratory).
Transportation to the laboratory: The clinic needs to notify the laboratory before a sample is ready and the laboratory will offer to arrange sample pickup. Carriage is at Room Temperature.
Turnaround time: Report TAT is 10 working days.

Important notes:

Unlabelled, mislabelled or damaged samples will not be accepted.
Samples not accompanied by the relevant “Test Requisition Form” will not be processed.
The report for samples accompanied by an incomplete “Test Requisition Form” will not be released until the form is completed (see section 3).
When the outside ambient temperature exceeds 35°C please contact the laboratory for further instructions on how to send the samples.

3. Referrals

Before referrals can be made, clinics need to complete the "Clinic Enrolment Form (CEF)" which can be downloaded from the Igenomix UK website or requested by email from info.uk@igenomix.com and support.uk@igenomix.com. Once the form is completed it should be sent by email to info.uk@igenomix.com and support.uk@igenomix.com. For all tests except PGD the test-specific Test Requisition and Informed Consent forms need to be completed, placed in a plastic sleeve and included in the kit along with the sample to be sent to the laboratory. These forms can be downloaded from the Igenomix UK website or requested by email from lab.uk@igenomix.com. For PGD: the test-specific Test Requisition form, Informed Consent form and a genetics report (specifying the pathogenic mutation(s)/chromosomal abnormality) need to be sent by email to lab.uk@igenomix.com prior to sending the sample (please email lab.uk@igenomix.com or call +44(0)2080689410 for additional information). 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 both the patient and the referring clinician.

4. Accreditation and enrolment in external assessment schemes

The laboratory is working towards achieving accreditation for ISO 15189:2012. The laboratory participates in the national UK External Quality Assessment Schemes (UK NEQAS) for molecular genetics).