St George's University Hospitals NHS
NHS Foundation Trust

## *SW Thames Regional Genetics Laboratory*

# The SAFE Test Laboratory
# User's Manual

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| **Author(s)** | Daria Freydina |
| **Authorised by** | Rachel Dunn |
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## 1 Introduction

The St George's Antenatal Fetal Evaluation (SAFE) test laboratory is located at St George's University Hospitals NHS FT and is part of the South West Thames Regional Genetics Laboratory.

The SAFE test laboratory runs the CE-IVD IONA® screening test developed by Premaitha Health. It is an *in vitro* nucleic acid screening test that indicates the likelihood of a woman carrying a fetus with trisomy 21, 18 or 13. The test is intended to be offered by a clinician to estimate the chance of an affected pregnancy. The test has a sensitivity and specificity of >99% for Patau's, Edwards' and Down's syndrome. The sensitivity is reduced to 95% in the case of dichorionic diamniotic twin pregnancies and vanishing/demised twin.

The SAFE test analyses maternal plasma samples for fetal aneuploidies, using automated next generation sequencing.

This type of technology enables a patient to gain accurate and reliable screening information, which can then be used in conjunction with other clinical and personal information and beliefs to make decisions on further tests if recommended.

This laboratory does not perform tests for any other disease/genetic condition and the SAFE test is not a diagnostic test. An invasive test should be recommended to confirm the presence of fetal Chromosome 21, 18 or 13 Trisomy, should the SAFE test indicate a high chance report.

The following details are provided for the users to aid their referral process.

## 2 Contact information

### 2.1 Postal address

All samples and correspondence should be addressed to:

Genetics - the SAFE test Laboratory
Jenner Wing – Basement – Room 01.242
St George's University Hospitals NHS FT
Blackshaw Road
London
SW17 0QT

### 2.2 Other contact information

**Telephone**: +44 (0) 20 8725 5864 /+44 (0) 20 8725 5874
**Fax**: +44 (0) 20 8725 2138
**Email**: thesafetest@nhs.net/ theSAFEtest-report@nhs.net
**Website**: www.theSAFEtest.co.uk

## 3 Key People

| Name | Description | Contact details |
|---|---|---|
| John Short | Consultant Clinical Scientist | John.Short@stgeorges.nhs.uk |
| Rachel Dunn | Lead Technician | Rachel.Dunn@stgeorges.nhs.uk |
| Basky Thilaganathan | Professor & Consultant Obstetrician Lead | basky.thilaganathan@nhs.net/ Baskaran.Thilaganathan@stgeorges.nhs.uk |
| Joanne Hargrave | SAFE Test Midwife | Joanne.Hargrave@stgeorges.nhs.uk 07876710540 |

## 4 Laboratory hours of operation

The laboratory is open Monday – Friday, 9.00 am to 5.00 pm excluding bank holidays. Samples will not be received outside of these times.

## 5 Clinical services offered by the SAFE test laboratory

### 5.1 Principals of the testing procedure

The testing is based on IONA® test proprietary to Premathia Ltd. No other genetic tests are carried out within this current workflow.

The analysis is performed on cell-free placental DNA from maternal blood samples. Samples are taken in Streck tubes and transported to the laboratory for processing. The plasma is separated from the other blood components and maternal and fetal DNA is extracted. The DNA is then barcoded (for identification), amplified and processed enabling Next Generation Sequencing (NGS) on the ION Proton. The automated analysis step takes the NGS data and directly measures the change in the proportion of chromosome 21, 18 and 13. This data is then combined with the background risk provided (either maternal age, combined test results or quadruple test results) to provide a risk score. This is then reported as a likelihood chance.

### 5.2 Tests offered

The laboratory performs screening on peripheral blood of pregnant women to analyse the chance of a pregnancy affected with either Down's syndrome (T21), Patau's syndrome (T13), or Edwards' syndrome (T18). The SAFE test is suitable for women who are at least 10 weeks pregnant with either a singleton or twin pregnancy. The SAFE test is not suitable for multiple pregnancies greater than twins or if the mother has cancer or a chromosomal or genetic abnormality (including Down's syndrome).The accuracy of the SAFE test may be affected if the mother has recently undergone a blood transfusion in the last 3 months or had transplant surgery, immunotherapy or stem cell therapy prior to the blood sample taken. Results may be confounded in the case of placental mosaicism, partial trisomy or translocations, interuterine fetal demise/Vanishing twin or if the mother has cancer.

The SAFE test has a detection rate of over 99% for Down's syndrome, 99% for Edward's Syndrome and 99% for Patau Syndrome.

In some instances, a diagnostic test such as chorionic villus sampling **(**CVS**)** or amniocentesis should be considered. It is recommended that all screening options, risk factors and results are discussed with a healthcare provider. In the event of a high-chance result (indicating that there is an increased chance that a baby will have Down's, Edwards' or Patau's syndrome) it is important to verify and confirm the high-chance result by CVS or amniocentesis.

The SAFE test offers optional testing for private referrals to determine the baby's sex with a sensitivity of over 99%. However, in about 3% of cases, it is not possible to issue a fetal sex report because of natural sex chromosome variations in the placenta. The SAFE test is not suitable for detection of sex chromosome abnormalities and sex determination is not currently available for multiple births (two or more babies) except for identical twin pregnancies.

### 5.3 Specimen requirements

| Specimen | Sample Collection | Transportation |
|---|---|---|
| **STRECK (Cell-free DNA BCT CE)** | Collect **one tube** of 10ml STRECK blood per patient; ensure tube is **labelled** with 3 identifiers. Smaller volumes are accepted, but this may adversely affect the result of tests performed, ie test failure. | Transport at room temperature (6-37deg), stable for up to 14 days at room temperature. |

## 6 Requesting tests

All requests should be made using the SAFE test consent form; informed consent for testing should be filled in for each patient. Printable copies of this form are available from the MyNIPT portal or directly from the SAFE test Lab. All parts of this form must be completed.

Prior to signing informed consent for genetic testing, details should be explained to the patient by informed medical personnel (e.g. midwife, sonographer). The patient(s) should also be informed of the turnaround times of the screening test.

The following guidelines should be used for completing any consent form.

| | Essential | Desirable |
|---|---|---|
| On -Streck tube/ (blood bottle) | • Patients full name – spelt correctly<br>• Date of Birth<br>• Hospital or NHS number<br>• Date and Time of sampling | |
| On Referral form | • Patients full name – spelt correctly<br>• Date of Birth<br>• Age<br>• Current gestation age by USS<br>• If IVF pregnancy – age of mother/donor at egg harvest<br>• Chorionicity details<br>• Vanishing Twin<br>• Referring hospital details and name of referrer<br>• Blood draw date<br>• Patient consent/ signature<br>• Clinician signature | • Patient label<br>• Patients address and contact number<br>• Maternal weight and height<br>• Ethnic Group<br>• Prior screening test results<br>• Relevant medical history |

**Please confirm the patient identity before taking the sample**

## 7 Sampling handling information

Prepare the sample as detailed below. **All samples should be labelled with at least 3 identifiers (First name, surname, date of birth and hospital no) or they may be rejected.**

- Complete a 'Patient Consent' form for each sample collected.
- Draw 10mL blood sample from pregnant woman into a 'Streck' blood tube. Ensure the tube is in date and not damaged.
- Mix immediately by inverting several times (x10).
- Record onto blood sample tube:
    - Patient ID (inclusive of name and ID number), patient date of birth, blood draw date, If not posted immediately store at room temperature (6-37ºC) (**do not refrigerate**).
- Place the blood sample tube into transport packaging including absorbent padding, place into the biohazard bag.

- Place biohazard bag and 'Patient Consent' form into the transport container (for clinics outside of St Georges Hospital) labelled with the SAFE test address and a UN3373 Biological substance category B label (information provided below).

**Sample collection component check list:**

- Blood tube - Cell-Free DNA BCT® ("Streck").
- Absorbent and protective outer packaging (tube cradle or outer tubing supplied)
- Biohazard bag.
- Outer transport packaging for clinics external to St Georges Hospital
- 'Patient Consent' form.
- Brochure information for NHS and Private Patients.

Additional sampling handling information is available in the document below and is also available on the MyNIPT Portal.


## 8 Transportation of SAFE test samples

Prior to transportation, ensure the patient consent form and blood bottle have been completed with the correct patient information.

Place the sample into the absorbent and protective packaging. The sample and consent form will then be placed into the bio-hazard bag. The bio-hazard bag has a slot specifically for the paper consent form.

The biohazard bag will then be placed into the transport packaging, and sealed securely. The transport packaging must be UN3373, and is provided by the laboratory. Send the sample to:

Genetics - the SAFE test Laboratory
Jenner Wing – Basement – Room 01.242
St George's University Hospitals NHS FT
Blackshaw Road
London
SW17 0QT

- **NOTE**: If a courier is used for delivery please specify delivery directly to the SAFE Test Lab or to the CENTRAL PATHOLOGY RECEPTION at St George's Hospital.
- Register the sample on the **My NIPT™ portal.**

## UN3373 - Summary of Packing Instruction 650 (PI650)

SAFE test sample transport should comply with UN3373, details below;

The packaging needs to be strong enough to withstand shocks normally encountered during transport, transfer and mechanical handling. It should prevent loss of contents due to vibration, or change in temperature, humidity or pressure. There are 3 major components:

- **Primary leak-proof container** (i.e. sample/blood tube) – each sample must be individually wrapped to prevent contact if multiple samples are sent in one package.

- Absorbent material (tissue paper or cotton wool) – enough to absorb the entire contents of the primary containers.
- **Secondary packaging** – leak proof to protect the outer packaging. Any paperwork should be outside this container.
- Cushioning material – to secure the secondary packaging within the outer packaging.
- **Outer packaging** – This must be rigid with at least one surface having a minimum dimension of 100x100 mm. They must pass a "drop test" of 1.2 meters when containing primary and secondary packaging. They must be labelled with the following symbol and text:

**BIOLOGICAL SUBSTANCE, CATEGORY B**


The sides of the diamond must be at least 50mm, the width of the line at least 2mm and the text within and adjacent to the diamond at least 6mm high. For full instructions go to www.hse.gov.uk/biosafety/biologagents.pdf.

If samples are being transported from hot climates please contact the SAFE test laboratory for advice on appropriate transport methods to ensure the samples arrive in an adequate state to process.

## 9 SAFE test laboratory criteria for accepting and rejecting samples

Samples will be checked against a set of criteria [GEN-SAFE-LAB-01].The receipt of unsuitable samples may result in sample rejection, re-sampling request, poor sample quality, delays in tests/results and/or possible delivery of an incorrect diagnosis. . If you are unsure of any aspect of sample collection or form filling, please contact the laboratory for further advice.

| Criteria for Rejecting Bloods | Samples for SAFE test analysis |
|---|---|
| **Less than 3 identifiers** | Samples inadequately labelled with less than 3 identifiers. Note on referral form and inform senior member of staff. These will likely be rejected. |
| **Broken tubes** | All blood samples in broken tubes should be rejected and should be handled as per SOP GEN-ALL-H&S-02. Note on referral form and query with senior staff member if sample discard is required. |
| **Compromised samples** | Samples taken in the incorrect tube or transported incorrectly (e.g. received not at room temperature, on ice or refrigerated) or received compromised (cracked tube). Note on referral form and inform senior member of staff. These will likely be rejected and require a re-draw. Inform clinic on the MyNIPT portal. |
| **Clotted samples** | Unsuitable for SAFE test analysis and a repeat sample in an appropriate tube should be requested. Inform senior member of staff and they will inform booking in staff if sample discard is required. |
| **Old samples** | DNA can be extracted from the plasma <14 day Streck samples. If the sample is outside of this criteria, inform a senior member of staff and a repeat sample will be requested. They will inform booking in staff if sample discard is required.<br>Samples in EDTA tubes will be rejected. |

| | |
|---|---|
| | Streck tube out of date. |
| **Gestational Age** | Less than 10 weeks gestation. |
| **Heparin** | If a patient is on a dose of more than 7500iu of Fragmin (Dalteparin) or anti-coagulating drug, this could lead to an invalid result. Consult with a clinical member of staff. |
| **Multiple pregnancies** | Test is not suitable for multiple pregnancies (greater than twins). |
| **Cancer** | If the patient has a current cancer then this is likely to affect the cfDNA in the maternal blood stream and the result. If current cancer is indicated or information is not provided then this should be queried and a clinician consulted. |
| **Genetic Disorder** | If indicated and detail not provided, query and consult with clinician. |
| **Transplant or immunotherapy** | If indicated and detail not provided, query and consult with clinician. |
| **Blood transfusion** | If indicated and within 3 months the sample should be rejected. |

## 10 Factors known to significantly affect the performance of the examination

The following key factors may affect the performance of our tests or interpretation of the results achieved:

**Specimen factors:**

- Low blood volume – inadequate quantity of DNA.
- Clotted blood – low quality/quantity of DNA.
- Incorrect type of specimen container.
- Delayed sample transport to lab.

**Clinical factors:**

- Incorrect/inaccurate clinical information/diagnosis, medical history.
- Presence of low level mosaic mutations in founder individuals.
- The SAFE test is not suitable for multiple pregnancies (greater than twins).
- If the mother has cancer or a chromosomal or genetic abnormality (including Down's syndrome).
- Unsuitable for mothers who have undergone a blood transfusion in the last 3 months, or had transplant surgery, immunotherapy or stem cell therapy.
- Less than 10 weeks of pregnancy (gestation age must be confirmed by scan prior to testing)

## 11 Results and reporting

- Only senior staff can authorise test results.
- Test results, consisting of a report per patient, are uploaded on to the **My NIPT™ portal** as soon as the test is completed and reports are generated and authorised.
  **My NIPT™ portal - https://mynipt.com**
  - If you are unable to download reports from the portal please contact the safe test laboratory or the portal hosts; support@bluehub.co.uk.
  - For advice regarding use of the portal please contact the SAFE test laboratory or Premaitha on +44 (0) 161 232 5600 or email techsupport@premaitha.com
- Urgent reports can be faxed or emailed from theSAFEtest@nhs.net to a secure location upon request.
- No telephone reports are issued because of the risk of error in verbal transmission.

- Amended reports are issued in cases where an error has been discovered in an already released report or when additional information is obtained/ additional testing is completed where new information needs to be added to an already released report.
- Amended reports are marked as “revision 2 or 3 … etc.” compared to the original statement “revision 1” and are accompanied by a cover letter stating the amendment to the original report.

**Low Chance:** means that it is very unlikely that your pregnancy is affected by trisomy 21, 18 or 13, and therefore very unlikely that your baby has Down’s, Edwards’ or Patau’s syndrome.

**High Chance:** means that your pregnancy is at increased risk for trisomy 21, 18 or 13 and that the result should be confirmed by an invasive diagnostic test, such as amniocentesis or CVS to give a definitive diagnosis.

**Failed Test:** in a very small number of cases tests may need repeating due to insufficient placental DNA in the mother’s blood. Under these rare occasions another blood sample will be required or alternative testing will be recommended. The current test failure rate is <0.5%.

## 12 Expected turn-around times

Please note the following comments:
- Turn-around times are from receipt in the laboratory until a report is available electronically.
- Most samples are processed on the same day that they are received.
- The minimum processing time for a sample in the laboratory is 72 hours.
- An additional day of testing is required for requests that include fetal sex determination.

## 13 Reports available on request

- External quality assurance.
- Turn-around time compliance.
- Accreditation information.

## 14 The laboratory’s policy on protection of personal information

The SAFE test laboratory complies with the guidelines and policies of St George’s Hospitals NHS Foundation Trust. Please see the St Georges University Hospital FT website for details of how the trust complies with the Data Protection Act etc.

## 15 The laboratory’s complaints procedure

If there is an issue that needs to be raised with the department please contact the laboratory on 02087255864 and ask to speak to the laboratory manager. Alternatively email theSAFEtest@nhs.net. All complaints will be forwarded to the Head of the Laboratory and Quality Manager and wherever possible they will be dealt with straightaway.

In cases of a formal complaint through the Trust, the Trust Complaints and Concerns policy and procedure (Org 2.6) will be followed. Please also see trust website for the complaints process.

## 16 Clinical advice and interpretation

The SAFE test laboratory is contactable for any clinical advice during operational hours. Information leaflets are also available in the lab and in clinics offering the test.