FOR CLINICAL LABORATORIES

the IONA® test

non-invasive prenatal screen: safe, fast, accurate

The advanced NIPT solution for clinical laboratories

The IONA® test is a CE-IVD prenatal screening test which is offered to pregnant women to estimate the risk that their fetus may be affected with:

- Trisomy 21 (Down's syndrome)
- Trisomy 18 (Edwards' syndrome)
- Trisomy 13 (Patau's syndrome)

Fetal sex determination is optional

Key features of the IONA® test:

Excellent support

- CE-IVD: no tech transfer required, no hidden costs
- World class technical support and training
- Verified and validated - so you don't have to
- Backup service laboratory

Robust and reliable

- >99% detection and <1% false positive rate
- Highly scalable workflow to match your demands
- Low re-draw rate <0.5%
- Measures fetal fraction, requiring as little as ≥2%

Fast and easy to use

- 3 day turnaround time
- IONA® Software for analysis - trusted and reliable reporting
- Premaitha® Workflow Manager for complete paper-free sample tracking

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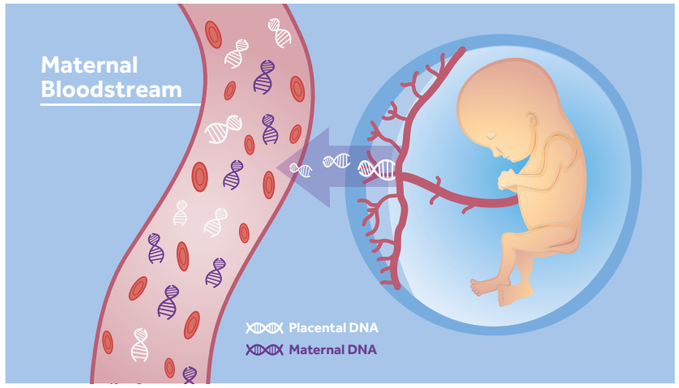
Technology

During pregnancy, the placenta leaks fetal cell-free DNA which circulates in the maternal bloodstream. As a result, a maternal blood sample contains a mixture of fetal and maternal circulating DNA. The IONA® test directly measures the amount of this cell-free DNA and can detect small changes in the chromosomal ratios when fetal trisomy 21, 18 or 13 is present. The IONA® test employs the latest advances in Next Generation Sequencing (NGS) in both a fully automated or manual standardised workflow.

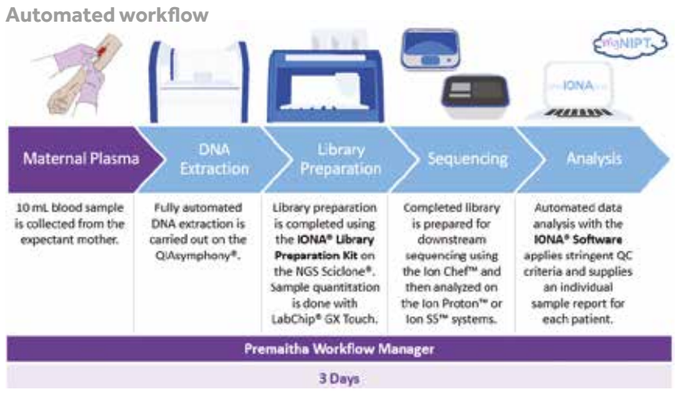


CE-IVD: what does it mean?

The IONA® test is a CE-marked *in vitro* diagnostic product which meets the requirements laid out in the European In Vitro Diagnostic Medical Devices Directive (98/79/EC). The IONA® test system meets the stringent regulatory requirement for a non-invasive screening test and has been externally reviewed by a Notified Body. This is substantially more rigorous than a self-certification CE mark, in line with the IONA® test's classification under Annex II list B of the Directive. The IONA® test received its CE mark in February 2015. This ensures a high-quality robust and reproducible screening test with verification and clinical validation already performed to enable fast implementation with confidence.

The IONA® test workflow

The IONA® test has been validated on a highly flexible and scalable workflow, suitable for low to high volume sample throughput. It enables clinical laboratories to meet and grow with their rising demands and is available as both an automated and manual workflow. Every IONA® test system comes with the fully validated and robust IONA® Software for easy and automated results analysis.
The IONA® test has been validated on the Ion Proton™ and Ion S5™ systems from Thermo Fisher Scientific.



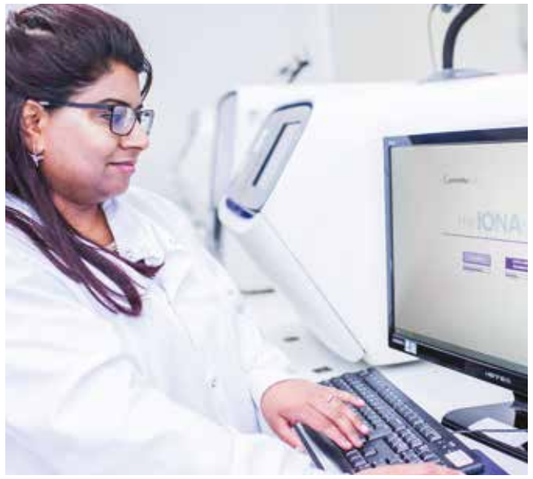
Quality control and fetal fraction

The detection of fetal fraction is an important part of a robust sample QC pipeline. Regardless of sequencing depth, it is not possible to completely remove the uncertainty of false negative results. The IONA® test has been optimised to deliver the most accurate results while simultaneously keeping the number of sample failures, due to low fetal fraction, at a minimum. This is achieved by using a unique approach of two fetal fraction evaluations.

All samples must have ≥2% fetal fraction. In addition, all samples at risk of a false negative or false positive result are evaluated using our proprietary dynamic fetal fraction assessment. This adapts the level of required fetal fraction for the sample to the quality of the sequencing data. Unlike other methods available, less than 0.5% of samples do not generate a reliable result when analysed using the IONA® test. The IONA® test employs a new fetal fraction enrichment method which ensures a low failure rate.

IONA® Software for analysis

This state of the art dedicated bioinformatics solution, for cfDNA analysis in prenatal screening, was custom built by Premaitha as an essential element of the IONA® test.



The medical device grade software employs highly efficient, multi-core analysis algorithms that interprets sequenced DNA fragments and clinical data to produce a printable report. It contains built-in fully automated QC checks and has been verified and validated in compliance with medical device development standards. Test result reports can be customised and provided in local language formats.

The IONA® test is the only NIPT with the option to incorporate the prior risk from the combined test into the analysis. The software provides fast, user-friendly data entry and operation, with no requirement for bioinformatics personnel. Installation, connection to all components of the IONA® workflow, and training is fully covered by the Premaitha technical support team. The IONA® Software provides local and secure data; it is not cloud-based.

Premaitha® Workflow Manager

This is part of the IONA® automated workflow and is a custom-built information management system for comprehensive clinical sample and patient data tracking from receipt to result. The Premaitha® Workflow Manager interfaces with all instruments in the IONA® workflow, covering all stages: DNA extraction, library preparation, sequencing chip preparation, sequencing and analysis to produce the test result. This is the optimal paper-less solution, minimising the need for labour intensive manual tracking.

Instrumentation providers

Premaitha works directly with its technology and instrumentation providers, to offer a complete assay package for clinical testing laboratories, enabling customers to quickly establish routine prenatal screening with a simple and standardised workflow.

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IONA® test results

The relative amounts of chromosomes 21, 18 and 13 are used to calculate a risk score which predicts the presence of a trisomy. This can then be integrated with a prior risk, such as the first trimester background risk of the mother, to give an adjusted probability of the fetus being affected.

The IONA® test report gives a clear, easy to interpret, result of high risk or low risk for each trisomy. High risk results should be confirmed with a follow up diagnostic test. Risk scores can be combined with other markers (e.g. biochemical) to provide the most comprehensive probability assessment.

TRISOMY	BACKGROUND RISK	The IONA® test RISK SCORE	CLINICAL SUMMARY
TRISOMY 21	1 : 307	> 95%	HIGH RISK INVASIVE TEST RECOMMENDED
TRISOMY 18	1 : 797	1 : 516,727 (0.0002%)	LOW RISK
TRISOMY 13	1 : 2487	< 1 : 1,000,000 (<0.0001%)	LOW RISK

Fetal Fraction	4%
Fetal Sex	Female

Enabling service laboratory

To support our customers during installation and to offer a back-up solution for peace of mind, we have a CQC (Care Quality Commission) registered Premaitha NIPT clinical service laboratory.

Premaitha is ISO 13485:2003 certified and the IONA® test is a CE-marked *in vitro* diagnostic test ensuring reliability and giving confidence in the IONA® test results.

MyNIPT®

MyNIPT® is a data exchange portal that enables the exchange of patient results easily and securely between the laboratory and the clinic. Healthcare professionals can track the status of the submitted samples and communicate with the laboratory. Every IONA® laboratory customer has access to the portal enabling them to manage their own clinic users. The portal interface can be branded with your own laboratory logo.

Clinical performance

The IONA® test	Detection rate (Sensitivity)	False Positive Rate (FPR)
Trisomy 21 (Down's syndrome)	>99%	<1%
Trisomy 18 (Edwards' syndrome)	>99%	<1%
Trisomy 13 (Patau's syndrome)	>99%	<1%

Premaitha have demonstrated that the IONA® test can use First Trimester Combined Test results modified by the generated risk score, further tailoring the test results for the individual, and, allowing for contingent prenatal aneuploidy screening.

Optional fetal sex determination has an accuracy rate of >99%

1. Clinical evaluation of the IONA test: a non-invasive prenatal screening test for Trisomy 21, 18 and 13. Papageorghiou A, Khalil A, Forman M, Hulme R, Mazey R, Mousa HA, Johnstone ED, McKelvey A, Cohen KE, Risley M, Denman W, Kelly B. Ultrasound Obstet Gynecol.2016, 47(2), 188-193. Published online at www.wileyonlinelibrary.com. Doi: 10.1002/uog.15791.

2. IONA test for first-trimester detection of trisomy 21, 18 and 13. L. Poon LC, Dumidrascu-diris D, Francesco C, Fantasia I, Nicolaides KH. Ultrasound, Obstet Gynecol, 2016, 47 (2), 184-187. Published online at www.wileyonlinelibrary.com. Doi: 10.1002/uog.15749.

3. The IONA Test: Development of an Automated Cell-Free DNA-Based Screening Test for Fetal Trisomies 13, 18, and 21 That Employs the Ion Proton Semiconductor Sequencing Platform. Crea F, Forman M, Hulme R, Old R.W, Ryan D, Mazey R, Risley M.D. Fetal Diagn Ther. 2017. Published online at www.karger.com. DOI: 10.1159/000455025.

The IONA® test: what is included?

The IONA® test has been validated on the Ion Proton™ and Ion S5™ systems from Thermo Fisher™.

Price per sample includes the following for 192 samples:

- IONA® Library Preparation Kit
- QIASymphony® Circulating Nucleic Acid Kits (QIAGEN)
- Ion PI Chip Kit v3/Ion 540™ Chip Kit
- IC PI Hi-Q Chef/Ion 540™ Kit - Chef
- Licence code
- Instructions for Use
- IONA® plastic consumables
- Premaitha® Workflow Manager
- IONA® Software
- Technical support
- MyNIPT®

Technical support

Premaitha is dedicated to providing a comprehensive training programme for new laboratories and their staff with ongoing technical support available once the IONA® test is fully operational.

- Premaitha coordinates installation of all new instrumentation into the customer laboratory and configures the IONA® system with server and software.
- Premaitha works with instrumentation partners on Installation Qualification (IQ) and Operational Qualification (OQ).
- Bespoke technical lab training for up to four members of the technical team onsite at the Premaitha training suite.
- Performance Qualification (PQ).
- Ongoing technical support via telephone, video conference, email or site visits.

How to order

Please call or email to arrange a technical discussion with the IONA® team to find out more about offering the IONA® NIPT service in your clinical laboratory.

T: +44 (0) 161 667 6865

E: iona@premaitha.com

www.premaitha.com

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