Seraseq®

Trisomy 18 Male - Matched Reference Material

Package Insert

PLEASE NOTE:
THESE REAGENTS MUST NOT BE SUBSTITUTED FOR THE MANDATORY POSITIVE AND NEGATIVE CONTROL REAGENTS PROVIDED WITH MANUFACTURED TEST KITS.

NAME AND INTENDED USE

The Seraseq® Trisomy 18 Male - Matched Reference Material is formulated for use with whole genome or targeted Next Generation Sequencing (NGS) assays or microarray assays that screen for Trisomy 18 (Edwards Syndrome) chromosomal abnormality in cell-free fetal DNA (cfDNA). The Seraseq Trisomy 18 Male - Matched Reference Material, created with matched (or related) maternal-fetal source material, is intended as a reference material for researchers and Non-Invasive Prenatal Testing (NIPT) labs to monitor library preparation, sequencing, and detection performance.
For Research Use Only. Not for use in diagnostic procedures.

SUMMARY

A well-designed quality control program can provide added confidence in the reliability of results obtained for unknown specimens. The use of independent reference products may provide valuable information concerning assay sensitivity and bioinformatics pipeline analysis.

PRINCIPLES OF THE PROCEDURE

Seraseq Trisomy 18 Male - Matched Reference Material is ready to use in NGS or microarray assays starting with DNA extraction similar to an actual test sample. The Reference Material contains processed human cfDNA derived from matched maternal-fetal source material and is formulated in a commutable matrix (simulated plasma) that is compatible with varying shotgun sequencing and microarray-based methods following extraction.

REAGENTS

Item No. 0720-0171. 1 vial, 1 mL per vial, 20 ng/mL concentration.

WARNINGS AND PRECAUTIONS

For Research Use Only. Not for use in diagnostic procedures.
CAUTION: Handle Seraseq Trisomy 18 Male - Matched Reference Material and all materials derived from human blood products as though they are capable of transmitting infectious agents. Seraseq Trisomy 18 Male - Matched Reference is manufactured using processed human cfDNA. Purified cfDNA mixture is formulated in a commutable matrix (simulated plasma) containing human protein isolates (SeraCare's SeraCon™ Matribase).

Safety Precautions

Use Center for Disease Control and Prevention (CDC) recommended universal precautions for handling reference materials and human specimens[1]. Do not pipette by mouth; do not smoke, eat, or drink in areas where specimens are being handled. Clean any spillage by immediately wiping up with 0.5% sodium hypochlorite solution. Dispose of all specimens and materials used in testing as though they contain infectious agents.

Handling Precautions

Do not use Seraseq Trisomy 18 Male - Matched Reference Material beyond the expiration date shown on the vial label. Avoid contamination of the product when opening and closing the vials.

STORAGE INSTRUCTIONS

Store Seraseq Trisomy 18 Male - Matched Reference Material refrigerated at 2 - 8°C. Do not freeze. Samples are designed to be single use.

INDICATIONS OF REAGENT INSTABILITY OR DETERIORATION

Seraseq Trisomy 18 Male - Matched Reference Material is a mixture of human genomic DNA (maternal and fetal). It should appear as a clear to pale yellow liquid. Alterations in this appearance may indicate instability or deterioration of the product and vials should be discarded.

PROCEDURE

Materials Provided

Seraseq Trisomy 18 Male - Matched Reference Material is produced from cfDNA extracted from a pregnant patient source sample carrying a male fetus with confirmed trisomy 18. Material is further processed to maintain natural cfDNA size profile of both fetus and maternal DNA of approximately 170 base pairs in average (Figure 1). The DNA is stabilized and introduced into a dilution of SeraCare's SeraCon™ Matribase (simulated plasma). One (1) mL is provided per tube at 20 ng/mL concentration.

Materials Required but not Provided

Refer to instructions supplied by manufacturers of the test kits to be used.

Instructions for Use

Seraseq Trisomy 18 Male - Matched Reference Material may be inserted into workflows in a manner consistent with plasma fractions prior to extractions. Mix by vortexing to ensure a homogeneous solution. Do not centrifuge. Following extraction, Seraseq® Trisomy 21 Male - Matched Reference Material must go through the entire library preparation and sequencing steps in parallel with the test specimens. Refer to your usual assay procedures in order to determine the amount of material to use. Each vial is intended for a single use.

Quality Control

Seraseq Trisomy 18 Male - Matched Reference Material does not have assigned values for trisomy or fetal fraction. There are many reasons why assays may observe variations in performance, which may or may not be of significance. It is therefore recommended that each laboratory qualify the use of each lot of Seraseq Trisomy 21 Male - Matched Reference Material with each assay system prior to its routine use.

INTERPRETATION OF RESULTS

Detection of aneuploidy may vary with different NGS and microarray assays and different test reagent lots. Since the reference material does not have an assigned value, the laboratory must establish an acceptable range for each lot of Seraseq Trisomy 18 Male - Matched Reference Material. When results for the product are outside of the established acceptance range, it may indicate unsatisfactory test performance. Possible sources of error include: deterioration of test kit reagents, operator error, faulty performance of equipment, contamination of reagents, or change in bioinformatics pipeline parameters.

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LIMITATIONS OF THE PROCEDURE

Seraseq Trisomy 18 Male - Matched Reference Material MUST NOT BE SUBSTITUTED FOR THE CONTROL REAGENTS PROVIDED WITH MANUFACTURED TEST KITS.

TEST PROCEDURES provided by manufacturers must be followed closely. Deviations from procedures recommended by test kit manufacturers may produce unreliable results. Seraseq Trisomy 18 Male - Matched Reference Material is not a calibrator and should not be used for assay calibration. Note that the Seraseq Trisomy 18 Male - Matched Reference Material may not be compatible with certain NIPT methods based on the specific assay design and methodology.

Adverse shipping and storage conditions or use of outdated product may produce erroneous results.

EXPECTED RESULTS

Specific detection of chromosomal abnormality will vary among different assays, different procedures, different lot numbers, and different laboratories. Each laboratory should establish its own range of acceptable values.

SPECIFIC PERFORMANCE CHARACTERISTICS

Seraseq Trisomy 18 Male - Matched Reference Material has been designed for use with whole genome or targeted NGS assays or Microarray assays for the purposes of assessing assay characteristics. The product is manufactured from purified human genomic DNA. Although designed to produce a positive Trisomy 18 result, Seraseq Trisomy 18 Male - Matched Reference Material does not have assigned values. Procedures for implementing a quality assurance program and monitoring test performance on a routine basis must be established by each individual laboratory.

REFERENCES

1. Siegel JD, Rhinehart E, Jackson M, Chiarello L, and the Healthcare Infection Control Practices Advisory Committee, 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings.

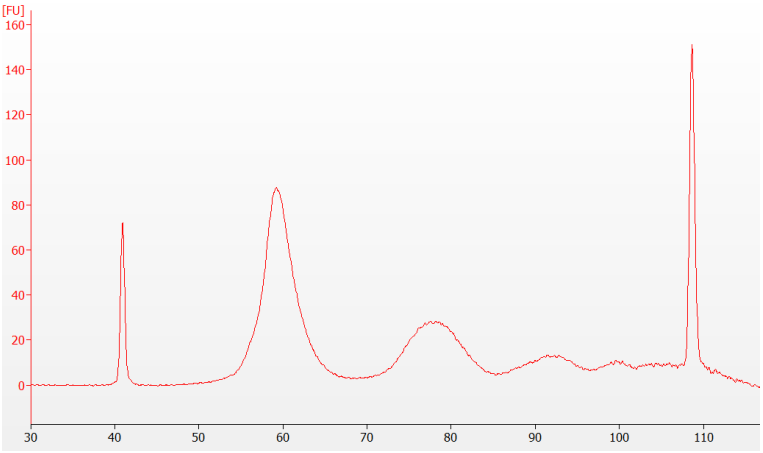

Figure-1: Representative cfDNA size distribution for Seraseq® Trisomy 18 Male - Matched Reference Material.

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PRODUCT SHEET

Seraseq® NIPT Reference Materials

ASSAY VALIDATION AND DAILY-RUN QC MATERIAL FOR NON-INVASIVE PRENATAL TESTING (NIPT)

HIGHLIGHTS

SINGLE-VIAL FORMAT OF PLASMA-LIKE MATERNAL-FETAL cfDNA

UNIQUE ANEUPLOIDY REFERENCE MATERIALS FOR COMMON TRISOMIES, MICRODELETIONS. NIPT-TESTED MATERIALS ASSURING PLOIDY AND FETAL FRACTION LEVELS

HIGH-QUALITY MANUFACTURED REFERENCE MATERIAL SAVES TIME AND COST PROCURING SAMPLES OR PRODUCING HOMEBREW REAGENTS WITH SPECIFIC VARIANTS

INTRODUCTION

Non-invasive Prenatal Testing (NIPT) continues to expand globally as the market shifts to covering a greater portion of the average risk population. Given the clinical implications of the test result, it is extremely critical that NIPT assays report back presence or absence of aneuploidies in an accurate and consistent manner. Reporting problems in assays are often related to low fetal fraction, process variation or bioinformatics, and can result in false negatives, false positives or no results. Matched maternal-fetal reference materials derived from pregnant maternal plasma enable accurate assessment of a broad range of NIPT assays, including those based on counting methods, SNPs, as well as differences in the length of maternal and fetal cfDNA.

The Seraseq NIPT reference materials portfolio consists of two product versions:

- Matched (or related) maternal and fetal cfDNA, derived from pregnancy plasma source samples
- Unmatched (or unrelated) fetal DNA, derived from aneuploid trophoblast cell lines, blended with maternal female genomic DNA

The portfolio of reference materials includes the most frequent chromosomal aneuploidies (such as Trisomy 21 and Trisomy 18) as well as the most frequent microdeletion – 22q11 or DiGeorge Syndrome. These materials are purpose-built to enable monitoring of a full NIPT process from extraction to reporting results. These materials are Research Use Only and not for In Vitro Diagnostic Use.

PRODUCT BENEFITS

- Develop, validate, monitor and troubleshoot your NIPT assay with a single sample
- Technology agnostic reference materials compatible with a broad range of NIPT assay methods (see Table 1)
- Save time, cost and increase QC consistency with a convenient full-process workflow control
- Eliminate need to find, source and maintain remnant samples
- Maintain regulatory compliance with a robust and consistently manufactured third-party QC material

PRODUCT FEATURES

- Collection of common chromosomal aneuploidies – trisomy 21, 18 and 13 as well as Euploid
- Assess expanded conditions such as 22q11 microdeletions (or DiGeorge Syndrome)
- Proprietary method maintains native cfDNA size profile of ~170 bp size distribution and natural maternal-fetal size difference
- Scalable technology allows for easy customization of fetal fraction, concentration and material formulation (either in plasma or fragmented DNA in buffer format)
- Long shelf life product allows for repeated use of the same lot for training, validation or assay performance assessment
- Ensure lot-to-lot consistency with materials manufactured in GMP-compliant and ISO 13485-certified facilities

PRODUCT DESIGN

Our first-generation (unmatched) products were created with a robust biosynthetic technology from unrelated maternal-fetal source materials (see Figure 1B). They are compatible with counting based assays (MPSS method) or amplification assays that do not require related maternal-fetal source samples.

However, as the NIPT assays in the market shifted towards SNP and Paired-End assays that require matched (or related) maternal-fetal source material, we developed our 2nd generation products with an in-house developed proprietary technology (See Figure 1A). This technology utilizes source plasma material obtained from pregnant patients (through an external collaboration) with a known condition as confirmed by NIPT or amniocentesis.

Both types of products are encapsulated and formulated in plasma matrix and need to be processed similarly to a patient specimen.

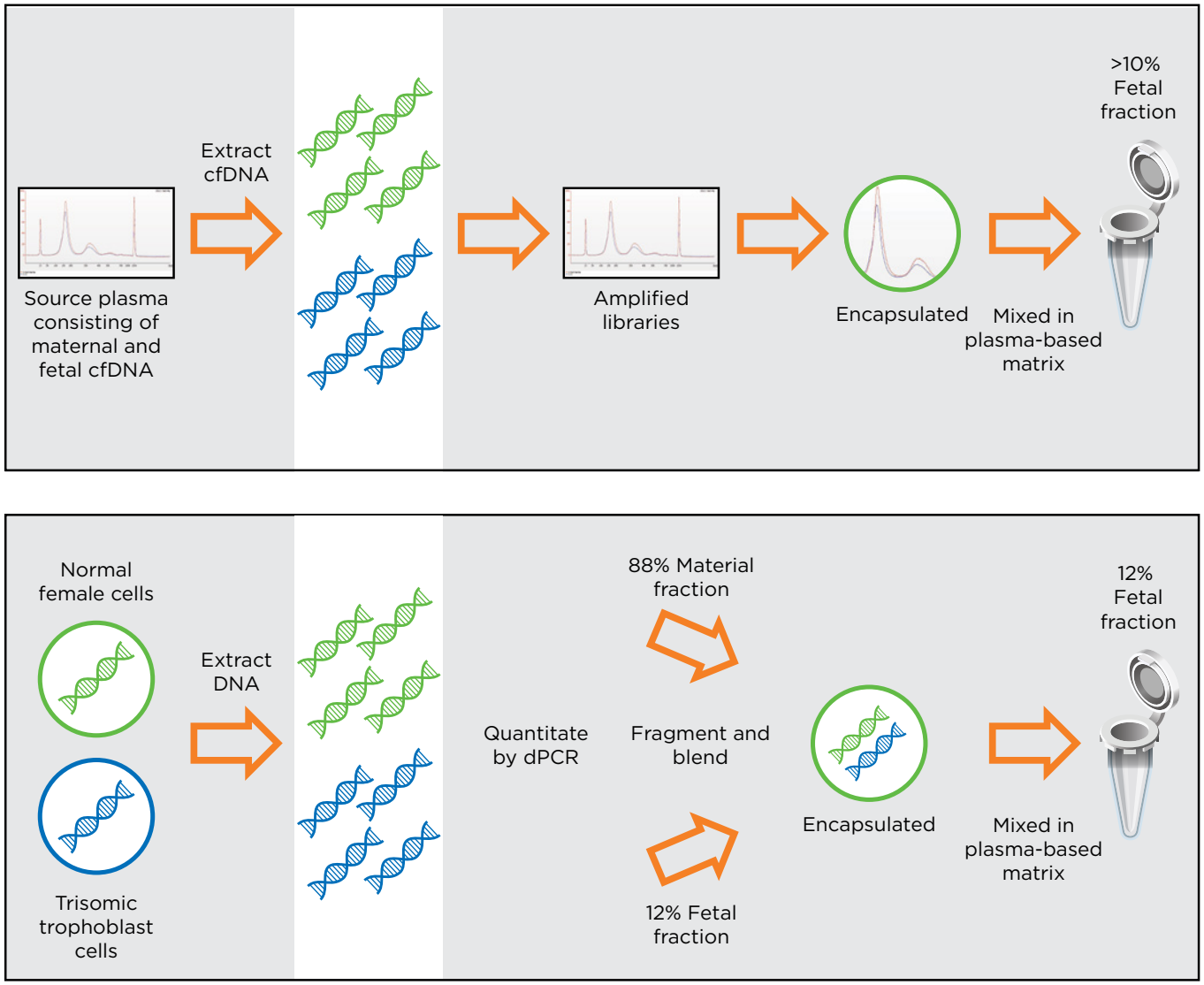
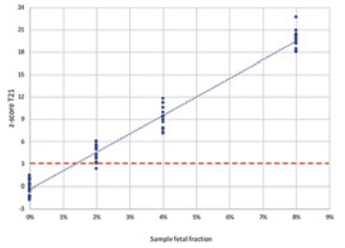


FIGURE 1: Creation of the NIPT reference materials.
Top (1A) — Matched materials prepared from a sample of maternal plasma containing maternal and fetal cfDNA. Plasma samples were collected from pregnant women, cfDNA was isolated, amplified via a proprietary method, encapsulated and formulated in a plasma matrix. Bottom (1B) – Unmatched materials were prepared by mixing fetal gDNA isolated from trophoblasts and an unrelated female (maternal) sample, then fragmented to ~170 bp size profile, encapsulated and formulated in a plasma matrix.

REAL-WORLD APPLICATION OF THE NIPT REFERENCE MATERIALS

The Seraseq NIPT reference materials have been successfully used in numerous labs across the world for a variety of applications ranging from new assay development to proficiency assessment and routine run QC:

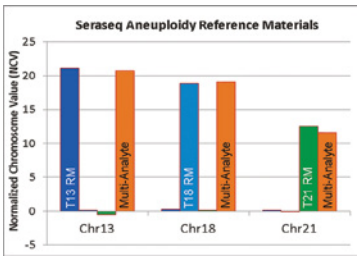
2A



Assay Development

- Enables limit of detection (LOD) studies and test range validity at varying fetal fraction levels. (Figure 2A)[1]
- Expedite new assay development and protocol optimization

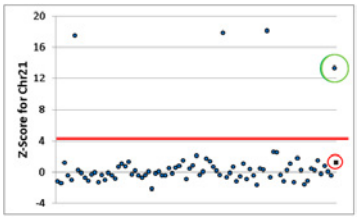
2B



Analytical Validation

- Confirm analytical performance and ability to correctly identify all the chromosomal aneuploidies (Figure 2B)
- Perform External Quality Assessment (EQA) and proficiency testing
- Conduct new assay installation and training

2C



Routine Run QC

- Produces patient-like performance for monitoring daily run performance. As shown in Figure 2C, when used as run controls, they cluster together with the patient samples (for both trisomy and euploid) providing a clear indication that these materials behave like patient samples.
- Customizable technology allows for specific volume, concentration and fetal fraction levels as required

FIGURE 2: Application of Trisomy 21 linearity panel and Multi-Analyte reference materials.
2A (Top). Trisomy 21 Reference Materials at fetal fractions 0%, 2%, 4% and 8% were analyzed to evaluate ability to measure samples with low fetal fraction (Vanadis NIPT System, PerkinElmer). 2B (Middle). Plot of multi-analyte reference material (12% T13, T18, & T21 fetal fraction in a single tube format) compared to the single analyte reference materials demonstrating excellent correlation. 2C (Bottom). Plot of samples run at Lab Cerba demonstrating majority of NIPT results being euploid with only 4 being T21 positive. The samples circled represent SeraCare T21 reference materials and their similarity to actual specimens.

COMPATIBILITY OF THE NIPT REFERENCE MATERIALS WITH EXISTING ASSAYS

	MPSS	MPSS — Pair End	Array	SNP	Non-NGS
Test examples	Verifi™, Iona®, MaterniT®	VeriSeq™	Harmony®	Panorama®	Vanadis®
Matched Maternal-fetal NIPT reference materials	✔	✔*	✔	✔	✔
Unmatched Maternal-fetal NIPT reference materials	✔	✖	✖	✖	✔

*** The 22q11 microdeletion size is approximately 2Mb, which is below the current 7Mb detection limit for VeriSeq NIPT v2[2].**
TABLE 1: NIPT tests which were shown to work with Seraseq NIPT reference materials by our customers. Blue check mark implies compatibility, while red cross mark indicates that the materials are not suitable for a given test

ABOUT SERACARE

TRUSTED SUPPLIER TO THE DIAGNOSTIC TESTING INDUSTRY FOR OVER 30 YEARS.

HIGH-QUALITY CONTROL PRODUCTS, RAW BIOLOGICAL MATERIALS, AND IMMUNOASSAY REAGENTS.

INNOVATIVE TOOLS AND TECHNOLOGIES TO PROVIDE ASSURANCE IN DIAGNOSTIC ASSAY PERFORMANCE AND TEST RESULTS.

FOR MORE INFORMATION, PLEASE VISIT OUR WEBSITE: WWW.SERACARE.COM.

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RELIABLE, CONSISTENT REFERANCE MATERIAL

As a manufactured control reference material, developed under cGMP compliance in ISO 13485 certified facilities, Seraseq NIPT Reference Materials provide a consistent source of reference material for your NIPT assay. This not only ensures a reliable supply which is consistent from lot-to-lot; it also eliminates the need to obtain, characterize, blend, and document your own mixes of cell lines, saving you time and resources in your assay development and validation efforts.
Not for In Vitro Diagnostic Use. Research Use Only.

ORDERING INFORMATION

Matched NIPT Reference Materials

Material #	Product	Fill Size
0720-0169	Seraseq Euploid Male – Matched Reference Material	1 vial x 1 mL
0720-0170	Seraseq Euploid Female – Matched Reference Material	1 vial x 1 mL
0720-0167	Seraseq Trisomy 21 Male – Matched Reference Material	1 vial x 1 mL
0720-0168	Seraseq Trisomy 21 Female – Matched Reference Material	1 vial x 1 mL
0720-0171	Seraseq Trisomy 18 Male – Matched Reference Material	1 vial x 1 mL
0720-0172	Seraseq Trisomy 18 Female – Matched Reference Material	1 vial x 1 mL
0720-0173	Seraseq 22q11 Male - Matched Reference Material	1 vial x 1 mL
0720-0779	Seraseq Trisomy 13 Male - Matched Reference Material	1 vial x 1mL

Unmatched NIPT Reference Materials

Material #	Product	Fill Size
0720-0020	Aneuploidy Negative (Euploid) Reference Material	1 vial x 1 mL
0720-0019	Seraseq® Trisomy 21 Aneuploidy Reference Material,	1 vial x 1 mL
0720-0018	Seraseq® Trisomy 18 Aneuploidy Reference Material	1 vial x 1 mL
0720-0017	Seraseq® Trisomy 13 Aneuploidy Reference Material	1 vial x 1 mL

Custom NIPT Materials

The above products can be customized with regard to fetal fraction level, concentration, volume and format (DNA mix or plasma). Other conditions, including Sex Chromosome Aneuploidies (SCA) are available. Please contact SeraCare for any specific conditions.	Custom

LEARN MORE

To learn more about Seraseq NIPT Reference Materials and SeraCare's product offering for reproductive health, visit https://www.seracare.com/Controls---Reference-Materials-NGS-Reproductive-Health/.

Contact us at 508.244.6400 and 800.676.1881 or email info@seracare.com.

REFERENCES
1. Dahl, F et al. (2018) Imaging single DNA molecules for high precision NIPT. Scientific Reports 8:4549
2. Illumina VeriSeq https://science-docs.illumina.com/documents/RGH/veriseq-nipt-solution-v2-data-sheet-1000000032015/veriseq-nipt-solution-v2-data-sheet.pdf

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