Seraseq®
Pan-RAS DNA Mutation Mix

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® Pan-RAS DNA Mutation Mix is intended for use with Next Generation Sequencing (NGS) assays that identify DNA variants present in cancer which may aid in treatment decisions and confirm an NGS assay is functioning as intended. The Seraseq Pan-RAS DNA Mutation Mix is intended as a quality reference material for translational and disease research testing and monitors library preparation, sequencing, and variant allele detection under a given set of bioinformatics pipeline parameters.
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 accuracy and bioinformatics pipeline analysis.

PRINCIPLES OF THE PROCEDURE

Seraseq Pan-RAS DNA Mutation Mix is ready-to-use in Next Generation Sequencing (NGS) assays in steps that follow DNA isolation; no further purification or DNA isolation is needed. The reference materials should follow the same workflow as unknown samples. The product contains DNA at a concentration of 25 ng/µL. The Reference Material is formulated in 1 mM Tris / 0.1 mM EDTA pH 8.0, which is a buffer that is compatible with both PCR-based target amplification and hybridization-based target selection methods.

Seraseq Pan-RAS DNA Mutation Mix contains 47 mutations (not including those present in the GM24385 background) that are associated with cancer. The product is formulated to simulate DNA isolated from a tumor. The variant allele frequency is confirmed by droplet digital PCR and reported in the batch-specific technical product report.

REAGENTS

Table 1. Seraseq Pan-RAS DNA Mutation Mix

Material No.	Product
0710-4228	Seraseq® Pan-RAS DNA Mutation Mix
0710-4229	Seraseq® Pan-RAS DNA Wild Type

WARNINGS AND PRECAUTIONS

For Research Use Only. Not for use in diagnostic procedures.
CAUTION: Handle Seraseq Pan-RAS DNA Mutation Mix and all materials derived from human blood products as though it is capable of transmitting infectious agents. Seraseq Pan-RAS DNA Mutation Mix is manufactured using genomic DNA extracted from the human cell line GM24385, which is a B-lymphocytic, male cell line from the Personal Genome Project offered by the NIGMS Human Genetic Cell Repository (https://catalog.coriell.org/1/NIGMS). Purified genomic DNA is formulated in a 1 mM Tris / 0.1 mM EDTA pH 8.0 aqueous buffer.

Safety Precautions
Use Centers 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
Avoid contamination of the product when opening and closing the vials.

STORAGE INSTRUCTIONS

Store Seraseq Pan-RAS DNA Mutation Mix frozen at -20 °C or colder. Once opened, a vial can be thawed and re-frozen up to five (5) times. Sub-aliquoting of the product into low DNA binding tubes may be advisable to limit the number of freeze/thaw cycles to five (5) or less.

INDICATIONS OF REAGENT INSTABILITY OR DETERIORATION

Seraseq Pan-RAS DNA Mutation Mix is a mixture of human genomic DNA and synthetic DNA constructs. It should appear as a clear liquid. Alterations in this appearance may indicate instability or deterioration of the product and vials should be discarded.

PROCEDURE

Materials Provided
Seraseq Pan-RAS DNA Mutation Mix is a mixture of human genomic DNA and synthetic DNA constructs in a 1 mM Tris / 0.1 mM EDTA pH 8.0 buffer. Twenty (20) µL is provided per tube and the concentration is 25 ng/µL.

Materials Required but not Provided
Refer to instructions supplied by manufacturers of the test kits to be used.

Instructions for Use
Allow the product vial to come to room temperature before use. Mix by vortexing to ensure a homogeneous solution and spin briefly. Seraseq Pan-RAS DNA Mutation Mix should be integrated into library preparation after the DNA isolation step. If a DNA shearing step is part of the workflow, Seraseq Pan-RAS DNA Mutation Mix should be sheared and go through the target selection and library preparation in parallel with test specimens. Refer to standard assay procedures in order to determine the amount of material to use.

Quality Control
Although Seraseq Pan-RAS DNA Mutation Mix is designed to simulate a tumor sample with multiple variant allele frequencies, the product does not have assigned values for mutation frequencies. There are many reasons why assays may observe deviation from the representative data which may or may not be of significance. It is therefore recommended that each laboratory qualify the use of Seraseq Pan-RAS DNA Mutation Mix with each assay system prior to its routine use.

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INTERPRETATION OF RESULTS
Detection of the variants within Seraseq Pan-RAS DNA Mutation Mix may vary with different types of tests and different test kit lots. Since the reference material does not have an assigned value, the laboratory must establish a range for each lot of Seraseq Pan-RAS DNA Mutation Mix. 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.

LIMITATIONS OF THE PROCEDURE
Seraseq Pan-RAS DNA Mutation Mix MUST NOT BE SUBSTITUTED FOR THE CONTROL REAGENTS PROVIDED WITH MANUFACTURED TEST KITS.

TEST PROCEDURES and *INTERPRETATION OF RESULTS* provided by manufacturers of test kits must be followed closely. Deviations from procedures recommended by test kit manufacturers may produce unreliable results. Seraseq Pan-RAS DNA Mutation Mix is not a calibrator and should not be used for assay calibration. Adverse shipping and storage conditions or use of outdated product may produce erroneous results.

EXPECTED RESULTS
Specific detection of variants and variant allele frequencies will vary among different assays, different procedures, different lot numbers, and different laboratories. Each laboratory should establish its own acceptance criteria. For example, the acceptable range for each variant might include all values within two standard deviations of the mean of 20 data points obtained in 20 runs[2]. Table 2 lists the variants in the product and their target allele frequencies (verified by digital PCR).

SPECIFIC PERFORMANCE CHARACTERISTICS
Seraseq Pan-RAS DNA Mutation Mix has been designed for use with NGS sequencing procedures for the purposes of evaluating assay performance. Seraseq Pan-RAS DNA Mutation Mix 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.
2. Statistical Quality Control for Quantitative Measurements: Principles and Definitions; Approved Guideline– Fourth Edition. CLSI document C24, 2016.

Table 2: List of Mutations Incorporated

Gene	Nucleotide change	Protein change	Type of nucleotide alteration
HRAS	c.37G>C	p.G13R	SNV
HRAS	c.182_183delinsGT	p.Q61R	SNV
KRAS	c.34G>T	p.G12C	SNV
KRAS	c.34G>C	p.G12R	SNV
KRAS	c.34G>A	p.G12S	SNV
KRAS	c.34_35delinsTT	p.G12F	INDEL
KRAS	c.35G>A	p.G12D	SNV
KRAS	c.35G>T	p.G12V	SNV
KRAS	c.35G>C	p.G12A	SNV
KRAS	c.37G>C	p.G13R	SNV
KRAS	c.37G>A	p.G13S	SNV
KRAS	c.38G>C	p.G13A	SNV
KRAS	c.38G>A	p.G13D	SNV
KRAS	c.38G>T	p.G13V	SNV
KRAS	c.38_39GC>AG	p.G13E	MNV
KRAS	c.180_181TC>AA	p.Q61K	MNV
KRAS	c.181C>A	p.Q61K	SNV
KRAS	c.182A>T	p.Q61L	SNV
KRAS	c.182A>G	p.Q61R	SNV
KRAS	c.183A>C	p.Q61H	SNV
KRAS	c.183A>T	p.Q61H	SNV
NRAS	c.34G>T	p.G12C	SNV
NRAS	c.34G>C	p.G12R	SNV
NRAS	c.34G>A	p.G12S	SNV
NRAS	c.35G>A	p.G12D	SNV
NRAS	c.35G>C	p.G12A	SNV
NRAS	c.35G>T	p.G12V	SNV
NRAS	c.37G>T	p.G13C	SNV
NRAS	c.37G>C	p.G13R	SNV
NRAS	c.37G>A	p.G13S	SNV
NRAS	c.38G>C	p.G13A	SNV
NRAS	c.38G>A	p.G13D	SNV
NRAS	c.38G>T	p.G13V	SNV

Gene	Nucleotide change	Protein change	Type of nucleotide alteration
NRAS	c.181C>G	p.Q61E	SNV
NRAS	c.181C>A	p.Q61K	SNV
NRAS	c.181_182delinsAG	p.Q61R	INDEL
NRAS	c.182A>T	p.Q61L	SNV
NRAS	c.182A>C	p.Q61P	SNV
NRAS	c.182A>G	p.Q61R	SNV
NRAS	c.183A>C	p.Q61H	SNV
NRAS	c.183A>T	p.Q61H	SNV
NRAS	c.183A>G	p.Q61Q	SNV
BRAF	c.1799T>A	p.V600E	SNV

Translocation	5' Transcript	3' Transcript
EML4::ALK	NM_019063.5	NM_004304.5
ETV6::NTRK3	NM_001987.5	NM_002530.4
FGFR2::BICC1	NM_000141.5	NM_001080512.3
NCOA4::RET	NM_001145263.2	NM_020975.6

NOTE: Above list does not include variants present in the GM24385 background. Substitution refers to single nucleotide variant; Indels are defined as deletion/insertions less than 10 base pairs, and Large deletions or insertions are larger than 10 base pairs.