Mimix™ Geni™ Onco Mix 1 DNA/RNA FFPE Reference Standard

IVD

For In Vitro Diagnostic Use

REF HD852-IVD Mimix™ Geni™ Onco Mix 1 DNA/RNA FFPE Reference Standard

Intended Use

The Mimix™ Geni™ OncoMix 1 DNA/RNA FFPE Reference Standard is a commutable control material comprising a formalin-fixed paraffin-embedded (FFPE) curl made from a multiplex of 7 engineered cell lines from the GM24385 Genome in a Bottle Consortium Cell line (GIAB), containing 5 single nucleotide polymorphisms (SNPs) and 2 gene fusions. It is intended for quantitative and/or qualitative monitoring of next-generation sequencing (NGS) or droplet digital polymerase chain reaction (ddPCR) assays designed to detect somatic mutations and gene fusions in genomic DNA (gDNA) or RNA from human samples for *in vitro* diagnostic use.

The gDNA or RNA obtained from Geni OncoMix 1 DNA/RNA FFPE Reference Standard can be used to monitor NGS or ddPCR workflows, test performance, assay variation and helps identify increases in random or systematic errors. This product is for professional laboratory use only.

Summary and Explanation

NGS assays are widely adopted by researchers as well as clinical and diagnostic laboratories to analyze the genetic make-up of patient-derived samples, making it useful to gain insightful data on common or rare diseases[1]. Providing high-throughput data, NGS helps identify genetic differences in patients or any genetic changes introduced as certain diseases progress[2]. Similarly, digital PCR workflows, including ddPCR, are commonly used to enhance traditional PCR performance by allowing absolute quantification and offering greater sensitivity for low-abundance targets[3].

The Mimix™ Geni™ Onco Mix 1 DNA/RNA FFPE Reference Standard enables direct analysis of patient-derived DNA samples against seven cancer-related somatic mutations for fast and accurate results for cancer detection assays and workflow. The product is designed to fit into NGS and ddPCR workflows to help accurately analyze patient-derived samples.

Geni™ Onco Mix 1 DNA/RNA FFPE Reference Standard is a curl mimicking the patient tissue sections, sectioned from an FFPE block derived from seven independently engineered GM24385 cell lines via cell pellet collection and blending followed by fixation in 4% paraformaldehyde (PFA) and paraffin embedding. Each FFPE block contains approximately $3x10^8$ cells, which corresponds to approximately $3.5 x10^5$ cells per section. Individual curls from this product can be used to extract either DNA or RNA.

The multiplex reference standard contains seven clinically relevant cancer mutations: Two single-nucleotide variants (SNVs) (V600E and S249C), one multi-nucleotide variant (MNV) (V659E), two indels (A763_Y764insFQEA and I843del/I843_D846del), and two gene fusions (TPM3-NTRK1 and CCDC6-RET). These variants are present at allelic frequencies ranging from 9.42% to 13.48% (Table 1) for supporting assay development and validations. RNA expression levels of the fusions are quantified at ≥40 copies/ng for TPM3-NTRK1and ≥4 copies/ng for CCDC6-RET (Table 2).

This product has been developed in collaboration with the Medical Device Innovation Consortium (MDIC) and the National Institute of Standards and Technology (NIST) as part of the Somatic Reference Samples (SRS) Initiative led by MDIC to help clinical diagnostic labs improve the accuracy of their cancer diagnostic assays.

Principles of Operation

The Mimix™ Geni™ Onco Mix 1 DNA/RNA FFPE Reference Standard contains a single curl suitable for gDNA or RNA extraction, derived directly from engineered GM24385 cell lines to mimic patient samples. No synthetic DNA is incorporated into this product. The FFPE curl is intended to be integrated into the customer's workflow for DNA or RNA extraction. Each batch of Mimix™ Geni™ Onco Mix 1 DNA/RNA FFPE contains seven variants confirmed by ddPCR and RNA expression of two fusions confirmed by RT-ddPCR. This provides an accurate and reliable set for comparison to any NGS assay's performance.

In addition to ddPCR, RT-ddPCR and NGS, further quality control of this product was performed via agarose gel electrophoresis, fluorometric analysis and automated electrophoresis-based analysis.

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Table 1: Verified variants and the corresponding allelic frequencies (AF) confirmed by ddPCR.

Chromosome	Gene	Variant	Variant Type	Expected Allelic Frequency (%)	Acceptance criteria (%)	
					Low	High
Chr17	ERBB2	V659E	MNV	10.82%	8.65%	12.98%
Chr7	BRAF	V600E	SNV	9.75%	7.80%	11.70%
Chr7	EGFR	A763_Y764insFQEA	INDEL	9.42%	7.53%	11.30%
Chr4	PDGFRA	I843del/ I843_D846del	INDEL	11.51%	9.21%	13.81%
Chr4	FGFR3	S249C	SNV	10.15%	8.12%	12.17%
Chr1	TPM3-NTRK1	Fusion	Fusion	13.48%	10.78%	16.17%
Chr10	CCDC6-RET	Fusion	Fusion	11.22%	8.98%	13.46%

Table 2: Verified expression levels of the RNA Fusions.

Chromosome	Fusion	Expression Category	Acceptance criteria
Chr1	TPM3-NTRK1	Medium	≥40 copies/ng
Chr10	CCDC6-RET	Low	≥4 copies/ng

Material Provided

Mimix™ Geni™ Onco Mix 1 DNA/RNA FFPE Reference Standard

- Catalogue/Model number: HD852-IVD
  One vial, 1x FFPE curl, 15 µm thickness.

⚠ Precautions and Warning

- This product is not classified as dangerous; however, users are advised to handle all materials as potentially biohazardous, following standard laboratory safety procedures.
- Dispose of all waste materials in accordance with local regulations.
- Avoid contamination of the product when opening and closing the vial by making sure that the curl is intact and sits at the bottom of the vial.
- Inspect the curl for any signs of melting before opening.

Storage and Handling

- Store unopened at 2 to 8 °C.
- Do not use this product beyond the expiration date printed on the product label.
- Please see the following instructions for handling:
  - Open the tube by twisting and lifting the lid.
  - If needed, please remove the curl carefully without destruction by using suitable forceps (e.g. anatomical forceps) and transfer the curl appropriately.
  - If the whole curl is to be removed from the vial, we recommend all handling takes place at temperatures below room temperature (~15-25 °C).
  - If the curl does not need to be transferred, please keep it in the vial and perform your assay accordingly (e.g. gDNA extraction or RNA extraction).

Quality Control and Performance Characteristics

Variant detection and fusion expression levels when using the Mimix™ Geni™ Onco Mix 1 DNA/RNA FFPE Standard may vary depending on the library preparation method, sequencing platform, and bioinformatics pipeline used for NGS assays, as well as primer/probe set, analysis type/platform, and assay conditions for ddPCR or RT-ddPCR. The expected variant frequency and fusion expression of the Onco Mix 1 DNA/RNA FFPE provided can be used to compare each subsequent run.

The acceptance criteria for QC procedures followed are described below (Table 3). Users should note that results will vary depending on the equipment and workflow used. Users are expected to perform their own validation. The below reported data were obtained using the validated equipment and workflow as specified for each quality control test.

Table 3. List of quality control tests applied and the corresponding acceptance criteria.

Format	Test name	Test purpose	Acceptance criteria
DNA	Fluorometric analysis	Evaluate the quantity and quality of FFPE DNA	dsDNA yield ≥400ng per section
	ddPCR	Measure the stability of AF	Within the accepted target range. Refer to Table 1.
RNA	Fluorometric analysis	Evaluate the quantity of FFPE RNA	RNA yield ≥100ng per section
	Automated electrophoresis-based analysis	Evaluate the integrity of the FFPE RNA	DV200 ≥ 65%
	Fusion-specific RT-ddPCR	Measure the stability of RNA fusion expression	Within the accepted target range. Refer to Table 2.

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The **gDNA yield** obtained from the Mimix™ Geni™ Onco Mix 1 DNA/RNA FFPE Reference Standard is shown in Figure 1.

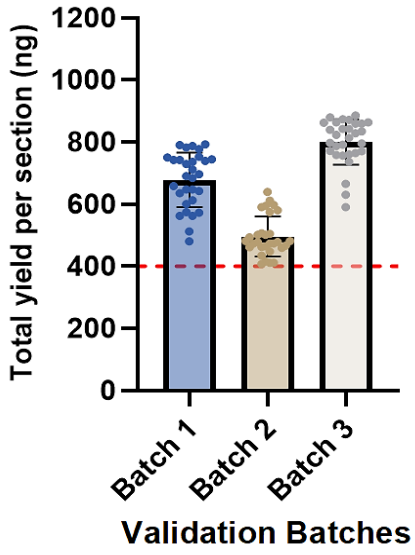


Figure 1. DNA yield per section from three batches of the Mimix™ Geni™ Onco Mix 1 DNA/RNA FFPE Reference Standard. The red dotted line indicates the acceptance criteria of 400 ng

The **RNA yield** obtained from the Mimix™ Geni™ Onco Mix 1 DNA/RNA FFPE Reference Standard is shown in Figure 2.

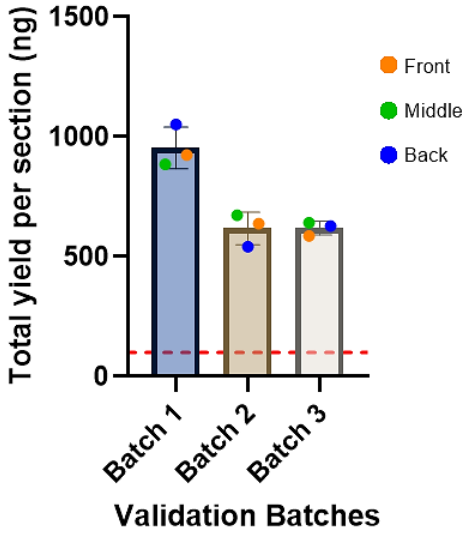


Figure 2. Average RNA yield per section from three batches of the Mimix™ Geni™ Onco Mix 1 DNA/RNA FFPE Reference Standard. Each data point represents 10 pooled sections from different positions in FFPE block. The red dotted line indicates the acceptance criteria of 100 ng.

The **% Allelic frequency (AF) of seven DNA variants** in the Mimix™ Geni™ Onco Mix 1 DNA/RNA FFPE Reference Standard is shown in Figure 3.

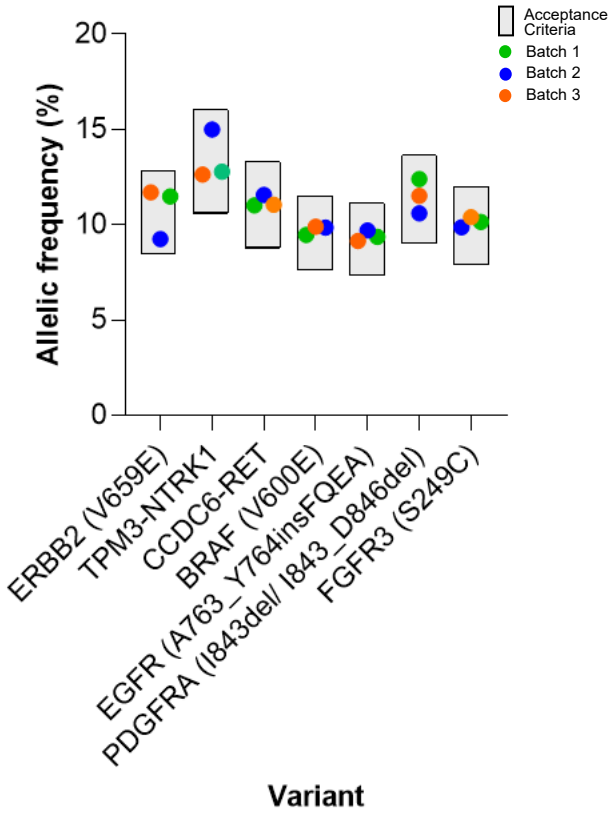


Figure 3. Graph illustrating the % AF of seven DNA Variants in the Mimix™ Geni™ Onco Mix 1 DNA/RNA FFPE Reference Standard across three batches.

RNA expression levels of TPM3-NTRK1 and CCDC6-RET fusions in the Mimix™ Geni™ Onco Mix 1 DNA/RNA FFPE Reference Standard are presented in Table 4.

Table 4. RNA expression levels of fusions in Mimix™ Geni™ Onco Mix 1 DNA/RNA FFPE Reference Standard for three batches.

Fusion	RNA Expression Level (copies/ng)		
	Batch 1	Batch 2	Batch 3
TPM3-NTRK1	101.98	76.81	48.69
CCDC6-RET	15.19	8.32	6.87

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Limitations

- The Mimix™ Geni™ Onco Mix 1 DNA/RNA FFPE Reference Standard is not to be used as a substitute for the internal controls provided by manufacturers within their IVD assay kits.

Technical Support

Scientific support
Tel: 800-235-9880 (Option 2) Or 303-604-9499 (Option 2)
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Email: technical.horizon@revvity.com

Customer support

Tel: 800-235-9880 (Option 1) Or 303-604-9499 (Option 1)
Fax: 1-800-292-6088 Or 303-604-9680
Email: orders.horizon@revvity.com

Batch-specific whole exome sequencing data is provided upon purchase as an online link.

References

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2. Boycott K, Hartley T, Adam S, et al. The clinical application of genome-wide sequencing for monogenic diseases in Canada: Position Statement of the Canadian College of Medical Geneticists. *J Med Genet*. 2015;52(7):431-437. doi:10.1136/jmedgenet-2015-103144

3. Mirabile A, Sangiorgio G, Bonacci PG, et al. Advancing Pathogen Identification: The Role of Digital PCR in Enhancing Diagnostic Power in Different Settings. *Diagnostics (Basel)*. 2024;14(15):1598. Published 2024 Jul 25. doi:10.3390/diagnostics14151598

Glossary

IVD In Vitro Diagnostic Medical Device

REF Catalogue Number

Manufacturer

Temperature Limit

Caution

Consult instructions for use

Use-by date

UDI Unique device identifier

QTY Quantity

CONTROL + Positive control

Trademark and Patent information

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