

Product Data Sheet:

fastGEN POLE Cancer kit

Catalogue number:

RDNGS0004

For research use only!

For professional use.

ENG

**B
G** | **BioVendor
R&D[®]**

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1. INTENDED USE	3
2. STORAGE, EXPIRATION	4
3. INTRODUCTION	5
4. TEST PRINCIPLE	6
5. PRECAUTIONS	6
6. TECHNICAL HINTS	7
7. REAGENT SUPPLIED	8
8. RECOMMENDED MATERIAL (NOT SUPPLIED)	9
9. PREPARATION OF REAGENTS	10
10. PREPARATION OF SAMPLES	11
11. ASSAY PROCEDURE	12
12. RESULTS EVALUATION	18
13. KIT LIMITATIONS	20
14. KIT CHARACTERISTICS	20
15. FAQ	21
16. REFERENCES	22
17. EXPLANATION OF SYMBOLS	23

1. INTENDED USE

RDNGS0004 BioVendor fastGEN POLE Cancer kit is intended for rapid preparation of the sequencing library required for *POLE* (DNA polymerase epsilon, catalytic subunit; exons 9, 11, 13, 14) gene genotyping by fast massively-parallel next-generation sequencing (NGS) using the Illumina® instrument. Sequencing data are analysed online by GENOVESA software, fastGEN module.

The information about the mutation status of *POLE* gene is required for appropriate tumour (especially endometrial) therapy indication and possibly for evaluating the prognosis of the disease.

Abbreviations

Ct	cycle threshold
Cp	Abs Quant/2 nd derivation max
DNA	deoxyribonucleic acid
FAM/SYBR	6-carboxyfluorescein/asymmetrical cyanine dye
FFPE	Formalin-fixed, paraffin-embedded samples
LoD	limit of detection
NC	negative control
NGS	Next Generation Sequencing
PC	positive control
PCR	polymerase chain reaction
<i>POLE</i>	DNA polymerase epsilon catalytic subunit
qPCR	quantitative polymerase chain reaction
RFU	relative fluorescent unit
Tm	Tm Calling (melting temperature)

Features

- **European Union: For research use only!**
- **Rest of the world: For research use only!**
- Total preparation time is less than 3 hours including **less than 30 minutes of hands-on time.**
- Technology is based on the **fast and robust single-step preparation** of sequencing libraries for tumour marker (*POLE*) genotyping.
- Kit contains **complete Master Mixes** including indexes supplied in a ready to use format and **sequencing primers.**
- In the procedure of fastGEN POLE Cancer kit, **simple addition of isolated DNA** to the Master Mix, and analysis in a Real-Time PCR cyclers is required.
- The input material for sequencing library preparation is isolated DNA.
- The kit capacity is 16 reactions/samples with the unique combination of indexes for one sequencing run.
- Sequencing data are analysed online in fastGEN module of GENOVESA software.

2. STORAGE, EXPIRATION

Store the kit at $-20\text{ }^{\circ}\text{C}$. Under these conditions, all components are stable until the expiration date (see label on the box).

- fastGEN POLE Cancer kit is delivered frozen at $-20\text{ }^{\circ}\text{C}$.
- After delivery, store the fastGEN POLE Cancer kit at $-20\text{ }^{\circ}\text{C}$.
- **Protect kit components from light.**
- Avoid repeated freeze-thaw cycles.
- Do not use expired kits or components.

3. INTRODUCTION

Personalized therapy can provide an opportunity for patients with various types of cancer to prolong and improve their quality of life. To effectively set up the therapy, it is necessary to distinguish patients who will benefit from treatment from patients for whom the therapy is not adequate. Appropriate predictive molecular markers can increase the overall efficiency and reduce the financial costs of therapy [1, 2].

Endometrial (uterus or *corpus uteri*) cancer is the sixth most common type of tumour in women, with more than 417,000 new cases reported in 2020. Molecular classification of endometrial carcinoma is becoming an important part of the diagnostic process with direct therapeutic implications [3, 4]. Only those tumours that have at least one of the defined hot-spot pathogenic mutations (variants) in the exonuclease domain of *POLE* gene in exons 9–14 should be assessed as POLE-ultramutated tumours. The list of these variants represents the current situation and may further change with the development of scientific knowledge [5, 6].

Currently, genotyping methods based on the NGS sequencing technologies are available, and specific probes or primers for each acceptable mutation variant are not required, thus the risk of false-negative results is reduced.

The NGS genotyping is based on the preparation of a suitable double-stranded DNA construct (sequencing library), which must contain:

- a target sequence for genotyping (DNA locus)
- an adapter sequence for sequencing primers annealing
- the index sequence, unique per sample and run, which serves to identify the corresponding DNA sample (patient) and sequencing result, and thus allows parallel sequencing of multiple samples (typically more than ten per run)
- a sequence for binding the DNA construct to the surface of the sequencing flow cell

4. TEST PRINCIPLE

The fastGEN POLE Cancer kit is developed for the determination of clinically relevant *POLE* mutation status by NGS. The input material is DNA isolated from tumour tissue. Workflow is also suitable for DNA isolated from FFPE tissue samples. During NGS, short amplicons obtained by a single PCR with hybrid primers with tags, in which up to 170 bp length sequences are amplified and sequenced with high coverage. The use of short amplicons increases the DNA amplifiability and diagnostic yield. Master Mixes are supplied as ready to use, thus the total time and the risk of error is reduced. Sequencing data are analysed online in fastGEN module of GENOVESA software.

In the procedure of the fastGEN POLE Cancer kit, only the addition of isolated DNA to a specific Master Mix and amplification in Real-Time PCR thermocycler is required.

Sequencing data are analysed online in fastGEN module of GENOVESA software, which is a part of a complex solution.

5. PRECAUTIONS

- **For professional use only.**
- fastGEN POLE Cancer kit components do not contain infectious material.
- Samples used for the fastGEN POLE Cancer kit should be treated as potentially infectious and standard safety precautions must be followed.
- Do not drink, eat, or smoke in areas where biological material is handled.

6. TECHNICAL HINTS

- The kit is intended for use with isolated DNA.
- The kit is intended for use by professional users in an adequate laboratory environment.
- Before and after each test, the working environment must be decontaminated with standard RNase, DNase disinfectant. Working in an unsuitable environment can lead to contamination of the kit components.
- The fastGEN POLE Cancer kit is intended for 16 reactions to test mutations in the POLE gene.
- The fastGEN POLE Cancer kit Master Mixes are supplied in separate test tubes for each sample. Aliquotation and repeated thawing is not recommended. Multiple thawing cycles can negatively affect the quality of the test.
- Thaw the individual components right before use. Minimize the time reagents are at room temperature. The use of cooling racks is recommended.
- Vortex and centrifuge reagents gently before using.
- Perform the qPCR preparation and post-amplification steps in separated laboratory areas.
- Avoid the contamination of samples and reagents. For this purpose, use disposable tips for each sample and reagent.
- Do not mix reagents with different lot numbers.
- Dispose of the used and unused material in accordance with the legislation.

7. REAGENT SUPPLIED

The **fastGEN POLE Cancer kit** is supplied in a ready to use format to perform 16 reactions for the *POLE* gene (Table 1). Kit includes **specific Master Mixes** containing all the necessary reaction components and **sequencing primers** for *POLE* gene.

Table 1: fastGEN POLE Cancer kit components.

fastGEN POLE Cancer kit components	Index sequences	Volume per 1 tube (µl)	Number of tubes	State
POLE Cancer kit Master Mix i730	AGACGCGC	18	1	ready to use
POLE Cancer kit Master Mix i731	CATGGACC	18	1	ready to use
POLE Cancer kit Master Mix i741	CGTTGGTT	18	1	ready to use
POLE Cancer kit Master Mix i743	GACCAGTT	18	1	ready to use
POLE Cancer kit Master Mix i744	AAGTTCTT	18	1	ready to use
POLE Cancer kit Master Mix i746	TCTCTATT	18	1	ready to use
POLE Cancer kit Master Mix i747	CTACTGGT	18	1	ready to use
POLE Cancer kit Master Mix i748	AATACGGT	18	1	ready to use
POLE Cancer kit Master Mix i751	CCGGAAGT	18	1	ready to use
POLE Cancer kit Master Mix i753	GCTTCTCT	18	1	ready to use
POLE Cancer kit Master Mix i754	AGCGATCT	18	1	ready to use
POLE Cancer kit Master Mix i757	GTACCTTG	18	1	ready to use
POLE Cancer kit Master Mix i761	ATGGTTGG	18	1	ready to use
POLE Cancer kit Master Mix i764	TTCTTGCG	18	1	ready to use
POLE Cancer kit Master Mix i767	GAGCTACG	18	1	ready to use
POLE Cancer kit Master Mix i768	GACTGCAG	18	1	ready to use
R1SP		12	1	to be diluted
R2SP POLE Cancer		20	1	to be diluted
ISP POLE Cancer		20	1	to be diluted

8. RECOMMENDED MATERIAL (NOT SUPPLIED)

Chemicals

- Examined DNA (standard concentration of at least 10–200 ng/μl according to the spectrophotometer, or 1 ng/μl according to the fluorometer Qubit HS assay; less concentrated DNA can be examined in a special mode, see Table 2).
- Standardized sample containing the required variants of the examined POLE gene (suitable as a positive control).
- Water for molecular biology (Nuclease Free Water, also suitable as a negative control).
- Illumina sequencing kit
- Qubit® dsDNA HS Assay Kit (Life Technologies)
- NaOH (p.a.)
- Tween 20
- Purification kit for DNA pool
- Commercially available surface decontamination solutions

Equipment

- 0.2 ml tubes and 1.5 – 2 ml tubes appropriate for nucleic acids (RNase + DNase free, low binding nucleic acid tubes)
- PCR tubes/strips/plates for use in a Real-Time PCR thermocycler (appropriate for working with nucleic acids)
- Adhesive PCR seals
- Racks for tubes
- Cooling racks/refrigerator/freezer/box with ice
- Single-use sheets suitable for optical instruments
- Pipette tips with filters
- Protective equipment (gloves, clothes)

Instruments

- Automatic pipettes for 0.2 – 1 000 μl volumes
- Real-Time PCR thermocycler
- Flowbox/PCR box
- Fluorometer
- Vortex, combi-spin (centrifuge and vortex), centrifuge
- Illumina®, Inc. sequencing machine

9. PREPARATION OF REAGENTS

Prepare the appropriate number of tubes with Master Mixes needed for testing.

Do not use components after the expiration date marked on the label.

Reagents are supplied as ready to use or must be diluted.

fastGEN POLE Cancer kit: Master Mix

For *POLE* gene genotyping let the appropriate number of POLE Cancer kit Master Mixes tubes thaw and keep them cool until use.

Sequencing primers

Before sequencing library denaturation, let primers thaw and keep them cool until use:

- 1 tube: R1SP
- 1 tube: R2SP for POLE Cancer kit
- 1 tube: ISP for POLE Cancer kit

Recommended:

It is recommended to add the positive control (PC, standardized sample containing the required variants of target genes, not supplied in the kit) and the negative control (NC) into each run using the fastGEN POLE Cancer kit to assess the proper preparation and to eliminate the risk of contamination. In case of non-compliance, false positive or negative results cannot be ruled out.

Handle the positive control with care and **pipette it as the last one**. Improper handling may result in contamination of the test and false positive results. If contamination is suspected, repeat the test.

10. PREPARATION OF SAMPLES

Work at the appropriate PCR box

- Use isolated DNA as input sample.
- Assess the appropriate dilution according to the DNA concentration, see Table 2.
- Obtainment of the proper amount of input DNA:

A) **High concentration DNA** samples – dilute 5x (1 μ l DNA + 4 μ l H₂O).

B) **Common concentration DNA** samples – do not dilute

C) **Very low concentration DNA** samples – do not dilute and include duplicates into the analysis (pipet 5 μ l of DNA into tubes with two different Master Mixes).

- Pipette **5 μ l DNA** prepared according to Table 2 into each reaction.
- The sample is **prepared for analysis**. Follow the chapter 11. Assay Procedure.

Table 2: Appropriate DNA dilution.

	Nanodrop concentration	Qubit HS concentration	Dilution	Dilution
A	>200 ng/ μ l	>20 ng/ μ l	5 x	1 μ l DNA + 4 μ l H ₂ O
B	10–200 ng/ μ l	1–20 ng/ μ l	No dilution	5 μ l DNA
C	<10 ng/ μ l	<1 ng/ μ l	No dilution	5 μ l DNA in duplicates

Recommended:

Positive control (PC)

PC is not included in the kit. Analysis of positive control is recommended for each run.

Prepare the PC similarly to DNA samples.

Precaution: Do not open the tube with positive control during PCR preparation. Pipette the PC as the last one. Inappropriate manipulation can result in contamination and false-positive results. If contamination is suspected, repeat the test.

11. ASSAY PROCEDURE

Using the NGS technology, multiple DNA segments are sequenced with coverage of thousands of reads per sample. Therefore, the method is highly sensitive and somatic mutations with frequency from 1 % (or from 5 %) can be detected.

Up to 16 samples can be processed in parallel.

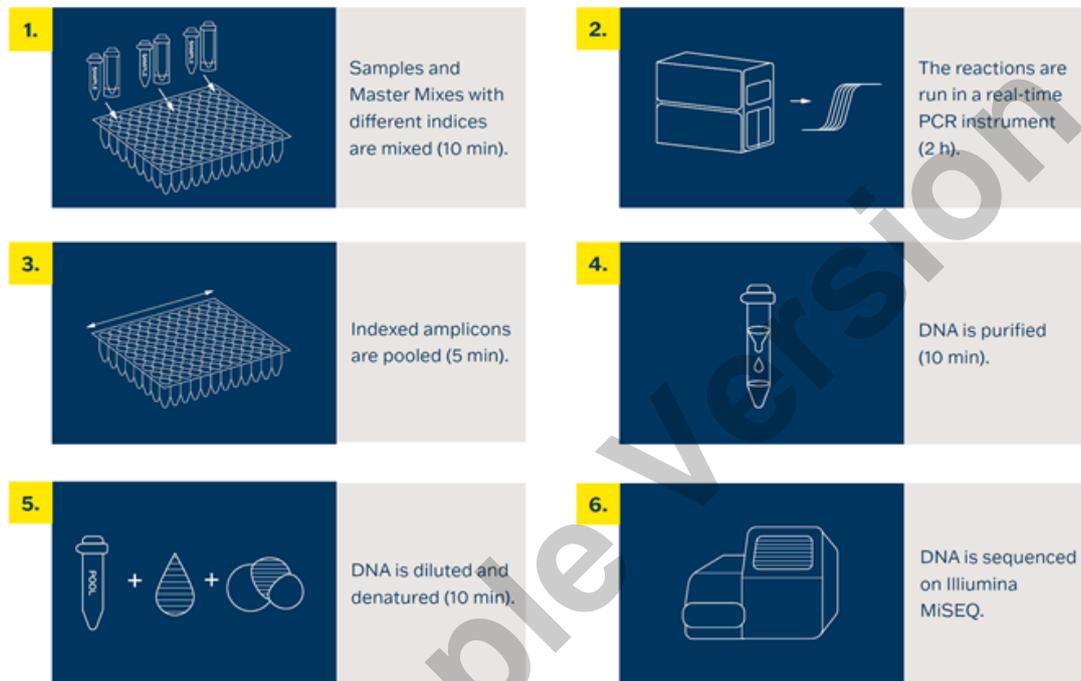


Figure 1: Workflow of genotyping using the fastGEN kit.

11.1 DNA library preparation

11.1.1 Preparation of examined DNA

Use the PCR box.

- Prepare samples.
- Vortex and centrifuge DNA samples shortly.
- Add **5 µl of DNA of the appropriate concentration** (see chapter 10) into the PCR plate or strip.
- Recommendation:
 - Include positive (PC) and negative (NC) control.
 - Use **5 µl of positive DNA with appropriate concentration** as a positive control (see chapter 10).
 - Use **5 µl of molecular grade water** as a negative control.

11.1.2 Preparation of Master Mixes

Use the PCR box in the pre-PCR room.

- Mark the PCR plate or the strip.
- Briefly vortex and centrifuge the Master Mixes when thawed.
- Add **15 µl** of Master Mix to each sample or control.
- The total volume per PCR reaction is **20 µl**.
- Use only **one** Master Mix per position.
- The number of samples analysed simultaneously in one run is 16, including controls.
- Master Mixes have to be opened one by one right before being added into the sample. Close the tube with Master Mix immediately after use. Do not open tubes with various Master Mixes simultaneously to avoid cross-contamination.
- Seal the plate or close the tubes, vortex gently and spin down (15s; 280x g).

11.1.3 qPCR

Set the cycling conditions according to Table 3.

Table 3: qPCR amplification program.

Step	Time	Temperature	
Denaturation	2 min	95 °C	
Amplification	15 s	95 °C	40 cycles
	30 s	62 °C	
	30 s	72 °C*	
Final elongation	5 min	72 °C	
Melting curve acquisition		60 °C → 95 °C	

* FAM/SYBR signal detection

- Set sample names into qPCR software.
- Start the run.
- Export and analyse qPCR results. Keep Ct values for later control.

11.2 Sequencing machine preparation

- We recommend doing this step-in advance.
- During the qPCR run, perform “maintenance wash” of the sequencing machine, and thaw the cartridge.

11.3 Pooling the amplicons, purification and quantification

Use the appropriate box in the post-PCR room and **keep amplicons and DNA pool on ice at all times, with the exception of denaturation step – see the chapter 11.4.3 DNA pool denaturation.**

11.3.1 Pooling

- Centrifuge plates/strips briefly after the qPCR run.
- For genotyping **POLE** gene in one library:
 - Mix the individual amplicons of all samples into one DNA pool in the same ratio.

Example: For 16 samples, mix the individual amplicons in an amount of 3 µl. You get a DNA pool in a volume of 48 µl.

- The final volume of the DNA pool should follow recommendations from the user manual of the purification kit.

Recommended: If the Ct of the sample is > 31 or even > 34, double or triple the volume of the sample added into the final DNA pool.

- Use the new 1.5 ml tube for DNA pool purification.
- Store the plate/strip with samples in the freezer in case of repeated purification.

11.3.2 DNA pool purification

- Follow instructions from the user manual of the purification kit.
- Store the purified DNA pool according to the user manual of the purification kit.

11.3.3 DNA pool quantification

- Assess the mass concentration of the purified DNA pool fluorometrically.
- Recommended DNA pool mass concentration is approximately 40–80 ng/μl; the minimum concentration is 10 ng/μl.
- Assess the DNA pool molarity (molar concentration) according to the equation:

$$c[nM] = \frac{\rho_i \left[\frac{ng}{\mu l} \right] \times 10^6}{(660 \times 230)}$$

- ρ_i is the DNA mass concentration
- 230 is the average DNA molecule length (bp) after indexing
- 660 g/mol is the average molar mass of 1 base pair (bp)

11.4 Preparation for sequencing run

11.4.1 Run assignment

To assign the run, use the SampleSheet „fastGEN-sample-sheet.xlsx“ from www.biovendor.com and edit it (date, run ID, sample identification using the indexes). The sample sheet can be downloaded from GENOVESA software, module fastGEN.

11.4.2 Purified DNA pool dilution

- Dilute the DNA pool (sequencing library) with molecular grade water to a final concentration of **2 nM**.
- The final library concentration should be between 1.6 nM – 2.4 nM.
- Verify the concentration of diluted DNA pool by Qubit HS or other techniques. Use at least 10 μl of diluted DNA pool.
- Dilution should correspond to the raw sequencing density of 1 000–1 200 K/mm². In the case of non-optimal cluster density (>1 200 K/mm²), it is recommended to decrease the final pool concentration to 1.8 nM and increase to 2.2 nM if the raw density is <1 000 K/mm². To facilitate the dilution, use the tool “fastGEN-pool-dilution.xlsx”, available at www.biovendor.com
- Otherwise, the DNA pool has to be diluted repeatedly, and concentration has to be assessed again.

11.4.3 DNA pool denaturation

- Prepare fresh 0.2 M NaOH solution: 480 µl H₂O + 20 µl 5 M NaOH.
- Mix **10 µl of diluted DNA pool with 10 µl of freshly prepared 0.2 M NaOH (1:1)**. It is necessary to use fresh NaOH solution.
- Incubate for **5 min at room temperature**.

11.4.4 Sequencing primers dilution

- Prepare new tubes for sequencing primers dilution. During denaturation, dilute sequencing primers:
 - **Read1 sequencing primers (R1SP):** 3 µl R1SP + 597 µl HT1
 - **Index sequencing primers (ISP):** 6 µl ISP POLE Cancer + 594 µl HT1
 - **Read2 sequencing primers (R2SP):** 6 µl R2SP POLE Cancer + 594 µl HT1

11.4.5 Denatured DNA pool dilution

Dilute the denatured DNA pool by cooled HT1 solution from a refrigerator in ratio 1:100 (e.g., 10 µl DNA pool + 990 µl HT1) – **the resulting 10 pM DNA pool is prepared for sequencing cartridge**.

Keep the DNA pool in the refrigerator before sequencing.

11.4.6 Sequencing cartridge preparation

- Check that the cartridge is completely thawed and turn it over 3x to mix the content.
- Pipette 600 µl of the diluted 10 pM DNA library and diluted sequencing primers into the sequencing cartridge into positions 17-20 in this order:
 - Position 17: DNA library in HT1
 - Position 18: R1SP diluted in HT1
 - Position 19: ISP diluted in HT1
 - Position 20: R2SP diluted in HT1
- Prepare the sequencing flowcell according to the appropriate user manual.
- Run the sequencing program (Illumina software). Follow the manufacturer's recommendation for machine usage.

Note: If you mix several DNA libraries, follow the recommendations for mixing libraries „fastGEN-pool-mix.docx”, which are available at www.biovendor.com, or contact the application specialists.

12. RESULTS EVALUATION

For sequencing raw data interpretation, use the fastGEN POLE module of the GENOVESA software, which is available at www.biovendor.com

GENOVESA fastGEN module

fastGEN module is the cloud, all-in-one solution for sequencing raw data analysis (FASTQ files) with technical and application support provided in the English language.

Software enables:

- Advanced quality control of raw sequencing data
- Automated warnings for insufficiently covered regions
- Simple filtration of relevant variants
- Monthly updates of annotation databases
- Customization
- Saving patient's data and variants into the intern database
- One-click report generation

12.1 *POLE* genotyping

POLE genotyping result is considered as positive (pathogenic mutation detected in the exonuclease domain), if a non-synonymous mutation for **codon 286, 411, 297, 459, 456, 367, 424, 295, 436, 444, 368 of *POLE* was detected with a frequency $\geq 5\%$** [3, 4].

If the *POLE* variants are detected with a frequency from 1 - 5 %, we recommend retesting in duplicate or verifying results with another method. In the case of repeated confirmation of the variant, the sample is considered positive. In case of repeated confirmation of the wt form of *POLE*, the sample is considered negative.

Genotyping of samples with extremely low DNA concentration (<10 ng/ μ l; spectrophotometrically) is valid if the results of both replicates processed with different Master Mixes match.

12.2 Negative result

If none of the variants is detected or the frequency is lower than the threshold, genotyping result is negative (no mutation is detected).

Recommended:

12.3 PC and NC interpretation

The inclusion of positive and negative control for each run of the test (a group of samples measured simultaneously) is recommended to verify that the DNA library preparation has been performed correctly and to avoid technical issues.

Positive control must meet the following criteria:

- In the qPCR amplification step, the Ct of PC is at least 3 Ct lower than NC ($Ct_{PC} + 3 \leq Ct_{NC}$).
- After the sequencing data evaluation, frequencies of *POLE* gene variants are as expected.

Negative control must meet the following criteria:

- In the qPCR amplification step, the NC is not detected, or the Ct value is at least 3 Ct higher than the sample/PC with the highest Ct.

If PC or NC does not meet any of the parameters, analysis was not performed correctly, and it is necessary to interpret the effect on results properly. You can contact the application specialists at www.biovendor.com.

For more information see chapter 15. FAQ

13. KIT LIMITATIONS

- The fastGEN POLE Cancer kit was validated on DNA samples isolated from FFPE tumour tissue.
- The result of genotyping is affected by the quality of the sample. Proper collection, transport, DNA isolation, and sample storage are crucial for test performance.
- Genotyping results should be interpreted by a healthcare professional.
- The fastGEN POLE Cancer kit is designed for rapid preparation of the sequencing library required for the *POLE* gene genotyping using the NGS technology.
- The method is intended for examination of the mutation status of tumour tissue samples, a negative result does not exclude mutations below the LoD.

All instructions in this document should be followed when performing the test. Otherwise, the quality and reliability of the results can be affected.

14. KIT CHARACTERISTICS

Analytical sensitivity and specificity of the BioVendor fastGEN POLE Cancer kit was determined. The LoD for kit was determined, and the crossreactivity of primers was verified (*in silico*). The repeatability and robustness of the method were tested using a series of identical samples in three independent experiments with a defined change of conditions. The diagnostic accuracy (sensitivity and specificity) of the tests was determined based on the analysis of clinical and reference samples with a known mutation status. The results of *POLE* genotyping were correct in all samples, including repeated measurements (sensitivity and specificity 100 %).

15. FAQ

1. How many samples can be sequenced in one run?

It is necessary to obtain 100 000 – 130 000 pair-end reads per sample, if allele frequency is 1-5 % and coverage is 1,000x. Thus, it is possible to sequence up to 16 samples with MiSeq, Reagent kit v2 Nano with 2 mil pair-end reads output. It is possible to analyse up to 128 samples using the MiniSeq Mid-Output kit with 16 mil pair-end reads output.

2. Is it possible to use a different tool for data analysis?

Yes. It is possible to use Illumina® Experiment Manager.

3. Which sequencing machine is appropriate for sample analysis by fastGEN kits?

Illumina® brand sequencing machines should be used to sequence the fastGEN sequencing libraries.

4. Is it possible to combine several kits for genotyping?

Yes, it is possible to combine all fastGEN kits. If you mix several pools, follow the recommendation „fastGEN-pool-mix.docx”, which is available at www.biovendor.com, or contact the application specialists.

5. How should the results be interpreted if PC or NC does not meet quality criteria?

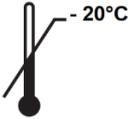
There can be several reasons for the non-standard results of PC and NC. We recommend the PC verification (targeted genes and their variants must contain mutations). Further, verify technical settings and check if a manual error has occurred. In case of ambiguity, contact customer support.

16. REFERENCES

For more references see our websites www.biovendor.com.

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17. EXPLANATION OF SYMBOLS

	Catalogue number
	Batch code
	Use by date
	Upper limit temperature
	Manufacturer
 www.biovendor.com	Read electronic instructions for use - eIFU
	The content is sufficient for 16 tests



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