APPROVED BY
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August 28, 2017

INSTRUCTION

Kit for mutation detection in *EGFR* gene based on real-time PCR (Test-EGFR)

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Version 4 – revised on 28/08/2017

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1. Intended use

Kit is intended for in vitro diagnostic use by trained personnel in medical institutions and clinical diagnostic laboratories of oncological profile when examining patients with Stage III-IV metastatic non-small cells lung cancer (NSCLC). It is aimed for identification of L858R, T790M mutations and deletions (del) in *EGFR* exon 19. Testing is carried out by real-time allele-specific PCR in free circulating DNA test with tumor DNA isolated from blood plasma. The purpose is identification of targeted therapy by EGFR small molecule tyrosine kinase inhibitors and response monitoring.

Clinical relevance of the test is identification of targeted therapy and response monitoring in disease – metastatic non-small cells lung cancer (NSCLC) of III-IV stage using the method of polymerase chain reaction (PCR) with hybridization-fluorescent detection of L858R, T790M activating mutations and deletions in *EGFR* exon 19.

Application area – clinical laboratory diagnostics, oncology.

Materials for PCR procedure are tests of free circulating DNA with tumor DNA isolated from blood plasma.

Testing for detection of L858R, T790M mutations and deletions in *EGFR* exon 19 is recommended to perform on advanced (III- IV stage) non-small cells lung cancer (NSCLC), as circulating tumor DNA has not got into blood flow at early neoplastic proliferation.

Determination principle.

Testing is carried out by real-time allele-specific PCR. *EGFR* PCR-products are identified at 5′-exonuclease reaction by FAM labeled probe. Kit contains reagents for testing of L858R, T790M mutations and deletions in *EGFR* exon 19 and reagents for internal endogenous control (*Norm*). Internal endogenous control (*Norm*) allows detecting PCR inhibitors that may cause false-negative result. PCR Mix consists of all necessary reagents. Kit includes Positive Control (PC) and No Template Control (NTC). As PC it is used 5% PC that is mix of genomic DNA from Jurkat human cell culture with concentration of 400 GE/ µl (genome-equivalent per µl) and artificial-synthesized insertion with 300 bps size in plasmid vector pAL-TA with concentration 20 GE/µl containing equimolar mixture of L858R, T790M mutations and deletions.

PC concentration is selected based on concentration average values of free circulating DNA (200-500 copies/µl of DNA solution) isolated from blood plasma.

Genomic DNA from Jurkat human cells culture used for obtaining PC, control sample of sensitivity and external amplification control, has negative *EGFR* status on L858R, T790M mutations and deletions in exon 19.

Deionized water is used as NTC.

Deletions in exon 19 (Del19) or replacement of L858R in exon 21 are *EGFR* activating mutations related to sensitivity to tyrosine kinase inhibitors. Tumors with mutations Del19 or L858R are more sensitive to tyrosine kinase inhibitors therapy.

Prescribing of tyrosine kinase inhibitors therapy to NSCLC patients with *EGFR* mutations is effective method that may lead to reduction of tumor sizes and disease control for an extended period.

Mutation T790M is resistant to tyrosine kinase inhibitors and responsible for resistance to tyrosine kinase inhibitors therapy. T790M mutation detection allows optimizing therapeutic approach, discovering non-sensitive to therapy tumors and assigning other chemotherapy. It is clinically and economically profitably, taking into account necessity of long-term application and high cost of therapy.[1]

Indication for use. The kit «Test-EGFR» is recommended to patients with Stage III- IV non-small cells lung cancer for possible application of targeted therapy by EGFR small molecule tyrosine kinase inhibitors and response monitoring.

The kit is intended for professional use only in medical institutions and clinical diagnostic laboratories of oncology profile. Potential users are doctor of clinical diagnostic laboratory and laboratory technicians.

Total time of the testing procedure is 2-2.5 hours.

[1] Real-time PCR and digital PCR approach for detecting EGFR status in plasma of patients with NSCLC / M. Gordiev [et al.] // Journal of Thoracic Oncology. - 2016. - V 11. - N 4. - p. 124-125. doi:10.1016/S1556-0864(16)30263-5.

2. Kit characteristics

«Test-EGFR» kit is produced in two versions:

1) «Test-EGFR-12» for 12 tests;

2) «Test-EGFR-24» for 24 tests.

Each kit «Test-EGFR-12» for 12 tests contains reagents that allows testing of 12 samples including PC and NTC.

Each kit «Test-EGFR-24» for 24 tests contains reagents that allows testing of 24 samples including PC and NTC.

Kit composition:

Kits for 12 and 24 tests include:

No.	Reagent	Description	Version	
			«Test-EGFR-12»	«Test-EGFR-24»
1	PCR Mix Norm, **Norm**	Pink-colored transparent liquid	1 tube, (192 µl)	1 tube, (384 µl)
2	PCR mix del, **del**	Pink-colored transparent liquid	1 tube, (288 µl)	2 tubes (288 µl each)
3	PCR mix L858R, **L858R**	Pink-colored transparent liquid	1 tube, (288 µl)	2 tubes (288 µl each)
4	PCR mix T790M, **T790M**	Pink-colored transparent liquid	1 tube, (288 µl)	2 tubes (288 µl each)
5	PC 0,5%, **К+ 0,5%**	Transparent colorless liquid	1 tube, (400 µl)	2 tubes (400 µl each)
6	PC 5%, **К+ 5%**	Transparent colorless liquid	1 tube, (400 µl)	2 tubes (400 µl each)
7	PC-1к 0%, **К+ 1к 0%**	Transparent colorless liquid	1 tube, (150 µl)	2 tubes (150 µl each)
8	PC-10к 0%, **К+ 10к 0%**	Pink-colored transparent liquid	1 tube, (150 µl)	2 tubes (150 µl each)
9	NTC, **К-**	Transparent colorless liquid	1 tube, (1600 µl)	2 tubes (1600 µl each)
10	Taq-polymerase, **Taq**	Transparent colorless liquid	1 tube, (55 µl)	1 tube, (110 µl)

Note:

- PC 0,5% - contains 400 GE/µl of DNA without mutation and 2 GE/µl with L858R, T790M mutations and deletions in the equimolar concentration;

- PC 5% - contains 400 GE/µl of DNA without mutation and 20 GE/µl with L858R, T790M mutations and deletions in the equimolar concentration;

- PC-1κ 0% - contains 100 GE/μl of DNA without mutation (1000 GE for one reaction);

- PC-10κ 0% - contains 1000 GE/μl of DNA without mutations (10000 GE for one reaction).

The kits are supplied in two versions, for 12 and 24 tests including all positive and negative controls. That is, even if tests with all reagent controls are performed individually, the kit version «12» or «24» includes sufficient amount of reagents for testing 12 and 24 clinical specimens, respectively. It is permissible to test several clinical specimens simultaneously. In such case, the kit version «12» makes it possible to analyze up to 24 clinical specimens and the kit version «24» makes it possible to analyze up to 48 clinical specimens because consumption of reagents for positive and negative controls is reduced when several specimens are tested simultaneously.

3. Operating principle

Detection of L858R, T790M mutations and deletions (del) in *EGFR* exon 19 at nucleic acids specimen received from clinical specimen, using the method of polymerase chain reaction (PCR) with hybridization-fluorescent detection includes three stages:

1) DNA PCR-amplification;

2) hybridization-fluorescent detection performed during PCR;

3) interpretation of results.

DNA samples are used for amplification reactions of *EGFR* gene sites in the reaction buffer, using primers, which are specific for these DNA sites, and Taq-polymerase enzyme. The reaction mixture for amplification includes allele-specific primers and fluorescent-labeled oligonucleotide probes that are hybridized with the complementary site of the amplified DNA-target and destroyed by Taq-polymerase resulting increased fluorescence intensity. This enables to observe specific amplification product accumulation by measuring the fluorescent signal intensity. The fluorescent signal is detected directly during PCR using an amplifier with a system for fluorescent signal detection in «real-time» mode.

4. Analytical and diagnostic characteristics

4.1 Analytical characteristics

Analytical specificity	Specific to L858R, T790M mutations and deletions in *EGFR* exon 19
Analytical sensitivity	1 copy of *EGFR* gene to 1 μl of DNA solution
Range of measured DNA concentrations	from 1 to 1000 copies of *EGFR* gene to 1 μl of DNA solution
Regular test results	Absence of L858R, T790M mutations and deletions (del) in *EGFR* exon 19

4.2 Diagnostic characteristics

Diagnostic specificity – 96,0 % with 90 % confidence interval;

Diagnostic sensibility – 88,1 % with 90 % confidence interval

Percent of false-negative results – 11,9 % with 90% confidence interval.

Specificity of analysis is determined by oligonucleotide primers matched to homologous genes regions and by specific fluorescent oligonucleotide probes for hybridization with complementary regions of amplicons (specific amplification products). It excludes cross-reactions.

5. List of risks

Border risk zone includes:

- loss of functional properties of the reagents included in the kit, due to transportation, storage or operation under inappropriate conditions,
- utilization of the kit with violation of safety and deactivation measures;
- crossover contamination of the samples;
- contamination of materials by inhibitors;

- contamination of reaction mixes with DNA samples by PC 0,5% or 5% tubes or PCR products;

- failure to meet the requirements for sample preparation, testing procedure and utilization because of unqualified personnel.

No risks have been identified in the unacceptable zone.

The total residual risk of using the medical product « Kit for mutation detection in *EGFR* gene based on real-time PCR (Test-EGFR) by TS 9398-004-97638376-2015 in the versions: 1) «Test-EGFR-12» for 12 tests, 2) «Test-EGFR-24» for 24 tests» produced by TestGene LLC, is acceptable, and the benefit of its using exceeds the risk.

6. Precautions for handling

Class depending on the potential risk of use is 2b in accordance with the nomenclature classification of medical devices approved by order of the Ministry of Health of the Russian Federation of 06.06.2012 N 4n.

All components and reagents contained in composition of «Test-EGFR» are of 4 hazard class (low-hazard substances) in accordance with GOST 12.1.007-76 «Occupational safety standards system. Noxious substances. Classification and general safety requirements».

Reagents included in «Test-EGFR» kit have low vapor pressure and eliminate the possibility of inhalation toxicity.

Reagents included in «Test-EGFR» kit are not toxic as they are prepared by mixing of separate nontoxic components.

The work shall be carried out in a laboratory performing bimolecular (PCR) testing of clinical material in compliance with the sanitary and epidemiologic rules SanPiN 2.1.7.2790-10 «Sanitary and Epidemiologic Requirements to the address with Medical Waste Products». The following requirements should always be fulfilled during the work:

- Dispose of unused reagents in accordance with p. 4.28 of SanPiN 2.1.7.2790-10 «Sanitary and Epidemiologic Requirements to Handling of Medical Waste».

ATTENTION! When discarding waste products after amplification (tubes containing PCR products), it is not allowed opening the tubes

and spray their contents because this may result in contamination of the laboratory area, equipment and reagents with PCR products.

- Use the kit strictly for its intended use as per this instruction.
- Admit only specially trained staff to the work with the kit.
- Do not use the kit after the expiry date.
- Avoid contact with skin, eyes and mucous membranes. In case of contact, wash immediately the affected area with water and seek medical attention.

7. Required equipment and materials

Equipment:

1. PCR-box (e.g., BAV-PCR-Laminar-S, Laminar Systems, Russia).
2. Vortex (e.g., TETA-2, Biocom, Russia).
3. Kit of electronic or automatic variable volume dispensers (e.g., Eppendorf, Germany).
4. Refrigerator with a temperature from +2 to +8°C with a freezing chamber (max minus 16 °C).
5. Cycler of rotary type, e.g., Rotor-Gene 3000 or 6000 (Corbett Research, Australia), or amplifier of plate type, e.g. Real-Time CFX96 Touch (BioRad, USA), DTprime (DNA-Technology, Russia), or equivalent ones.

Materials and reagents not included in the kit:

1. Disposable tips with an aerosol barrier of up to 200 µl, up to 100 µl, up to 20 and 10 µl (e.g., Axygen, USA).
2. Racks for tips (e.g., Axygen, USA) and 0.5 (0.2 ml) microtubes (e.g., InterLabService, Russia).
3. An individual coat and disposable gloves.
4. Container with a cover for disinfecting solution.
5. Disposable polypropylene tubes for PCR:

a) 0.2 ml tubes (flat cap, not stripped), (e.g., Axygen, USA) for placing in a rotor for 36 tubes – for devices for real-time PCR with detection through the tube bottom (e.g., Rotor-Gene).

b) 0.2 ml tubes (domed cap) (e.g., Axygen, USA) for devices for real-time PCR with detection through the cap (e.g., CFX96, DTprime).

8. Test samples

PCR material is free circulating DNA tests with tumor DNA isolated from blood plasma.

8.1 Obtaining of free circulating DNA tests isolated from blood plasma

To extract free circulating DNA from blood plasma, it is recommended using the following kits of reagents:

- Kit for DNA isolation from blood plasma (DNA-Plasma-M) by TS 9398-002-97638376-2015 in the versions: 1) "DNA-Plasma-M-50" for 50 preparations, 2) "DNA-Plasma-M-100" for 100 preparations (TestGene, Russia),
- Kit for free-circulating DNA isolation from blood plasma (DNA-Plasma-M-RT) by TS 21.20.23-010-97638376-2017 (TestGene, Russia),
- Kit for RNA/DNA extraction from clinical material AmplyPrime MAGNO-sorb by TS 9398-004-09286667-2012 (Nextbio, Russia)
- NucleoSpin® Blood (MACHEREY-NAGEL, Germany)
- QIAamp Circulating Nucleic Acid Kit, QIAamp UltraSens Virus Kit (QI-Aamp, Germany)

or analogous kits intended for circulating nucleic acids extraction from biological fluids.

ATTENTION! In case of obtaining of free circulating tumor DNA from blood plasma, we recommend to comply with the following plasma obtaining procedure. To obtain plasma, take the blood (not less than 8–10 ml) in a tube containing EDTA or CPDA. Turn over the closed tube with blood several times. It is necessary to separate plasma and transfer it in a new tube within 24 h after taking the blood. For this purpose, centrifuge the tube containing blood for 10–15 min at 2000–3000 g, after that take top plasma layer carefully and transfer it in a separate disposable tube; avoid getting of buffy coat and layers containing erythrocytes in the collected material. Centrifuge the plasma for 15 minutes at 13000 g or for 10 minutes at 16000 g (if a high-speed centrifuge is not available it is permissible to perform the second centrifugation at 3000 g), take the top

layer again in a separate tube without touching the precipitate on the tube bottom. The obtained plasma may be used for DNA isolation or frozen at a temperature not higher than minus 70 °C for subsequent use.

The DNA should be isolated from not less than 2 ml of plasma (the recommended quantity is 3-5 ml) and dissolved in final volume of not less than 100 µl.

8.2 Interfering substances and limitations of sampling material use.

Biological material used for PCR-testing and containing excess of admixtures in the form of mucus, blood, purulence etc. may cause amplification inhibition.

For nucleic acids specimens' extraction from clinical sample necessary for PCR purity tests, it is recommended to use extraction kits specified in p. 8.1 of this instruction.

For efficiency control of DNA extraction and possible PCR inhibition it is used external amplification control (РС-10к 0%). It is represented genomic DNA from Jurkat human cells culture with concentration 1000 EGFR gene copies per 1 µl. It is necessary to add 10 µl of DNA to amplification reaction with primers on «Norm» for amplification external control. Reaction passage is indicative of effective nucleic acids extraction and absence of PCR-inhibitors.

Non-reactiveness result should be considered as inaccurate. In this case, it is recommended making additional DNA extraction for this sample for PCR-testing.

Limitations for testing material use:

- Blood plasma samples taken in heparin tubes as anticoagulant is not suitable for testing.

- Testing material is not suitable for use if storage and transportation conditions are violated (temperature, duration, multiple freezing and thawing).

- Samples contaminated with outside biological material are not allowed for using.

- Not use laky and chylous blood. It may cause inaccurate results while testing.

8.3 Storage conditions of testing samples

The obtained DNA shall be stored at a temperature of +4°C and used for testing within 12 hours.

9. Preparation of the components for testing

ATTENTION! When working with DNA, you shall use only disposable sterile plastic consumables with special labeling «DNAse-free».

Preparation of tubes for amplification

The selection of the tubes for amplification depends on a cycler used. Disposable tips with filters shall be used for putting the reagents, DNA samples and control specimens in the tubes.

ATTENTION! The reaction mixture components should be mixed just before performing testing. Mix the reagents calculated for the required number of reactions, including testing and control specimens, according to calculation tables.

1. Before starting the work, you should completely unfreeze all the reagents at room temperature and precipitate drops from tube caps.

2. Mix the contents of the tubes thoroughly (by shaking the tubes in the vortex for several seconds or by turning them over 10 times) after unfreezing, shake off the tube contents to the bottom using a centrifuge.

3. Take the required quantity of tubes for amplification of the test and control DNA samples. Select the type of tubes, strips or plates depending on a device used.

10. Testing procedure

The PCR-test consists of the following stages:

A) DNA PCR-amplification;

B) «real-time» hybridization-fluorescent detection of amplification products;

C) interpretation of results (specified in Section 11).

A) DNA PCR-amplification

(performed in area for PCR – room for PCR-amplification)

Total reaction volume: 20 µl.

ATTENTION! It is prohibited to change the reaction volume. If the volume is changed, the method sensitivity will decrease greatly!!!

1. To prepare the reaction mixture mix all necessary components in separate sterile tubes as calculated for one reaction according to calculation tables. Use a separate tip with an aerosol barrier for each reaction component of each sample.

2. When working with small volumes of viscous liquids (such as Taq-polymerase), it is recommended to prepare a mix for 5 to 10 reactions in order to take not less than 1 µl of the liquid using an automatic pipette. Take the required volume from the tube while not sinking the tip deeply in the reagent so that not to take excessive enzyme volume because of its getting on the external tip surface.

Preparation of reaction mixes (calculated for one specimen)

Test	Master mix			
	Reaction mixture (µl)	**Taq (µl)**	**Water (µl)**	**Total quantity of tubes**
Norm	4	0,2	5,8	4
del	4	0,2	5,8	6
L858R	4	0,2	5,8	6
T790M	4	0,2	5,8	6

Recommended arrangement of reactions

96-well plate												
Test	1	2	3	4	5	6	7	8	9	10	11	12
Norm	NTC	PC-1к	PC-10к	S1			S2			S3		
del	NTC	PC-0,5%	PC-5%	S1	S1	S1	S2	S2	S2	S3	S3	S3
L858R	NTC	PC-0,5%	PC-5%	S1	S1	S1	S2	S2	S2	S3	S3	S3
T790M	NTC	PC-0,5%	PC-5%	S1	S1	S1	S2	S2	S2	S3	S3	S3

3. Put 10 µl of each master mix in the respective wells as per the recommended arrangement of reactions.

4. Put 10 µl of deionized water in each NTC reaction.

5. Put 10 µl of PC standard mixture in each PC reaction.

6. Put 10 µl of the specimens in each control and mutation reaction.

7. Seal the PCR-plate/close the tubes; make sure that all the covers or the film fit tightly.

8. Remove the PCR-plate/ tubes in order to collect the reaction mixture on the well bottom, while preserving the correct orientation of the plate or tube series.

B) «Real-time» hybridization-fluorescent detection of amplification products;

1. Place the tubes into the reaction module of a device for «real-time» PCR. Pay attention to the fact that the devices for «real-time» PCR

shall be maintained, calibrated and used in accordance with the manufacturer's recommendations. The use of this kit in a non-calibrated device may affect the test performance.

2. Program the device for fulfillment of a relevant amplification and fluorescent signal detection program as per the description for this device.

Amplification program for DNA-Technology devices

Stage	Temperature, °C	Time	Total cycle number
1	95	2 min	1
2	94	10 s	60
3	62 ;, ;	60 s	

Amplification program for other devices

Stage	Temperature, °C	Time	Total cycle number
1	95	2 min	1
2	94	10 s	60
3	60 ;, ;	60 s	

3. Start amplification program with fluorescent signal detection at stage 3.

4. After completing the program, analyze the results.

11. Recording and interpretation of results

Record the results with the use of software of the device used for performing PCR with detection in «real-time» mode. Analyze fluorescent signal accumulation curves by one channel:

– the channel **FAM/Green** in the reaction mixture *Norm* records a signal evidencing the accumulation of DNA amplification products of normal *EGFR* gene variant.

– the channel **FAM/Green** in the reaction mixtures *del, L858R, T790M* records a signal evidencing the accumulation of DNA amplification products of mutant *EGFR* gene variants and deletions in exon 19.

The results are interpreted based on the presence (or absence) of intersection of the fluorescence curve with a threshold line set at an appropriate level, which determines the presence (or absence) of a threshold cycle value «C_t» for the given DNA sample.

Interpretation of results of control specimens

The result of the PCR-test is considered correct if reactions «Norm», «del», «L858R», «T790M» are held in tubes with relevant PC not later than 38 cycle.

Correct results for NTC mean absence of reaction in NTC tubes.

Interpretation of results in test samples

Interpretation of results for test specimens is performed only if results for NTC and PC are correct.

The obtained results are interpreted based on the data of fluorescent signal level relative to the background for the respective channels for control specimens and DNA samples isolated from the test specimens. The interpretation is performed using software of the device used.

The principle for interpretation of results is:

– the mutant DNA of *EGFR* gene is detected if for the given sample the signals by FAM channel in two specimen tubes out of three are higher than the preset threshold value and the signal by FAM channel in the tube *Norm* is higher than the preset threshold value.

– the mutant DNA of *EGFR* gene is not detected if the signal by FAM channel in three specimen tubes is lower than the mandatory threshold value for the given sample, and the signal by FAM channel in the tube *Norm* is higher than the mandatory threshold value.

– The testing result is invalid if the signal by FAM channel in the tube *Norm* is lower than the mandatory threshold value for the given sample.

If an invalid result is obtained for the sample, it is necessary to repeat PCR-test of the respective test specimen starting from repeated DNA isolation from the tissue/plasma specimen, or reject the sample as unsuitable for this type of testing.

- The testing result is doubtful if the signal by FAM channel in the tube *Norm* and the threshold cycle value "Ct" for this tube is more than 38 for the given sample, or the signals by FAM channel are higher than the preset threshold value only in one tube out of three.

If a doubtful result is obtained for the sample, it is required to repeat PCR-testing of the respective test sample. If the doubtful result is repeated, it is necessary to repeat PCR-testing of the respective test sample starting from repeated DNA isolation from the sample.

The kit is unsuitable for further use if the signal by FAM channel in the reaction mixtures *Norm* in PC tubes is lower than the preset threshold value and such result is steadily reproduced.

12. Storage, transportation and usage conditions

Storage. The kit of reagents shall be stored at a temperature from minus 18 to minus 25°C. Store on the working table at a temperature of +4 °C with the use of «ice-bath» for not more than 10 minutes. Avoid repeated thawing-freezing.

PCR Mix Norm, del, L858R, T790M store in a light-proof place.

Transportation. The kit of reagents shall be transported at a temperature from minus 18 to minus 25°C. It is permissible to transport the kit at a temperature from 2 to 8 °C for not more than 3 days or at a temperature of up to 25°C for not more than 1 day.

Shelf life. 12 months. The kit of reagents shall not be used after the expiry date.

Shelf life of opened kit components. 12 months, provided that the kit components are stored at a temperature from minus 18 to minus 25°C.

13. Utilization

Kits that have become unusable because of shelf life expiration, are subject to utilization in accordance with the requirements to the address with medical waste.

Liquid components are eliminated by draining into the sewage system with a preliminary watering of the reagent with tap water 1: 100 and removal of the rest of the packages as industrial or household garbage.

Consumer package of «Test-EGFR» kit is subject to mechanical destruction with removal of residues as industrial or household garbage.

Personnel carrying out the destruction of the kit must comply with the safety rules for carrying out a particular method of destruction.

14. Warranty obligations, contact information

The manufacturer guarantees the conformity of «Test-EGFR» kit to technical requirements under transportation, storage and operation conditions established by technical specification.
If there are any complaints regarding the quality, undesired events that may cause adverse event (incident), send the information to the address:

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