VENTANA pan-TRK (EPR17341) Assay

REF 790-7026

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IVD Σ 50

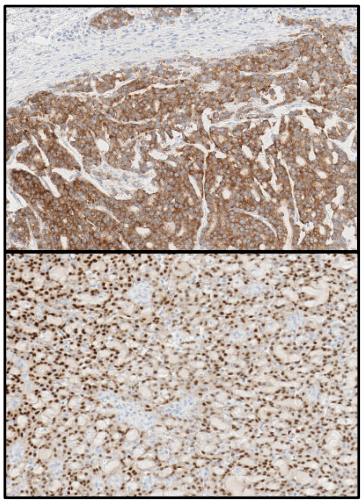

Figure 1. VENTANA pan-TRK (EPR17341) Assay staining of EML4-NTRK1 fusion in colorectal cancer (top) and ETV6-NTRK3 fusion in mammary analogue secretory carcinoma (bottom).

INTENDED USE

VENTANA pan-TRK (EPR17341) Assay is intended for the immunohistochemical detection of the C-terminal region of the tropomyosin receptor kinase (TRK) proteins A, B and C, which is known to be conserved across wild-type and chimeric fusion proteins, in formalin-fixed, paraffin-embedded (FFPE) neoplastic tissues stained with BenchMark IHC/ISH instruments.

This product should be interpreted by a qualified pathologist in conjunction with histological examination, relevant clinical information, and proper controls.

This antibody is intended for *in vitro* diagnostic (IVD) use.

SUMMARY AND EXPLANATION

VENTANA pan-TRK (EPR17341) Assay is a rabbit monoclonal primary antibody directed against the C-terminal region of TRK A, B and C proteins. In normal physiology, TRK receptors are preferentially expressed in tissues of neural origin, and help regulate cell differentiation and survival; they also play a physiological role in the development of the central and peripheral nervous systems.[1,2,3,4] Multiple isoforms of all three TRK proteins (A, B, and C) have been identified in neuronal and non-neuronal tissue. Many of these have truncations of the N-terminal or C-terminal regions.[5,6] This has, in part, resulted in inconsistencies in literature-reported prevalence of TRK protein expression across tissue types.

The antibody epitope of VENTANA pan-TRK (EPR17341) Assay is located downstream of the tyrosine kinase within the 3' region of the human neurotrophic tyrosine receptor kinase genes (NTRK 1, 2, and 3). The epitope is also conserved across all three of the TRK proteins. The assay has been designed to detect presence of C-terminal protein expression, and is thus able to detect TRK-fusion as well as wild-type protein expression.

Wild-type TRK protein expression in most solid tumors is generally minimal and of low prevalence. However, wild-type TRK protein expression can be substantial in some neuroendocrine tumor tissues.

Tumors harboring an NTRK fusion typically have appreciable levels of TRK domain expression. NTRK1, NTRK2, and NTRK3, which encode the TRK A, B, and C proteins, respectively, are oncogenes that can be activated and drive cancer progression when chromosomal rearrangements lead to their aberrant juxtaposition with other genes such as ETV6, EML4, LMNA, and TPM3. These oncogenic fusions generally retain the 3' region of NTRK encoding the full kinase domain and some 5' protein-coding sequence of an unrelated gene such as ETV6. The resulting overexpressed and constitutively active TRK fusion proteins in turn generate aberrant signaling through downstream pathways.[7,8,9] The ability of these fusion proteins to signal in a ligand-independent fashion has been shown to transform cells in preclinical models. TRK fusion proteins appear to demonstrate oncogene addiction behavior, similar to other fusion proteins in cancer, such as those involving ABL, ALK, and ROS1.[10]

NTRK fusion proteins have been identified in a wide range of commonly occurring tumors, such as lung cancer, thyroid cancer and sarcoma at low frequencies.[8,11-15] In very rare tumors, such as infantile fibrosarcoma, secretory/juvenile breast cancer, and mammary analogue secretory cancers (MASC, secretory carcinoma) of the salivary glands, NTRK fusion proteins are likely to be the defining genetic feature.[15-19]

The following fusion partner-specific staining patterns have been reported with this antibody clone: all 5 LMNA-NTRK1 fusions stained displayed nuclear membrane accentuation, all 4 TPM3 fusions stained displayed cellular membrane accentuation, and half (3/6) of ETV6-NTRK3 fusions displayed nuclear staining.[20]

Additional fusion partners have been reported in literature, but have not been tested with the VENTANA pan-TRK (EPR17341) Assay.[7,21,22]

PRINCIPLE OF THE PROCEDURE

VENTANA pan-TRK (EPR17341) Assay binds to the TRK epitope in paraffin-embedded tissue sections. The specific antibody can be visualized using OptiView DAB IHC Detection Kit (Cat. No. 760-700 / 06396500001). Refer to the OptiView DAB IHC Detection Kit package insert for further information.

In addition to staining with VENTANA pan-TRK (EPR17341) Assay, a second slide should be stained with Rabbit Monoclonal Negative Control Ig (Cat. No. 790-4795 / 06683380001).

REAGENT PROVIDED

VENTANA pan-TRK (EPR17341) Assay contains sufficient reagent for 50 tests.

One 5 mL dispenser of VENTANA pan-TRK (EPR17341) Assay contains approximately 140 µg of a rabbit monoclonal antibody.

The antibody is diluted in 0.05 M Tris buffered saline, 0.01 M EDTA, 0.05% Brij-35 with 0.3% carrier protein and 0.05% sodium azide, a preservative.

Total protein concentration of the reagent is approximately 10 mg/mL. Specific antibody concentration is approximately 28 µg/mL. There is no known non-specific antibody reactivity observed in this product.

VENTANA pan-TRK (EPR17341) Assay is produced as a Protein A purified recombinant rabbit monoclonal antibody.

Refer to the OptiView DAB IHC Detection Kit package insert for detailed descriptions of: Principle of the Procedure, Material and Methods, Specimen Collection and Preparation for Analysis, Quality Control Procedures, Troubleshooting, Interpretation of Results, and General Limitations.

MATERIALS REQUIRED BUT NOT PROVIDED

Staining reagents, such as VENTANA detection kits and ancillary components, including negative and positive tissue control slides, are not provided.

Not all products listed in the package insert may be available in all geographies. Consult your local support representative.

The following reagents and materials may be required for staining but are not provided:

1. Recommended control tissue
2. Microscope slides, positively charged
3. Drying oven capable of maintaining a temperature of 60°C ± 5°C
4. Bar code labels
5. Xylene (Histological grade)
6. Ethanol or reagent alcohol (Histological grade)
   - 100% solution: Undiluted ethanol or reagent alcohol
   - 95% solution: Mix 95 parts of ethanol or reagent alcohol with 5 parts of deionized water
   - 80% solution: Mix 80 parts of ethanol or reagent alcohol with 20 parts of deionized water
7. Deionized or distilled water
8. Rabbit Monoclonal Negative Control Ig (Cat. No. 790-4795 / 06683380001)
9. OptiView DAB IHC Detection Kit (Cat. No. 760-700 / 06396500001)
10. EZ Prep Concentrate (10X) (Cat. No. 950-102 / 05279771001)
11. Reaction Buffer Concentrate (10X) (Cat. No. 950-300 / 05353955001)
12. LCS (Predilute) (Cat. No. 650-010 / 05264839001)
13. ULTRA LCS (Predilute) (Cat. No. 650-210 / 05424534001)
14. Cell Conditioning Solution (CC1) (Cat. No. 950-124 / 05279801001)
15. ULTRA Cell Conditioning Solution (ULTRA CC1) (Cat. No. 950-224 / 05424569001)
16. Hematoxylin II (Cat. No. 790-2208 / 05277965001)
17. Bluing Reagent (Cat. No. 760-2037 / 05266769001)
18. Permanent mounting medium (Permount Fisher Cat. No. SP15-500 or equivalent)

19. Cover glass (sufficient to cover tissue, such as VWR Cat. No. 48393-060)
20. Automated coverslipper (such as the Tissue-Tek SCA Automated Coverslipper)

STORAGE

Upon receipt and when not in use, store at 2-8°C. Do not freeze.

To ensure proper reagent delivery and the stability of the antibody, replace the dispenser cap after every use and immediately place the dispenser in the refrigerator in an upright position.

Every antibody dispenser is expiration dated. When properly stored, the reagent is stable to the date indicated on the label. Do not use reagent beyond the expiration date.

SPECIMEN PREPARATION

Routinely processed, formalin-fixed, paraffin-embedded tissues are suitable for use with this primary antibody when used with VENTANA detection kits and BenchMark IHC/ISH instruments. The recommended tissue fixative is 10% neutral buffered formalin.[23] Slides should be stained immediately, as antigenicity of cut tissue sections may diminish over time.

It is recommended that positive and negative controls be run simultaneously with unknown specimens.

WARNINGS AND PRECAUTIONS

1. For *in vitro* diagnostic (IVD) use.
2. For professional use only.
3. When used according to instructions, this product is not classified as a hazardous substance. The preservative in the reagent is sodium azide. Symptoms of overexposure to sodium azide include skin and eye irritation, and irritation of mucous membranes and upper respiratory tract. The concentration of sodium azide in this product is 0.05% and does not meet the OSHA criteria for a hazardous substance. Build-up of sodium azide may react with lead and copper plumbing to form highly explosive metal azides. Upon disposal, flush with large volumes of water to prevent azide accumulation in plumbing.[24] Systemic allergic reactions are possible in sensitive individuals.
4. Positively charged slides may be susceptible to environmental stresses resulting in inappropriate staining of any IHC assay (for example, lack of primary antibody or counterstain on the tissue). Ask your Roche representative for a copy of "Impacts of Environmental Stresses on IHC Positively Charged Slides" to better understand how to use these types of slides.
5. Materials of human or animal origin should be handled as biohazardous materials and disposed of with proper precautions.
6. Avoid contact of reagents with eyes and mucous membranes. If reagents come in contact with sensitive areas, wash with copious amounts of water.
7. Avoid microbial contamination of reagents as it may cause incorrect results.
8. Consult local and/or state authorities with regard to recommended method of disposal.
9. For supplementary safety information, refer to the product Safety Data Sheet and the Symbol and Hazard Guide located at www.ventana.com.

STAINING PROCEDURE

VENTANA primary antibodies have been developed for use on BenchMark IHC/ISH instruments in combination with VENTANA detection kits and accessories. Refer to Table 1 for recommended staining protocols.

This antibody has been optimized for specific incubation times but the user must validate results obtained with this reagent.

The parameters for the automated procedures can be displayed, printed and edited according to the procedure in the instruments Operator's Manual. Refer to the OptiView DAB IHC Detection Kit package insert for more details regarding immunohistochemistry staining procedures.

Table 1. Recommended staining protocol for VENTANA pan-TRK (EPR17341) Assay with OptiView DAB IHC Detection Kit on BenchMark IHC/ISH instruments.

Procedure Type	Method	
	GX and XT	ULTRA
Deparaffinization	Selected	Selected
Cell Conditioning (Antigen Unmasking)	CC1, 92 minutes	ULTRA CC1 88 minutes, 100°C
Antibody (Primary) or Rabbit Monoclonal Negative Control Ig	32 minutes, 37°C	16 minutes, 36°C
Pre-primary Peroxidase Inhibitor	Selected	
Counterstain	Hematoxylin II, 4 minutes	
Post Counterstain	Bluing, 4 minutes	

Due to variation in tissue fixation and processing, as well as general lab instrument and environmental conditions, it may be necessary to increase or decrease the primary antibody incubation, cell conditioning or protease pretreatment based on individual specimens, detection used, and reader preference. For further information on fixation variables, refer to "Immunohistochemistry Principles and Advances".[25]

POSITIVE TISSUE CONTROL

Optimal laboratory practice is to include a positive control section on the same slide as the test tissue. This helps identify any failures applying reagents to the slide. Tissue with weak positive staining is best suited for quality control. Control tissue may contain both positive and negative staining elements and serve as both the positive and negative control. Control tissue should be fresh autopsy, biopsy, or surgical specimen, prepared or fixed as soon as possible.

Known positive tissue controls should be utilized only for monitoring performance of reagents and instruments, not as an aid in determining specific diagnosis of test samples. If the positive tissue controls fail to demonstrate positive staining, results of the test specimen should be considered invalid.

Examples of positive control tissues for this antibody are cerebellum or appendix.

STAINING INTERPRETATION / EXPECTED RESULTS

Staining with the VENTANA pan-TRK (EPR17341) Assay was observed in multiple localizations (nuclear, cytoplasmic and membranous).

SPECIFIC LIMITATIONS

The VENTANA pan-TRK (EPR17341) Assay has not been optimized to delineate between TRK wild-type and chimeric-fusion proteins.

This antibody has been optimized for a 16-minute incubation time on the VENTANA BenchMark ULTRA instrument and 32-minute incubation time on the BenchMark GX and BenchMark XT instruments in combination with the OptiView DAB IHC Detection Kit, but the user must validate results obtained with this reagent.

Sections approximately 3-6 µm in thickness should be cut and mounted on positively charged slides.

All assays might not be registered on every instrument. Please contact your local Roche representative for more information.

PERFORMANCE CHARACTERISTICS

Staining tests for specificity, sensitivity, and repeatability were conducted and the results are listed in Table 2, Table 3, Table 4, Table 5, and in the Precision section.

Sensitivity and Specificity

Table 2. Specificity of VENTANA pan-TRK (EPR17341) Assay was determined by testing formalin-fixed, paraffin-embedded normal tissues.

Tissue	# positive / total cases	Tissue	# positive / total cases
Adrenal gland	0/3	Nerve	0/2
Bladder	0/23	Ovary	0/2
Breast	0/3	Pancreas	0/3
Cerebellum	3/3	Parathyroid	0/3
Cerebrum	3/3	Pericardium (Cardiac)	0/1
Cervix	0/1	Prostate	0/4
Colon	0/15	Salivary gland	0/3
Endometrium (Uterus)	0/2	Skeletal muscle	0/1
Esophagus	0/3	Skin	0/2
Heart	0/3	Small intestine	0/3
Hypophysis	3/3	Spleen	0/3
Kidney	0/3	Stomach	0/3
Liver	0/3	Testis	0/3
Lung	0/3	Thymus gland	0/3
Lymph node	0/2	Thyroid	0/13
Mesothelium (Cardiac)	0/1	Tonsil	0/3
Myeloid (Bone Marrow)	0/3		

Table 3. Sensitivity of the VENTANA pan-TRK (EPR17341) Assay was determined by testing a variety of formalin-fixed, paraffin-embedded neoplastic tissues.

Pathology	# positive / total cases
Adenocarcinoma (Bladder)	0/2
Adenocarcinoma (Colorectal)	0/98
Adenocarcinoma (Esophagus)	0/1
Adenocarcinoma (Lung)	0/1
Adenocarcinoma (Prostate)	0/2
Adenocarcinoma (Small Intestine)	0/1
Basal Cell Carcinoma (Skin)	0/1
Border Nevus (Skin)	0/1
Clear Cell Carcinoma (Kidney)	0/1
Clear Cell Carcinoma (Uterus)	0/1
Compound Nevus (Skin)	0/8
Dermatofibrosarcoma Protuberans (Fibrous tissue)	0/10
Diffuse B-Cell Lymphoma (Lymph Node)	0/2
Diffuse B-Cell Lymphoma (Spleen)	0/1
Ductal Adenocarcinoma (Pancreas)	0/1
Embryonal Carcinoma (Testis)	0/1
Embryonal Rhabdomyosarcoma (Striated Muscle)	1/1
Endometrioid Adenocarcinoma (Uterus)	0/1
Fibrosarcoma (Fibrous Tissue)	0/8
Gastrointestinal Stromal Tumor (GIST) (Colorectal)	0/2
Gastrointestinal Stromal Tumor (GIST) (Small Intestine)	1/1
Glioblastoma (Cerebrum)	1/2
Hepatoblastoma (Liver)	0/1
Hepatocellular Carcinoma (Liver)	0/1
Hodgkin's Lymphoma (Lymph Node)	0/1
Intradermal Nevus (Skin)	0/6
Intraductal Carcinoma (Breast)	0/1
Invasive Ductal Carcinoma (Breast)	0/2
Islet Cell Tumor (Pancreas)	0/1
Leiomyosarcoma (Bladder)	0/1
Leiomyosarcoma (Smooth muscle)	1/19
Liposarcoma (Adipose)	0/18
Malignant Melanoma (Esophagus)	0/2
Malignant Melanoma (Rectum)	0/13
Malignant Melanoma (Skin)	0/42
Malignant Melanoma (Stomach)	0/2
Malignant Melanoma (Vulva)	0/4
Malignant Mesothelioma (Peritoneum)	0/1
Medullary Carcinoma (Thyroid)	0/1
Meningioma (Cerebrum)	1/1
Metastatic Malignant Melanoma (Lymph Node)	0/21
Mucinous Adenocarcinoma (Colorectal)	0/7
Mucinous Adenocarcinoma (Ovary)	0/1
Mucinous Adenocarcinoma (Stomach)	0/1
Neuroblastoma (Retroperitoneum)	1/1
Neurofibroma (Nerve)	0/1
Papillary Adenocarcinoma (Colorectal)	0/2
Papillary Carcinoma (Thyroid)	1/45
Pleomorphic Rhabdomyosarcoma (Retroperitoneum)	0/1
Rhabdomyosarcoma (Skeletal Muscle)	2/19
Sebaceous Nevus (Skin)	0/1

Pathology	# positive / total cases
Seminoma (Testis)	0/1
Serous Papillary Adenocarcinoma (Ovary)	0/1
Signet Ring Cell Carcinoma (Colorectal)	0/2
Small Cell Undifferentiated Carcinoma (Lung)	0/1
Squamous Cell Carcinoma (Bladder)	0/1
Squamous Cell Carcinoma (Cervix)	0/2
Squamous Cell Carcinoma (Esophagus)	0/1
Squamous Cell Carcinoma (Lung)	0/1
Squamous Cell Carcinoma (Skin)	0/1
Thyroid Follicular Carcinoma (Thyroid)	0/19
Undifferentiated Carcinoma (Thyroid)	0/6
Urothelial Carcinoma (Bladder)	0/58

Table 4. Protein expression detected using VENTANA pan-TRK (EPR17341) Assay in cell lines containing TRK fusions.

Pathology	Fusion Type	Detected by VENTANA pan-TRK (EPR17341) Assay
Colorectal Carcinoma	KM-12* (TPM3-NTRK1)[21,26-28]	✓
Acute Myeloid Leukemia	MO-91* (ETV6-NTRK3)[28,29]	✓

*tumor derived cell lines

Table 5. Protein expression detected using VENTANA pan-TRK (EPR17341) Assay in tumors containing TRK fusions. Next generation sequencing reported from external laboratory developed test using Oncomine Focus Assay[30-33]

Pathology	Fusion Type	Detected by VENTANA pan-TRK (EPR17341) Assay
Colorectal Carcinoma	TPM3-NTRK1	✓
	EML4-NTRK1	
Mammary Analogue Secretory Carcinoma (MASC)	ETV6-NTRK3	✓

Precision

Precision studies for the VENTANA pan-TRK (EPR17341) Assay were completed to demonstrate:

- Between lot precision of the antibody.
- Within run and between day precision on a BenchMark GX, BenchMark XT, BenchMark ULTRA instrument.
- Between instrument precision on the BenchMark GX, BenchMark XT, BenchMark ULTRA instrument.
- Between platform precision between the BenchMark GX, BenchMark XT, BenchMark ULTRA instrument.

All studies met their acceptance criteria.

REFERENCES

1. Barbacid M, Lamballe F, Pulido D, Klein R. The trk family of tyrosine protein kinase receptors. Biochim Biophys Acta. 1991;1072(2-3):115-27.
2. Barbacid M. Structural and functional properties of the TRK family of neurotrophin receptors. Ann NY Acad Sci. 1995;766:442-58.
3. Lemmon MA, Schlessinger J. Cell signaling by receptor tyrosine kinases. Cell. 2010;141(7):1117-34. (doi: 10.1016/j.cell.2010.06.011)
4. Klein R, Jing SQ, Nanduri V, O'Rourke E, Barbacid M. The trk proto-oncogene encodes a receptor for nerve growth factor. Cell. 1991;65(1):189-97.
5. Eide FF, Vining ER, Eide BL, Zang K, Wang XY, Reichardt LF. Naturally occurring truncated trkB receptors have dominant inhibitory effect on brain-derived neurotrophic factor signaling. J Neurosci. 1996;16(10):3123-29.
6. Luberg K, Park R, Aleksejeva E, Timmusk T. Novel transcripts reveal a complex structure of the human TRKA gene and imply the presence of multiple protein isoforms. BMC Neurosci. 2015;16:78. (doi: 10.1186/s12868-015-0215-x)
7. Greco A, Mariani C, Miranda C, et al. The DNA rearrangement that generates the TRK-T3 oncogene involves a novel gene on chromosome 3 whose product has potential coiled-coil domain. Mol Cell Biol. 1995;15(11)6118-27.
8. Bongarzone I, Vigneri P, Mariani L, Collini P, Pilotti S, Pierotti MA. RET/NTRK1 rearrangements in thyroid gland tumors of the papillary carcinoma family: correlation with clinicopathological features. Clin Cancer Res. 1998;4(1):223-8.
9. Stransky N, Cerami E, Schalm S, Kim JL, Lengauer C. The landscape of kinase fusions in cancer. Nat Commun. 2014;5:4846. (doi: 10.1038/ncomms5846)
10. Brzezińska E, Karbownik M, Migdalska-Sek M, Pastuszak-Lewandoska D, Włoch J, Lewiński A. Molecular analysis of the RET and NTRK1 gene rearrangements in papillary thyroid carcinoma in the Polish population. Mutat Res. 2006;599(1-2):26-35.
11. De Braud FG, Pilla L, Niger M, et al. Phase 1 open label, dose escalation study of RXDX101, an oral pan-trk, ROS1, and ALK inhibitor, in patients with advanced solid tumors with relevant molecular alterations: Journal of Clinical Oncology - published online before print January 31, 2017. (doi: 10.1200/jco.2014.32.15_suppl.2502)
12. Fernandez-Cuesta L, Peifer M, Lu X, et al. Cross-entity mutation analysis of lung neuroendocrine tumors sheds light into their molecular origin and identifies new therapeutic targets. [abstract]. In: Proceedings of the 105th Annual Meeting of the American Association for Cancer Research; 2014 Apr 5-9; San Diego, CA. Philadelphia (PA): AACR; Cancer Res 2014;74(19 Suppl):Abstract nr 1531. (doi: 10.1158/1538-7445.AM2014-1531)
13. Leeman-Neill RJ, Kelly LM, Liu P, et al. ETV6-NTRK3 is a common chromosomal rearrangement in radiation-associated thyroid cancer. Cancer. 2014;120(6):799-807.
14. Ross J.S, Wang K, Gay L, et al. New routes to targeted therapy of intrahepatic cholangiocarcinomas revealed by next-generation sequencing. Oncologist. 2014;19(3):235-42.
15. Argani PM, Fritsch M, Kadkoi SS, et al. Detection of the ETV6-NTRK3 chimeric RNA of infantile fibrosarcoma/cellular congenital mesoblastic nephroma in paraffin-embedded tissue: application to challenging pediatric renal stromal tumors. Mod Pathol. 2000;13(1):29-36.
16. Bishop JA, Yonescu R, Batista D, Begum S, Eisele DW, Westra WH. Utility of mammaglobin immunohistochemistry as a proxy marker for the ETV6-NTRK3 translocation in the diagnosis of salivary mammary analogue secretory carcinoma. Hum Pathol. 2013;44(10):1982-8.
17. Bourgeois JM, Knezevich SR, Mathers JA, Sorensen PH. Molecular detection of the ETV6-NTRK3 gene fusion differentiates congenital fibrosarcoma from other childhood spindle cell tumors. Am J Surg Pathol. 2000;24(7):937-46.
18. Rubin BP, Chen CJ, Morgan TW, et al. Congenital mesoblastic nephroma t(12;15) is associated with ETV6-NTRK3 gene fusion: cytogenetic and molecular relationship to congenital (infantile) fibrosarcoma. Am J Pathol. 1998;153(5):1451-8.
19. Tognon C, Knezevich SR, Huntsman D, et al. Expression of the ETV6-NTRK3 gene fusion as a primary event in human secretory breast carcinoma. Cancer Cell. 2002;2(5):367-76.
20. Hechtman JF, Benayed R, Hyman DM, et al. Pan-Trk immunohistochemistry is an efficient and reliable screen for the detection of NTRK fusions. Am J Surg Pathol. 2017;41(11):1547-51.
21. Vaishnavi A, Capelletti M, Le AT, et al. Oncogenic and drug-sensitive NTRK1 rearrangements in lung cancer.Nat Med. 2013;19(11):1469-1472.

22. Passiglia F, Caparica R, Giovannetti E, et al. The potential of neurotrophic tyrosine kinase (NTRK) inhibitors for treating lung cancer. Expert Opin Investig Drugs. 2016;25(4):385-92.
23. Carson F, Hladik C. Histotechnology: A Self Instructional Text, 3rd edition. Hong Kong: American Society for Clinical Pathology Press; 2009.
24. Department of Health, Education and Welfare, National Institute of Occupational Safety and Health, Rockville, MD. Procedures for the decontamination of plumbing systems containing copper and/or lead azides. DHHS (NIOSH) Publ No. 78-127, Current 13. August 16, 1976.
25. Roche PC, Hsi ED. Immunohistochemistry-Principles and Advances. Manual of Clinical Laboratory Immunology, 6th edition. In: NR Rose, ed. ASM Press; 2002.
26. Creancier L, Vandenberghe I, Gomes B, et al. Chromosomal rearrangements involving the NTRK1 gene in colorectal carcinoma. Cancer Letters. 2015;365:107-111.
27. Murphy D, Ely H, Shoemaker R, et al. Detecting gene rearrangements in patient populations through a 2-step diagnostic test comprised of rapid IHC enrichment followed by sensitive next-generation sequencing. Appl Immunohistochem Mol Morphol. 2017; 25(7): 513-523.
28. Doebele RC, Davis LE, Vaishnavi A, et al. An onogenic NTRK fusion in soft tissue sarcoma patient with response to the tryopomyosin-related kinase (TRK) inhibitor LOXO-101. Cancer Discovery. 2015;5(10):1049-57.
29. Taipale M, Krykbaeva I, Whitesell L, et al. Chaperones as thermodynamic sensors of drug-target interactions reveal kinase inhibitor specificities in living cells. Nat Biotech. 2013;31:630-7.
30. Passinen-Sohns A, Koelzer VH, Frank A, et al. Single-Center Experience with a Targeted Next Generation Sequencing Assay for Assessment of Relevant Somatic Alterations in Solid Tumors. Neoplasia. 2017;19(3):196-206.
31. Oncomine™ Focus Assay, Part I: Library Preparation USER GUIDE. Document number: MAN0015819.B.0.
32. Oncomine™ Focus Assay Part II: Plan a Run, Template Preparation, and Sequencing USER GUIDE. Document number. MAN0015820.A.0.
33. Velizheva NP, Rechsteiner MP, Valtcheva N, et al. Targeted next-generation-sequencing for reliable detection of targetable rearrangements in lung adenocarcinoma—a single center retrospective study. Path research and prac. 2018;214:572-578.

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