anti-PRAME (EPR20330) Rabbit Monoclonal Primary Antibody

REF 790-7149

09592237001

IVD Σ 50

REF 790-7150

09592245001

IVD Σ 250

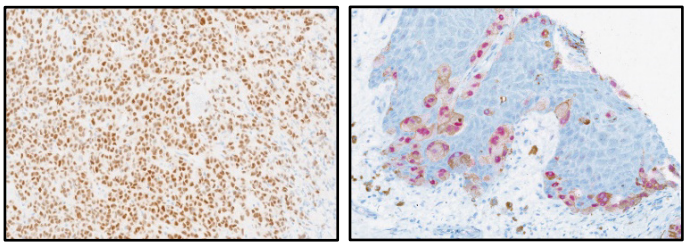

Figure 1. Anti-PRAME (EPR20330) antibody staining of melanoma with OptiView DAB IHC Detection Kit (left) and staining of melanoma with *ultra*View Universal Alkaline Phosphatase Red Detection Kit (right).

INTENDED USE

Anti-PRAME (EPR20330) Rabbit Monoclonal Primary Antibody (anti-PRAME (EPR20330) antibody) is intended for laboratory use in the qualitative immunohistochemical detection of PRAME by light microscopy in sections of formalin-fixed, paraffin-embedded tissue stained on a BenchMark IHC/ISH instrument.

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

Preferentially expressed antigen in melanoma (PRAME) is a 58 kDa cancer testis antigen and is located on chromosome 22 (22q11.22).[1] First characterized in 1997, the *PRAME* gene encodes the human leucocyte antigen HLA-A24.[2,3] PRAME is typically not expressed in normal human tissues, with the exception of testes, though limited expression in ovary, placenta, adrenal gland, and endometrium has been observed.[2,4] Cellular expression of PRAME has been detected in the nuclear and cytoplasmic compartments as well as on the cell membrane.[5-8] The variance in cellular distribution is not understood; however, different epitopes of the PRAME gene may be disparately expressed depending on cell type and physiological condition.[8] Under normal physiological conditions, PRAME is a transcriptional regulator involved in germline development and gametogenesis.[9] Beyond embryogenesis, the function of PRAME in normal human tissues is not yet well understood. When overexpressed, PRAME is a dominant repressor of retinoic acid receptor signaling and inhibits retinoic acid-induced differentiation, growth arrest, and apoptosis; contributing to tumorigenesis.[5]

Melanocytic neoplasms are a heterogeneous group of lesions that include benign and malignant tumors, which are categorized and subtyped according to the World Health Organization guidelines.[10,11] PRAME is generally overexpressed in melanomas (i.e., malignant melanocytic tumors). When immunoreactivity is considered diffuse (i.e., nuclear staining in > 75% of tumor cells), PRAME expression has been observed in 50-100% of malignant melanomas, excluding desmoplastic subtypes.[4,13-17,20,22-25] Additional studies have reported 92% and 94% of malignant melanoma cases expressed PRAME, although the threshold for positivity was lower (i.e., nuclear staining in 50% and 60% of tumor cells).[18,19]

Benign nevi are clonal proliferations of melanocytic cells with mutated oncogenes that are often considered simulators of melanoma with low malignant potential.[10,11] The majority of benign nevi lack nuclear PRAME staining; although, some of these melanocytic lesions exhibit what is described as focal immunoreactivity (i.e., ≤ 75% nuclear staining in tumor cells). When > 75% is used as the threshold for positivity, 90-100% of benign nevi specimens are either negative or focally positive for PRAME.[4,13,14,16,18,20,21,24,25,27-30] Therefore, the detection of PRAME by IHC with anti-PRAME (EPR20330) antibody may be used as an aid to differentiate between benign and malignant melanocytic neoplasms. This antibody may complement findings from routinely used H&E and ancillary IHC panels.

PRINCIPLE OF THE PROCEDURE

Anti-PRAME (EPR20330) antibody binds to the PRAME antigen in formalin-fixed, paraffin-embedded (FFPE) tissue sections. This antibody can be visualized using OptiView DAB IHC Detection Kit (Cat. No. 760-700 / 06396500001), *ultra*View Universal Alkaline Phosphatase Red Detection Kit (Cat. No. 760-501/ 05269814001) or *ultra*View Universal DAB Detection Kit (Cat. No. 760-500 / 05269806001). Refer to the respective method sheet for further information

MATERIAL PROVIDED

Anti-PRAME (EPR20330) antibody contains sufficient reagent for 50 tests.

One 5 mL dispenser of anti-PRAME (EPR20330) antibody contains approximately 58.5 µg of a rabbit monoclonal antibody.

Anti-PRAME (EPR20330) antibody contains sufficient reagent for 250 tests.

One 25 mL dispenser of anti-PRAME (EPR20330) antibody contains approximately 292.5 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.

Specific antibody concentration is approximately 11.7 µg/mL. There is no known non-specific antibody reactivity observed in this product.

Anti-PRAME (EPR20330) antibody is a recombinant species monoclonal antibody produced as purified cell culture supernatant.

Refer to the appropriate VENTANA detection kit method sheet 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 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 method sheet 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. Rabbit Monoclonal Negative Control Ig (Cat. No. 790-4795 / 06683380001)
4. OptiView DAB IHC Detection Kit (Cat. No. 760-700 / 06396500001)
5. *ultra*View Universal Alkaline Phosphatase Red Detection Kit (Cat. No. 760-501 / 05269814001)
6. *ultra*View Universal DAB Detection Kit (Cat. No. 760-500 / 05269806001)
7. Amplification Kit (Cat. No. 760-080 / 05266114001 (50 test))
8. EZ Prep Concentrate (10X) (Cat. No. 950-102 / 05279771001)
9. Reaction Buffer Concentrate (10X) (Cat. No. 950-300 / 05353955001)
10. LCS (Predilute) (Cat. No. 650-010 / 05264839001)
11. ULTRA LCS (Predilute) (Cat. No. 650-210 / 05424534001)
12. Cell Conditioning Solution (CC1) (Cat. No. 950-124 / 05279801001)
13. ULTRA Cell Conditioning Solution (ULTRA CC1) (Cat. No. 950-224 / 05424569001)
14. Hematoxylin II (Cat. No. 790-2208 / 05277965001)
15. Bluing Reagent (Cat. No. 760-2037 / 05266769001)
16. Antibody Diluent (Cat. No. 251-018 / 05261899001)
17. General purpose laboratory equipment
18. BenchMark IHC/ISH instrument

STORAGE AND STABILITY

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 FFPE 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.[31] Sections should be cut at approximately 4 µm in thickness and mounted on positively charged slides. 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. **CAUTION**: In the United States, Federal law restricts this device to sale by or on the order of a physician. (Rx Only)
4. Do not use beyond the specified number of tests.
5. Positively charged slides may be susceptible to environmental stresses resulting in inappropriate staining. Ask your Roche representative for more information on how to use these types of slides.
6. Materials of human or animal origin should be handled as biohazardous materials and disposed of with proper precautions. In the event of exposure, the health directives of the responsible authorities should be followed.[32,33]
7. Avoid contact of reagents with eyes and mucous membranes. If reagents come in contact with sensitive areas, wash with copious amounts of water.
8. Avoid microbial contamination of reagents as it may cause incorrect results.
9. For further information on the use of this device, refer to the BenchMark IHC/ISH instrument User Guide, and instructions for use of all necessary components located at dialog.roche.com.
10. Consult local and/or state authorities with regard to recommended method of disposal.
11. Product safety labeling primarily follows EU GHS guidance. Safety data sheet available for professional user on request.
12. To report suspected serious incidents related to this device, contact the local Roche representative and the competent authority of the Member State or Country in which the user is established.

STAINING PROCEDURE

Anti-PRAME (EPR20330) antibody has been developed for use on BenchMark IHC/ISH instruments in combination with VENTANA detection kits and accessories. Refer to the tables below 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 instrument User Guide. Refer to the appropriate VENTANA detection kit method sheet for more details regarding immunohistochemistry staining procedures.

For more details on the proper use of this device, refer to the inline dispenser method sheet associated with P/N 790-7149 and P/N 790-7150.

Table 1. Recommended staining protocol for anti-PRAME (EPR20330) antibody with OptiView DAB IHC Detection Kit on BenchMark IHC/ISH instruments.

Procedure Type	Method		
	GX	XT	ULTRA or ULTRA PLUS [a]
Deparaffinization	Selected	Selected	Selected
Cell Conditioning (Antigen Unmasking)	CC1, 64 minutes,	CC1, 64 minutes,	ULTRA CC1, 64 minutes, 100 °C
Antibody (Primary)	32 minutes, 37 °C	48 minutes, 37 °C	32 minutes, 36 °C
Pre-Primary Peroxidase Inhibitor	Selected		
Counterstain	Hematoxylin II, 4 minutes		
Post Counterstain	Bluing, 4 minutes		

[a] Concordance was demonstrated between BenchMark ULTRA and BenchMark ULTRA PLUS instruments using representative assays.

Table 2. Recommended staining protocol for anti-PRAME (EPR20330) antibody with *ultra*View Universal DAB Detection Kit on BenchMark IHC/ISH instruments.

Procedure Type	Method		
	GX	XT	ULTRA or ULTRA PLUS [a]
Deparaffinization	Selected	Selected	Selected
Cell Conditioning (Antigen Unmasking)	CC1, Standard	CC1, Standard	ULTRA CC1, Standard, 95 °C
Antibody (Primary)	32 minutes, 37 °C	32 minutes, 37 °C	32 minutes, 36 °C
Amplification	Selected	Selected	Selected (Rabbit Amp)
ultraBlock with Antibody Diluent	none	none	8 minutes
Counterstain	Hematoxylin II, 4 minutes		
Post Counterstain	Bluing, 4 minutes		

[a] Concordance was demonstrated between BenchMark ULTRA and BenchMark ULTRA PLUS instruments using representative assays.

Table 3. Recommended staining protocol for anti-PRAME (EPR20330) antibody with *ultra*View Universal Alkaline Phosphatase Red Detection Kit on BenchMark IHC/ISH instruments.

Procedure Type	Method		
	GX	XT	ULTRA or ULTRA PLUS [a]
Deparaffinization	Selected	Selected	Selected
Cell Conditioning (Antigen Unmasking)	CC1, Standard	CC1, Standard	ULTRA CC1, Standard, 95 °C
Antibody (Primary)	32 minutes, 37 °C	32 minutes, 37 °C	32 minutes, 36 °C
Amplification	Selected	Selected	none
ultraBlock with Antibody Diluent	8 minutes	8 minutes	none
Counterstain	Hematoxylin II, 4 minutes		

Procedure Type	Method		
	GX	XT	ULTRA or ULTRA PLUS [a]
Post Counterstain	Bluing, 4 minutes		

[a] Concordance was demonstrated between BenchMark ULTRA and BenchMark ULTRA PLUS instruments using representative assays.

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." [34]

NEGATIVE REAGENT CONTROL

In addition to staining with anti-PRAME (EPR20330) antibody, a second slide should be stained with the appropriate negative control reagent. The negative tissue control should be used only to monitor performance of processed tissues, test reagents, and instruments and not as an aid in formulating a specific diagnosis of the test specimen.

POSITIVE TISSUE CONTROL

A positive tissue control must be included with every staining run. 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 in a manner identical to test sections.

Known positive tissue controls should be utilized only for monitoring the correct 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 normal testis and positively staining melanomas.

STAINING INTERPRETATION / EXPECTED RESULTS

The cellular staining pattern for anti-PRAME (EPR20330) antibody is nuclear in seminiferous tubules of testis and tumor cells of melanoma. Membranous staining in Leydig cells of testis and cytoplasmic staining in sebaceous glands of skin may also be present. Nuclear staining may also be present in squamous cells and lymphocytes.

SPECIFIC LIMITATIONS

OptiView DAB IHC Detection Kit is generally more sensitive than *ultra*View Universal DAB Detection Kit and *ultra*View Universal Alkaline Phosphatase Red Detection Kit. The user must validate the results obtained with this reagent and detection systems.

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

PERFORMANCE CHARACTERISTICS

ANALYTICAL PERFORMANCE

Staining tests for sensitivity, specificity, and precision were conducted and the results are listed below.

Sensitivity and Specificity

Table 4. Sensitivity/Specificity of anti-PRAME (EPR20330) antibody was determined by testing FFPE normal tissues.

Tissue	# positive / total cases	Tissue	# positive / total cases
Cerebrum	0/3	Small intestine	0/4
Cerebellum	0/4	Colon	0/4
Brain [a]	1/1	Rectum	0/3
Adrenal gland [b,c]	1/4	Liver	0/4
Ovary	0/4	Salivary gland	0/3
Pancreas	0/4	Kidney	0/6
Parathyroid gland	0/3	Prostate	0/4
Pituitary gland	0/3	Bladder	0/3
Testis [d]	13/15	Ureter	0/2
Thyroid	0/4	Endometrium [g]	3/4
Breast [e]	1/3	Fallopian tube	0/3
Spleen	0/3	Placenta	0/3
Tonsil	0/3	Cervix	0/4
Thymus [f]	1/3	Skeletal muscle	0/3
Bone marrow	0/3	Skin	0/13
Lung	0/4	Nerve	0/3
Heart	0/3	Spinal cord	0/2
Esophagus	0/4	Mesothelium	0/3
Stomach	0/4		

[a] Weak staining of neurons
[b] Tissue evaluated includes normal and hyperplasia.
[c] Medullary cells
[d] Germ cells of seminiferous tubules
[e] Scattered ductal and lobular epithelial cells
[f] Rare epithelial cells
[g] Glandular epithelial cells

Table 5. Sensitivity/Specificity of anti-PRAME (EPR20330) antibody was determined by testing a variety of FFPE neoplastic tissues.

Pathology	# positive / total cases
Meningioma (Cerebellum)	0/2
Meningioma (Brain)	0/1
Astrocytoma (Brain)	0/1
Adenocarcinoma (Head and neck)	0/1
Squamous cell carcinoma (Head and neck)	0/1
Adenoma (Adrenal gland)	0/1
Adrenocortical carcinoma (Adrenal gland)	0/1
Granulosa cell tumor (Ovary)	0/1
Adenocarcinoma (Ovary)	0/1
Endometrioid adenocarcinoma (Ovary)	1/1
Adenocarcinoma (Pancreas)	0/1
Seminoma (Testis)	0/2

Pathology	# positive / total cases
Adenoma (Thyroid)	0/3
Follicular carcinoma (Thyroid)	0/1
Papillary adenocarcinoma (Thyroid)	0/1
Fibroadenoma (Breast)	0/2
Invasive ductal carcinoma (Breast)	0/3
Metastatic breast ductal carcinoma (Lymph node)	0/1
Small cell carcinoma (Lung)	0/1
Squamous cell carcinoma (Lung)	0/2
Adenocarcinoma (Lung)	1/1
Metastatic cancer (Lung)	0/1
Squamous cell carcinoma (Esophagus)	0/3
Metastatic esophagus squamous cell carcinoma (Lymph node)	0/1
Adenocarcinoma (Stomach)	1/3
Adenoma (Small intestine)	0/1
Adenocarcinoma (Small intestine)	0/1
Adenoma (Colon)	0/1
Adenocarcinoma (Colon)	0/3
Metastatic colon signet ring cell carcinoma (Ovary)	0/1
Metastatic colon adenocarcinoma (Liver)	0/1
Adenocarcinoma (Rectum)	0/3
Hepatocellular carcinoma (Liver)	0/4
Pleomorphic adenoma (Head and neck, salivary gland)	0/1
Adenoid cystic carcinoma (Head and neck, salivary gland)	1/1
Clear cell carcinoma (Kidney)	0/2
Adenocarcinoma (Prostate)	0/2
Squamous cell carcinoma (Cervix)	0/2
Adenocarcinoma (Endometrium)	2/2
Squamous cell carcinoma (Skin)	2/8
Basal cell carcinoma (Skin)	4/7
Melanoma in situ (Skin)	18/18
Melanoma (Skin)	61/80
Melanoma (Head and neck)	0/1
Melanoma (Eye)	3/3
Melanoma (Rectum)	4/5
Melanoma (Anus)	0/1
Metastatic melanoma (Brain)	2/2
Metastatic melanoma (Ear)	1/2
Metastatic melanoma (Testis)	0/1
Metastatic melanoma (Liver)	0/2
Metastatic melanoma (Parotid gland)	2/2
Metastatic melanoma (Mediastinum)	2/2
Metastatic melanoma (Soft tissue)	1/1
Metastatic melanoma (Lymph node)	35/47
Dysplastic nevus (Skin)	0/1
Spitz nevus (Skin) [a]	4/5
Blue nevus (Skin) [a]	1/4
Deep penetrating nevus (Skin)	0/5
Acral nevus (Skin) [a]	1/2
Junctional nevus (Skin)	0/2
Intradermal nevus (Skin) [a]	2/14
Compound nevus (Skin)	0/6
Congenital nevus (Skin) [a]	2/10
B-Cell Lymphoma; NOS (Lymph node)	0/1
Hodgkin lymphoma (Lymph node)	0/1
Anaplastic large cell lymphoma (Lymph node)	0/1
Urothelial carcinoma (Bladder)	1/3
Osteosarcoma (Bone)	1/1
Chondrosarcoma (Bone)	0/1

[a] Weak focal staining

PRAME expression in melanocytic neoplasms may exhibit variable percent tumor positivity. Refer to Table 6 for positive staining tumor cell percentages (categorized by quartiles) observed in melanocytic neoplasms found in Table 5.

Table 6. Percent positive tumor cell staining in FFPE melanocytic neoplasms.

Tissues	Percent Tumor Cells Staining [a] # of cases exhibiting staining percentage / total # of cases (%)				
	< 1%	1-25%	26-50%	51-75%	> 75%
Melanoma	22/90 (24.4%)	7/90 (7.8%)	4/90 (4.4%)	5/90 (5.6%)	52/90 (57.8%)
Melanoma in situ	0/18 (0%)	1/18 (5.6%)	0/18 (0%)	0/18 (0%)	17/18 (94.4%)
Metastatic melanoma [b]	16/58 (27.6%)	4/58 (6.9%)	8/58 (13.8%)	8/58 (13.8%)	22/58 (37.9%)
Melanocytic nevi	42/49 (85.7%)	6/49 (12.3%)	0/49 (0%)	0/49 (0%)	1/49 (2.0%)

[a] Percent tumor cell staining presented for all staining intensities.

[b] One positive case had high melanin pigment which impacted ability to determine percent tumor staining.

Precision

Precision studies for anti-PRAME (EPR20330) antibody were completed to demonstrate:

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

All studies met their acceptance criteria.

Precision on the BenchMark ULTRA PLUS instrument was demonstrated using representative assays. Studies included Within-run Repeatability, Between-day and Between-run Intermediate Precision. All studies met their acceptance criteria.

CLINICAL PERFORMANCE

Clinical performance data relevant to the intended purpose of anti-PRAME (EPR20330) antibody were assessed by systematic review of the literature. The data gathered support the use of the device in accordance with its intended purpose.

REFERENCES

1. Hermes N, Kewitz S, Staege MS. Preferentially Expressed Antigen in Melanoma (PRAME) and the PRAME Family of Leucine-Rich Repeat Proteins. Curr Cancer Drug Targets. 2016;16(5):400-414.
2. Ikeda H, Lethé B, Lehmann F, et al. Characterization of an Antigen That Is Recognized on a Melanoma Showing Partial HLA Loss by CTL Expressing an NK Inhibitory Receptor. Immunity. 1997;6(2):199-208.
3. Xu Y, Zou R, Wang J, et al. The Role of the Cancer Testis Antigen PRAME in Tumorigenesis and Immunotherapy in Human Cancer. Cell Prolif. 2020;53(3).
4. Lezcano C, Jungbluth AA, Nehal KS, et al. PRAME Expression in Melanocytic Tumors. Am J Surg Pathol. 2018;42(11):1456-1465.
5. Epping MT, Wang L, Edel MJ, et al. The Human Tumor Antigen PRAME Is a Dominant Repressor of Retinoic Acid Receptor Signaling. Cell. 2005;122(6):835-847.
6. Proto-Siqueira R, Figueiredo-Pontes LL, Panepucci RA, et al. PRAME Is a Membrane and Cytoplasmic Protein Aberrantly Expressed in Chronic Lymphocytic Leukemia and Mantle Cell Lymphoma. Leuk Res. 2006;30(11):1333-1339.
7. Wadelin FR, Fulton J, Collins HM, et al. PRAME Is a Golgi-Targeted Protein That Associates with the Elongin BC Complex and Is Upregulated by Interferon-Gamma and Bacterial PAMPs. PLoS One. 2013;8(2):e58052-e58052.
8. Pankov D, Sjöström L, Kalidindi T, et al. In Vivo Immuno-Targeting of an Extracellular Epitope of Membrane Bound Preferentially Expressed Antigen in Melanoma (PRAME). Oncotarget. 2017;8(39):65917-65931.
9. Kern CH, Yang M, Liu WS. The PRAME Family of Cancer Testis Antigens Is Essential for Germline clinics Development and Gametogenesis†. Biol Reprod. 2021;105(2):290-304.
10. Elder D, Massi D, Scolyer R, et al. WHO (2018) Classification of Skin Tumors. Vol 11. 4 ed. Lyon France: LWW; 2018.
11. Ferrara G, Argenziano G. The WHO 2018 Classification of Cutaneous Melanocytic Neoplasms: Suggestions from Routine Practice. Front Oncol. 2021;11.
12. Lezcano C, Jungbluth AA, Busam KJ. PRAME Immunohistochemistry as an Ancillary Test for the Assessment of Melanocytic Lesions. Surg Pathol Clin. 2021;14(2):165-175.
13. Googe PB, Flanigan KL, Miedema JR. Preferentially Expressed Antigen in Melanoma Immunostaining in a Series of Melanocytic Neoplasms. Am J Dermatopathol. 2021;43(11):794-800.
14. Alomari AK, Tharp AW, Umphress B, et al. The Utility of PRAME Immunohistochemistry in the Evaluation of Challenging Melanocytic Tumors. J Cutan Pathol. 2021.
15. Lezcano C, Jungbluth AA, Busam KJ. Comparison of Immunohistochemistry for PRAME with Cytogenetic Test Results in the Evaluation of Challenging Melanocytic Tumors. Am J Surg Pathol. 2020;44(7):893-900.
16. Gassenmaier M, Hahn M, Metzler G, et al. Diffuse PRAME Expression Is Highly Specific for Thin Melanomas in the Distinction from Severely Dysplastic Nevi but Does Not Distinguish Metastasizing from Non-Metastasizing Thin Melanomas. Cancers. 2021;13(15).
17. Tio D, Willemsen M, Krebbers G, et al. Differential Expression of Cancer Testis Antigens on Lentigo Maligna and Lentigo Maligna Melanoma. Am J Dermatopathol. 2020;42(8):625-627.
18. Raghavan SS, Wang JY, Kwok S, et al. PRAME Expression in Melanocytic Proliferations with Intermediate Histopathologic or Spitzoid Features. J Cutan Pathol. 2020;47(12):1123-1131.
19. Gradecki SE, Valdes-Rodriguez R, Wick MR, et al. PRAME Immunohistochemistry as an Adjunct for Diagnosis and Histological Margin Assessment in Lentigo Maligna. Histopathology. 2021;78(7):1000-1008.
20. Šekoranja D, Hawlina G, Pižem J. PRAME Expression in Melanocytic Lesions of the Conjunctiva. Histopathology. 2021.
21. LeBlanc RE, Miller DM, Zegans ME. PRAME Immunohistochemistry Is Useful in the Evaluation of Conjunctival Melanomas, Nevi, and Primary Acquired Melanosis. J Cutan Pathol. 2021.
22. Toyama A, Siegel L, Nelson AC, et al. Analyses of Molecular and Histopathologic Features and Expression of PRAME by Immunohistochemistry in Mucosal Melanomas. Mod Pathol. 2019;32(12):1727-1733.
23. Lezcano C, Müller AM, Frosina D, et al. Immunohistochemical Detection of Cancer-Testis Antigen PRAME. Int J Surg Pathol. 2021.
24. See SHC, Finkelman BS, Yeldandi AV. The Diagnostic Utility of PRAME and p16 in Distinguishing Nodal Nevi from Nodal Metastatic Melanoma. Pathol Res Pract. 2020;216(9).
25. Lezcano C, Pulitzer M, Moy AP, et al. Immunohistochemistry for PRAME in the Distinction of Nodal Nevi from Metastatic Melanoma. Am J Surg Pathol. 2020;44(4):503-508.
26. Gradecki SE, Slingluff CL, Jr., Gru AA. PRAME Expression in 155 Cases of Metastatic Melanoma. J Cutan Pathol. 2021;48(4):479-485.
27. Lohman ME, Steen AJ, Grekin RC, et al. The Utility of PRAME Staining in Identifying Malignant Transformation of Melanocytic Nevi. J Cutan Pathol. 2021;48(7):856-862.
28. Parra O, Lefferts JA, Tafe LJ, et al. Cross-Reactivity of NRASQ61R Antibody in a Subset of Spitz Nevi with 11p Gain: A Potential Confounding Factor in the Era of Pathway-Based Diagnostic Approach. Hum Pathol. 2021;112:35-47.
29. Umano GR, Errico ME, D'Onofrio V, et al. The Challenge of Melanocytic Lesions in Pediatric Patients: Clinical-Pathological Findings and the Diagnostic Value of PRAME. Front Oncol. 2021;11.
30. Ruby KN, Li Z, Yan S. Aberrant Expression of HMB45 and Negative PRAME Expression in Halo Nevi. J Cutan Pathol. 2021;48(4):519-525.
31. Carson F, Hladik C. Histotechnology: A Self Instructional Text, 3rd edition. Hong Kong: American Society for Clinical Pathology Press; 2009.
32. Occupational Safety and Health Standards: Occupational exposure to hazardous chemicals in laboratories. (29 CFR Part 1910.1450). Fed. Register.
33. Directive 2000/54/EC of the European Parliament and Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work.
34. Roche PC, Hsi ED. Immunohistochemistry-Principles and Advances. Manual of Clinical Laboratory Immunology, 6th edition. In: NR Rose, ed. ASM Press; 2002.

NOTE: A point (period/stop) is always used in this document as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

The summary of safety and performance can be found here:

https://ec.europa.eu/tools/eudamed

Symbols

Ventana uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see dialog.roche.com for definition of symbols used):

GTIN	Global Trade Item Number
UDI	Unique Device Identification
	Indicates the entity importing the medical device into the European Union

INTELLECTUAL PROPERTY

CONTACT INFORMATION

Ventana Medical Systems, Inc.
1910 E. Innovation Park Drive
Tucson, Arizona 85755
USA
+1 520 887 2155
+1 800 227 2155 (USA)

www.roche.com

EC REP

Roche Diagnostics GmbH
Sandhofer Strasse 116
D-68305 Mannheim
Germany
+800 5505 6606

CE 0123