New biomarker: Ventana FOLR1 in ovarian cancer diagnostics

Advancing Tubo-Ovarian Cancer Management Beyond Chemotherapy

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MC-PL-01395

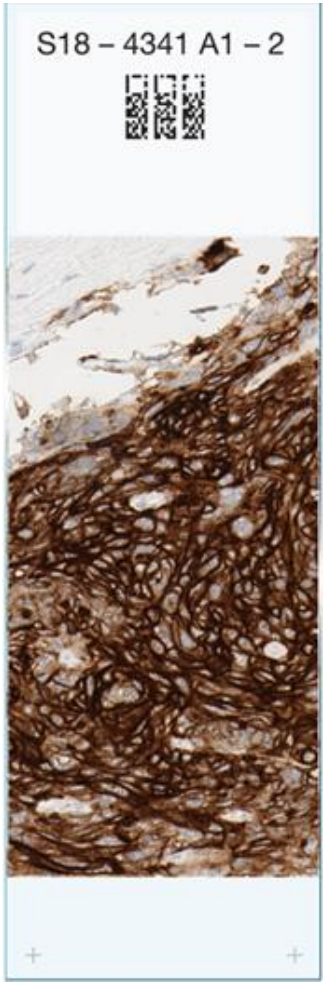
29.05.2026 Warsaw Poland.

Disclaimer

- Emilia Andersson is a full time employee of Roche Diagnostics
- The VENTANA FOLR1 (FOLR1-2.1) RxDx Assay is approved in the EU and Roche Diagnostics is providing this medical and scientific education to prepare pathologists to be confident in the interpretation of the VENTANA FOLR1 Assay to ensure there is no delay in identifying patients eligible for mirvetuximab soravtansine

VENTANA FOLR1 (FOLR1-2.1) RxDx Assay is a qualitative immunohistochemical assay using mouse monoclonal anti-FOLR1 clone FOLR1-2.1 intended for use in the assessment of folate receptor alpha (FOLR1) in formalin-fixed, paraffin-embedded epithelial ovarian cancer, including primary peritoneal cancer and primary Fallopian tube cancer (EOC) tissue specimens by light microscopy. The OptiView DAB IHC Detection Kit is used for staining on a BenchMark ULTRA instrument. FOLR1 expression is determined by the percentage of tumor cells (% TC) with membrane staining
at 2+ and 3+ intensity levels. VENTANA FOLR1 (FOLR1-2.1) RxDx Assay is indicated as an aid in identifying patients with EOC who may be eligible for treatment with the therapy listed in Table 1 for the indication and FOLR1 status in accordance with the approved therapeutic product labeling.

- **This presentation is for educational purposes only**

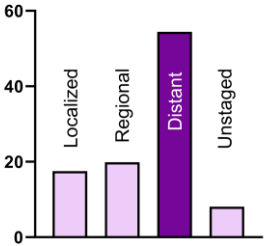


VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

Disease context

Tubo-Ovarian cancer (OC) background

Disease Burden[2]



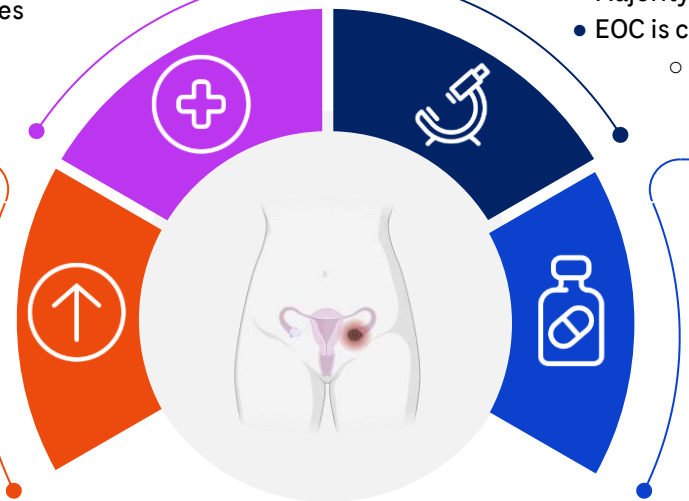
- Asymptomatic in early stages
- Majority of diagnosis occurs at advanced stages

Histology

- OC can be of epithelial, mesenchymal, sex cord stromal and germ cell origin
- Majority of cases are epithelial ovarian cancers (EOC)
- EOC is comprised of 5 distinct subtypes[3]
  - High-grade serous (HGSOC), low-grade serous, endometrioid, clear call & mucinous

Epidemiology[1]

- 300 000 new cases per year
- 8th most common cancer in women worldwide
- Over 200,000 deaths per year
- Number of annual deaths is projected to increase 50% by 2040



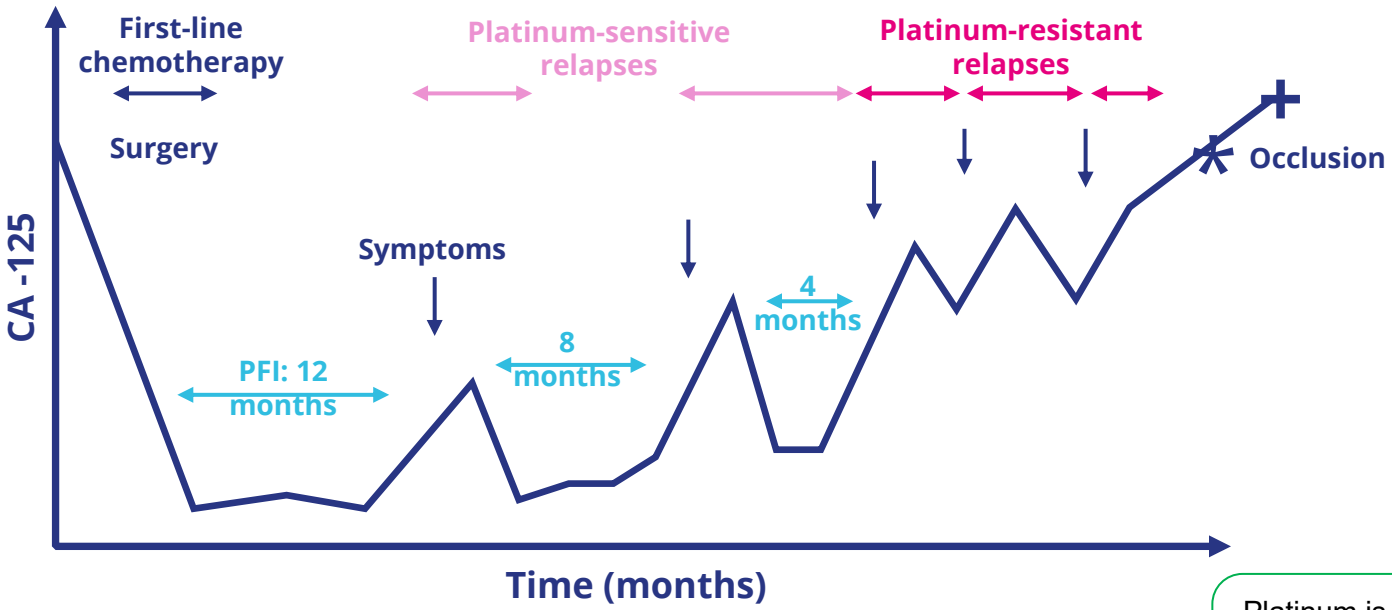
HGSOC & Treatment[4,5]

- **Accounts for 75% of all OC & 90% of all mortalities[6]**
- Molecular testing for BRCA ½ and HRD recommended for all OC patients to guide 1L treatment
- **Surgery** → platinum/taxane chemotherapy +/- bevacizumab (anti-VEGF)
- **Maintenance:** bevacizumab +/- PARPi

1 Globocan database, https://gco.iarc.fr/, accessed June 2023, SEER database, https://seer.cancer.gov/, accessed June 2023
2 SEER database: https://seer.cancer.gov/, accessed in Jan. 2022
3 De Leo, A, et al. What Is New on Ovarian Carcinoma: Integrated Morphologic and Molecular Analysis Following the New 2020 World Health Organization Classification of Female Genital Tumors. Diagnostics. 2021; 11(4):697. https://doi.org/10.3390/diagnostics11040697

4 NCCN Guidelines for Epithelial Ovarian Cancer Version 1.2022 (www.NCCN.org)
5 Ledermann, J. A., et al. (2013). "Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up." Ann Oncol 24 Suppl 6: vi24-32.DOI: 10.1093/annonc/mdt333
6 Lheureux, S., et al. (2019). "Epithelial ovarian cancer." Lancet 393(10177): 1240-1253.DOI: 10.1016/S0140-6736(18)32552-2

Advanced ovarian cancer: a “chronic” disease with multiple relapses



PFI: platinum-free interval or duration of disease control without chemotherapy.

- Length of response shortens with each line of therapy
- Shorter platinum-free interval, lower chance of response, and shorter PFS
- Around 20% relapse within 6 months of 1st line therapy

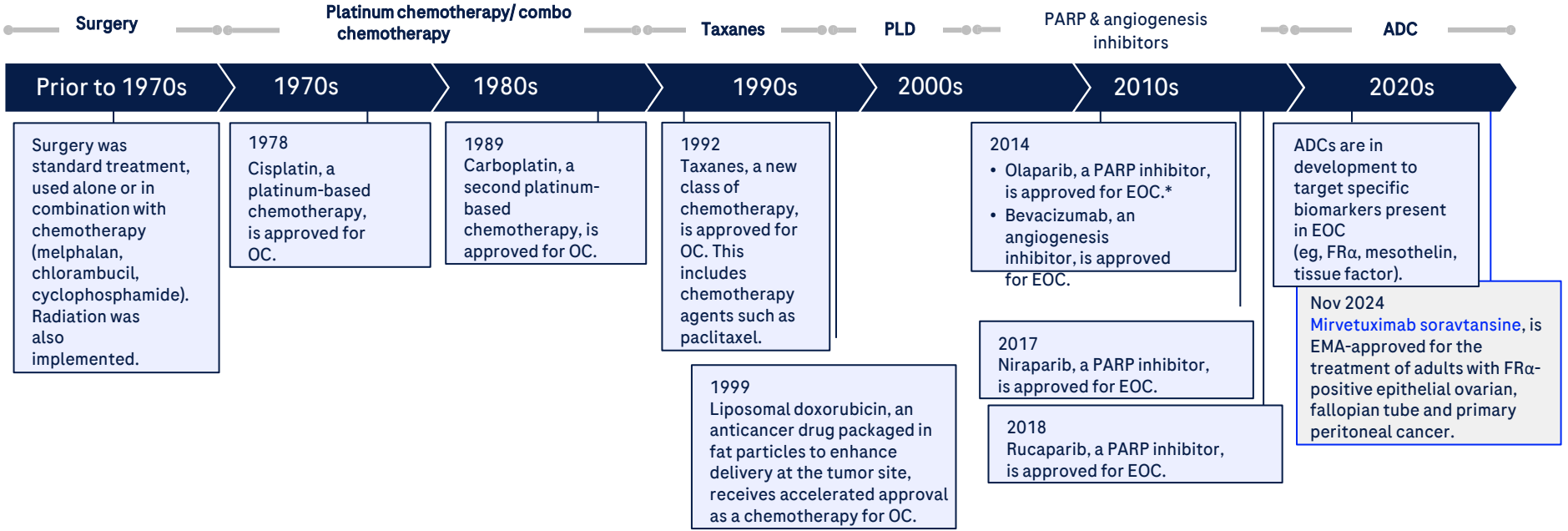
Platinum is not the best option when:

- Progression during platinum
- Early symptomatic progression
- Platinum intolerance

González-Martín, A., et al. *Annals of Oncology* 34.10 (2023): 833-848.

Du Bois a, Pfisterer J. Zentralbl Gynakol. 2004;126:312-4.

Advancements in Treatment for Ovarian Cancer[1-4]



1. Ovarian cancer progress timeline. American Society of Clinical Oncology. Accessed July 21, 2022. https: //www.asco.org/research-guidelines/cancer-progress-timeline/ovarian-cancer 2. Drugs@FDA: FDA-approved drugs. US Food and Drug Administration. Accessed March 31, 2022. https: //www.accessdata.fda.gov/scripts/cder/daf/ 3. Lheureux S, et al. *CA Cancer J Clin*. 2019;69(4):280-304. 4. Manzano A, Ocaña A. *Cancers (Basel)*. 2020;12(8):2223.

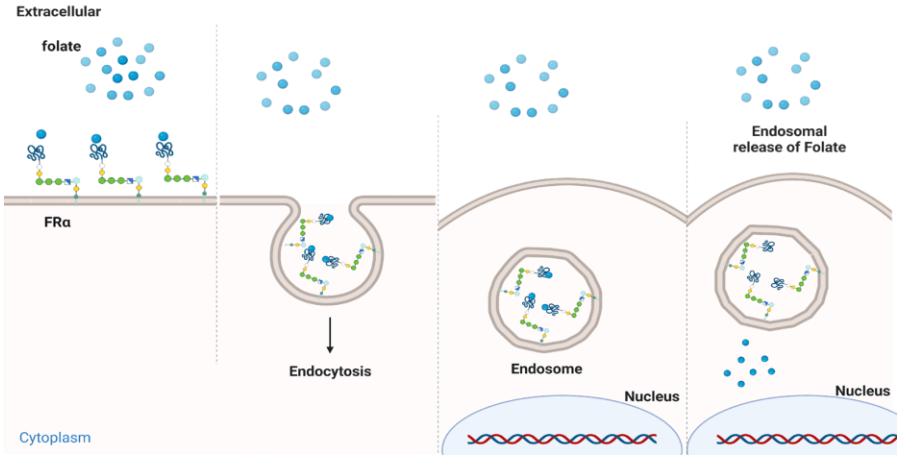
Folate receptor-alpha (FRα)

Background and therapeutic targeting in cancer

- Folate is a water soluble vitamin essential for **DNA and RNA synthesis** in normal cell **growth and development**

- Expression of membrane bound cell surface **FRα** is high during periods of rapid cell growth and division, such as **pregnancy and embryogenesis,** but is **limited** in most (not all) **adult tissues**, as they utilize an alternative transporter for folate uptake

- Due to FRα's role in cell growth, FRα is **overexpressed in certain cancers**
  The combination of restricted expression in normal tissue and overexpression in tumor tissue makes FRα an ideal clinical **target**



Tumors shown to overexpress* FRα:

Breast,	Lung,	Endometrial,	Ovarian
35-70%	15-75%	20-50%	75-90%

*derived from the literature using different detection techniques, numbers of specimens and thresholds for determining expression

Scaranti M, Cojocaru E, Banerjee S, Banerji U. Exploiting the folate receptor α in oncology. Nature reviews clinical oncology. 2020;17(6):349-359

Review of Folate receptor-alpha (FRα) targeting clinical trials

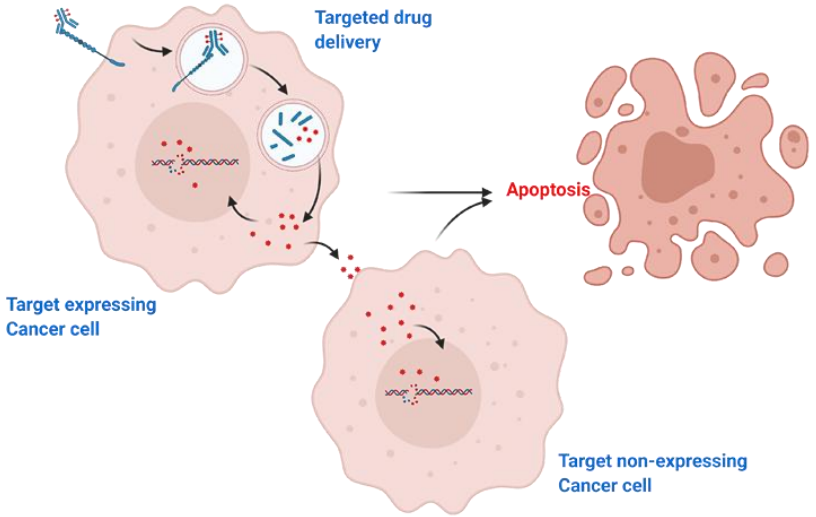
Mirvetuximab soravtansine

Mirvetuximab soravtansine-gynx (ELAHERE®)

Drug mechanism

- ELAHERE is an antibody-drug conjugate (ADC) targeting the FRα protein[1] on the cell surface and is internalized by the cell
- As the ADC is broken down, the cytotoxic drug is released, resulting in cell death including bystander effects due to diffusion of toxic metabolites
- By selectively targeting tumors express FRα, physicians can target the patient's cancer and reduce unwanted drug side effects
- Efficacy correlates directly with FRα protein expression levels

  Identifying the level of FRα present in a patient's tumor is critical to ensure efficacy of ELAHERE



Developed by ImmunoGen, Inc. (now AbbVie)

1 Matulonis UA, et al., Efficacy and Safety of Mirvetuximab Soravtansine in Patients With Platinum-Resistant Ovarian Cancer With High Folate Receptor Alpha Expression: Results From the SORAYA Study. J Clin Oncol. 2023 Jan 30:JCO2201900. doi: 10.1200/JCO.22.01900. PMID: 36716407..

Phase 2 & 3 MIRV Clinical Development Timeline

Overview of key clinical trials

FORWARD 1
Double arm

Did not meet primary endpoint but promising activity in a predefined subset of patients with high FOLR1 expression

SORAYA
Single arm

Robust evidence for the efficacy of mirvetuximab soravtansine vs historical data

Led to accelerated conditional FDA approval Nov 2022

MIRASOL
Double arm

Confirmatory study.

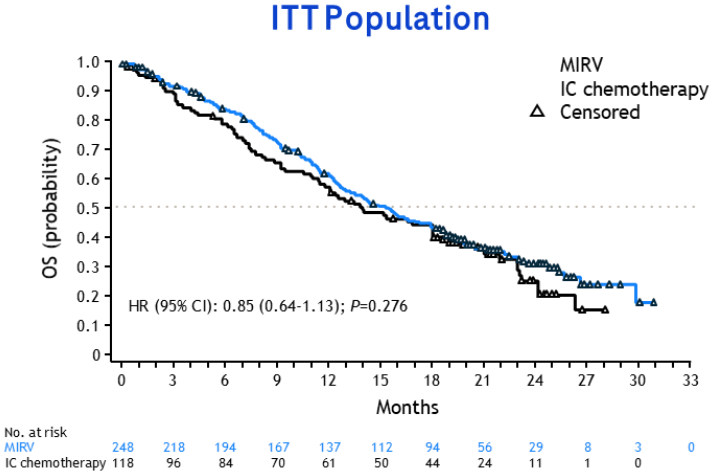
Led to full FDA approval Mar 2024 and EMA approval Nov 2024

All trials used the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay to determine patient FRα expression

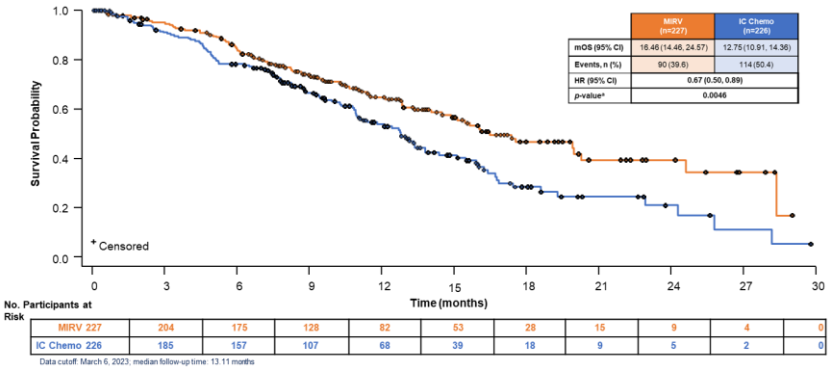
VENTANA® FOLR1 (FOLR1-2.1) RxDx Assay

The cutoff for eligibility

- FORWARD 1 trial: Negative results
  - Patient selection: (**≥50%** with membrane staining visible at 10x)



- MIRASOL trial: Positive results
  - Patient selection: (**≥75%** of cells with ≥2+ membrane staining intensity)



Phase III, randomized trial of mirvetuximab soravtansine versus chemotherapy in patients with platinum-resistant ovarian cancer: primary analysis of FORWARD I. Moore, K.N. et al. Annals of Oncology, Volume 32, Issue 6, 757 - 765

MC-PL-01395

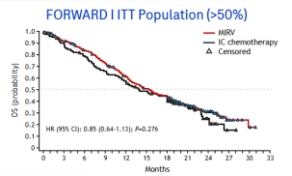
The 75% cutoff for eligibility emphasize the importance of using a clinically validated assay

Including patients with low FOLR1 expression as per CDx, does not translate in benefit from treatment.

Study 1

FORWARD1

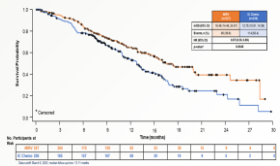
Applied **50% cutoff** but failed to meet primary endpoint



Study 2

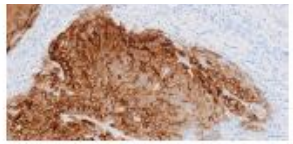
MIRASOL

Applied **>75% cutoff** and met primary endpoint



FDA and EMA approval 2024

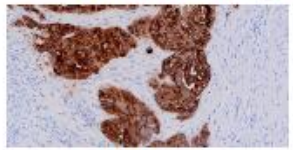
Commercially available RTU 1



False Positive

FOLR1 Negative

Commercially available RTU 2



False Positive

FOLR1 Negative

	False positive	False negative
Commercially available RTU 1	40%	0%
Commercially available RTU 2	26%	14%

Two analytically validated assays compared to the FOLR1 RxDx Assay

Deutschman, Emily, Regan Fulton, and Callum M. Sloss. "Evaluation of Laboratory-Derived Immunohistochemical Assays for Folate Receptor α Expression in Epithelial Ovarian Cancer and Comparison With a Companion Diagnostic." Archives of Pathology & Laboratory Medicine (2025).

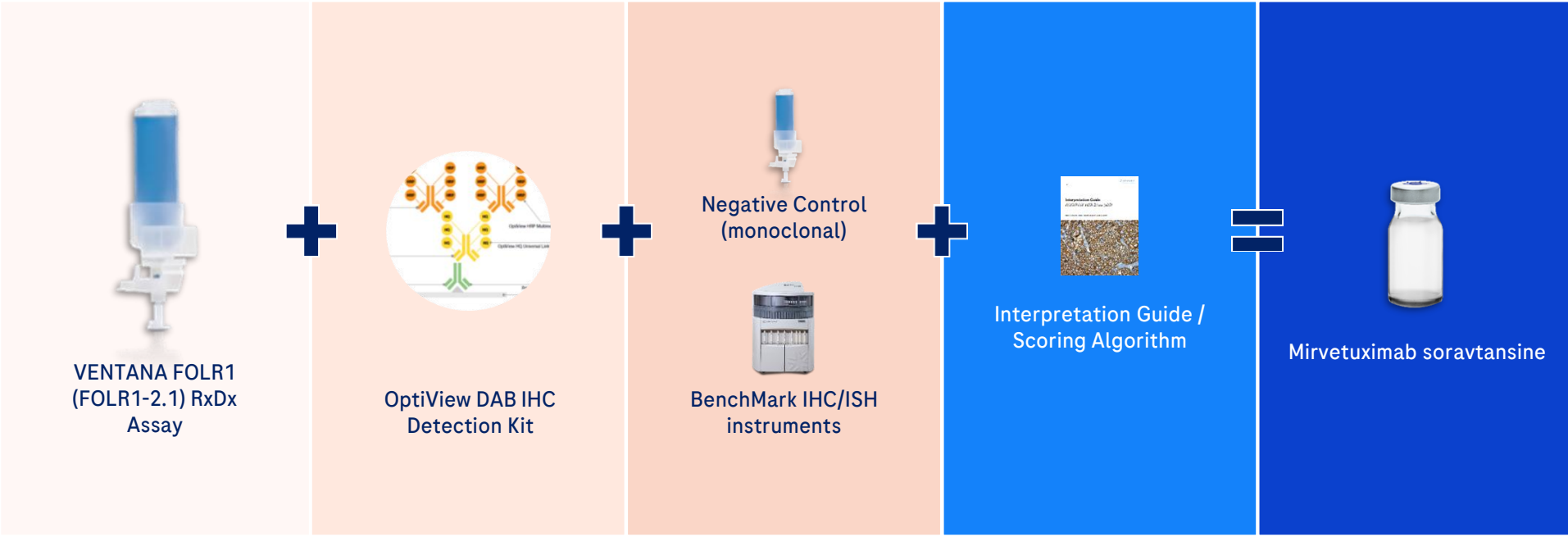
VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

Analytically and **clinically** validated IHC assay to detect FRα in epithelial ovarian, primary peritoneal, and primary fallopian tube cancer.

VENTANA FOLR1 (FOLR1-2.1) RxDx Assay is the first and only FDA- and CE-IVD approved IHC companion diagnostic for determining FRα protein expression in high grade EOC patients who may benefit from ELAHERE therapy.

VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

Assay configuration



VENTANA FOLR1 (FOLR1-2.1) RxDx Assay [package insert]. Tucson, AZ. Ventana Medical Systems, Inc. 2022.

VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

Specimen Types

Validated specimens

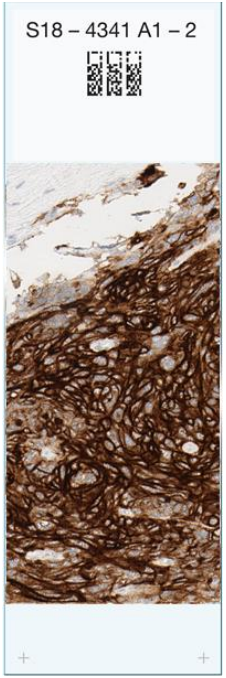
- Primary ovarian cancer, fallopian tube cancer and primary peritoneal cancer
- Formalin-fixed and paraffin embedded
- Archival or fresh tissues from resections, excisions, and biopsies
- Primary and metastatic sites

Non-validated specimens

- Cytology samples
- Decalcified metastatic bone lesions

System level control

- Fallopian tube with 2+ staining intensity in the epithelial cells



VENTANA FOLR1 (FOLR1-2.1) RxDx Assay Interpretation Guide for Epithelial Ovarian Cancer, Primary Peritoneal, and Fallopian Tube Cancer

Estrogen-Mediated Repression of FOLR1

Cell culture models and clinical studies confirm that **Estrogen Receptor (ER) signaling actively represses** the FOLR1 gene.

The Biological Mechanism:

High Serum Estrogen → ER Binding to FOLR1 Promoter → Transcriptional Repression → Low Basolateral Protein Expression.

Pregnancy Effect:

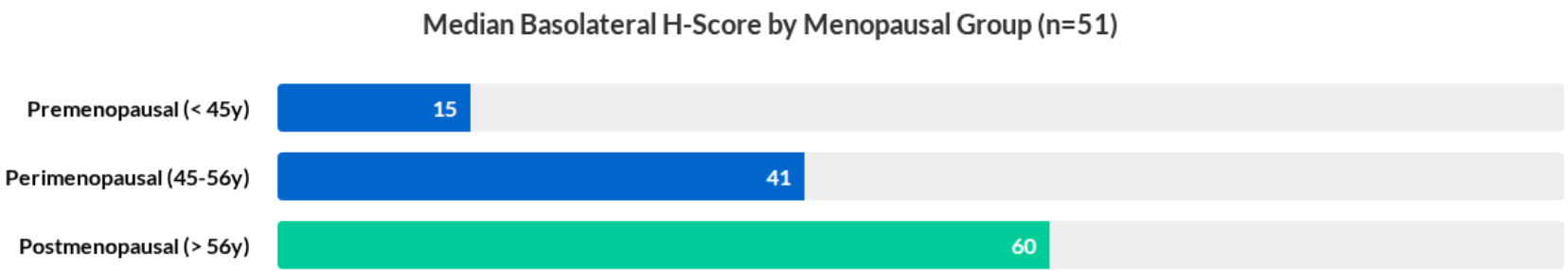
2nd/3rd trimester serum estrogen is >500-fold higher than postmenopausal levels, causing profound FOLR1 repression in normal fallopian tissue.

Tamoxifen Effect:

Patients on Tamoxifen (ER antagonist) show significantly **higher** FOLR1 expression, as the estrogenic repression is pharmacologically blocked

Nasdala A, et al. J Pathol Clin Res 2026

Impact of Menopause on Basolateral IHC



Graph created based on Nasdala A, et al. J Pathol Clin Res 2026

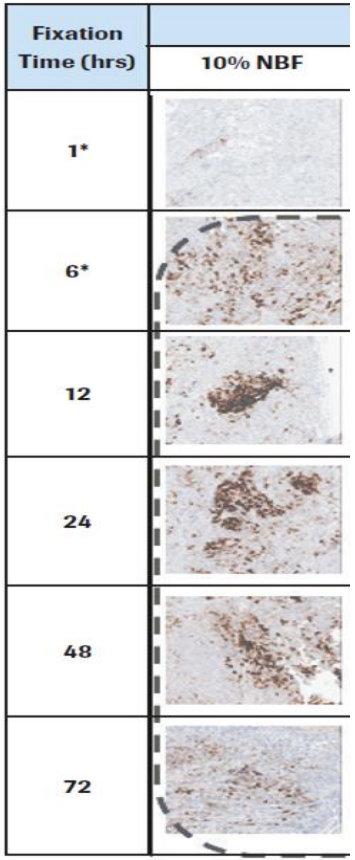
VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

Specimen Pre-analytical Factors

Specimens should be:

- Fixation (12-72 hours) with 10% neutral buffered formalin
- 6 hour minimum fixation for small biopsies
- Sectioned at a thickness of 4µm and placed onto positively charged slides
- Cut slide stability: no more than 45 days

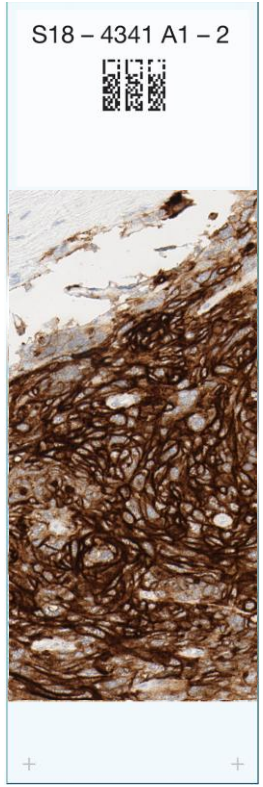
*Fixation with alcohol based fixatives is not recommended



VENTANA FOLR1 (FOLR1-2.1) RxDx Assay Interpretation Guide for Epithelial Ovarian Cancer, Primary Peritoneal, and Fallopian Tube Cancer
VENTANA FOLR1 (FOLR1-2.1) RxDx Assay Package Insert

VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

Staining Interpretation



VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

Scoring Criteria

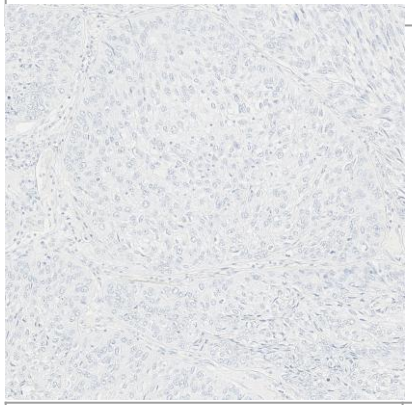
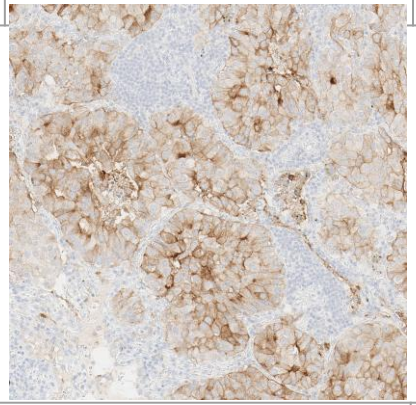
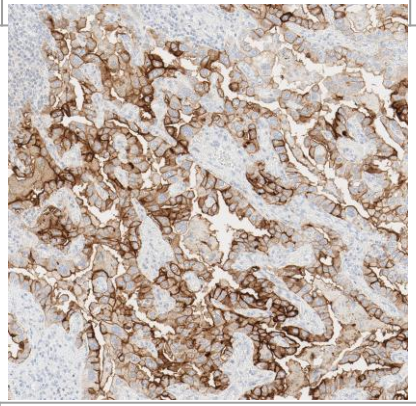
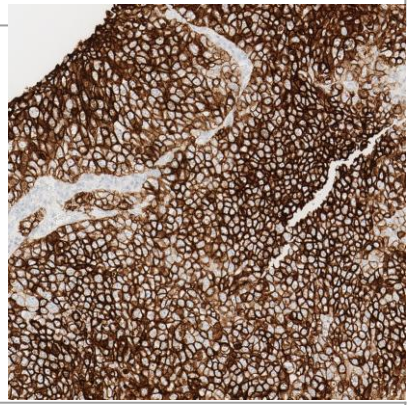
- **membrane** staining is included in scoring
  - **Partial** and/or **complete**
  - **Apical, circumferential** distribution

  - When variable intensities are seen in a single cell, the **highest intensity** is scored

- Excluded from scoring:
  - Necrotic, crushed or cauterized cells
  - Cytoplasmic staining

VENTANA® FOLR1 (FOLR1-2.1) RxDx Assay

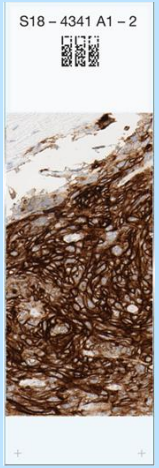
Tumor cell intensity characteristics

0	1+	2+	3+
			
Absence of any detectable signal. Negative cases may still exhibit pale grey cytoplasmic and/or membranous discoloration.	Signal intensity is characterized by **a faint gold/light brown hue**	Signal intensity is characterized by a **chocolate brown to thickened dark brown, black hue**	

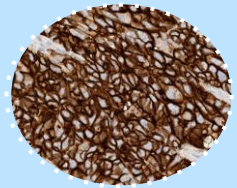
Note: Relative ease of visualization of membrane staining can be impacted by presence/absence of concurrent cytoplasmic staining and its intensity

VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

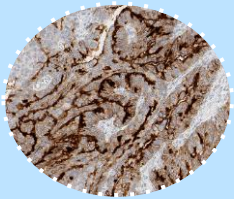
Staining Characteristics



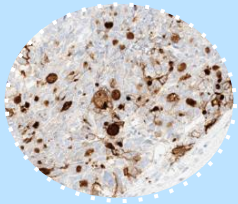
Membrane Staining



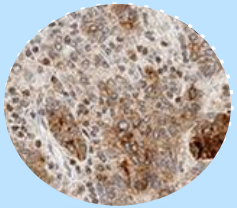
Apical Staining



Dot Like Staining



Though rare, EOC cases can exhibit dot-like or apical staining that can make interpretation challenging. Both are considered as membranous staining.



Cytoplasmic

FRα cytoplasmic staining should not be scored

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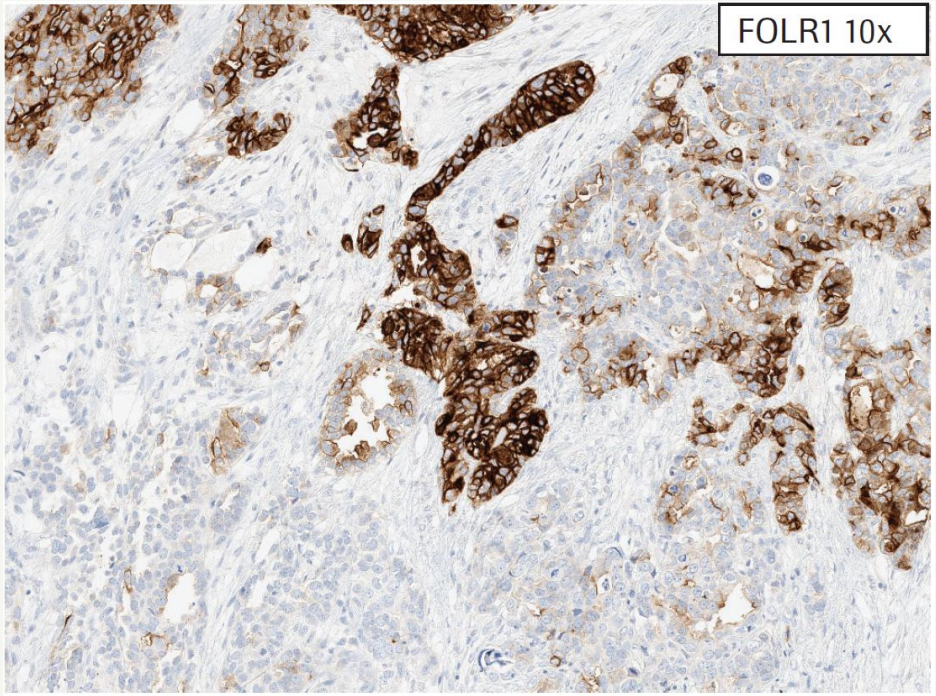
VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

Heterogeneity

Heterogeneous Staining:

Pay attention to non staining areas.

Risk of overscoring



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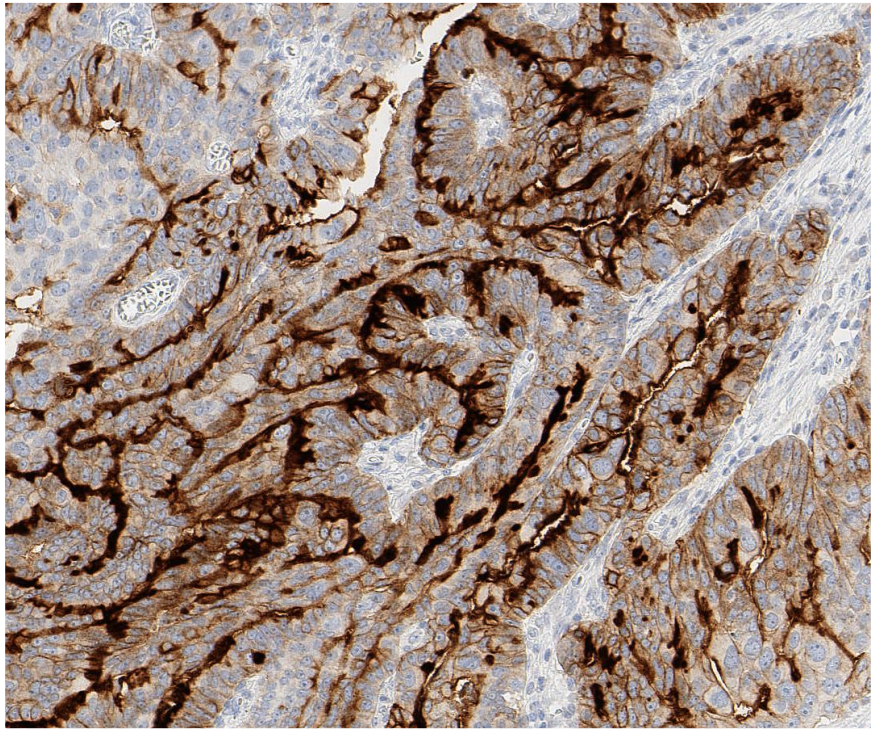
VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

Apical staining

Apical Staining:

When there is apical staining in a cell, the entire cell should be **considered positive.**
When variable intensities are seen in a single cell, **the highest intensity is scored**
Risk of underscoring



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VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

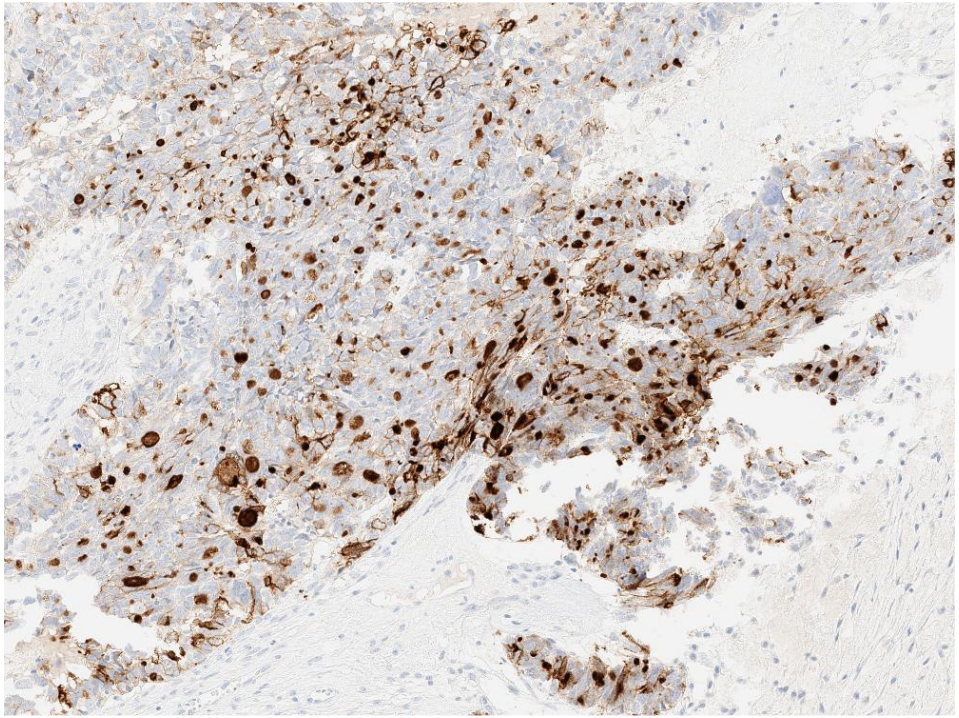
Dot-like staining pattern

Dot-like Pattern Staining:

Apical staining in gland forming morphology.
The entire cell should be **considered positive.**

When variable intensities are seen in a single cell, **the highest intensity is scored**

Risk of underscoring



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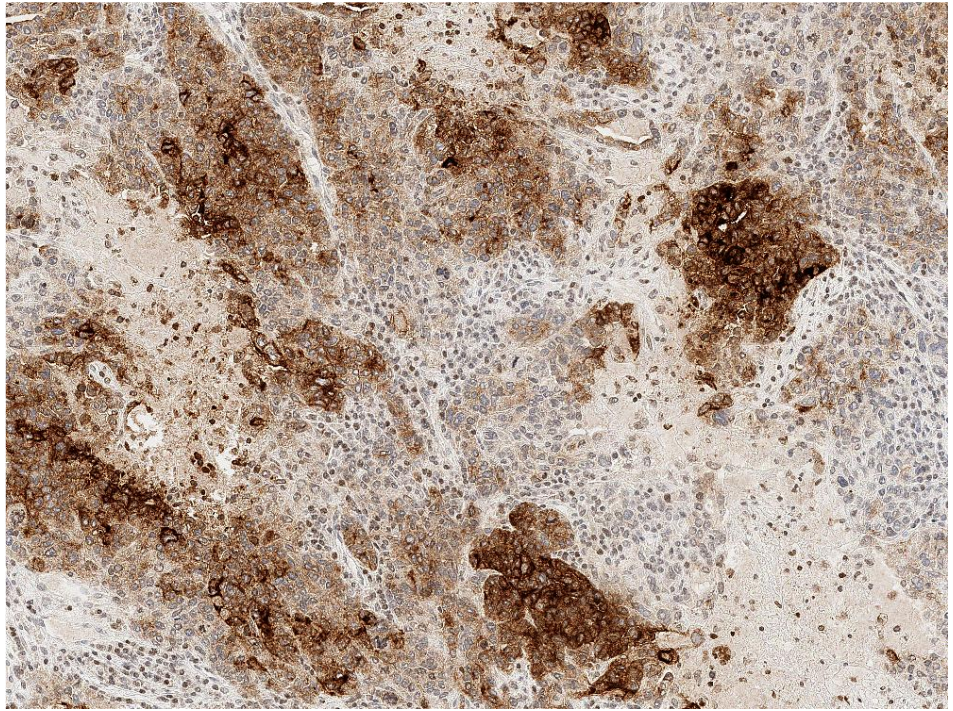
VENTANA FOLR1 (FOLR1-2.1) RxDx Assay [Interpretation Guide]. Tucson, AZ. Ventana Medical Systems, Inc.

VENTANA FOLR1 (FOLR1-2.1) RxDx Assay

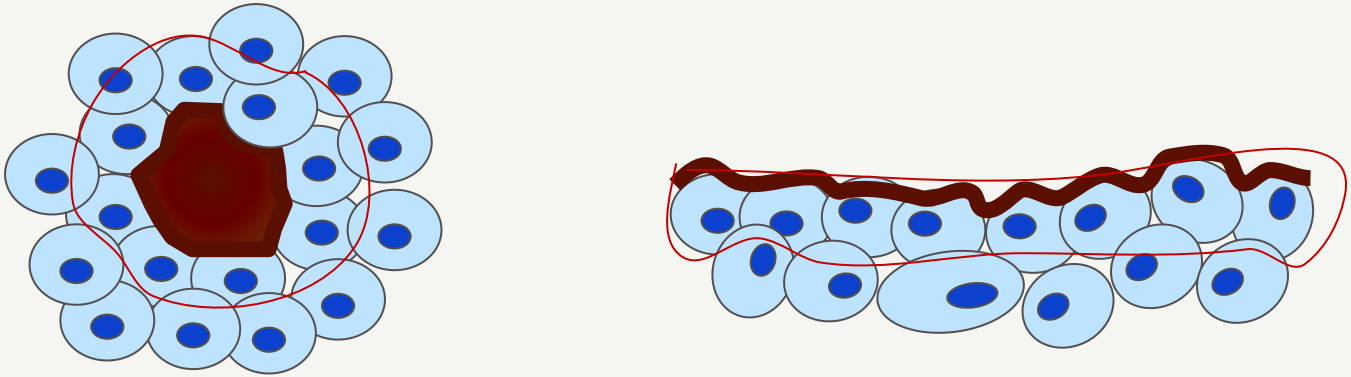
Cytoplasmic and membrane staining

Cytoplasmic Staining:
Only include cells with membrane staining.
Risk of overscoring



VENTANA FOLR1 (FOLR1-2.1) RxDx Assay [Interpretation Guide]. Tucson, AZ. Ventana Medical Systems, Inc. 2022.

Dot-like and apical staining pattern



All cells touching the “dot” or the apical surface are included in the scoring

Positivity rate seems to be higher in primary vs metastatic tissue

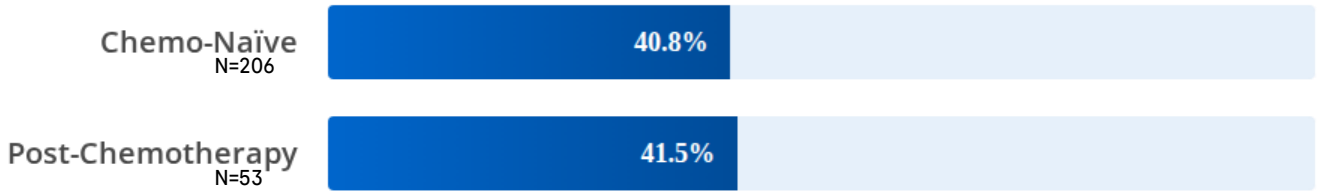
New data from an Asian cohort (Chen et al. 2026) validates previous Western findings (Previs et al.), demonstrating global consistency in biomarker prevalence.

Study	Region	N	Positivity Rate*	Key Observation
Previs et al.	USA	432	36.3%	Primary tumors (44.4%) > Metastatic (32.5%)
Chen et al. (2026)	China	313	**40.9%**	Primary tumors (44.2%) > Metastatic (32.2%)

*Positivity defined as ≥75% of tumor cells staining at ≥2+ intensity.

1. Previs RA, et al. Analysis of real world FRa testing in ovarian, fallopian tube, and primary peritoneal cancers. *Gynecol Oncol*. 2025;192:102-110.
2. Chen X, et al. Performance of the VENTANA FOLR1 Assay for folate receptor alpha: Real-world evidence from 313 Chinese participants. *Pathol Res Pract*. 2026;279:156359.

No significant Impact of Chemotherapy on FRα Expression



Key Finding: *Treatment status does not significantly alter FRα expression. The positivity rate in post-chemotherapy samples is statistically comparable to chemo-naïve samples.*

Chen X, et al. Performance of the VENTANA FOLR1 Assay for folate receptor alpha: Real-world evidence from 313 Chinese participants. Pathol Res Pract. 2026;279:156359 (Table 3).

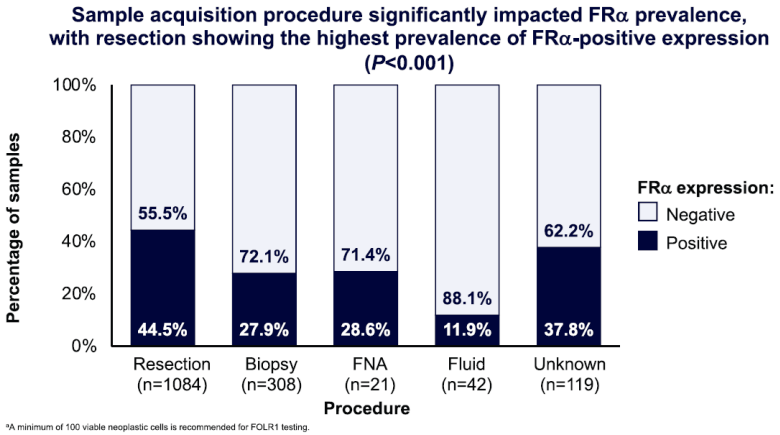
Optimizing Specimen selection

Resection vs. Biopsy

Due to tumor heterogeneity, the type of specimen collected significantly impacts the likelihood of a positive result.

- **Excision/Resection:** Highest yield.
- **Biopsy:** Significantly lower yield.
- **Fluid:** Lowest yield.

Figure 4. FRα Prevalence Among Ovarian Cancer Samples by Acquisition Procedure[a] (n=1574)



Recommendation: Prioritize excision or resection samples from primary tumor whenever possible to minimize the risk of false negatives due to sampling error.

Krivak et al, Real-World analysis of Folate receptor Alpha expression in pan-tumor samples from over 6000 patients in the US.Abstract 5568

For more cases and background

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Thank you

for your attention

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