Endometriosis: Challenges in Diagnosis

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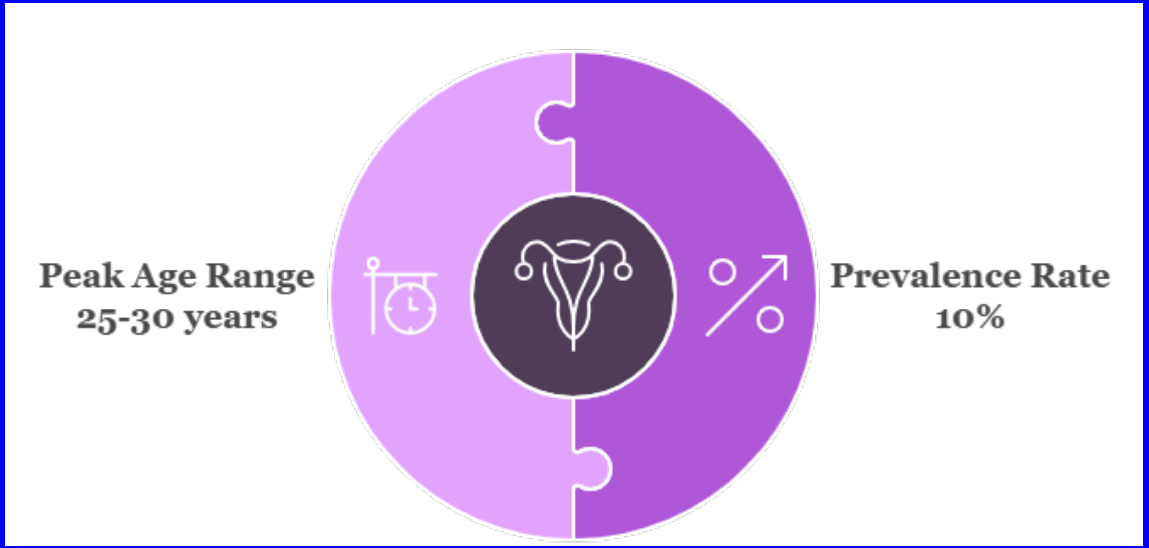
Disclosures

Contracted Research (Principal Investigators must provide information, even if received by the institution): AbbVie, Organon

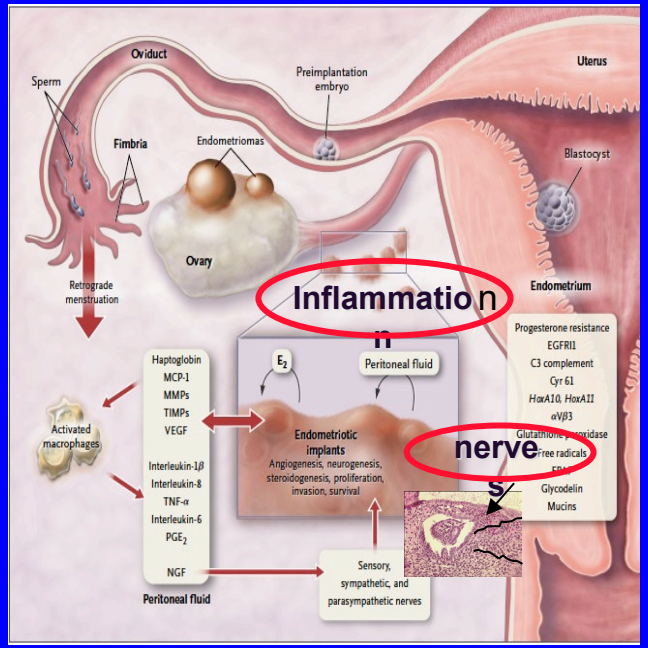
Prevalence

Endometriosis is a public health disorder affecting **~ 250 million** women globally and **~ 10 million** women in the United States.



Challenges in diagnosing endometriosis

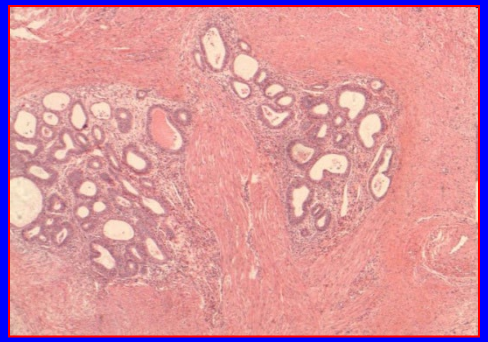
- 6.7-11 years from symptom onset to definitive diagnosis and treatment
- Many PCPs unfamiliar with disease
- Symptoms are nonspecific or associated with other disorders
- Social norms inhibit conversation
- Pain is subjective
- Survey of n = 7,025 women
  - 65% misdiagnosed
  - 46% saw ≥ 5 MDs to get correct diagnosis

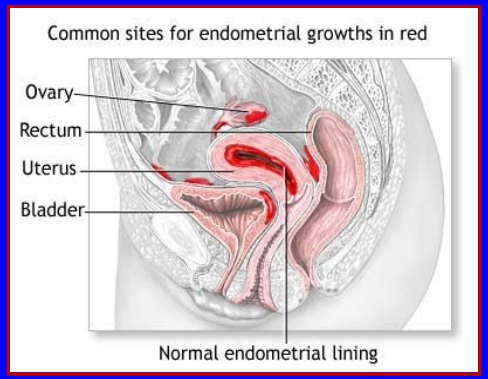


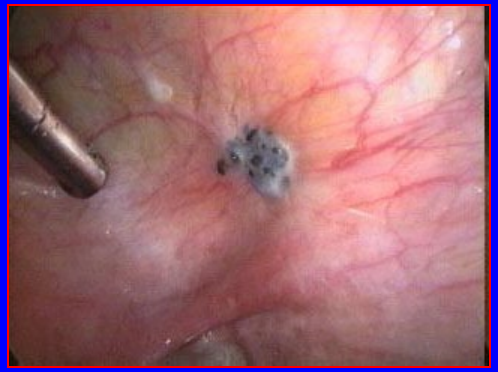
Early diagnosis and treatment can reduce uncertainty, discomfort, disease progression, and later complications

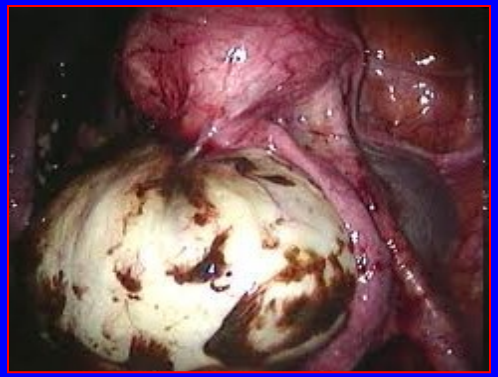
(Ballard et al, 2006; Nnoaham et al 2011; May et al 2011; Rogers et al, 2013)

Endometriosis is Ectopic Endometrial Glands and Stroma









Clinical Presentation

- **Pain**
- **Infertility**
- **Asymptomatic**

Disease Stage does not explain pain symptoms.

Percentage at Each Stage

	Stage				
	I	II	III	IV	*P*
Dysmenorrhea	73	86	72	85	.68
NM Pelvic pain	38	46	36	41	.21
Dyspareunia	30	25	36	29	.91

Fedele L et al. *Fertil Steril*. 1990;53(1):155-158.

What you see
in the pelvis is just part
of the disease.

Symptoms Associated with Endometriosis

Endometriosis is a systemic disease!

Taylor HS et al. Lancet 2021;397(10276):839-852.

Endometriosis:
A Chronic Systemic Disease

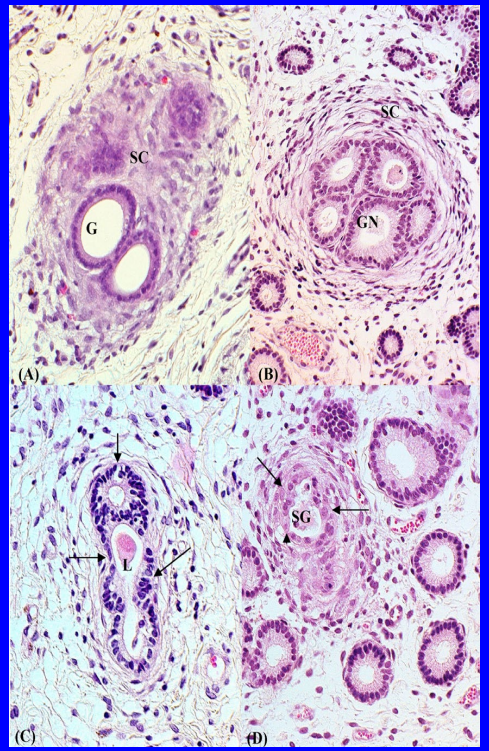
- Varied presentation and diffuse symptoms have traditionally made it difficult for some practitioners to make the diagnosis.

Current limitations in endometriosis diagnosis:

- No non-invasive diagnostic tests
- Requirement for surgical diagnosis is a barrier to timely diagnosis and therapy

Diagnosis

- Gold standard:
  - Direct visualization of endometriotic lesions
  - Laparoscopy or laparotomy
- Signs and symptoms
  - Secondary dysmenorrhea
  - Dyspareunia
  - Infertility
- Gynecological examination
- Imaging:
  - Ultrasonography
  - MRI
  - CT
- Serum biomarkers



Clinical Presentation

Symptoms vary but typically reflect area of involvement and may include:

- Dysmenorrhea
- Cylical/noncylical pelvic pain
- Lower abdominal or back pain
- Dyschezia, often with cycles of diarrhea/constipation
- Bloating, nausea, and vomiting
- Inguinal pain
- Dysuria
- Dyspareunia
- Nodules may be felt upon pelvic exam
- Typically develops on pelvic structures, ie, rectovaginal septum, bladder, bowel, intestines, ovaries, and fallopian tubes
- Ovaries most common locations; gastrointestinal tract, urinary tract, soft tissues, and diaphragm follow
- Imaging may indicate pelvic mass/endometriomas.
- Less commonly found in distant regions, eg, diaphragm, lungs (inducing catamenial pneumothorax), and rarely, areas far outside abdominopelvic region

Physical Findings

- **Physical Examination**
  - **Pelvic tenderness**
  - **Uterosacral nodularity**
  - **Fixed or retroverted uterus**
- **Limitations of Physical Exam**
  - **May be normal**
  - **Deep lesions not palpable**

Chronic Pelvic Pain Associated with Endometriosis

- Cyclic
- Progressive: over time, pain worsens or changes in character
- Cyclic bladder- and bowel-associated symptoms (nausea, distention, and early satiety)

Chronic Pelvic Pain Syndromes Confused with Endometriosis

Other gynecologic conditions:

- Pelvic inflammatory disease
- Pelvic adhesions
- Ovarian cysts or masses (including ovarian cancer)
- Leiomyomata
- Adenomyosis
- History of sexual abuse

Non-gynecologic conditions:

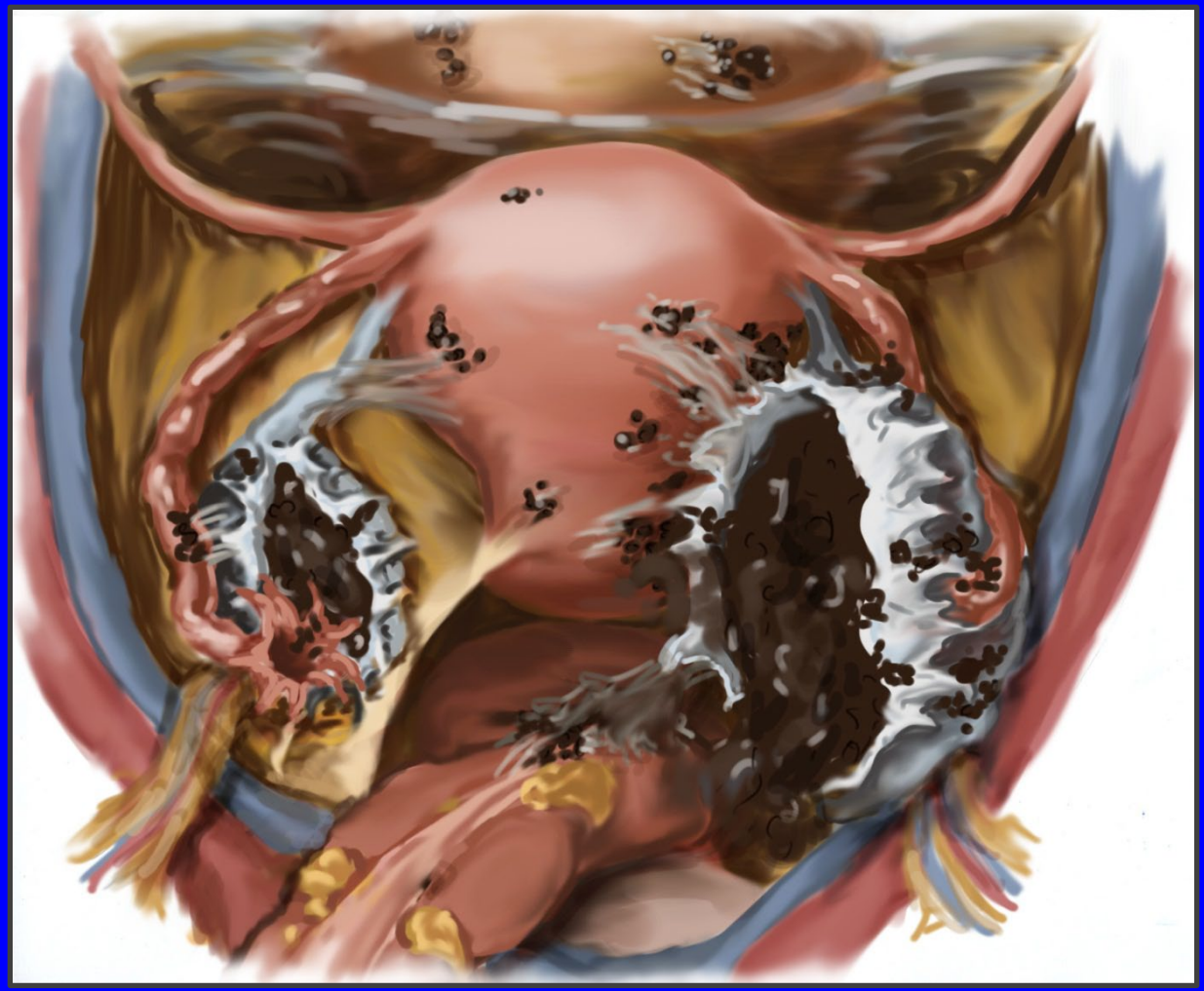
- Irritable bowel syndrome
- Inflammatory bowel disease
- Interstitial cystitis
- Myofascial pain
- Depression

Endometriosis is a biologically complex, chronic, systemic disease;

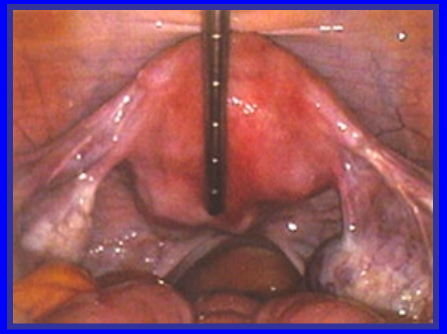
however clinically it is easily recognized and treated.

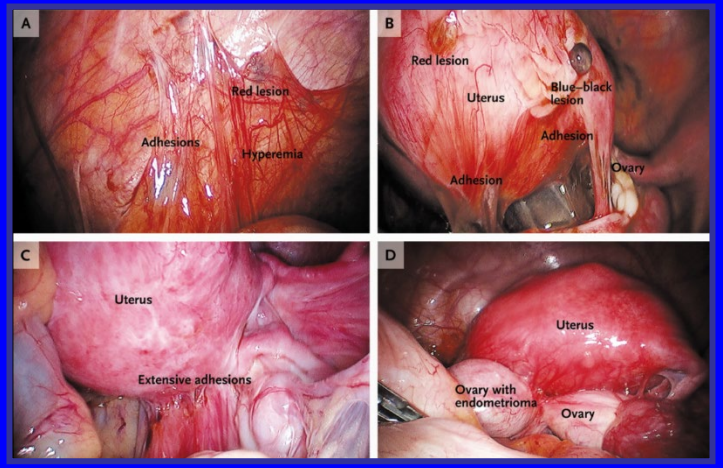
Laparoscopy/laparotomy

- Pros:
  - “Gold standard”
  - Can also remove lesions
- Cons
  - Invasive procedure
  - Has its own risks/morbility
  - Costly
  - Still difficult to detect microscopic and/or subperitoneal lesions
  - Accuracy depends on the skill levels of surgeons

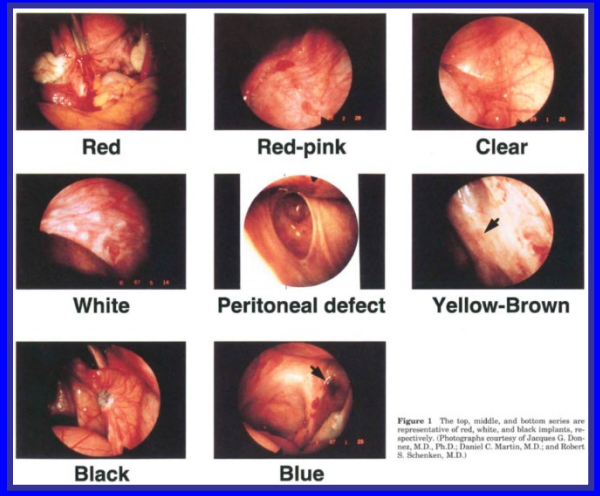


Surgical Diagnosis





Giudice L. *N Engl J Med.* 2010;*362*(25):2389–2398



Subtleties in appearance can lead to misdiagnosis

Normal Peritoneum has Endometriosis in 25% of Women with PP

- **Unsuspected endometriosis documented in visually normal peritoneum.**

Murphy AA, Green WR, Bobbie D, dela Cruz ZC, Rock JA.
Fertil Steril. 1986;46(3):522-4

Only 45% of Visualized Endometriosis Confirmed by Histology

- A prospective study of 44 patients undergoing laparoscopy for the evaluation of chronic pelvic pain.
- The positive predictive value was 45%.

Walter AJ et al. Am J Obstet Gynecol. 2001;184(7):1407-11

Clinical Presentation

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Laparoscopy/laparotomy

- Pros:
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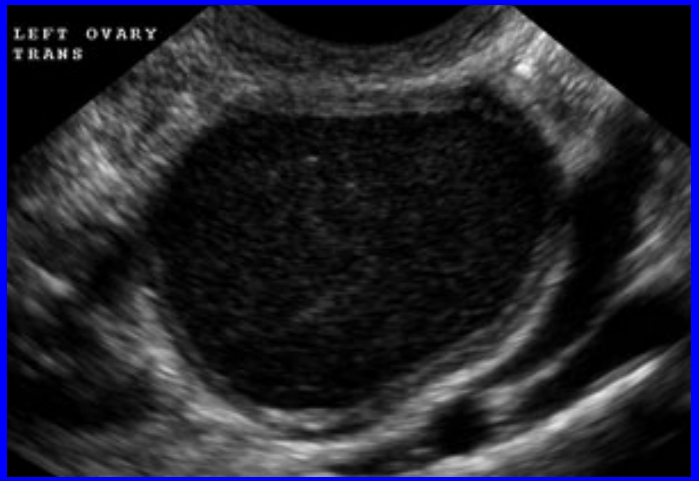
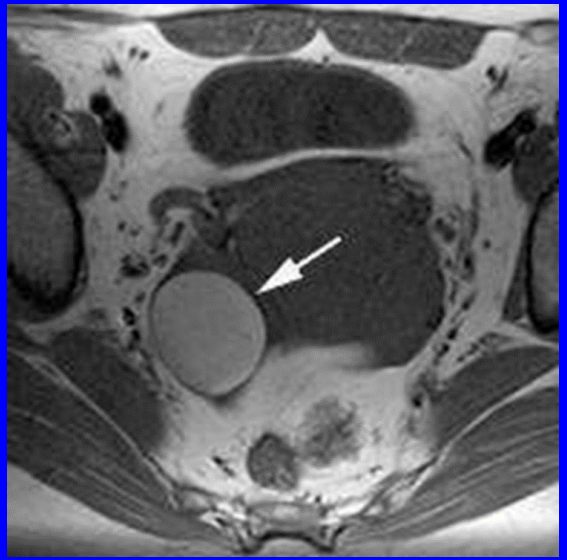
  - Can also remove lesions
- Cons
  - Invasive procedure
  - Has its own risk of morbility and, rarely, mortality
  - Costly
  - Still difficult to detect microscopic and/or subperitoneal lesions
  - Accuracy depends on the skill levels of surgeons

Major Barrier to Early Diagnosis

Endometriosis – U/S or MRI





Transvaginal Ultrasound

- First-line imaging
  - Best for endometriomas
  - “Ground-glass” appearance
- Ultrasound Limitations
  - Poor for superficial disease
  - Operator dependent

MRI in Endometriosis

Deep infiltrating disease

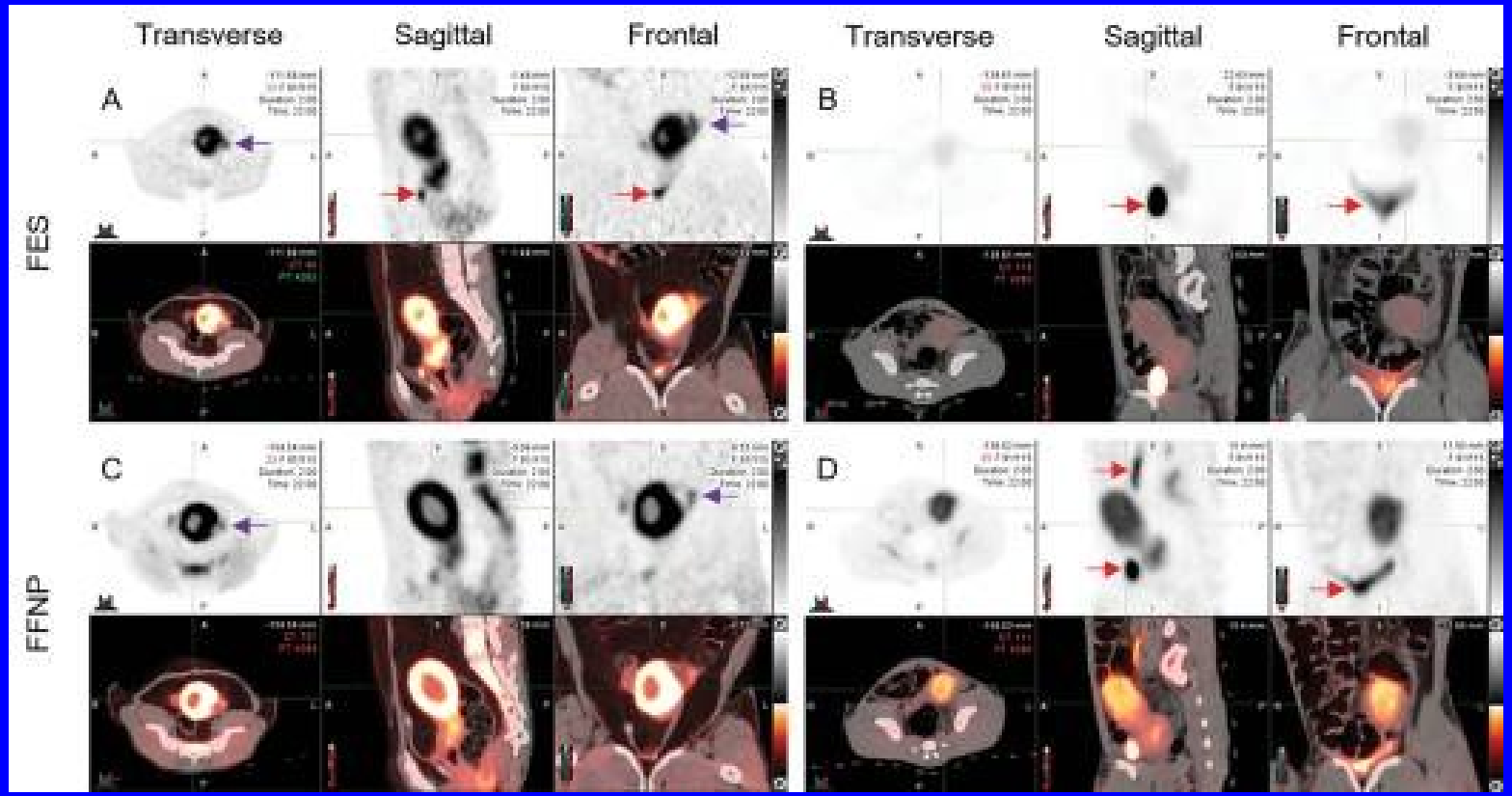
Pre-surgical mapping

High soft-tissue contrast

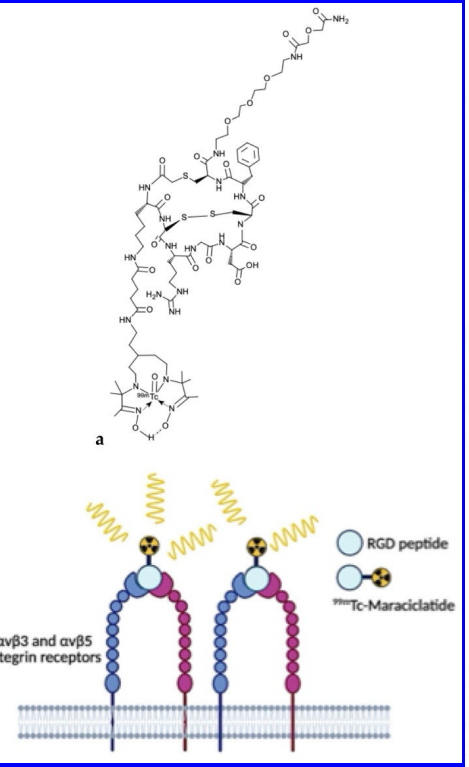
- MRI Findings
- Endometriomas
- Deep nodules
- Adhesions

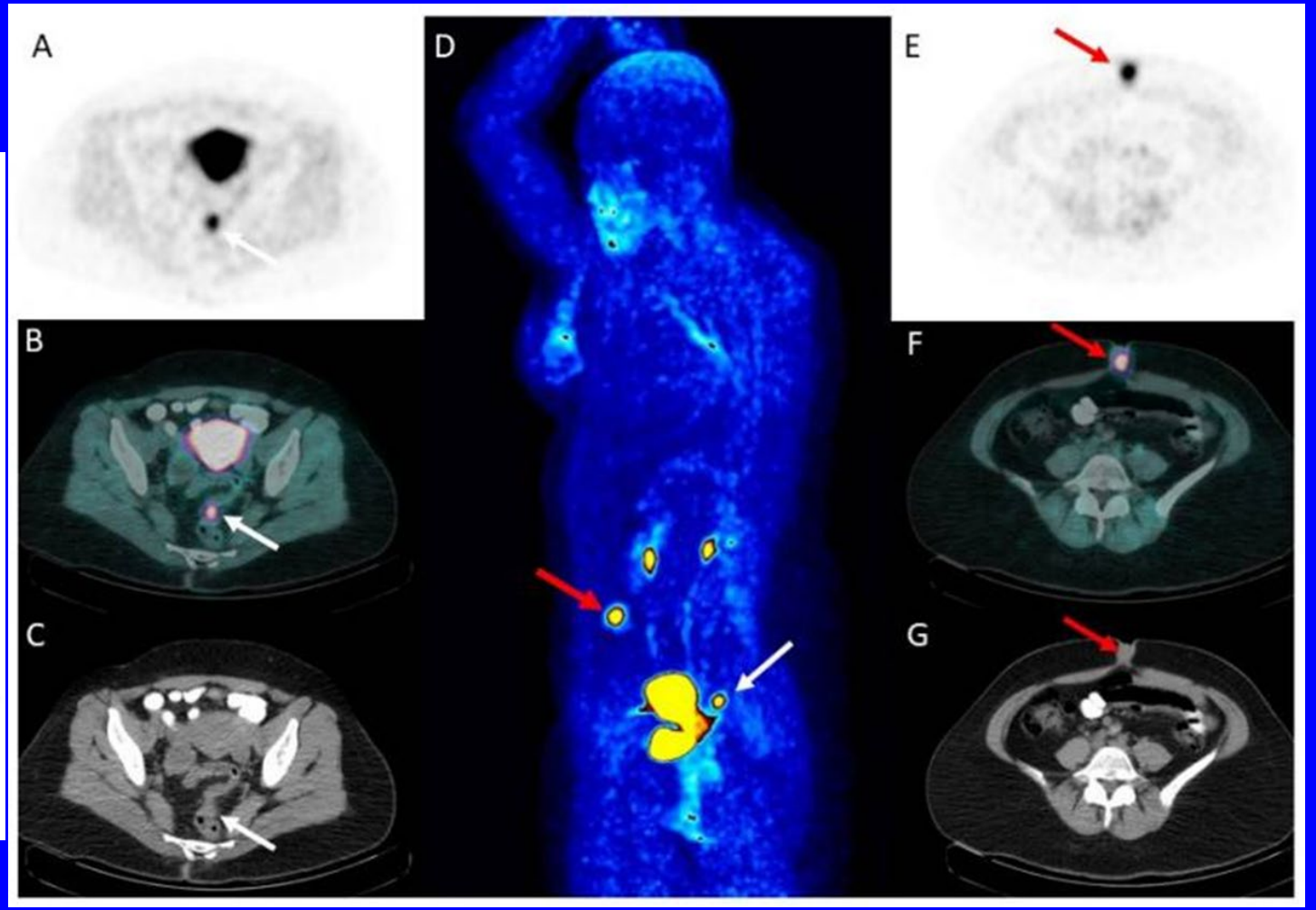
PET

16α-[18F]fluoroestradiol (FES) and 21-[18F]fluoro-furanyl-nor-progesterone (FFNP) in NHP



PET


a
RGD peptide
^{99m}Tc-Maraciclatide
αvβ3 and αvβ5
tegrin receptors


A
B
C
D
E
F
G

Endometriosis Biomarkers

Summary of Biomarker Uses:

- Risk assessment Biomarkers:
  - Identify those at risk for development of disease
  - Opportunity for monitoring or prophylactic therapy
- Diagnostic Biomarker:
  - Diagnostic clarity
  - Early diagnosis
  - Monitor asymptomatic, high-risk individuals

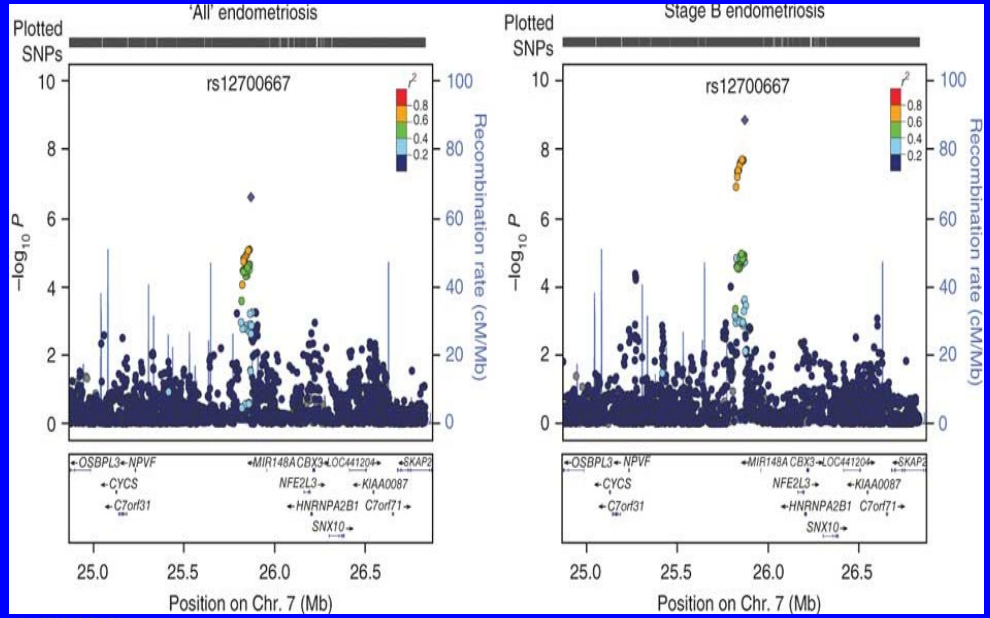
- **Prognostic Biomarker**
  - Predict disease outcome
  - Monitor disease recurrence
  - Predict disease free interval
- **Predictive Biomarker**
  - Choose optimal therapy
  - Monitor therapy response
  - Alter therapy in setting of emerging resistance

Types of biomarkers by clinical application

- Biomarkers of risk
- Biomarkers for early detection/diagnosis
- Disease outcomes: prognostic biomarkers
- Treatment outcome: predictive biomarkers

Risk Assessment Biomarkers

- Family History
- Exposures and Environmental Factors
- Genetics



Fowler et al. Nature Genetics 2011;43:437–44

Genetic Tests

Exome sequencing

“Low-Frequency, Damaging Mutations in Hundreds of Genes Are Risk Factors for Endometriosis”

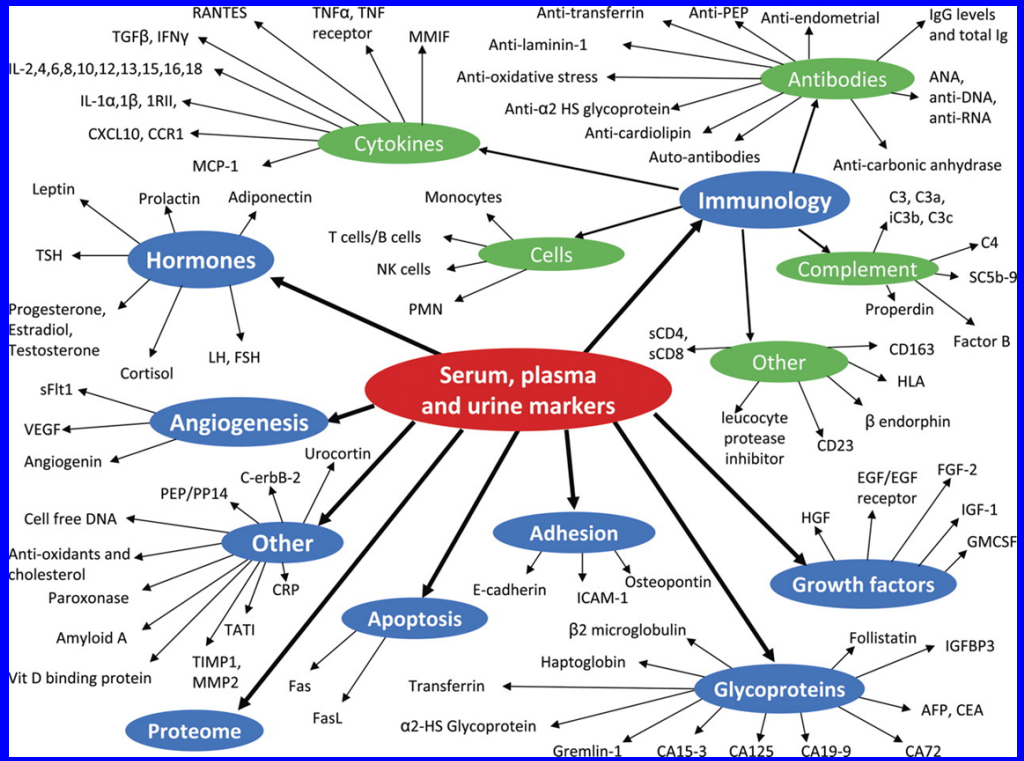
Society of Reproductive Investigation
Annual Meeting 2018

Types of biomarkers by clinical application

- Biomarkers of risk
- Biomarkers for early detection/diagnosis
- Disease outcomes: prognostic biomarkers
- Treatment outcome: predictive biomarkers

Serum Biomarkers

- Over 200 different serum biomarkers have been proposed, yet none have adequate specificity and sensitivity.



Where are we now with biomarkers?

The most widely-used at present is CA-125, a marker that is inadequate on its own in terms of sensitivity and specificity

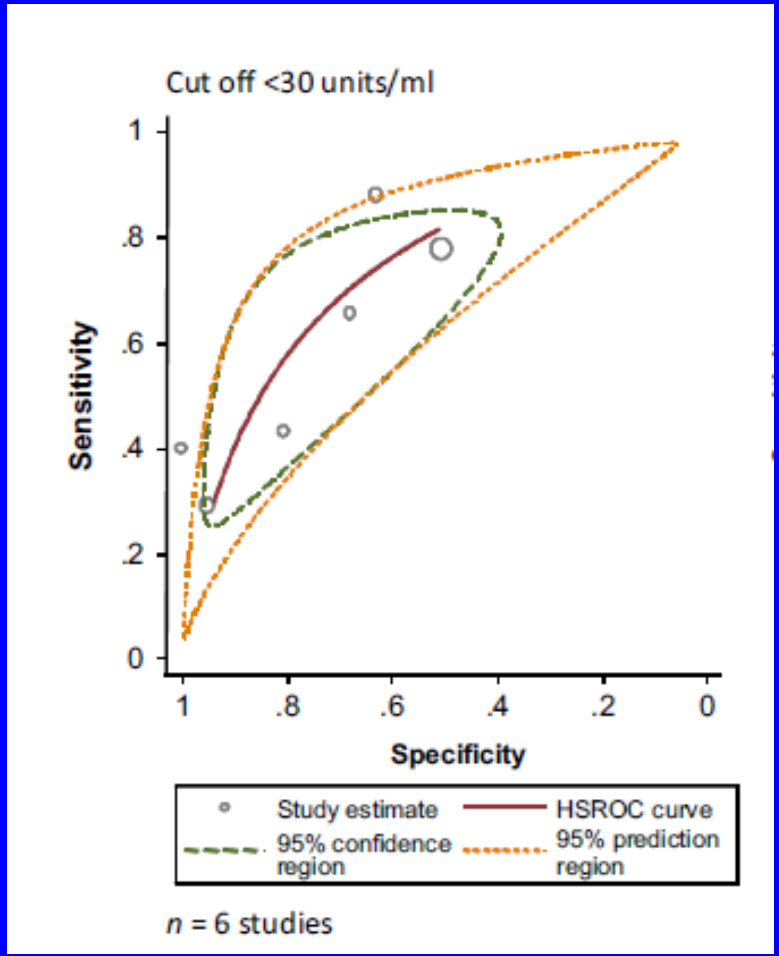
Biomarker	Sensitivity	Specificity
Anti-endometrial antibodies	81%	75%
IL-6	63%	69%
CA 19-9	36%	87%
CA 125 (low cutoff)	70%	64%
CA 125 (high cutoff)	50%	91%

CA-125

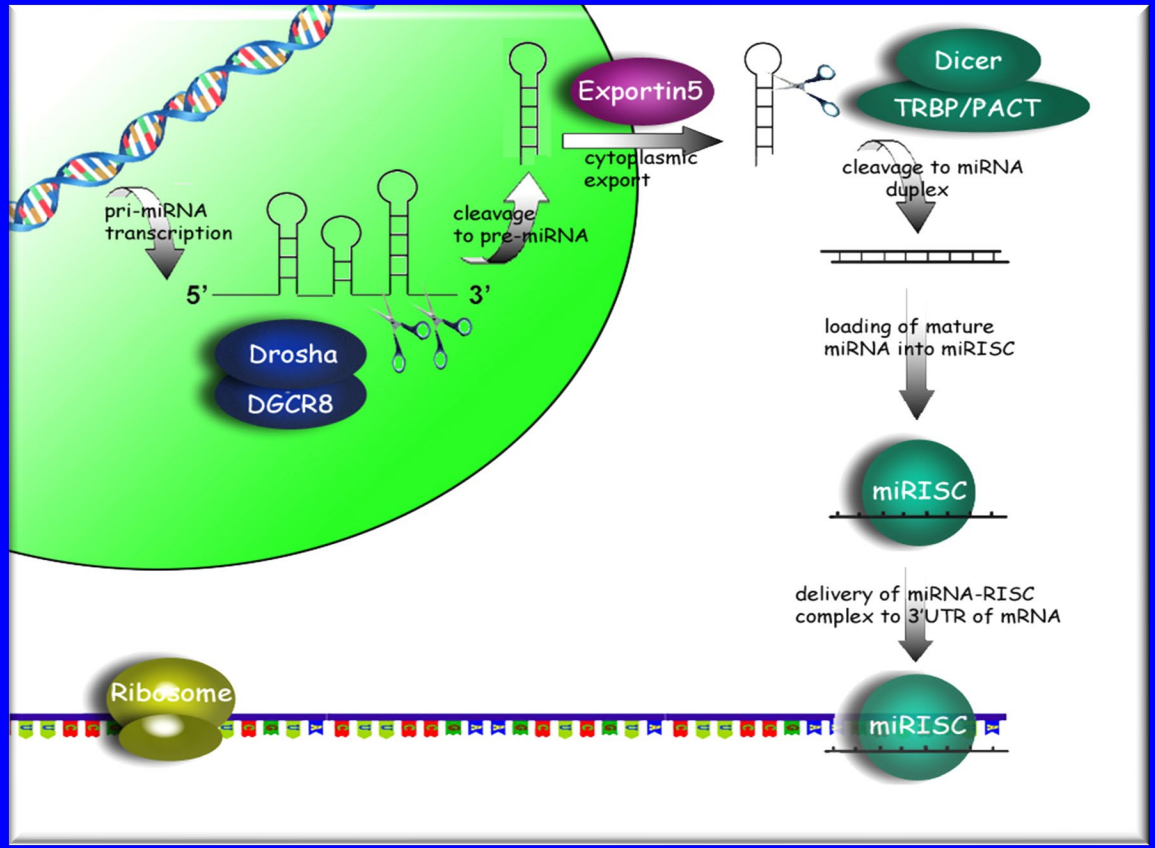
Medscape® www.medscape.com

Reference (*n* = Number of Patients)	Assay;Timing of Sample Collection	Stage	Sensitivity (%)	Specificity (%)
Barbieri et al, 1986[91]	Standard assay; timing of	All	17	96
(*n* = 147)	sample collection unknown	III+IV	54	96
Patton et al, 1986[177]	Standard assay; timing of	All	14	93
(*n* = 113)	sample collection unknown	III+IV	18	93
Pittaway and Fayez, 1986[92]	Standard assay (cutoff level	All	17	93
(*n* = 414)	30 IU/mL); follicular phase	III+IV	42	93
Koninckx et al, 1992[94]	Standard assay; late luteal	All	13	96
(*n* = 259)	phase	III+IV	31	94
O'Shaughnessy et al, 1993[96]	Standard assay; menstrual	All	27	100
(*n* = 100)		III+IV	67	100
Hornstein et al, 1995[97]	Standard assay; early	All	16	92
(*n* = 123)	follicular phase	III+IV	40	92
	CA 125 II assay; early	All	23	94
	follicular phase	III+IV	60	94
Medl et al, 1997[114]	Standard assay; timing of	All	36	92
(*n* = 368)	sample collection unknown	III+IV	44	86
Chen et al, 1998[107]	CA 125 II assay;	All	61	88
(*n* = 157)	luteal phase	III+IV	87	88

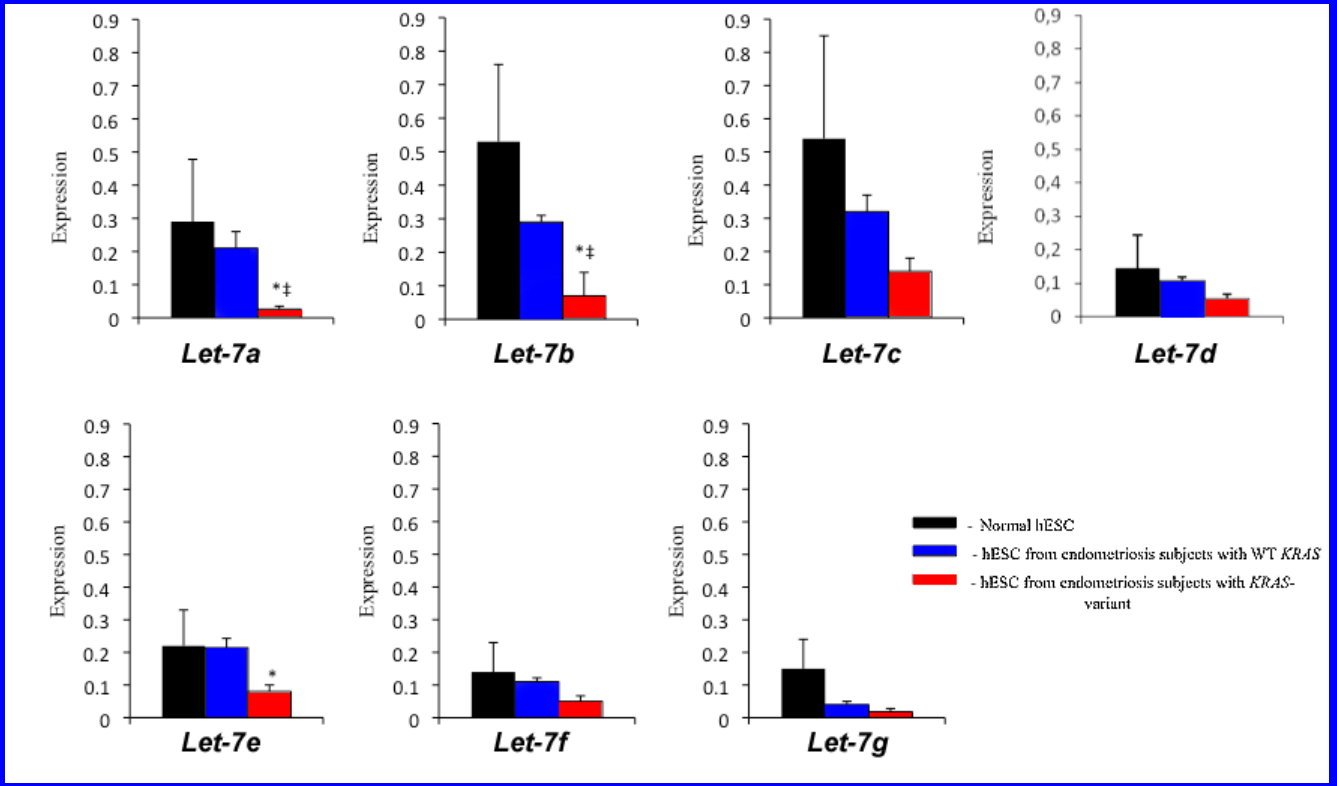
Source: Semin Reprod Med © 2003 Thieme Medical Publishers



Micro RNA (MiRNA)

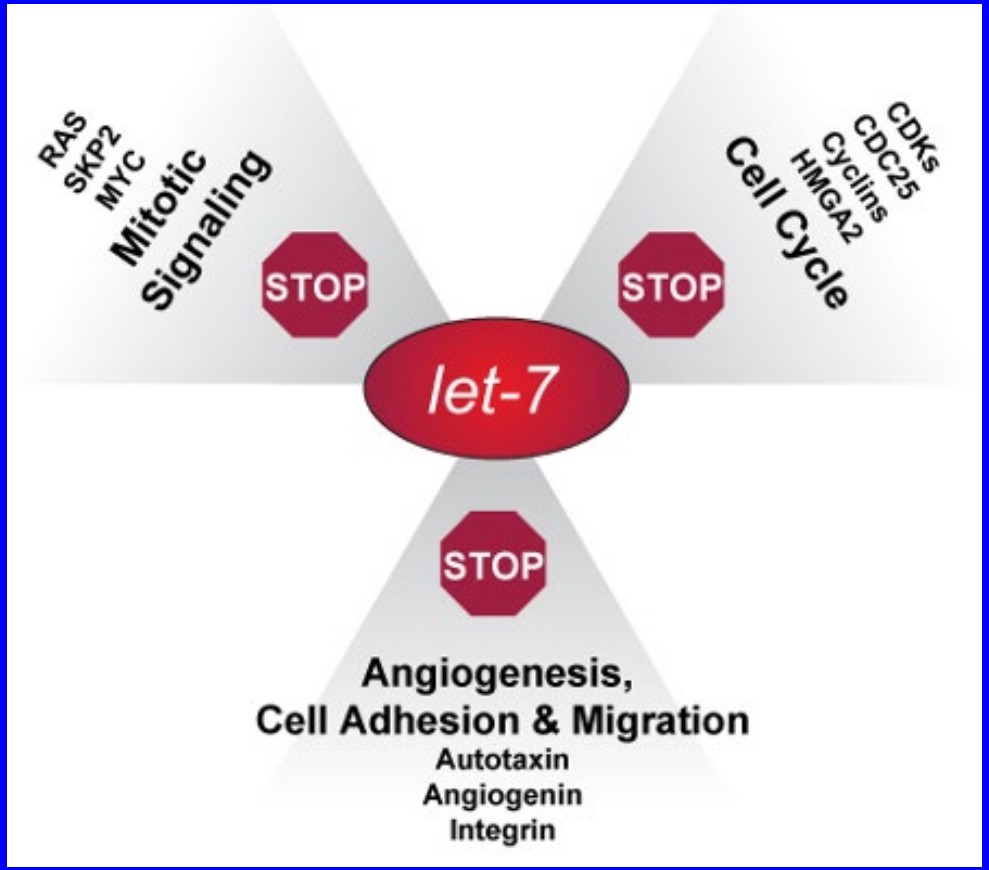


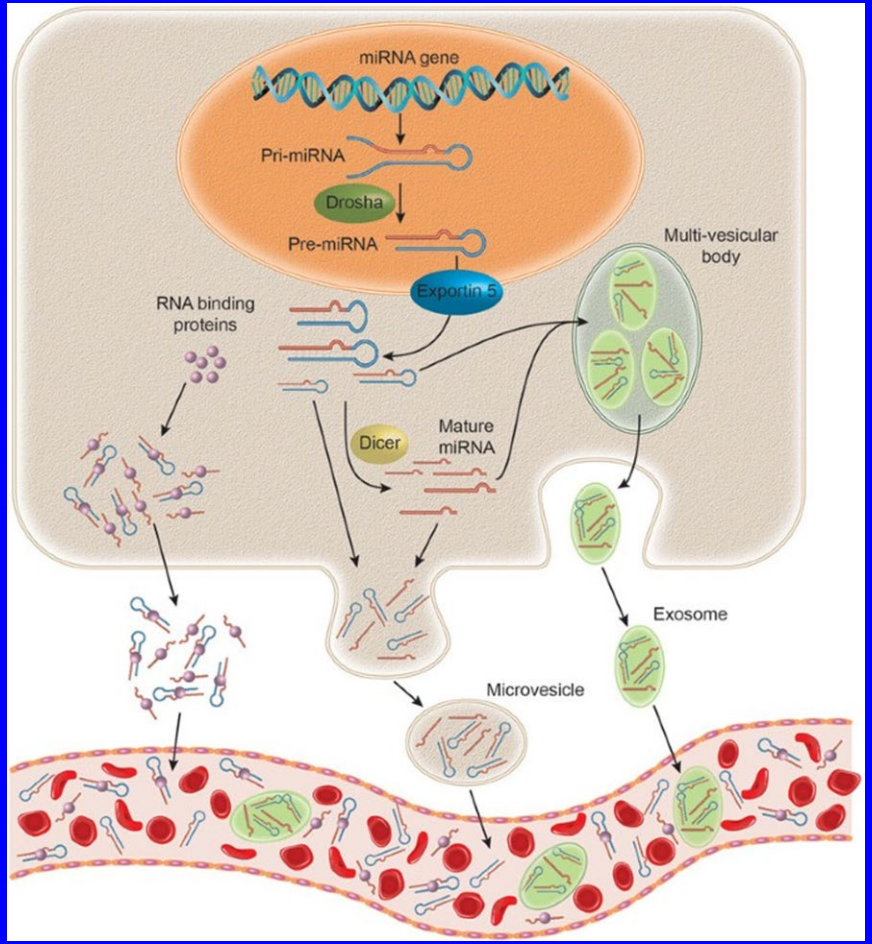
Decreased Let-7 micro RNAs in Endometriosis



Grechukhina et al, EMBO Mol Med 2012;4(3):206-217

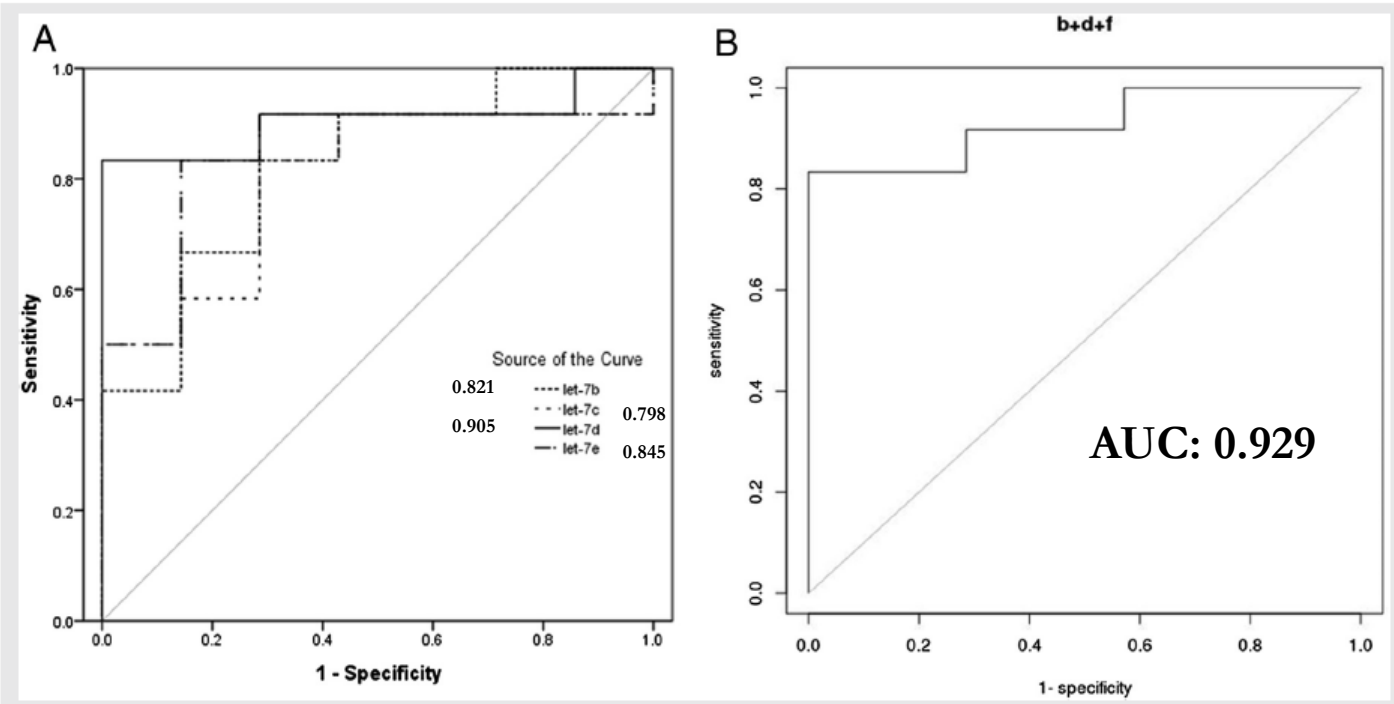
Let-7 signaling

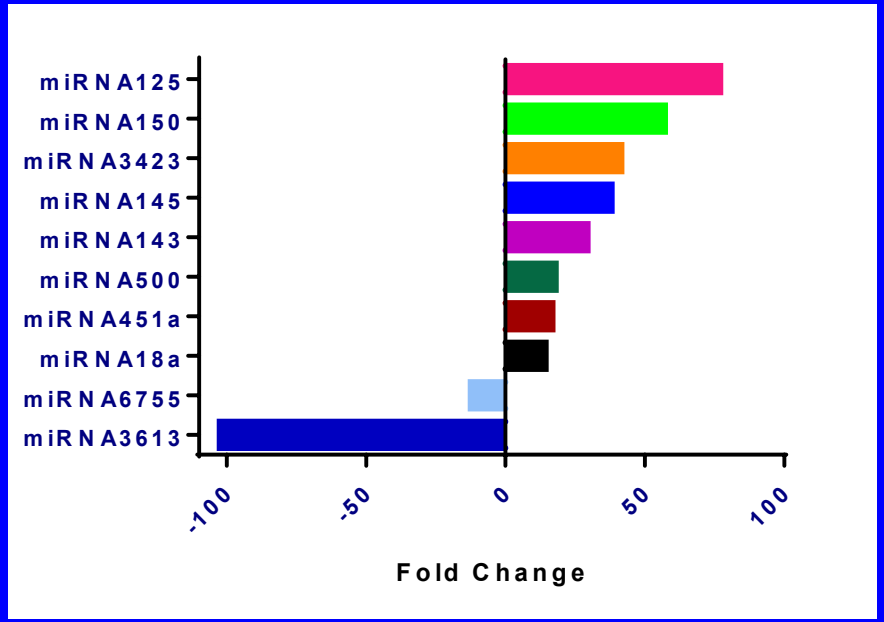



miRNA gene
Pri-miRNA
Drosha
Pre-miRNA
Exportin 5
Multi-vesicular body
RNA binding proteins
Dicer
Mature miRNA
Exosome
Microvesicle

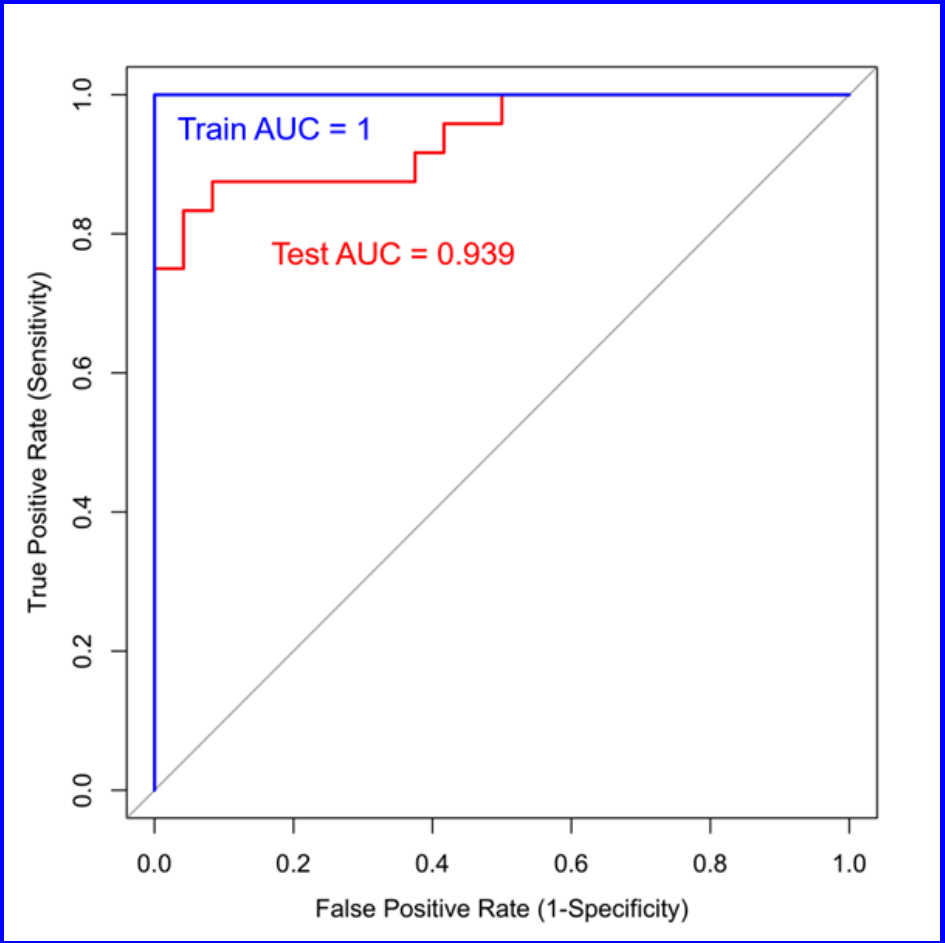
Circulating miRNAs as Serum Biomarkers of Endometriosis

ROC Curves of let7 During the Proliferative Phase of Menstrual Cycle

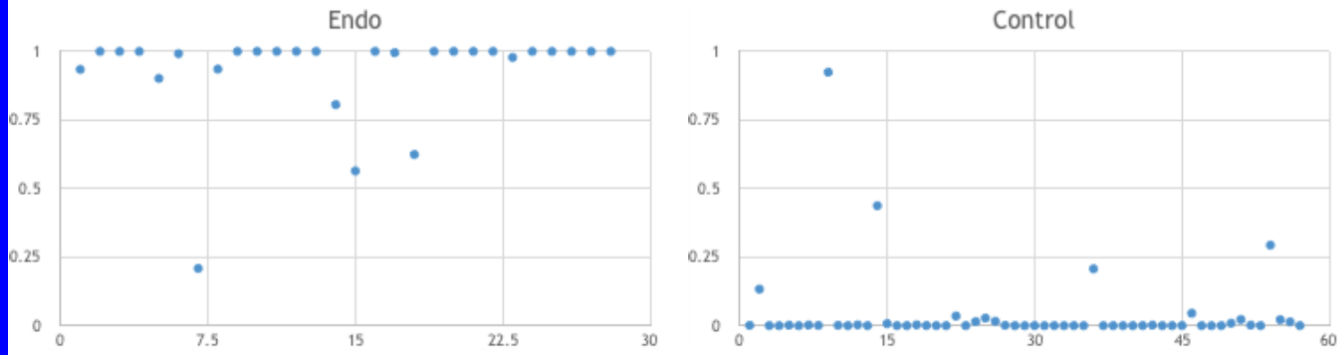




Cosar et al, Fertil Steril 2016

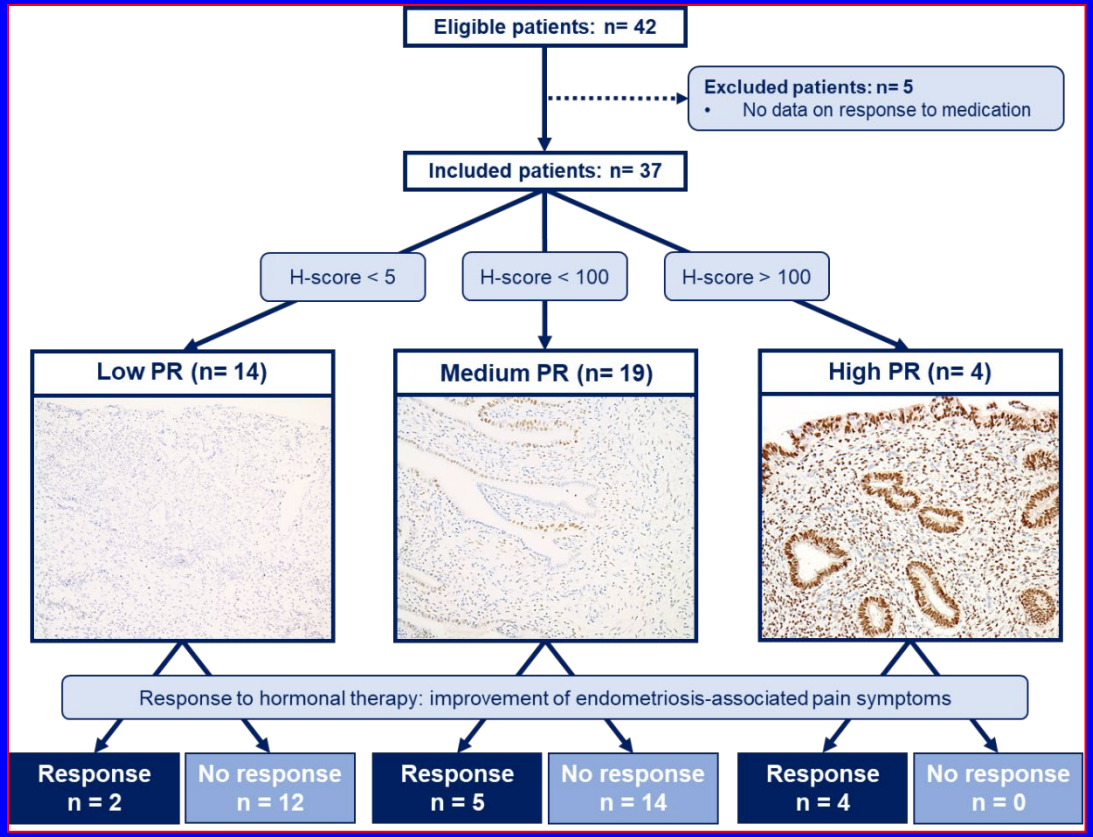

Train AUC = 1
Test AUC = 0.939
True Positive Rate (Sensitivity)
False Positive Rate (1-Specificity)
0.0
0.2
0.4
0.6
0.8
1.0

5 marker model

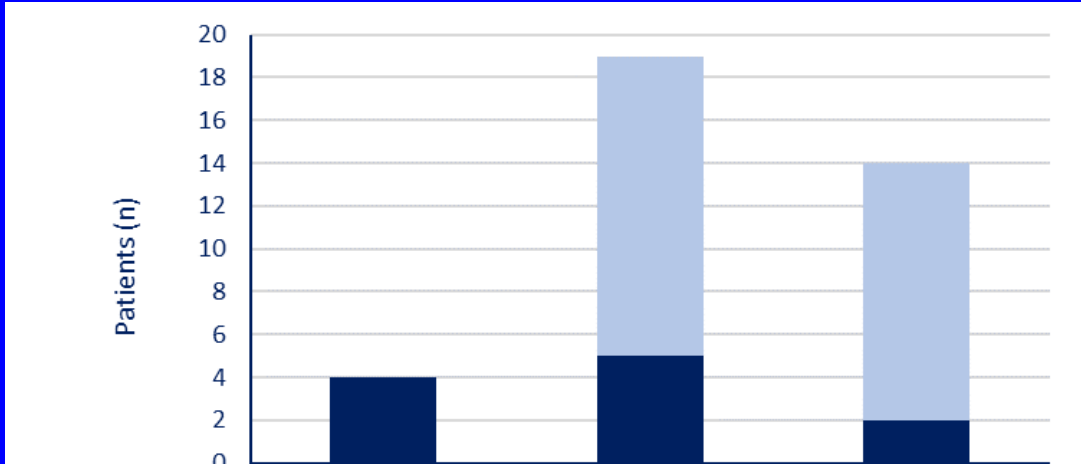


- Algorithm able to provide clear distinction between endometriosis and other benign gynecological pathologies
- Only 1 false positive and 1 false negative observed in above analysis of algorithm performance in prospective dataset

Markers of Progestin Resistance



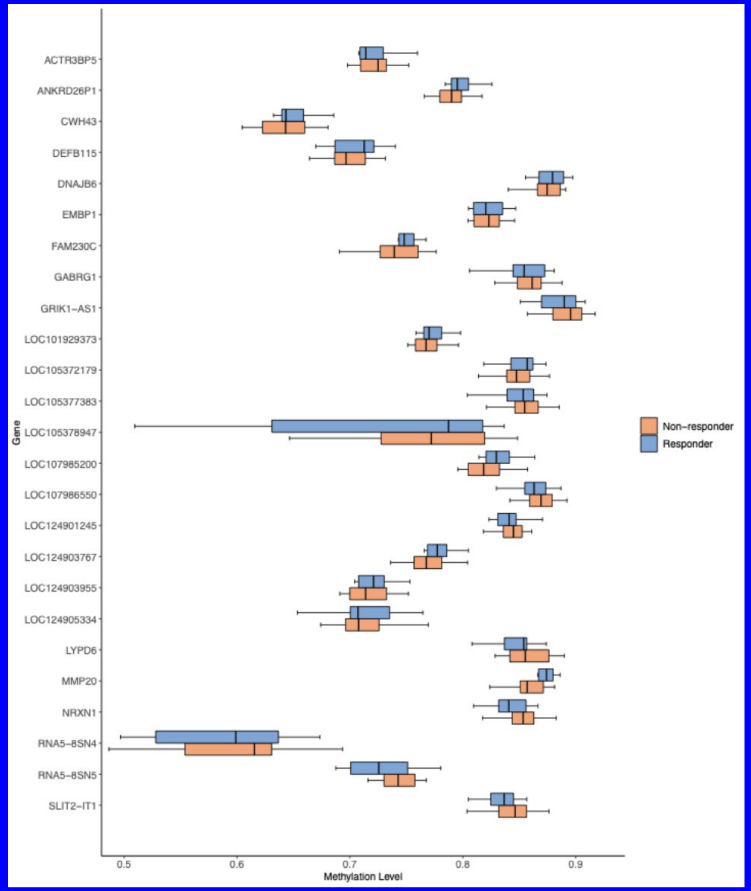
Flores V at al JCEM 2017



	High PR	Medium PR	Low PR
Response rate	100%	26%	14%
No Response	0	14	12
Response	4	5	2

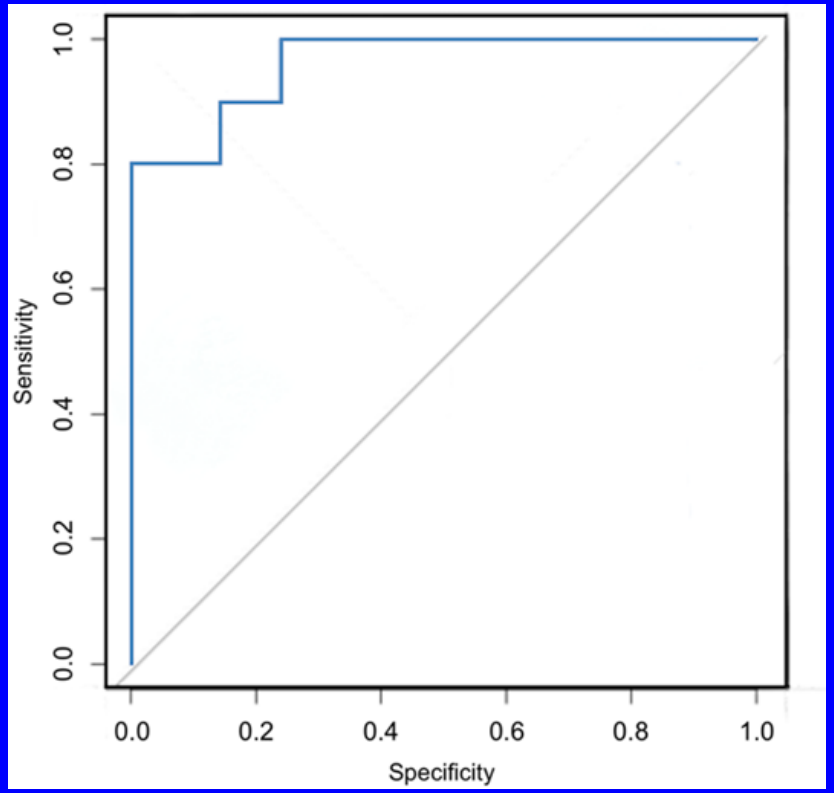
- PR status was significantly associated (**p= 0.004**) with response to progestin therapy.
- All patients with high PR responded to progestin therapy.
- 86% of patients in the low PR group did not respond to progestin therapy.
- The medium PR group had a response rate of 26%

Epigenetic Marks in Leukocytes

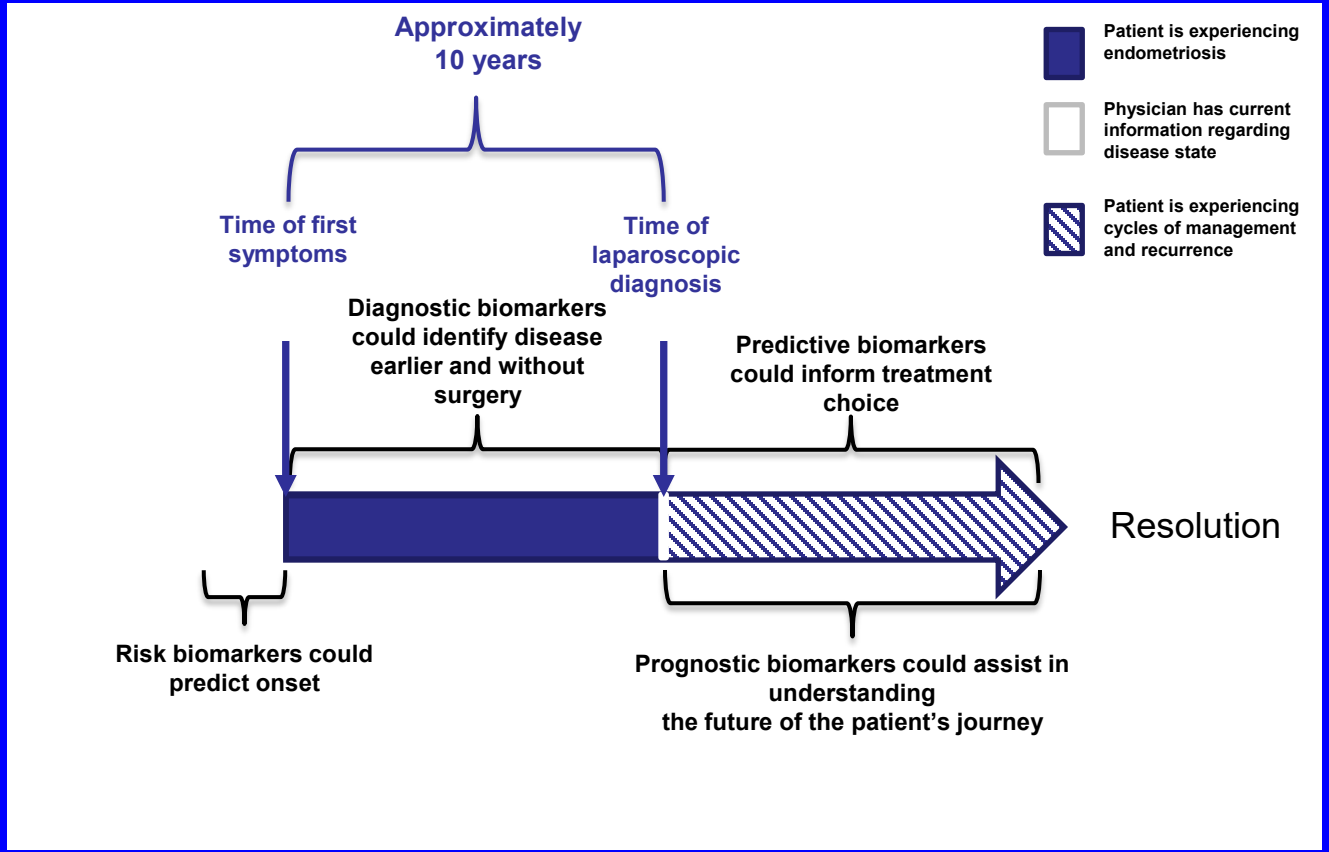


Cevik et al. Biomarkers Res 2026

Epigenetic Biomarkers of Progesterone Resistance in Peripheral Blood



Changing the Timeline



Clinical Diagnosis

- **Cyclic**
- **Progressive**: over time, pain worsens or changes in character