

Salivary micro-RNA test for the diagnosis of endometriosis (Endotest)



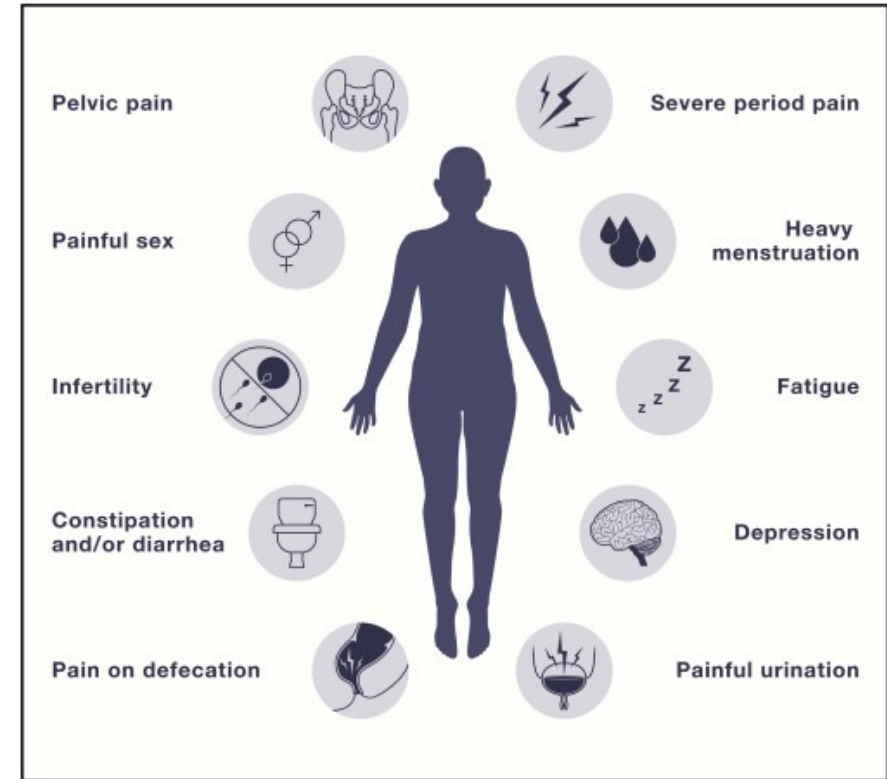
**S. Bendifallah, A.Spiers, L.Delbos, M.Poilblanc, F.Golfier,
S.Suisse, Ph. Descamps (*Paris-Lyon-Angers*)**

Conflicts of interest

None

Endometriosis a Complex Disease

- Endometriosis is a common disease affecting **5-10% of women of reproductive age globally**
- Endometrial-like tissue outside the uterine cavity
- Characterized mainly by symptoms of **pain and infertility**.
- Three subtypes ; **peritoneal endometriosis, deep endometriosis and endometrioma**.



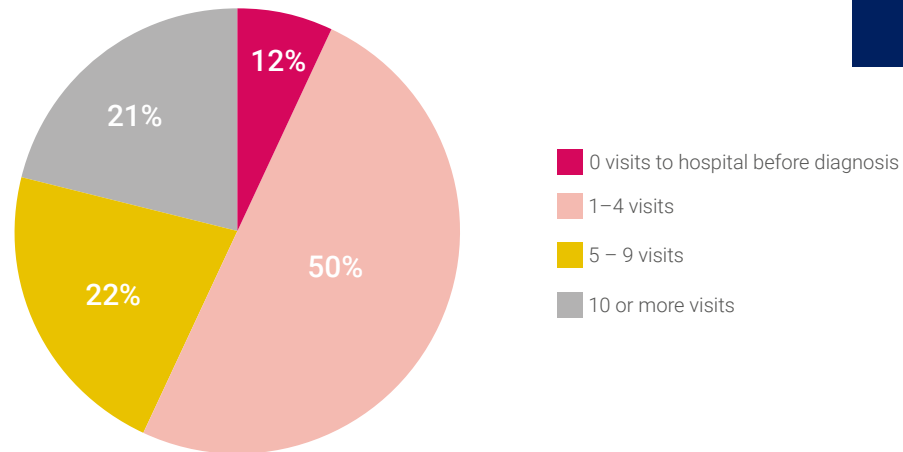
Saunders, Philippa T K, and Andrew W Horne.
“Endometriosis: Etiology, pathobiology, and therapeutic prospects.” *Cell* vol. 184,11 (2021): 2807-2824. doi:10.1016/j.cell.2021.04.041

A Delayed Diagnosis....



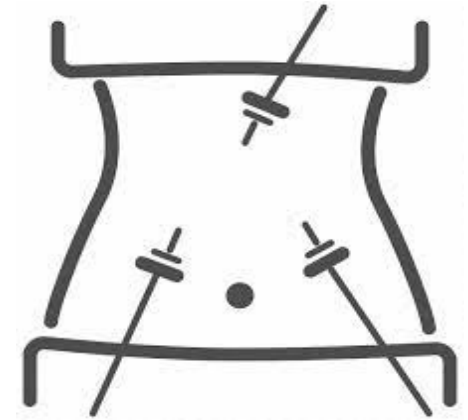
7 Years
is the average
Time to
diagnosis

If you have been diagnosed, approximately how many times did you visit the Doctors in hospital with your symptoms of endometriosis, before you received a diagnosis for endometriosis?



40% >5-10
Consultations

25%



A Delayed diagnosis

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Endometriosis

Krina T. Zondervan, D.Phil., Christian M. Becker, M.D.,
and Stacey A. Missmer, Sc.D.

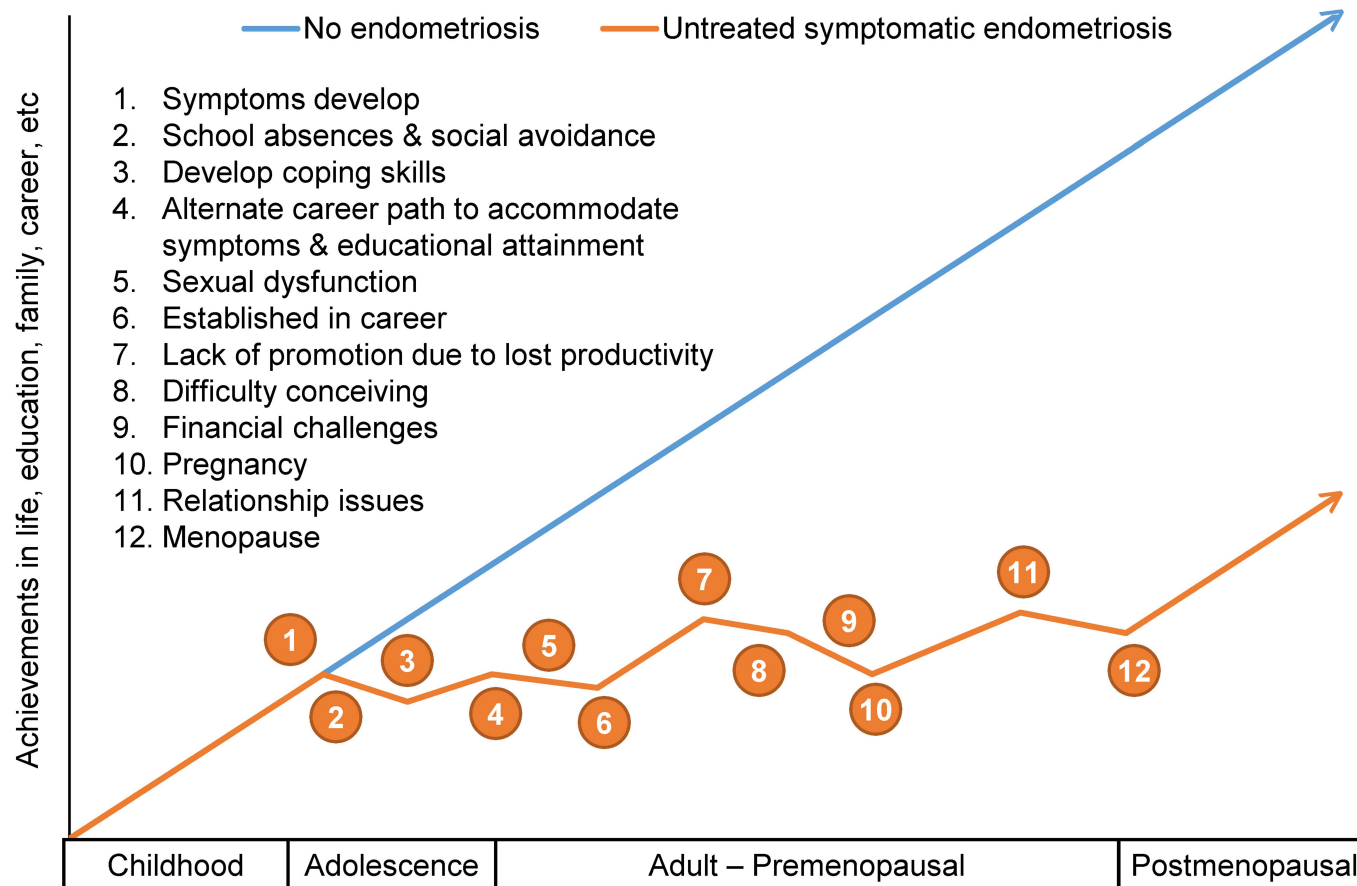
**7-10
years.....**



Figure 5. The Diagnostic Challenge in Endometriosis.

Consequences of Delayed Diagnosis....

Life Course Impact of Untreated Symptomatic Endometriosis




Wandering

Suffering

InvestigationS

Discrepancy

Questionnaires for Endometriosis screening


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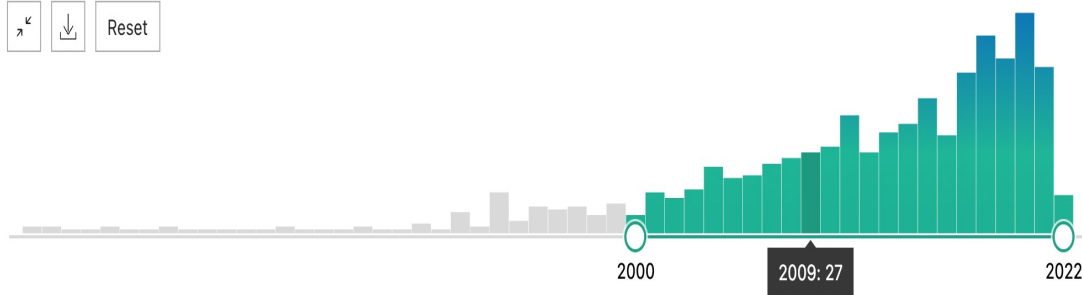
Sorted by: Most recent 

Display options 

RESULTS BY YEAR

634 results

Page 1 of 64



Patient-completed or symptom-based screening tools for endometriosis: a scoping review

Eric Surrey¹ · Cathryn M. Carter² · Ahmed M. Soliman³ · Shahnaz Khan⁴ · Dana B. DiBenedetti⁴ · Michael C. Snabes³

Feb 2017

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Abstract

Purpose The objective of this review was to evaluate existing patient-completed screening questionnaires and/or symptom-based predictive models with respect to their potential for use as screening tools for endometriosis in adult women. Validated instruments were of particular interest.

Methods We conducted structured searches of PubMed and targeted searches of the gray literature to identify studies reporting on screening instruments used in

all studies, as most studies focused on diagnosis versus screening.

Conclusions This literature review did not identify any fully validated, symptom-based, patient-reported questionnaires for endometriosis screening in adult women.

Keywords Endometriosis · Patient-reported · Screener · Self-administered · Symptoms

Endometriosis Diagnostics

Patient-completed or symptom-based screening tools for endometriosis: a scoping review

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Abstract

Purpose The objective of this review was to evaluate existing patient-completed screening questionnaires and/or symptom-based predictive models with respect to their potential for use as screening tools for endometriosis in adult women. Validated instruments were of particular interest.

Methods We conducted structured searches of PubMed and targeted searches of the gray literature to identify studies reporting on screening instruments used in endometriosis. Studies were screened according to inclusion and exclusion criteria that followed the PICOS (population, intervention, comparison, outcomes, study design) framework.

Results A total of 16 studies were identified, of which 10 described measures for endometriosis in general, 2 described measures for endometriosis at specific sites, and 4 described measures for deep-infiltrating endometriosis. Only 1 study evaluated a questionnaire that was solely patient-completed. Most measures required physician, imaging, or laboratory assessments in addition to patient-completed questionnaires, and several measures relied on complex scoring. Validation for use as a screening tool in adult women with potential endometriosis was lacking in

all studies, as most studies focused on diagnosis versus screening.

Conclusions This literature review did not identify any fully validated, symptom-based, patient-reported questionnaires for endometriosis screening in adult women.

Keywords Endometriosis · Patient-reported · Screener · Self-administered · Symptoms

Introduction

Endometriosis is a painful, inflammatory condition characterized by the development of endometrial-like tissue outside the uterus [1]. Endometriotic lesions may occur at various anatomic sites, including the pelvic peritoneum and the ovary [2]. Deep-infiltrating endometriosis occurs in the pelvic structures below the surface of the peritoneum. More rarely, endometriosis lesions of the bladder, ureter, or extrapelvic sites may also occur [2].

An estimated 10% of women of reproductive age are affected by endometriosis [3]. Endometriosis causes considerable clinical, economic, and humanistic burden. Clinical symptoms include chronic pelvic pain, dysmenorrhea, and infertility [3], and endometriosis may increase a woman's risk of cancer or autoimmune disorders [4, 5]. Numerous studies have demonstrated the considerable economic burden associated with endometriosis [6–8]. Hospitalizations, especially those related to surgical intervention, are a primary direct cost driver for endometriosis [6, 7, 9, 10]. Moreover, endometriosis has a significant social and psychological impact on the lives of women across several domains, including quality of life, intimate relationships, fertility, education and work, and emotional well-being [11, 12].

A new validated screening method for endometriosis diagnosis based on patient questionnaires

Charles Chapron,^{a,b,c,1} Marie-Christine Lafay-Pillet,^{b,1} Pietro Santulli,^{a,b,c} Mathilde Bourdon,^{a,b} Chloé Maignien,^b Antoine Gaudet-Chardonnet,^b Lorraine Maitrot-Mantelet,^b Bruno Borghese,^{a,b,c} and Louis Marcellin,^{a,b,c}

Early identification of women with endometriosis by means of a simple patient-completed questionnaire screening tool: a diagnostic study

Arnaud Fauconnier, M.D., Ph.D.,^a Hocine Driouche, M.Sc.,^b Cyrille Huchon, M.D., Ph.D.,^a Joseph Du Cheyron, B.Sc.,^b Emilie Indersie, Ph.D.,^c Yasmine Candau, M.B.A.,^c Pierre Panel, M.D.,^d and Xavier Fritel, M.D., Ph.D.^e

No evidence that questionnaires reduce the time to diagnosis

2022

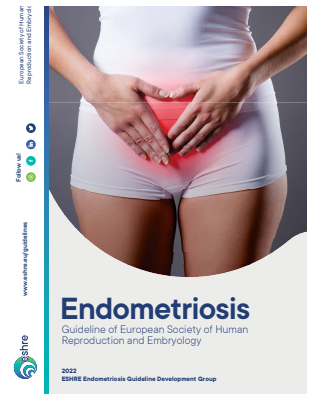
Not reliable enough

2017-2022

Surrey et al.

No fully validated questionnaire for endometriosis screening

2000-2017



ESHRE guidelines

✉ Cathryn M. Carter
ccarter@rti.org

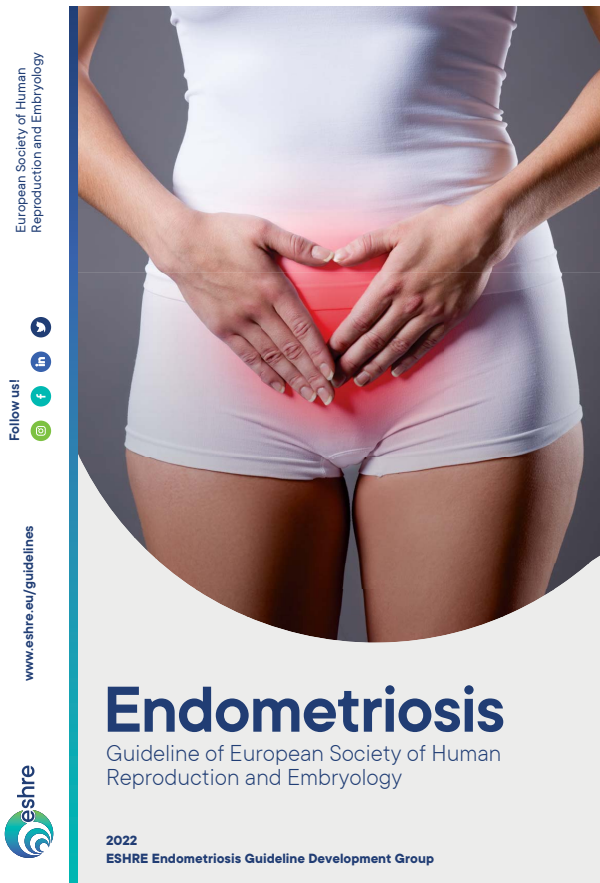
¹ Colorado Center for Reproductive Medicine, Lone Tree, CO, USA

² RTI Health Solutions, 3055 Boardwalk Street, Suite 105, Ann Arbor, MI 48106, USA

³ AbbVie, North Chicago, IL, USA

⁴ RTI Health Solutions, Research Triangle Park, NC, USA

Diagnostic Algorithms in 2023



DIAGNOSIS OF ENDOMETRIOSIS

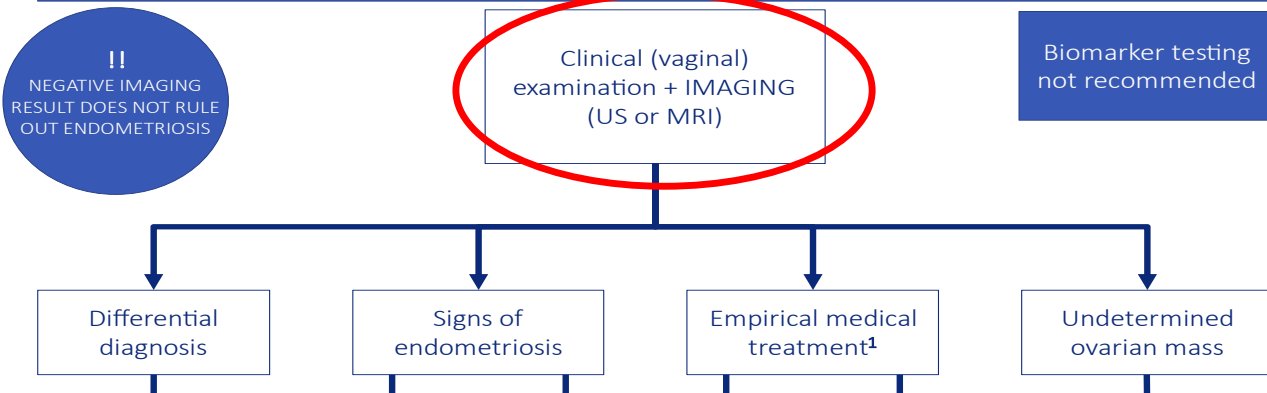
SIGNS AND SYMPTOMS

Consider Endometriosis when the woman reports one or more of these symptoms

Dysmenorrhoea	Shoulder tip pain
Deep dyspareunia	Catamenial pneumothorax
Dysuria	Cyclical cough/haemoptysis /chest pain
Dyschezia	Cyclical scar swelling and pain
Painful Rectal bleeding	Fatigue
Haematuria	Infertility

A symptom diary or app can be helpful in the history taking process

Explore a diagnosis of endometriosis



2022 ESHRE recommendations: Diagnosis of endometriosis

Clinicians should not use measurement of biomarkers in endometrial tissue, blood, menstrual or uterine fluids to diagnose endometriosis.

⊕⊕⊕○

ESHRE 2022 Guidelines

Recommendations (5-7)

Clinicians are recommended to use imaging (US or MRI) in the diagnostic work-up for endometriosis, but they need to be aware that a negative finding does not exclude endometriosis, particularly superficial peritoneal disease.

⊕⊕○○

In patients with negative imaging results or where empirical treatment was unsuccessful or inappropriate, the GDG recommends that clinicians consider offering laparoscopy for the diagnosis and treatment of suspected endometriosis.

GPP

The GDG recommends that laparoscopic identification of endometriotic lesions is confirmed by histology although negative histology does not entirely rule out the disease.

GPP



Endometriosis

Guideline of European Society of Human Reproduction and Embryology

2022
ESHRE Endometriosis Guideline Development Group

ESHRE 2022 Guidelines

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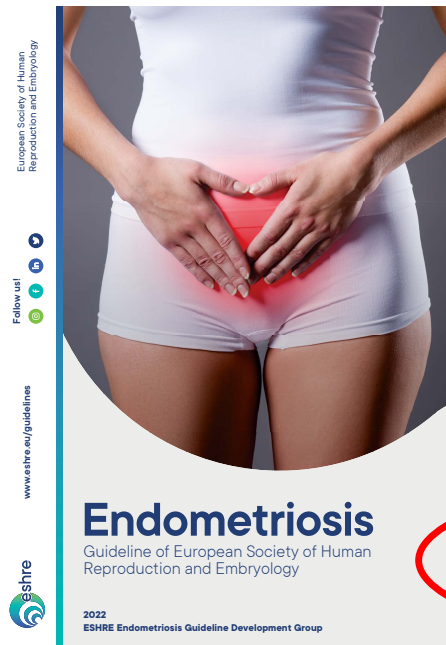
⊕⊕○○

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GPP




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GPP

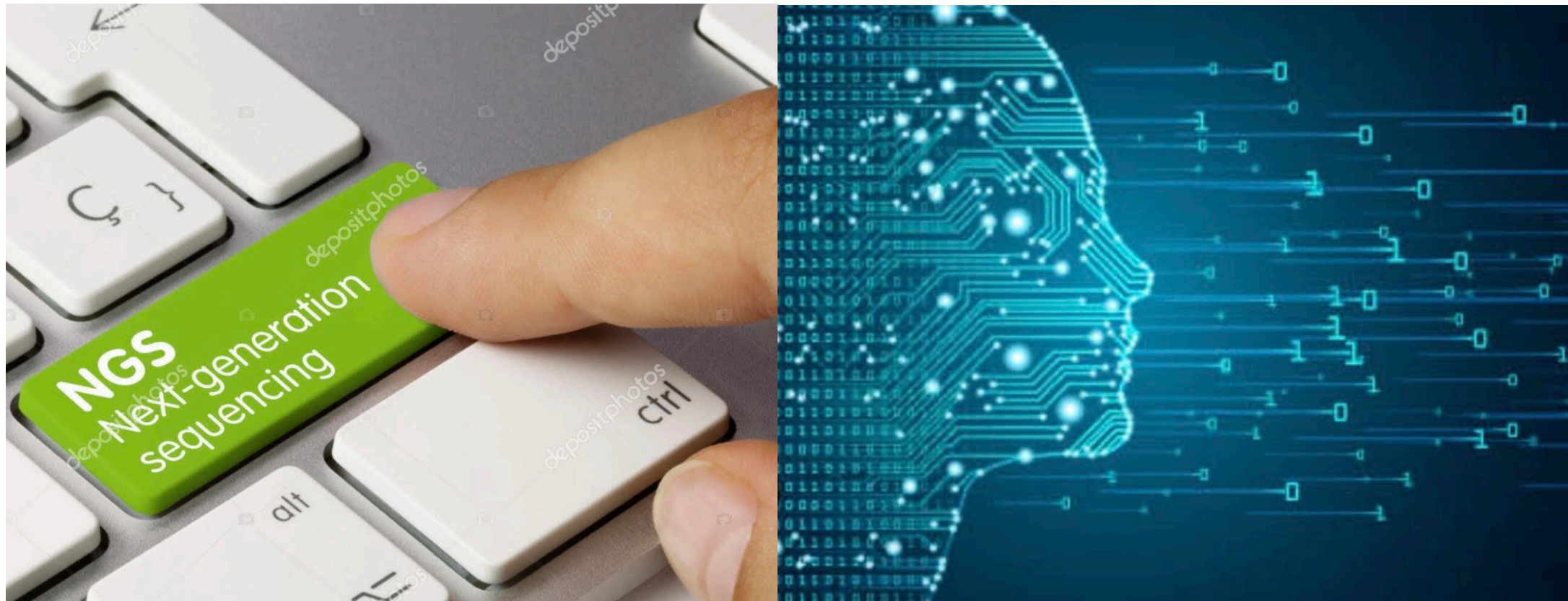


Endometriosis Diagnostic Tests



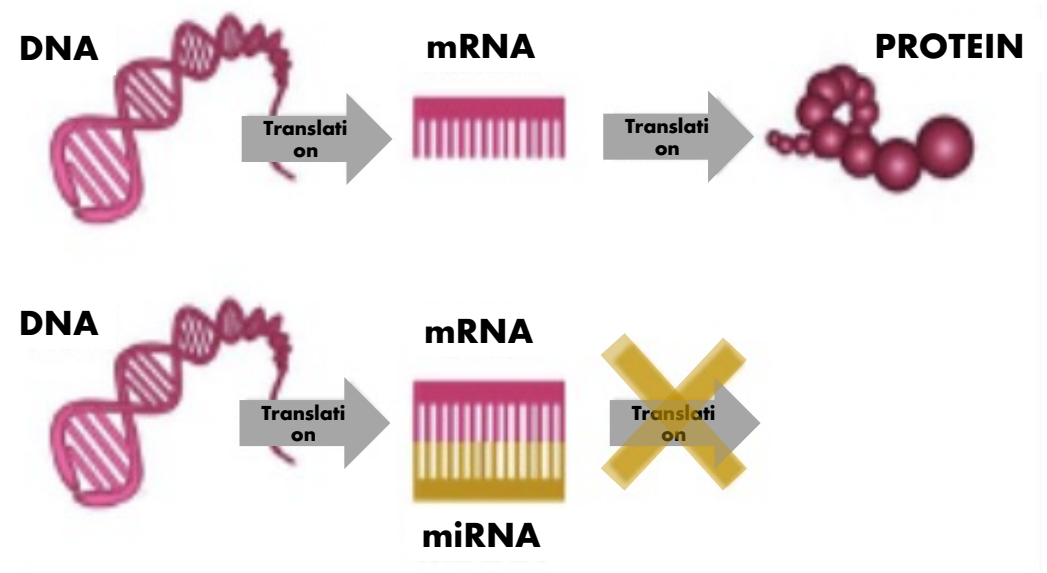
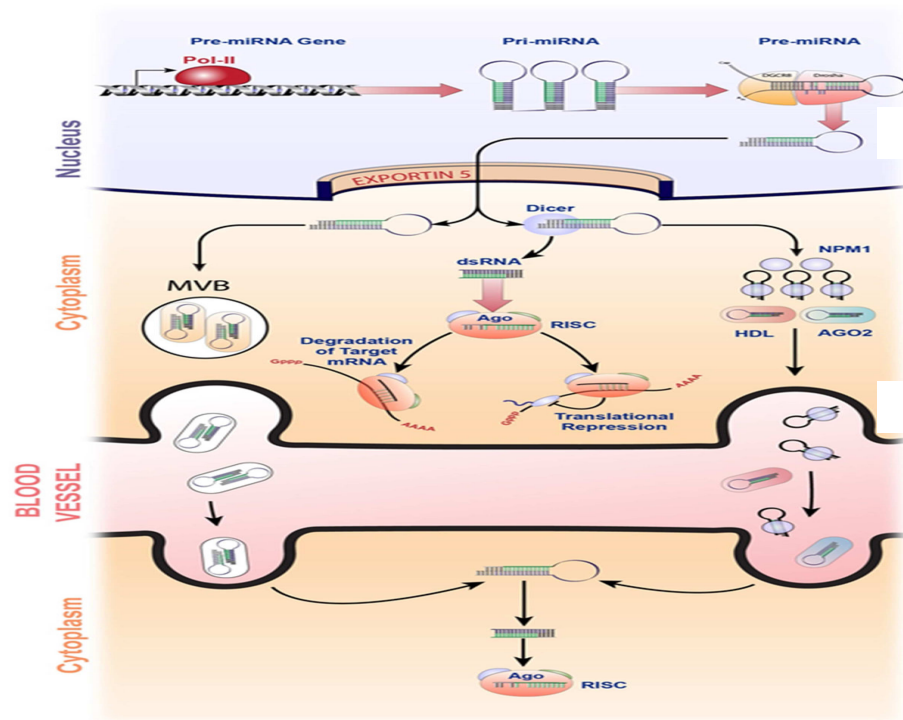
Endometriosis test	 Medical questionnaire	 Ultrasound imaging	 MRI imaging	 Blood test	 Surgery and pathology	
General value	++	++	+++	-	++++	
Performance value						
- Sensitivity	76-98%	65-79%	79%	63%	90-94%	
- Specificity	20-58%	91-95%	72%	69%	40-79%	
Reliability	Very Low specificity	Low accuracy for early stage lesion	Low accuracy for early stage lesion	-	Yes	
	+	++	++		++++	
Reproducibility	+	+	+++	-	+++	
Be simple, safe	++++	++	+++	+++	+	
Acceptability	++++	+++	++	++	+	
Detect disease early in its natural history	+	++	+	-	++++	

miRNA – NGS and AI

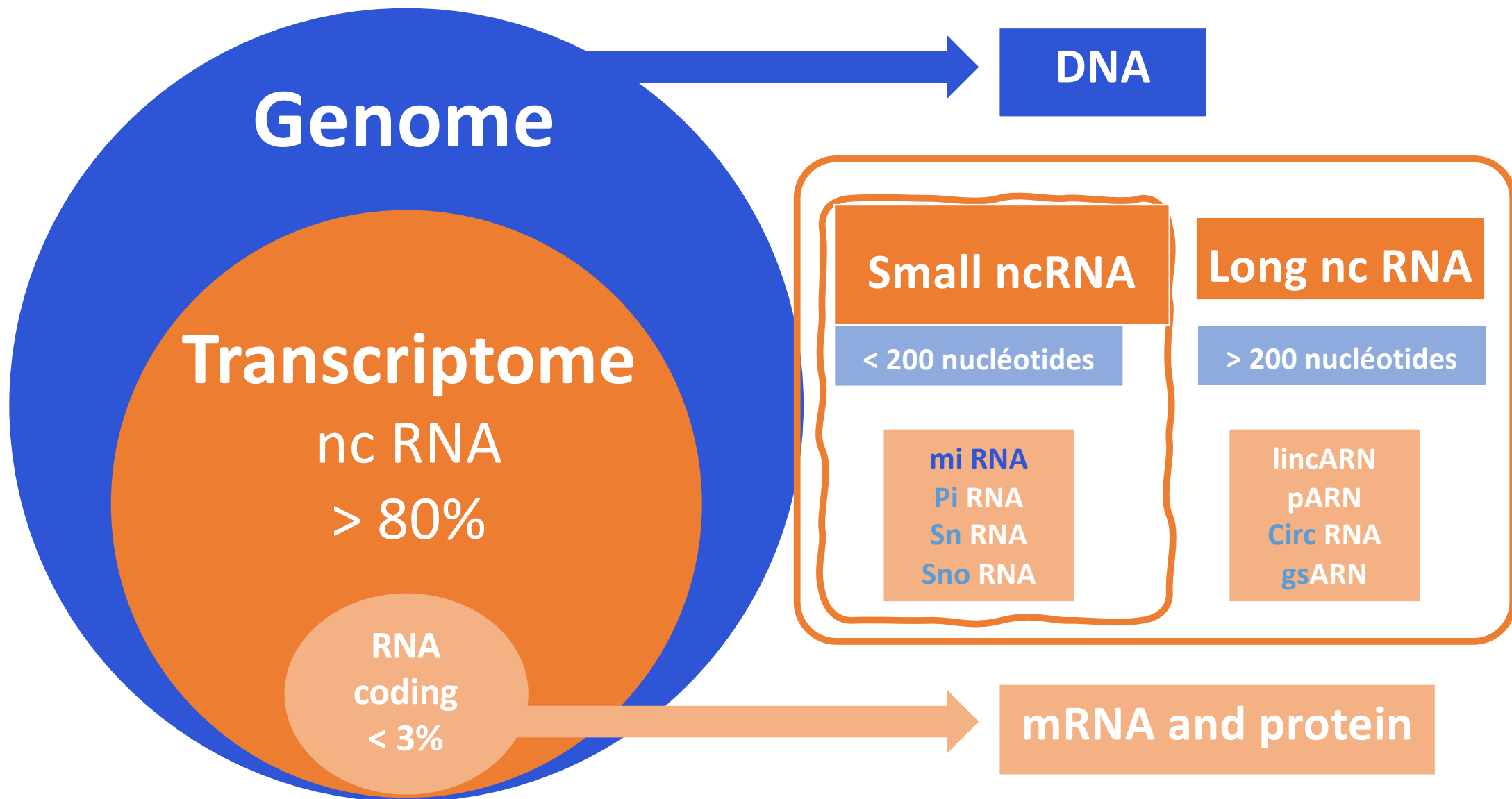


Biosynthesis of miRNAs

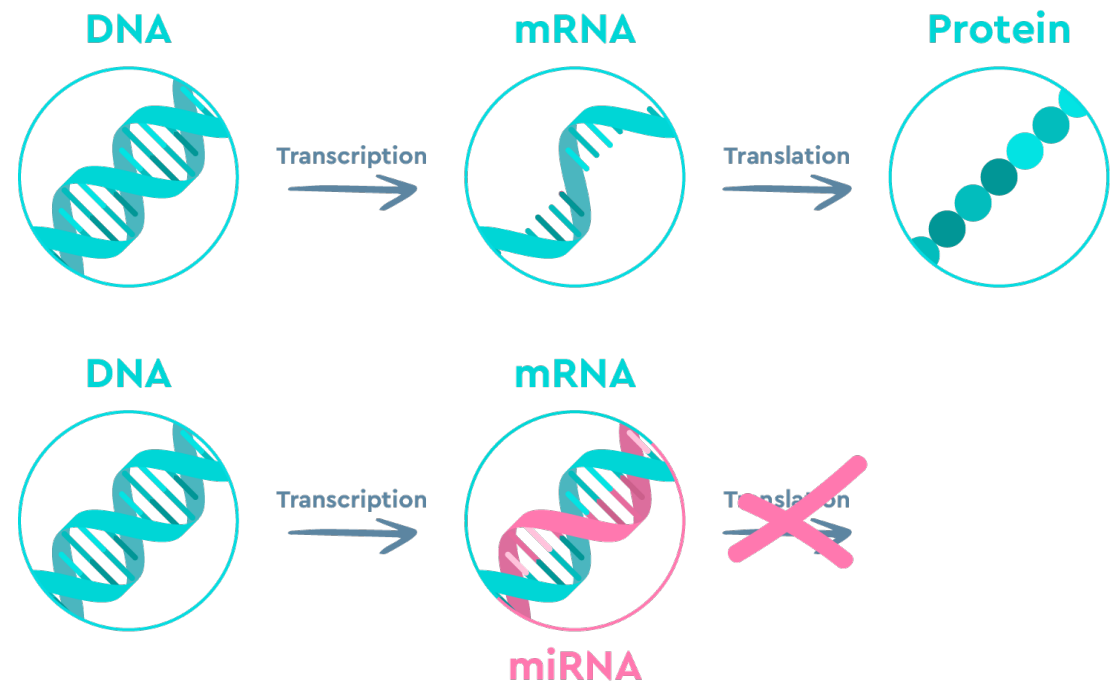
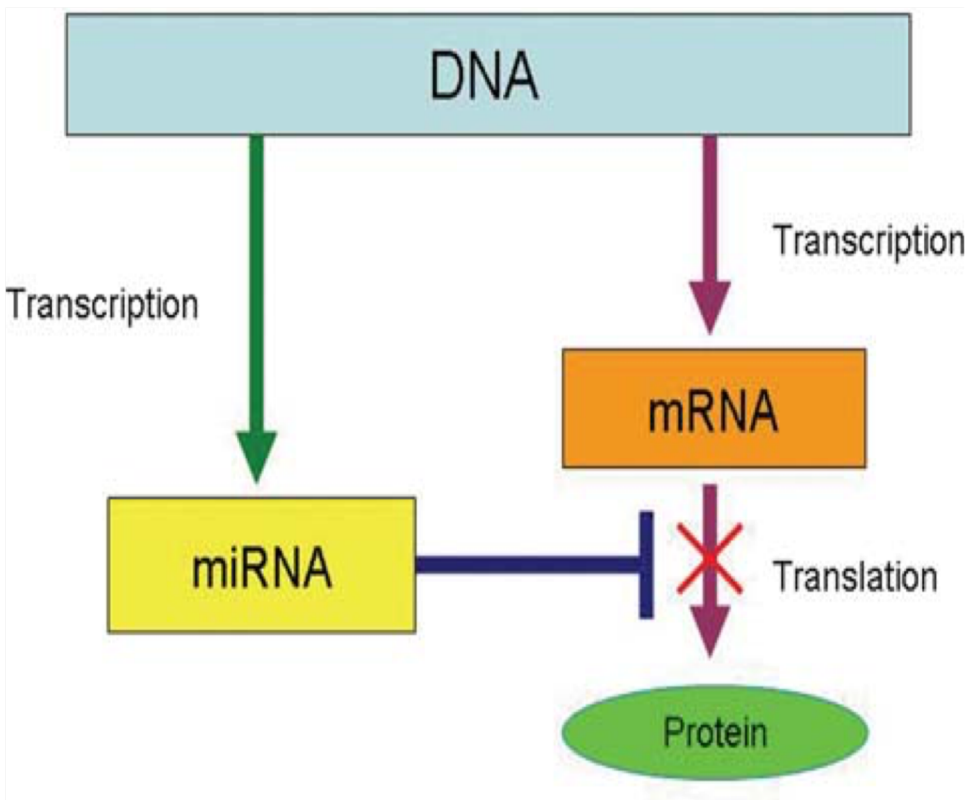
Detection in biofluids



Regulation of gene expression by miRNA

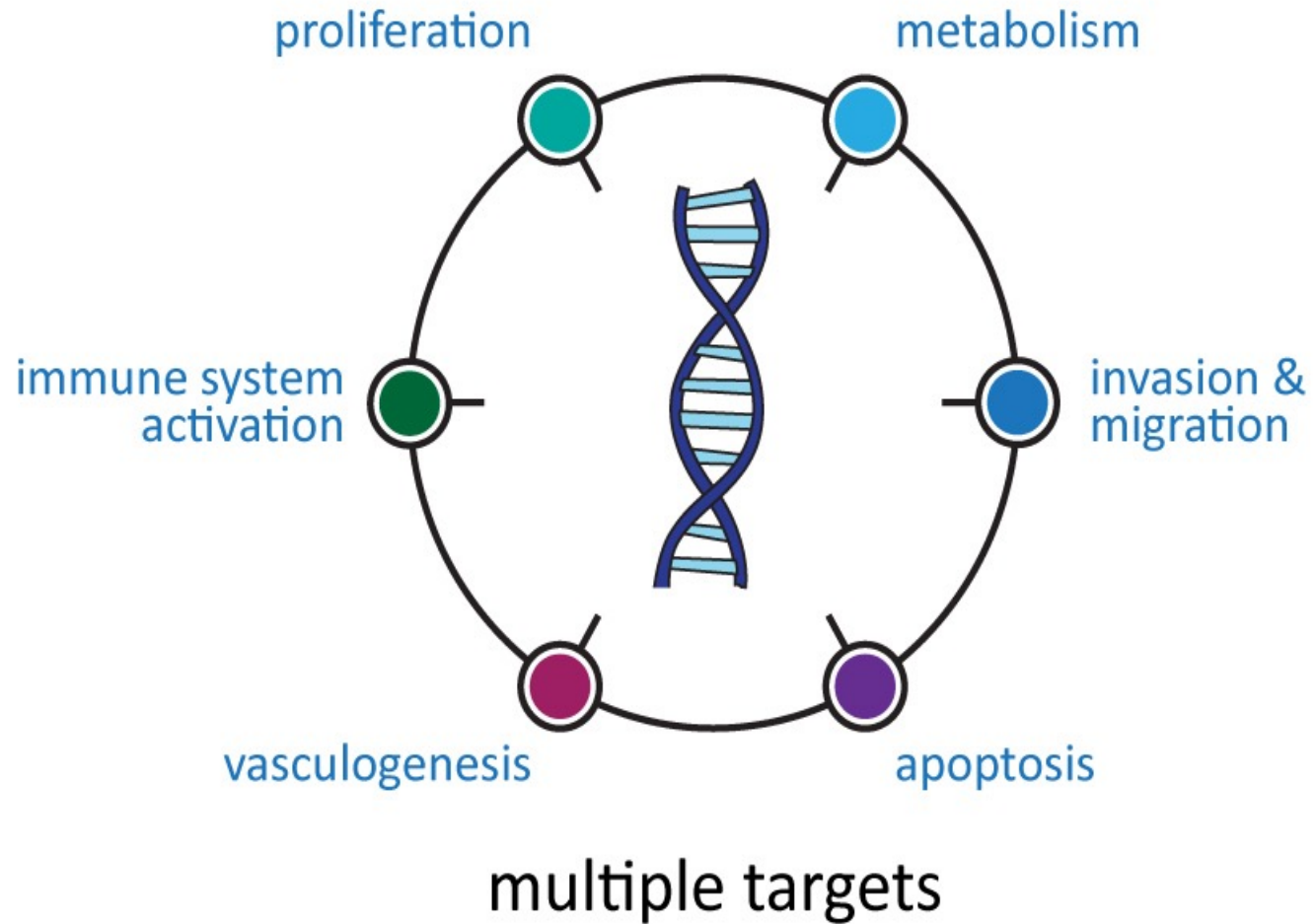


Regulation of Gene Expression by miRNA



Guo, Sun-Wei. "Epigenetics of endometriosis." *Molecular human reproduction* vol. 15,10 (2009): 587-607.
doi:10.1093/molehr/gap064

miARNs function



Cancer
Neurology
Auto immune

The pioneers....

Individual analysis of 6 mi-RNA

No exhaustive analysis of mi-RNome

No NGS, no AI

Circulating MicroRNAs Identified in a Genome-Wide Serum MicroRNA Expression Analysis as Noninvasive Biomarkers for Endometriosis

Wen-Tao Wang,* Ya-Nan Zhao,* Bo-Wei Han, Shun-Jia Hong, and Yue-Qin Chen

Department of Obstetrics and Gynecology, Sun Yat-sen Memorial Hospital (Y.-N.Z., S.-J.H.), Key Laboratory of Gene Engineering of the Ministry of Education, and State Key Laboratory for Biocontrol (W.-T.W., B.-W.H., Y.-Q.C.), Sun Yat-sen University, Guangzhou 510120, China

Context: There is currently no reliable noninvasive biomarker for the clinical diagnosis of endometriosis. Previous analyses have reported that circulating microRNAs (miRNAs) can serve as biomarkers for a number of diseases.

Objective: The study aims to detect the serum miRNAs that are differentially expressed between endometriosis patients and negative controls to evaluate the potential of these miRNAs as diagnostic markers for endometriosis.

Design: A total of 765 serum miRNAs were profiled using a TaqMan microRNA array in a pool of 10 endometriosis patients and a pool of 10 negative controls, and a set of selected miRNAs were further analyzed in a validation cohort consisting of sera from 60 patients and 25 controls including 10 samples used in array profiling.

Results: The relative expression levels of miR-199a and miR-122 were found to be up-regulated in endometriosis patient samples compared with control samples, whereas miR-145*, miR-141*, miR-542-3p, and miR-9* were down-regulated in endometriosis patients. Importantly, the relative expression of miR-199a ($P < 0.05$) and miR-122 can be used to discriminate between severe and mild endometriosis. We also found that miR-199a is well correlated with pelvic adhesion and lesion distribution ($P < 0.05$) and associated with hormone-mediated signaling pathways. Furthermore, we investigated the diagnostic value of these molecules and confirmed the optimal combination of miR-199a, miR-122, miR-145*, and miR-542-3p with area under the curve of 0.994 (95% confidence interval = 0.984–1.000, $P < 0.001$) and a cutoff point (0.4950) of 93.22% sensitivity and 96.00% specificity.

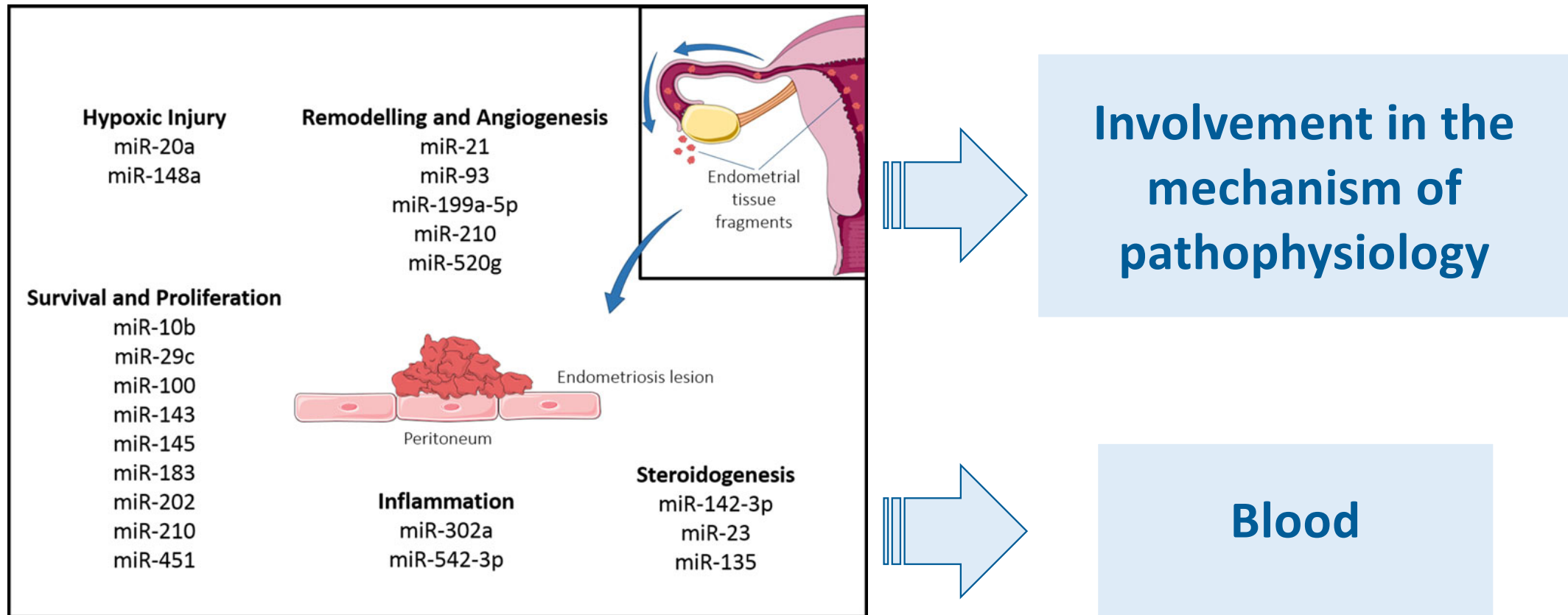
Conclusions: Our study demonstrated that the circulating miRNAs miR-199a, miR-122, miR-145*, and miR-542-3p could potentially serve as noninvasive biomarkers for endometriosis. miR-199a may also play an important role in the progression of the disease. This is the first report that circulating miRNAs serve as biomarkers of endometriosis. (*J Clin Endocrinol Metab* 98: 281–289, 2013)

Non-coding RNAs in endometriosis: a narrative review

2018

Human Reprod. Update

Kavita Panir ^{1,*}, John E. Schjenken¹, Sarah A. Robertson¹,
and M. Louise Hull^{1,2,3}



Accurate diagnosis of endometriosis using serum microRNAs

2020 AJOG

Sarah Moustafa, MD; Martina Burn, MD¹; Ramanaiah Mamillapalli, PhD¹; Sepide Nematian, MD; Valerie Flores, MD; Hugh S. Taylor, MD

TABLE 2
ROC analysis of individual miRNAs

ROC model	Area	SE	95% Wald confidence limits	Optimal cutoff	Correct, %	Sensitivity, %	Specificity, %
miR_125b	0.73	0.05	0.63—0.83	0.084	68.0	56.1	78.0
miR_150	0.68	0.06	0.57—0.78	0.44	63.9	20.0	94.7
miR_342	0.92	0.04	0.86—0.99	0.085	90.8	90.0	91.2
miR_451a	0.84	0.04	0.76—0.92	0.35	79.8	90.0	72.9
miR_3613	0.76	0.05	0.66—0.85	0.014 ^a	74.0	92.7	61.0
let_7b	0.78	0.05	0.69—0.87	0.012 ^a	73.7	82.5	67.8

Article

Clues for Improving the Pathophysiology Knowledge for Endometriosis Using Serum Micro-RNA Expression

Yohann Dabi ^{1,2,3}, Stéphane Suisse ⁴, Ludmila Jornea ⁵, Delphine Bouteiller ⁶, Cyril Touboul ^{1,2,3}, Anne Puchar ¹, Emile Daraï ¹ and Sofiane Bendifallah ^{1,2,*}

¹ Department of Obstetrics and Reproductive Medicine, Hôpital Tenon, Sorbonne University, 4 Rue de la Chine, 75020 Paris, France; yohann.dabi@gmail.com (Y.D.); cyril.touboul@gmail.com (C.T.); anne.puchar@aphp.fr (A.P.); emile.darai@aphp.fr (E.D.)

² Clinical Research Group (GRC) Paris 6, Centre Expert Endométriose (C3E), Sorbonne University (GRC6 C3E SU), 4 Rue de la Chine, 75020 Paris, France

³ Cancer Biology and Therapeutics, Centre de Recherche Saint-Antoine (CRSA), Sorbonne University, INSERM UMR_S_938, 75020 Paris, France

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⁵ Paris Brain Institute—Institut du Cerveau—ICM, Inserm U1127, CNRS UMR 7225, AP-HP—Hôpital Pitié-Salpêtrière, Sorbonne University, 4 Rue de la Chine, 75020 Paris, France; ludmila.jornea@icm-institute.org

⁶ Genotyping and Sequencing Core Facility, iGenSeq, Institut du Cerveau et de la Moelle Épinrière, ICM, Hôpital Pitié-Salpêtrière, 47–83 Boulevard de l'Hôpital, 75013 Paris, France; delphine.bouteiller@icm-institute.org

* Correspondence: sofiane.bendifallah@aphp.fr; Tel.: +331-5601-7000

Article

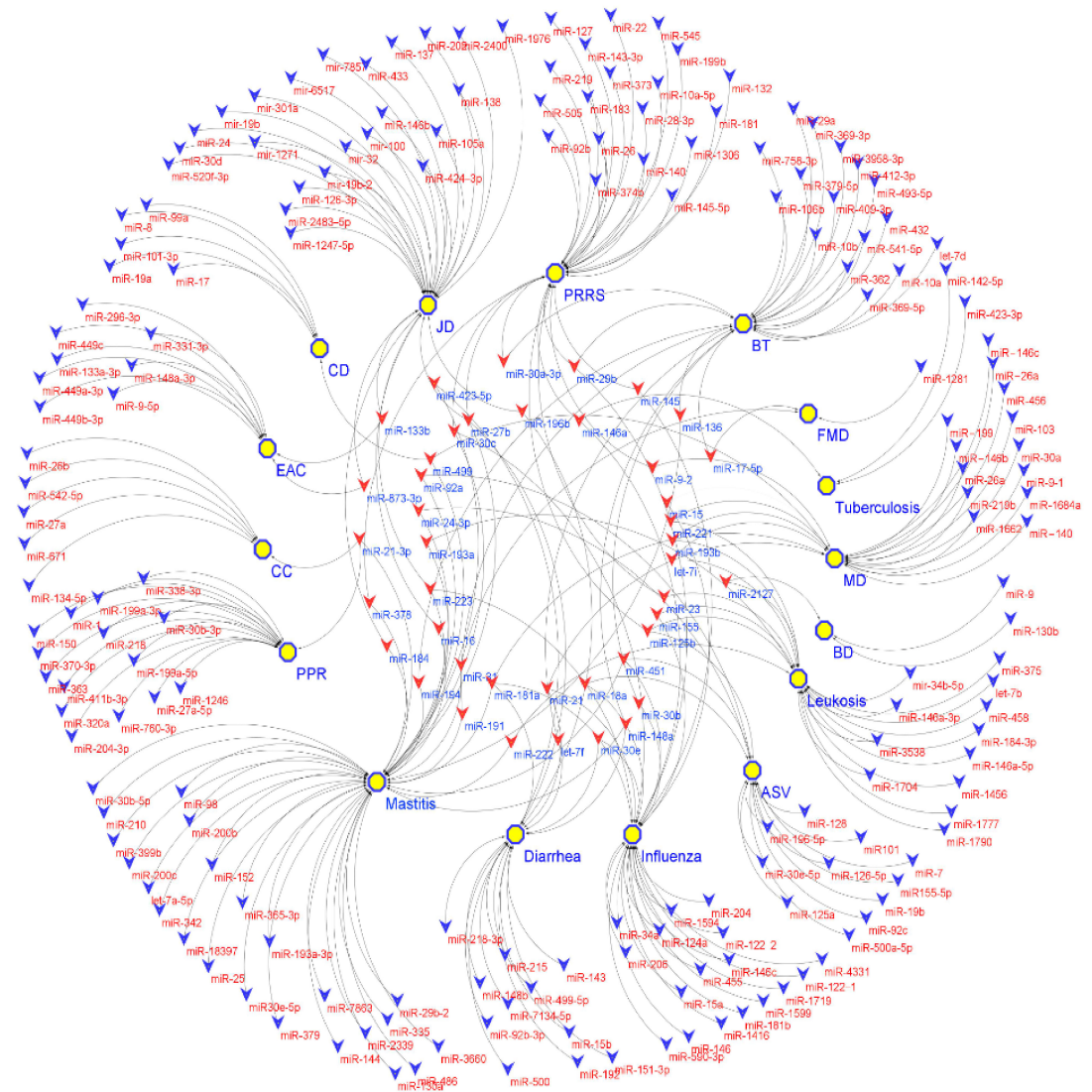
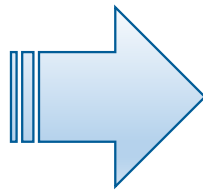
Clues for Improving the Pathophysiology Knowledge for Endometriosis Using Serum Micro-RNA Expression

Yohann Dabi ^{1,2,3}, Stéphane Suisse ⁴, Ludmila Jornea ⁵, Delphine Bouteiller ⁶, Cyril Touboul ^{1,2,3}, Anne Puchar ¹, Emile Darai ¹ and Sofiane Bendifallah ^{1,2,*}

**Diagnostic
Cartography**

**Phenotypic
Cartography**

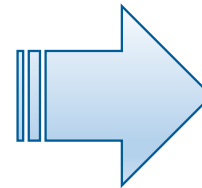
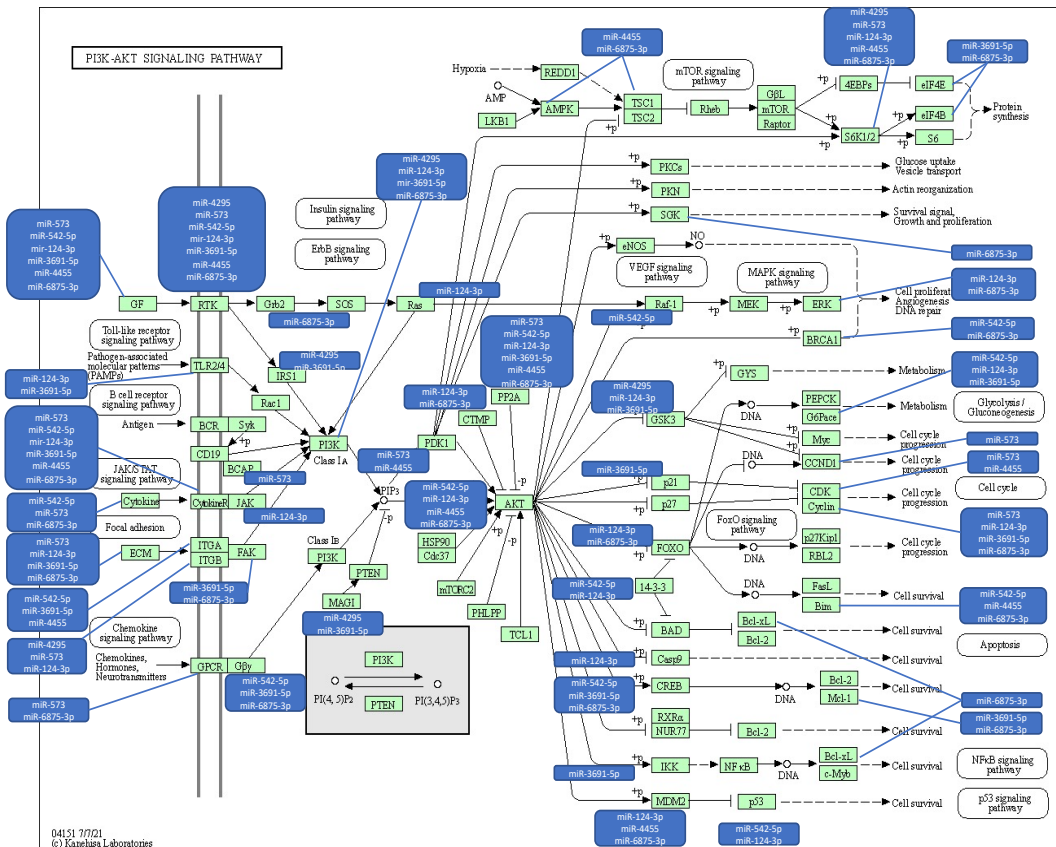
**Evolutionary
Cartography**



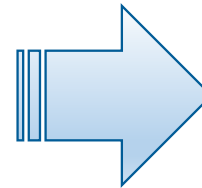
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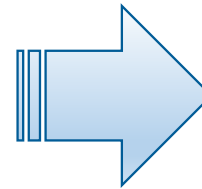
2022 Diagnostics



> 2600 Biomarkers



Signalisation



Heterogeneity



OPEN

MicroRNome analysis generates a blood-based signature for endometriosis

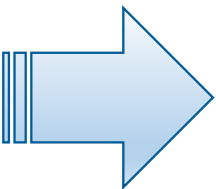
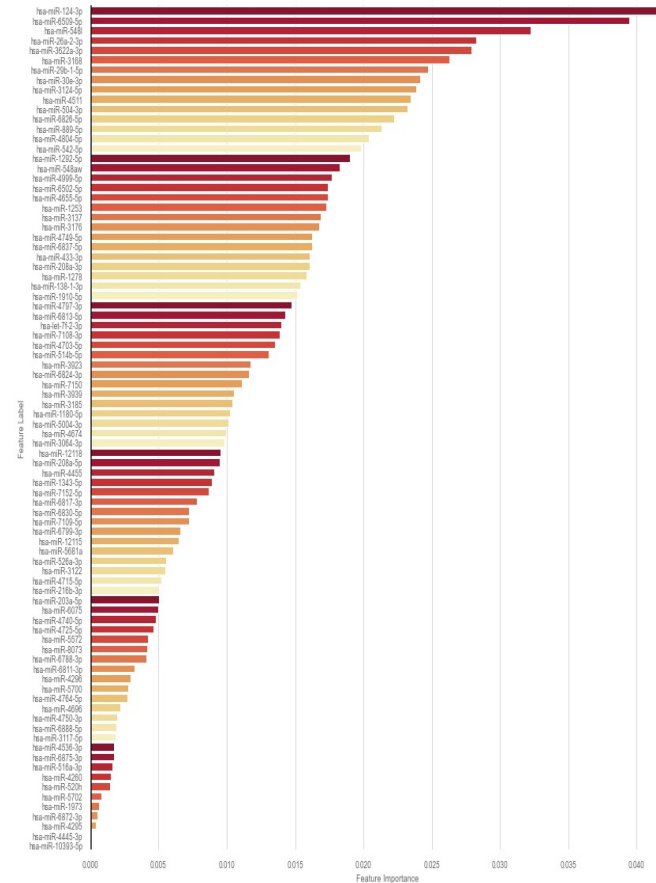
Sofiane Bendifallah^{1,2✉}, Yohann Dabi^{1,2,3}, Stéphane Suisse², Ludmila Jornea⁴, Delphine Bouteiller⁵, Cyril Touboul^{1,2}, Anne Puchar^{1,2} & Emile Darai^{1,2}

Endometriosis, characterized by endometrial-like tissue outside the uterus, is thought to affect 2–10% of women of reproductive age: representing about 190 million women worldwide. Numerous studies have evaluated the diagnostic value of blood biomarkers but with disappointing results. Thus, the gold standard for diagnosing endometriosis remains laparoscopy. We performed a prospective trial, the ENDO-miRNA study, using both Artificial Intelligence (AI) and Machine Learning (ML), to analyze the current human miRNome to differentiate between patients with and without endometriosis, and to develop a blood-based microRNA (miRNA) diagnostic signature for endometriosis. Here, we present the first blood-based diagnostic signature obtained from a combination of two robust and disruptive technologies merging the intrinsic quality of miRNAs to condense the endometriosis phenotype (and its heterogeneity) with the modeling power of AI. The most accurate signature provides a sensitivity, specificity, and Area Under the Curve (AUC) of 96.8%, 100%, and 98.4%, respectively, and is sufficiently robust and reproducible to replace the gold standard of diagnostic surgery. Such a diagnostic approach for this debilitating disorder could impact recommendations from national and international learned societies.



MicroRNome analysis generates a blood-based signature for endometriosis

2022 Nature Scientific Reports



2600 Biomarkers

86 Biomarkers

Sensitivity 96.7%, specificity 100%

Accuracy > 98%

Overview of miRNAs for the non-invasive diagnosis of endometriosis: evidence, challenges and strategies.

A systematic review

2021 Einstein Journal

Total	EU versus EN	EC versus EN	EC versus EU	Plasma	Serum	Blood	PF
6	miR-145	miR-145	miR-145	miR-145	miR-145		Wang et al. ⁽¹⁾ et al. ⁽⁴⁵⁾ Cos
5		miR-200b	miR-200b	miR-200b			Saare et al. Filigheddu et
5	miR-424		miR-424		miR-424	miR-424	Braza-Boils e Wang et al. ⁽⁵²⁾
4	miR-199a	miR-199a			miR-199a		miR-199a Wang et al. ⁽¹⁾
4		miR-141	miR-141	miR-141	miR-141		Wang et al. Rekker et al. ⁽⁶⁾
4		miR-20a		miR-20a	miR-20a	miR-20a	Zhao et al. ⁽³⁷⁾
4		miR-200a	miR-200a	miR-200a			Saare et al. ⁽³⁾ et al. ⁽⁵⁷⁾
3	miR-29c	miR-29c	miR-29c				Braza-Boils e
3	miR-34c	miR-34c	miR-34c				Braza-Boils e
3		miR-200c	miR-200c				Liang et al. ⁽³⁸⁾
3		miR-21	miR-21			miR-21	Haikal et al.
3	miR-126		miR-126			miR-126	Liu et al. ⁽²⁰⁾ C
3			miR-16	miR-16		miR-16	Yang et al. ⁽⁴³⁾
3			miR-451a		miR-451a		miR-451a Nothnick et a
3	miR-9		miR-9		miR-9		Wang et al. ⁽¹⁾

Likewise, none of the papers examined investigated miRNAs in saliva. To date, there are no scientifically proven salivary biomarkers for endometriosis. Saliva is a suitable and desirable medium for biomarker detection^(96,97) and its applicability to the diagnosis of endometriosis has been explored previously.^(98,99) Saliva is widely available and can be easily collected in a non-invasive manner, at low cost and with minimal discomfort. Therefore, it is an ideal fluid for biomarker investigation and is attracting great interest in the public health sector. The use of saliva for miRNA identification could be a potential non-invasive solution to overcome current barriers to the diagnosis of endometriosis.

Article

Salivary MicroRNA Signature for Diagnosis of Endometriosis

Sofiane Bendifallah ^{1,2,*}, Stéphane Suisse ³, Anne Puchar ^{1,2}, Léa Delbos ^{4,5}, Mathieu Poilblanc ^{6,7}, Philippe Descamps ^{4,5}, Francois Golfier ^{6,7}, Ludmila Jornea ⁸, Delphine Bouteiller ⁹, Cyril Touboul ^{1,2}, Yohann Dabi ^{1,2} and Emile Daraï ^{1,2}

2022 Journal of
Clinical Medicine

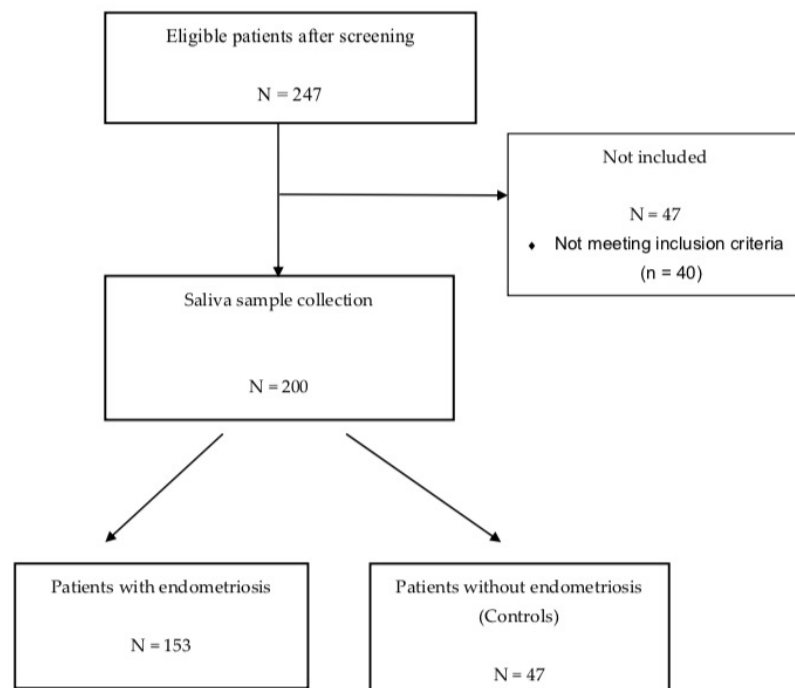


Figure 1. Flow chart of ENDO-miRNA study.





Article

Salivary MicroRNA Signature for Diagnosis of Endometriosis

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2022 Journal of
Clinical Medicine

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	Control Patients N (%) N = 47	Patients with Endometriosis N (%) N = 153	
Age (years) (mean ± SD)	30.92 (13.79)	31.17 (13.78)	0.1912
Age range			
- Less than 30 years	72% (34)	63% (96)	
- Over 30 years	28% (13)	37% (57)	0.294
BMI (body mass index) (mean ± SD)	24.84 (11.10)	24.36 (8.38)	0.525
Infertility			
- Yes	17% (8)	24% (36)	
- No	83% (39)	76% (117)	0.556
rASRM classification			
- I–II	-	52% (80)	-
- III–IV	-	48% (73)	
Control diagnoses			
- No abnormality	51% (24)	-	-
- Leiomyoma	2% (1)		
- Cystadenoma	11% (5)		
- Teratoma	23% (11)		
- Other gynecologic disorders	13% (6)		
Dysmenorrhea	100%	100%	
Abdominal pain outside menstruation			
- Yes	66% (21)	71% (89)	0.6905
Pain suggesting sciatica			
- Yes	31% (10)	56% (70)	0.0214
Lower back pain outside menstruation			
- Yes	62% (20)	81% (101)	0.0498
Right shoulder pain during menstruation			
- Yes	9% (3)	21% (26)	0.2184
Blood in the stools during menstruation			
- Yes	12% (4)	24% (30)	0.2425
Blood in urine during menstruation			
- Yes	25% (8)	17% (21)	0.4172
Diagnostic method			
- Surgery	47 (100)	83 (54.2)	
- Magnetic Resonance Imaging	-	70 (45.8)	-

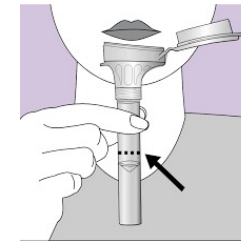
Population Characteristics

Article

Salivary MicroRNA Signature for Diagnosis of Endometriosis

Sofiane Bendifallah ^{1,2,*}, Stéphane Suisse ³, Anne Puchar ^{1,2}, Léa Delbos ^{4,5}, Mathieu Poilblanc ^{6,7},
Philippe Descamps ^{4,5}, Francois Golfier ^{6,7}, Ludmila Jornea ⁸, Delphine Bouteiller ⁹, Cyril Touboul ^{1,2},
Yohann Dabi ^{1,2} and Emile Daraï ^{1,2}

2022



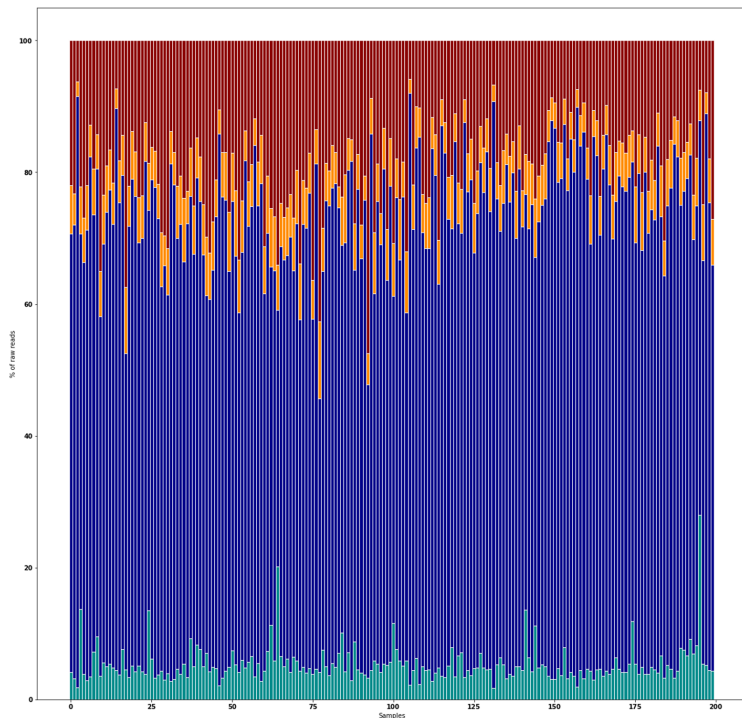
109 Biomarkers, Accuracy > 98%

Sensitivity 96.7%, specificity 100%

All stages

Simplicity

Reliability



Article

A Bioinformatics Approach to MicroRNA-Sequencing Analysis Based on Human Saliva Samples of Patients with Endometriosis

Sofiane Bendifallah ^{1,2,3,*}, Yohann Dabi ^{1,2,3}, Stéphane Suisse ⁴, Ludmila Jornea ⁵, Delphine Bouteiller ⁶, Cyril Touboul ^{1,2,3}, Anne Puchar ¹ and Emile Daraï ^{1,2}

- ¹ Department of Obstetrics and Reproductive Medicine, Hospital Tenon, Sorbonne University, 4 rue de la Chine, 75020 Paris, France; yohann.dabi@gmail.com (Y.D.); cyril.touboul@gmail.com (C.T.); anne.puchar@aphp.fr (A.P.); emile.darai@aphp.fr (E.D.)
- ² Clinical Research Group (GRC) Paris 6; Endometriosis Expert Center (C3E), Sorbonne University (GRC6 C3E SU), 75020 Paris, France
- ³ Cancer Biology and Therapeutics, Centre de Recherche Saint-Antoine (CRSA), Sorbonne University, INSERM UMR_S_938, 75020 Paris, France
- ⁴ Ziwig Health, 19 rue Reboud, 69003 Lyon, France; stephane@ziwig.com
- ⁵ Paris Brain Institute-Institut du Cerveau-ICM, Sorbonne University, Inserm U1127, CNRS UMR 7225, AP-HP-Hôpital Pitié-Salpêtrière, 75013 Paris, France; ludmila.jornea@icm-institute.org
- ⁶ Genotyping and Sequencing Core Facility, iGenSeq, Institut du Cerveau et de la Moelle Épinrière, ICM, Hôpital Pitié-Salpêtrière, 47-49 Boulevard de l'Hôpital, 75013 Paris, France; delphine.bouteiller@icm-institute.org
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Citation: Bendifallah, S.; Dabi, Y.; Suisse, S.; Jornea, L.; Bouteiller, D.; Touboul, C.; Puchar, A.; Daraï, E. A Bioinformatics Approach to MicroRNA-Sequencing Analysis Based on Human Saliva Samples of Patients with Endometriosis. *Int. J. Mol. Sci.* **2022**, *23*, 8045. <https://doi.org/10.3390/ijms23148045>

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Abstract: Endometriosis, defined by the presence of endometrium-like tissue outside the uterus, affects 2–10% of the female population, i.e., around 190 million women, worldwide. The aim of the prospective ENDO-miRNA study was to develop a bioinformatics approach for microRNA-sequencing analysis of 200 saliva samples for miRNAome expression and to test its diagnostic accuracy for endometriosis. Among the 200 patients, 76.5% (n = 153) had confirmed endometriosis and 23.5% (n = 47) had no endometriosis (controls). Small RNA-seq of 200 saliva samples yielded ~4642 M raw sequencing reads (from ~13.7 M to ~39.3 M reads/sample). The number of expressed miRNAs ranged from 1250 (outlier) to 2561 per sample. Some 2561 miRNAs were found to be differentially expressed in the saliva samples of patients with endometriosis compared with the control patients. Among these, 1.17% (n = 30) were up- or downregulated. Among these, the F1-score, sensitivity, specificity, and AUC ranged from 11–86.8%, 5.8–97.4%, 10.6–100%, and 39.3–69.2%, respectively. Here, we report a bioinformatic approach to saliva miRNA sequencing and analysis. We underline the advantages of using saliva over blood in terms of ease of collection, reproducibility, stability, safety, non-invasiveness. This report describes the whole saliva transcriptome to make miRNA quantification a validated, standardized, and reliable technique for routine use. The methodology could be applied to build a saliva signature of endometriosis.

Keywords: endometriosis; miRNA; NGS; bioinformatics; saliva

2022 International Journal of Molecular Science

Saliva > Blood

- Ease of collection
- Non invasive
- Safety
- Stability
- Reproducibility

ARTICLE



Endometriosis-associated infertility diagnosis based on saliva microRNA signatures

[Yohann Dabi](#) • [Stéphane Suisse](#) • [Anne Puchar](#) • ... [Cyril Touboul](#) • [Emile Daraï](#) • [Sofiane Bendifallah](#)  

October 2022

FULL LENGTH ARTICLE | [ARTICLES IN PRESS](#)

Endometriosis-associated infertility diagnosis based on saliva microRNA signatures

[Yohann Dabl](#) • [Stéphane Suisse](#) • [Anne Puchar](#) •
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[Julie Haury](#) • [Francois Golfier](#) • [Ludmila Jornea](#) •
[Delphine Bouteiller](#) • [Cyril Touboul](#) • [Emile Daraï](#) •
[Sofiane Bendifallah](#)   • [Show less](#)

Published: September 26, 2022 •

DOI: <https://doi.org/10.1016/j.rbmo.2022.09.019>

153 patients diagnosed with endometriosis

24 % were infertile, 76 % were fertile

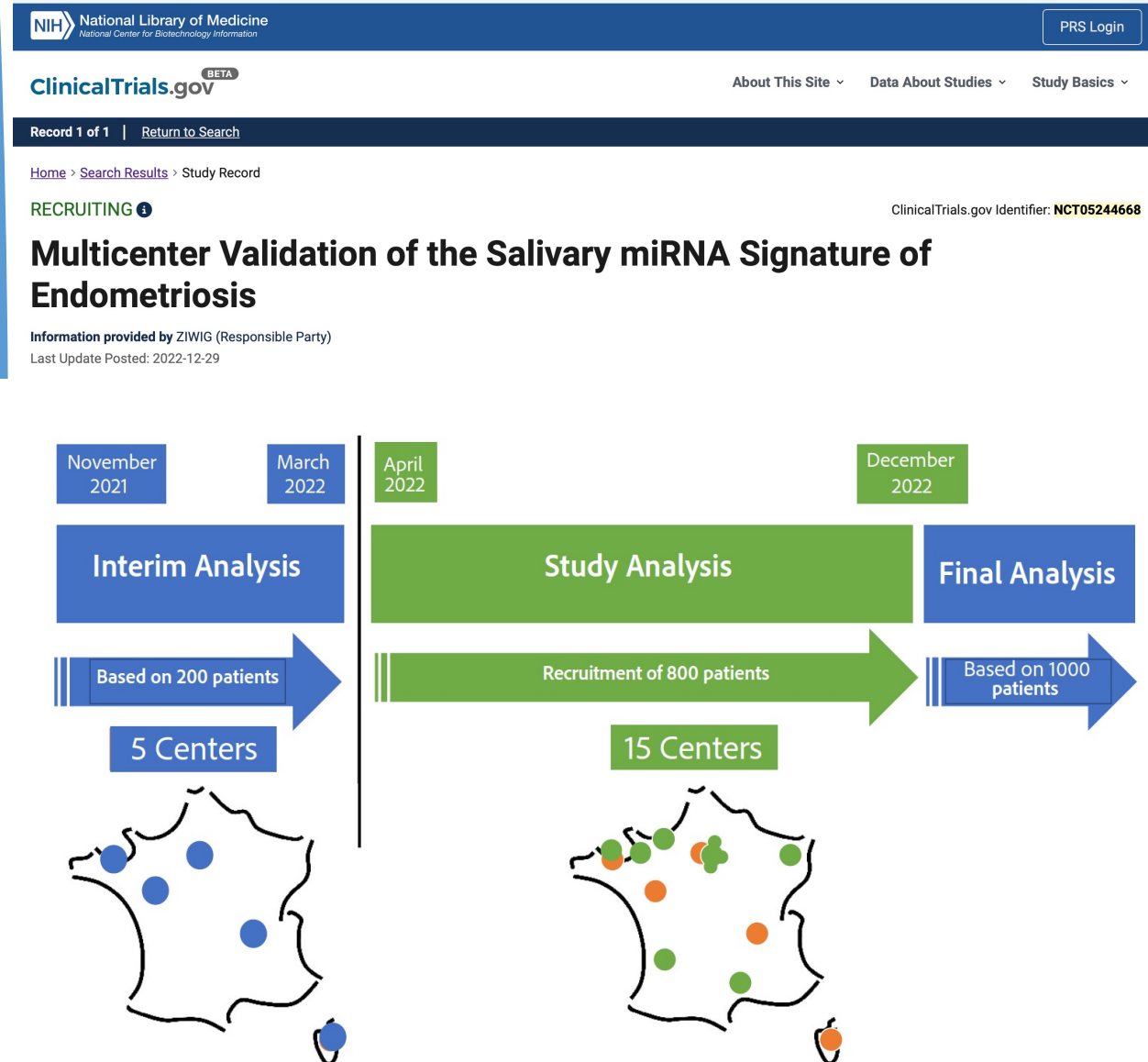
Of the 2561 known mi-RNA, the feature selection method generated a **signature of 34 miRNAs linked to endometriosis associated infertility.**

Those results still require external validation before using the signature in routine practise.

miRNA Salivary Signature for the Diagnosis of Endometriosis

NCT 05244668

« 1000 Study »



miRNA Salivary
Signature for the
Diagnosis of
Endometriosis
**External Validation
Study**

NCT 05244668

Interim analysis

« » »

Study Design

Time perspective : **Prospective**

Locations : **Multicenter**

(15 centres across France)

Cohort : 1150 patients

Eligibility criteria :

- 18 to 43 years old (Adult)
- Suspected/ Diagnosed Endometriosis

Primary outcome :

**Assess diagnostic accuracy of miRNA Salivary
Signature**

Epidemiologic, clinical, and saliva sequencing data
were collected between **Nov. 2021 and March 2022.**



Publication in NEJM Evidence

June 9, 2023

DOI : 10.1056/EVIDoa2200282



Published June 9, 2023

[DOI: 10.1056/EVIDoa2200282](https://doi.org/10.1056/EVIDoa2200282)

ORIGINAL ARTICLE

Validation of a Salivary miRNA Signature of Endometriosis — Interim Data

Sofiane Bendifallah, M.D., Ph.D.,^{1,2,3} Yohann Dabi, M.D.,^{1,2,3} Stéphane Suisse,⁴ Léa Delbos, M.D.,^{5,6} Andrew Spiers, M.D.,⁴ Mathieu Poilblanc, M.D.,^{7,8} Francois Golfier, M.D., Ph.D.,^{7,8} Ludmila Jornea, Msc.,⁹ Delphine Bouteiller, M.D.,¹⁰ Hervé Fernandez, M.D., Ph.D.,¹¹ Alexandra Madar, M.D.,¹ Erick Petit, M.D.,¹² Frédérique Perotte,¹² Raffaèle Fauvet, M.D., Ph.D.,¹³ Michael Benjoar, M.D.,¹⁴ Cherif Akladios, M.D., Ph.D.,¹⁵ Vincent Lavoué, M.D., Ph.D.,¹⁶ Thomas Darnaud, M.D.,¹⁷ Benjamin Merlot, M.D.,¹⁸ Horace Roman, M.D., Ph.D.,¹⁸ Cyril Touboul, M.D., Ph.D.,^{1,2,3} and Philippe Descamps, M.D., Ph.D.^{5,6}

miRNA Salivary Signature for the Diagnosis of Endometriosis External Validation Study

ORIGINAL ARTICLE

Validation of a Salivary miRNA Signature of Endometriosis — Interim Data

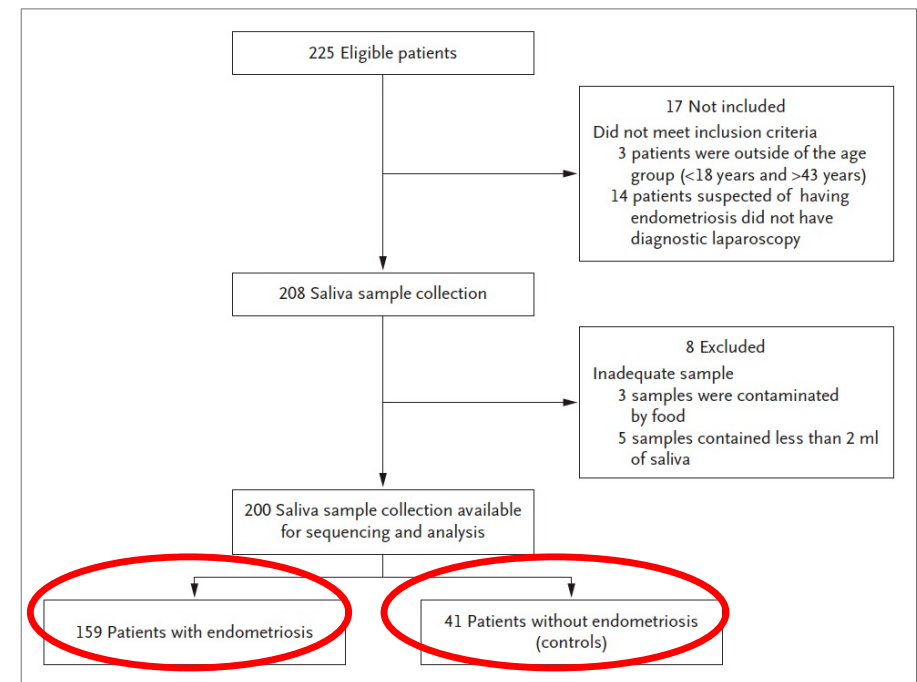


Figure 2. Flow Chart of the Interim Analysis of the ENDOMiRNA Saliva Test Study. This flow chart shows the recruitment of patients and provides the details of noninclusion and exclusion.

miRNA Salivary Signature for the Diagnosis of Endometriosis External Validation Study

ORIGINAL ARTICLE

Validation of a Salivary miRNA Signature of Endometriosis — Interim Data


Accuracy of the Saliva-Based Diagnostic Signature for Endometriosis

With an overall population prevalence of 79.5%, the diagnostic signature composed of 109 miRNAs (random forest model) against the validation cohort obtained a sensitivity of 96.2% (95% CI, 93.7 to 97.3%), specificity of 95.1% (95% CI, 85.2 to 99.1%), PPV of 95.1% (95% CI, 85.2 to 99.1%), NPV of 86.7% (95% CI, 77.6 to 90.3%), positive likelihood ratio of 19.7 (95% CI, 6.3 to 108.8), negative likelihood ratio of 0.04 (95% CI, 0.03 to 0.07), and AUC of 0.96 (95% CI, 0.92 to 0.98).

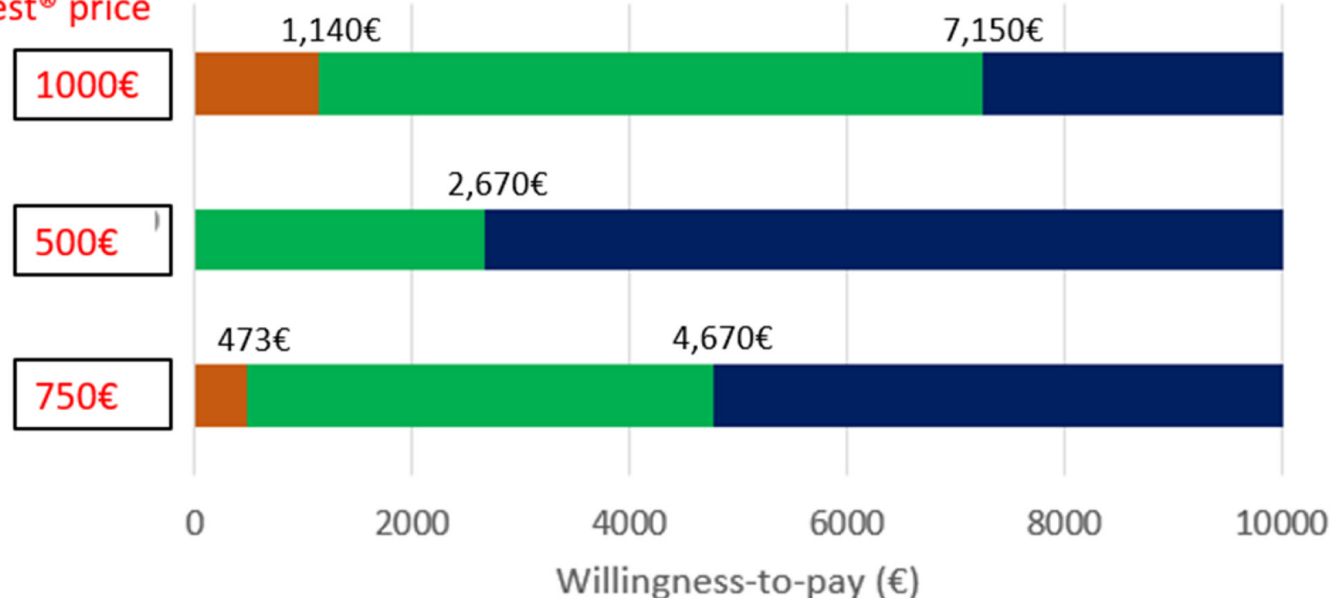
Interim Data Analysis - Results :

- **Sensitivity of 96.2%** (95% CI: 93.7%-97.3%)
- **Specificity of 95.1%** (95% CI: 85.2%-99.1%)

Saliva microRNA signature to diagnose endometriosis: A cost-effectiveness evaluation of the Endotest®

Clement Ferrier^{1,2} | Sofiane Bendifallah^{1,2} | Stéphane Suisse³ | Yohann Dabi^{1,2} |
Cyril Touboul^{1,2} | Anne Puchar^{1,2} | Kevin Zarca^{4,5} | Isabelle Durand Zaleski^{4,5} 

Endotest® price



+ Health care cost impact

Results


With an Endotest® priced at €750, the cost per correctly diagnosed case was €1542, €990, €919 and €1000, respectively, for strategies I, II, III and IV. Strategy I was dominated by all other strategies. Strategies IV, III and II were, respectively, preferred for a willingness-to-pay threshold below €473, between €473 and €4670, and beyond €4670 per correctly diagnosed case. At a price of €500 per Endotest®, strategy I was dominated by all other strategies. At €1000, the ICERs of strategies II and III were €724 and €387 per correctly diagnosed case, respectively, compared with strategy I.

Conclusion

The present study demonstrates the value of the Endotest® from an economic perspective.

miRNA Salivary Signature for the Diagnosis of Endometriosis Cost-Effectiveness Study

DOI : 10.1111/1471-0528.17348

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> [BJOG](#). 2023 Mar;130(4):396-406. doi: 10.1111/1471-0528.17348. Epub 2022 Dec 19.

Saliva microRNA signature to diagnose endometriosis: A cost-effectiveness evaluation of the Endotest®

Clement Ferrier ^{1 2}, Sofiane Bendifallah ^{1 2}, Stéphane Suisse ³, Yohann Dabi ^{1 2}, Cyril Touboul ^{1 2}, Anne Puchar ^{1 2}, Kevin Zarca ^{4 5}, Isabelle Durand Zaleski ^{4 5}

Affiliations + expand
PMID: 36424910 DOI: 10.1111/1471-0528.17348

Study Design

Comparison of 4 diagnostic pathways :

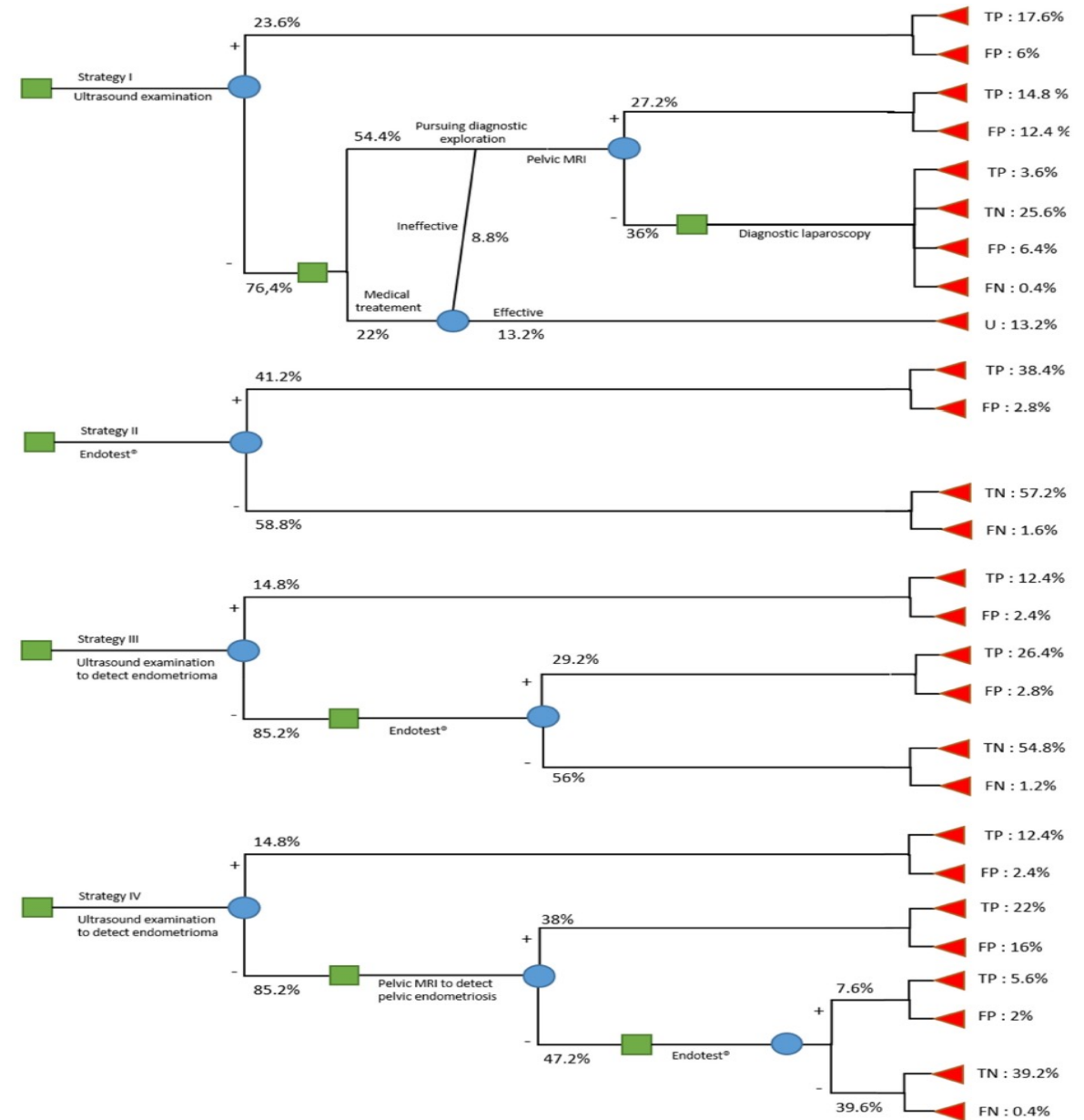
- 1 - Current French Guidelines
- 2 - Endotest
- 3 - Ultrasound -> Endotest
- 4 - Ultrasound -> MRI -> Endotest

www.ziwig.com

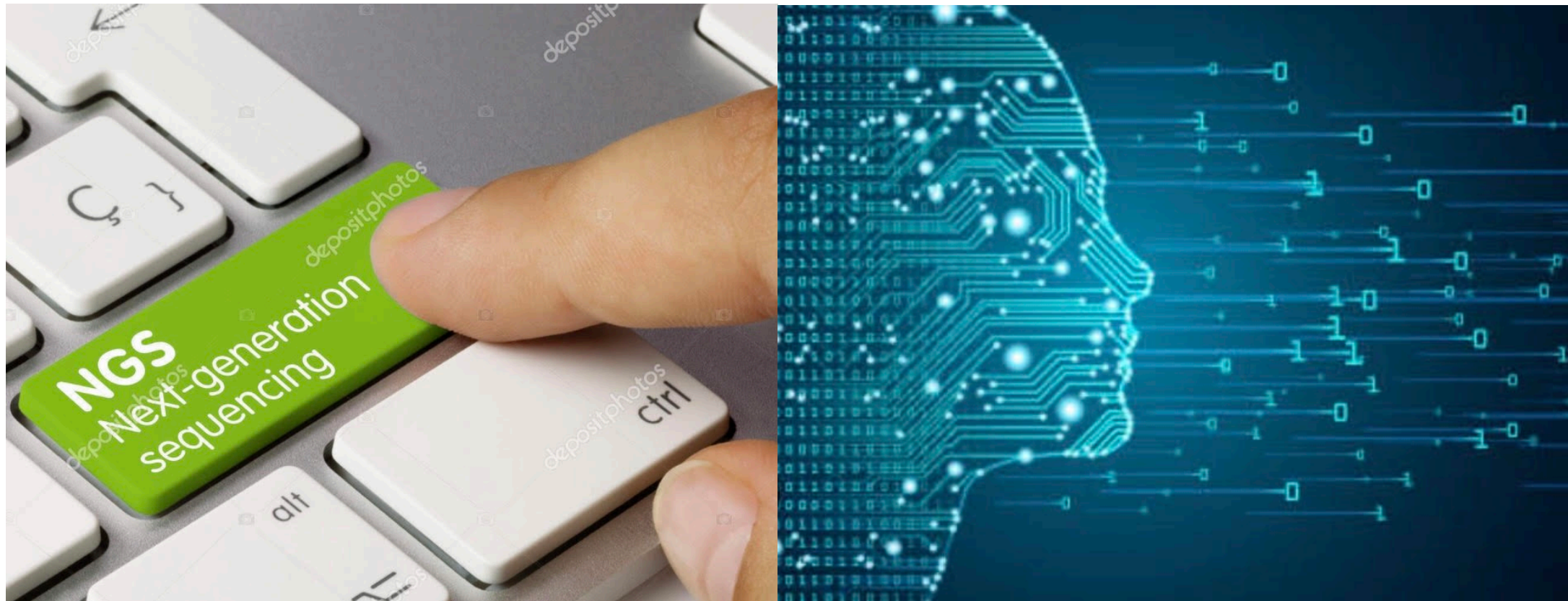
miRNA Salivary Signature for the Diagnosis of Endometriosis

Cost-Effectiveness Study

DOI : 10.1111/1471-0528.17348

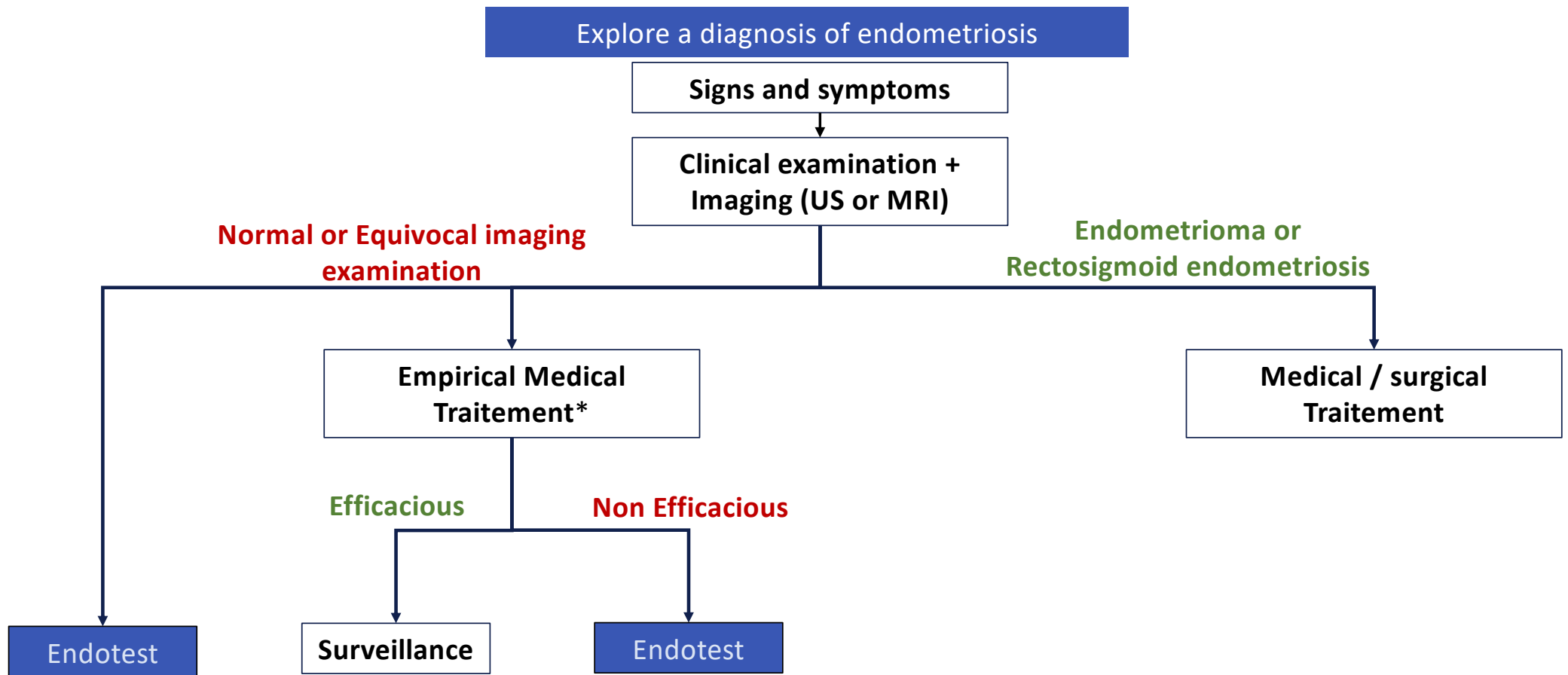


Endotest: Indications



Endotest® Kit







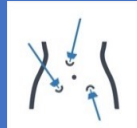



** The Endotest can be offered to patients who do not wish to take empirical medical treatment*

Conclusions (1)

- **Endotest** is a salivary mi-RNA non invasive diagnostic test, should not be used for screening
- **Interim results of the external validation** confirm the relevance of the signature **Spe : 95,1, Se :96,2** (*June 9th 2023-NEJM-Evidence*)
- **Endotest is available** *in Switzerland since october 2022, in Germany since December 2022, and in total 10 European countries in 1st semester 2023*

Endometriosis Diagnostic Tests

Endometriosis test						
	Medical questionnaire	Ultrasound imaging	MRI imaging	Blood test	Surgery and pathology	Saliva Test
General value	++	++	+++	-	++++	+++++
Performance value						
- Sensitivity	76-98%	65-79%	79%	63%	90-94%	> 95%
- Specificity	20-58%	91-95%	72%	69%	40-79%	> 95%
Reliability	Very Low specificity	Low accuracy for early stage lesion	Low accuracy for early stage lesion	-	Yes	Yes
	+	++	++		++++	++++
Reproducibility	+	+	+++	-	+++	+++++
Be simple, safe	++++	++	+++	+++	+	+++++
Acceptability	++++	+++	++	++	+	+++++
Detect disease early in its natural history	+	++	+	-	++++	+++++



Accuracy



Reliability

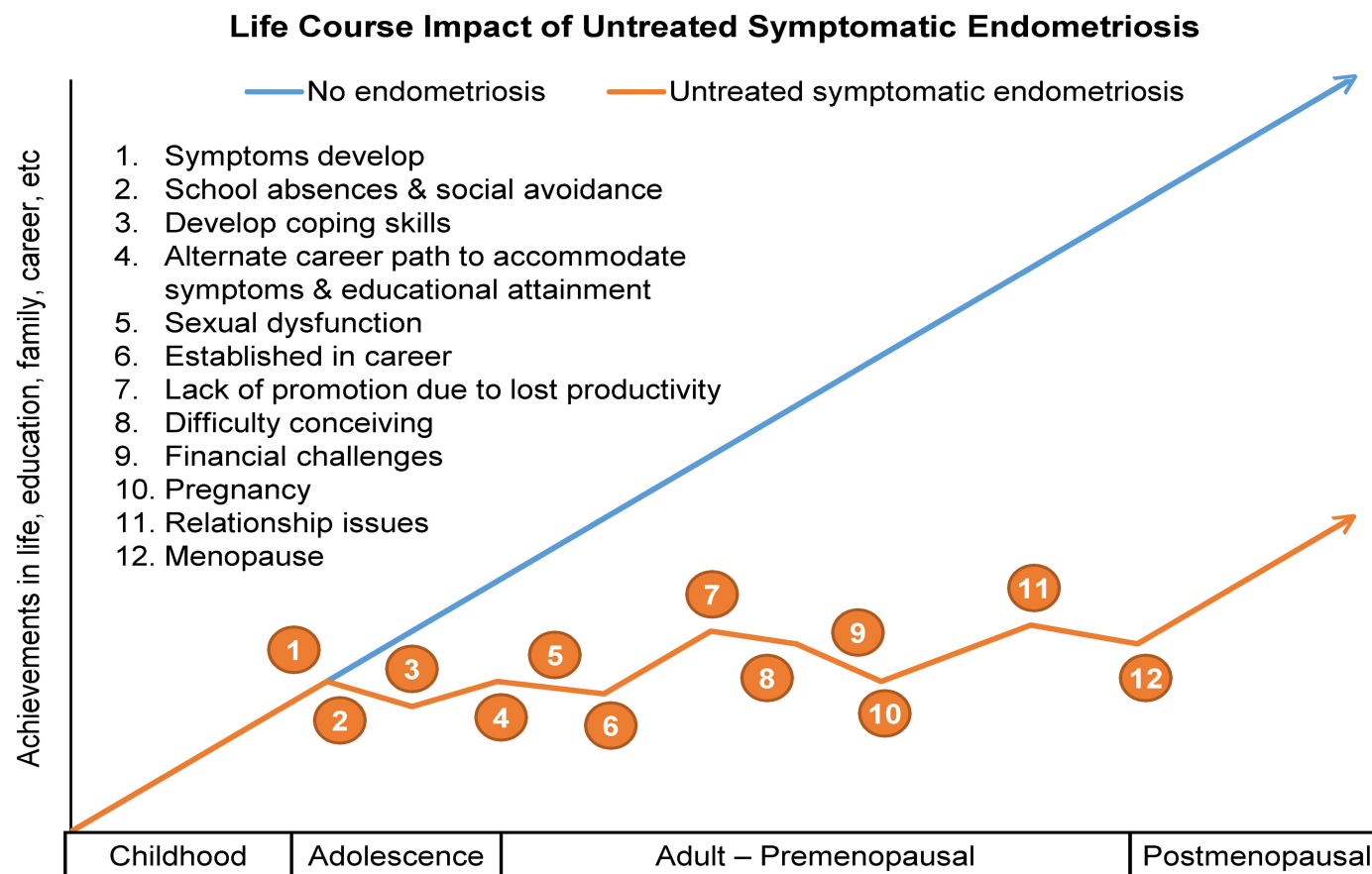


Simplicity



Non invasive

Consequences of **EARLY** Diagnosis....



Pain

Quality
of life

Pathway

Conclusions (2)

- **AI** : Promizing path to revolutionize women's health
- **Gyn RNA study** : salivary test able to give several diagnosis
- **Next steps** :
 - . Informations from the 1000 study (Phenotypes)
 - . Teenagers study
 - . Fertility
 - . Adenomyosis
 - . Ovarian cancer



2022-23



16 publications



Published June 9, 2023

[DOI: 10.1056/EVIDoa2200282](https://doi.org/10.1056/EVIDoa2200282)



ORIGINAL ARTICLE

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Awards 2022



**BFM Business prize for the
therapeutic
advance of the year 2022**



Innovation Award 2022



**Académie Nationale de
Chirurgie
et des pratiques opératoires innovantes**

ANC Innovation Award 2022



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Research paper

A diagnostic miRNA signature for pulmonary arterial hypertension using a consensus machine learning approach



Journal of Ambient Intelligence and Humanized Computing
<https://doi.org/10.1007/s12652-021-03091-2>

ORIGINAL RESEARCH



MicroRNA expression classification for pediatric multiple sclerosis identification

Gabriella Casalino¹ · Giovanna Castellano¹ · Arianna Consiglio² · Nicoletta Nuzziello² · Gennaro Vessio¹



Salivary miRNAs as non-invasive biomarkers of hepatocellular carcinoma: a pilot study

Arshiya Mariam¹, Galen Miller-Atkins¹, Amika Moro², Alejandro I. Rodarte², Shirin Siddiqi², Lou-Anne Acevedo-Moreno², J. Mark Brown^{3,4}, Daniela S. Allende⁵, Federico Aucejo² and Daniel M. Rotroff^{1,6}

¹ Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, Ohio, United States

² Department of General Surgery, Cleveland Clinic, Cleveland, Ohio, United States

³ Department of Cardiovascular and Metabolic Sciences, Cleveland Clinic, Cleveland, Ohio, United States

⁴ Center for Microbiome and Human Health, Cleveland Clinic, Cleveland, Ohio, United States

⁵ Department of Pathology, Cleveland Clinic, Cleveland, Ohio, United States

⁶ Endocrinology and Metabolism Institute, Cleveland Clinic, Cleveland, Ohio, United States

Identifying Potential miRNA Biomarkers for Gastric Cancer Diagnosis Using Machine Learning Variable Selection Approach

Neda Gilani^{1*}, Reza Arabi Belaghi^{2,3}, Younes Aftabi⁴, Elnaz Faramarzi⁵, Tuba Edgünlü⁶ and Mohammad Hossein Somi⁵

The mi-RNA revolution !....

Review

MicroRNA as a Potential Therapeutic Molecule in Cancer

Joanna Szczepanek ^{1,*} , Monika Skorupa ^{1,2}  and Andrzej Tretyn ² 

Table 4. Clinical trials of miRNA therapy in oncology (based on <https://clinicaltrials.gov>, accessed on 10 January 2022).

Therapeutic Agent	Drug Name (Sponsor)	Clinical Trial Number	Phase Status	Cancer
miR-34 mimic	MRX34 (Mirna Therapeutics, Inc.)	NCT01829971	Terminated (Five immune-related serious adverse events) Withdrawn	Primary liver cancer, SCLC, lymphoma, melanoma, multiple myeloma, renal cell carcinoma, NSCLC
miR-34 mimic	MRX34 (Mirna Therapeutics, Inc.)	NCT02862145	Withdrawn (five immune-related serious adverse events in Phase 1 study)	Melanoma
miR-16 mimic	TargomiRs/MesomiR-1 (Asbestos Diseases Research Foundation)	NCT02369198	Completed	Malignant pleural mesothelioma, non-small-cell lung cancer
anti-miR-155	Cobomarsen/MRG-106/Vorinostat (miRagen Therapeutics, Inc.)	NCT03713320 NCT03837457	Terminated (terminated early for business reasons, not due to concerns regarding safety or lack of efficacy.) Terminated (study no longer needed because eligible subjects may receive treatment with cobomarsen in a crossover arm of the SOLAR clinical trial (NCT03713320))	Cutaneous T-cell lymphoma



What is the Next step ?



Review

RNA-Targeting CRISPR–Cas Systems and Their Applications

Michał Burmistrz *, Kamil Krakowski and Agata Krawczyk-Balska

Department of Molecular Microbiology, Biological and Chemical Research Centre, Faculty of Biology,
University of Warsaw, 02-089 Warsaw, Poland; k.krakowski@student.uw.edu.pl (K.K.); akra@biol.uw.edu.pl (A.K.-B.)

* Correspondence: m.burmistrz@biol.uw.edu.pl

Received: 14 January 2020; Accepted: 4 February 2020; Published: 7 February 2020



Abstract: Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)–CRISPR-associated (Cas) systems have revolutionized modern molecular biology. Numerous types of these systems have been discovered to date. Many CRISPR–Cas systems have been used as a backbone for the development of potent research tools, with Cas9 being the most widespread. While most of the utilized systems are DNA-targeting, recently more and more attention is being gained by those that target RNA. Their ability to specifically recognize a given RNA sequence in an easily programmable way makes them ideal candidates for developing new research tools. In this review we summarize current knowledge on CRISPR–Cas systems which have been shown to target RNA molecules, that is type III (Csm/Cmr), type VI (Cas13), and type II (Cas9). We also present a list of available technologies based on these systems.

Keywords: CRISPR–Cas; RNA; Cas9; Cas13; Cmr; Csm

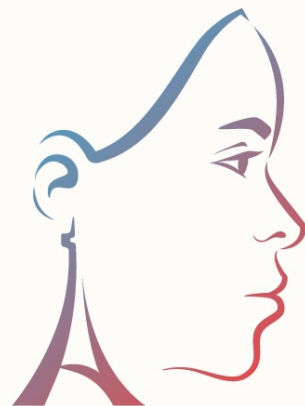
Thank you for your attention !



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