



Ziwig Endotest®

A saliva test for the early and reliable diagnosis
of endometriosis

Women suffering from endometriosis, for the most part, go through a long period of doctor-hopping (over a period of 8 to 12 years on average)¹. During this time they see multiple physicians and undergo numerous tests and examinations before a diagnosis, which sometimes requires surgery, is finally reached.

A global innovation now allows women suffering from endometriosis to avoid this tortuous medical journey. A French team, made up of expert doctors specialized in endometriosis, engineers in artificial intelligence and medical researchers has recently developed a saliva based diagnostic test that uses Next Generation Sequencing of microRNAs.



This simple and non-invasive test, called Ziwig Endotest[®], allows for the early detection of all types of endometriosis with a performance that exceeds that of conventional diagnostic tests²⁻⁶ (sensitivity 97%, specificity 100%, diagnostic accuracy AUC 98%⁴).

Ziwig Endotest[®] has been validated by one of the largest clinical trials ever carried out in this field⁶ in collaboration with 15 French centers specialized in endometriosis. The Diagnostic performance was tested firstly on blood samples⁶, and then on saliva samples⁴. This tool is set to revolutionize the diagnosis of, and the care for, endometriosis by providing a reliable and rapid diagnosis to healthcare professionals who prescribe the test.

Ziwig Endotest[®] has obtained the CE label.

Endometriosis, a scarcely known disease

Endometriosis affects about 10% of women of childbearing age in the UAE, i.e. about 150,000¹¹ women. It potentially affects all women and can appear as early as from adolescence.

Endometriosis is characterized by the presence of endometrial-like epithelium and/or stroma outside of the uterine cavity (womb). The growth of these tissue fragments is frequently associated with an inflammatory process⁷. During menstruation, endometriosis lesions can react to variations in hormonal levels, leading to acute inflammation, bleeding, severe pain and many other symptoms.

Endometriosis can be completely asymptomatic, and is sometimes diagnosed during a consultation prompted by difficulty in conceiving. In fact, a significant proportion of patients with endometriosis also suffer from infertility.

Main symptoms of endometriosis:

- Severe menstrual pain
- Pain during sexual intercourse
- Pelvic pain outside of menstruation
- Pain in the right shoulder
- Digestive problems
- Intense fatigue
- Urinary disorders
- Infertility
- Pain during defecation
- Alternating diarrhea – constipation

A major impact on personal and social life



**Endometriosis
causes a
significant
deterioration in
quality of life.**

Pain is responsible for a disruption in sleep that induces chronic fatigue and symptoms of psychological distress (irritability, depression, etc.). This can have a significant impact on overall well-being, as well as on personal and public relationships. The repercussions of endometriosis on a patient's working life is also considerable, with a marked increase in repeated scholar or professional absenteeism.

Moreover, the persistence of pain can induce a phenomenon of hypersensitization: pain perception thresholds decrease over time leading to the onset of chronic pain.

This can occur at any stage of endometriosis and chronic pain can persist even after lesions have been treated.

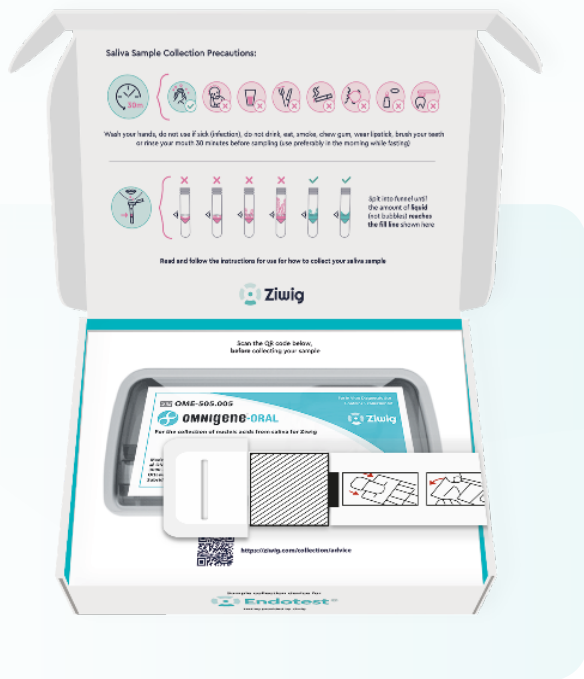
A saliva test, why and when?

Compared to current methods, Ziwig Endotest® represents a major innovation in the detection of endometriosis⁵. Patient care will be greatly improved via the reduction of the average time to diagnosis from several years to a few days¹. Ziwig Endotest® paves the way for the early treatment of endometriosis and represents a major paradigm shift in clinical practice².

The advantages of Ziwig Endotest®:

- Clear Positive/negative result
- Rapid diagnosis
- All forms of endometriosis can be diagnosed²⁻⁶
- High reliability: close to 100% (sensitivity of 97%, specificity of 100%, diagnostic accuracy (AUC) of 98%)⁴
- Simple and non-invasive sample collection





When to prescribe the saliva test?

It is essential to remove any doubts of the possibility of endometriosis as soon as possible. The prescription of Ziwig Endotest® is recommended for women between 18 and 43 years of age, presenting one or more symptoms suggestive of endometriosis^{4,9}.

Suggestive symptoms include⁹:

- Chronic pelvic pain
- And/or dysmenorrhea
- And/or abdominal pain outside of menstruation
- And/or pain suggestive of sciatica
- And/or lumbar pain outside of menses
- And/or pain in the right shoulder during menstruation
- And/or blood in stool during menstruation
- And/or blood in urine during menstruation
- And/or pain during urination, defecation
- And/or alternating diarrhea/constipation
- And/or dyspareunia.



Ziwig Endotest® is not intended to replace diagnosis by pelvic medical imaging. Medical imaging remains essential after diagnosis for lesion description, mapping, and classification.

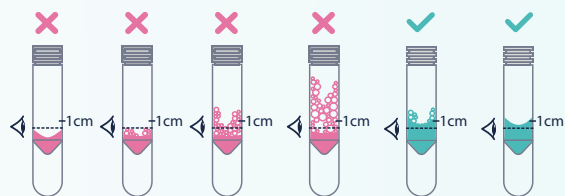
Instructions for collecting saliva samples

30 minutes before sampling:

- Wash your hands
- Do not use if you are sick (infection)
- Do not eat or drink
- Do not smoke
- Do not chew gum
- Do not wear lipstick
- Do not brush your teeth



The quantity of liquid must be sufficient and exceed the filling line by at least 1cm (not including bubbles).



1. Spit in the funnel until the amount of liquid (without bubbles) reaches 1 cm above the filling line.



2. Close the tube tightly by pressing strongly on the funnel cap until you hear a clear click.



3. Unscrew the funnel from the tube.



4. Close the tube with the small cap



5. Shake the capped tube for 5 seconds.

Treatment and care

Currently, endometriosis remains without a complete cure. However, early diagnosis allows for targeted care that can slow or even stop the worsening of pain and other symptoms, thereby greatly improving patient quality of life. Furthermore, an optimized treatment strategy can be implemented in case of associated infertility.

In addition to the analgesic treatment and supportive care adapted to each patient, hormonal treatments, which are based on the use of estrogen-progestin contraceptives or progestins, aim to block menstruation. These treatments reduce the intensity of symptoms and their consequences on quality of life. As a second-line treatment, it is also possible to use GnRH analogues, with the effect of putting patients in a state of reversible menopause. This treatment is always combined with an "add-back therapy" to avoid hot flashes.

Surgical treatment is considered when medical treatments are insufficient to alleviate pain⁸. The objective of surgery is to remove or electro-coagulate endometriosis lesions and correct anatomical abnormalities caused by the disease. The procedure is most often performed by laparoscopy.

Sciences



Ziwig Endotest® uses two cutting-edge technologies: Next Generation Sequencing and artificial intelligence. Through a simple saliva sample, 109 different microRNAs are analyzed to detect endometriosis.

The development of a non-invasive test for the diagnosis of endometriosis has been the subject of intense medical research for many years. More than 100 biomarkers have been evaluated over the last decades. Among them, a new class of molecules first described in 1993, microRNAs, has emerged as a promising option, supported by a growing number of studies on tumors and neurodegenerative disorders.

MicroRNAs are small non-coding RNAs. They participate in gene expression: when a microRNA binds to its target, a specific messenger RNA, it blocks or stimulates its translation into protein and/or causes its destruction.

MicroRNAs are also released into the extracellular environment through different transport structures that protect them from ribonucleases present in the circulation and give them a remarkable stability. These circulating microRNAs are found in varying amounts in body fluids (blood, urine, breast milk, tears, saliva, etc.).

In recent years, there has been increasing evidence of the contribution of microRNAs in the pathophysiological mechanisms of endometriosis. A direct link has been proven between the dysregulation of certain microRNAs and the development of endometriosis lesions¹⁰.

The studies on Ziwig Endotest® have been published in international peer-reviewed scientific journals.

Find all the publications and their summary on the website www.ziwig.com



November 2022

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

<https://doi.org/10.1111/1471-0528.17348>



October 2022

Endometriosis-associated infertility diagnosis based on saliva microRNA signatures

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



International Journal of
Molecular Sciences

July 2022

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

<https://doi.org/10.3390/ijms23148045>



diagnostics

May 2022

Endometriosis Associated-miRNome Analysis of Blood Samples: A Prospective Study

<https://doi.org/10.3390/diagnostics12051150>



March 2022

MicroRNome analysis generates a blood-based signature for endometriosis

<https://doi.org/10.1038/s41598-022-07771-7>



Journal of
Clinical Medicine

January 2022

Salivary MicroRNA Signature for Diagnosis of Endometriosis

<https://doi.org/10.3390/jcm11030612>



diagnostics

January 2022

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

<https://doi.org/10.3390/diagnostics12010175>



January 2022

Machine learning algorithms as new screening approach for patients with endometriosis

<https://doi.org/10.1038/s41598-021-04637-2>

About Ziwig

Ziwig Endotest® has been developed by Ziwig®, a French company whose ambition is to improve women's health through a holistic approach and the development of products, services and a care ecosystem guided by science and the unique biology of each individual. This approach is supported by ongoing research excellence and is based on the close collaboration of medical experts and engineers specialized in cutting-edge technologies such as artificial intelligence and Next Generation human RNA Sequencing.

Its functioning is based on an ecosystem, driven by the quest for excellence and patient centered, that uses disruptive technologies. This contributes to the emergence of precision medicine that is individualized, predictive and participatory, serving women's well-being and quality of life.

www.ziwig.com

Acknowledgements

Ziwig®'s ambition to foster research and treatment of endometriosis and to change the way we understand this debilitating disease that affects so many women around the world, would never have succeeded without all the women and men who believed in our project.

They fought alongside us to make this innovation possible. On behalf of all those who will benefit from our progress, we thank them!



Ziwig Endotest® wins
the Prix Galien 2022

Bibliographic references

1. <https://solidarites-sante.gouv.fr/soins-et-maladies/prises-en-charge-specialisees/endometriose>
2. Machine learning algorithms as new screening approach for patients with endometriosis. Bendifallah S & al. Sci Rep. 2022 Jan 12;12(1):639. doi: 10.1038/s41598-021-04637-2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8755739/pdf/41598_2021_Article_4637.pdf
3. Clues for Improving the Pathophysiology Knowledge for Endometriosis Using Serum Micro-RNA Expression. Dabi Y & al. Diagnostics (Basel). 2022 Jan 12;12(1):175. doi: 10.3390/diagnostics12010175. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8774370/pdf/diagnostics-12-00175.pdf>
4. Salivary MicroRNA Signature for Diagnosis of Endometriosis. Bendifallah & al. J Clin Med. 2022 Jan 26;11(3):612. doi: 10.3390/jcm11030612. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8836532/pdf/jcm-11-00612.pdf>
5. MicroRNome analysis generates a blood-based signature for endometriosis. Bendifallah S & al. Sci Rep. 2022 Mar 8;12(1):4051. doi: 10.1038/s41598-022-07771-7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8902281/pdf/41598_2022_Article_7771.pdf
6. Endometriosis Associated-miRNome Analysis of Blood Samples:A Prospective Study Bendifallah S & al. Diagnostics. 2022; 12(5):1150. <https://doi.org/10.3390/diagnostics12051150>
7. International working group of AAGL ESGE ESHRE and WES, et al., 2021.
8. Haute Autorité de Santé. Prise en charge de l'endométriose. Fiche de synthèse. Décembre 2017. https://www.has-sante.fr/upload/docs/application/pdf/2018-01/prise_en_charge_de_lendometriose_-_demarche_diagnostique_et_traitement_medical_-_fiche_de_synthese.pdf
9. <https://www.eshre.eu/Guidelines-and-Legal/Guidelines/Endometriosis-guideline.aspx>
10. Panir K et al. Hum Reprod Update 2018;24(4):497-515.
11. <https://worldpopulationpyramid.info/United-Arab-Emirates/2023/>