ENDOMETRIAL MICROBIOME METAGENOMIC ANALYSIS (EMMA)

Patient information		Sample information		Clinic information	
Unique pat id:	xxxxxx	**Date received:**	xxxxx	**Clinic:**	xxxxxx
Patient name:	xxxxxx	**Report date/time:**	xx/xx/xxxx xx:xx	**Clinician:**	xxxxx
Patient DOB:	xxxxxxxx	**Sample type:**	Endometrial Biopsy		
Allergic to antibiotics	Unknown	**Cycle type:**	Natural		
		No. Biopsy:	1		
		Date of biopsy:	xx/xx/xxxx		

EMMA TEST RESULT ABNORMAL ENDOMETRIAL MICROBIOME.

ALICE TEST RESULT NEGATIVE FOR BACTERIAL PATHOGENS CAUSING CHRONIC ENDOMETRITIS

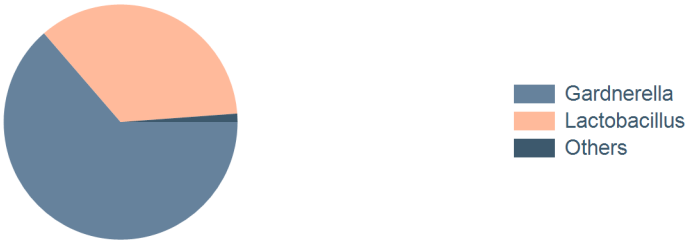
EMMA

Most abundant bacteria	%
Lactobacillus	**35,21% ***
Gardnerella	63,63%
Others	1,16%

** For reference intervals, please refer to Moreno et al., Am J Obstet Gynecol. 2016.*

ALICE

Chronic Endometritis pathogens	%
Enterobacteriaceae	**Not Detected**
Escherichia	Not Detected
Klebsiella	Not Detected
Enterococcus	Not Detected
Chlamydia	Not Detected
Mycoplasma	Not Detected
Neisseria	Not Detected
Ureaplasma	Not Detected
Streptococcus	Not Detected
Staphylococcus	Not Detected



INTERPRETATION OF YOUR RESULT AND RECOMMENDATION

DNA from bacterial pathogens of the reproductive tract has been detected in a significant amount in the endometrial sample.

Antibiotic therapy followed by probiotic treatment is recommended before continuing with ART. Please find below the suggested therapy based on the bacteria detected. We also recommend the analysis of a second sample after treatment, to confirm the restoration of a favourable environment for implantation.

SUGGESTED THERAPY

Metronidazole 500mg/12h for 7 days followed by probiotic treatment is recommended. A list with recommended probiotics of vaginal administration is provided at the end of this report.

COMMENTS

Allergy information: Cefditoren, Cefixime or Amoxycillin are contraindicated in patients with allergy to beta-lactam; Azithromycin is contraindicated in patients with allergy to macrolides; Doxycycline is contraindicated in patients with allergy to tetracyclines; Metronidazole is contraindicated in patients with allergy to nitroimidazoles.

TEST DESCRIPTION

EMMA (Endometrial Microbiome Metagenomic Analysis) is a molecular tool used to determine whether the uterine microbial environment is optimal for endometrial health. This molecular method is based on detecting and measuring the amount of bacterial DNA present in the endometrial sample. Therefore, EMMA helps to determine when the endometrium presents a physiological bacterial flora.

ALICE (Analysis of Infectious Chronic Endometritis) is a molecular microbiology tool used to diagnose chronic endometritis (CE), a subclinical infection of the endometrium that has been associated to infertility, especially repeated implantation failure and recurrent pregnancy loss. This molecular method is based on detecting and measuring bacterial DNA from the most frequent CE-causing pathogens as: Enterobacteriaceae, Streptococcus, Staphylococcus, Enterococcus, Mycoplasma, Ureaplasma, Chlamydia and Neisseria). Therefore, ALICE provides information about the pathogens causing the disease (either culturable or non-culturable) to guide and personalize therapy for those patients with asymptomatic chronic endometritis.

TESTING METHODOLOGY

The EMMA test utilizes Next Generation Sequencing to provide microbiome information in endometrial tissue by analyzing the complete bacterial profile in the uterine cavity.

The ALICE test utilizes Next Generation Sequencing to provide a molecular diagnosis of chronic endometritis in endometrial tissue by analyzing the presence of the 10 aforementioned bacteria causing the disease.

The technology used for these purposes is based on DNA extraction followed by amplification and barcoded sequencing of the bacterial 16S ribosomal RNA gene that enables the taxonomic assignment and relative quantification of each bacteria present in a sample. After receiving the endometrial biopsy and extracting the genetic material (bacterial DNA), sample minimum quality requirements are evaluated before use of the diagnosis tools.

TEST LIMITATIONS

The aim of this test is to provide physicians with an objective molecular diagnosis of the patient's endometrial microbial health, including those pathogens causing chronic endometritis. Depending on the result of this analysis, the physician may use it to improve the uterine microbial health.

EMMA results may vary depending on different factors such as hormonal changes, antibiotic intake, sexual activity, hygiene, etc.

The result of ALICE only informs about the most frequent pathogens causing the disease. A negative result in the ALICE report does not exclude the presence of microbial pathogens in the uterine cavity other than the ones detailed in the test description.

Following the recommendations indicated in this report does not guarantee successful pregnancy. Failed implantation may be caused by other factors such as displaced window of implantation, poor embryo quality, genetic abnormalities, or previous pathologies.

This test has not been cleared or approved by the Food and drug Administration (FDA). The FDA has determined such approval is not necessary. Prior consenting is required to confirm understanding of the risks, benefits and limitations to this testing.

This technology is intended for the identification of bacteria at the genus level, although the species level can be defined in some cases. The correct identification of the species is clinically relevant for the detection of pathogens causing serious diseases as Mycobacterium tuberculosis, Chlamydia trachomatis, Neisseria gonorrhoeae. If DNA from those bacterial genus containing serious pathogenic species are found, we recommend to confirm the diagnosis with a specialist in infectious diseases. Also, this test is not intended for the diagnosis of sexually transmitted infections (STIs), if there is any suspect of these types of diseases or the patient has a risk of suffer STIs, please consult with a specialist in infectious diseases to offer an appropriate clinical management.

LEGAL/QUALITY

IGENOMIX, SL will only release the report once a completed Test Requisition Form is received. The clinic/clinician/certified health professional requesting the test is responsible for obtaining and taking custody of "Informed Consent" from the patient as depicted by national guidelines and/or legislation.
This text is not subject to preclearance by the US Food and Drug Administration (FDA) or to special controls by the FDA.

EXEMPTION CLAUSE OF DIAGNOSTIC LIABILITY

The genetic diagnosis services carried out by IGENOMIX, SL are exclusively intended to be interpreted by qualified/certified health professionals. The result obtained by this test and the information that could be derived from it, cannot be considered in any case as substitute of genetic counselling or medical treatment by a trained professional neither represent itself a medical enquiry. Any result should be interpreted in the context of all available clinical findings, within the general context of a medical enquiry, which must be conducted by genetic diagnosis and / or clinical trained professionals. IGENOMIX, SL is not responsible for the use made by the contracting party of their services, neither the obtained results by means of their study analysis, nor the harmful temporary consequences diverted by its use, making specific discretion of taking appropriate legal measures assuming an improper use of those mentioned studies and analysis.

INFORMATION

Scientific evidence:
Evidence that the endometrial microbiota has an effect on implantation success or failure. Moreno I, Codoñer FM, Vilella F, Valbuena D, Martinez-Blanch JF, Jimenez-Almazán J, Alonso R, Alamá P, Remohí J, Pellicer A, Ramon D, Simon C. Am J Obstet Gynecol. 2016 Dec;215(6):684-703.
The diagnosis of chronic endometritis in infertile asymptomatic women: a comparative study of histology, microbial cultures, hysteroscopy, and molecular microbiology. Moreno I, Cicinelli E, Garcia-Grau I, Gonzalez-Monfort M, Bau D, Vilella F, De Ziegler D, Resta L, Valbuena D, Simon C. Am J Obstet Gynecol. 2018; 218(6): 602.e1-602.e16.

SIGNED

Pilar Lopez,

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COUNTERSIGNED

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LIST OF RECOMMENDED PROBIOTICS:

Asia
Lactoflora. Lactoshop. Vaginal capsules.
Gynolact vaginal tablets N8 Vitabalans. Gynolact. Vaginal suppositories.
Invag. Biomed (imported from Europe). Vaginal capsules.

Europe
Muvagyn. Casen Laboratories. Vaginal suppositories.
GineCanesflor. Bayer. Vaginal capsules.
Physioflor or Physioflor LP. IPRAD Laboratories. Vaginal capsules.
Gynoflor. Medinova AG. Vaginal tablets.
Vagi-flora. Assos Pharma. Vaginal capsules.
Invag. Biomed. V
Gynolact vaginal tablets N8 Vitabalans. Gynolact. Vaginal suppositories.
Normogin 40mg. Baldacci Laboratory. Vaginal tablets
Acidif CV. Biohealth. Vaginal tablets
Feb-rin. Ferring. Vaginal capsules.

Middle East
Gynoflor. Medinova AG. Vaginal tablets.
Purfem. Aralez Pharmaceuticals. Vaginal ovules with applicator.

North America
Canada
MediGYNE. Saforelle. Vaginal suppositories
Purfem. Bifodan. Vaginal ovules with applicator.
Canesflor. Bayer. Vaginal capsules.
Provacare probiotic vaginal care. Provacare. Vaginal ovules.

US
Purfem. Aralez Pharmaceuticals. Vaginal ovules with applicator.
Flora Femme Antimicrobials. FloraFemme. Vaginal capsules.
Canesflor. Bayer. Vaginal capsules.

Mexico
Florgynal. Farmasa. Vaginal capsules.
Gynophilus. ELEA. Vaginal capsules.

South America
Purfem. Aralez Pharmaceuticals. Vaginal ovules with applicator
Canesflor. Bayer. Vaginal capsules.
Lactinex. Omega Laboratory. Vaginal ovules.
Florgynal. Farmasa. Vaginal capsules.
Gynophilus. Synthon Chile. Vaginal capsules.
Isadin a barcilus or Isadin Plus. ISDIN Laboratories. Vaginal capsules.

These probiotics are commercially available in pharmacies, parapharmacies and online shops. Use these probiotics following the manufacturer's instructions.

In case that no vaginal Lactobacilli probiotics are available in your area, you can also order your pharmacist to prepare vaginal suppositories or capsules containing L. crispatus, L. rhamnosus, L. gasseri and L. plantarum (10^9 CFUs each). In this case, probiotic suppositories or capsules should be inserted pushing it high into the vagina (one every day for 10 days at bedtime).