HYSPLANT 1
INTERDISCIPLINARY INNOVATION PROJECT
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Final report Hysplant 1

Introduction

Hysplant is a project of IBEC (Institut de Bioenginyeria de Catalunya) that initially aimed to develop a new imaging method capable of identifying the embryos with the highest implantation potential, which is critical in the IVF (in vitro fertilization) cycle.

This technology was developed using hyperspectral imaging, so the research team is currently working on new uses of this technology, including early detection of uterine diseases. For this reason, our team has conducted a market study on the most effective possible uses, through interviews with doctors and patients.

By means of this imaging method it is possible to detect cells with a behavior or physical aspect peculiar to the rest and thus analyze them by means of artificial intelligence, which would make it possible to obtain instant results, without the need for interpretation by the physician, and above all to reduce time and costs for the patient. It is also important to note that this requires an optical device to obtain the hyperspectral image in the uterus.

Initial Phase - Endometriosis

In the first meeting with the researchers, they explained to us how the technology worked and what were their expectations from us. We were a bit confused at the start since we had done research about fertilization because we thought they would be still working on that area, but we managed to adapt quickly. We started looking into several diseases to see how the patient journey was and what were the methods being used in the diagnosis and treatment. At first, we decided to dig deep on endometriosis since in the meeting it seemed like the researchers focus was on this specific disease and there was obviously a problem since in several forums and articles we could see that it was a disease very difficult to diagnose (Annex 1).

To research about endometriosis we started with the definition of various hypotheses (Annex 2) which then we would try to validate with as many interviews with doctors and patients as we could, a general survey for the patients that were not willing to have an interview and more secondary research. These hypotheses were all about the problems associated with how is endometriosis currently treated, and we were trying to assess if Hysplant's technology

could do better than that, our hypotheses were that right now the disease takes too much time to diagnose, that there is very low awareness about what is endometriosis and how its treated even from the doctors side and this diagnose is too laborious (which is expensive and can produce human errors since doctors need to analyze the results after making the tests), too invasive (the methods used now are very uncomfortable and sometimes harmful for the women), too expensive and has a relatively low accuracy.

To validate these hypotheses we interviewed 20 patients and surveyed 29 more found on social media, support groups and other communities and also interviewed 5 doctors contacted through Doctoralia. We obtained several insights from each source. According to the surveys (which was responded from endometriosis patients all over the world), the average age was 36, the average time to diagnose was 9 years (which is astonishing and possibly confirmed our hypothesis), it took less than a weekend for the majority of the surveyed to get the results after the diagnosis test (which is not bad at all), lots of them found the diagnosis process to be very invasive being those laparoscopies and transvaginal ultrasounds, the thing they disliked the most about the process were the time it took to diagnose, the invasiveness, the psychological support and the medical professional service (attitude, engagement). (Annex 3)

Other insights we obtained from the interviews are that there is no screening for uterine pathologies if the women are asymptomatic, most agree that there should not be surgery to diagnose it and if it has to be done skip the ultrasound since it only wastes time, although accuracy is still more important than time, the majority also point out that there is very low awareness about endometriosis not only from the general public but also by doctors that some of them do not even know what it is or how to treat it and do not consider it as a possibility.

After all this research we decided that endometriosis was not the right disease to focus on for the technology since according to the interviews with the doctors and additional research (NHS UK, 2022), although the current technology can detect endometriosis as soon as symptoms appear and even if our technology would allow us to detect the disease on very early stages, there would have to be regular screenings in order to be detected since women would not notice it and even if it were, there is no treatment available as of now. Another constraint is that most doctors are not even aware of the fact that endometriosis comes from inside the uterus initially, which could make them feel as if there was no need for this technology. Another reason was that the other team was already doing their research on

endometriosis, so it would be more interesting for the researchers to have two different projects.

Phase Two - Uterus Cancer Research

After looking for other uterine diseases, we decided to focus on uterine/endometrial cancer, since the others were very mild or just too rare to have a feasible market. Uterine cancer is a relatively common disease with 382,069 new cases and 89,929 deaths in only 2018 (National Library of Medicine, 2019), it also shares some similarities with endometriosis since both disease are in the endometrium, involve endometrial tissue, are influenced by estrogen and spread throughout the body. (Annex 4)

The hypotheses were basically the same we defined with endometriosis. In the initial research where we analyzed the current diagnosis process, we found out that they used transvaginal ultrasounds that had high false-positive test results and the risks coming from that include anxiety and complications from biopsies. On the other hand we have endometrial sampling by hysteroscopy or direct biopsy which has a lot of false negatives (you have the disease but test negative) and very few false positives (you don't have the disease but test positive), it requires general anesthesia most of the time and could cause cancer dissemination. It also can suffer from technical failure or intolerable pain that affects up to 31% of the women, finally it also has huge financial implications for health service providers.

Technologies Review

Transvaginal ultrasound
Transvaginal ultrasound (TVU) is a procedure used to examine the vagina, uterus, fallopian tubes, and bladder. It is also called endovaginal ultrasound. An ultrasound transducer (probe) is inserted into the vagina and used to bounce high-energy sound waves (ultrasound) off internal tissues or organs and make echoes. The echoes form a picture of body tissues called a sonogram. The doctor can identify tumors by looking at the sonogram. TVU is commonly used to examine women who have abnormal vaginal bleeding. For women who have or are at risk for hereditary non-polyposis colon cancer, experts suggest yearly screening with transvaginal ultrasound, beginning as early as age 25 (*Endometrial Cancer Screening (PDQ®)–Patient Version*, 2021).

Endometrial Sampling

Most of the time, you can get this test done in your doctor's office. You won't need anesthesia, but your doctor may suggest you take an over-the-counter pain reliever 30 minutes before your visit. The procedure usually takes 10 to 15 minutes. You'll lay on an exam table with your feet resting in stirrups, just like you would for a Pap smear. Your doctor will insert a device called a speculum into your vagina. This holds it open during the procedure. After your cervix is cleaned, your doctor will insert a very thin, flexible tool to gently suction out a tissue sample from the lining (endometrium) of your uterus. This will then be sent to a lab so it can be looked at under a microscope and tested for abnormal cells like cancer (*What Is an Endometrial Biopsy*, 2017).

Hysteroscopy with Direct Sampling
Under the hysteroscopy, the symptom of endometrial cancer is: An endometrial cavity showing focal or extended polypoid, papillary, nodular, or mixed patterns of mucosal overgrowth showing friable/cerebroid consistence, surface necrosis appearing as avascular whitish-grayish tissue, and an overt atypical vascular network.

Based on the custom of each participating center, hysteroscopy was carried out either as outpatient office intervention with or without anesthetic local support and as inpatient procedure accomplished in a surgical room under general anesthesia or conscious sedation. All procedures were assisted by a video camera and were conducted by using a fluid distending medium delivered by a pressure bag or a peristaltic pump. Normal saline or hypotonic solutions were used according to the use of bipolar or monopolar technology, respectively. Endometrial biopsies were carried out by using one of the following hysteroscopes: (1) 12–16 Fr rigid hysteroscopes with a 5-Fr operative channel; (2) 16 Fr mini-resectoscopes armed with a mini-loop electrode; and (3) 26–27 Fr resectoscopes armed with a loop electrode. The vaginoscopic technique was routinely used to gain uterine entering [23] with the exception of patients treated under general anesthesia by 26–27 Fr resectoscopes, in whom cervical dilatation was done before hysteroscopy assessment. The cutting devices used for endometrial sampling included (1) mechanical tools such as sharp scissors and grasping forceps and (2) electrosurgical tools such as 5 Fr co-axial or angled bipolar electrodes, bipolar or monopolar loops, and bipolar or monopolar mini-loops. After a hysteroscopy inspection suggestive for EC, based on the responsible hysteroscopist's judgment, one or more endometrial biopsies under vision were accomplished, addressing the tissue sampling to the viable tissue showing the most predictive features of malignancy. When hysteroscopy view was consistent with hyperplasia or polyp, biopsies targeted to the most significant mucosal abnormality or a full polypectomy were carried out, respectively (Garuti, 2020b).

The steps we followed for the research were similar to endometriosis with over 24 interviews but this time focusing more on the patient journey. Out of the 24 women, all of them said it took too long for the final results and sought more than one doctor's opinion, 88% went to more than one facility and underwent strong discomfort, 25% went under anesthesia and 21% experienced failure in the biopsy (not enough sample collected or too much pain to

continue). We also had a survey, which was less effective since the support groups and communities are more closed and not willing to post any survey or accept you into the discussions. (Annex 5) As in endometriosis, lots of women stated that they did not understand why they still had to do ultrasounds and previous steps instead of directly doing the biopsy if it was clear to the doctor that they had cancer. Some of them also complained about having misdiagnosis, for example, 2 of them were told they did not have cancer (after doing the tests) when they actually had it.

After analyzing and extracting conclusions from all the testimonies, we had to provide a value proposition for diagnosing uterine cancer using our technology. Our technology used as a diagnostic tool could provide higher accuracy, and faster results (since AI is the one analyzing the test, not the doctor itself which also brings a more objective point of view and avoids human error), it is also a less invasive solution, will replace the multistep process since being less invasive/costly could avoid this multistep process, and it has a low failure rate compared to biopsy.

After defining our value proposition, we wanted to make a prototype that was able to portray it and show the patient journey, so we contacted a video animator on Fiverr to help us create a video that could portray the patient journey and how it could be improved with Hysplant's technology. We also thought of making a physical prototype portraying the device that could enter the uterus and allow for the imaging, but we ended up not doing it since it would take too much time and was not that useful.

This project has been a very long journey where we have learned to work in a diverse team where everyone can contribute within their area of knowledge and provide their best to the team, we also got to know how to interview properly since we only had done a few of them during our studies but in this project, we had to step it up and make over 30 of them. We also learned how to use design thinking in our future projects to build a customer journey to have a better understanding of a business problem and how to build a prototype to validate/portray our value proposition. Overall, we think doing this project was one of the best parts of our master's since it was very different from everything we had been doing, and we got to meet a diverse group of people that we would not have had the chance to, we really appreciate that a company can trust a group of students to help in a project like this and that our universities offered us this opportunity to work in a real-life environment.

Patient - Doctors Testimonies

Endometriosis Patient:
- Patient (52 years old)

Menstruation within 14 years, from the beginning many pains (menstruation not abundant but very painful, in addition to pains such as gastroenteritis and the appearance of clots). She has private medicine.

In the first examinations she was diagnosed with ovarian cysts, and was only given painkillers to relieve the pain (detected by transvaginal ultrasound). At the age of 26, the pain became unbearable and she accepted hormone treatment. With revisions every 3 months, where already in this opportunity they detected another cyst of 6*6 dimension, with which they extirpated it by laparoscopy. In spite of this, the intense pain continued.

Then a second operation, after consulting with different gynecologists, where they removed the endometrial tissue, leaving only a part of the left ovary, the fallopian tubes retracted, damaged the right ureter, and additionally formed a petrified blood clot as a result of the same.

Endometriosis Patient:
- Patient (44 years old)

Diagnosed with endometriosis since the age of 18. Symptoms such as vomiting, dizziness and a lot of pain. Went to hospital for check-ups (through Social Security), and additionally had check-ups in private hospitals. With the transvaginal ultrasound it was not clear, but at first they suspected polycystic ovaries. She has a diagnosis of infertility due to endometriosis. She has undergone 3 surgeries to remove endometrial tissue adhesions. Her physician indicated that, despite early detection, there is currently no treatment to prevent the disease from progressing, only pain relief through contraceptives.

Gynecologist:
- Dr. Herraiz Martinez

He experienced the introduction of hysteroscopy in the early 1980s. To make diagnoses inside the uterus, first by ultrasound with a vaginal probe and to confirm it by diagnostic hysteroscopy. It may happen that very small polyps, small septa/altered uterus are not detected by Transvaginal Ultrasound (it can be done at any time and at any age). In the case of Endometriosis, it is mainly observed through Laparoscopy.

Gynecologist:
- Dra. Kovaleva Irishina

There is currently no systematic screening for uterine pathology in asymptomatic women. Contour alterations (congenital anomalies) are diagnosed by 3D ultrasound or MRI. Myomas that do not protrude into the uterine cavity are not visible by hysteroscopy. The procedure for their diagnosis is 2D ultrasound.

Endometrial Cancer Patient:
- Patient

Interview Highlights:
- Early control since 15 years old
- Papilloma virus (she did not have the vaccine at the time of contracting it). When it was detected, she had a "Conization" (they remove some tissue from the lower part). Recurrent controls
- After a few months, as a control, she underwent a Transvaginal Ultrasound (to

closely observe two nodules that were visualized during the controls)
- Surgical hysteroscopy without anesthesia to remove the tumors, but because of their location they could not be removed. After 3 months, she was operated on, applying a "curettage".
- Treatment by means of daily oral medication.
- For the Controls: Cornier (procedure without anesthesia, where cells are extracted to check if no cancer cells appear, very painful, with results in about 2 weeks).

- Patient
  Interview Highlights:

- Visited 3 doctors and 2 hospitals during the whole diagnosis process.
- The initial diagnosis is from the yearly cervix screening which is recommended to females over 50 years. Unfortunately, I had to wait for one month for an appointment in the public hospital after the initial diagnosis. Waited for another two weeks for the result.
- The cost was covered by the public health care but I prefer to pay an extra $500 to have the result immediately.

References

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- Garuti, G. (2020b, July 19). Hysteroscopic view with targeted biopsy in the assessment of endometrial carcinoma. What is the rate of underestimatated diagnosis? The results of a multicenter Italian trial - Gynecological Surgery. SpringerOpen. https://gynecolsurg.springeropen.com/articles/10.1186/s10397-020-01077-0

Annex

Annex 1 (World Health Organization)

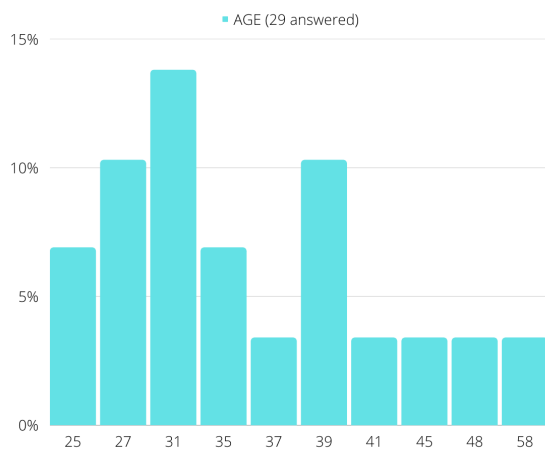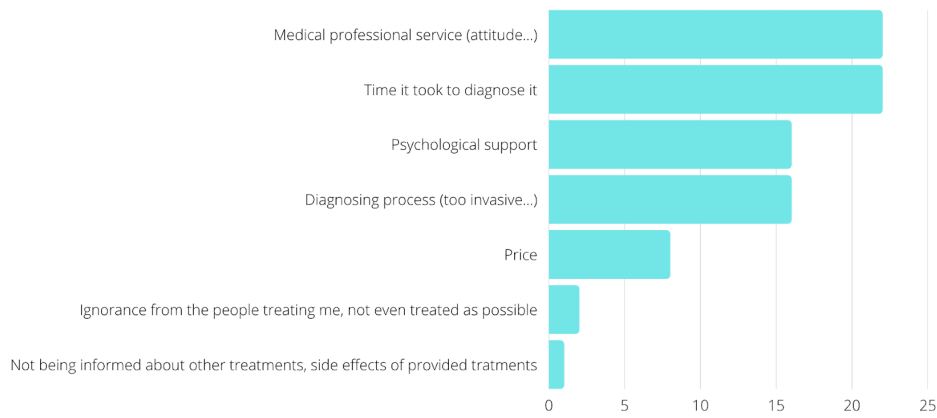1 to 10 women get affected by endometriosis during their reproductive years (ages of 15 to 49)

10% women of reproductive age get affected

■ 176 million affected
■ Unaffected
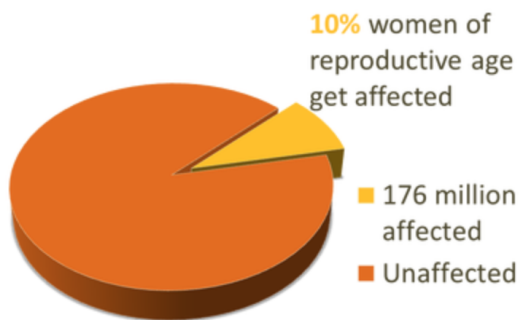
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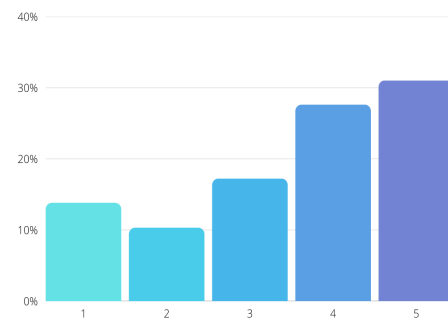

HYPOTHETICAL PROBLEMS

01 **Late Diagnosis**
Great majority of patients don't get diagnosed until months after first symptoms and do not get regular screenings.

02 **Laborious**
Doctors need to analyze the results after making the test which can be subjective.

03 **Too Invasive**
Women feel very uncomfortable while doing the tests to diagnose the disease.

04 **Too expensive**
The current diagnose methods are very expensive for the patients.

05 **Low awareness**
Most women do not know about uterine cancer and how to prevent it.

06 **Low accuracy**
Current technology may misdiagnose
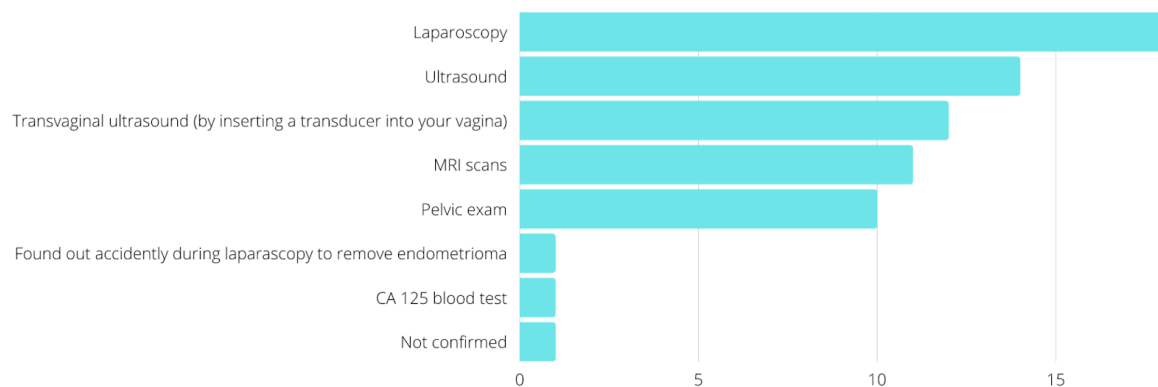
Annex 3 (Endometriosis survey results)

What parts of the process did you dislike the most? (aside from the disease itself) (29 answered)

- Medical professional service (attitude...): ~22
- Time it took to diagnose it: ~22
- Psychological support: ~16
- Diagnosing process (too invasive...): ~16
- Price: ~8
- Ignorance from the people treating me, not even treated as possible: ~2
- Not being informed about other treatments, side effects of provided tratments: ~1
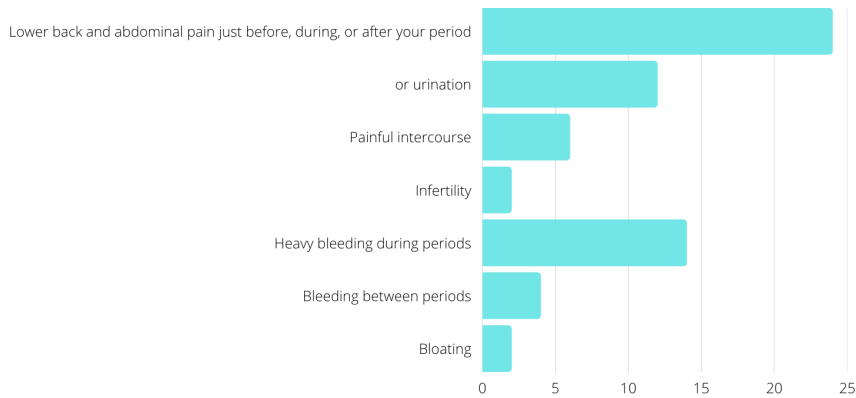
AGE (29 answered)

How invasive did you find the diagnose process to be? (29 answered)

Which procedures did they use to diagnose your endometriosis? (29 answered)

- Laparoscopy: ~18
- Ultrasound: ~14
- Transvaginal ultrasound (by inserting a transducer into your vagina): ~12
- MRI scans: ~11
- Pelvic exam: ~10
- Found out accidently during laparascopy to remove endometrioma: ~1
- CA 125 blood test: ~1
- Not confirmed: ~1

Which were the first symptoms you noticed
(29 answered)

Lower back and abdominal pain just before, during, or after your period

or urination

Painful intercourse

Infertility

Heavy bleeding during periods

Bleeding between periods

Bloating

0 5 10 15 20 25

Annex 4 (National Cancer Institute)

Estimated New Cases in 2022	65,950
% of All New Cancer Cases	3.4%

Estimated Deaths in 2022	12,550
% of All Cancer Deaths	2.1%

5-Year Relative Survival

81.3%

2012–2018

ENDOMETRIAL CANCER STATS

- Endometrial cancer is the sixth most common cancer affecting women globally
- Most women present early following the onset of postmenopausal bleeding (PMB)
- 20% of women present with advanced disease, for whom 5-year survival rates are just 15%
- New strategies to facilitate early diagnosis are urgently needed to enable curative hysterectomy for women who present with biologically aggressive diseases.
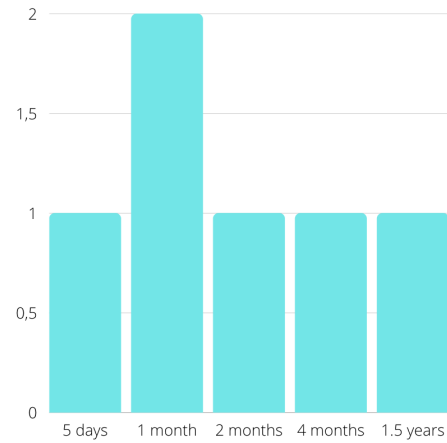
CASES
382 000 NEW CASES

DEATHS
89 900 PERSONS IN 2018

PROPORTION OF ALL CASES
20%
OF WOMEN PRESENT WITH ADVANCED DISEASE

TREND OVER TIME
15%
CHANGE IN UTERINE CANCER INCIDENCE RATE SINCE THE EARLY 1990S

Annex 5

How much time did it take to get the results after the tests?

How long it took from the first symptoms until you got diagnosed?

Treatment depends on cancer stage, diagnose tools :