III. Endo-Detect

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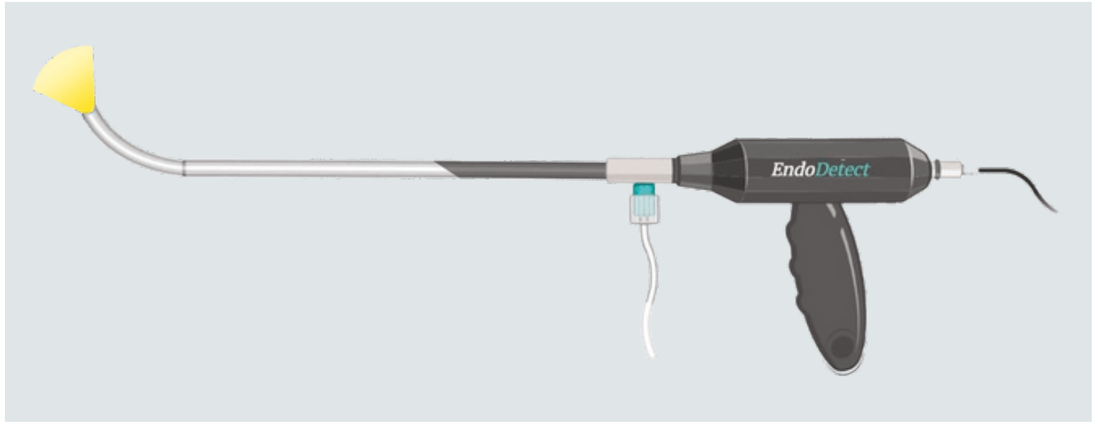


PROBLEM STATEMENT

"There is no way of detecting Endometriosis without surgery".

NEED STATEMENT

"A need to develop a minimally invasive, cost-effective diagnostic tool to detect endometriosis in a more time-efficient manner."

BACKGROUND

Disease Aetiology and Patient Cohort: Endometriosis is a painful disorder that occurs when endometrial tissue occurs outside of the uterine cavity. Characterised by painful menstrual periods, endometrial tissue can irritate surrounding tissue to cause scarring and adhesions between pelvic tissue and organs. While also causing infertility, the disease is estimated to affect upwards of 10% of women of childbearing age. Endometriosis is a hidden disease, with current clinical practice lacking non-surgical means for detection. This project aimed to solve needs related to the diagnosis and monitoring of this pathology.

USER REQUIREMENTS

Practitioner User Requirements:	Patient User Requirements:
Time-Effectiveness:	
Minimal Processes Involved in Testing Procedure.	Shortened Length of Time For Diagnosis.
Indication / Definitive Answer of Endometrial Tissue Present.	
Cost-Effectiveness:	
Similar or Lower Costs Than Current Diagnostic Methods	Costs in Line With Routine Check-Up (e.g. Hormonal Tests).
Minimal Overhead Costs (E.G. Labour) Required.	Can Be Performed in GP Office.
Encourage the Use Of Early Testing At First Consultation	Minimal Number of Consultation Necessary.
Ease of Use:	*Minimally-Invasive:*
Minimal Training Necessary for Physicians.	Minimal Pain or Discomfort to the Patient
Obey by Ergonomic Principles.	Minimal Hospital Stay and Recovery Time
Intuitive Functionality.	Minimal Regulatory Standards Required for Approval.

USER STORIES

"As a woman experiencing painful menstrual periods, I want a non-surgical diagnostic tool that can quickly and accurately detect endometriosis, so that I can get the treatment I need without having to undergo surgery."

"As a woman with endometriosis, I want a cost-effective diagnostic tool that is available to me without a long wait, so that I can get a diagnosis and start treatment as soon as possible."

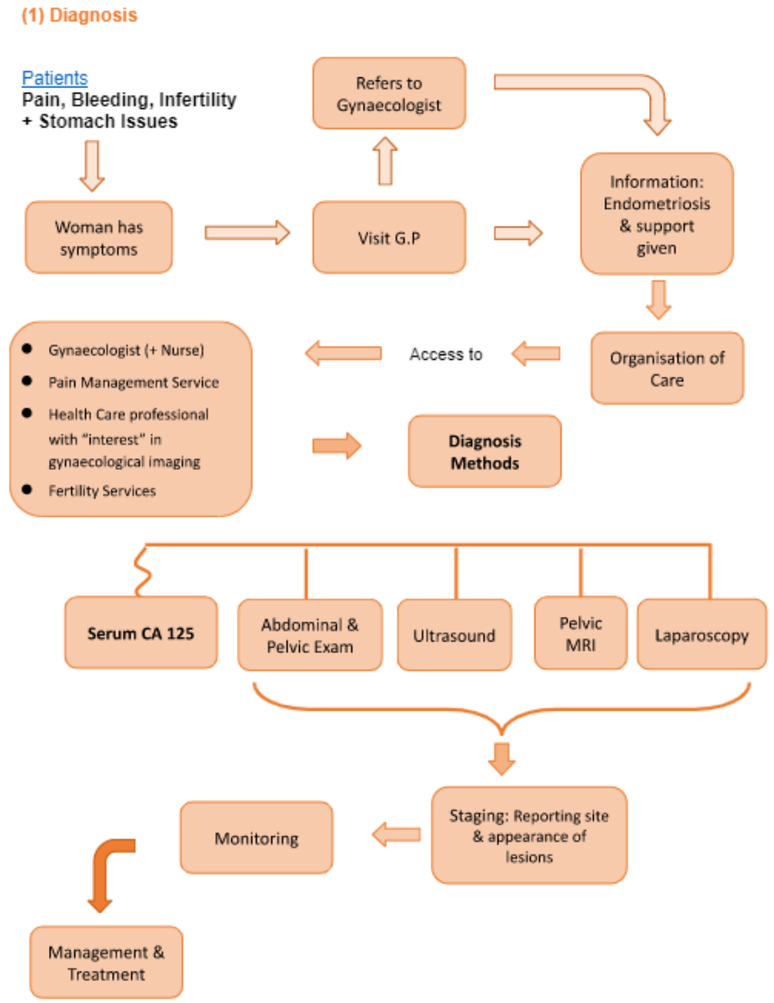
"As a woman with endometriosis, I want a minimally invasive diagnostic tool that is less painful and risky than surgery, so that I can get a diagnosis without experiencing additional discomfort or complications."

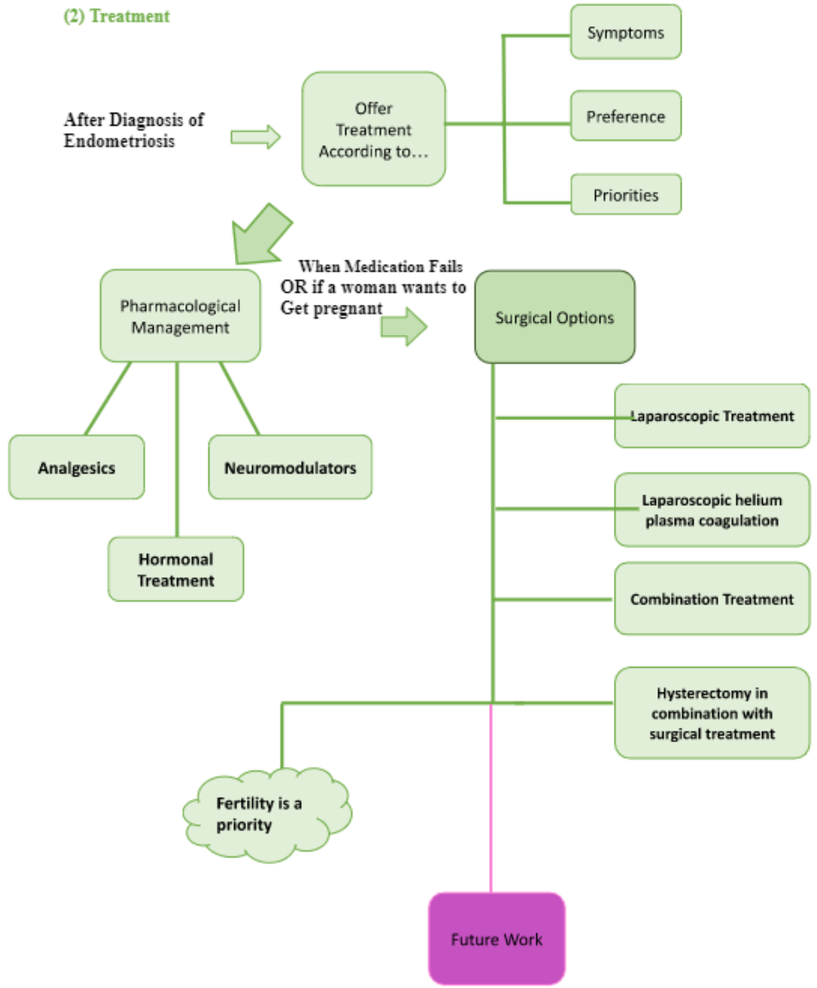
"As a healthcare provider, I want a diagnostic tool that can accurately detect endometriosis without the need for surgery, so that I can provide my patients with a more efficient and effective diagnostic process.

"As a healthcare provider, I want a diagnostic tool that is cost-effective and minimally invasive, so that I can offer my patients a more affordable and comfortable diagnostic experience.

PATIENT JOURNEY

Developing the patient journey map allowed the team to get a fuller understanding of the diagnosis and treatment processes. Exposing pain points also unveiled opportunities to best disrupt the market.





CONCEPT GENERATION

CONCEPT SCREENING

Three favouring concepts are outlined below. Each of which were measured against the user requirements.

Concept 1 - "**Nano-Particles**" *(Figure 1)*
This concept was in part inspired by recently demonstrated in a study to selectively bind to endometrial tissue (Moses et al., 2020). Nanoparticles have found medical applications in imaging and photothermal therapy in recent times. Within oncology, their use is particularly attractive due to their tendency to accumulate in highly vascularised areas pertaining to tumours. Similarly, endometrial tissue also occurs highly vascularised, hence the suggestion that it would be a suitable candidate using techniques borrowed from diagnostics developed for studying cancer cells. Should a nanoparticle model be developed to specifically bind to endometrial tissue, a combination device was conceived to image the presence of endometriosis in the pelvic region

Concept 2 - "**Bioimpedence**" (Figure 2)
Whilst current procedures depend on physicians being able to visually differentiate between endometrial and healthy tissue, diagnosis through bioimpedance could enhance their capability. The principle of bioimpedance allows tissue types to be identified by their varying conductive properties compared to surrounding tissue, acting as a 'digital signature'. Factors affecting impedance include structural make up including composition and vascularity, and ratios between protein, water, and electrolyte content. The proposed concept would use external anterior and posterior electrodes to measure the bioimpedance of affected regions. Whilst Halonen (Halonen et al., 2019) supported this hypothesis through the identification of tissue types, this would be a first of its kind in application to the diagnosis of Endometriosis.

Concept 3 - "**Hormone Patch**" (Figure 3)
A minimally invasive transdermal patch that provides continuous monitoring of a patient's hormonal levels. Altered estrogen and progesterone levels have been found to be associated with endometriosis (Marquardt et al., 2019). A painless microneedle patch would be placed on the skin. The microneedles of a suitable length will be subject to blood contact with an actuator that is calibrated to react according to the presence of said hormones.

An IOT device will emit a signal to a smart device that interprets the results over time. This product could help diagnose endometriosis, or even track the regrowth of endometrial tissue after surgery. Transdermal microneedling has been demonstrated for blood-glucose monitoring, and there is a precedent that it could be redesigned for hormonal applications (Xue et al., 2018).

Figure1

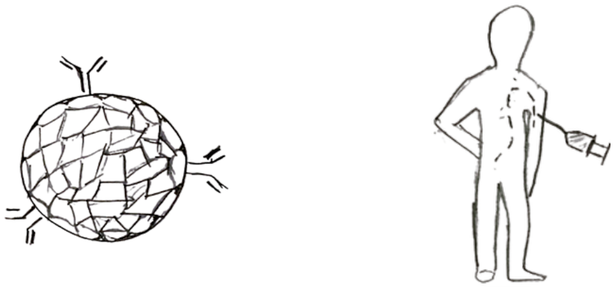


Figure 2

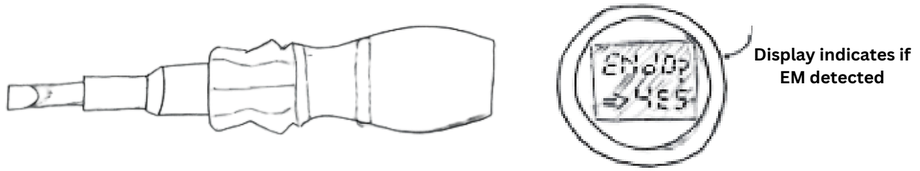
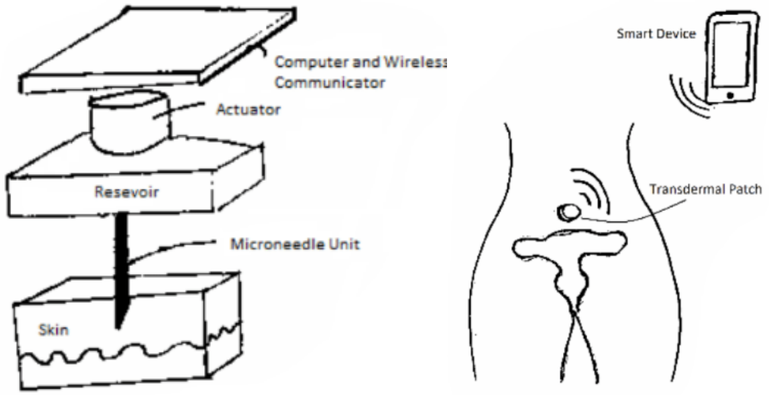


Figure 3



CONCEPT SELECTION

On this occasion, despite a marginally lower score, the nanoparticle imaging concept was selected given that few steps would be required to carry out the procedure, unlike the hormonal patch, which would not have to control for variation throughout the hormonal cycle. All concepts would expectantly reduce the time between the first consultation and diagnosis.

As for Cost Effectiveness, Bioimpedence scored lower than its counterparts for such a device may act as an additional instrument during laparoscopic surgery rather than eliminate the need for the procedure. The hormonal patch scored the highest due to the relatively low costs of micro-needle patch devices.

Again the hormonal patch scored highest for being the most minimally invasive of all the three procedures. This was followed by the nanoparticles which require an endoscopic procedure and bioimpedance which would involve a surgical incision. Despite not achieving the highest score, the team rationalised our nanoparticle concept as having the most promise due to an established body of literature in research backing the claim that it would work.

	Nanoparticles	Bio-Impedence	Hormone Patch
Practitioner User Requirements:			
Time-Effectiveness:			
Minimal Processes Involved in Testing Procedure.	4	3	5
Indication / Definitive Answer of Endometrial Tissue Present.	5	2	3
Cost-Effectiveness:			
Similar or Lower Costs Than Current Diagnostic Methods	5	2	5
Minimal Overhead Costs (E.G. Labour) Required.	4	2	5
Encourage the Use Of Early Testing At First Consultation	3	2	5
Ease of Use:			
Minimal Training Necessary for Physicians.	5	4	5
Obey by Ergonomic Principles	5	4	5
Intuitive Functionality.	5	4	5
Patient User Requirements:			
Time-Effectiveness:			
Shortened Length of Time For Diagnosis.	4	3	3
Cost-Effectiveness:			
Costs in Line With Routine Check-Up (e.g. Hormonal Tests).	3	2	3
Minimal Touch Points in Patient Journey	4	3	4
Minimal Number of Consultation Necessary	4	3	4
Minimally-Invasive:			
Minimal Pain or Discomfort to the Patient	4	3	4
Minimal Hospital Stay and Recovery Time	4	3	5
Minimal Regulatory Standards Required for Approval.	2	3	3
Total	61	43	64

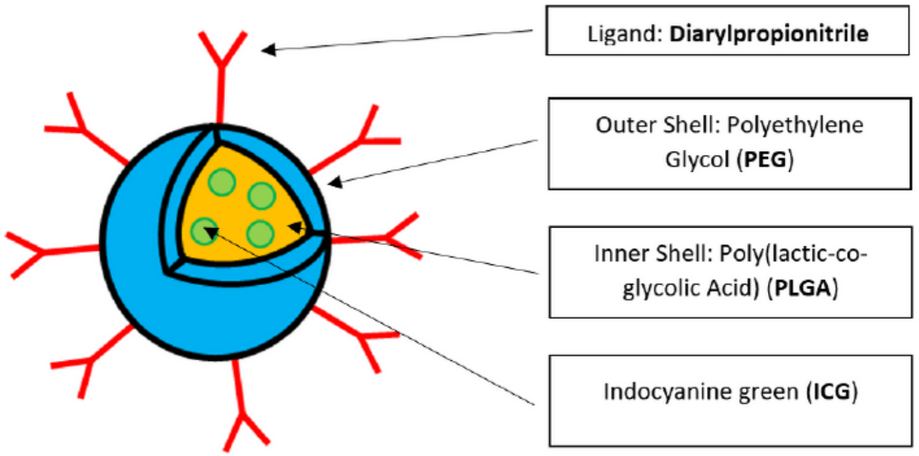
NANOPARTICLE DESIGN

The Diarylpropionitrile ligand actively targets the endometrial cell receptor. The target receptor estrogen receptor beta (ERβ), is found in higher concentrations within endometriotic tissue than in healthy endometrial tissue.

Polyethylene glycol (PEG) outer shell coats the particle in order to improve the blood circulation half-life. PEG encapsulation or "PEGylation" common NP surface modification which also improves ligand grafting to nanoparticles.

PLGA is the selected nanoplatform. It is part of the polymeric nanomaterial family, proving to be versatile (targeting modifications, imaging) and efficient with minimal toxicity. (Danhier et al., 2012, Lamberti et al., 2014).

Indocyanine green (ICG) (Hu et al., 2020) dye is the only FDA-approved dye able to be imaged with the proposed imaging modality

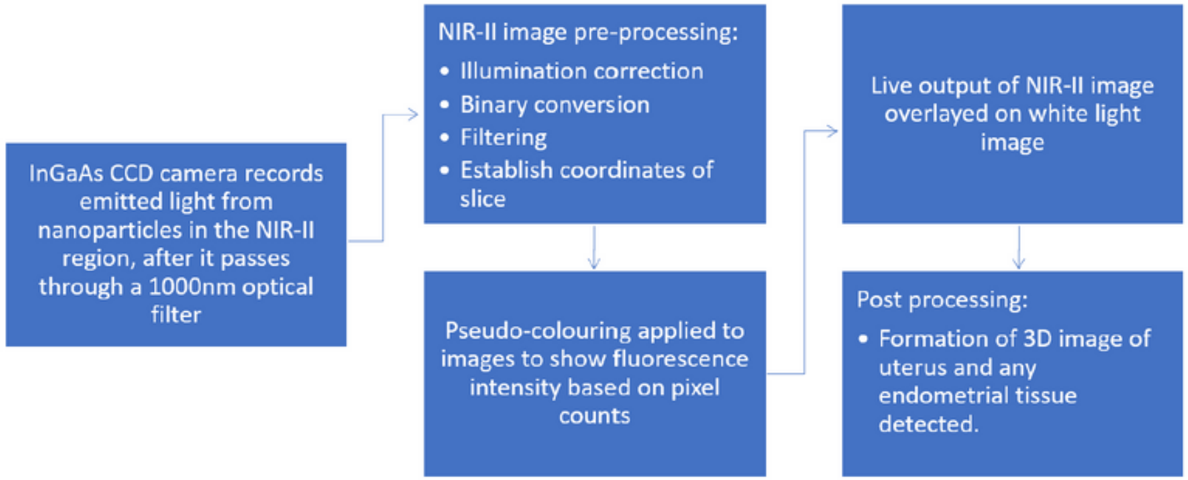


IMAGING MODALITY

Choosing the best imaging modality considers engineering variables such as nanoparticle design, characteristics of the tissue assessed, and attainable image resolution. Cost and settings are equally important. For example, Magnetic Resonance Imaging (MRI) produces high-definition quality imaging at a cost and requires a hospital setting. In contrast, a sonar would produce a relatively low-quality image, it can be performed at minimal cost within a GP surgery.

Near Infra-Red (NIR) is similar akin to visible light with a longer wavelength (>700nm). The window for NIR-II (1000-1700nm) in particular has been shown to produce high quality *in vivo* imaging due to minimal opacity and light scattering through biological tissue. This imaging modality has a range of depth of centimetres (Sheng et al., 2020)

This imaging modality is used to provide real time imaging and / or the formulation of 3D image as seen below.

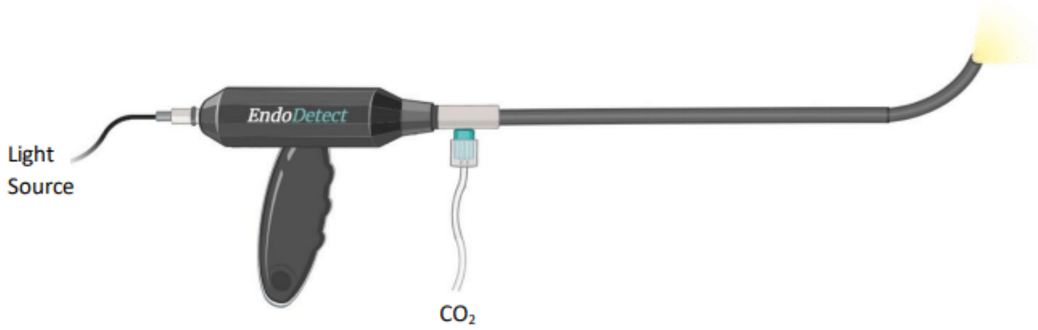


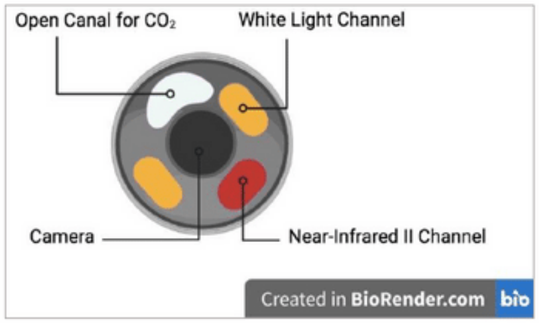
THE SCOPE

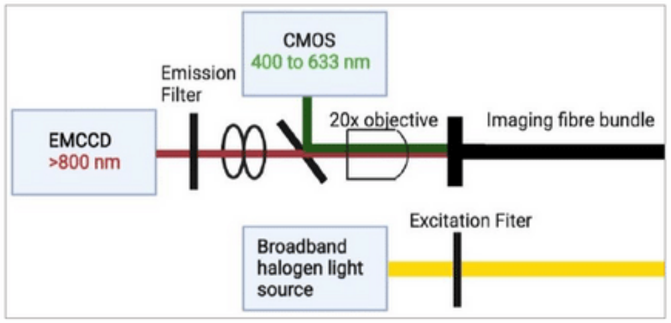
A modified hysteroscope design allows the physician to achieve specific visualization of the NIR-II excited nanoparticles in the pelvic area.

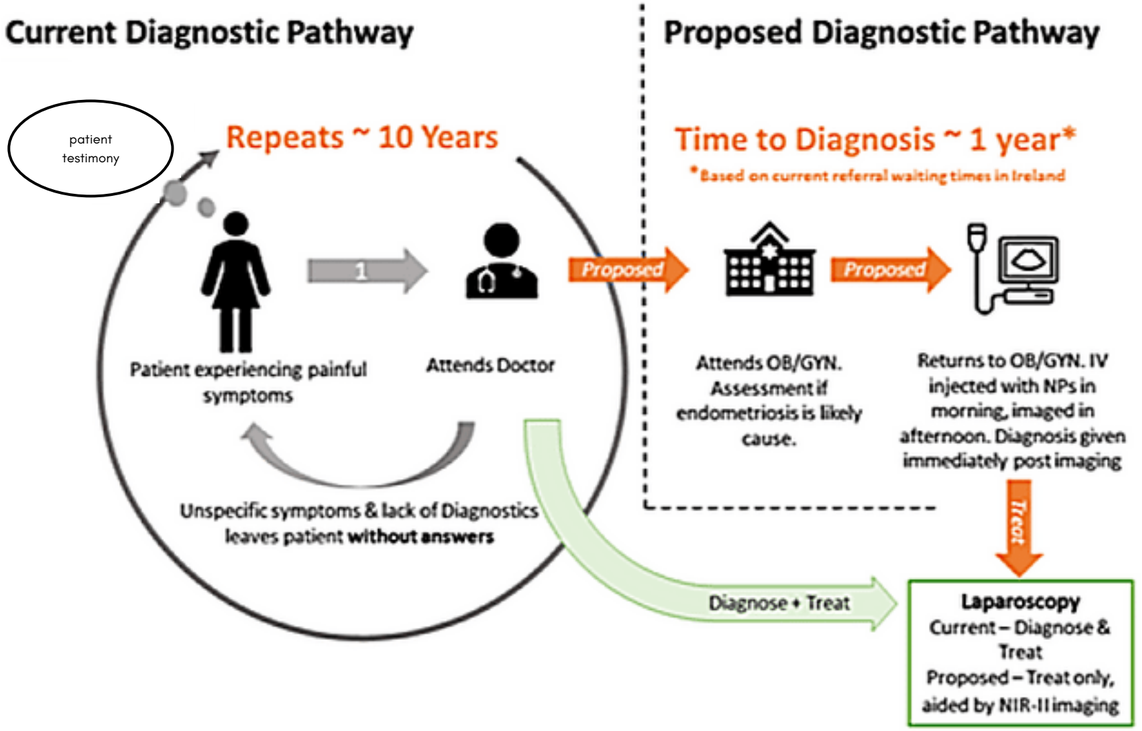
The scope device is designed to provide both optical and NIR-II. Optical mode allows the physician to direct the probe to the uterus and inspect proximal tissue as necessary. Switching to NIR-II mode allows visualisation of suspected endometriosis within the myometrium and beyond. The option of inflating the uteral cavity is possible using the CO2. Also, the probe's end can be flexed to control the angle of the camera

NOTE: Even with the use of laparoscopic surgery, it has not been possible up to this point to visualise endometriosis within the myometrium without a hysterectomy.









RISK MANAGEMENT

Following a thorough FMEA analysis, risks shown to have high RPN scores are mitigated for with a control strategy

Design element	Failure mode	Effect of failure	RPN	Current risk control	Additional risk controls/alterations in design
NP	Not reaching the target tissue	No signal detection / inconclusive results	16	Delay time of administration and acquisition of images	**Thorough testing to proof this prior to application**
NP	Harm to patient	Toxic, allergic reaction	24	Minimum therapeutic dose to receive signal	**Patient selection after allergy test**
NP	Not being specific enough	Unable to diagnose	27	Designing a very specific NP for ER-β; set threshold for definitive signal	**Selection of a very specific ligand to maximise efficiency**
NIR-II	Unable to detect signal	Unable to diagnose	27	No saline fluid usage to inflate the uterus; flexible top part of endoscope to get as close to tissue as possible	**Specific training to aim for maximal possibility to detect signal**
Bending section	breaking / fracture / wear debris, rubber tear at distal end	Open surgery to retrieve parts, risks associated with open surgery	12	Mechanical testing, regular servicing	**Selection of material to withstand the loads/ cyclic movements,**

ADDRESSING KEY REQUIREMENTS

1. Time Effectiveness

- No elective surgery needed
- Accessible treatment means reduced time to diagnosis
- Unambiguous diagnosis
- Fewer consultation steps for diagnosis

2. Cost Effectiveness

- Lower cost than laparoscopic surgery
- Minimal overhead costs
- Encourages early testing at first consultation
- Costs in line with routine check-up (e.g. hormonal testing)

3. Ease of Use

- Minimal training necessary (similar to hysteroscope)
- Intuitive functioning with ergonomic design

4. Minimally Invasive

- Minimal discomfort to the patient
- No surgery means minimal recovery and hospital stay
- FDA 510k clearable due to a simlar design to the hysteroscope