Project Notes:

Project Title: Using MicroRNAs and Deep Learning to Noninvasively Diagnose Gynecologic Conditions
Name: Palak Yadav

Contents:

Knowledge Gaps:
This list provides a brief overview of the major knowledge gaps for this project, how they were resolved and where to find the information.

Knowledge Gap	Resolved By	Information is located	Date resolved
What are lesions and their role in endometriosis?	I searched the histology of endometrial tissue	https://www.healthline.com/health/endometriosis/endometriosis-lesions#definition	9/14/23
How does bioinformatics work?	- Analyze large sets of genome - Can be used in cancer treatment to alter genetic base pairs - Large, centralized databases - Find patterns between large data sets to identify biomarkers, targets, etc.	What is Bioinform… https://www.yourgenome.org/facts/what-is-bioinformatics-and-how-do-we-use-it/ https://www.pnnl.gov/explainer-articles/bioinformatics	10/25/23
What are microRNAs?	Reading articles	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10296063/	10/28/23
How to develop machine learning models	Reading articles, watching videos, and asking seniors for help.	https://pubmed.ncbi.nlm.nih.gov/36829667/	11/20/23

Literature Search Parameters:
List of keywords and databases used during this project.

Database/search engine	Keywords	Summary of search
Nature Journal	Cancer photodynamic therapy	- Ovarian cancer background - Microscopy development
Boston Children's	Endometriosis	- Genetic markers - Overall background - Development theories
Google Scholar	DNA Methylation + epigenetic factors influencing mental health	The main emphasis is on methylation of cytosine in DNA, which is the best understood epigenetic modification. We conclude by considering whether targeting epigenetic modification by nutritional means might reasonably be applied more widely in the treatment of mental disorders.
Frontiers	Machine Learning, miRNA	A lot of the methods focus on identifying significant miRNAs in a sample and then applying ML models to determine differentially expressed miRNAs.
Google Scholar	Meta-analysis of endometriosis	- Subset of systematic reviews - A way to analyze qualitative and quantitative study data from several studies used to establish a statistical strong conclusion - Purposes: - Find statistical significance

		with results that may be contradicting - Accurate magnitude estimation - Detailed analysis of harms, safety data and benefits - Analyze subgroups with individual numbers that are not statistically significant -

Article #0 Notes: Template

Article notes should be on separate sheets

KEEP THIS BLANK AND USE AS A TEMPLATE

Source Title	
Source citation (APA Format)	
Original URL	
Source type	
Keywords	
#Tags	
Summary of key points + notes (include methodology)	
Research Question/Problem/ Need	
Important Figures	
VOCAB: (w/definition)	
Cited references to follow up on	
Follow up Questions	

Article #1 Notes: Photodynamic Therapy For Cancer

Source Title	Photodynamic Therapy for Cancer
Source citation (APA Format)	Dolmans, D., Fukumura, D. & Jain, R. Photodynamic therapy for cancer. *Nat Rev Cancer* 3, 380–387 (2003). https://doi.org/10.1038/nrc1071
Original URL	https://www.nature.com/articles/nrc1071
Source type	Journal Article
Keywords	Photochemical internalization, photosensitizer, PDT, cytotoxicity, vascular culture, immune response

Summary of key points + notes (include methodology)	Photodynamic therapy is used to target and treat tumors. It involves two components: a photosensitizer that localizes to the target cell and the administration of light of a specific wavelength. A cellular response is induced and oxygen availability plays a key role.
	
	Reduces toxicity improves efficiency
	Mechanism of PDT:
	- A photosensitizer is administered through intravenous injections or topical application
	- A light of a specific wavelength is used to activate the photosensitizer, which causes it to get activated and release energy
	- Oxygen in the area is thereby activated, turning into Reactive Oxygen Species (ROS) which facilitates the mediation of cellular toxicity
	- There are two potential outcomes of oxygen once the singlet state is converted to a triplet state
	  - It can react with a substrate and transfer hydrogen atoms to form radicals and Type 1 oxygenated products
	  - Energy is transferred to oxygen and singlet oxygen becomes ROS (Type 2)
	- Because ROS have high reactivity and short-life, only cells close to ROS production are impacted
	  - <0.04 us have a half life of singlet oxygen
	  - < 0.02 um is the radius of action
	
	Key factors that influence cytotoxicity and photodamage:
	- Biodistribution: the timing of light exposure plays a key role in PDT effects

- Shorter time intervals lead to greater accumulation whereas longer time intervals (24-72 hours) lead to localization of MV6401 to extravascular compartment and a slower leakage
- Type of photosensitizer
- Extra and intra cellular localization
- Total dosage
  - Fractionated drug dose is more effective than single dose as it attacks through several compartments
  - PS is sent to targeted parts through the use of conjugated antibodies that recognizes tumor antigens such as ED-B domain
- Light exposure
- Fluence rate
- Oxygen availability

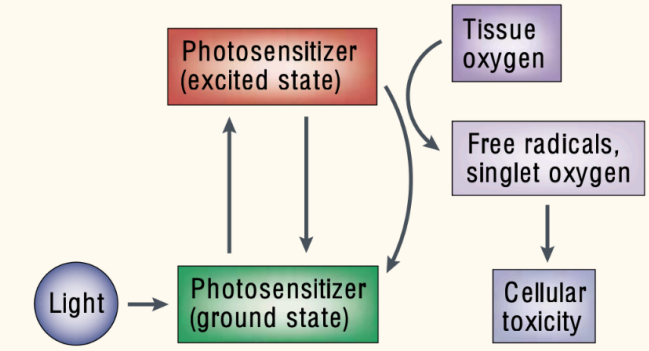
PDT effects on tumors:
- ROS produced by PDT kills tumors
- PDT damages tumors associated vasculature which leads to tumor infarction
- PDT activates immune response

Limitations:
- PDT can be ineffective due to the non homogenous distribution and increasing distance from the vascular supply (low oxygen)
- A long term response to PDT is microvascular damage and hypoxia

Overcoming limitations:
- Decrease light fluence and oxygen consumption
- Fractionate PDT light delivery to allow reorganization

Vascular damage:
- PDT causes microvascular collapse, anoxia, and hypoxia,
  - Examples: benzoporphyrin derivative, HPD, photofrin
- Can also cause endothelial growth factors to increase such as VEGF and cyclooxygenase (COX-2) due to ROS and hypoxia induced

PDT effects:
- When PDT is administered in normal Balb/C vs immunodeficient mice, there is a tumor higher recurrence in

	the latter - Immune response in addition to PDT is necessary to destroy a greater majority of tumor cells - PDT vaccines with greater tumor specificity have been developed - They are a combination of photofrin and lystate which leads to a cytotoxic T-cell response and IL-12 expression Photosensitizer cons: - Made of 60 compounds which can be hard to reproduce - 630 nm absorption is needed which is very low and required higher doses of administration - Not very selective - Long lasting photosensitive
Research Question/Problem/ Need	How does photodynamic therapy influence the viability of cancer cells?
Important Figures	 Figure 1 | **Mechanism of action of photodynamic therapy (PDT).** PDT requires three elements: light, a photosensitizer and oxygen. When the photosensitizer is exposed to specific wavelengths of light, it becomes activated from a ground to an excited state. As it returns to the ground state, it releases energy, which is transferred to oxygen to generate reactive oxygen species (ROS), such as singlet oxygen and free radicals. These ROS mediate cellular toxicity.

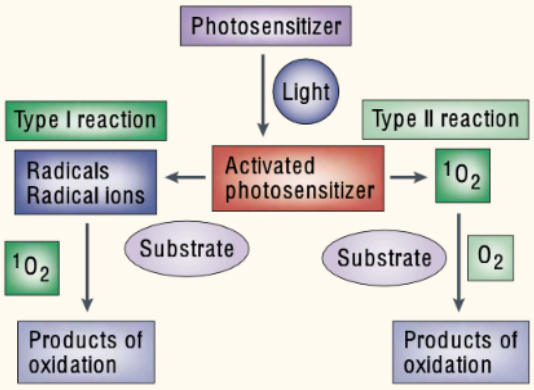


Figure 2 | **Type I and type II reaction in photodynamic therapy (PDT).** There are two types of reaction during PDT. Following the absorption of light, the sensitizer is transformed from its ground state into an excited state. The activated sensitizer can undergo two kinds of reaction. First, it can react directly either with the substrate, such as the cell membrane or a molecule, transferring a hydrogen atom to form radicals. The radicals interact with oxygen to produce oxygenated products ($^1O_2$) (type I reaction). Alternatively, the activated sensitizer can transfer its energy directly to oxygen, to form singlet oxygen ($^1O_2$) — a highly reactive oxygen species. These species oxidize various substrates (type II reaction).

Table 1 | **Photosensitizers for malignant diseases**

Sensitizer	Trade name	Potential indications	Activation wavelength
HPD (partially purified), porfimer sodium	Photofrin	Cervical*, endobronchial*, oesophageal*, bladder* and gastric cancers*, and brain tumours	630 nm
BPD-MA	Verteporfin	Basal-cell carcinoma	689 nm
m-THPC	Foscan	Head and neck tumours*, prostate and pancreatic tumours	652 nm
5-ALA	Levulan	Basal-cell carcinoma, head and neck, and gynaecological tumours Diagnosis of brain, head and neck, and bladder tumours	635 nm 375–400 nm
5-ALA-methylesther	Metvix	Basal-cell carcinoma*	635 nm
5-ALA benzylesther	Benzvix	Gastrointestinal cancer	635 nm
5-ALA hexylesther	Hexvix	Diagnosis of bladder tumours	375–400 nm
SnET2	Purlytin	Cutaneous metastatic breast cancer, basal-cell carcinoma, Kaposi's sarcoma, prostate cancer	664 nm
Boronated protoporphyrin	BOPP	Brain tumours	630 nm
HPPH	Photochlor	Basal-cell carcinoma	665 nm
Lutetium texaphyrin	Lutex	Cervical, prostate and brain tumours	732 nm
Phthalocyanine-4	Pc 4	Cutaneous/subcutaneous lesions from diverse solid tumour origins	670 nm
Taporfin sodium	Talaporfin	Solid tumours from diverse origins	664 nm

*Indications that are registered in one or more countries (all other indications are in development). 5-ALA, 5-aminolevulinic acid; BPD-MA, benzoporphyrin derivative-monoacid ring A; HPD, haematoporphyrin derivative; HPPH, 2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide-alpha; mTHPC, meta-tetrahydroxyphenylchlorin; SnET2, tin ethyl etiopurpurin.

VOCAB: (w/definition)	Photodynamic therapy: PDT or photodynamic light therapy is a treatment used to kill the disease and bacteria with the use of light Sensitizer: a substance that causes exposed individuals to develop an allergic reaction in normal tissue after repeated exposure to the

	substance. Cytotoxicity: damage to cells
Cited references to follow up on	Daniell, M. D. & Hill, J. S. A history of photodynamic therapy. *Aust. NZ J. Surg.* 61, 340–348 (1991). Ackroyd, R., Kelty, C., Brown, N. & Reed, M. The history of photodetection and photodynamic therapy. *Photochem. Photobiol.*74, 656–669 (2001).
Follow up Questions	1. What factors influence drug light interval? Why is a longer time interval more efficient? 2. Why is oxygen and conversion of ROS important and connected to cytotoxic species? 3. How does PS identify and locate specific cells? 4. How are controls and variables determined and maintained in various experiments? (for ex, how to create an experiment to find the optimal time interval) 5. What is the PDT vaccine composed of? Why is DPT vaccine more effective than lystate made from tours that have been exposed to UV?

Article #2 Notes: Study links cadmium levels in women's urine to endometriosis

Source Title	Study links cadmium levels in women's urine to endometriosis
Source citation (APA Format)	Michigan State University. (2023, July 24). Study links cadmium levels in women's urine to endometriosis. *ScienceDaily*. Retrieved December 15, 2023 from www.sciencedaily.com/releases/2023/07/230724122643.htm
Original URL	https://www.sciencedaily.com/releases/2023/07/230724122643.htm
Source type	News Article
Keywords	Endometriosis, cadmium, environmental factors
Summary of key points + notes (include methodology)	Endometriosis is a condition in women where the tissue that resembles the lining of the uterus appears on the outside of the uterus. This results in chronic pain that negatively impacts all aspects of one's life. Studies are showing that exposure to the toxic metal cadmium can result in the development of endometriosis. Levels of estrogen are too high, causing hormonal imbalance. Cadmium is considered a "metallic estrogen" - a hormone that behaves like estrogen. Cadmium can be found in cigarette smoke and even contaminated food like spinach and lettuce. The research was conducted amongst 20 to 54 years old. Various biological markers were analyzed from their urine samples and four classes of exposure were established. The findings proved the following: - Participants in the 2nd and 3rd quartile were twice as likely to have been diagnosed with endometriosis than 1st - In the 4th quartile, there was a 60% increase in prevalence Cadmium increases the prevalence of endometriosis due to its biological interaction. It binds to estrogen receptors and increases the proliferation of endometrial in both in vitro and in vivo studies. WHO has declared cadmium as one of the top 10 public health concerns. Cadmium has been shown to accumulate in kidneys as well and tends to linger as it has a longer biological half-life due to inefficient mechanisms. Currently, endometriosis can only be diagnosed with surgical visuals.

	Past studies have resulted in mixed results due to sample population, and cadmium measurement tools. This study selected a more diverse and well-represented population of the US. Methodology: - Cross-sectional study from data from four cycles of the National health and Nutrition Examination Survey - 20-54 year old women who have been surgically diagnosed with endo - Urinary cadmium measured through inductively coupled plasma spectrometry - Using statistical strategies such as log-binomial regression to find a correlation to find ratio Limitations: - Self report misclassification Urinary cadmium was measured by inductively coupled plasma–mass spectrometry,
Research Question/Problem/ Need	Is exposure to toxic metal cadmium associated with increased endometriosis prevalence among a nationally representative sample of the US population?
Important Figures	Professors to research: - Kristen Upson MSU - National Health and Nutrition Examination Survey - Marc Laufer
VOCAB: (w/definition)	**Metalloestrogen:** a hormone that can act like estrogen
Cited references to follow up on	https://academic.oup.com/humrep/advance-article/doi/10.1093/humrep/dead117/7227951
Follow up Questions	- What interventions can be taken to decrease cadmium exposure? - What populations are at more risk? - What genes are activated? - Will treatments that seek to lower the levels of estrogen

	negatively impact other parts of the body? - How are various bodily fluids and tissues collected and tested?

Article #3 Notes: Endometriosis Is More Than Just 'Painful Periods'

Source Title	**Endometriosis Is More Than Just 'Painful Periods'**
Source citation (APA Format)	MACMILLAN, C. (2017, August 17). *Endometriosis Is More Than Just "Painful Periods."* Yale Medicine. https://www.yalemedicine.org/news/endometriosis-is-more-than-painful-periods
Original URL	https://www.yalemedicine.org/news/endometriosis-is-more-than-painful-periods
Source type	Journal article
Keywords	Endometriosis, treatment, diagnosis
Summary of key points + notes (include methodology)	**Summary:** - Endometriosis is a painful, progressive disease in women where the lining of the uterus occurs on the outside, causing the monthly period cycle to become more painful and complicated, and unfortunately, the disease can become worse over time, spreading to other parts of the body through white blood cells. - Numerous studies are trying to uncover the cause behind this, from genetic markers, to nerve conduction such as pain over-stimulation, weight problems, depression, anxiety, and more. - Currently treatment involves surgery and hormonal treatments, however, more research needs to be done to find effective and efficient diagnosis tools and treatments that do not have long term detrimental impacts.
Research Question/Problem/ Need	How can treatment and diagnostic tools for endometriosis be improved?
Important Figures	None
VOCAB:	**laparoscopic excision surgery**

(w/definition)	- allows for the removal of lesions without removing or harming the uterus
Cited references to follow up on	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5737931/
Follow up Questions	- What do research models for studying this disease look like? - How are marginalized groups taken into consideration? - What patterns and genetic patterns are seen amongst various women with this condition? - What role does genetic vs environmental factors play at activating the genes for this disease?

Article #4 Notes: Cell protector: Bio-inspired solar devices boost stability, efficiency

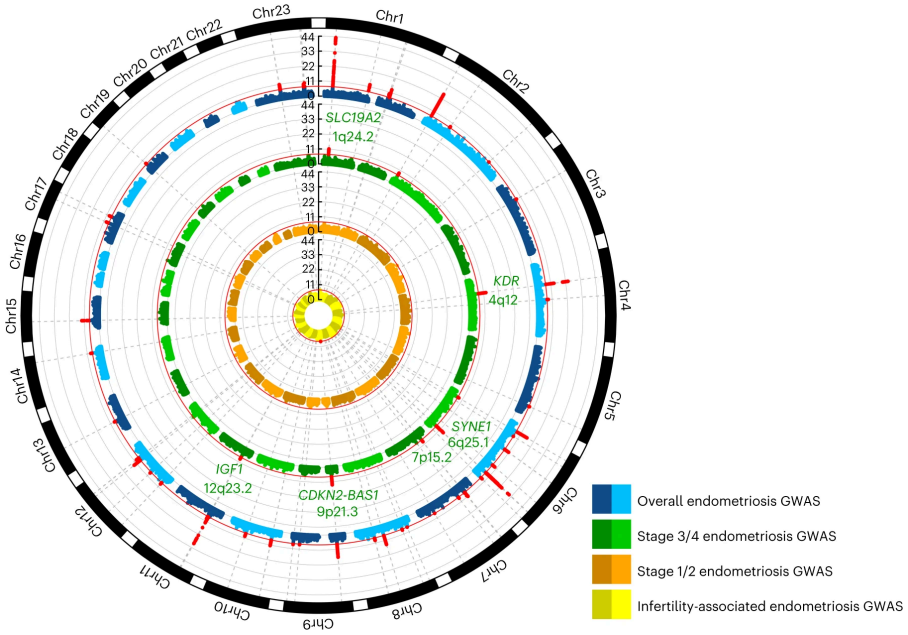
Source Title	Cell protector: Bio-inspired solar devices boost stability, efficiency
Source citation (APA Format)	Carroll, M. *Cell protector: Bio-inspired solar devices boost stability, efficiency | Penn State University*. (n.d.). Www.psu.edu. Retrieved August 21, 2023, from https://www.psu.edu/news/research/story/cell-protector-bio-inspired-solar-devices-boost-stability-efficiency/
Original URL	https://www.psu.edu/news/research/story/cell-protector-bio-inspired-solar-devices-boost-stability-efficiency/
Source type	News article
Keywords	Earth and Mineral Sciences, Materials Science and Engineering, Materials Research, Solar Energy, Efficiency
Summary of key points + notes (include methodology)	A recent study developed more efficient solar devices by combining perovskite solar cell material and synthesized versions of natural lipid biomolecules. Previously it has been a challenge to protect such devices against moisture and degradation, however the current biomaterials create a nano-layered protection by creating an emulsion (separation of water and oil materials). More research is being docuted to improve the interface, electronic properties, cost, biomolecules and more to bring these devices to market.
Research Question/Problem/ Need	How can technology be improved by incorporating biological phenomenons?
Important Figures	 The solar devices were tested in Pennsylvania from October through

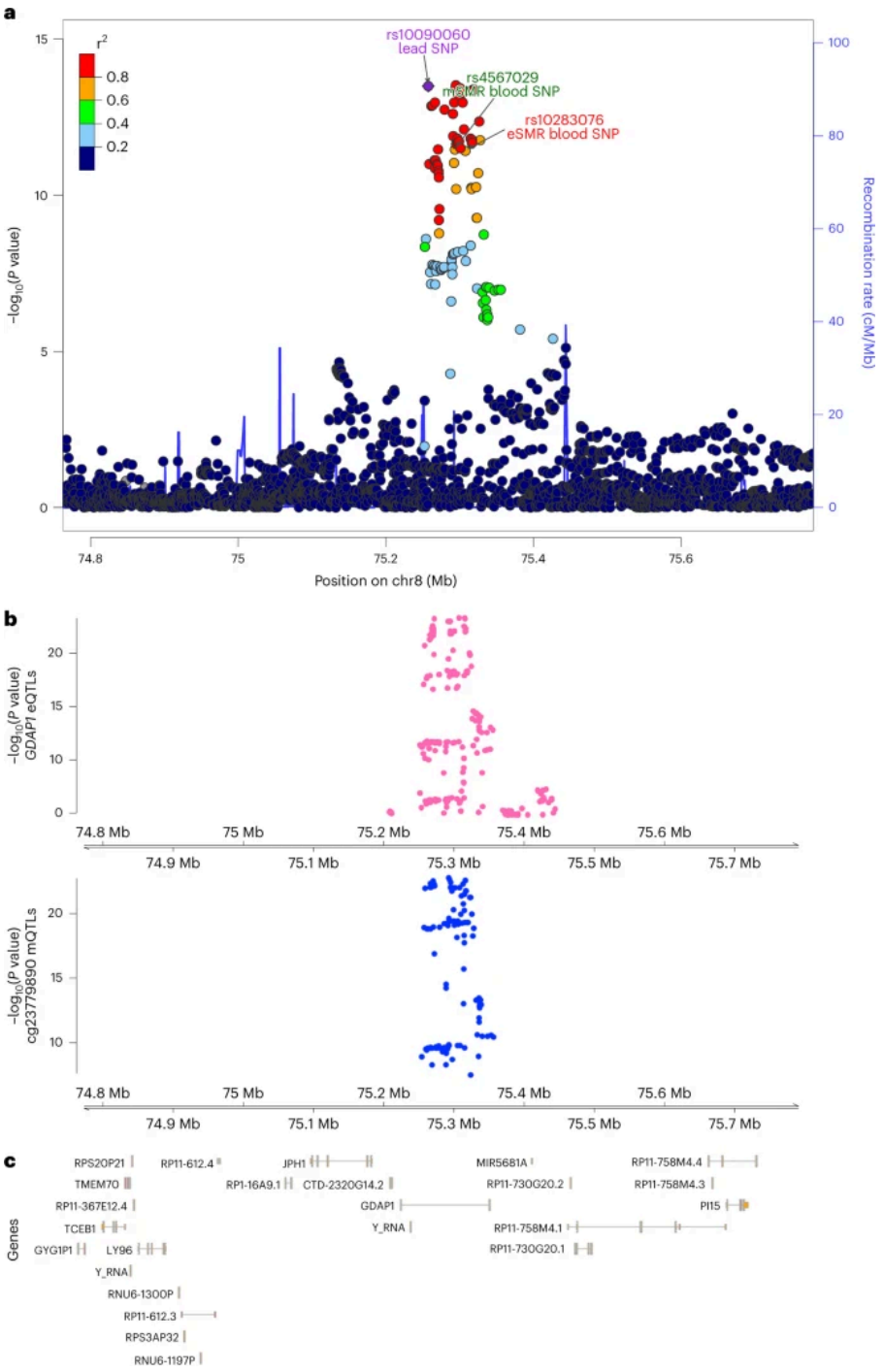
	February. The devices showed consistent efficiency of more than 19% for more than 116 days of continuous use in natural weather conditions, including snow and humidity. Credit: Provided by Luyao Zheng
VOCAB: (w/definition)	**Perovskite**: - calcium titanium oxide mineral composed of calcium titanate - used in sensors and catalyst electrodes, certain types of fuel cells, solar cells, lasers, memory devices and spintronics applications. **Emulsion**: - Mixture of 2 or more liquids that do not mix
Cited references to follow up on	https://www.ems.psu.edu/
Follow up Questions	- How are biomolecules sustained in artificial settings? - Why is it so important to create a strong emulsion on the outside of the solar cell? - Where will these solar devices be used? - Will certain parts of the device need to be replaced? - What biomolecules could be incorporated to decrease the current shortcomings?

Article #5: The genetic basis of endometriosis and comorbidity with other pain and inflammatory conditions

Source Title	The genetic basis of endometriosis and comorbidity with other pain and inflammatory conditions
Source citation (APA Format)	Rahmioglu, N., Mortlock, S., Ghiasi, M. *et al.* The genetic basis of endometriosis and comorbidity with other pain and inflammatory conditions. *Nat Genet* 55, 423–436 (2023). https://doi.org/10.1038/s41588-023-01323-z
Original URL	https://www.nature.com/articles/s41588-023-01323-z
Source type	Journal Article
Keywords	Endometriosis, genetics,
Summary of key points + notes (include methodology)	● American Society of Reproductive Medicine (rASRM) criteria ● Stage 1/2 disease features: ○ superficial peritoneal lesions and minimal adhesions ● stage ¾: ○ cystic ovarian endometriosis (endometrioma) ○ extensive scarring ○ Fibrosis ○ Adhesions ● Causes: ○ **50% heritable and 26% common genetic variation** ● Case study of 17,504 women with endometriosis and 191,596 control ○ Identified 19 distinct association genome-wide significance ○ 13 loci that are 1 MB apart ○ 1.75% phenotypic variance ● Unknowns:

	○ Potential involvement of sex steroid hormone signaling ○ WNT wingless related integration site signal ○ Cell adhesion/migration ○ Cell growth and carcinogenesis ○ Inflammation related pathways ● Results: ○ Determine pathogenesis and subphenotypes of endometriosis ○ Fine map causal variants and functional effects ● **BMF → BCl2 modifying factor** ○ Codes for glycoprotein and is associated with the sex hormone ○ Plays a role in binding globulin and regulating bioavailability of estrogen and testosterone ● SRP14 affects endometriosis related pain and helps regulate DHEA-sulfate ○ DHEA is a neurosteroid and acts as neurotrophin which plays a role in binding and activating nerve growth factors ● NGF expression helps mediate local nerve density around endometrial lesions. Three variants were shared with pain traits: rs1352889 at BSN/ 3p21.31 and rs10828249 at MLLT10/10p12.31 with multi-site chronic pain; and rs12030576 at NGF/1p13.2 with migraine and dysmenorrhea. Loci shared with uterine fibroids (3), menstrual cycle length (2), age at menarche (1), age at menopause (1), BMI (2), type 2 diabetes (1), and asthma (1) are discussed in Supplementary Text. Detailed genomic enrichment analyses for endometriosis with each of these traits and conditions is required to fully elucidate the biological basis for their genetic correlations.

	The 9 shared lead SNPs between endometriosis and MCP or migraine are eQTLs in diverse tissues (Supplementary Tables 31–32). Rs1352889 regulates the expression of multiple genes (UBA7, AMT, RNF123, ARIH2) involved in the ubiquitin system, an important cellular mechanism that may be associated with the immune-mediated survival of endometrial implants in ectopic locations48. - Rs12580862 → expression of Estrogen Regulated Growth Inhibitor MHC II gene polymorphisms
Research Question/Problem/ Need	What genetic factors and cellular pathways are involved in the onset of endometriosis?
Important Figures	 Circular Manhattan plots for genome-wide association analysis for overall endometriosis (blue), rASRM stage 3/4 disease (green), rASRM stage 1/2 disease (orange) and endometriosis-associated infertility (yellow). Genome-wide significant signals are marked in red and their chromosomal location is denoted with dotted gray lines. The six loci with substantially larger effect sizes in rASRM stage 3/4 versus rASRM stage 1/2 analysis are annotated in green.

	
VOCAB: (w/definition)	Lesions: the regions of the uterus and other reproductive organs that experience abnormal endometrial growth rASRM: a classification system for endometrial stages based on changes in the reproductive organs

	Case ascertainment: a methodology/tool used in disease detection. There are two types of case ascertainment: active and passive. Methylation: the DNA is chemically altered by adding an extra methyl group to move the process of cell division forward Summary data-based Mendelian randomization: a type of gene profiling program that analyze genome databases and its association with trait expression
Cited references to follow up on	Zondervan, K. T., Becker, C. M. & Missmer, S. A. Endometriosis. *N. Engl. J. Med.* 382, 1244–1256 (2020). Revised, A. S. R. M. American society for reproductive medicine classification of endometriosis: 1996. *Fertil. Steril.* 67, 817–821 (1997).
Follow up Questions	1. How can presence of specific genetic markers be linked to symptoms reported by patients later diagnosed with endometriosis? 2. How can the genes highlighted in this research be targeted to develop diagnostic or treatments? 3. What genes overlap between endometriosis and other conditions? Is there a pattern between the prevalence of two conditions?

Article #6: Does Nutrition Affect Endometriosis?

Source Title	Does Nutrition Affect Endometriosis?
Source citation (APA Format)	Helbig, M., Vesper, A. S., Beyer, I., & Fehm, T. (2021). Does Nutrition Affect Endometriosis?. *Geburtshilfe und Frauenheilkunde*, *81*(2), 191–199. https://doi.org/10.1055/a-1207-0557
Original URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7870287/
Source type	Journal article
Keywords	Endometriosis, nutrition, diet, fruits, fatty acids, vegetable, meat, alcohol, lifestyle, caffeine, dairy, vitamins,

Summary of key points + notes (include methodology)	**Abstract**:
	- Hormone-related, chronic inflammation
	- Currently, no scientific or proven data to confirm a specific diet or lifestyle
	- In general, fish oil capsules showed a positive impact on endometrial symptoms, whereas alcohol, red meat, and trans fat had a negative impact
	- The impact of fruits, dairy products, unsaturated fats, soy products and coffee were unclear
	- Need to conduct further studies
	
	Background:
	- Need to conduct more research to better understand the pathogenesis and etiology of the condition
	- Some factors that influence pathogenesis:
	  - Immunological
	  - Endorical
	  - Genetic
	  - Inflammation
	- Common symptom
	  - Dysmenorrhoea
	  - Dyspareunia
	  - Dysuria
	  - Dyschezia
	- Ways to confirm diagnosis: laparoscopy with biopsy

Pathogenesis of Endometriosis and Potential Dietary Strategies:

- Potential theories on development:
    - Sampson 1921 transplantation/implantation theory
        - Menstruation causes endometrial cells to spread due to antegrade and retrograde
    - Tissue injury and repair hypothesis:
        - The endometrium can have micro traumas caused by muscle movements, resulting in cells to become loose
        - Intrauterine movement: a type of repair mechanism that causes more endometrial cells to be lost
    - Metaplasia Theory by R. Meyer (1919)
        - Stem cells grow into endometrial cells due to estrogen
        -

Methods:

Preliminary:

- literature search using the key words listed
- 2 meta analysis
- 6 case control studies
- 2 randomized trials
- 4 prospective cohort studies

Included in the article is a chart that highlights the setup of past experiments

Review

1. Do certain foods pose a risk of developing endometriosis?

Vegetables:

- May reduce risk of developing endo
- contribute to DNA methylation of specific genes
- Pesticides may be harmful and help it grow

2 Major case control studies - both had conflicting results

- Parazzini → observed lower risk
- Trabert → observed little difference between high and low amounts
- Nurse Health Study II (2018) → no shown benefits of vegetable rich diet
- Contradictory results: Cruciferous vegetables showed to increase endometrial system
    - Potential paths of research: linkage between presence of endometriosis and gastrointestinal symptoms
    - "On the contrary, women consuming ≥ 1 portion cruciferous vegetables per day had a 13% higher risk of developing endometriosis (95% CI 0.95–1.34; p trend = 0.03)"

Fruits:

- Antioxidants help reduce inflammation by reducing oxygen free radicals
    - One study showed higher, and the other showed lower risk

- One specifically: citrus fruits lowered chances of endometriosis as they prevent inflammation

Vitamins:

- None of the three studies analyzed showed a statistically significant link between vitamin rich diet and endometriosis development

Fats:

- Saturated fats:
  - Animal-derived products
  - Some pros: create higher plasma concentration of oestradiol (steroid hormone)
  - Linked to estrogen dependent diseases
  - Further exploration: does increased intake of saturated fats be linked to development of endometriosis
  - Case studies showed contradictory results
  - Nurses Health Study II (2018) → more than 2 portions of red meat increased chances of endo by 56%
- Trans fat was shown to have a negative impact
- Polyunsaturated: contain ROS that regulate prostaglandins and cytokines which are inflammatory chemicals
- Omega-3 and omega-6 showed to decrease chances of endo
  a. Coffee/caffeine can increase the availability of estrogen and estrogen, which can lead to higher concentration of sex-hormone binding proteins. Also lowers the availability of testosterone.

Dairy Products (contain vitamin D and magnesium)

- Activate immunosuppressive regulatory T-cells, secrete interleukin-10
- Inhibit proinflammatory interleukin-17 and T-helper cells
- Potential application to endometriosis occurrence
- Low fat dairy consumption may decrease
- Vitamin D deficiency → increase risk of inflammatory disease
- Inverse relation between vitamin D and endometriosis
  - High levels of vitamin D plasma was correlated with 24% lower risk of endo
- Magnesium → relaxation impact on smooth muscle; antispasmodic effect
  - Research potential impact on pathogenesis, specifically retrograde menstruation

Fiber:

- High fiber = rich in complex carbs & low glycemic index
- Insulin causes the growth of endometrial cells; therefore, foods that are classified as high glycemic index increase the levels of insulin → hyperinsulinism decreases levels of the sex hormone that binds with globin → hyperestrogenism → endo

Soy and phytoestrogens:

- May cause endometriosis developments

	- Isoflavone and daidzein concentration in urine → only applied to women with higher levels of endometriosis
	- Animal model conclusion:
	  - isoflavones genistein and puerarin turns off aromatase and decrease expression of estrogen receptor
	
	Coffee and caffeine
	- Caffeinated drinks increase estrogen availability and sex-hormone binding protein
	- Decrease testosterone
	- However, in-depth meta analysis showed no link between endometriosis and caffeine
	
	Does diet influence endometriosis symptoms or the postoperative condition (therapeutic approach)?
	
	- More omega-3 fatty acids elevate pain symptoms
	- Fish oil and vitamin B reduces dysmenorrhoea symptoms
	
	Hormone therapy vs diet related measures vs placebo:
	- 222 women with rASRM stage III-IV endometriosis
	- Observed for 12 months after surgery using visual analogue scale for evaluating pain levels
	- SF-36 score for evaluation of quality of life
	- Post-operative intervention groups
	  - Placebo n=110
	  - Hormone replacement (GnRH analogues/estro progestin and=77
	  - Diet n = 35
	- Symptoms analyzed:
	  - Dyspareunia
	  - Dysmenorrhea
	  - Chronic
	- Findings: receiving hormone suppressants and diet related treatments showed similar pain reductions
	
	Findings:

Research Question/Problem/ Need	This study seeks to identify a linkage between nutrition and endometriosis and if diet and lifestyle can be used a preventive strategy.

Important Figures

Table 1 Overview of the studies and articles included in this review.

Literature	Structure
Case-control studies	
Britton et al., 2000	Case study group (n = 673): Women aged between 18 and 74 with confirmed endometrial cysts (n = 280) and women with benign ovarian tumours (n = 393) Control group (n = 351): Women without ovarian or endometrial tumours
Parazzini et al., 2004	Case study group (n = 504): Women aged between 20 and 65 with confirmed endometriosis Control group (n = 504): Women aged between 20 and 61 with no gynaecological disorders
Heilier et al., 2007	Case study group (n = 176): Women with confirmed endometriosis Control group (n = 88): Women without endometriosis
Tsuchiya et al., 2007	Case study group (n = 79): Women with confirmed endometriosis Control group (n = 69): healthy women
Trabert et al., 2011	Case study group (n = 284): Women aged between 20 and 65 with confirmed endometriosis Control group (n = 660): healthy women
Savaris et al., 2011	Case study group (n = 25): Women with confirmed endometriosis, grades I–IV Control group (n = 20): Women with no gynaecological disorders
Khanaki et al., 2012	Case study group (n = 64): Women with confirmed endometriosis Control group (n = 74): Women of childbearing age with no gynaecological disorders
Prospective cohort studies Evaluation of the Nurses' Health Study II; premenopausal women aged between 25 and 42	
Missmer et al., 2010	586153 person-years; 1199 cases with endometriosis confirmed by laparoscopy Control group (n = 69510): healthy women
Harris et al., 2013	737712 person-years; 1385 cases with endometriosis confirmed by laparoscopy

Table 1 Overview of the studies and articles included in this review.

[illegible]	[illegible] Control group (n = 69510): healthy women
Harris et al., 2013	737712 person-years; 1385 cases with endometriosis confirmed by laparoscopy Control group (n = 70556): healthy women
Harris et al., 2018	840012 person-years; 2609 cases with endometriosis confirmed by laparoscopy Control group (n = 70385): healthy women
Yamamoto et al., 2018	1019294 person-years; 3800 cases with endometriosis confirmed by laparoscopy Control group (n = 81908): healthy women
Cross-sectional study	
Hopeman et al., 2015	205 people from the database, 25 of whom had histologically confirmed endometriosis
Randomised studies	
Deutch et al., 2007	78 women aged between 16 and 39 with dysmenorrhoea treated for three months either with placebo (n = 18), seal oil capsules (n = 23), fish oil capsules (n = 19) or with fish oil capsules and vitamin B_{12} (n = 18)
Sesti et al., 2013	222 women with endometriosis grade III–IV who were treated postoperatively with immunosuppressives (n = 69), dietary supplements (n = 35) or with placebo (n = 110)
Meta-analyses	
Chiaffarino et al., 2014	6 case-control studies, 2 cohort studies
Parazzini et al., 2013	14 case-control studies, 1 cohort study
Reviews	
Hansen et al., 2007	23 studies, of which n = 12 "Endometriosis and diet" and n = 11 "Dysmenorrhoea and diet"
Parazzini et al., 2013	11 case-control studies, 2 prospective cohort studies
Jurkiewicz-Przondziono et al., 2017	12 case-control studies, 2 prospective cohort studies

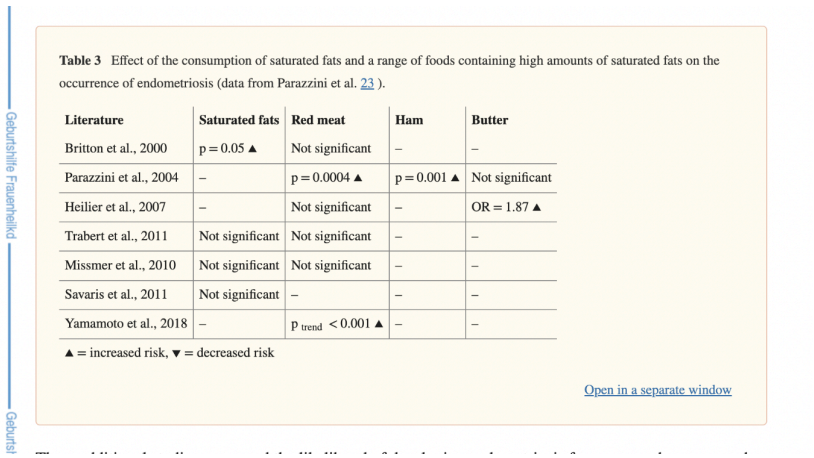
<table>
<tr><td></td><td>


Table 3 Effect of the consumption of saturated fats and a range of foods containing high amounts of saturated fats on the occurrence of endometriosis (data from Parazzini et al. 23).

Literature	Saturated fats	Red meat	Ham	Butter
Britton et al., 2000	p = 0.05 ▲	Not significant	–	–
Parazzini et al., 2004	–	p = 0.0004 ▲	p = 0.001 ▲	Not significant
Heilier et al., 2007	–	Not significant	–	OR = 1.87 ▲
Trabert et al., 2011	Not significant	Not significant	–	–
Missmer et al., 2010	Not significant	Not significant	–	–
Savaris et al., 2011	Not significant	–	–	–
Yamamoto et al., 2018	–	$p_{trend} < 0.001$ ▲	–	–

▲ = increased risk, ▼ = decreased risk

Open in a separate window
</td></tr>
<tr><td>VOCAB:
(w/definition)</td><td>

- Pathogenesis: describes the way a disease develops
- Etiology: describes the causation of a disease
- Meta-analysis: a type of data analysis procedure to find correlation between two studies

</td></tr>
<tr><td>Cited references to follow up on</td><td>

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2730449/
https://pubmed.ncbi.nlm.nih.gov/28718209/

Parazzini F, Chiaffarino F, Surace M. Selected food intake and risk of endometriosis. *Hum Reprod Oxf Engl.* 2004;19:1755–1759. [PubMed] [Google Scholar]

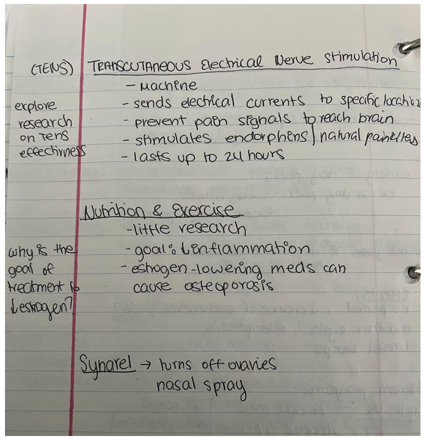
</td></tr>
<tr><td>Follow up Questions</td><td>

- What is the etiology and pathogenesis of endometriosis?
- Why are several of the studies contradictory?
- What new approaches can be taken to understand the correlation between nutrition and

</td></tr>
</table>

Article #7: Center for Young Women's Health

Source Title	Center For Young Women's Health Guides
Source citation (APA Format)	*Health Guides – Center for Young Women's Health*. (n.d.). Retrieved October 14, 2023, from https://youngwomenshealth.org/health-guides-index/
Original URL	https://youngwomenshealth.org/health-guides-index/ PDF: https://youngwomenshealth.org/wp-content/uploads/2014/10/Endometriosis-Teen.pdf
Source type	Informational Health Guides
Keywords	Endometriosis, Adosclences, symptoms, pain management
Summary of key points + notes (include methodology)	Endometriosis key facts: - Lining of the uterus found outside the normal location - The amount of endometrial tissue - It is a type of inflammatory condition - Several theories for development - Treatment is targeted towards pain management

<table>
<tr>
<td></td>
<td>


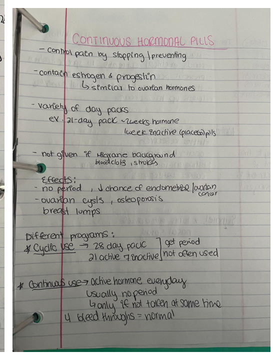
(TENS) TRANSCUTANEOUS Electrical Nerve Stimulation
- machine
- sends electrical currents to specific locations
- prevent pain signals to reach brain
- stimulates endorphins } natural painkillers
- lasts up to 24 hours

explore research on TENS effectiveness

Nutrition & Exercise
- little research
- goal: ↓ inflammation
- estrogen-lowering meds can cause osteoporosis

why is the goal of treatment to ↓ estrogen?

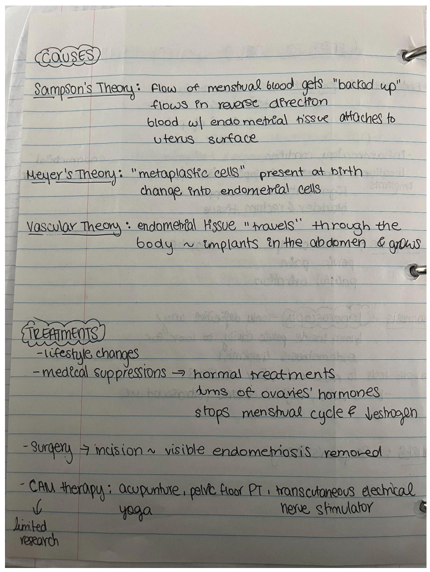
Synarel → turns off ovaries
nasal spray



CONTINUOUS HORMONAL PILLS
- control pain by stopping / preventing
- contain estrogen & progestin
  ↳ similar to ovarian hormones
- variety of day packs
  ex. 21-day pack ~ 2 weeks hormone
  1 week inactive (placebo) pills
- not given if migraine background
  blood clots, strokes

Effects:
- no period, ↓ chance of endometrial / ovarian cancer
- ovarian cysts, osteoporosis
  breast lumps

Different programs:
* Cyclic use → 28 day pack
  21 active 7 inactive } get period
  not often used
* Continuous use → active hormone everyday
  usually no period
  ↳ only if not taken at same time
  ↳ bleed throughs = normal



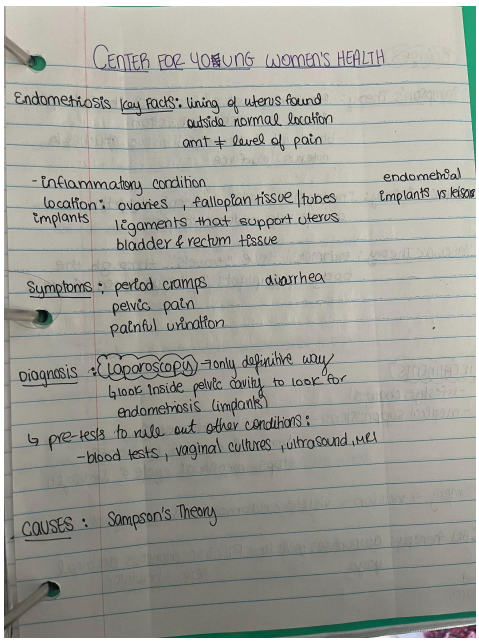
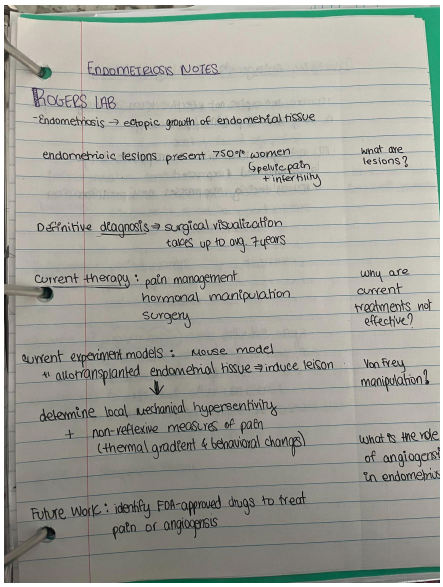
CAUSES

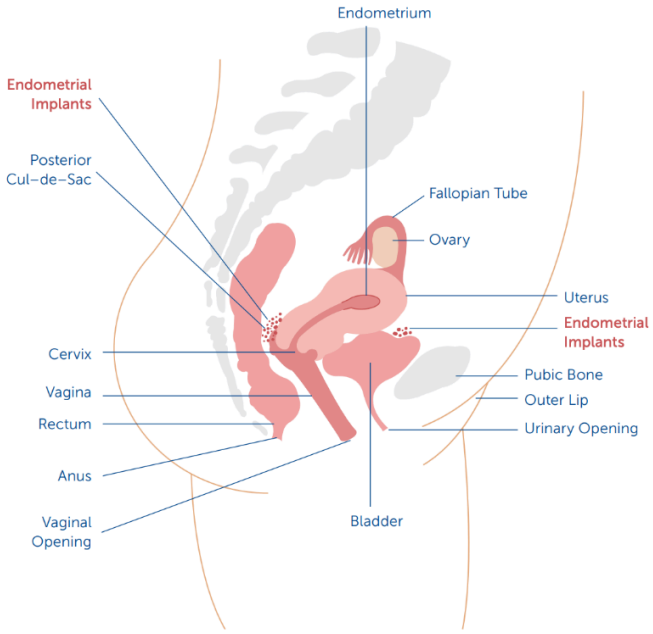
Sampson's Theory: flow of menstrual blood gets "backed up"
flows in reverse direction
blood w/ endometrial tissue attaches to uterus surface

Meyer's Theory: "metaplastic cells" present at birth
change into endometrial cells

Vascular Theory: endometrial tissue "travels" through the body ~ implants in the abdomen & grows

TREATMENTS
- lifestyle changes
- medical suppressions → hormonal treatments
  turns off ovaries' hormones
  stops menstrual cycle & ↓ estrogen
- Surgery → incision ~ visible endometriosis removed
- CAM therapy: acupuncture, pelvic floor PT, transcutaneous electrical nerve stimulator
  yoga
  ↓ limited research
</td>
</tr>
</table>

	 CENTER FOR YOUNG WOMEN'S HEALTH Endometriosis key facts: lining of uterus found outside normal location amt ≠ level of pain - inflammatory condition location: ovaries, fallopian tissue/tubes, ligaments that support uterus, bladder & rectum tissue implants endometrial implants vs lesions Symptoms: period cramps, diarrhea, pelvic pain, painful urination Diagnosis: (Laparoscopy) → only definitive way ↳ look inside pelvic cavity to look for endometriosis (implants) ↳ pre-tests to rule out other conditions: - blood tests, vaginal cultures, ultrasound, MRI CAUSES: Sampson's Theory  ENDOMETRIOSIS NOTES BROGERS LAB - Endometriosis → ectopic growth of endometrial tissue endometriotic lesions present 750+ women ↳ pelvic pain + infertility what are lesions? Definitive diagnosis ⇒ surgical visualization takes up to any 7 years Current therapy: pain management, hormonal manipulation, surgery why are current treatments not effective? current experiment models: mouse model + allotransplanted endometrial tissue ⇒ induce lesion Von Frey manipulation? determine local mechanical hypersensitivity + non-reflexive measures of pain (thermal gradient & behavioral changes) what is the role of angiogenesis in endometriosis Future Work: identify FDA-approved drugs to treat pain or angiogenesis
Research Question/Problem/ Need	Provide a thorough understanding of endometriosis and information available to patines

Important Figures	
VOCAB: (w/definition)	- Allotransplant - Lesions - local mechanical hypersensitivity
Cited references to follow up on	Ballweg, Mary Lou, and The Endometriosis Association. Endometriosis—The Complete Reference for Taking Charge of Your Health Mills, Dian Shepperson MA, and Vernon, Michael PhD HCLD. Endometriosis: A Key to Healing Through Nutrition. Thorsons, 2002.
Follow up Questions	- What are lesions and their role in endometriosis? - What is local mechanical hypersensitivity and von Frey stimulation? - What is the prevalence of diagnosis given a family history of endometriosis?

Article #8: Heritability of Endometriosis

Source Title	Heritability of Endometriosis
Source citation (APA Format)	Saha, R., Pettersson, H. J., Svedberg, P., Olovsson, M., Bergqvist, A., Marions, L., Tornvall, P., & Kuja-Halkola, R. (2015). Heritability of endometriosis. *Fertility and Sterility*, *104*(4), 947–952. https://doi.org/10.1016/j.fertnstert.2015.06.035
Original URL	https://www.fertstert.org/article/S0015-0282(15)00462-8/fulltext#sectitle0050
Source type	Journal article
Keywords	Concordance, endometriosis, heritability, twins

Summary of key points + notes (include methodology)	Experiment set-up:
	1. Patients: 28,370 women who are either monozygotic or dizygotic twins; self-reported endometriosis
	
	Results:
	- Probandwise concordance:
	  - 0.21 for MZ → also had higher within-pair tetrachoric correlation
	  - 0.10 for DZ twins
	- 47% caused by additive genetic factors
	- 53% caused by unique environmental effects
	
	Conclusions: genetics greatly influence the etiology and overall phenotypic nature of endometriosis
	
	General background:
	- Most common benign gynecologic disease
	- Ectopic endometrial tissue outside the uterus
	- Estimated 50% infertile women may have this condition
	- Endometriosis is a binary trait

Heritability patterns:

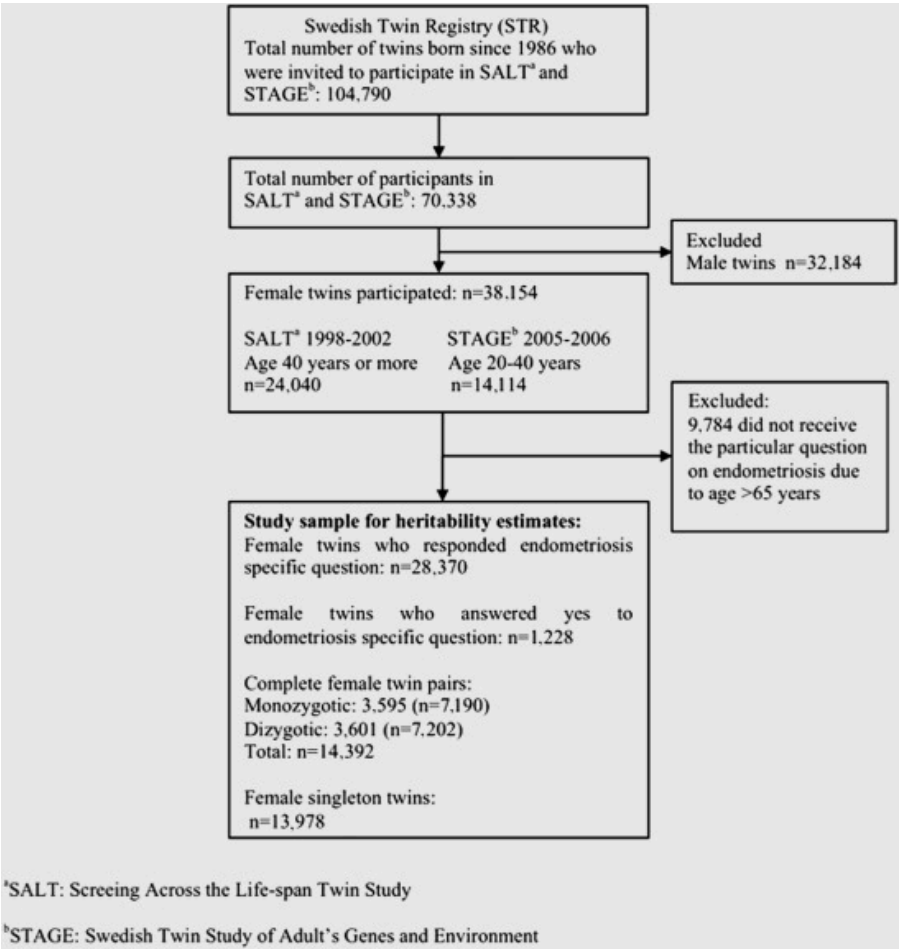
- Highest concordance in MZ twins
- 3-15% higher risk in first-degree relatives
- MZ twins have 2 times greater risk than DZ twins
- Genetic component contributes to 50% phenotypic variability
- Studies have tried to find loci that may be linked to endometriosis ang genes that could to be used as potential targets
- No specific environmental factor has been identified; could be anything from chemicals to food

Methods:

- 2 cross sectional surveys
    - Screening Across the Lifespan Twin (SALT)
    - Swedish Twin Study of Adult Genes and Environments (STAGE)
- Participants 38,154 female twins
    - Answered question: “Have you ever been diagnosed with endometriosis?”
- Validation of Self Reported Data and Twin Status
    - 1,228 women gave consent for their medical records to be used in this study
- Protocol:
    - Visible lesions, histologic reports, and clinical diagnosis reports
- Statistical analysis:
    - Age → mean and standard deviation
    - Out of all the women reported, only those with 95% confidence interval (CI) were incorporated in the calculation
    - Probandwise concordance:
        - 2 x 2 contingency tables for MZ and DZ twins pairs
        - Formula: 2K/(2K+D)
        - K = number of concordant twin pairs
        - D = discordant twin pairs
        - Liability correlation for each zygosity group

	- Genetic contribution to endometriosis development is caused by higher concordance rates and liability correlations
	- Genetic Modeling
	  - Variation in the population categorized in groups of:
	  - Additive genetic factors (A)
	  - Environmental factors similar between twins (C)
	  - Differing Environmental factors (E)
	
	Results:
	Validation of Self-reported by Medical Records
	- 82% confirmed cases

Research Question/Problem/ Need	The goal of this study was to understand the influence of genetic factors on the development of endometriosis.

Important Figures	

VOCAB: (w/definition)	• Concordance: given the probability a pair of individuals will have a phenotype given that they share a gene
	• Zygosity: genetic makeup of a pregnancy
	  ○ Monozygotic twins: division of a zygote arising from the fertilization of an ovum by one sperm.
	  ○ Dizygotic twins: fertilization of separate ova by separate sperm.

Cited references to follow up on	Endometriosis and adenomyosis: shared pathophysiology - Fertility and Sterility https://doi.org/10.1016/j.fertnstert.2023.03.006 Gut dysbiosis-derived β-glucuronidase promotes the development of endometriosis Wei et al. Fertility and SterilityMay 12, 2023
Follow up Questions	1. What is probandwise in meta-analysis?

	2. What is zygosity and why must silico markers have high accuracy? 3. What does binary trait mean and its genetic significance?

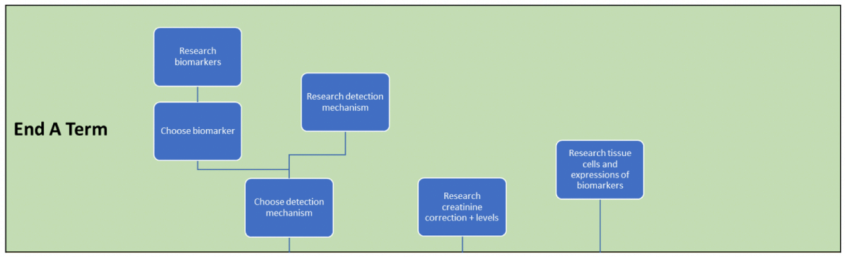
Article #9: Elagolix as a Novel Treatment for Endometriosis-Related Pain

Source Title	Elagolix as a Novel Treatment for Endometriosis-Related Pain
Source citation (APA Format)	Fantasia, H. C. (2019). Elagolix as a Novel Treatment for Endometriosis-Related Pain. *Nursing for Women's Health*, *23*(4), 366–369. https://doi.org/10.1016/j.nwh.2019.05.004
Original URL	https://www.sciencedirect.com/science/article/abs/pii/S1751485119301114?via%3Dihub
Source type	Journal Article
Keywords	Endometriosis, treatment, hormonal therapy
Summary of key points + notes (include methodology)	Overview of Elagolix: - Gonadotropin-releasing hormone (GnRH) receptor antagonist - Able to bind to GnRH receptors in the pituitary glands - Goal is to inhibit the production of luteinizing hormone & follicle-stimulating hormones - Results in the overall reduction of estradiol and progesterone - Estrogen is suppressed → pelvic pain reduces Dosage and Administration - Can be used orally - 150-200 mg - Same time without food - Efficacy does seem to be influenced by weight/body mass Potential Adverse Effects: - Decrease in menstrual cycle duration and bleeding as estrogen and progesterone levels are suppressed - Early pregnancy loss Drug Interactions: - Cytochrome P450m family 3, subfamily A (CYP3A) inducer

	- May reduce concentration of other medications that are of the family stated above - Plasma concentration of elagolix can increase by the presence of rifampin, cyclosporine, and gemfibrozil
Research Question/Problem/ Need	To evaluate the efficiency of Elagogix as a treatment
Important Figures	***need to borrow through a library to gain access to the whole document — request on hold ******
VOCAB: (w/definition)	- Gonadotropin-releasing hormone: a type of regulator in the reproductive axis - Used by the pituitary gland to produce follicle-stimulating hormone and luteinizing hormone, all of which ultimately produce estrogen, testerone, and other sex hormones
Cited references to follow up on	Elagolix Treatment in Women With Heavy Menstrual Bleeding Associated With Uterine Fibroid: A Systematic Review and Meta-analysis Elagolix treatment in women with heavy menstrual bleeding associated with uterine fibroid: a systematic review and meta-analysis
Follow up Questions	- How can the properties of elagonix be found in other drugs or foods to serve as a preventive strategy?

Article # 10: Developing and Validating a Non-Invasive Diagnostic Test for Endometriosis

Source Title	Developing and Validating a Non-Invasive DiagnosticTest for Endometriosis A Major Qualifying Project Report: Submitted to the faculty of Worcester Polytechnic Institute In partial fulfillment of the Degree of Bachelor of Science
Source citation (APA Format)	Gannon, A., Tremblay, K., Chen, B., & Neidig, L. (2022, April 28). Developing and Validating an Endometriosis Diagnostic Test. Digitalwpi.wpi.edu. https://digitalwpi.wpi.edu/concern/student_works/k0698b902?locale=it
Original URL	https://digitalwpi.wpi.edu/pdfviewer/vm40xv876
Source type	Filed Patent + Senior Thesis
Keywords	Endometriosis, noninvasive
#Tags	Endometriosis diagnosis, noninvasive tests, biomarker
Summary of key points + notes (include methodology)	**Biomarkers for Endometriosis:** ● Aromatase ○ Estrogen producer ○ Angiogenesis ○ Increases estradiol hormones ○ High concentration in endometrial tissues ○ Blood detection tests can be unreliable ● Prostaglandin-E2 ○ Mediates pain ○ Increases levels of aromatase ● Mi12-20a and mRNA have shown to be involved in the pathways for endo related angiogenesis ○ However, biomarkers for angiogenesis do not always show up in urine tests ○ HIFI-A & VEGF-A only show up in the blood ● **sFlt-1 (**critical marker in device detection) ○ Protein isoform of vascular endo growth factor (VEGFR) ○ 3 main domains ■ Intracellular ■ Transmember ■ Extracellular ○ Transmember & Extracellular → lacking in soluble VEGFR ■ Replaced by 31 amino acid sequence which prevent binding to cell membrane

	○ Currently, unknown why it is found in urine after corrected for creatinine **Design Project:** - Detect sFlt-1 Levels and creatinine in expected levels for patients with endo - MMP-9 and VDBP as other potential biomarkers **Design Criteria:** 1. Non-Invasive - Current options such as laparoscopy and pelvic exams are inaccessible - Goal is to create a method that provides samples non invasively 2. Consistent and Quantifiable Results a. Ultrasound imaging and pelvic exams ⟶ delayed diagnosis and misdiagnosis b. Protein biomarkers are better as they are invasive, objective, and replicable and reliable when examining multiple areas 3. Unobtrusive a. Maintain the physical and mental well being of the patient 4. Painless a. No after effects or rest necessary 5. Simple and Easy to Use **Method Evaluation** 1. Pugh selection matrix ⟶ rank 2. Risk evaluation matrix ⟶ compares multiple solutions with the criteria stated by the pugh selection matrix 3. Algorithmic diagnostic method
Research Question/Problem/ Need	Currently, there are no safe and accessible diagnosis tools for endometriosis. The object of this project is to analyze different biomarkers in urine samples of those with endometriosis and develop a urine analysis test.
Important Figures	 Figure 8 - A clip of the planned flow chart for the team to work on for the end of A-term.

	Monetary Cost	Feasibility	Research Cost	Return on Investment	Intellectual Property	Market Need	Development Cost
Non-Invasive	2	2	2	1	1	1	9
Consistent & Quantifiable Results	2	3	2	1	1	1	10
Unobtrusive	1	2	3	2	1	2	11
Painless	2	2	1	2	2	2	11
Simplicity & Ease of Use	3	3	4	1	1	1	13

Figure 9 - Pugh selection matrix of proposed device criteria.

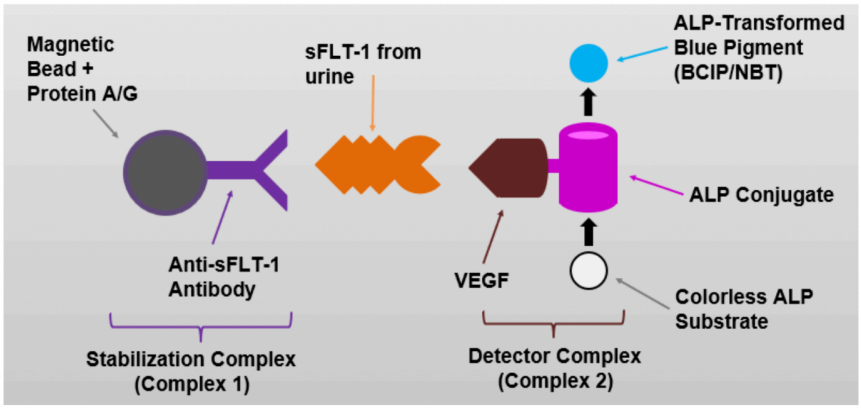


Figure 14 - The planned sFlt-1 detection method. Full detection chain unlinked to indicate individual sections of the chain.

VOCAB: (w/definition)	1. sFlt-1: a type of tyrosine kinase-1 which contains properties that support angiogenesis 2. Angiogenesis: the process by which new blood vessels are formed; play a key role in the abnormal growth of cells 3. VEGFR: growth receptors factors that are highly expressed during angiogenesis 4. Protein isoform: types of protein that are similar but contain slight difference in the chemical makeup; deveried from the same base
Cited references to follow up on	Agrawal, S., Tapmeier, T., Rahmioglu, N., Kirtley, S., Zondervan, K., & Becker, C. (2018b).The miRNA Mirage: How Close Are We to Finding a Non-Invasive DiagnosticBiomarker in Endometriosis? A Systematic Review. International Journal of MolecularSciences, 19(2), 599.https://doi.org/10.3390/ijms19020599 Urinary vitamin D-binding protein is elevated in patients with endometriosis | Human Reproduction | Oxford Academic Evaluation of Serum and Urinary Angiogenic Factors in Patients with Endometriosis - Cho - 2007 - American Journal of Reproductive Immunology - Wiley Online Library
Follow up Questions	1. How can the expression of Vitamin D Binding Protein be studied further to

	better understand the role of nutrition and endometriosis? 2. How can the limitations of the project be improved? 3. How can angiogenesis be controlled with environmental factors? 4. How can the levels of creatine be used to eliminate other reproductive diseases? 5. Research what the amino acid sequences are, significance, and how it can be controlled with diet?

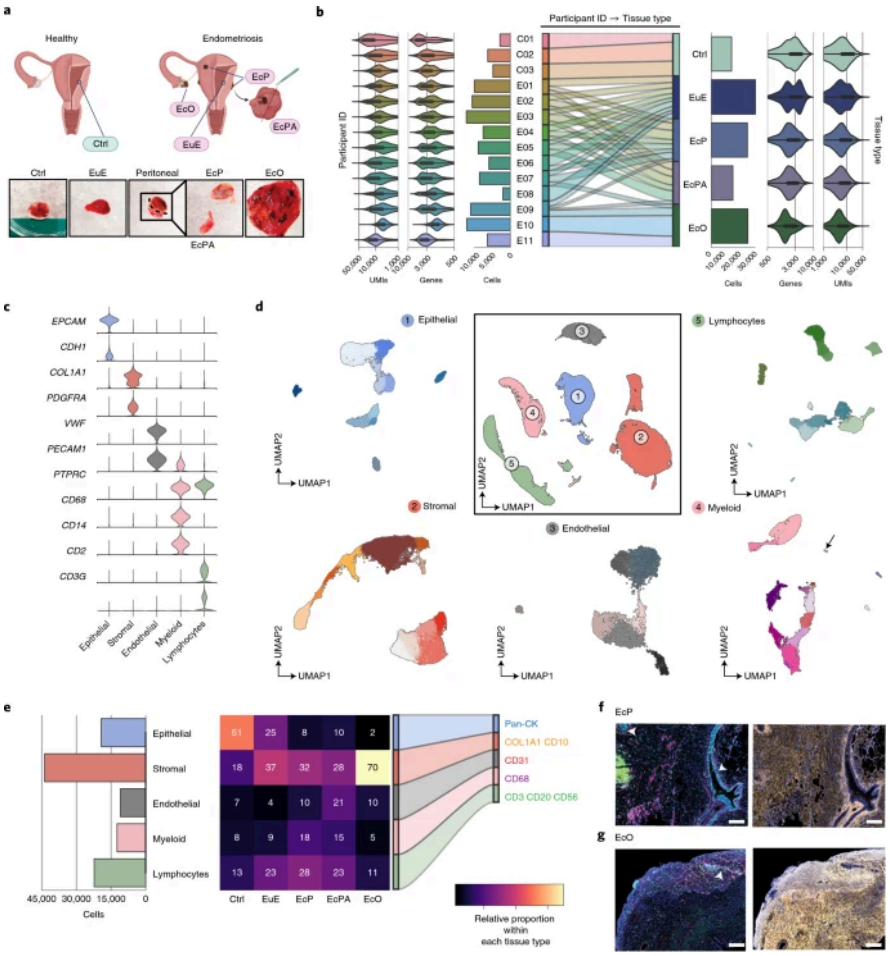
Article #11: Single-cell analysis of endometriosis reveals a coordinated transcriptional programme driving immune tolerance and angiogenesis across eutopic and ectopic tissues

Source Title	Single-cell analysis of endometriosis reveals a coordinated transcriptional programme driving immune tolerance and angiogenesis across eutopic and ectopic tissues
Source citation (APA Format)	Tan, Y., Flynn, W.F., Sivajothi, S. *et al.* Single-cell analysis of endometriosis reveals a coordinated transcriptional programme driving immune tolerance and angiogenesis across eutopic and ectopic tissues. *Nat Cell Biol* 24, 1306–1318 (2022). https://doi.org/10.1038/s41556-022-00961-5
Original URL	https://www.nature.com/articles/s41556-022-00961-5
Source type	Journal Article
Keywords	Endometriosis, RNA-seq, single cell transcriptomes, organoids
Summary	This research focuses on single-cell transcriptome analysis of peritoneal and ovarian lesions, eutopic endometrium, and organoids, which contains thousands of cells. The goal is to identify specific cell types that play a role in angiogenesis and immune cell trafficking. The findings highlight the immunotolerant peritoneal niche, the differences between eutopic endometrium and lesions, and describes epithelial cell interaction. This research supports future works in identifying therapeutics and diagnostics.
notes (include methodology)	Main: - There is little knowledge on the etiology and the molecular/genetic markers and drivers of this condition - Definitive diagnosis needs surgery such as laparoscopy which can be invasive and expensive - There are no treatments that are effective in promoting lesion clearance

	- Oral contraceptives help with pain management but not with targeting the lesions
	
	Immune cells
	- currently at the center of emerging research due their role in promoting endometrium development
	- Single-cell RNA sequencing + organoid culture systems provide greater understanding of the endometrial microenvironment
	- Similar model can be used to understand the dynamic nature of the endometrium during menstrual cycle and pregnancy
	
	Methods: Single-cell transcriptome analysis was conducted on tissues using mechanical and enzymatic digestion. Specific cell-types were identified using clustering methods. Gene expression analysis, gene set enrichment, and ligand-receptor analysis were conducted.
	
	- Analyze transcriptomes of endometrium and endometriosis lesions through scRNA-seq and hyperlexed antibody imaging
	- Individuals receive oral treatment
	- Goal is to understand the changes in the microenvironment and cellular surface
	  - Looked at:
	  - Eutopic endometrium
	  - Peritoneal lesions
	  - Ovarian lesions
	  - Human-derived organoids
	  - Impacted:
	  - Cellular changes
	  - Immunomodulatory macrophages
	  - Immunotolerant dendritic cells (DCs)
	  - Vascular changes
	  - Found cellular component which may open doors to better understanding this condition:
	  - Endometriosis-specific perivascular population
	  - Tertiary lymphoid structure present
	  - Progenitor-like epithelia cell population

	Results:
	- scRNA-seq and imaging mass cytometry tissue analysis from 14 biopsies
	- Control: healthy eutopic endometrium
	- Experimental: stage II-IV endometriosis; most receiving similar hormonal treatment
	  - Eutopic endometrium (EuE)
	  - Ectopic peritoneal lesions (EcP)
	  - Adjacent regions (EcPA) → help understand the environment for lesion evolution
	- 108,497 cellular transcriptomes developed
	  - 9186 unique transcript
	  - 2823 genes per cell
	  - 5 types of predominant cell types:
	  - Epithelial, stromal, endothelial, lymphocyte, myeloid
	  - Total of 58 subpopulations
	- Subtype results:
	  - EuE
	  - Differs greatly from control
	  - Stroma and lymphocytes replace the epithelial
	  - Greater expression of cell-cycle-related genes + endometrial fibroblasts growth
	  - Stratification of biopsies in two groups of immune cell and fibroblast abundance
	  - Osteoglycin expression
	  - NOTE: osteoglycin controls insulin levels, bone mass, and food intake

Research Question/Problem/ Need	How can immune cells and organoid culture of those with endometriosis improve the understanding of the pathology and microenvironment of endometriosis?

Important Figures	 Fig. 1: highlights the overall procedure and findings of the research. The margin (EcPA) was separated following macroscopic tissue assessment from the lesion (EcP) when possible and before single-cell dissociation, which helps identify unique markers. Five major cell types are identified in the UMAP, indicating the ones that are most impacted in endometriosis.
VOCAB: (w/definition)	**Lesions:** endometrium-like tissue found on the outside of the uterine cavity; within peritoneal cavity and on the surface of ovaries **Peritoneal lesions:** caused by carcinomas around the body **Single cell transcriptome:** the study of single-cell transcriptomics at the gene expression of individual cells. The purpose is to measure RNA sequence data.

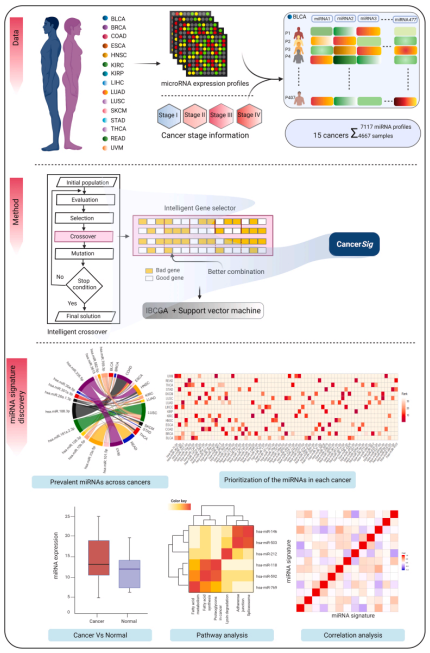
	Eutopic endometrium: Surface characterization of endometrium; its shapes and features determine the flow of endometrial cells, **Organoids:** artificial/lab based growth of organs and tissues **Perivascular mural cell**: important parts of the blood vessels that support the blood circulation.
Cited references to follow up on	Zou, G. et al. Cell subtypes and immune dysfunction in peritoneal fluid of endometriosis revealed by single-cell RNA-sequencing. *Cell Biosci.* 11, 98 (2021 Carbone, C. et al. Angiopoietin-like proteins in angiogenesis, inflammation and cancer. *Int. J. Mol. Sci.* 19, 431 (2018). Cheng, S. et al. A pan-cancer single-cell transcriptional atlas of tumor infiltrating myeloid cells. *Cell* 184, 792–809.e23 (2021). Ma, J. et al. Single-cell transcriptomic analysis of endometriosis provides insights into fibroblast fates and immune cell heterogeneity. *Cell Biosci.* 11, 125 (2021).
Follow up Questions	What components of RNA-seq data are important? Does RNA-seq data vary from cell types?

Article #12: Artificial intelligence-driven pan-cancer analysis reveals miRNA signatures for cancer stage prediction

Source Title	Artificial intelligence-driven pan-cancer analysis reveals miRNA signatures for cancer stage prediction
Source citation (APA Format)	Yerukala Sathipati, S., Tsai, M. J., Shukla, S. K., & Ho, S. Y. (2023). Artificial intelligence-driven pan-cancer analysis reveals miRNA signatures for cancer stage prediction. HGG advances, 4(3), 100190. https://doi.org/10.1016/j.xhgg.2023.100190
Original URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10130501/#mmc1
Source type	Journal Article
Keywords	Artificial Intelligence, Machine learning, Cancer diagnosis prediction, pan-cancer analysis, cancer early stage detection
Summary of key points + notes (include methodology)	This study uses miRNA profiles from at least 80 patients for each of the 15 types of cancers studied. After normalization methods are performed, a supervised learning method called CancerSig is applied to identify unique miRNA for multi-classification. **Aim**: develop a machine learning that helps identify stage-specific from 15 types, ranked the importance of each miRNA based on influence on cell survival with at least 84.27% accuracy **Database:** TCGA Atlas - Only selected cancers with more than 80 patients with miRNA profiles - 6758 samples across 15 types - Normalize with illumina HSeq 2000 Platform

	Methods:
	- Stage labels as input data
	- Analyze cancer-specific miRNA panel for prediction
	- IBCGA → selection
	- Support Vector and pan analysis
	
	Bi-Objective Combinatorial Optimization Problem
	- IBC GA: intelligent evolutionary algorithm
	- Goal: identify features
	- Uses orthogonal array crossover
	- C(n,m) [n = sample; m = IBCGA]
	
	Support Vector Machine:
	- Map data
	- Input higher dimensional space
	- Especially for small datasets
	Diana-miRPath: server to analyze miRNA signature downstream biological pathway
	
	Processing data: remove duplicate; no stage listed; miRNA not in 80% sample
	
	Results:
	- 3 key indicators for stage prediction:
	  - Hsa-let-7i-3p
	  - hsa-miR-362-3p
	  - hsa-miR-3651
	- Each cancer has 22 miRNA in a signature
	- Main Effect Difference (MED) → rank degree of contribution
	  - Breast cancer has 34 distinct miRNAs
	- Determine biological significance of each miRNA using the KEGG Pathway

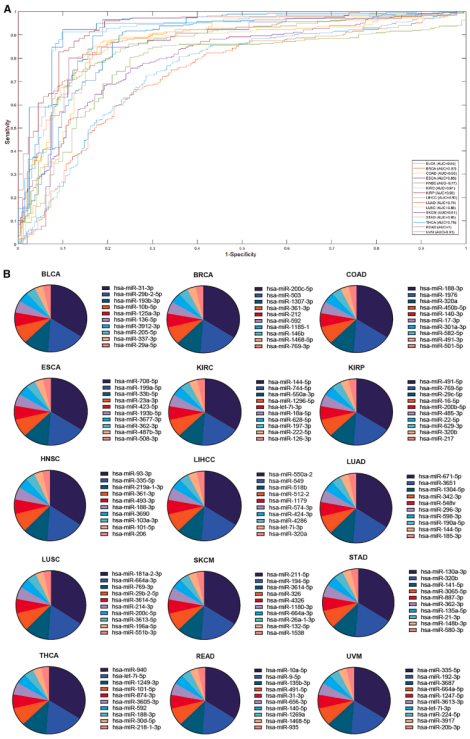
Research Question/Problem/ Need	Can miRNAs be used as a predictive marker for cancer stage prediction?
Important Figures	Schematic diagram of the CancerSig method and analysis of the panel of miRNAs



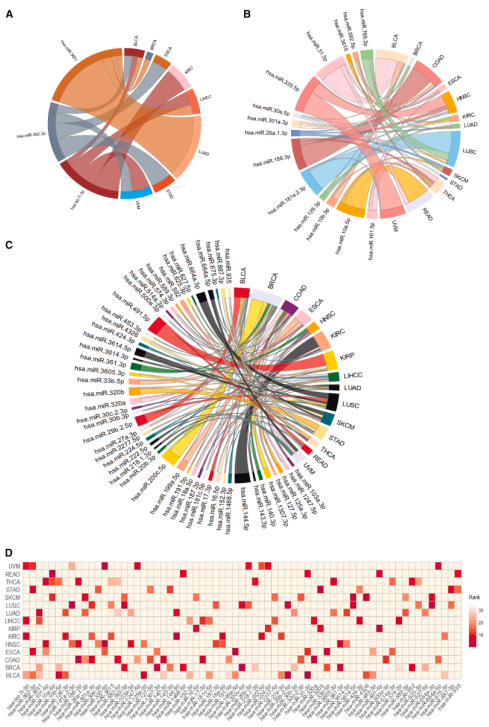
MicroRNA expression profiles of 15 cancer types along with cancer stage information are input in the workflow of the CancerSig method to identify miRNA signatures.

CancerSig prediction performance across cancers

(A) Evaluating the prediction performance of CancerSig using receiver operating characteristic (ROC) across 15 cancers. CancerSig obtained a mean area under the curve (AUC) of 0.80 across all cancers.



(B) Ranking of the relative miRNAs within the signature using MED analysis.

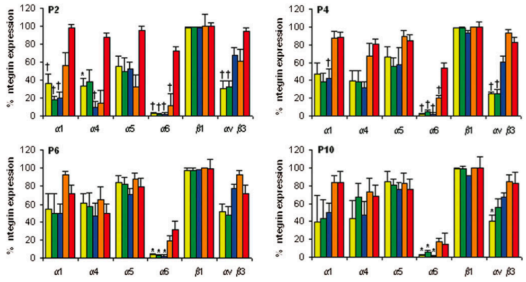
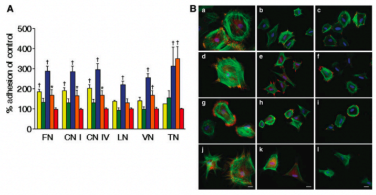
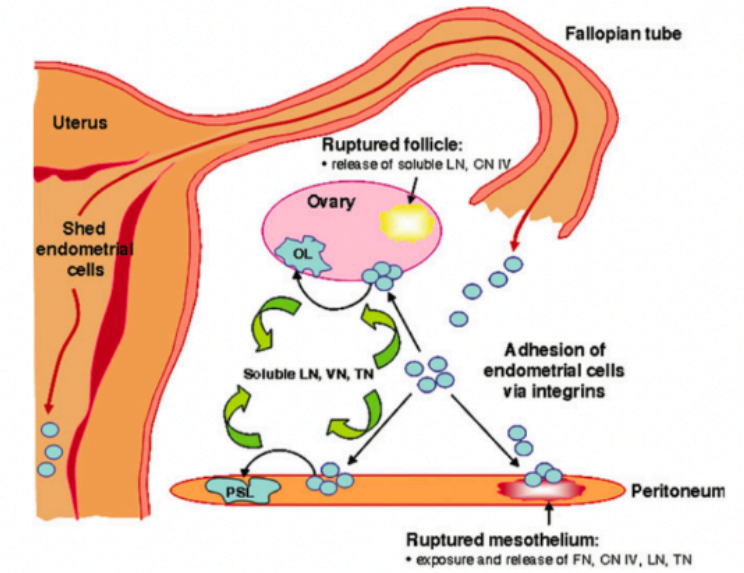
	 The predictive ability of miRNAs as a biomarker for cancer stage across cancer types (A) Three signature miRNAs and their contributions to stage prediction across eight cancer types. Each miRNA contributed to at least four cancers. The size of the line is proportional to the percent contribution toward the stage prediction. (B) Fourteen miRNAs contributed across cancers, and each miRNA contributed to at least three cancers. (C) Fifty miRNAs contributed to at least two cancers. (D) Heatmap showing 67 miRNAs and their ranks based on their predictive ability across 15 cancer types.
VOCAB: (w/definition)	Support Vector System: supervised learning model to classify different types miRNA: non-coding RNA that control gene expression
Cited references to follow up on	Satipati S.Y., Ho S.Y. Identification of the miRNA signature associated with survival in patients with ovarian cancer. *Aging*

	(Albany NY) 2021;13:12660–12690. [PMC free article] [PubMed] [Google Scholar] Noble W.S. What is a support vector machine? *Nat. Biotechnol.* 2006;24:1565–1567. [PubMed] [Google Scholar]
Follow up Questions	How can training bias, over/underfitting be prevented? Can the findings of this model be applied to the miRNAs from those with different ethnic backgrounds? How can geographic location, familia history, and symptoms be incorporated into this model?

Article #13 Notes: Endometrial cells from women with endometriosis have increased adhesion and proliferative capacity in response to extracellular matrix components: towards a mechanistic model for endometriosis progression

Source Title	Endometrial cells from women with endometriosis have increased adhesion and proliferative capacity in response to extracellular matrix components: towards a mechanistic model for endometriosis progression
Source citation (APA Format)	Richardson, M. R., Robbins, E. P., Vemula, S., Critser, P. J., Whittington, C., Voytik-Harbin, S. L., & Yoder, M. C. (2014). Angiopoietin-like protein 2 regulates endothelial colony forming cell vasculogenesis. Angiogenesis, 17(3), 675–683. https://doi.org/10.1007/s10456-014-9423-8
Original URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4063876/
Source type	Journal Article
Keywords	ANGPTL2, vasculogenesis, ECFC, MT1-MMP
#Tags	Endometriosis, ECM, proliferation,
Summary of key points + notes (include methodology)	Observation: - Increase in ECM expression and integrins in endometrial lesions - Results in increase in adhesion and proliferation - Application: understand pathology of ectopic cells as there is an elevated responsiveness in women with endometriosis Methods: - Analyzed expression of integrins in stromal cells from peritoneal, ovarian, and deep endometriotic lesions - From women with and without endometriosis - Used quantitative immunocytochemistry Background - Adhesion & proliferation likely occurs due to ECM components & integrin receptor interaction - Endometriotic lesions exhibit tumor characteristics → is endometriosis benign? **Ovarian cancer:**

	- Cells attach to mesothelial monolayer - Expose underlying ECM → mesothelium disrupted - Create opportunity for cell attachment, invasion, proliferation - Degradation of underlying peritoneal ECM causes mesothelium invasion Integrins - Increased Attachment - Endometrial stromal cells have different profiles than normal cells for integrin levels Soluble ECM components in peritoneal cavity may cause proliferative stimulus - Compared adhesive capacity of stromal cells w & w/o endometriosis - ESCs from deep infiltrating lesions → little difference - EScs form ovarian → 3 times greater attachment DNA synthesis: - Increase in DNA synthesis in response to ECM components from peritoneal surface, and less in deep infiltrating ESCs - ''Shows that ECM plays a role in proliferation eutopic ESCs exhibited a 2-fold increase in DNA synthesis in response to fibronectin and ESCs from women with endometriosis additionally responded with a 3-fold increase of DNA synthesis to collagen type IV. **Main conclusions:** 3 types of endometriotic lesions ESCS → abnormal intern profile Increased adhesive phenotype on ECM components Proliferative phenotype Great correlation/dependence on menstruation cycle Used ESS as it contained similar integrin expression Wanted to test whether imolites or soluble ECm components that greater influence to form lesions Great adherence to laminin → also shown to advance cancer phenotype – lesions may have similar cancerous phenotype
Research Question/Problem/ Need	Identify the potential of ECM components to modulate the adhesive and proliferative characteristics of stromal cells from endometriosis lesions and from women with and without endometriosis

Important Figures	 **Figure 1:** Integrin profile of cultured stromal cells Quantitative immunocytochemistry of integrin expression in eutopic and ectopic ESCs at passages 2, 4, 6 and 10. Data are expressed as percentage positive cells and bars represent mean ± SEM. Integrin expression was similar in the three different endometriotic lesions throughout passaging with loss of α6 in endometriotic versus control ESCs (*$P < 0.05$, †$P < 0.001$). ESCs were derived from peritoneal surface lesions (yellow, $n = 8$); deeply infiltrating lesions (green, $n = 5$); ovarian lesions (blue, $n = 10$); endometrium from women with endometriosis (orange, $n = 5$) and endometrium from control group (red, $n = 5$). P, passage number of cells  **Figure 2:** Quantitative and qualitative analyses of adhesion of eutopic and ectopic ESCs to ECM components (**A**) Percentage attachment compared with control ESCs (100% attachment). Bars represent mean ± SEM, and *$P < 0.05$ and †$P < 0.01$. ESCs were derived from peritoneal surface lesions (yellow, $n = 6$); deeply infiltrating lesions (green, $n = 8$); ovarian lesions (blue, $n = 8$); endometrium from women with endometriosis (orange $n = 5$) and endometrium from control group (red, $n = 5$). FN, fibronectin; CN I and IV, collagens I and IV; LN, laminin; VN, vitronectin; TN, tenascin-C. (**B**) Ovarian lesion ESCs (a, d, g, j) and eutopic ESCs derived from women with endometriosis (b, e, h, k) and without endometriosis (c, f, i, l) adherent to fibronectin (a–c), laminin (d–f), vitronectin (g–i) or tenascin-C (j–l) stained for vinculin (red) and actin (green) 
VOCAB: (w/definition)	Aberrant expression: - "Aberrant phenotype is a phenomenon of abnormal expression or loss of expression of cell specific lineage markers not associated with specific cell type. Aberrant phenotype expression due to genetic defects may be associated with unfavorable outcomes. It can be used to determine minimal residual disease status" Integrin receptor Proteolytic potential

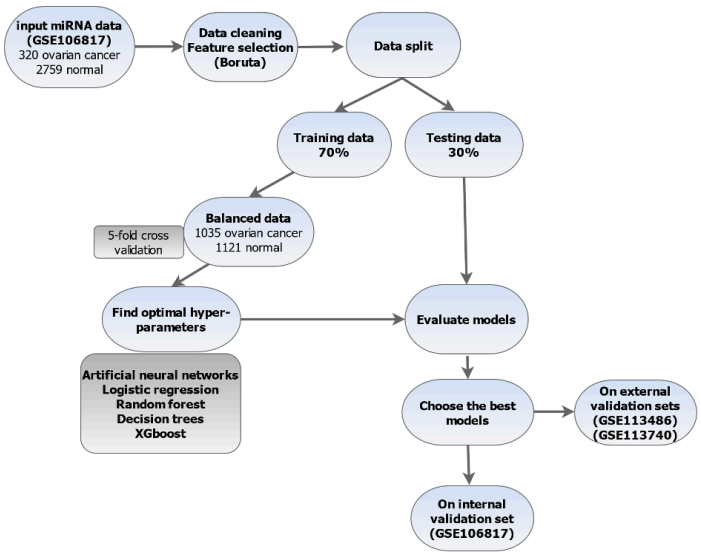
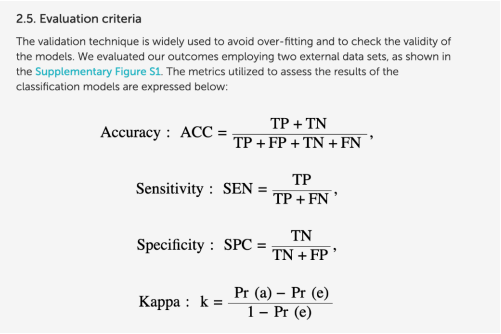
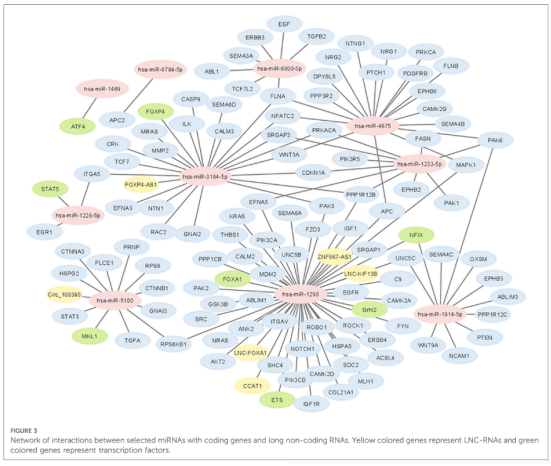
	- Protein breakdown
Cited references to follow up on	Czirok A, Little CD. Pattern formation during vasculogenesis. Birth Defects Res C Embryo Today. 2012;96(2):153–62. Kim I, et al. Molecular cloning, expression, and characterization of angiopoietin-related protein. angiopoietin-related protein induces endothelial cell sprouting. J Biol Chem. 1999;274(37):26523–8. Yancopoulos GD, et al. Vascular-specific growth factors and blood vessel formation. Nature. 2000;407(6801):242–8.
Follow up Questions	1. Is endometriosis benign or tumorous? 2. What aspects of regeneration are seen in endometriosis lesions? 3. How can adhesive and proliferative components of the endometrial ECM be connected to model organisms known for similar characteristics? 4. How can the mechanism of the ECM adherence be inhibited?

Article #14 Notes: Identifying potential circulating miRNA biomarkers for the diagnosis and prediction of ovarian cancer using machine-learning approach: application of Boruta

Source Title	Identifying potential circulating miRNA biomarkers for the diagnosis and prediction of ovarian cancer using machine-learning approach: application of Boruta
Source citation (APA Format)	Hamidi F, Gilani N, Arabi Belaghi R, Yaghoobi H, Babaei E, Sarbakhsh P and Malakouti J (2023) Identifying potential circulating miRNA biomarkers for the diagnosis and prediction of ovarian cancer using machine-learning approach: application of Boruta. *Front. Digit. Health* 5:1187578. doi: 10.3389/fdgth.2023.1187578
Original URL	https://www.frontiersin.org/journals/digital-health/articles/10.3389/fdgth.2023.1187578/full
Source type	Journal Article
Keywords	artificial intelligence, Boruta, biomarker, feature selection, Gene Expression Omnibus, ovarian cancer, oncology
#Tags	miRNA Machine learning
Summary	Diagnosing ovarian cancer is a challenge in gynecology due to its heterogeneous nature. miRNAs hold promise as diagnostic biomarkers. Boruta is a novel random forest feature selection in machine learning techniques that is designed to identify biomarkers using publicly accessible datasets, and applies 5-ML algorithms: logistic regression, random forest, decision trees, artificial neural networks, and XGBoost. 10 differentially expressed miRNAs were distinguished and the models achieved AUC of over 94%.
notes (include methodology)	Background: - 230,000 new cases and nearly 140,000 deaths per year - only 30% of advanced-stage ca - cancer patients live for nearly 5 years after receiving a prognosis - Need for improved screening methods - miRNA → control translation gene regulation; hold promise as diagnostic candidates

	- Knowledge gap:
	  - miRNAs are still insufficient for clinical applications that are due to large-scale non-validation and inconsistencies in the diagnosis of devices
	  - Failed to consider the nonlinear nature of bid data structure
	-
	Past studies miRNA:
	- has-miR-1228-5p and has-miR-6784-5p, has-miR-6784-5p, has-miR-6800-5p, and has-miR-5100 are indicating ovarian-associated cancer signature
	- miR-1290
	- 19 found using RF
	
	This study miRNA: (hsa-miR5100, hsa-miR-1343-3p, hsa-miR-1290, and hsa-miR-4787-3p → apply a novel ML model, identify new miRNAs, cross validation.
	
	Datasets: GSE113486, GSE113740, GSE113486
	
	Machine learning model:
	- random forest classifier → implemented in the Boruta package in R
	- help in the development of biomarkers for cancer diagnosis and prognosis.
	- Feature selection techniques to reduce overfitting and model complexity
	- CancerSEEK: sensitivity of 27% → increased to 52% when adding those detected by standard-of-care screening tests
	- CancerSEEK, when combined by PET-CT scan, showed a specificity of 99.6% and a positive predictive value (PPV) of 40.6%
	- sensitivities in the range of 80–100% for 10 out of 12 cancer types

Research Question/Problem/ Need	How can miRNA machine learning classification be used as an noninvasive diagnostic tool for ovarian cancer?

Important Figures	 flowchart of the research procedure.  2.5. Evaluation criteria The validation technique is widely used to avoid over-fitting and to check the validity of the models. We evaluated our outcomes employing two external data sets, as shown in the Supplementary Figure S1. The metrics utilized to assess the results of the classification models are expressed below: $$\text{Accuracy}: \ ACC = \frac{TP + TN}{TP + FP + TN + FN},$$ $$\text{Sensitivity}: \ SEN = \frac{TP}{TP + FN},$$ $$\text{Specificity}: \ SPC = \frac{TN}{TN + FP},$$ $$\text{Kappa}: \ k = \frac{Pr\,(a) - Pr\,(e)}{1 - Pr\,(e)}$$ Fig. 2: Evaluation Metrics  FIGURE 3 Network of interactions between selected miRNAs with coding genes and long non-coding RNAs. Yellow colored genes represent LNC-RNAs and green colored genes represent transcription factors. Fig. 3: interaction of proteins and genes identified from the classifier.
VOCAB: (w/definition)	**Kappa:** degree of agreement between a pair of variables **Cell-free DNA fragmentation:** short segments of the DNA that can be used in tests.

	Diagnostic Index: cut-off value to determine the significance of a disease.
Cited references to follow up on	Schwarzenbach, H.; Nishida, N.; Calin, G.A.; Pantel, K. Clinical Relevance of Circulating Cell-Free MicroRNAs in Cancer. Nature reviews. Clin. Oncol. 2014, 11, 145–156. Ritchie, M.E.; Phipson, B.; Wu, D.; Hu, Y.; Law, C.W.; Shi, W.; Smyth, G.K. Limma Powers Differential Expression Analyses for RNA-Sequencing and Microarray Studies. Nucleic Acids Res. 2015, 43, e47. Chen, X.; Gole, J.; Gore, A.; He, Q.; Lu, M.; Min, J.; Yuan, Z.; Yang, X.; Jiang, Y.; Zhang, T.; et al. Non-Invasive Early Detection of Cancer Four Years before Conventional Diagnosis Using a Blood Test. Nat. Commun. 2020, 11, 3475.
Follow up Questions	How are the ranking of the miRNA determined? Some diseases have common miRNAs. How is that taken into consideration? What are the specific mechanisms of the CancerSeek algorithm?

Article #15 Notes: MicroRNAs as Potential Biomarkers in Gynecological Cancers

Source Title	MicroRNAs as Potential Biomarkers in Gynecological Cancers
Source citation (APA Format)	Miśkiewicz, J., Mielczarek-Palacz, A., & Gola, J. M. (2023). MicroRNAs as Potential Biomarkers in Gynecological Cancers. *Bio Medicines*, *11*(6). https://doi.org/10.3390/biomedicines11061704
Original URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10296063/
Source type	Journal Article
Keywords	miRNA, gynecological cancers, biomarkers
#Tags	miRNA biology
Summary of key points + notes (include methodology)	Summary : - microRNAs are non-coding RNA that regulate gene expression and aberrant m-RNA has been linked to various health conditions - Can be tested in blood, plasma, peritoneal fluid, urine, etc. - Mediate translational repression and microRNA degradation - Transcribed by RNA polymerases II and III → series of cleavage events - miRNA prescourses categorization is unclear but speculations about the site of origin and sequence & thermodynamic stability - Regulatory function: performed through RNA inducing silencing complex (RISC) → activate target mRNA Background: - 1-5% of the genome - Regulate at least 30% of protein coding genes - 940 distinct miRNAs molecules Two pathways of biogenesis: 1. Canonical Pathway 2. Non-Canonical Pathway a. Dicer enzyme, Exportin 5, Drosha enzyme and AGO2. Regulation of Gene Expression 1. miRNA binds to 3'UTR and 5'UTR of target → represses translation of

	3'UTR and silencing genes in 5'UTR 2. Binds with promoter region and coding sequence → silencing effect → induces transcription 3. miRISC complex of the miRNA leader/guide strand and the AGO protein → activates AGO2 → mRNA degradation 4. Cancer → result of mutation in the sinking of oncogenes and tumor suppressors Ovarian Cancer - Heterogeneous nature → pathogenesis not defined - BRCA 1 and BRCA 2 gene mutations cause - Type II → genetically unstable; increase expression of HER2/neu & AKT genes, TP53 - miRNAs affecting the processes of proliferation, invasion, apoptosis, and control of the cell cycle have an altered profile - **miR-200 family → epithelial-mesenchymal transition (EMT)** - **miR-182 → migration, proliferation, and invasion processes** - **miR-93, miR-200c, miR-141, miR-492, miR-429, miR-155, miR-205, miR-200a, miR-200b** - **Deregulation of let-7 family** Gynecological Cancers: - antigen 125 (CA 125) → glycoprotein encoded by the MUC16 gene (most frequent serum maker for ovarian diagnosis) - WFDC2 (WAP Four-Disulfide Core Domain 2) → diagnosis and prognosis marker miR-200c-3p + miR-221-3p expression + CA-125 obtained significant diagnostic accuracy (AUC = 0.96) CA-125 and HE4 together with miRNA-205 significantly increased the AUC (0.951) Key miRNA: - Upregulated - miR-93 (ovarian and cervical cancer), miR-200a (ovarian, endometrial and cervical cancer), miR-200b (ovarian and cervical cancer), miR-200c (ovarian, endometrial and cervical cancer), miR-141 (ovarian and cervical cancer), miR-429 (ovarian and cervical cancer), miR-182 (ovarian and endometrial cancer), miR-182-5p (ovarian and vulvar cancer), miR-21-5p (ovarian and vulvar cancer), miR-205 (ovarian and endometrial cancer),

	miR-210 (endometrial and cervical cancer), and miR-183-5p (ovarian and vulvar cancer). - Downregulated - miR-152 (ovarian, endometrial, and cervical cancer), miR-214 (ovarian and cervical cancer), let-7a (ovarian and vulvar cancer), miR-145 (ovarian and cervical cancer), and miR-30c (endometrial and vulvar cancer). - PARP inhibitors → understand mechanism of chemoresistance Future works: - Need for more sensitive and specific markers - The markers stated here could serve as diagnostic marker in connection with other identified markers
Research Question/Problem/ Need	What does the levels of microRNA in body fluids indicate about the pathology of gynecological conditions?
Important Figures	Table 1 MicroRNAs with altered expression in ovarian cancer. 0:08 **Down-Regulated miRNAs** / **Up-Regulated miRNAs** miR-152, miR-214, miR-145, let-7a, let-7c, let-7b → miR-93, miR-200a, miR-325, miR-200c, miR-200b, miR-141, miR-492, miR-429, miR-182 — Braicu et al. [51] hsa-miR-1271-5p, hsa-miR-574-3p → hsa-miR-182-5p, hsa-miR-96-5p, hsa-miR-183-5p, hsa-miR-182-3p, hsa-miR-15b-5p, hsa-miR-141-5p, hsa-miR-135b-3p, hsa-miR-130b-5p — Wang et al. [61] miR-214, miR-31 → miR-155 — Mitra et al. [64] Table 5 MicroRNAs that are involved in gynecological cancer. **microRNA** / **Down-Regulated** / **Up-Regulated** miR-152 ↓ OC, EC, CC miR-214 ↓ OC, CC Let-7a ↓ OC, VC miR-145 ↓ OC, CC miR-30c ↓ EC, VC miR-93 ↑ OC, CC miR-200a ↑ OC, EC, CC miR-200b ↑ OC, CC miR-200c ↑ OC, EC, CC Tables of key miRNAs in gynecological conditions.
VOCAB: (w/definition)	**AGO2 protein**: family of proteins that play a role in RNA interference **Dicer-independent pathway:** dependent on AGO2 production to facilitate miRNA function **Glycoprotein:** combination of carbs and protein signaling

	Etiopathogenesis: the biological pathway features of the causation of a disease. **PARP inhibitors**: drugs used to target cancers, primarily ovarian cancer.
Cited references to follow up on	Saliminejad K., Khorram Khorshid H.R., Soleymani Fard S., Ghaffari S.H. An overview of microRNAs: Biology, functions, therapeutics, and analysis methods. *J. Cell. Physiol.* 2019;234:5451–5465. doi: 10.1002/jcp.27486 Shylasree T.S., Richa B., Lavanya G., Gulia S. Molecular Signatures of Gynecological Cancers: Clinicians Perspective. *Indian J. Surg. Oncol.* 2021;12((Suppl. 1)):103–110. doi: 10.1007/s13193-020-01271-8. He B., Zhao Z., Cai Q., Zhang Y., Zhang P., Shi S., Xie H., Peng X., Yin W., Tao Y., et al. miRNA-based biomarkers, therapies, and resistance in Cancer. *Int. J. Biol. Sci.* 2020;16:2628–2647. doi: 10.7150/ijbs.47203 Su Y.Y., Sun L., Guo Z.R., Li J.C., Bai T.T., Cai X.X., Li W.H., Zhu Y.F. Upregulated expression of serum exosomal miR-375 and miR-1307 enhance the diagnostic power of CA125 for ovarian cancer. *J. Ovarian Res.* 2019;12:6. doi: 10.1186/s13048-018-0477-x.
Follow up Questions	How can differential expression of miRNA be used to understand population observational studies? Are there differences in the miRNA expression that are collected from different types of bodily fluid? Has CA-125 proven to be an accurate diagnostic marker in experiments?

Article #16 Notes: Clinical use of artificial intelligence in endometriosis: a scoping review

Source Title	Clinical use of artificial intelligence in endometriosis: a scoping review
Source citation (APA Format)	Sivajohan, B., Elgendi, M., Menon, C. *et al.* Clinical use of artificial intelligence in endometriosis: a scoping review. *npj Digit. Med.* 5, 109 (2022). https://doi.org/10.1038/s41746-022-00638-1
Original URL	https://www.nature.com/articles/s41746-022-00638-1#cities
Source type	Nature Article
Keywords	Endometriosis, machine learning, artificial intelligence, review, prediction
#Tags	Endometriosis, ML

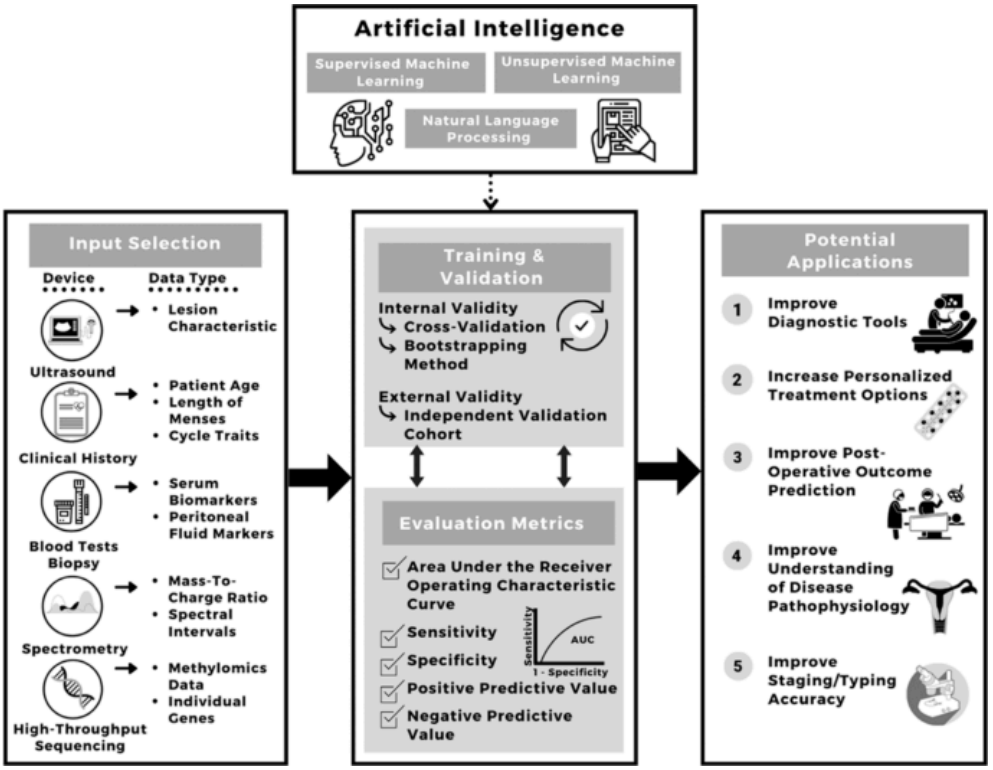
Summary of key points + notes (include methodology)	- AI models to predict and diagnosis based on data patterns
	
	Collecting Data:
	- 36 studies incorporated that used some type of AI approach to explore pathology, diagnostics, prediction, management 44.4% (n = 16) → predictive capabilities
	  - 47.2% (n=17) → diagnostic
	  - 8.33% (n=3) → improve disease understanding
	- Models used: logistic regression, decision tree algorithms, random forest, support vector machines
	- Data types:
	  - biomarkers
	  - Clinical variables
	  - Metabolite spectra
	  - Genetic variables
	  - Imaging data
	  - Mixed methods
	  - Lesion characteristic
	- provided evaluation metrics such as sensitivity and specificity: between 81.7% - 96.7%
	
	Background:
	- Affect 1/10 women – about 190 million women

- Often goes undiagnosed
- Causes great burden on the economy, family, quality of life
- Hard to develop a standard stage rank because of the variability amongst cases … clinical heterogeneity
    - 3 dominant phenotypes:
        - Superficial
        - Endometriomas
        - Deep endometriosis
- symptomatology depending on the type of endometriosis, location of implants, stage, and severity including but not limited to dysmenorrhea, dyspareunia, abdominal pain, chronic pelvic pain, menorrhagia, bowel symptoms, urinary symptoms, and subfertility or infertility
- Two major diagnostic tools: laparoscopy and Transvaginal ultrasonography

Specific studies:

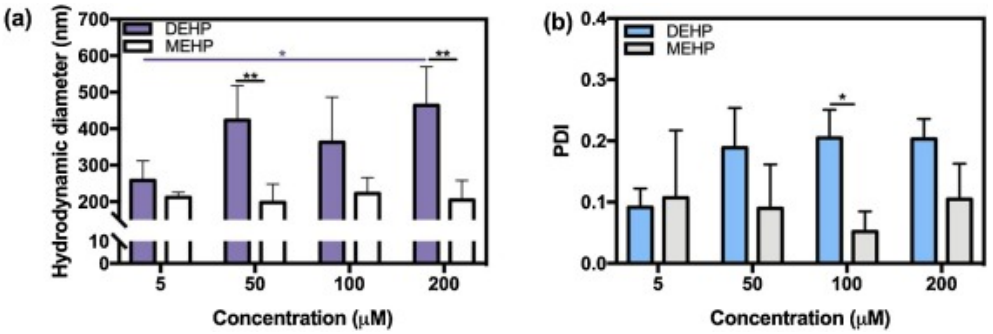
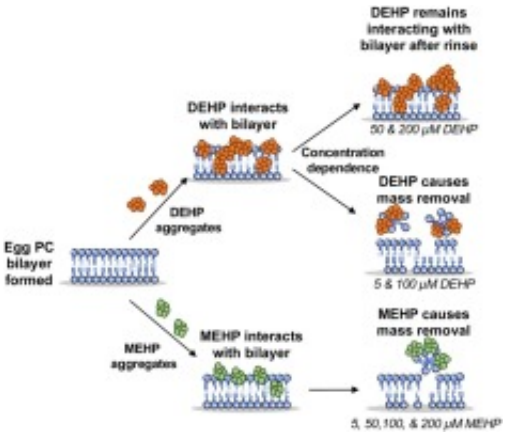
1. Biomarker as input
    a. Each study focused on different types of biomarkers
        i. Angiogenic factors
        ii. Cytokines
        iii. Serum microRNAs signatures
        iv. Metabolite biomarkers
        v. Plasma biomarkers collected in all phases of the menstrual cycle
2. Genetic maersk
    a. Large transcriptomics databases
    b. used genetic variables to build their predictive and diagnostic models, however, the type of input varied between individual gene candidates 52,56, large protein-coding gene datasets from transcriptomics and methylomics data53,55, and 16S rRNA gene amplicon data
    c. Clinical factors
        i. age, history of pelvic surgery, dysmenorrhea, and pelvic pain being
3. Metabolite spectra
    a. Looked at levels in serum
4. Imaging based models
    a. Not as accurate – only three so far
    b. Looked at adhesive properties on ultrasound

Takeaways:

	- The role of geographic variance not taken into account - Comorbidities?
Research Question/Problem/ Need	How has artificial intelligence been used in the detection of endometriosis?
Important Figures	 Overview of procedure
VOCAB: (w/definition)	Retrospective study: based on past trends
Cited references to follow up on	Bendifallah, S. et al. Machine learning algorithms as a new screening approach for patients with endometriosis. Sci. Rep. 12, 639 (2022). Wang, Y. F. et al. Mining medical data: A case study of endometriosis. *J. Med. Syst.* 37, 9899 (2013).
Follow up Questions	1. What are metabolite spectra and how are they important in understanding a disease? 2. How is family history taken into consideration?

Article #17 Notes: Investigating interactions of phthalate environmental toxicants with lipid structures

Source Title	Investigating interactions of phthalate environmental toxicants with lipid structures
Source citation (APA Format)	Bailey-Hytholt, C. M., Puranik, T., Tripathi, A., & Shukla, A. (2020). Investigating interactions of phthalate environmental toxicants with lipid structures. *Colloids and surfaces. B, Biointerfaces*, *190*, 110923. https://doi.org/10.1016/j.colsurfb.2020.110923
Original URL	https://www.sciencedirect.com/science/article/pii/S0927776520301533
Source type	Article
Keywords	Lipid vesiclesSupported lipid bilayersQuartz crystal microbalance with dissipationParallel artificial membrane permeability assayDi(2-ethylhexyl) phthalateMono(2-ethylhexyl) phthalate
#Tags	Lipids, environment
Summary of key points + notes (include methodology)	DEHP: - Di(2-ethylhexyl) phthalate - Type of plasticizer found in household products - Leaches from materials → health effects - Studies have found correlation between pregnant women urine and DEPH levels - Structural changes in A549 lung carcinoma cells migration, ROS production, neuron and glial cell signaling pathways Goal: - Understand how DEPH & metabolite interact with lipids/cell membrane Methods: - Light scattering → changes in size & polydispersity of egg pC vesicles (diff concentration for DEHP & MEHP) - migration: chitosan nanoparticle pre-treameten – absorb phthalates - Quartz crystal microbalance + dissipation monitoring (QCM-D) → indicates lipid removal based on concentration measured Results: - Both have low permeability but DEHP connected with bilayer - Expisre impacts many small molecules

	- Helpful in understanding public health and potential invention methods
Research Question/Problem/ Need	Understand how DEPP & metabolite interact with lipids/cell membrane and how the understanding of the mechanism can be used to improve public health
Important Figures	 Fig1. Shows the levels of DEHP and MEHP in different concentration levels  **Graphical Abstract**
VOCAB: (w/definition)	**Lipases**: assist in pancreatic secretion; enzyme that breaks down triglycerides into free fatty acids and glycerol; break ester bonds in triglycerides. **Phthalates**: endocrine disruption → impact human development **Endocrine disruptor:** causes dysregulation of the endocrine chemicals **Quartz crystal microbalance:** a way to measure low mass changes. **Glial cells:** considered the glue of the nervous system; physical and chemical support to neurons

Cited references to follow up on	Grindler, N. M., Vanderlinden, L., Karthikraj, R., Kannan, K., Teal, S., Polotsky, A. J., Powell, T. L., Yang, I. V., & Jansson, T. (2018). Exposure to Phthalate, an Endocrine Disrupting Chemical, Alters the First Trimester Placental Methylome and Transcriptome in Women. *Scientific Reports*, *8*(1), 6086. https://doi.org/10.1038/s41598-018-24505-w Braun, J. M., Sathyanarayana, S., & Hauser, R. (2013). Phthalate Exposure and Children's Health. *Current Opinion in Pediatrics*, *25*(2), 247–254. https://doi.org/10.1097/MOP.0b013e32835e1eb6 Bornehag, C.-G., Sundell, J., Weschler, C. J., Sigsgaard, T., Lundgren, B., Hasselgren, M., & Hägerhed-Engman, L. (2004). The Association between Asthma and Allergic Symptoms in Children and Phthalates in House Dust: A Nested Case–Control Study. *Environmental Health Perspectives*, *112*(14), 1393–1397. https://doi.org/10.1289/ehp.7187
Follow up Questions	How can understanding the impacts of environmental chemicals be linked to the onset of diseases? What are the broader implications of understanding the impacts of phthalate environmental toxicants? How can lipid structure damage lead to damage to other parts?

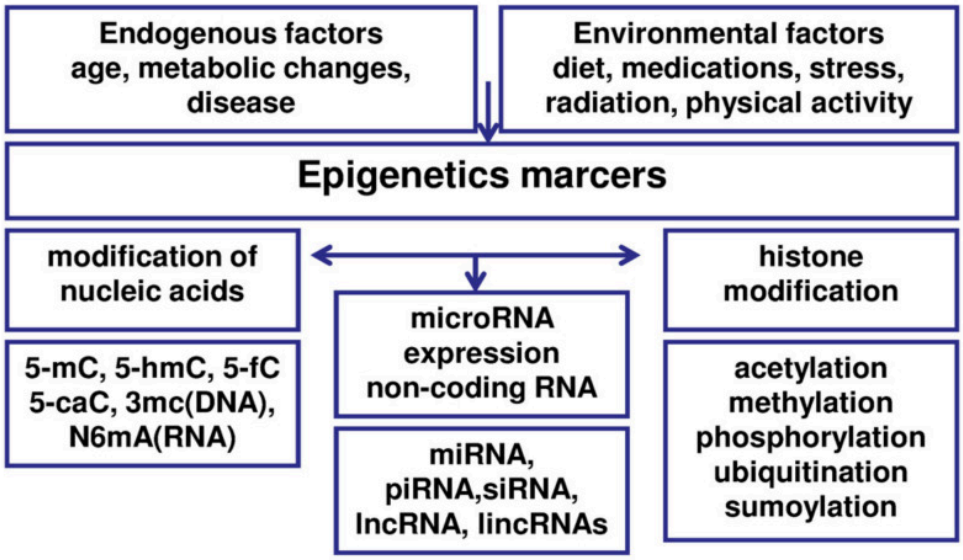
Article #18 Notes: Genetic, Epigenetic, and Steroidogenic Modulation Mechanisms in Endometriosis

Source Title	Genetic, Epigenetic, and Steroidogenic Modulation Mechanisms in Endometriosis
Source citation (APA Format)	Zubrzycka, A., Zubrzycki, M., Perdas, E., & Zubrzycka, M. (2020). Genetic, Epigenetic, and Steroidogenic Modulation Mechanisms in Endometriosis. *Journal of clinical medicine*, *9*(5), 1309. https://doi.org/10.3390/jcm9051309
Original URL	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7291215/#B14-jcm-09-01309
Source type	Journal Article
Keywords	endometriosis, genetics, epigenetics modifications, DNA methylation, histone proteins, microRNA
#Tags	Endometriosis
	The aim of this study is to understand the epigenetic and environmental factors of endometriosis. The heritability nature of endometriosis was understood, and important gene loci were identified in the pathology.

Summary of key points + notes (include methodology)	Endo GWAS studies:
	- Loci connected to matrix remodeling, transcription regulation, cell cycle, signaling, cell adhesion, inflammation, immunity, oxidative stress and steroid hormone receptors
	- Changes seen in: DNA methylation, histone modification, miRNA expression
	- GWAS + Snps + hapMap
	  - IL1A gene locus on 2q13 has also been confirmed recently by identifying genome-wide significant association between rs6542095 and endometriosis
	  - NP rs11556218 is associated with the development of endometriosis, probably as a result of the aberrant expression of interleukin-16 (IL-16), which activates T-lymphocytes, leading to

	the secretion of several pro-inflammatory cytokines, resulting in the survival of the ectopic endometrial tissue in the peritoneal cavity.
	- Identify SNPs → most common
	
	Familial studies:
	- Hereditary disorder + environmental triggers
	- No strong gene mutation have been identified
	- Polygenic inheritance → phenotypic features are transmitted
	- potential high-penetrance susceptibility loci and genes such as CYP2C19, INHBA, SFRP4, and HOXA10
	
	Steroidogenic Pathway:
	- estrogen -dependent disease → progesterone receptor suppression, abnormal growth
	- Inhibition of PGE2 biosynthesis → suppress endometriosis
	- SF-1 regulator pathway could be targeted for treatment
	- reduced levels of miR-23a and miR-23b expression in ectopic and eutopic endometrium,
	Results:
	- Endometriosis is linked to epigenetic disorders → environmental and intracellular factors
	  - Dna methylation → histone modification → miRNA expression
	  - Regulated by hypoxia, proinflammatory cytokines, and estradiol production

Research Question/Problem/ Need	How are epigenetic markers related to the pathology of endometriosis?

Important Figures	
VOCAB: (w/definition)	**Estradiol:** medication to help women manage post-menopausal symptoms **Methylation:** a process where methylation groups are added to the target molecules **Histone:** spools of DNA; provides structural support to chromosomes and different types of interactions play a role in gene expression. **Polymorphisms:** presence of specific types of DNA, most notably at the SNP level.
Cited references to follow up on	Kennedy S. The genetics of endometriosis. *Eur. J. Obstet. Gynecol. Reprod. Biol.* 1999;82:129–133. doi: 10.1016/S0301-2115(98)00213-9. Tulandi T., Redwine D.B. Endometriosis: Advances and Controversies. Volume 3. Marcel Dekker; New York, NY, USA: 2004. pp. 55–56. Matalliotakis M., Zervou M.I., Matalliotaki C., Rahmioglu N., Koumantakis G., Kalogiannidis I., Prapas I., Zondervan K., Spandidos D.A., Matalliotakis I., et al. The role of gene polymorphisms in endometriosis. *Mol. Med. Rep.* 2017;16:5881–5886. doi: 10.3892/mmr.2017.7398
Follow up Questions	How can the epigenetic nature of endometriosis be observed in population behavior of the Nurses Health Study? What similarities are there between the genomic nature of endometriosis and cancers?

Article #19 Notes: Endometriosis and risks for ovarian, endometrial and breast cancers: A nationwide cohort study

Source Title	Endometriosis and risks for ovarian, endometrial and breast cancers: A nationwide cohort study
Source citation (APA Format)	Mogensen, J. B., Kjær, S. K., Mellemkjær, L., & Jensen, A. (2016). Endometriosis and risks for ovarian, endometrial and breast cancers: A nationwide cohort study. *Gynecologic Oncology*, *143*(1), 87–92. https://doi.org/10.1016/j.ygyno.2016.07.095
Original URL	https://www.sciencedirect.com/science/article/pii/S0090825816309647#bb0040
Source type	Journal
Keywords	Breast cancer, Endometrial cancer, Endometriosis. Cohort study, Gynecological cancer, Ovarian cancer
#Tags	Endometriosis, Breast Cancer, Ovarian Cancer
Summary of key points + notes (include methodology)	Background: - Endometriosis shares characteristics with invasive cancers - Epidemiology studies have shown increased risk of ovarian cancer amongst women with endo - Previous studies have been inclusive about correlation between endo and risk of cancer - This study aims to further explore this hypothesis on a nationwide cohort of Danish women with endo during 1977-2012 → one of the largest choro study on this topic Methods: - Women registered in the Danish National Patient Registry were considered. A filtration method was applied on those who emigrated or had undergone specific types of surgery

	- 45,790 women were diagnosed with endometriosis and further grouped into the specific types of varian, endometrial, and breast cancer - Standardized incidence ratios with 95% confidence intervals were computed between the observed and expected number Results: 1. Statistically significant increase for ovarian cancer 2. Endometrial cancer: risk statistically significant after 10 years of follow up; not convincing evidence at first diagnosis 3. Breast cancer: significant after diagnosis of ages 50 years or older 4. Risk for endometrioid- and clear-cell ovarian cancer in women with endometriosis. 5. endometriosis was associated with an excess risk for endometrial cancer, primarily type 1.
Research Question/Problem/ Need	What are the overall- and histotype-specific risks for these hormone-dependent cancers in women with endometriosis?
Important Figures	Table 1. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) for ovarian, endometrial and breast cancers among Danish women with endometriosis diagnosed in 1977–2012.

Cancer site	Total follow-up					Follow up ≥ 1 year after first diagnosis of endometriosis				
	PY	MFU (P10–P90) (years)	O	E	SIR (95% CI)	PY	MFU (P10–P90) (years)	O	E	SIR (95% CI)
Ovary	592,741	10.75 (0.26–29.33)	221	142.64	1.55 (1.35–1.77)	552,244	11.85 (2.11–29.07)	186	138.31	1.34 (1.16–1.55)
Endometrium	337,829	4.10 (0.01–22.73)	118	55.34	2.13 (1.77–2.55)	308,680	8.83 (1.35–25.86)	77	53.82	1.43 (1.13–1.79)
Breast	686,339	13.00 (2.53–30.22)	1452	1377.46	1.05 (1.00–1.11)	641,403	12.67 (2.34–29.42)	1397	1335.17	1.05 (0.99–1.10)

PY=person–years. MFU=median follow-up. P10=10th percentile. P90=90th percentile. O=observed. E=expected.

3.1. Endometriosis and risks for ovarian, endometrial and breast cancer

Table 4
Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) for histotypes of ovarian cancer among Danish women with endometriosis diagnosed in 1977–2012, by time since and age at first diagnosis of endometriosis. Cancers and person–years in the first year after a diagnosis of endometriosis were excluded.

	Serous			Mucinous			Endometrioid			Clear-cell		
	O	E	SIR (95% CI)	O	E	SIR (95% CI)	O	E	SIR (95% CI)	O	E	SIR (95% CI)
Time since endometriosis(years)												
1–4	13	7.69	1.69 (0.90–2.89)	3	2.30	1.30 (0.26–3.81)	5	2.36	2.12 (0.68–4.95)	2	0.97	2.07 (0.23–7.48)
5–9	15	11.24	1.33 (0.75–2.20)	3	3.02	0.99 (0.20–2.90)	4	3.35	1.19 (0.32–3.05)	8	1.41	5.69 (2.45–11.22)
≥10	42	47.87	0.88 (0.63–1.19)	4	8.09	0.49 (0.13–1.27)	19	11.38	1.67 (1.00–2.61)	15	4.49	3.34 (1.87–5.51)
Age at first endometriosis (years)												
<30	5	5.55	0.90 (0.29–2.10)	1	1.61	0.62 (0.01–3.46)	1	1.43	0.70 (0.01–3.90)	4	0.62	6.45 (1.73–16.51)
30–39	24	20.20	1.19 (0.76–1.77)	3	4.49	0.67 (0.13–1.95)	8	5.39	1.48 (0.64–2.93)	10	2.27	4.40 (2.11–8.09)
40–49	22	33.01	0.67 (0.42–1.01)	5	6.01	0.83 (0.27–1.94)	14	8.34	1.68 (0.92–2.82)	8	3.32	2.41 (1.04–4.75)
≥50	19	8.04	2.36 (1.42–3.69)	1	1.30	0.77 (0.01–4.27)	5	1.93	2.59 (0.83–6.03)	3	0.65	4.62 (0.93–13.51)

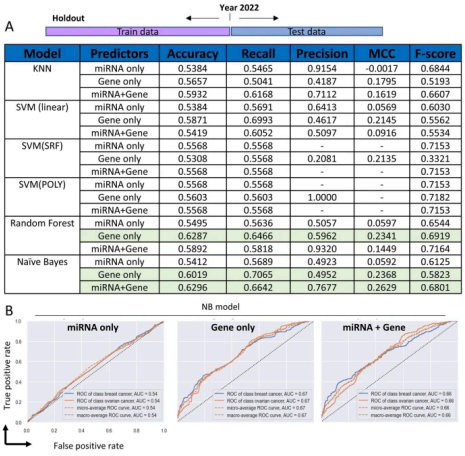
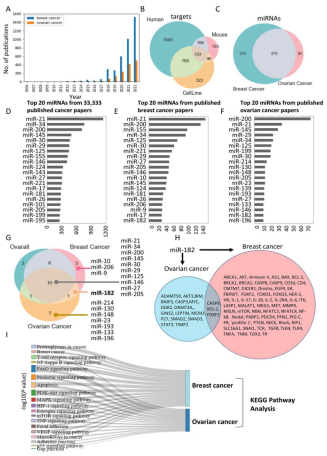
O = observed, E = expected.

VOCAB: (w/definition)	**Significant incidence ratio:** number of cases in a population **Confidence intervals:** probability of range of values falling within the specified range. **Histotype:** tissue type **Ascertainment**: the process of determining correlation between groups.
Cited references to follow up on	Ness, R. B. (2003). Endometriosis and ovarian cancer: Thoughts on shared pathophysiology. *American Journal of Obstetrics and Gynecology*, *189*(1), 280–294. https://doi.org/10.1067/mob.2003.408 A. Melin, P. Sparén, I. Persson, A. Bergqvist, Endometriosis and the risk of cancer with special emphasis on ovarian cancer, *Human Reproduction, Volume* 21, Issue 5, May 2006, Pages 1237–1242, https://doi.org/10.1093/humrep/dei462
Follow up Questions	Can the findings of this result be applied to other populations with varying ethnic groups? How can the population observations be correlated with the pathophysiology of each of these conditions?

Article #20 Notes: Identifying miRNA biomarkers for breast cancer and ovarian cancer: a text mining perspective

Source Title	Identifying miRNA biomarkers for breast cancer and ovarian cancer: a text mining perspective
Source citation (APA Format)	Li, X., Dai, A., Tran, R., & Wang, J. (2023a). Identifying miRNA biomarkers for breast cancer and ovarian cancer: a text mining perspective. *Breast Cancer Research and Treatment*, *201*(1), 5–14. https://doi.org/10.1007/s10549-023-06996-y
Original URL	https://link.springer.com/article/10.1007/s10549-023-06996-y
Source type	Journal Article
Keywords	microRNAs, Breast cancer, Ovarian cancer, Machine learning. Prediction model miR-182, miR-155
#Tags	Breast Cancer, Ovarian Cancer
Summary of key points + notes (include methodology)	1. miR-182 → highly specific to female cancers a. Targets regulation in breast and ovarian cancer b. Naive Bayes → promising prediction model c. 60% accuracy 2. miR-155 → breast cancer 3. miR-199 → ovarian Background: - miRNA: non coding RNA, post transcriptional gene regulation by binding to complementary sequence in target mRNAs → mRNA degradation/translation repression - with the breast cancer ranking as the second leading cause of cancer deaths in women and ovarian cancer often being undetected until it reaches an advanced stage - BRCA1 and BRCA2 gene mutation causes both disease

	- miR-21, miR-34a, miR-195, miR-10b, miR-127, miR-93, miR-210, miR-143, miR-145, and miR-125b have been extensively studied in both breast cancer and ovarian cancer, involving processes, such as cell proliferation, apoptosis, and angiogenesis
	- K-Nearest Neighbors (KNN) and Support Vector Machines (SVM) algorithms → similarity between samples to accurately classify breast cancer and ovarian cancer cases
	- Random Forest (RF) algorithm identifies crucial features for classification
	
	Methods:
	- Equal number of datasets for each cancer
	- Performance evaluated by ROC (receiver operating characteristic curve)
	- Area under under the curve (AUC)
	- Validation: time-based & cross-validation
	- p-value of < 0.05 was considered significant.
	-
	
	Frequency distribution:
	- miR-21, miR-34, miR-200, miR-145, and miR-30 were among the 20 most frequently referenced miRNAs
	- **breast cancer** studies were miR-21, miR-200, miR-155, miR-34, miR-125, and so on
	- **Ovarian cancer** miR-200, miR-21, miR-145, miR-29, miR-34,
	- miR-182: found in both; 63 & 19 unique genes
	  - FOXF2, CASP9, and BCL-2 – shared genes
	  - BRCA1, BRCA2, FOXO3, FBXW7, MET, AKT, TLR4, and TOX3 have been reported to occur at least twice in miR-182 studies of breast cancer.
	  - Both diseases may manifest due to shared mutations of OXF2 and involve cell proliferation and invasion in both ovarian cancer and breast cancer suggesting that miR-182 regulates both breast [35,36,37] and ovarian cancers [33] through similar signaling pathways.
	
	- **Naive Bayes** ML model seemed most promising; focused bio terms of those studies
	  - miR-155 (BC) and miR-199
	  - ER, HER-2, OVCAR3, TNM, EMT, SOX2, miR-155, PR, miR-199, and BRCA2 contribute the most to the prediction of breast cancer and ovarian cancer.

Research Question/Problem/ Need	This study aims to explore the role of miRNAs in the development of breast cancer and ovarian cancer.
Important Figures	 | Model	Predictors	Accuracy	Recall	Precision	MCC	F-score
---	---	---	---	---	---	---
KNN	miRNA only	0.5384	0.5465	0.9154	-0.0017	0.6844
	Gene only	0.5657	0.5041	0.4187	0.1795	0.5193
	miRNA+Gene	0.5932	0.6168	0.7112	0.1619	0.6607
SVM (linear)	miRNA only	0.5384	0.5691	0.6413	0.0569	0.6030
	Gene only	0.5871	0.6993	0.4617	0.2145	0.5562
	miRNA+Gene	0.5419	0.6052	0.5097	0.0916	0.5534
SVM(SRF)	miRNA only	0.5568	0.5568	-	-	0.7153
	Gene only	0.5308	0.5568	0.2081	0.2135	0.3321
	miRNA+Gene	0.5568	0.5568	-	-	0.7153
SVM(POLY)	miRNA only	0.5568	0.5568	-	-	0.7153
	Gene only	0.5603	0.5603	1.0000	-	0.7182
	miRNA+Gene	0.5568	0.5568	-	-	0.7153
Random Forest	miRNA only	0.5495	0.5636	0.5057	0.0597	0.6544
	Gene only	0.6287	0.6466	0.5962	0.2341	0.6919
	miRNA+Gene	0.5892	0.5818	0.9320	0.1449	0.7164
Naïve Bayes	miRNA only	0.5412	0.5689	0.4923	0.0592	0.6125
	Gene only	0.6019	0.7065	0.4952	0.2368	0.5823
	miRNA+Gene	0.6296	0.6642	0.7677	0.2629	0.6801	 Machine learning models for prediction of breast cancer and ovarian cancer. A Performance comparison of different classifiers for the developed machine learning models. B Receiver operating characteristic (ROC) curves of the Naïve Bayes model with the miRNA only, gene only, and miRNA + Gene  miRNA-155 plays a critical role in breast cancer. A Feature importance of Naïve Bayes model with combination of miRNAs and genes. B Bar graph shows the percentages of miR-155 and miR-199 studies in breast cancer and ovarian cancer, respectively. C Venn diagram shows overlap of miR-155-related genes in breast cancer and ovarian cancer. D Bar graph shows top 20 miR-155-related gene occurrences in breast cancer studies. E Bar graph shows miR-155 relevant KEGG signal pathways in breast cancer
VOCAB: (w/definition)	**Naive Bayes:** supervised machine learning algorithm, which is used for classification tasks, ex. text classification. **PI3K/AKT and MAPK signaling pathways:**
Cited references to follow up on	Lu C, Zhao Y, Wang J, Shi W, Dong F, Xin Y, Zhao X, Liu C (2021) Breast cancer cell-derived extracellular vesicles transfer miR-182-5p and promote breast carcinogenesis via the CMTM7/EGFR/AKT axis. Mol Med 27(1):78 Bearfoot JL, Choong DY, Gorringe KL, Campbell IG (2008) Genetic analysis of cancer-implicated MicroRNA in ovarian cancer. Clin Cancer Res 14(22):7246–7250 Silveri L, Tilly G, Vilotte JL, Le Provost F (2006) MicroRNA involvement in

	mammary gland development and breast cancer. Reprod Nutr Dev 46(5):549–556 Nguyen VHL, Yue C, Du KY, Salem M, O'Brien J, Peng C (2020) The role of microRNAs in epithelial ovarian cancer metastasis. Int J Mol Sci.
Follow up Questions	How are contradictory results of miRNA expression further evaluated? Are miRNA better equipped for diagnostic or monitor progression? How can bias be prevented in such datasets?

Patent #1: Classifiers for detection of endometriosis

Source Title	Classifiers for detection of endometriosis
Source citation (APA Format)	Taylor, H., & BOWERMAN, H. (n.d.). Classifiers for detection of endometriosis. Retrieved December 12, 2023, from https://patents.google.com/patent/US20230059244A1/en?q=(miRNA+machine+learnin+model)&oq=miRNA+machine+learning+model
Original URL	https://patents.google.com/patent/US20230059244A1/en?q=(miRNA+machine+learning+model)&oq=miRNA+machine+learning+model
Source type	Google Patent
Keywords	Endometriosis, machine learning, miRNA, classification
#Tags	Endometriosis patent
Summary	The goal of this patent is to develop a method for the classification, diagnostic, and monitoring of endometriosis. First, they generate a list of the top differentially expressed miRNA found in patients in endometriosis using PCR-RQ collection techniques and cross validating with previous studies. From there, a machine learning model of Random Forest was developed to provide at least an 80% specificity and AUC for the diagnosis of endometriosis. Finally, they hope to develop a network repository where patients can access their results from mobile applications.
notes (include methodology)	1. Background:

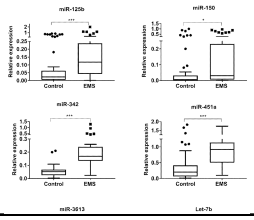
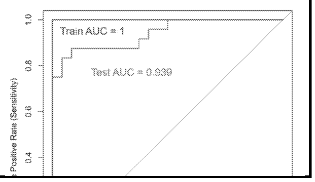
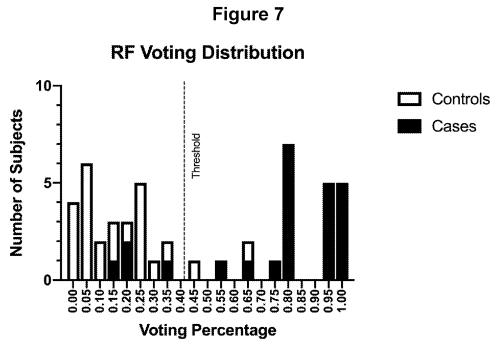
	a. Previously, CA-125 has been considered as a marker for endometriosis, however, it does not provide a strong sensitivity or specificity due to its prevalence in other cancerous conditions. 2. Develop a method to detect presence or absence of endometriosis in women a. Use bodily fluids to develop an expression profile of miRNAs that are found in endometriosis: miR-342 or miR-451a b. Utilize a machine learning model that determines a value of importance for each miRNA feature i. an importance measure is assigned to miR-342 and the importance measure assigned to miR-342 is greater than the importance measure assigned to miR-150, miR-3613, miR-451a, let-7b, or miR-125b; ii. an importance measure is assigned to miR-451a and the importance measure assigned to miR-451a is greater than the importance measure assigned to miR-3613, miR-125b, or let-7b; c. The machine learning model uses Random Forest Algorithm, KNN, SVM, and Naive Bayes i. Specificity of greater than 80% ii. The selected sample is premenopausal and may have received hormonal therapy iii. Trained on least 100 samples iv. AUC: greater than 0.85 3. Considerations of variation: a. Because miRNA levels can differ depending on factors such as the phase of the menstrual cycle, type of hormonal treatment 4. The final stage of this model is to develop a mobile application that connects various clinical centers in a geographic area and can provide a patient with the likelihood of them having endometriosis after their blood test or other bodily fluid sample has been collected.
Research Question/Problem/ Need	Develop a classification method for the detection of endometriosis using machine learning and miRNA levels to detect, predict, diagnose, and monitor the presence or absence of endometriosis.
Important Figures	Figure 1  Fig. 1: sequence listing of miRNAs that are efficient at identifying the presence or absence of endometriosis Figure 5 

	Fig. 5: Demonstrates the performance of the algorithm on an independent dataset. Train (n=100) and test (n=48) split performed on two previous retrospective studies.
	 Fig. 7: Demonstrates the specify and sensitivity levels of the Random Forest Algorithm.
	TABLE 2 ROC Analysis of Individual miRNAs Table 2: Highlights the top 6 miRNA used in the development of this model and the significance of each.

ROC Model	Area (AUC)	Standard Error	95% Wald Confidence Limits		Optimal cut-off ($2^{-\Delta CT}$ normalized expression values)	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*	74.0	92.7	61.0
let_7b	0.78	0.05	0.69	0.87	0.012*	73.7	82.5	67.8

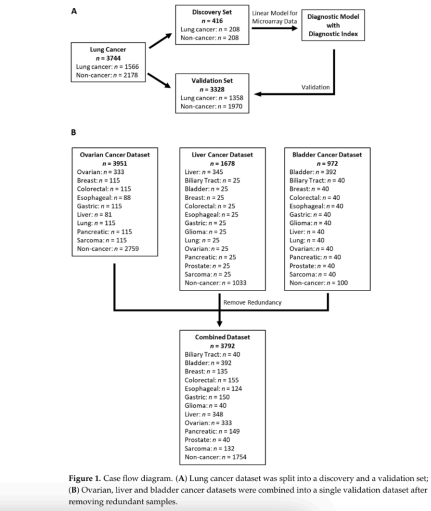
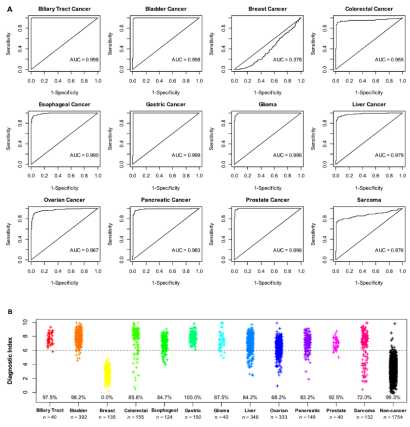
VOCAB: (w/definition)	**Cell-free:** nucleic acid not associated with a cell hen the nucleic acid was obtained. For example, such substances can be found in the blood or saved without being associated with a cell. **Cell-free sample:** biological fluid where cells are absent or parent in low levels so the miRNA levels only demonstrate the level in the liquid portion and not the cellular portion. Proceeded right after the sample is collected, and often goes through a centrifuge. **Non-coding RNA:** endogenous RNA that does not translate into a protein. **ROC:** **Random Forest Algorithm:** a type of machine learning algorithm that contains a series of decision trees that outputs classification and regression of the individual trees. **Support Vector Machine:** a type of supervised learning, that trains a subset and assigns them to one or two categories in a non-probabilistic binary linear classifier.

Cited references to follow up on	Weidhaas, J. B., & TAYLOR, H. S. (n.d.). *The kras-variant and endometriosis.* Retrieved December 15, 2023, from https://patents.google.com/patent/WO2012112883A1/en?q=(miRNA+machine+learning+model)&oq=miRNA+machine+learning+model Taylor, H., & CHO, S. (n.d.). *Circulating microrna as biomarkers for endometriosis.* Retrieved December 15, 2023, from https://patents.google.com/patent/WO2015148919A2/en?q=(miRNA+machine+learning+model)&oq=miRNA+machine+learning+model
Follow up Questions	1. Why was the specific train and test split selected? 2. Was the Random Forest model selected before or after comparing prototypes of several ML models? 3. What are the limitations of using a machine learning model such as RF? How can it be overcome? 4. How does this approach take into consideration that the raSAM ranking system for the different stages of endometriosis is unreliable due to the different physician practices?

Patent #2: A Novel Blood-Based microRNA Diagnostic Model with High Accuracy for Multi-Cancer Early Detection

Source Title	A Novel Blood-Based microRNA Diagnostic Model with High Accuracy for Multi-Cancer Early Detection
Source citation (APA Format)	Zhang, A., & Hu, H. (2022). A Novel Blood-Based microRNA Diagnostic Model with High Accuracy for Multi-Cancer Early Detection. *Cancers*, *14*(6), 1450. https://doi.org/10.3390/cancers14061450
Original URL	https://pubmed.ncbi.nlm.nih.gov/35326599/
Source type	Filed Patent (noted at the bottom of the article) + Article
Keywords	blood-based diagnostic model; microRNA; multi-cancer early detection; noninvasive.
#Tags	miRNA & Machine Learning
Summary	Developed a noninvasive diagnostic test for detecting multiple types of cancers. They used a serum-based 4-microRNA diagnostic model, and validated their findings with next generation sequencing-based tests. This model proved to perform at diagnosing 12 cancer types and holds potential to be feasibly implemented in a wide scale.
notes (include methodology)	Introduction: - 19.3 million new cancer cases and 10 million cancer deaths worldwide. Most common: - Breast (mammography for early screening), lung, colorectal, prostate, stomach - Early stage cancers are asymptotic, making it hard to diagnose - miRNAs: negative post-transcriptional regulation by binding to complementary sequences in the 3'untraslated region of mRNA molecules. - Control >50% of gene expression

	- Easily accessible due to circulation in bodily fluids & Stability in blood Study Design: Four microarray datasets from a Japanese nationwide research project "Development and Diagnostic Technology for Detection of miRNA in Body Fluids" Access Code: lung (GSE137140), ovarian (GSE106817), liver (GSE113740), and bladder (GSE113486) cancers. The goal is to improve efficiency and accuracy from previous 2-miRNA based model miRNA selection: - signal intensity was greater than mean plus two times standard deviation of the negative control signals, and in using the negative control signals the top and bottom 5% of the ranked signal intensities were removed. - Normalization across microarrays was achieved by calibrating according to three pre-selected internal control miRNAs (miR-149-3p, miR-2861, and miR-4463). Classification model: - (limma) Linear Model for Microarray Data → statistical significance of differential miRNA between cancer vs healthy - 10-fold cross validation based on area under the curve (AUC) e (AUC) of the Receiver's Operating Characteristics (ROC) curve analysis → performed to determine the optimal number of miRNAs for the be - Diagnostic Index: linear sum of miRNA expression levels weighted by limma statistics → determine cutoff point to prevent misclassification Statistical Analysis: - roc.test function with bootstrapping method from pROC → compare AUC of ROC curves - Use bioconductor limma package to evaluate sensitivity, specificity and ROC analysis Findings: - DId not perform well for breast cancer - Greater than 95% AUC - Unable to detect tissue origin, only the presence or absence of cancer.
Research Question/Problem/ Need	How can miRNA expression be used for multi-cancer detection of cancers?

Important Figures	 **Figure 1.** Case flow diagram. (**A**) Lung cancer dataset was split into a discovery and a validation set; (**B**) Ovarian, liver and bladder cancer datasets were combined into a single validation dataset after removing redundant samples. Development and validation of the 4-miRNA diagnostic model in the lung cancer data set.  **Figure 3.** Performance of 4-miRNA diagnostic model in the datasets of additional cancers. (**A**) ROC analysis; (**B**) distribution of diagnostic index the 4-miRNA model. The percentages shown in the graph were sensitivities of each cancer type and specificity of non-cancer controls. Different colors denoted different subject conditions. Fig. 2: Performance of 4-miRNA diagnostic model in the datasets of additional cancers. (A) ROC analysis; (B) distribution of diagnostic index the 4-miRNA model. The percentages shown in the graph were sensitivities of each cancer type and specificity of non-cancer controls. Different colors denote different subject conditions
VOCAB: (w/definition)	**ROS:** demonstrates a binary classifiers' performance on various thresholds. True vs false positive rates. **Area Under Curve (AUC):** the 2-D area under a graph calculated to determine the efficiency of a binary classifier. Used as a way to evaluate machine learning algorithms. **Sensitivity**: ability to designate an individual with disease as positive.

	Specificity: ability to designate an individual who does not have a disease as negative
Cited references to follow up on	Lennon, A.M.; Buchanan, A.H.; Kinde, I.; Warren, A.; Honushefsky, A.; Cohain, A.T.; Ledbetter, D.H.; Sanfilippo, F.; Sheridan, K.; Rosica, D.; et al. Feasibility of Blood Testing Combined with PET-CT to Screen for Cancer and Guide Intervention. Science 2020, 369, eabb9601. Nelson, H.D.; Fu, R.; Cantor, A.; Pappas, M.; Daeges, M.; Humphrey, L. Effectiveness of Breast Cancer Screening: Systematic Review and Meta-Analysis to Update the 2009 U.S. Preventive Services Task Force Recommendation. Ann. Intern. Med. 2016, 164, 244–255.
Follow up Questions	What does sensitivity based on methylation region mean? How is it measured? Why did breast cancer not perform well? What does this tell us about the nature of this cancer? How can this model be applied to other types of diseases?

Patent #3: Method to determine the risk of developing breast cancer by detecting the expression levels of microRNA (miRNA)

Source Title	Method to determine the risk of developing breast cancer by detecting the expression levels of microRNA (miRNA)
Source citation (APA Format)	Too, H.-P., Zhou, L., & Zou, R. (n.d.). *Método para determinar el riesgo de desarrollar cáncer de mama mediante detección de los niveles de expresión de microARN (miARN)*. Retrieved December 15, 2023, from https://patents.google.com/patent/ES2882104T3/en?q=(~patent%2fCA3163904A1)
Original URL	https://patents.google.com/patent/ES2882104T3/en?q=(~patent%2fCA3163904A1)
Source type	Google Patent
Keywords	miRNAs, breast cancer, algorithm, detection, prognosis, tissue classification
#Tags	miRNA Machine Learning, Breast Cancer
Summary	This patent designs a method to determine the risk of developing breast cancer or the presence/absence of the cancer by using the expression level of at least 5 miRNAs in body fluid. miRNAs were identified in samples by measuring their up or down regulation, with miR-409-3p being a promising candidate marker.
Summary of key points + notes (include methodology)	Background: - Mammography sensitivity 71% - 96%, specificity of 94 -97% → lower in younger women. False positives are common. Methods: - score based on the expression level of previously measured miRNAs to predict the likelihood that the subject will develop or have breast cancer - hsa-miR-409-3p (SEQ ID NO: 178), hsa-miR -382-5p (SEQ ID NO: 177), hsa-miR-375 (SEQ ID NO: 173), or hsa-miR-23a-3p (SEQ ID NO: 112) is downregulated in the subject, compared to a control. - Classification: C - control (non-cancer (normal) subjects), BC - all breast

cancer subjects, LA - luminal A subtype, HER - Her2 subtype, TN - triple negative subtype.

- RT-qPCR:
  - Isolate and purify miRNA from serum samples
  - Monitor up or down regulated miRNA at various stages: isolation, reverse transcription, augmentation, qPCR
- Subtype classification:
  - Luminal A Breast Cancer & Triple negative → Her2 overexpression & upregulated miRNAs from the table
  - The algorithm is pre trained with the specified list of miRNA and returns the probability of what category the patient miRNA expression may be

Cancer Risk Formula:
cancer risk score — 50' ^ ***K^X*** log_2 *miRNA copy*

log2 miRNAi_copy - log-transformed copy numbers (copies/ml serum) of the 12 individual miRNAs). Ki - coefficients used to weight multiple miRNA targets. Ki values were optimized using the support vector machine method and scaled to range from 0 to 100. Subjects with a cancer risk score of less than 0 will be considered 0 and subjects with a risk score of cancer greater than 100 will be considered 100.

Result: 141 new miRNAs for breast cancer were identified.

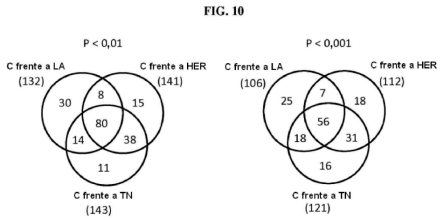
Research Question/Problem/ Need

How can miRNA expression be used to detect the risk of breast cancer?

Important Figures

Publicación	Regulado positivamente	Regulado negativamente	Muestra	Observaciones
Kodahl *et al.*	miR-423-5p, miR-425, miR-15a, miR-142-3p, miR-107, miR-18a	miR-365, miR-133a, miR-143, miR-145, miR-378, miR-139-5p, let-7b	Suero, 108 BC/ 75C	Comenzar con 174 miARN (qPCR), Cáncer de mama ER-positivo
Waters *et al.*	miR-138	-	Suero, 83 BC/83 C	Comenzar con 3 miARN basándose en modelo de murino
Si *et al.*	miR-21	miR-92a	Suero, 100 BC/20 C	Comenzar con 11 miARN,
Mar-Aguilar *et al.*	miR-10b, miR-21, miR-125b, miR-145, miR-155, miR-191, miR-382	-	Suero, 61 BC/10 C	Comenzar con 7 miARN,
Wang *et al.*	miR-182	-	Suero, 46 BC/58 C	Comenzar solo con un miARN,
Kumar *et al.*	miR-21, miR-146a	-	Plasma, 14 BC/8 C	Comenzar con los dos miARN
Chan *et al.*	miR-1, miR-92a, miR-133a, miR-133b	-	Suero, 132 BC/ 101 C	Validar 4 miARN basándose en micromatriz (1300 dianas)
Eichelser *et al.*	miR-34a, miR-93, miR-373	-	Suero, 120 BC/40 C	Comenzar con los 6 miARN
Liu *et al.*	miR-155	miR-205	Suero, 20 BC/10 C	Comenzar con los dos miARN
Sun *et al.*	miR-155	-	Suero, 103 BC/55 C	Comenzar solo con un miARN
Schwarzenbach *et al.*	miR-214	-	Suero, 102 BC/53 C	Comenzar con 4 miARN
van Schooneveld *et al.*	miR-452	miR-215, miR-299-5p, miR-411	Suero, 75 BC/20 C	Validar 4 miARN basándose en matriz de baja densidad (TaqMan)
Guo *et al.*	-	miR-181a	Suero, 152 BC/75 C	Comenzar solo con un miARN
Wu *et al.*	miR-222	-	Suero, 50 BC/50 C	Validar solo un miARN basándose en datos de secuenciación
Hu *et al.*	miR-16, miR-25, miR-222, miR-324-3p	-	Suero, 124 BC/ 124 C	Validar 10 miARN basándose en datos de secuenciación

Table 1:
List of upregulated and down regulated miRNAs.

	 Figure 10: Overlapping miRNAs; need to focus on differentially expressed miRNAs for improved subclassification
VOCAB: (w/definition)	**Differential Expression:** difference in cellular component in healthy versus experimental groups' miRNA **Her2:** human epidermal growth factor 2 → cell growth, mutated in cancer **Pretrained learning:** analyzes experimental data sets and makes predictions based on past sets. **RNA-seq:** RNA sequences data, where miRNAs are a subset of it.
Cited references to follow up on	Wu, H.-H., W.-C. Lin, and K.-W. Tsai, Advances in molecular biomarkers for gastric cancer: miRNAs as emerging novel cancer markers. Expert reviews in molecular medicine, 2014. 16. Kumar, S., et al., Overexpression of circulating miRNA-21 and miRNA-146a in plasma samples of breast cancer patients. Indian J Biochem Biophys, 2013. 50(3): p. 210-4. Cuk, K., et al., Circulating microRNAs in plasma as early detection markers for breast cancer. Int J Cancer, 2013. 132(7): p. 1602-12.
Follow up Questions	What are some limitations of relying on miRNA classification? Past studies have found it challenging to predict breast cancer - how does this invention overcome those challenges?