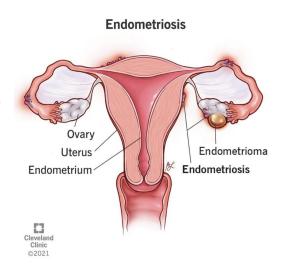
Interpreting Machine Learning Driven Features within Phenotype Groups for the Early Diagnosis of Endometriosis

What is Endometriosis?

- Chronic, autoimmune, inflammatory, estrogen-dependent, enigmatic, gynecological condition
- ★ Endometrium-like tissue growing outside of the lining of the uterus
- ★ Common symptoms: pelvic pain, painful periods, etc.
- ★ Common types of endometriosis
 - Peritoneal endometriosis (outer pelvic side walls)
 - Deep infiltrating endometriosis (inside the organs)
 - Ovarian endometrioma (on the walls of the ovaries)

Bulun SE, Yilmaz BD, Sison C, et al. Endometriosis. Endocrine Reviews. 2019;40(4):1048-1079. doi:https://doi.org/10.1210/er.2018-00242



Why is it considered an enigmatic condition?

- ★ Cause is unknown
 - Hypothesis: retrograde menstruation with endometrial cells
- ★ No 'clinically reliable' biomarkers to track its progression
- ★ No known cure
- ★ Noticeably ignored or misdiagnosed until later
- ★ Heterogeneous
 - Variety of symptoms and severity

Bulun SE, Yilmaz BD, Sison C, et al. Endometriosis. Endocrine Reviews. 2019;40(4):1048-1079. doi:https://doi.org/10.1210/er.2018-00242

9.

Tomassetti C, Johnson NP, Petrozza J, et al. An international terminology for endometriosis, 2021,. *Human Reproduction Open.* 2021;2021(4). doi:https://doi.org/10.1093/hropen/hoab029

How can this be addressed?

Machine Learning

a. Using classification machine learning algorithms to discover new ways to diagnose endometriosis without an invasive procedure

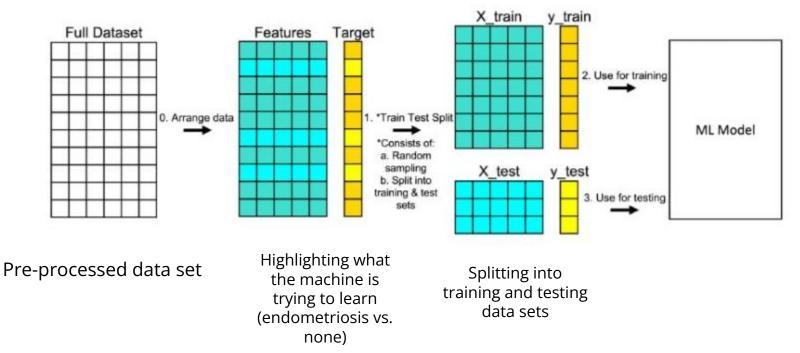
2. Computational Phenotyping

- a. Sorting patients into cohorts (with or without endometriosis) to try and understand the heterogeneity of the condition
 - i. Phenotype = period of time prior to diagnosis

3. Feature Extraction

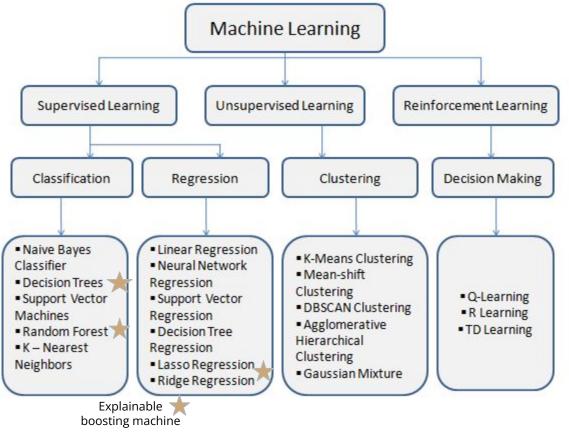
- a. Identifying and extracting relevant features from data within phenotype groups
 - i. Features = indicators of endometriosis

Process of Machine Learning



The objective: using machine learning models to extract key features that impact the phenotypic groups

Types of Machine Learning Models



Rajbanshi S. Machine Learning Algorithms | Introduction to Machine Learning. Analytics Vidhya. Published March 25, 2021. https://www.analyticsvidhya.com/blog/2021/03/everything-you-need-to-know-about-machine-learning/

Choosing the best model: Classification vs. Regression

Classification:

- Mapping function from input to get output
- Discrete class labels
- Data needs to have labels first
- Can have both discrete and real-valued variables

Regression:

- Estimating the mapping function
- Quantitative value
- Prediction based on "features"

Gupta S. Regression vs. Classification in Machine Learning: What's the Difference? Springboard Blog. Published October 6, 2021. https://www.springboard.com/blog/data-science/regression-vs-classification/

Machine Learning Models within this Project

- ★ Logistic Regression
- ★ Random Forest
- **★** XGBoost
- ★ Explainable Boosting Machine

What shows a model's effectiveness: Sensitivity, specificity, precision, negative predictive value, accuracy, ROC curve, etc.

Logistic Regression

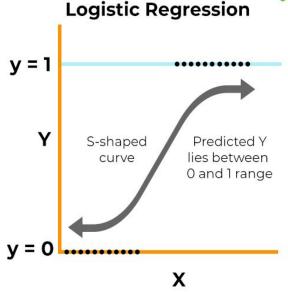
Using predictor variables (features) for binary prediction (endometriosis vs. no endometriosis)

Utilizes maximum likelihood function

Multivariable logistic regression

- Tests to see if the confounding variables' effect on the prediction is significant
- Model coefficient = holds weight to prediction
 - More weight = better predictor

Limitation(s): better for basic relationships



Meysami M, Kumar V, Pugh M, et al. Utilizing logistic regression to compare risk factors in disease modeling with imbalanced data: a case study in vitamin D and cancer incidence. *Frontiers in Oncology*. 2023;13. doi:https://doi.org/10.3389/fonc.2023.1227842

Rout AR. Advantages and Disadvantages of Logistic Regression. GeeksforGeeks. Published January 10, 2023.

 $\underline{https://www.geeks forgeeks.org/advantages-and-disadvantages-of-logistic-regression/}$

15.

Kanade V. What Is Logistic Regression? Equation, Assumptions, Types, and Best Practices. Spiceworks. Published April 18, 2022. https://www.spiceworks.com/tech/artificial-intelligence/articles/what-is-logistic-regression/

Random Forest

Random Forest Simplified Instance Random Forest Tree-1 Tree-2 Tree-n Class-B Majority-Voting Final-Class

Model that maximizes the prediction of multiple decision trees

Factors

- Node size
 - Increasing node size makes simpler trees and tones out irrelevant features
- Number of trees
 - More trees = more accuracy
- Number of features

Bootstrapping and Aggregating

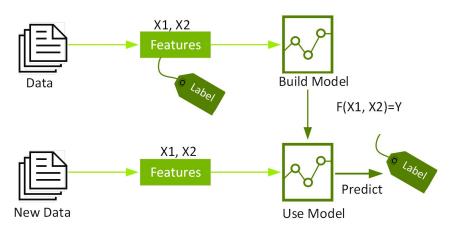
Limitation(s): more predictive trees results in slower run time

What does "node size" refer to in the Random Forest?. Cross Validated. Accessed July 10, 2024.

https://stats.stackexchange.com/questions/158583/what-does-node-size-refer-to-in-the-random-forest
Random Forest Algorithms: A Complete Guide | Built In. builtin.com. https://builtin.com/data-science/random-forest-algorithm#procon
Bootstrap Aggregation, Random Forests and Boosted Trees | QuantStart. Quantstart.com. Published 2013.
https://www.quantstart.com/articles/bootstrap-aggregation-random-forests-and-boosted-trees/

XGBoost

A collection of gradient boosted decision trees



Each tree is improved from the next by using the residual errors from the previous

Lower the loss function of each tree

SHAP values = evaluating the features that promote the prediction

- Greater the value, the better the feature

Better for 'non-linear' data

Limitation(s): prone to overfitting, needs structured data

Nvidia. What is XGBoost? NVIDIA Data Science Glossary. https://www.nvidia.com/en-us/glossary/xgboost/

Explainable Boosting Machine

Glassbox tree-based model best for human interpretation

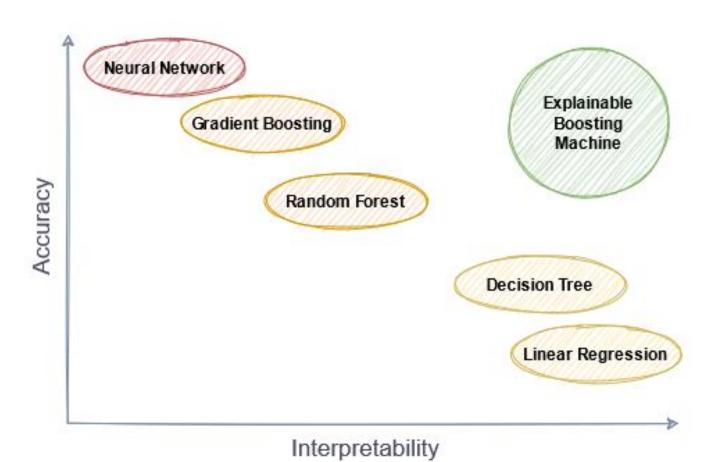
Uses gradient boosting and combines a number of decision trees (similar to XGBoost)

Generates "human-readable" results + provides 'explanations' for the predictions

Tests one feature at a time

Limitation(s): only explains the outer surface, not clear

Explainable Boosting Machine. interpret.ml. https://interpret.ml/docs/ebm.html Kübler DR. The Explainable Boosting Machine. Medium. Published April 13, 2021. https://towardsdatascience.com/the-explainable-boosting-machine-f24152509ebb



How the features are being interpreted

only looking at the top 20 features (features with positive coefficients/SHAP values)

Phenotype groups:

- 1: 3 yrs 2.5 yrs before diagnosis
- 2: 3 yrs 2 yrs before diagnosis
- 3: 3 yrs 1.5 yrs before diagnosis
- 4: 3 yrs 1 yr before diagnosis
- 5: 3 yrs 6 months before diagnosis
- 6: 3 yrs Date of Diagnosis

Types of Features:

- Evident Features
- Prominent Features
- Progressive Features
- Eccentric Features
- Outliers

Prominent Features

Features that go directly with known symptoms/ideologies of endometriosis or point strongly to a diagnosis of endometriosis

all found in the later groups; closer to the date of diagnosis

- ★ Female Infertility
- ★ Single Live Birth
- ★ Pelvic Pain
- ★ Heart Rate/Diastolic Blood Pressure under anesthesia
- ★ Ultrasonography for fetal biophysical profile
- **★** Ultrasound
- ★ Cervical cytology

Evident Features

Features that have a direct impact on endometriosis diagnosis

found in the vast majority of the groups

- ★ Mean Platelet Volume
- ★ Carbon/Oxygen in Blood
- ★ Glomerular Filtration Rate
- ★ Glucose in Blood/Serum/Urine
- ★ Hemoglobin
- **★** Globulin
- ★ DNA Bacteria found by probe detection

Mean Platelet Volume

Leading feature - found in groups L1 - L5, X1, X3, X4

Measurement of the average size of blood platelets

Higher MPV = faster platelet activation = inflammation

Can be used as an 'inexpensive' biomarker

Lale Bakir V, Dundar O, Bodur S, et al. Mean platelet volume as an inexpensive bio-marker of endometriosis. Int J Clin Exp Med. 2016;9(6):9431-9436. Accessed July 10, 2024. https://e-century.us/files/ijcem/9/6/ijcem0011915.pdf

Glucose in Serum/Urine/Blood

Serum - L1, X1 Urine - L3, X3 Blood - L5

- Endo patients often have lower glucose levels and higher insulin levels
 - Lower levels of glucose = risk of inflammation

Women with endometriosis are at risk for type 1 diabetes (autoimmune)

Chen JP, Zhang YY, Jin JN, et al. Effects of dysregulated glucose metabolism on the occurrence and ART outcome of endometriosis. *European Journal of Medical Research*. 2023;28(1):305. doi:https://doi.org/10.1186/s40001-023-01280-7 Duffin J, read W min. How Dysregulated Blood Sugar Can Worsen Endo Symptoms. Endometriosis.net. Published March 9AD.

Accessed July 10, 2024. https://endometriosis.net/living/diet-sugar

Xin Q, Li HJ, Chen HK, Zhu XF, Yu L. Causal effects of glycemic traits and endometriosis: a bidirectional and multivariate mendelian randomization study. *Diabetology & metabolic syndrome*. 2024;16(1). doi:https://doi.org/10.1186/s13098-024-01311-1

Carbon Dioxide/Oxygen in Blood

Carbon Dioxide - L1, L3, X1

- higher level indicates a higher hydrogen concentration (L1, x1)
 - Symptom: pH of arterial cord blood (L1, X1)

Oxygen -L2, L4, X2, X4

- insufficient amount = hypoxia
 - Endometrial cells under hypoxic stress outside uterus

Oxidative Stress

- Indicator of endometriosis
- Causes abnormally high SvO2 (measure of oxygen) L2, X2
- can lead to an increase of pH

Donnez J, Mercedes M, Donnez O, Dolmans MM. Oxidative stress in the pelvic cavity and its role in the pathogenesis of endometriosis. ScienceDirect. Published October 2016. https://www.sciencedirect.com/science/article/pii/S0015028216625050#:~:text=Endometriosis%20is%20a%20disorder%20associated,known%20to%20have%20deleterious%20effect Wu M, Hsiao K, Tsai S. Hypoxia: The force of endometriosis. *Journal of obstetrics and gynaecology research*. 2019;45(3):532-541. doi:https://doi.org/10.1111/jog.13900 Garcia AJ, Ramirez JM. Keeping carbon dioxide in check. *eLife*. 2017;6(e27563). doi:https://doi.org/10.7554/eLife.27563
Hu L, Li Y, Preliminary study on the effects of carbon dioxide and nitrogen pneumoperitoneums on endometriotic lesions. *Archives of Gynecology and Obstetrics*. 2012;286(2)

Hu L, Li L, Li Y. Preliminary study on the effects of carbon dioxide and nitrogen pneumoperitoneums on endometriotic lesions. *Archives of Gynecology and Obstetrics*. 2012;286 doi:https://doi.org/10.1007/s00404-011-2206-1

https://www.sciencedirect.com/science/article/pii/S2352513421002064

Glomerular Filtration Rate

Was at first positive in the first groups but then switched to negative as more time progressed (L1, L2, X1,)

Blood test that estimates how well the kidneys are filtering (per minute)

Glomerular Filtration Rate < 60 mL/min per 1.73 m² = chronic kidney disease

- Lower risk for women with endometriosis
 - Can be used to determine if the kidneys can be preserved during surgery for ureteral endometriosis

Ureteral endometriosis can result in loss of renal function = obstructed GFR

- Can result in high levels of urea nitrogen in serum/blood - L1, X1

Martínez-Zamora MA, Mensión E, Martínez-Egea J, et al. Risk factors for irreversible unilateral loss of renal function in patients with deep endometriosis. Scientific Reports. 2023;13(1):11940. doi: https://doi.org/10.1038/s41598-023-38728-z

Huang BS, Chang WH, Wang KC, et al. Endometriosis Might Be Inversely Associated with Developing Chronic Kidney Disease: A Population-Based Cohort Study in Taiwan. *International Journal of Molecular Sciences*. 2016;17(7):1079. doi:https://doi.org/10.3390/ijms17071079

Hemoglobin/Hematocrit

Hemoglobin - protein in blood that carries oxygen to cells - L4, X1

Hematocrit - percentage of red blood cells to total volume of blood - L4, L6

Blood markers are being used to help track the progression of endometriosis

- Examples of RBC indices = hemoglobin, hematocrit blood test, mean corpuscular volume, neutrophil-to-lymphocyte ratio, etc.
- Lower levels of RBC indices = more severe endometriosis (after laparoscopy)

Excessive hemoglobin = promotes oxidative stress and inflammation

Cho HY, Park ST, Park SH. Red blood cell indices as an effective marker for the existence and severity of endometriosis (STROBE). Medicine. 2022;101(42):e31157. doi: https://doi.org/10.1097/MD.000000000000001157 Value of endometriosis. ScienceDirect. Published September 14, 2001. https://www.sciencedirect.com/science/article/bii/S0015028201032113#:::tex!=Result(s):%20Pliother%20levels.hemoglobin

Nisenblat V, Bossuyt PM, Shaikh R, et al. Blood biomarkers for the non-invasive diagnosis of endometriosis. *Cochrane Database of Systematic Reviews*. 2016;(5). doi:https://doi.org/10.1002/14651858.cd012179

Obeagu EI, Igwe MC, Obeagu GU. Oxidative stress's impact on red blood cells: Unveiling implications for health and disease. *Medicine*. 2024;103(9):e37360. doi:https://doi.org/10.1097/MD.000000000037360

Bacterial pathogens found by Probe Detection

can be linked to inflammation

- ★ Streptococcus agalactiae L2, X3, X4
 - Found more in women with endometriosis
- Neisseria gonorrhoeae L4
 - Interact with endometrial cells
 - Can cause pelvic inflammatory disease (linked to endometriosis)

Moreno I, Cicinelli E, Garcia-Grau I, et al. The diagnosis of chronic endometritis in infertile asymptomatic women: a comparative study of histology, microbial cultures, hysteroscopy, and molecular microbiology. *American Journal of Obstetrics and Gynecology*. 2018;218(6):602.e1-602.e16. doi:https://doi.org/10.1016/j.ajog.2018.02.012

Christodoulides M, Everson JS, Liu BL, et al. Interaction of primary human endometrial cells with Neisseria gonorrhoeae expressing green fluorescent protein. *Molecular Microbiology*. 2000;35(1):32-43. doi:https://doi.org/10.1046/j.1365-2958.2000.01694.x

Progressive Features

Features that show an evident change as the date of diagnosis got closer

- ★ features regarding medications and pain remedies grow in strength
 - Group 1 + 2: multivitamins, witch hazel pads vs. Group 5 + 6: benzocaine, lidocaine hydrochloride injection
- ★ more features regarding emotion/mental besides physical are added
 - Group 1: General examination vs. Group 5: Little interest or pleasure in doing things in the past 2 weeks
 - More severe endometriosis = worse quality of life

25.Moradi M, Parker M, Sneddon A, Lopez V, Ellwood D. Impact of endometriosis on women's lives: a qualitative study. *BMC Women's Health*. 2014;14(1). doi:https://doi.org/10.1186/1472-6874-14-123

Eccentric Features

Features that seem irrelevant but still might have an effect on endometriosis diagnosis

- ★ Body height L1, L6, X1
 - taller women are at greater risk for endometriosis
- ★ Gestational age L5, X2, X4, X5
 - Women with endometriosis are more likely to have premature births
- **★** Viruses
 - Influenza endometriosis showing flu- like symptoms (L1, L2, X1)
 - Human papillomavirus higher risk within women with endometriosis (L6, X5)
 - Cytomegalovirus can infect endometrial cells
- ★ Women with endometriosis are more likely to be Rh-negative L6, X3, X6
 - can lead to problems during pregnancy

Farland LV, Missmer SA, Bijon A, et al. Associations among body size across the life course, adult height and endometriosis. *Human Reproduction*. 2017;32(8):1732-1742. doi:https://doi.org/10.1093/humrep/dex207

Breintoft K, Arendt LH, Uldbjerg N, Glavind MT, Forman A, Henriksen TB. Endometriosis and preterm birth: A Danish cohort study. *Acta Obstetricia et Gynecologica Scandinavica*. 2022;101(4):417-423. doi:https://doi.org/10.1111/aogs.14336

Rees A. Endometriosis: how the condition may be linked to the immune system. The Conversation.

https://theconversation.com/endometriosis-how-the-condition-may-be-linked-to-the-immune-system-203305. Published April 15, 2023.

Moslehi Z, Derakhshan R, Chaichian S, Mehdizadeh Kashi A, Sabet B, Rokhgireh S. Correlation of High-Risk Human Papilloma Virus with Deep Endometriosis: A Cross-Sectional Study. Silvestre S, ed. *BioMed Research International*. 2023;2023:1-6. doi:https://doi.org/10.1155/2023/6793898

Outliers

Measles

- Higher risk for women with endometrial cancer

Hepatitis B

- Can lead to endometrial carcinoma

Bordetella parapertussis

- No correlation with any gynecological issues/symptoms

Benharroch D, Kalinkovichi, Piura B, Shaco-Levy R, Gopas J. Evidence of measles virus antigens and RNA in endometrial cancer. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*. 2009;147(2):206-209. doi:https://doi.org/10.1016/j.ejogrb.2009.08.008

Jiang XF, Tang QL, Zou Y, et al. Does HBV Infection Increase Risk of Endometrial Carcinoma? *Asian Pacific Journal of Cancer Prevention*. 2014;15(2):713-716. doi:https://doi.org/10.7314/apjcp.2014.15.2.713

Thinking Bigger Picture...

- ★ Main categories: blood, kidney function, hormone production
- ★ The body reactiving out of a state trying to remain in homeostasis
 - Features that seem to contradict each other, but all could lead to endometriosis
- ★ Endometriosis and other conditions (i.e. STIs) showing symptoms in a similar manner

Questions to explore further

- Why are features more prominent in one model than the other?
- If one model deems a factor as positive and the other deems it as negative, which one do we go with?
- If a feature goes from positive to negative, how do we attest it?
- Are there more prominent features that the models are not picking up on?

Conclusion

- ★ Endometriosis is an enigmatic, gynecological, condition.
 - Machine learning is paving the way for inexpensive and noninvasive ways of diagnosis
- ★ ML models, such as Logistic Regression and XGBoost, are being used to extract phenotypic features to better the understanding of endometriosis
- ★ Majority of the features can be organized into these categories: Prominent, Evident, Progressive, Eccentric, and Outliers