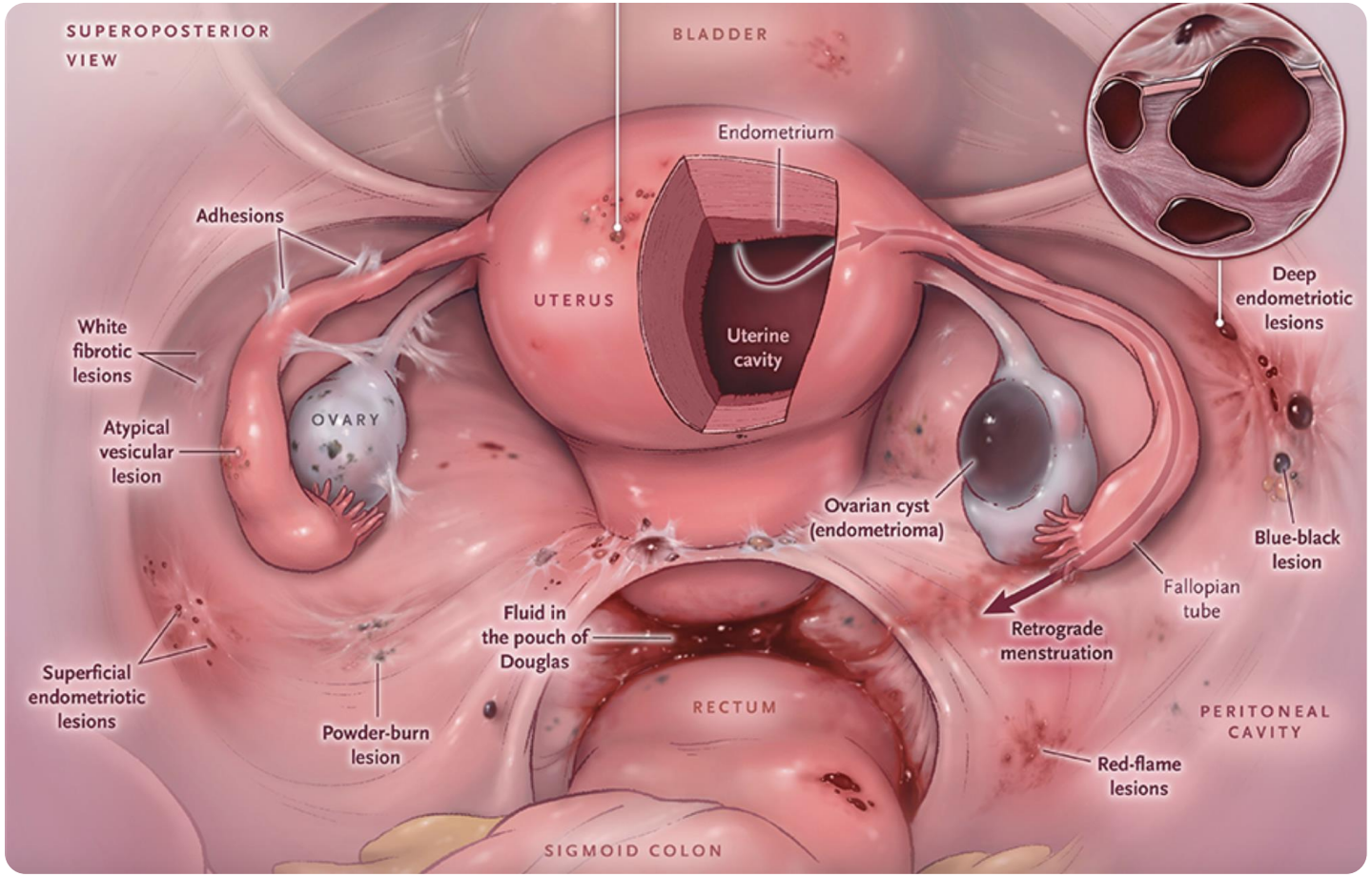
Zelia Soo, PhD candidate (University of Technology Sydney)

Identification of Endometriosis Gene-lists: An Example of Revolutionising Women's Health using Genomics and AI

Women's Health

Endometriosis

- Affects 10% of female population [1]
- Presence of endometrium-like tissue outside the uterus
- Complex symptomatic, pathobiological, and multisystemic disorder [2]
- Affects physical, mental, sexual, social well-being, and productivity
- $9.6B AUD cost of illness burden [3]
- Surgical visualisation diagnosis - laparoscopy

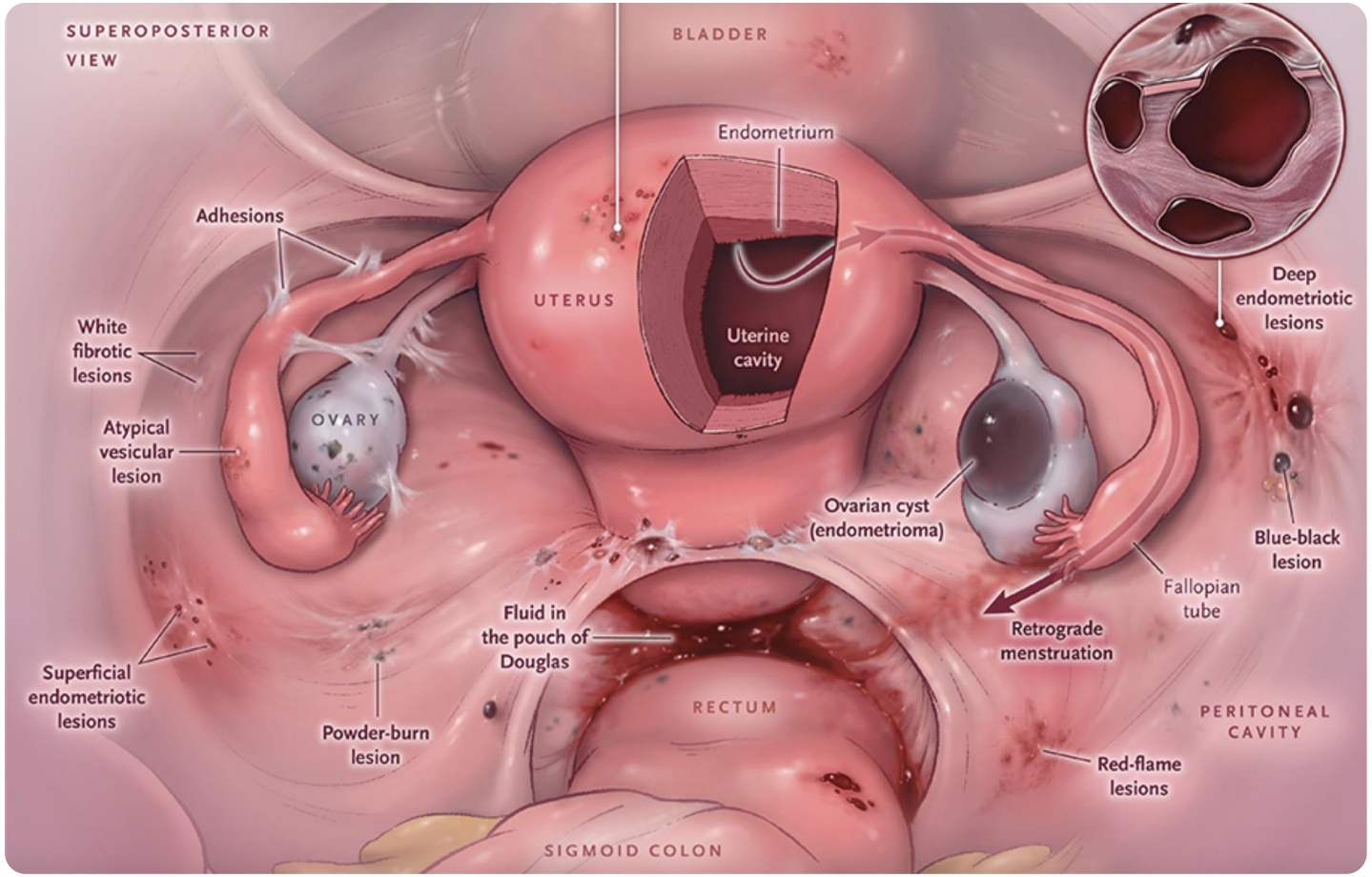


1: WHO. (2023)
2: Zondervan, K. (2020).
3:Armour M. (2022)

Women's Health

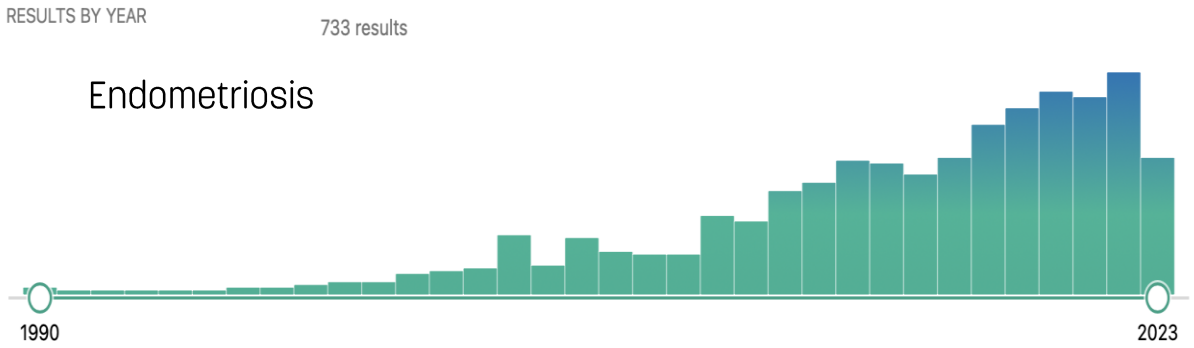
Endometriosis

- Significant knowledge gaps
- Endometriosis is known to consist of migration, implantation, growth, and invasion of endometrial tissue
- 2.2% disease variance linked to genetic causes via Genome-Wide Association Studies
- Estimated 26% common genetic variants cause of endometriosis [2]



2: Zondervan, K. (2020).

Research and Clinical Gap



Endometriosis HP:0030127

The growth of endometrial tissue outside the uterus.

Synonyms: *No synonyms found for this term.*

Comment: The main manifestations of endometriosis are chronic upper abdominal pain and infertility. Endometriosis occurs primarily on the pelvic peritoneum, ovaries, and rectovaginal septum, and in rare cases on the diaphragm, pleura, and pericardium. Endometriosis affects 6 to 10% of women of reproductive age, 50 to 60% of women and teenage girls with pelvic pain, and up to 50% of women with infertility. Peritoneal disease, which is dependent on estrogen for growth, derives from retrograde menstruation of steroid hormone sensitive endometrial cells and tissues, which implant on peritoneal surfaces and elicit an inflammatory response. This response is accompanied by angiogenesis, adhesions, fibrosis, scarring, neuronal infiltration, and anatomical distortion resulting in pain and infertility.

Pubmed References: *PMID:25221341*

Cross References: *MSH:D004715, SNOMEDCT_US:129103003, SNOMEDCT_US:396224008, UMLS:C0014175*

Export Associations

Disease Associations | **Gene Associations**

Gene Symbol	Associated Diseases
THOC6 [79228]	(ORPHA:363444) - THOC6-related developmental delay-mi... (OMIM:613680) - Beaulieu-Boycott-Innes syndrome

Displaying 1 out of 1.

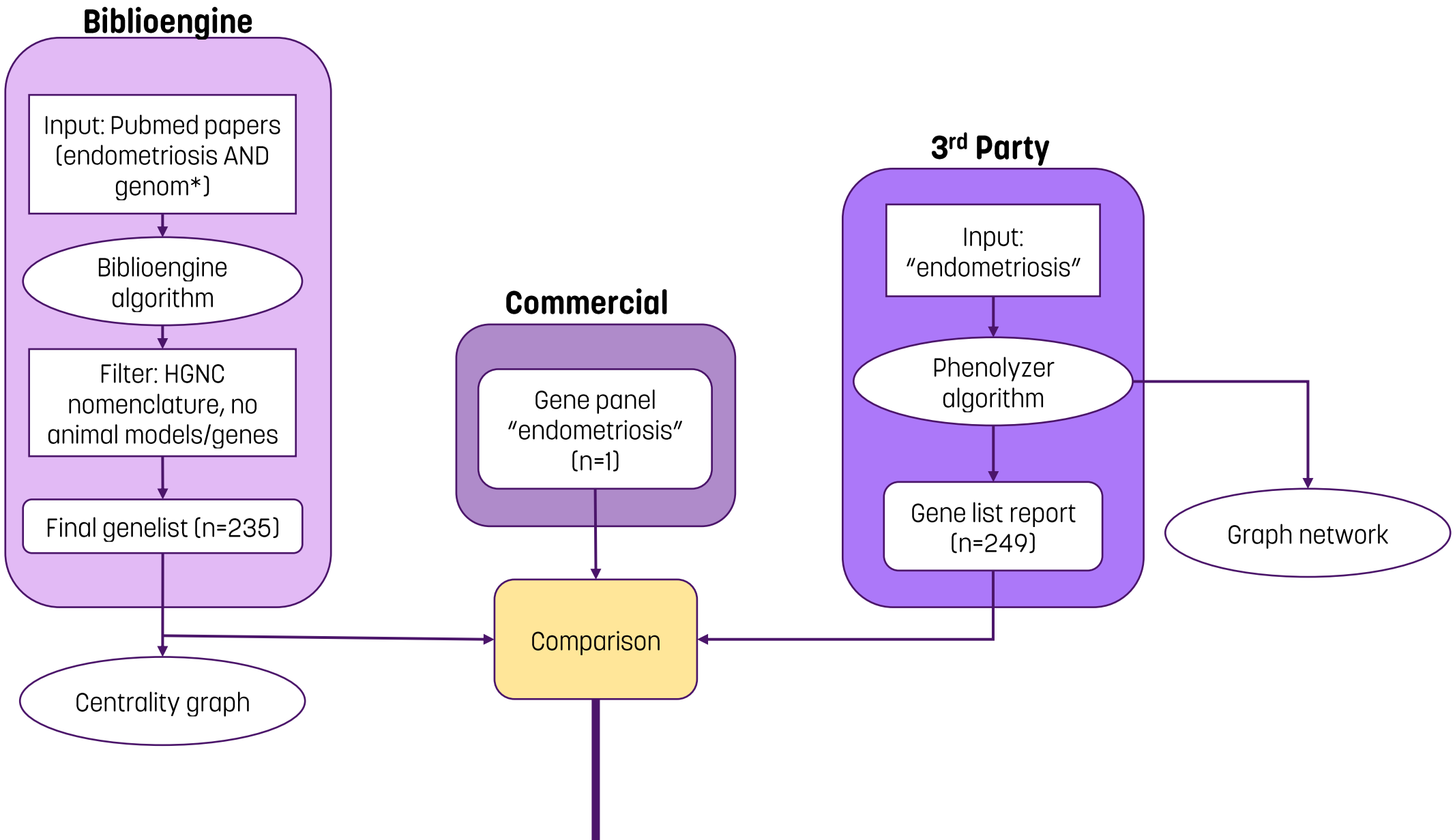
Aims

1. To run and compare the output of three gene-disease association algorithms focusing on endometriosis: an evidence-based artificial intelligence approach, a commercial gene panel maker, and a prior phenotype approach

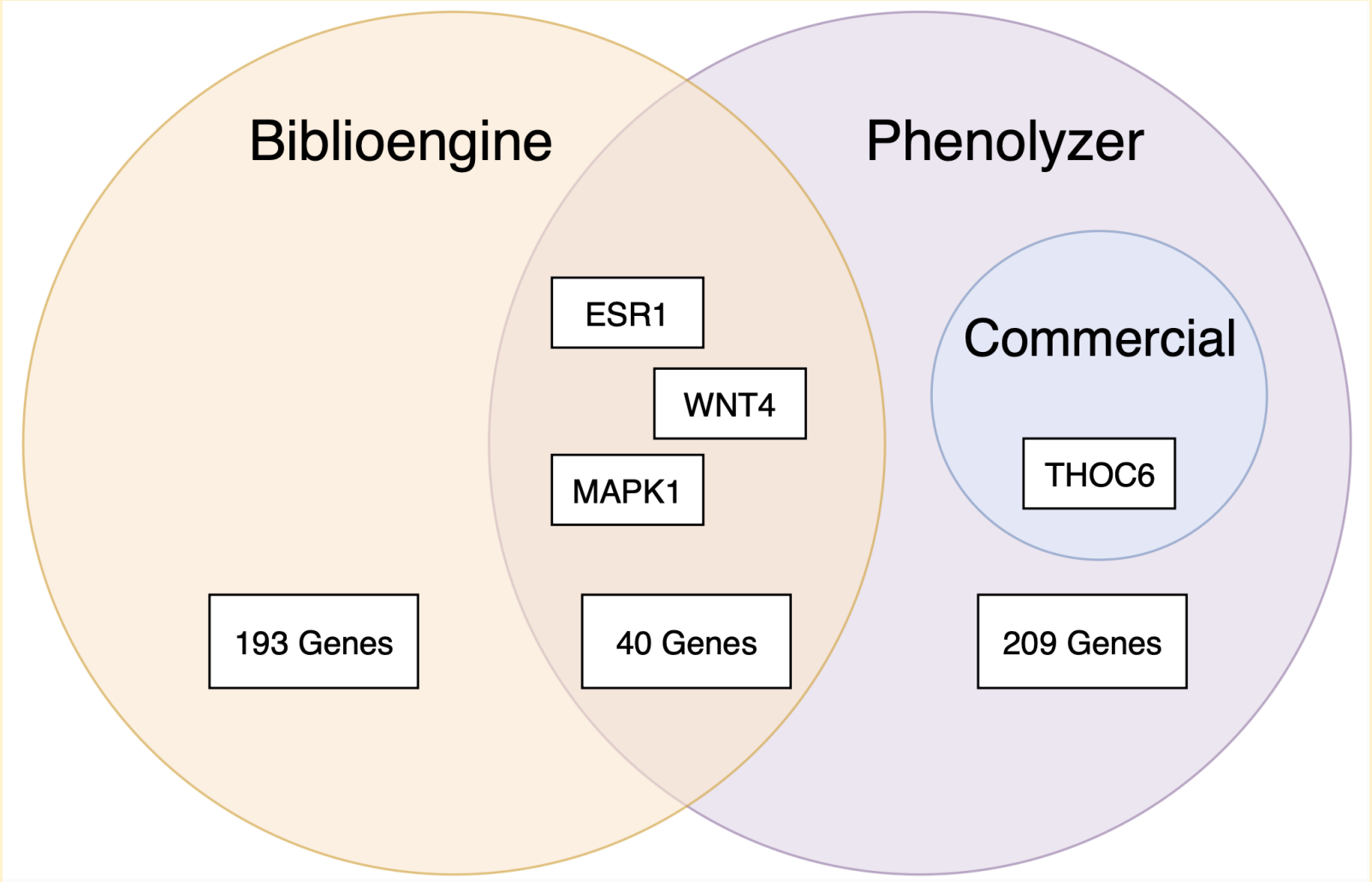
2. To help interpret whole human genome data and understand relevant molecular pathways

3. To outline a framework that could be used to understand other underrepresented diseases

Methodology



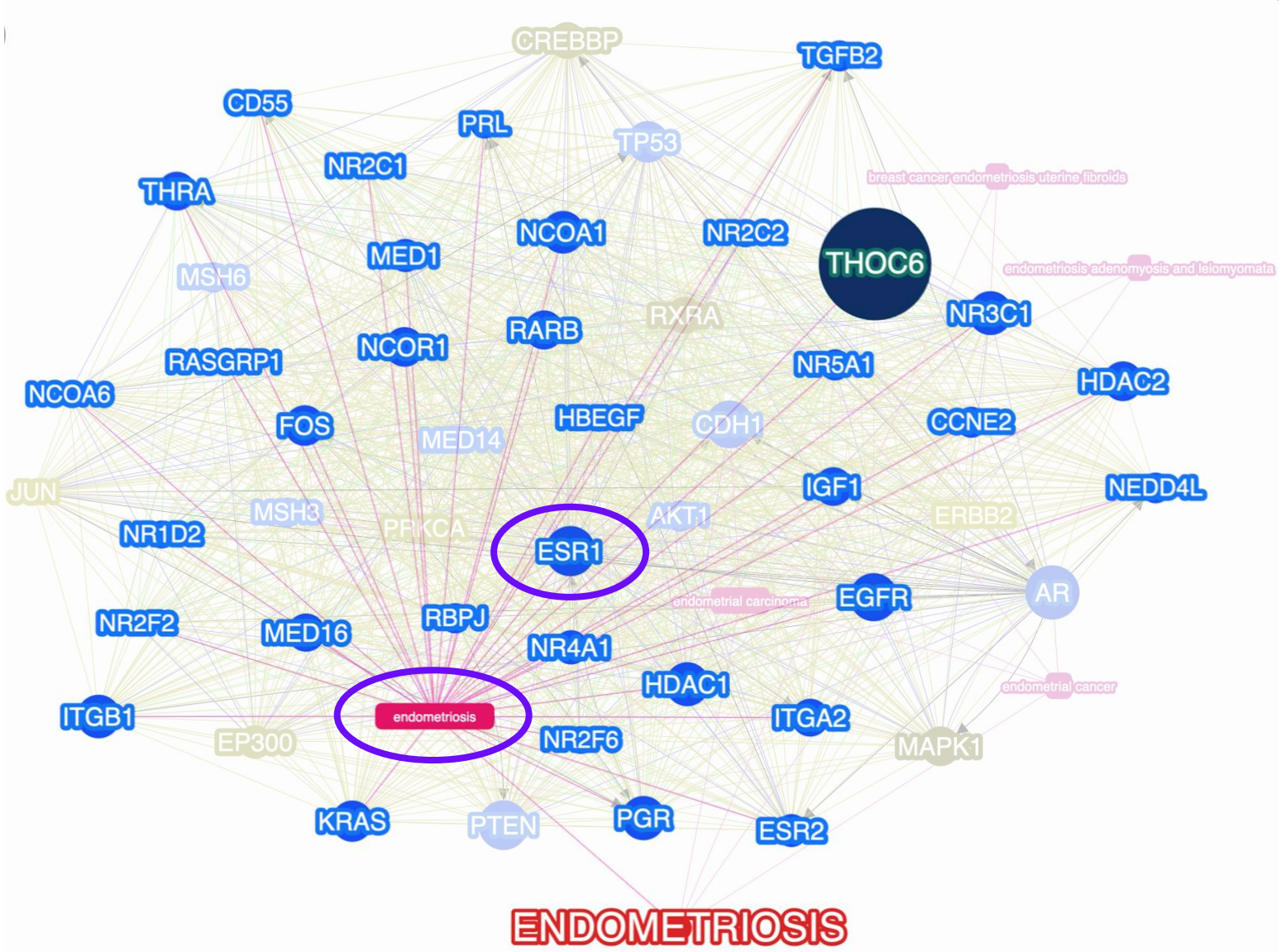
Results: Comparison



3rd Party

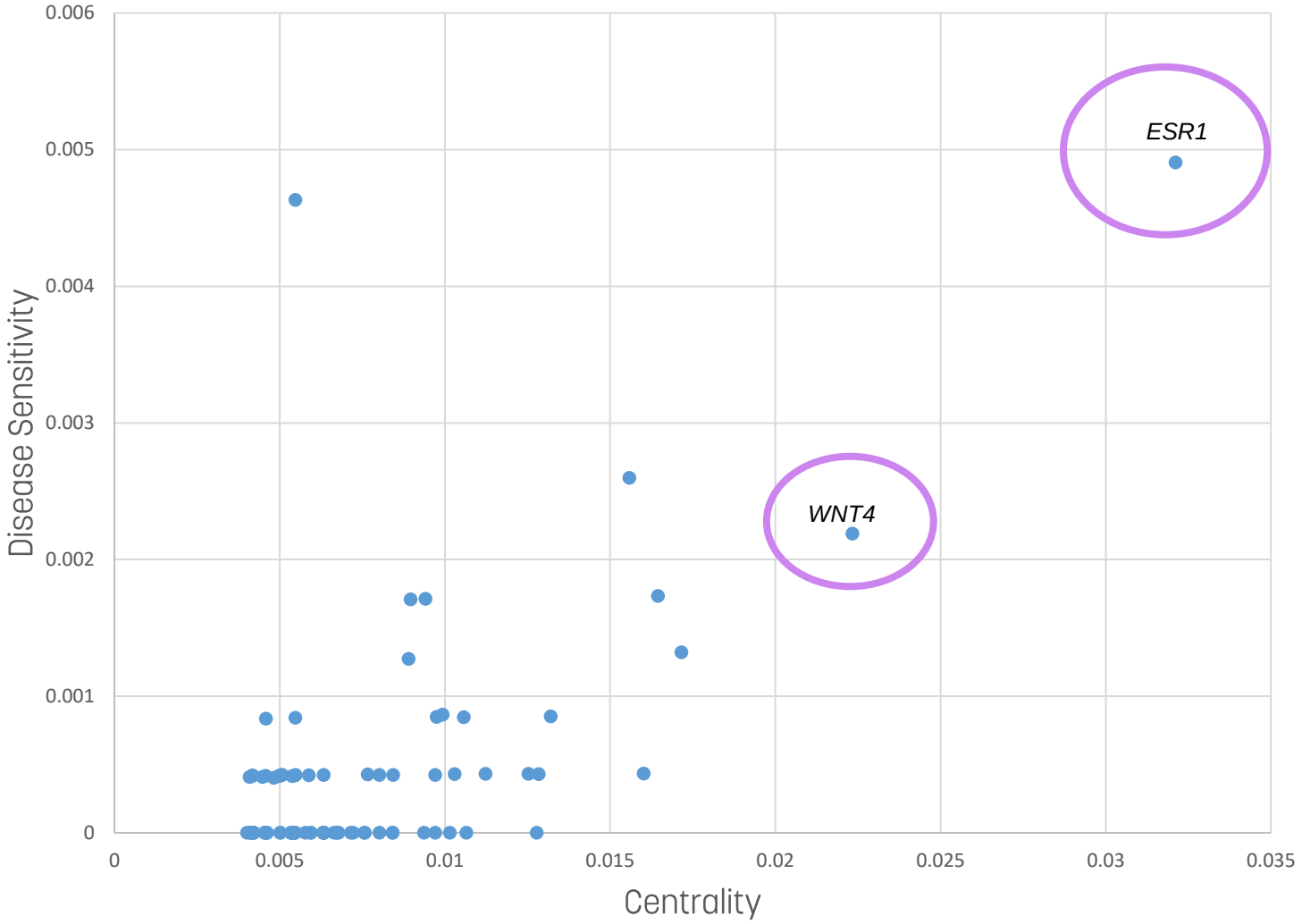
Graph Network

- 245 genes picked up relating to “Endometriosis”
- Top 50 genes depicted in graph network
  - Pink represents phenotypes based on search
  - Blue gene names are genes directly associated with phenotype
  - Khaki gene names are predicted genes



Yang H. et al. (2015).

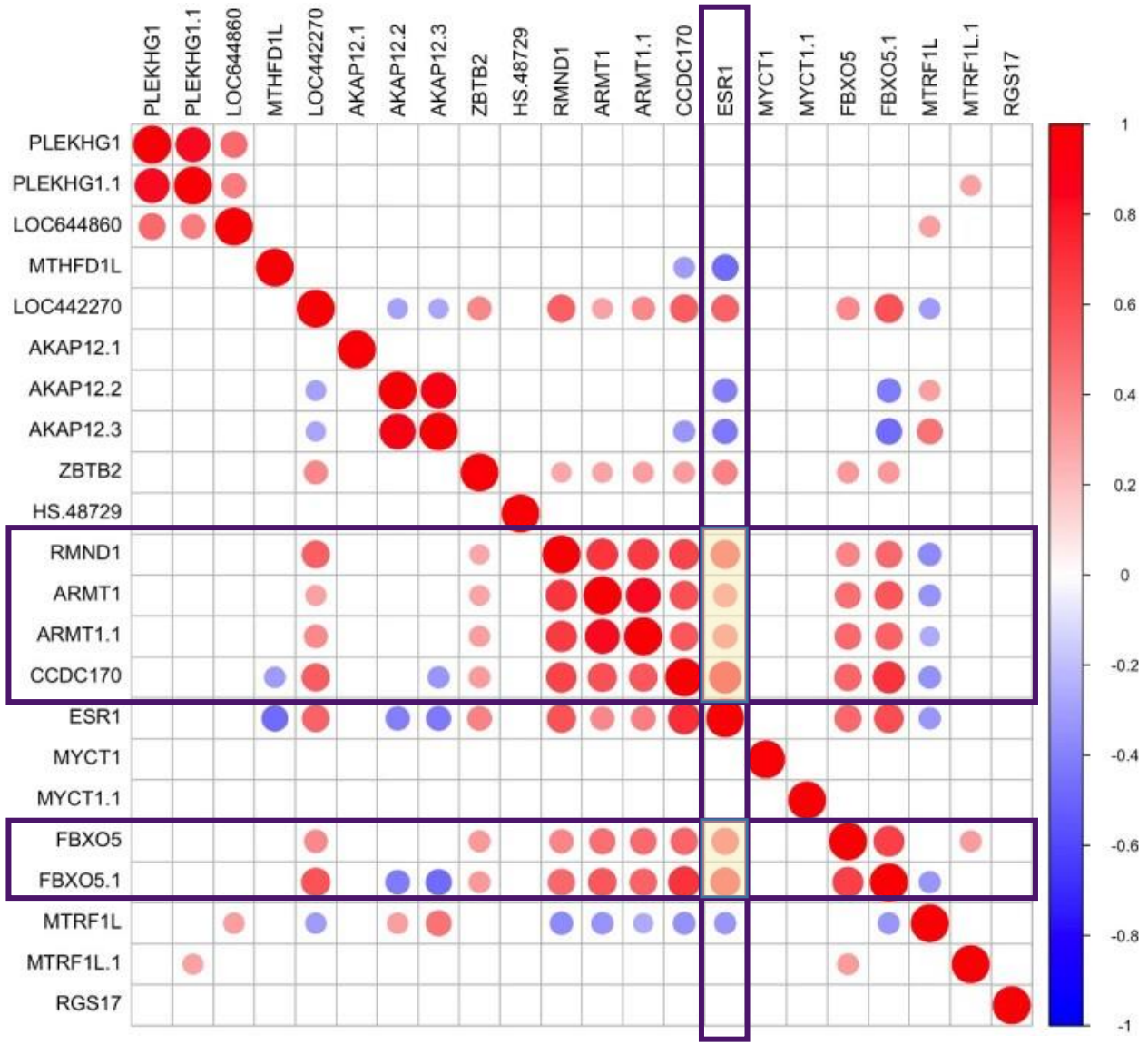
Biblioengine algorithm: Centrality graph



Results

ESR1

- Oestrogen receptor 1
- Oestrogen (E2) binds to ESR1 directly
- ESR1 and surrounding regions strongly associated with endometriosis
- RMND1, ARMT1, CCDC170 upstream, FBXO5 downstream positively correlated, suggesting coregulation
- Coregulated genes also impact ESR1 expression and can further exacerbate exhibited phenotype

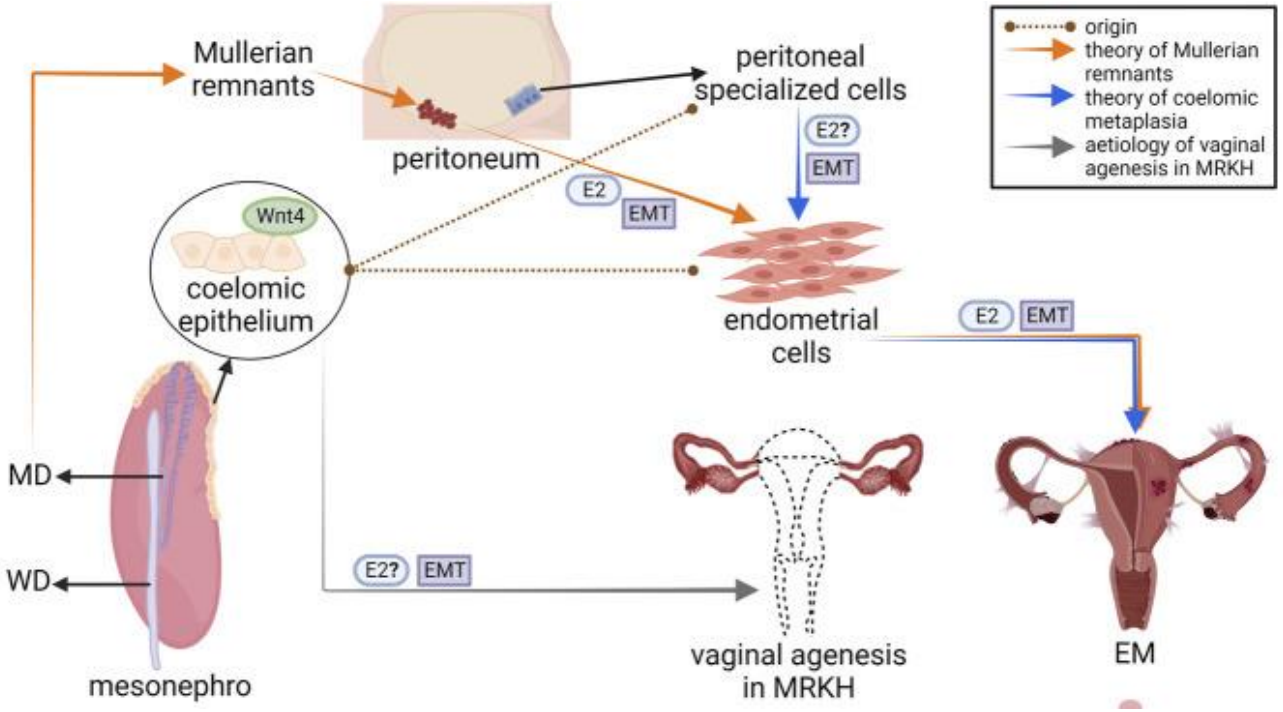


Marla S. (2021)

Results

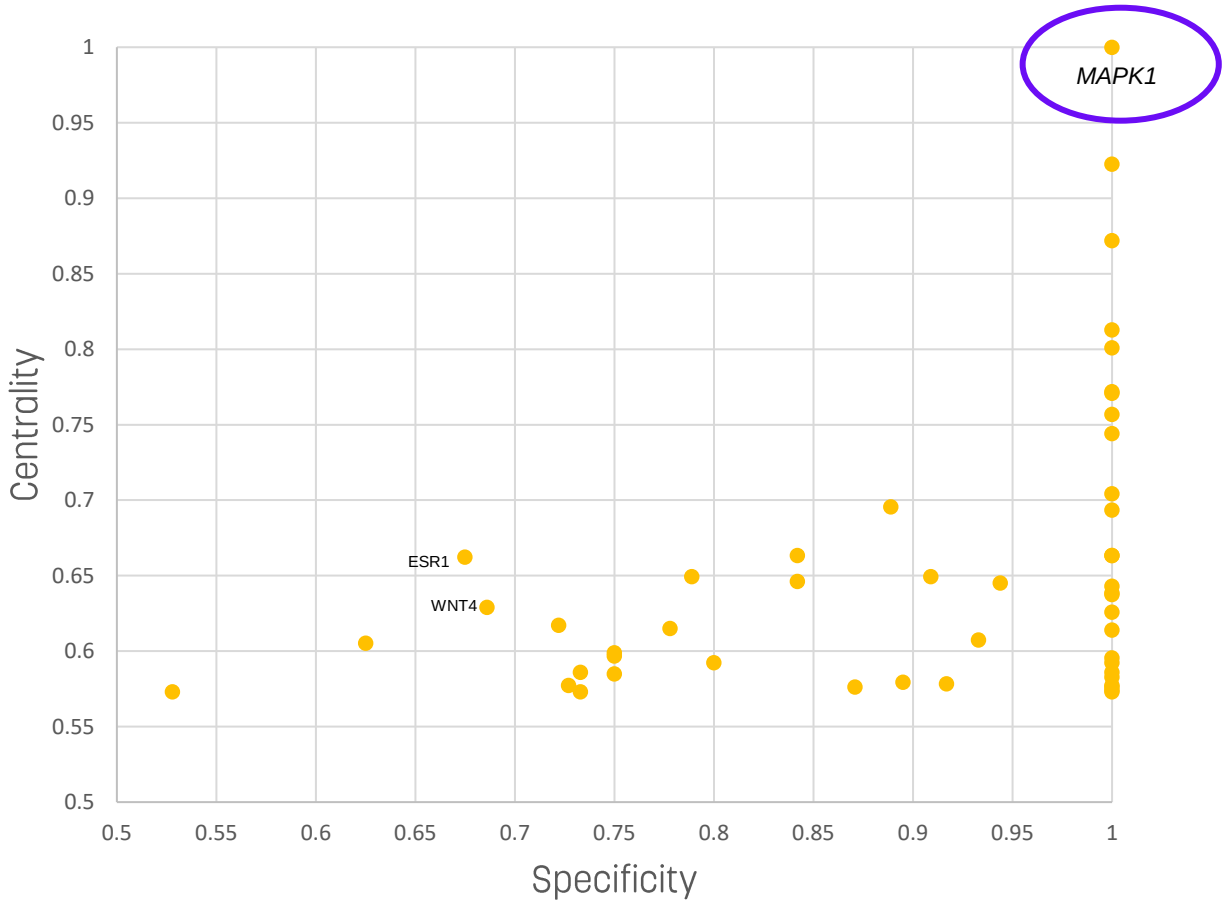
WNT4

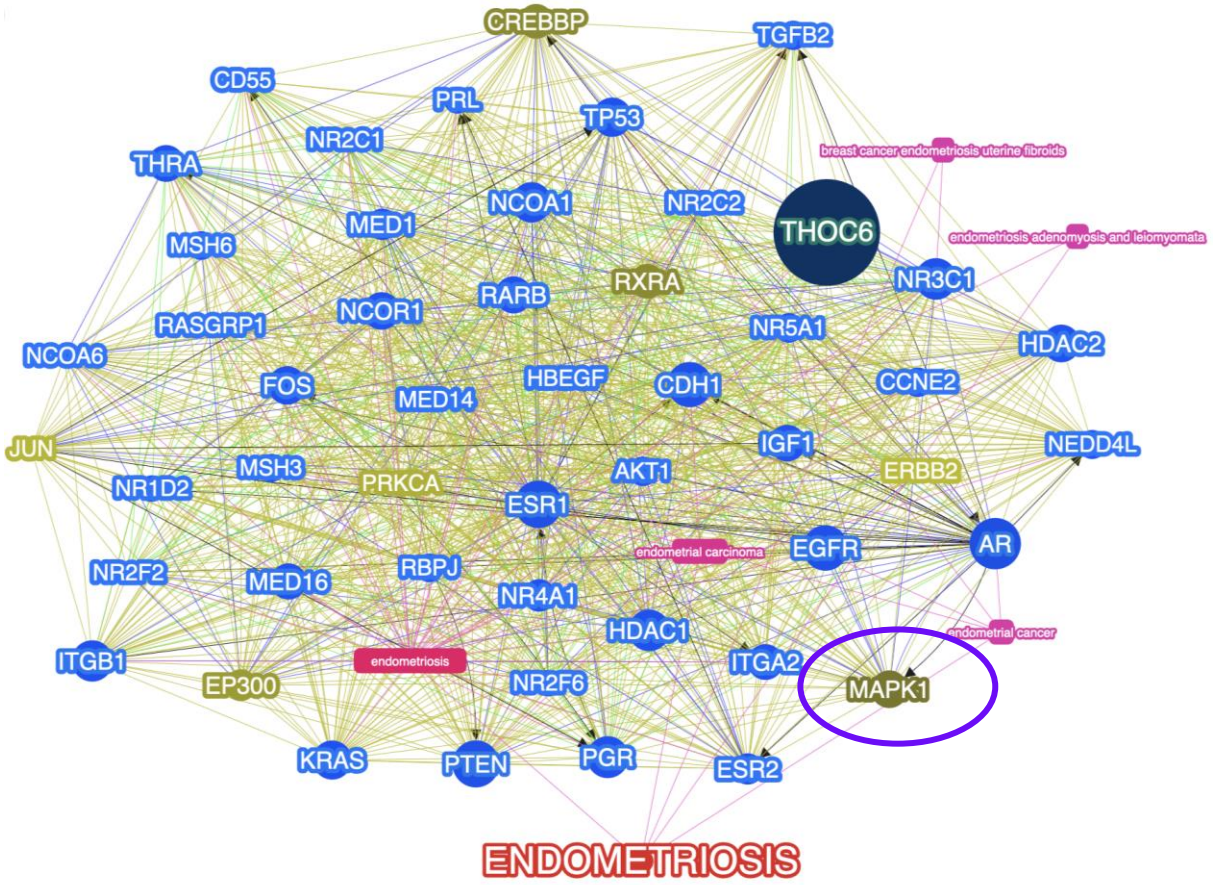
- Part of Wnt signalling family
- Promotes female sexual development
- Interactions with oestrogen inducing epithelial-mesenchymal transition (EMT)
- Correlation between EMT and development of endometriosis
- Wnt pathway may cause migration and multiple sites of lesions



Lih Yuan, T. (2022)

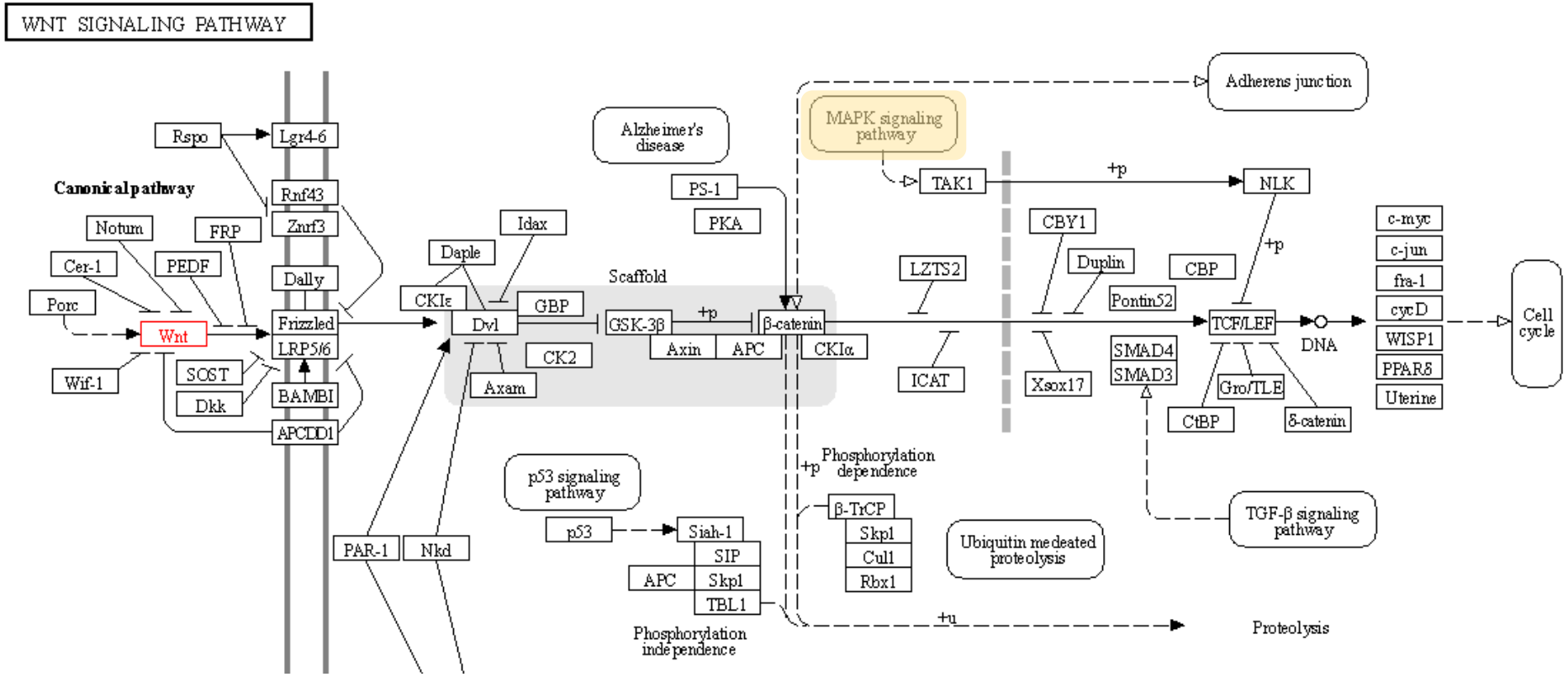
MAPK1 identified as a predicted endometriosis gene





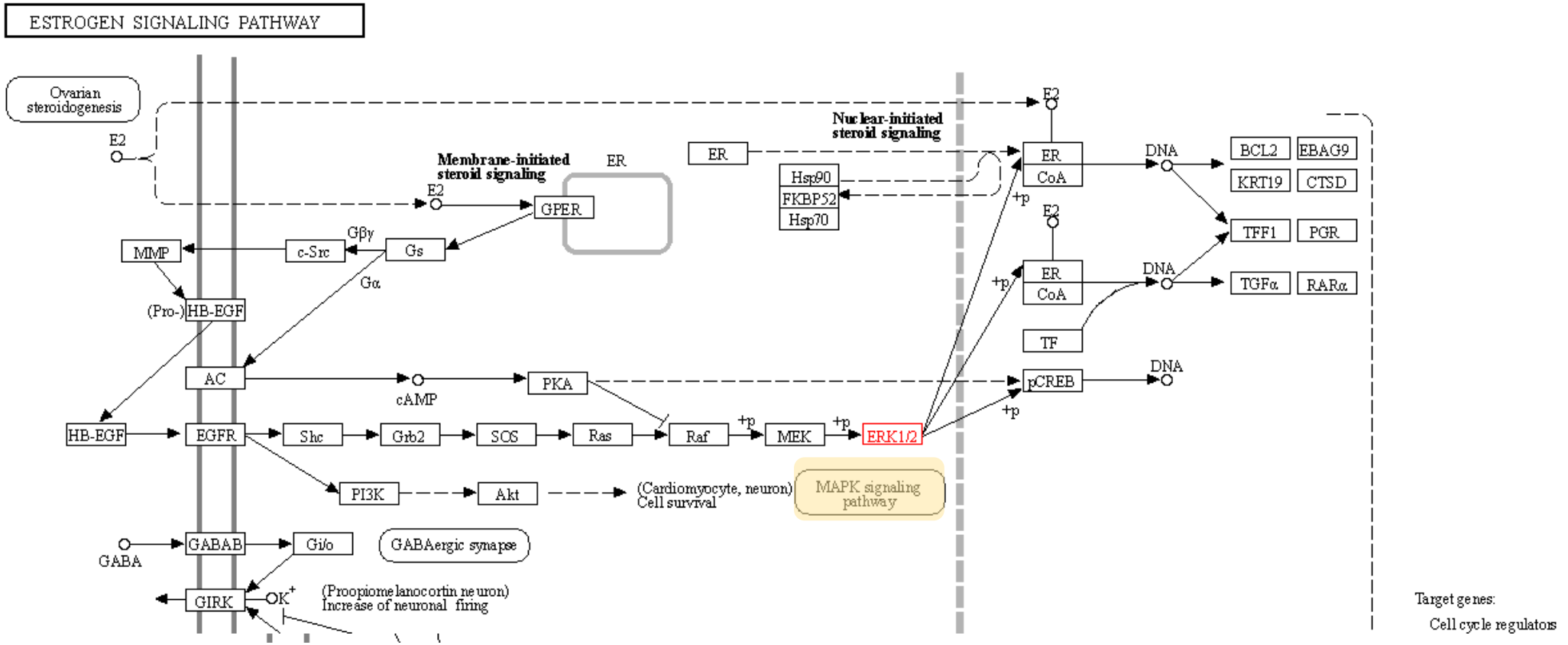
Results: *MAPK1*

- Mitogen-activated protein kinase 1
- MAPK pathway involved in cell survival mechanisms and apoptosis
- Mutations linked to lung and hepatocellular carcinomas
- Oestrogen stimulates Wnt signalling pathway leading to downstream effectors including MAPK1



Results: *MAPK1*

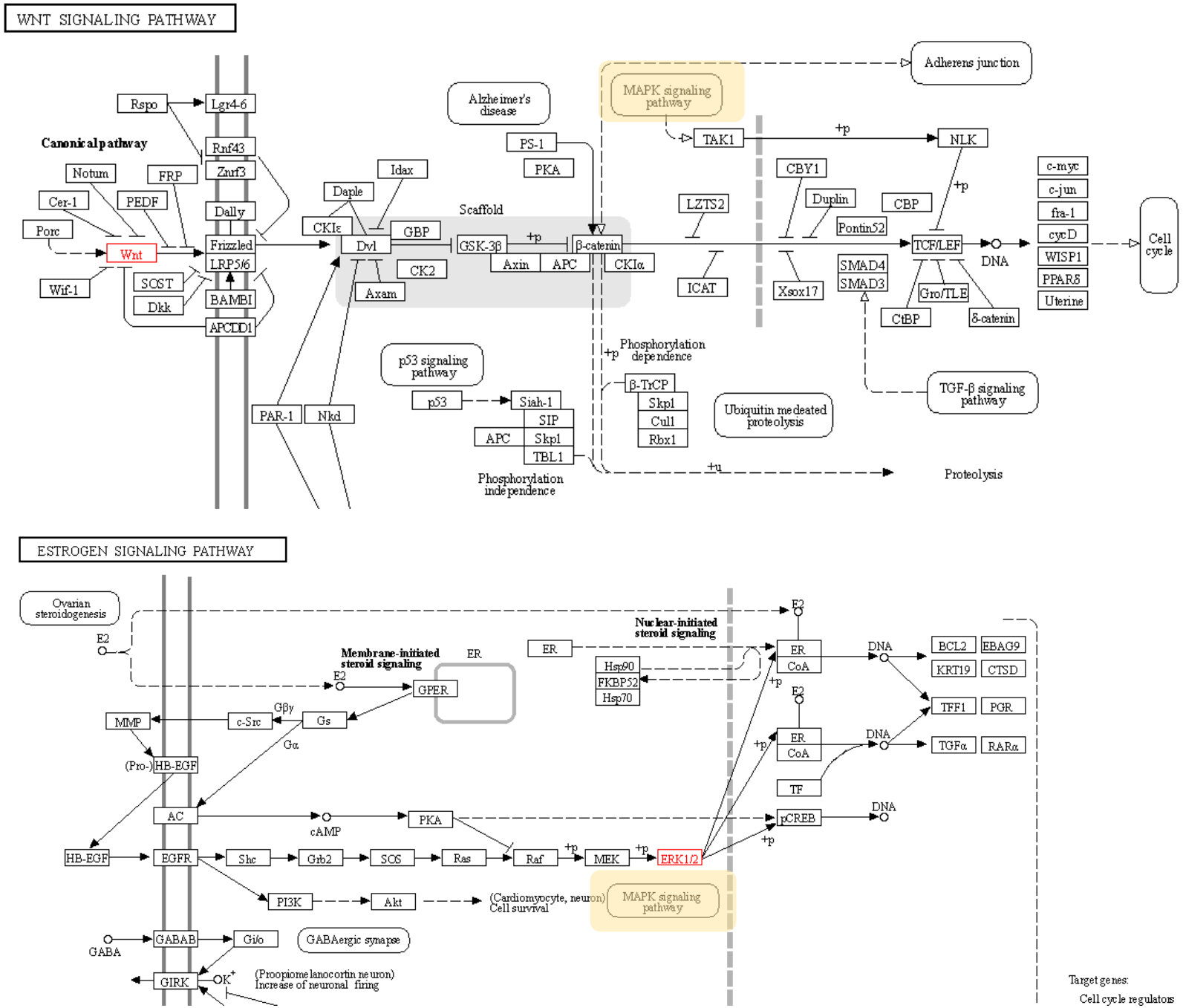
- Mitogen-activated protein kinase 1
- MAPK pathway involved in cell survival mechanisms and apoptosis
- Mutations linked to lung and hepatocellular carcinomas
- Oestrogen binding to ESR1 has downstream effect on MAPK pathway



Results

MAPK1

- Wnt and oestrogen signalling pathway associated with MAPK signalling pathway
- MAPK pathway directly affects endometriosis pathophysiology
- *MAPK1* expression increases in as severity of endometriosis increase
- *MAPK1* inhibitors – anti-inflammatory, anti-proliferative



Antonio LGL, (2023).

Conclusion

- 40 overlapping genes including *ESR1, WNT4, MAPK1* – key genes involved in endometriosis
- Potential to provide novel insight to endometriosis pathogenesis – further research and treatment
- AI Methodology easily adapted for any disease and any species

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  23Strands
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