Genetics of endometriosis

Molecular Diagnostics 2025 Symposium

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DISCLOSURE

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Other disclosures

Lecture fees Merck, Exeltis, Besins Health Care, Stragen

Endometriosis

CHRONIC MULTIFACTORIAL SYSTEMIC DISEASE

Inflammation / Progesterone resistance

Infertility / CVD / Low BMI / Fatigue

New!

CHRONIC PAIN

Dysmenorrhea / Pelvic, abdominal and back pain / Migraine

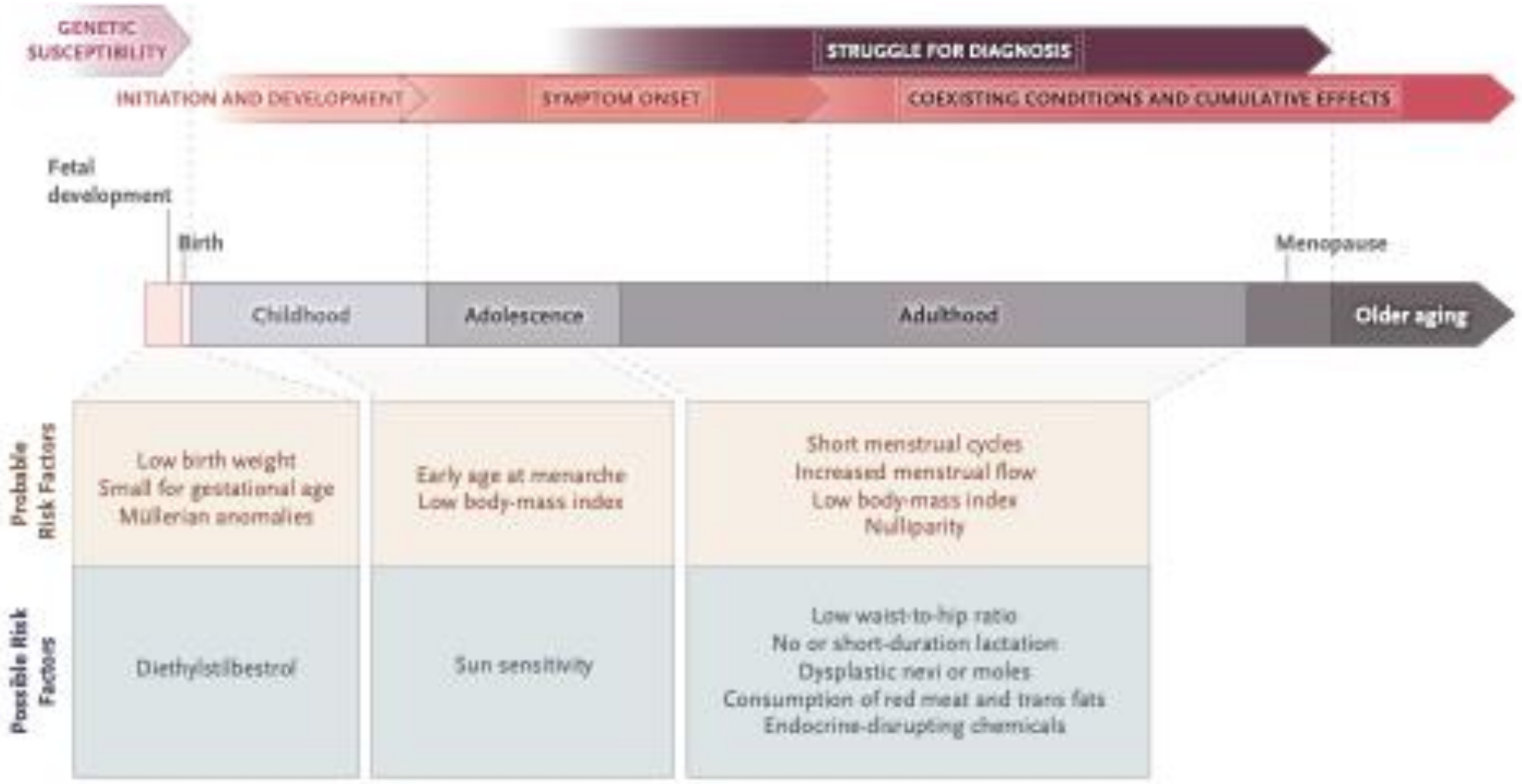
HORMONAL TREATMENT

Amenorrhea — Fertility treatments

PAIN MANAGEMENT PLAN

Chronic pain — Acute pain

Endometriosis across the Life Course



Endometriosis. K. T. Zondervan, C. M. Becker and S. A. Missmer. N Engl J Med 2020 Vol. 382 Issue 13 Pages 1244-1256

Pathogenesis of endometriosis

1) Endometrial tissue (endometriosis lesions) located outside the uterus, consisting of
   a. endometrial glands
   b. stromal cells
   c. fibrosis

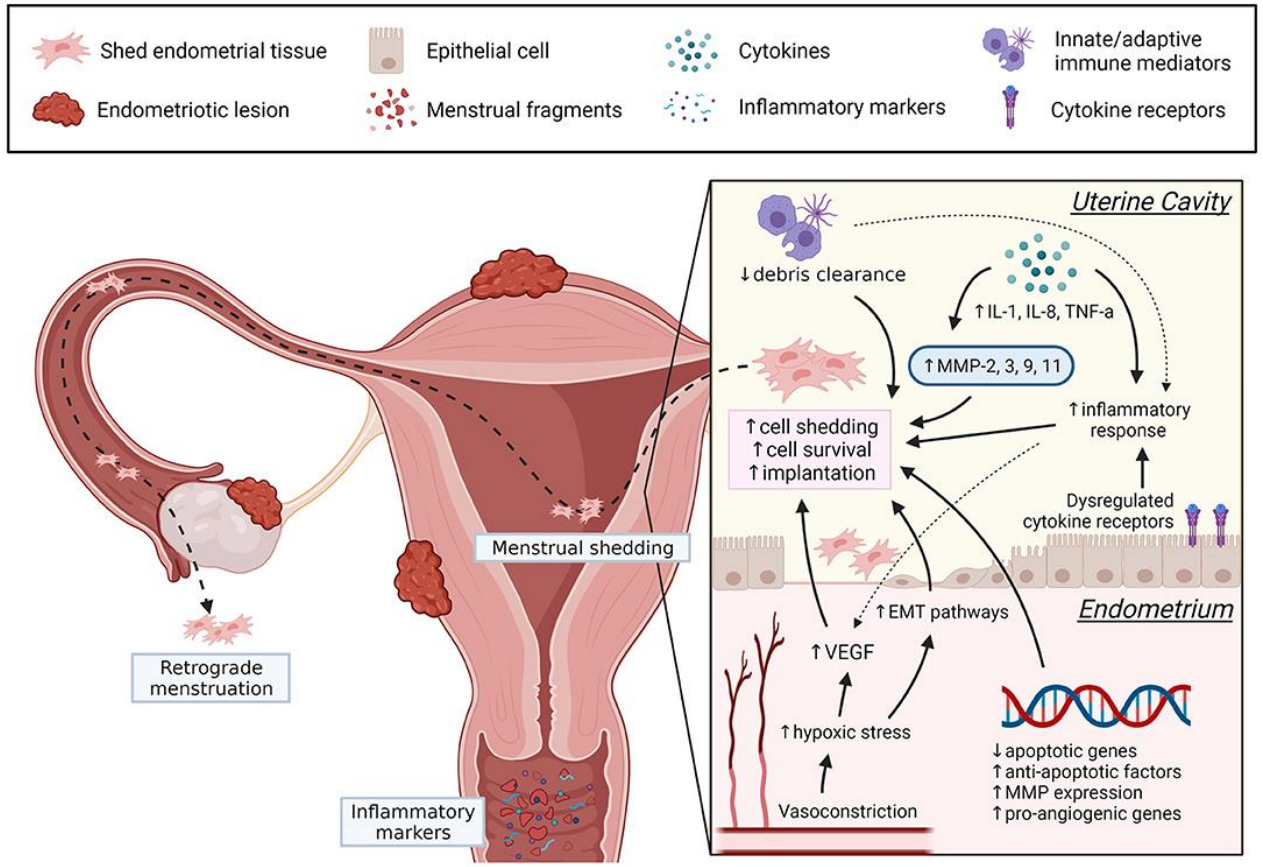
   ➔ Endometrial cells implant and form a cyst cavity bordered by glandular cells

2) Several dysregulated menstrual processes: angiogenesis, EMT, apoptotic regulators, inflammation, debris clearance, MMP

   ➔ May promote endometrial cell detachment, prolong endometrial cell survival and increase the likelihood for implantation following retrograde menstruation.

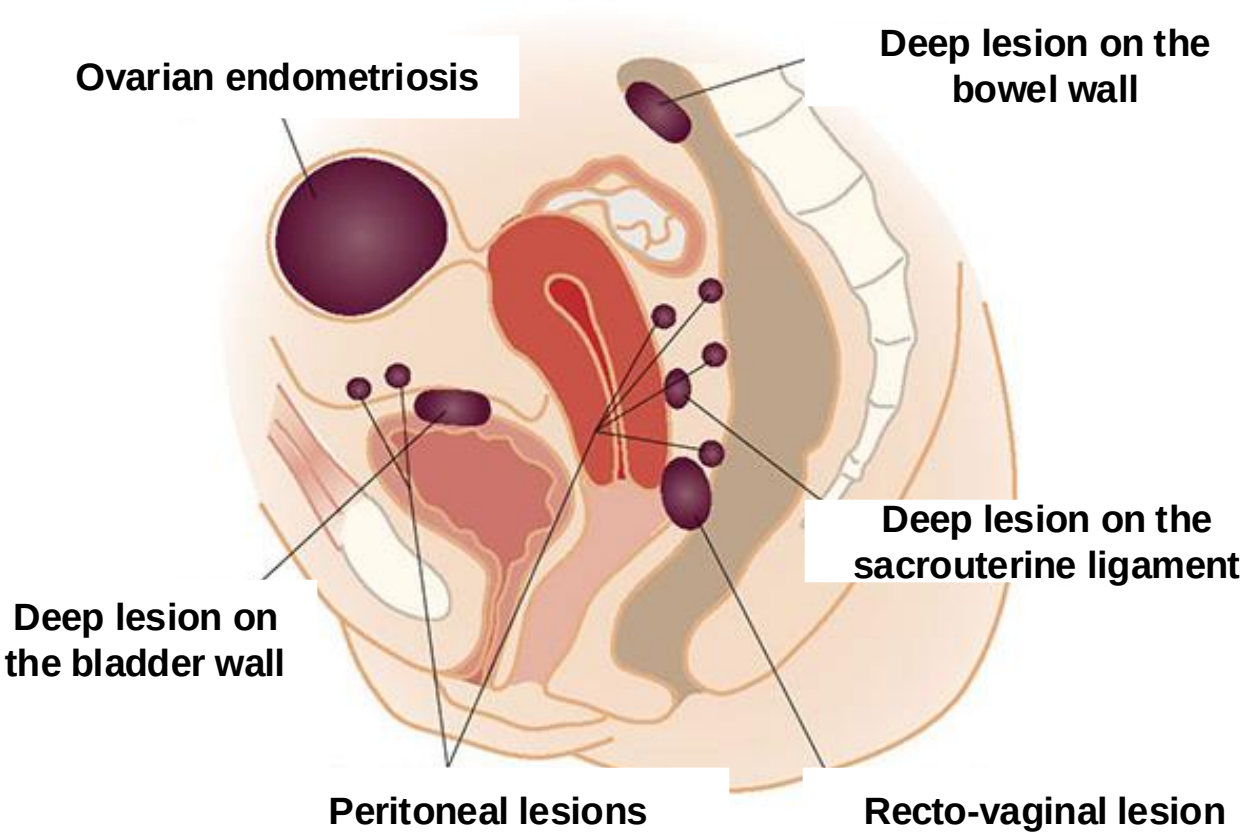
3) Causes adhesions between abdominal organs

4) Cyclic estrogen and progesterone secretion regulates glandular function. Endometriosis cells also produce their own estrogen via aromatase.



Kuan et al. Menstruation Dysregulation and Endometriosis Development. Front. Reprd. Health 2021

Endometriosis lesion sites



Ovaries

Recto-vaginal space (Fossa Douglas)

Sacrouterine ligaments

Rectum and sigma

Conjunctive of the bladder

Ligament latum

Fallobian tubes

→ **SAMPSON'S THEORY (RETROGRADE MENSTRUATION)**

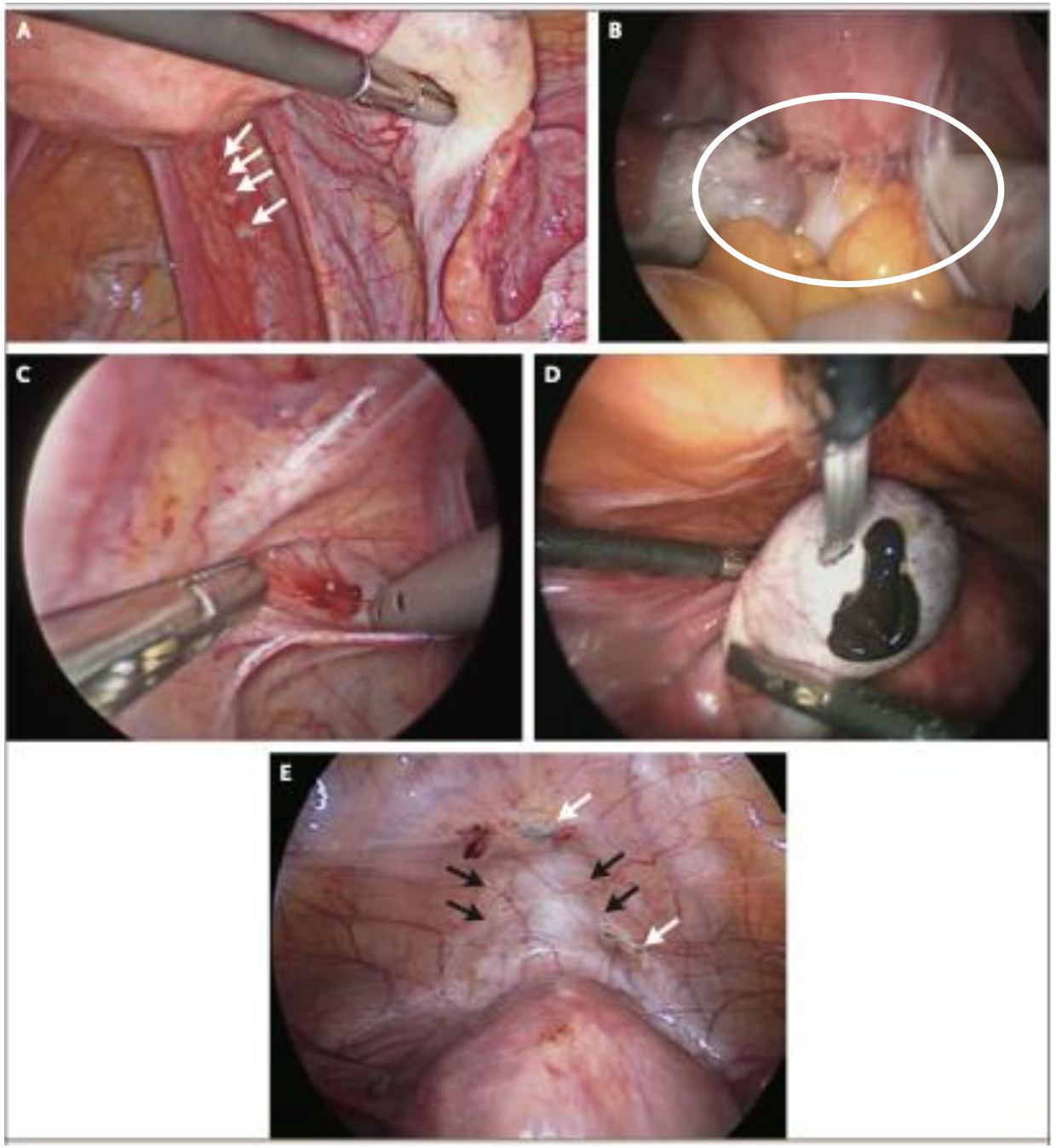
Extraperitoneal sites:

bowel, urinary tract, pulmonary system, CNS, skin

→ **VIA STEM CELLS/METAPLASIA**

Minimal peritoneal **LESIONS** (white arrows)

Bowel **ADHESIONS** to uterus, obliteration of recto-vaginal space



Superficial red peritoneal **LESION** and hyperemia

ENDOMETRIOMA (ovarian endometriosis), ”chocolate cyst”

CHARACTERISTICS OF ENDOMETRIOSIS LESIONS
Vascularization of lesions
Innervation of lesions
Scarring or adhesions within the pelvic cavity

LESION SIZE
Varies from millimeters to centimeters

DEEP bladder lesions (black arrows) and red, brown and black peritoneal **LESIONS** (white arrows)

Endometriosis. K. T. Zondervan, C. M. Becker and S. A. Missmer. N Engl J Med 2020 Vol. 382 Issue 13 Pages 1244-1256

CLASSIFICATION OF ENDOMETRIOSIS

According to lesion site

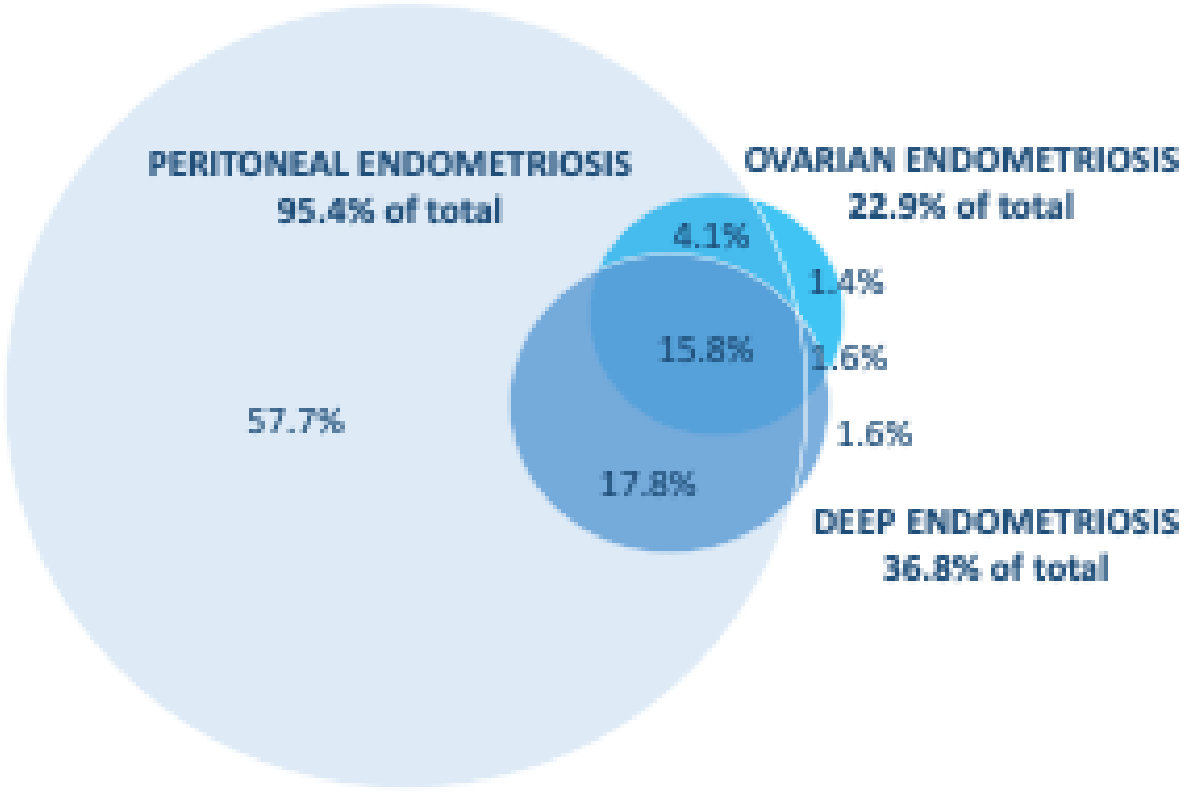


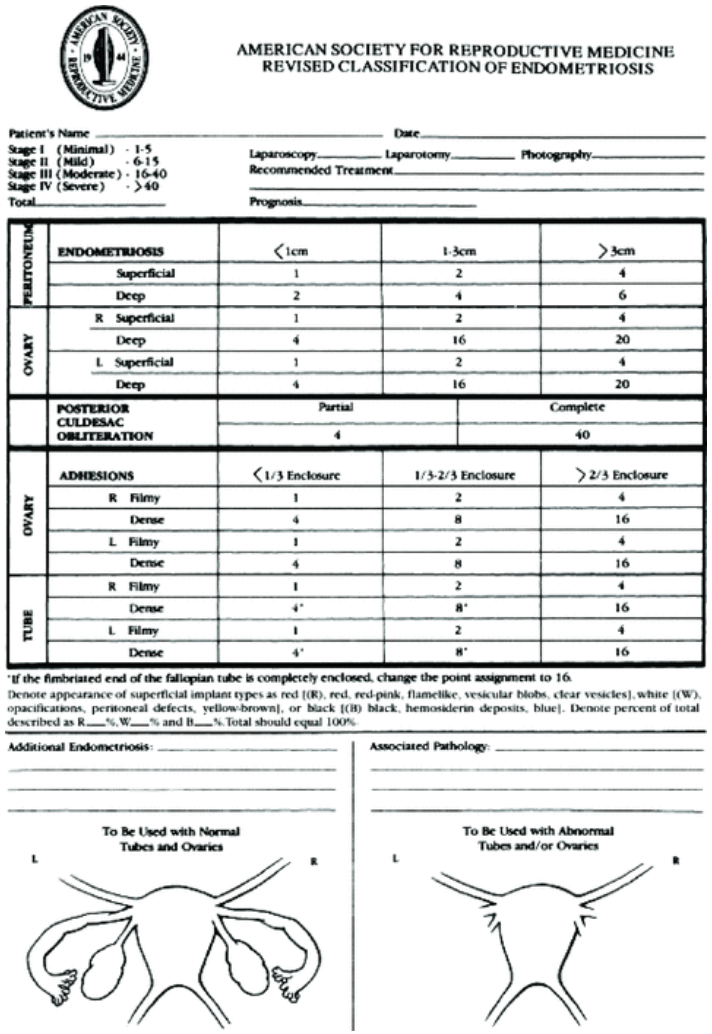
Figure 1. **Presentation of the prevalence and overlap of endometriosis lesion sites using venn diagrams**. Most patients with endometriosis have only peritoneal lesions, but those with ovarian endometriosis often have additionally peritoneal lesions and deep lesions. Patients with deep lesions often have peritoneal and ovarian lesions.

CLASSIFICATION OF ENDOMETRIOSIS

Grading according to lesion site, size, tissue depth and adhesions

Revised ASRM

Stage I – minimal	1-5
Stage II – mild	6-15
Stage III – moderate	16-40
Stage IV – severe	>40



AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE
REVISED CLASSIFICATION OF ENDOMETRIOSIS

Patient's Name _____ Date _____

Stage I (Minimal) - 1-5
Stage II (Mild) - 6-15
Stage III (Moderate) - 16-40
Stage IV (Severe) - >40
Total _____

Laparoscopy _____ Laparotomy _____ Photography _____
Recommended Treatment _____
Prognosis _____

	ENDOMETRIOSIS	<1cm	1-3cm	>3cm
PERITONEUM	Superficial	1	2	4
	Deep	2	4	6
OVARY	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20

	POSTERIOR CULDESAC OBLITERATION	Partial	Complete
		4	40

	ADHESIONS	<1/3 Enclosure	1/3-2/3 Enclosure	>2/3 Enclosure
OVARY	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
TUBE	R Filmy	1	2	4
	Dense	4*	8*	16
	L Filmy	1	2	4
	Dense	4*	8*	16

*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.

Denote appearance of superficial implant types as red [(R), red, red-pink, flamelike, vesicular blobs, clear vesicles], white [(W), opacifications, peritoneal defects, yellow-brown], or black [(B) black, hemosiderin deposits, blue]. Denote percent of total described as R___%, W___% and B___%. Total should equal 100%.

Additional Endometriosis: _____

Associated Pathology: _____

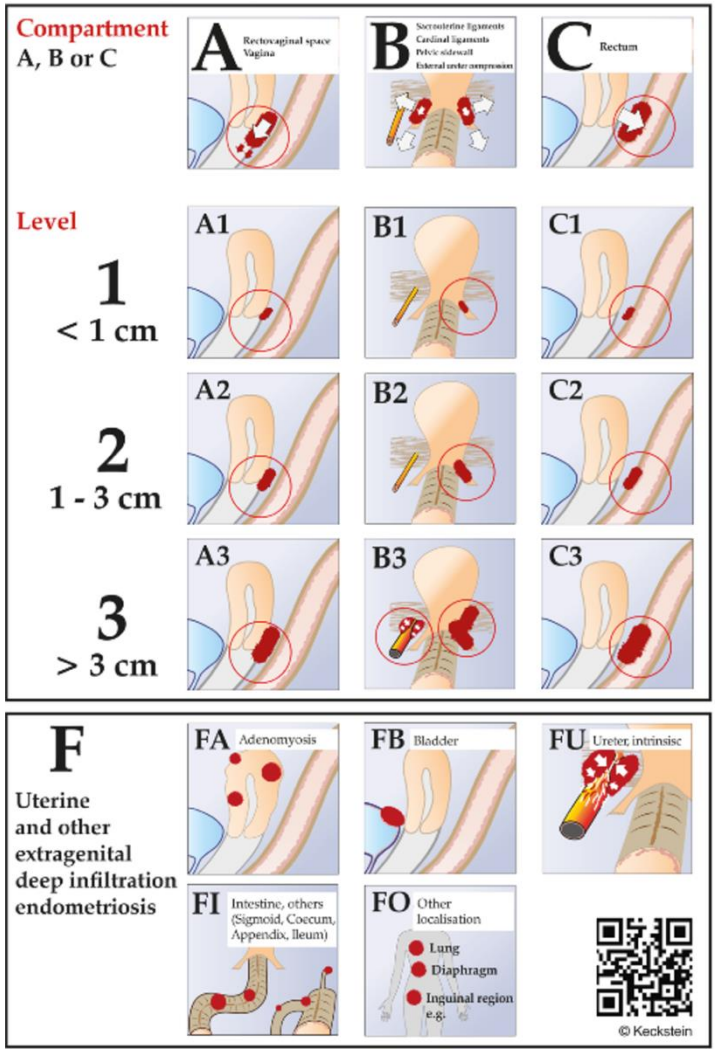
To Be Used with Normal Tubes and Ovaries

To Be Used with Abnormal Tubes and/or Ovaries

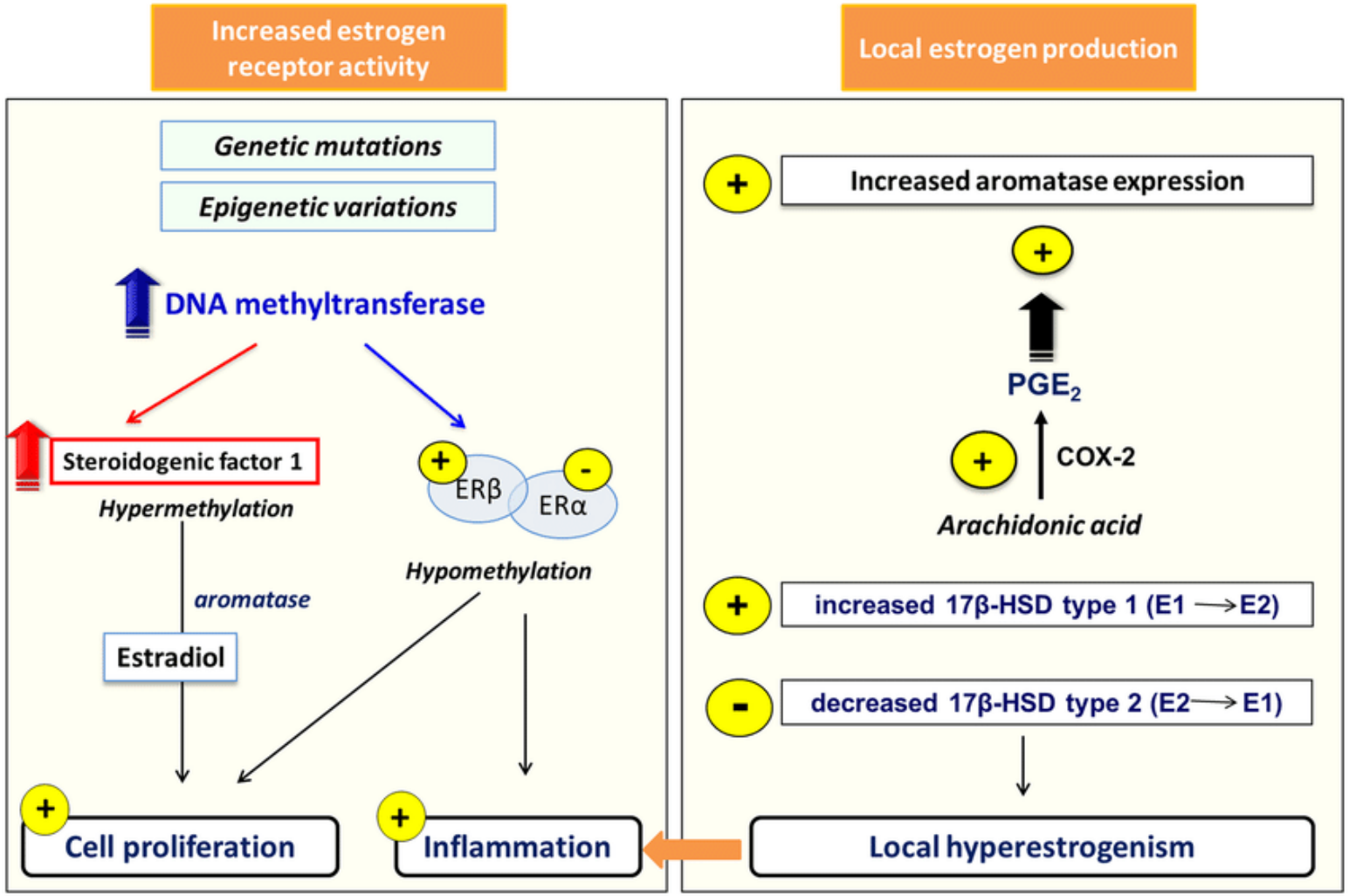
CLASSIFICATION OF ENDOMETRIOSIS

According to lesion site and tissue depth, specifically recto-vaginal disease

The ENZIAN-Score



ESTROGEN: a dominant role in endometriosis pathogenesis



17β-HSD
17β-hydroxysteroid dehydrogenase

E1, estrone

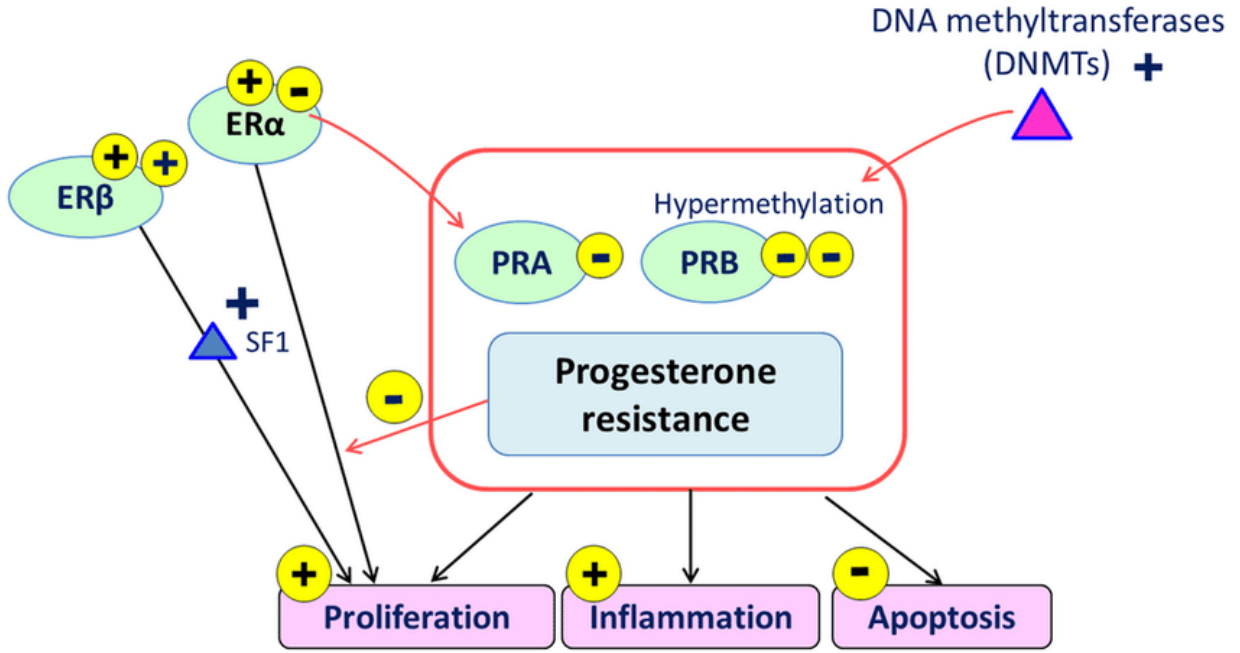
E2, estradiol

Vannuccini et al. Hormonal treatments for endometriosis: The endocrine background. Rev Endocr Metab Disord 2022

Mechanisms of progesterone-resistance in endometriosis

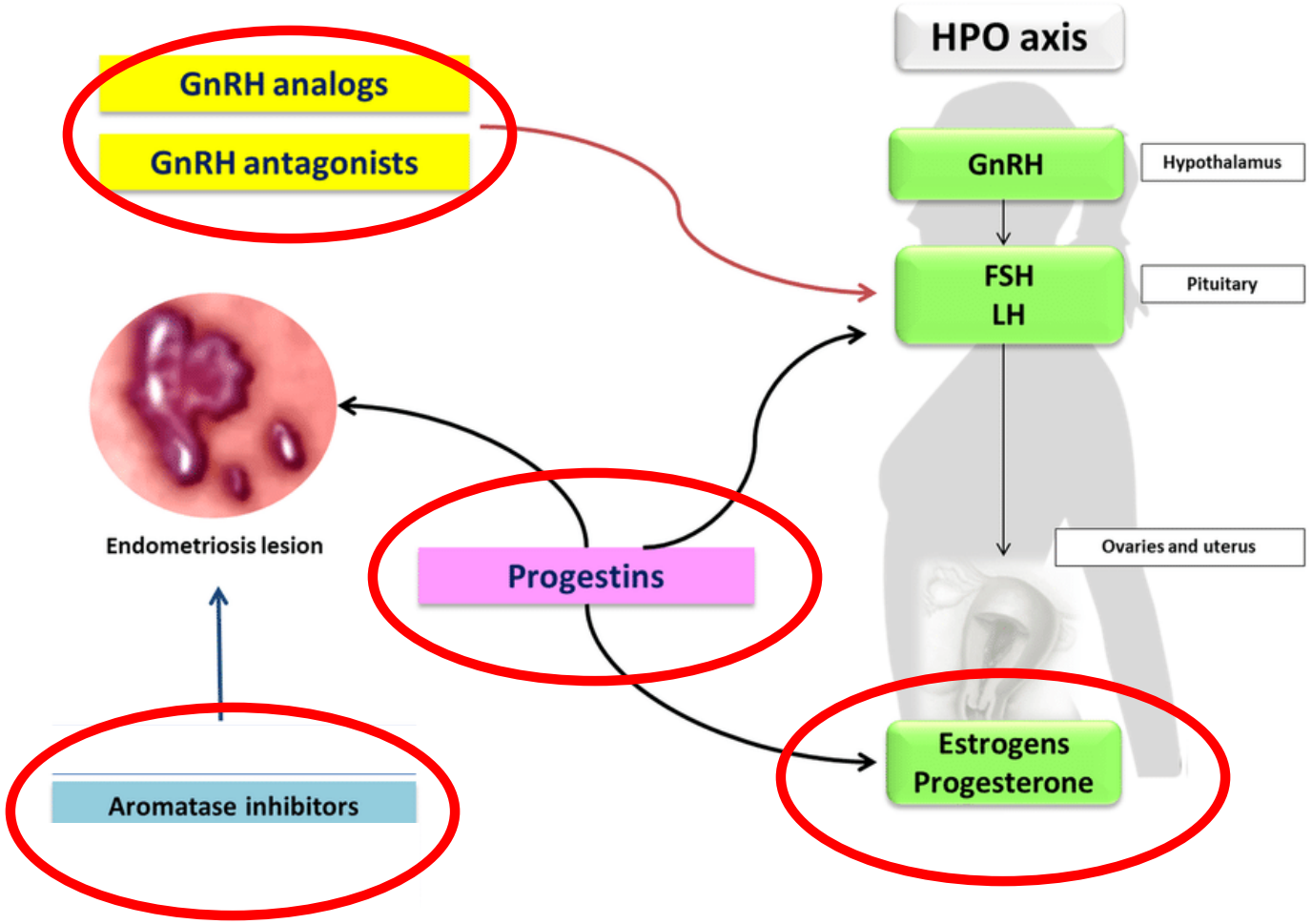
1) Dysregulation of progesterone signaling
2) Endometrial tissue inability to appropriately respond to progesterone

Well-established in both the endometriotic lesions and eutopic endometrium of women with endometriosis!



Vannuccini et al. Hormonal treatments for endometriosis: The endocrine background. Rev Endocr Metab Disord 2022

Hormonal targets of currently used drugs for endometriosis



Vannuccini et al. Hormonal treatments for endometriosis: The endocrine background. Rev Endocr Metab Disord 2022

Quality of life

COMMON SYMPTOMS (prevalence)

Dysmenorrhea (pain during menses) (70-80%)

Dyspareunia (pain during intercourse) (70-75%)

Chronic abdominal or pelvic pain (60%)

Dyschezia (pain during bowel movement) (40-70%)

Dysuria (pain while urinating) (6-68%)

Infertility (30-50%)

Rare symptoms

Shoulder stab or upper abdominal pain durin menses
Acute abdominal pain
Painful lump in abdominal wall
Bleeding from belly button
Sciatic pain
Loss of function of one kidney
Penumothorax

Suvitie. Milloin epäillä endometrioosia? [When to suspect endometriosis] Lääkärilehti 14-15/2020

Artist Ellie Kammer. An Australian artist hopes to raise global awareness about endometriosis by painting powerful images detailing her struggle with the illness.

Artist With Endometriosis Channels 'Desperation' Into Striking Portraits To Raise Awareness *'Painting made me feel powerful again.'* **By Rachel Moss**
Huffington Post UK 24/10/2017 12:23pm BST|**Updated** October 24, 2017

COMMON DISEASE

10% of reproductive-age women ➔ ~190 million women worldwide

2 to 11%	asymptomatic women
5 to 50%	infertile women
5 to 21%	women hospitalized for pelvic pain
49 to 75%	symptomatic adolescents, chronic pelvic pain and unresponsive pain to medical treatment

Zondervan, Becker, Missmer. Endometriosis. NEJM 2020

COMPARISON

Prevalence of **type 2 diabetes 6.28%**

Khan ert al. Epidemiology of Type 2 Diabetes – Global Burden of Disease and Forecasted Trends. J Epidemiol Glob Health. 2020

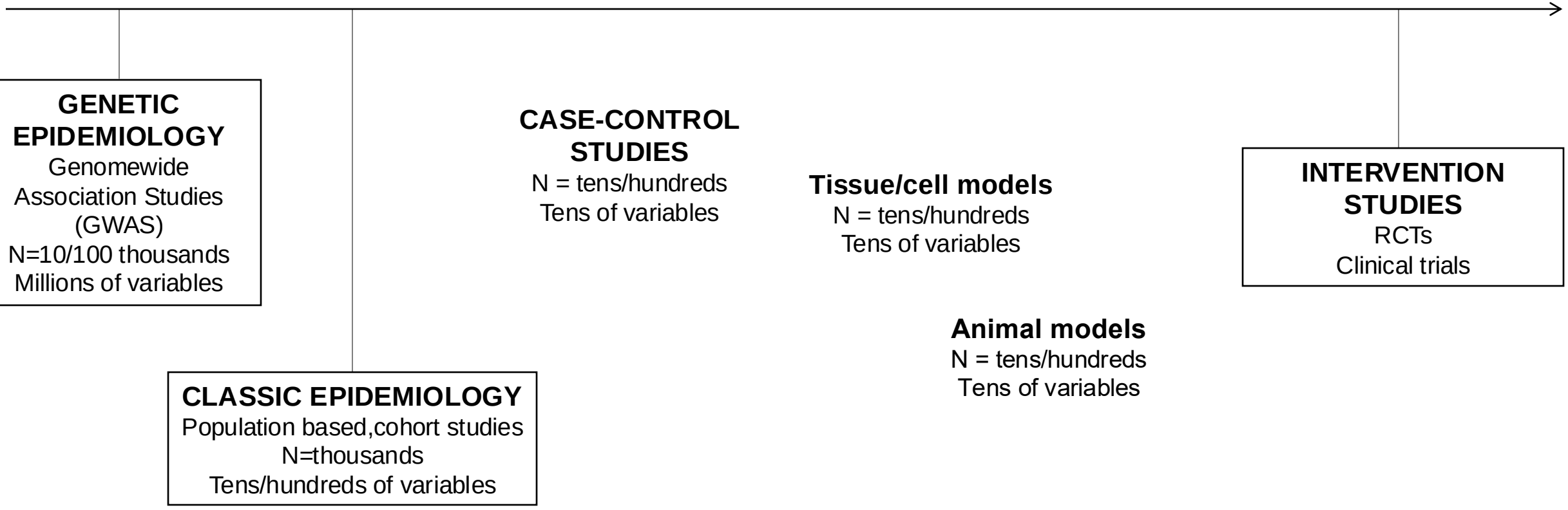
Prevalence of **asthma 5.4%**

Song et al. Global, regional, and national prevalence of asthma in 2019: a systematic analysis and modelling study. J Glob Health. 2022

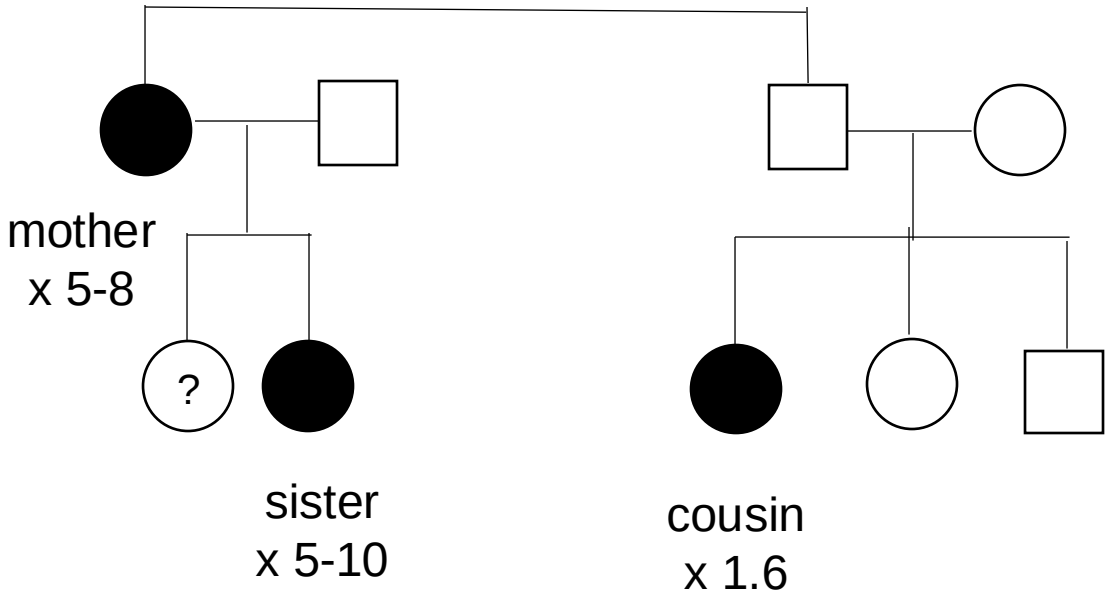
Research study designs by hypothesis level

Hypothesis free approach

Hypothesis driven approach



Increased disease risk by family history



Moen et al. The familial risk of endometriosis. ACTA Obstet Gynecol Scand 1993
Stefansson et al. Genetic factors contribute to the risk of developing endometriosis. Hum Reprod 2002
Kashima et al. Familial risk among Japanese patients with endometriosis. Int J Gynaecol Obstet 2004
Matalliotakis et al. Familial aggregation of endometriosis in the Yale series. Arch Gynecol Obstet 2008

Potential high-risk genetic variants for endometriosis

Only a few potential high-risk genetic variants have been identified:

1) Variants causing amino acid changes in the NPSR1 gene with association to reduction of inflammatory cell infiltrate and abdominal pain, have been identified in nine different families with endometriosis.

   (Tapmeier et al. Neuropeptide S receptor 1 is a nonhormonal treatment target in endometriosis. Sci Transl Med 2021)

2) Identified variants in three genes (FGFR4, NALCN, NAV2) by whole-exome sequencing that segregate with endometriosis using Finnish family (Fig. 1) data.

   (Nousiainen et al. Whole-exome sequencing reveals candidate high-risk susceptibility genes for endometriosis. Hum Genomics 2023)

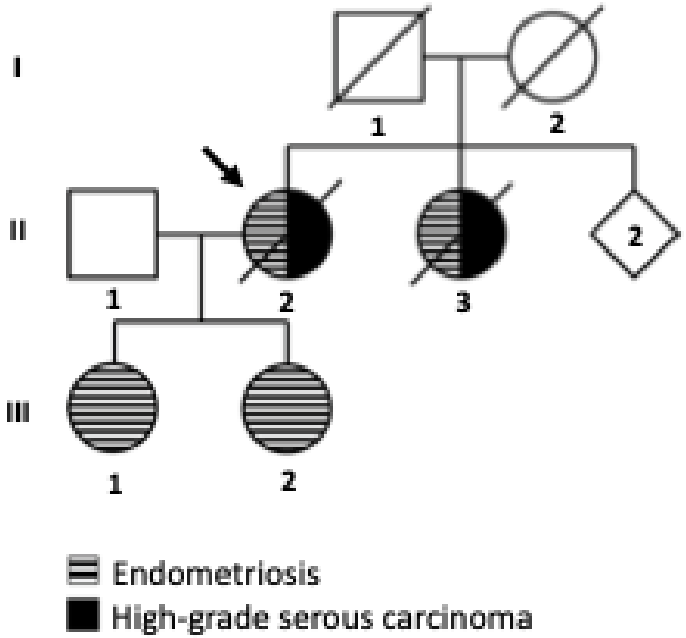


Fig. 1 Pedigree of the Finnish endometriosis family. Four women in two generations have been diagnosed with surgically verified endometriosis and two also with high-grade serous carcinoma (HGSC). The index patient is marked with an arrow. The pedigree has been slightly modified for anonymity

Endometriosis heritability

The relative contribution of genetic and environmental factors to the observed variation in a trait within a population

According to **twin studies**, the **heritability** of endometriosis (the proportion of disease risk due to genetic variation) **~ 50%**

Saha et al. Heritability of endometriosis. Fertil Steril 2015;104:947-52.

Common genetic variation accounts for **~ 26% of the risk of endometriosis**

Lee et al. Estimation and partitioning of polygenic variation captured by common SNPs for Alzheimer's disease, multiple sclerosis and endometriosis. Hum Mol Genet 2013; 22:832-41.

Common risk variants for multifactorial disease are detectable by sufficiently powered, population-based genome-wide association studies (GWAS)

Visscher et al. 10 Years of GWAS discovery: biology, function, and translation. Am J Hum Genet 2017;101:5-22.

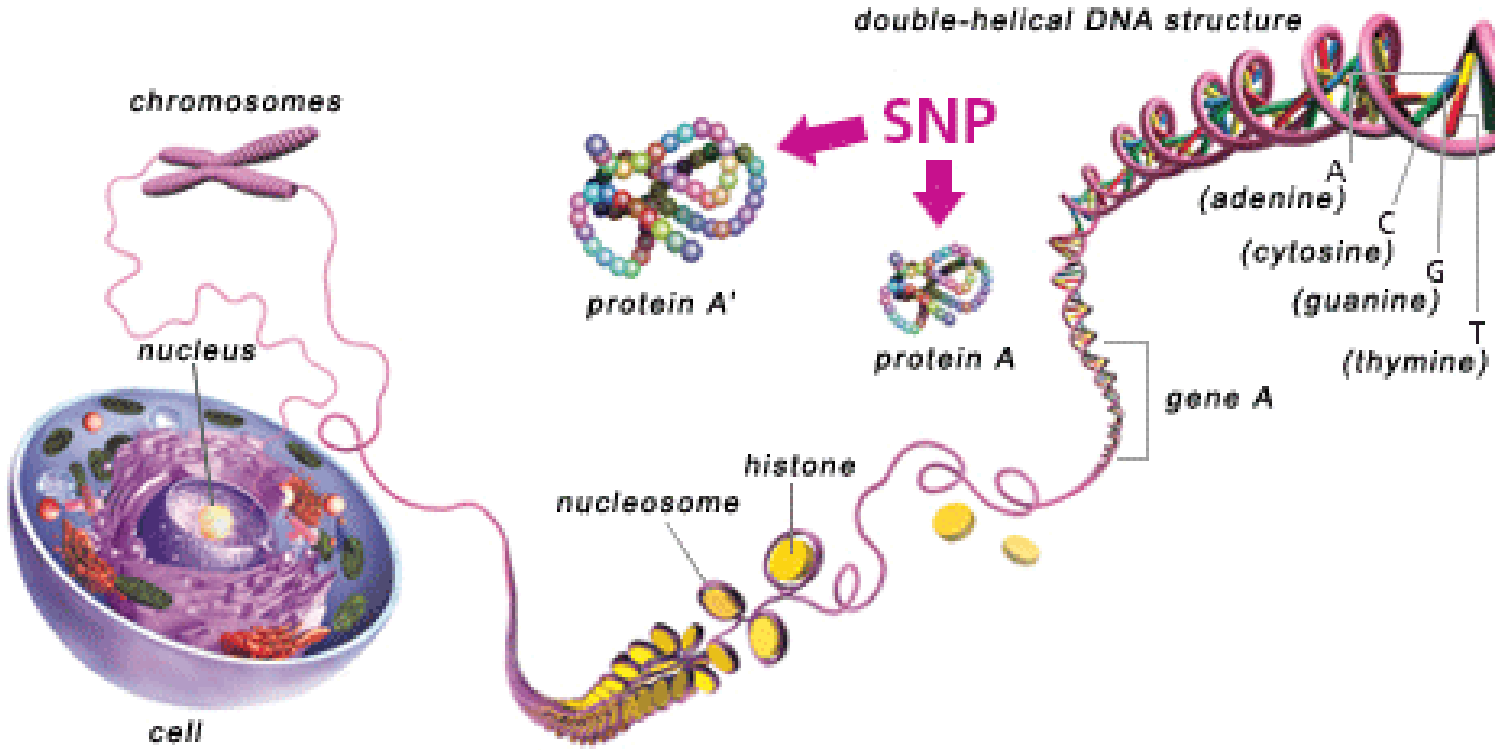
Genome-wide association studies (GWAS)

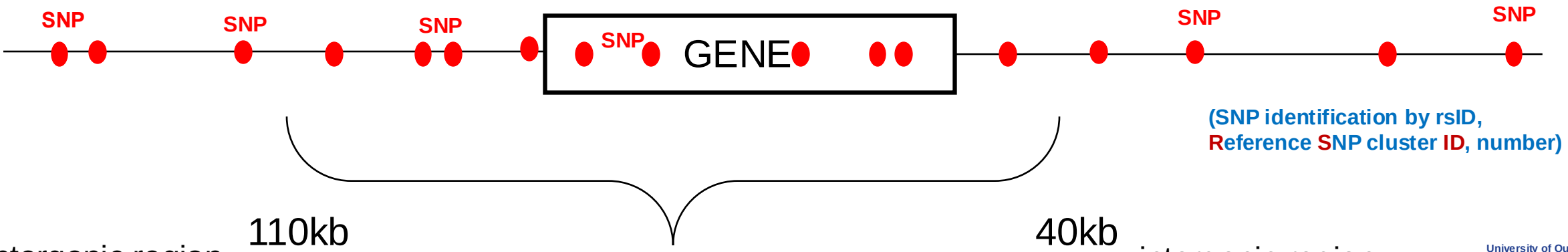
test millions of genetic variants (SNPs)
across many genomes (sample sets of hundreds of thousands)
to find those variants that are statistically ($P < 5 \times 10^{-8}$)
associated with a specific trait or disease

SNP single nucleotide variations (polymorphism)

- one SNP for every 500-1000 bases
- 3-5 million SNPs in the entire human genome, of which 500,000 SNPs are in gene regions
- are different between individuals

SNP in a gene can cause changes in the function, timing, or amount of the protein produced by that gene.


double-helical DNA structure
chromosomes
SNP
protein A'
protein A
A
(adenine)
C
(cytosine)
G
(guanine)
T
(thymine)
nucleus
gene A
histone
nucleosome
cell


SNP
SNP
SNP
SNP
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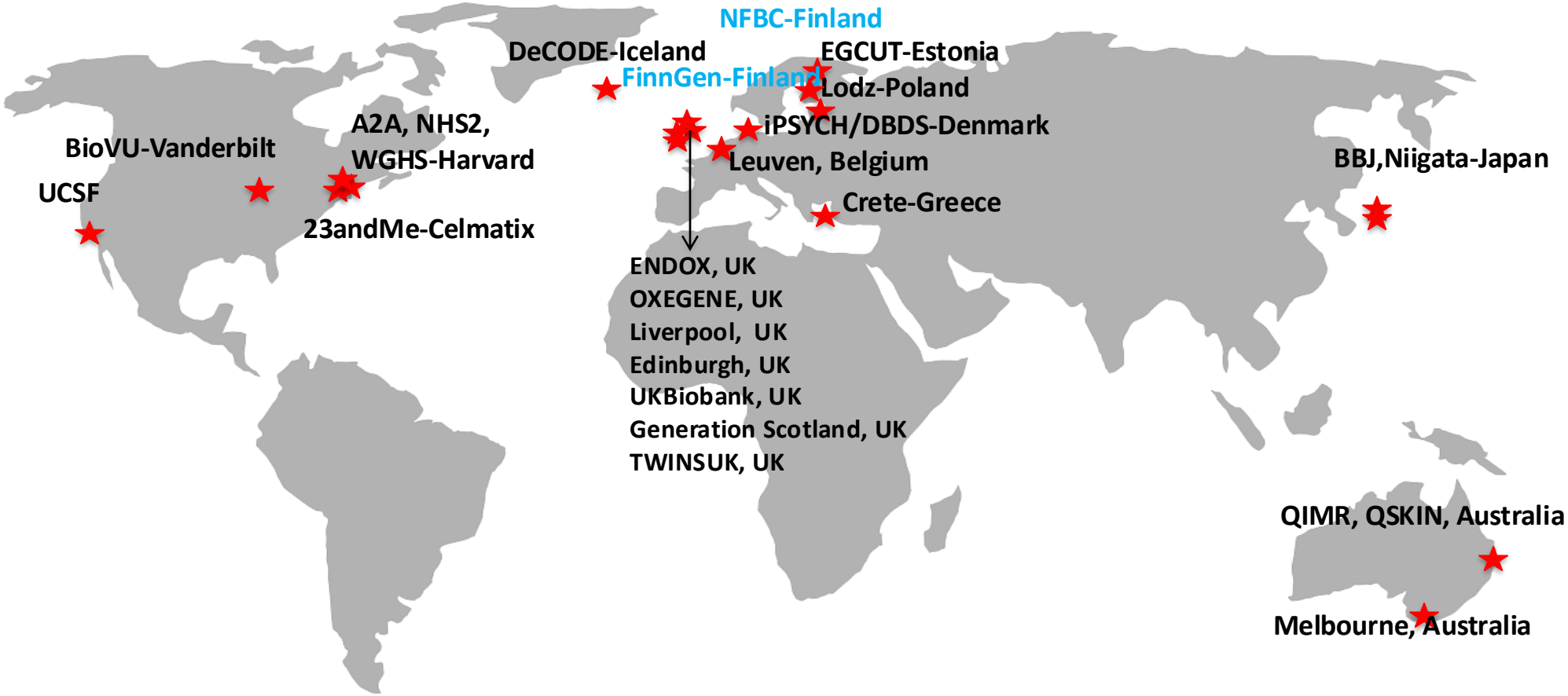
SNP
SNP
(SNP identification by rsID,
Reference SNP cluster ID, number)
110kb
40kb
intergenic region
intronic region
intergenic region

International Endometriosis Genomics Consortium (IEGC)



Prof Stacey Missmer, Michigan State Uni, USA

Prof Grant Montgomery, Uni of Queensland, Australia

Prof Andrew P. Morris, Uni of Liverpool, UK

Prof Krina Zondervan, Uni of Oxford, UK

GWAS	All Cases:Controls	Stage III/IV: Co	Stage I/II: Co	Infertile: Co
Total N (24 Studies)	60,674 : 701,926	4,045 : 379,898	3,916 : 184,014	3,060 : 221,674

	IEGC	International Endometriosis Genomics Consortium			
	Study acronym	**Study name**	**Ancestry**	**Total Case N**	**Total Control N**
1	23andMe	23andMe dataset	European	37 182	251 255
2	FinnGen	FinnGen	European	6 502	57 407
3	UKBiobank	UK Biobank dataset	European	6 611	196 188
4	QIMRHCS	Queensland Institute of Medical Research and Hunter Community Study	European	2 262	2 923
5	NHS2	Nurses' Health Study II	European	2 104	5 854
6	DECODE	DeCODE Genetics	European	1 857	132 978
7	EGCUT	The Estonian Biobank Cohort	European	1 716	35 176
8	WGHS	The Women's Genome Health Study	European	1 494	15 033
9	BBJ	BioBank Japan	Japanese	1 423	1 318
10	QSKIN	QSkin Sun and Health Study	European	1 038	7 604
...					
				~65,000	~760,000

FINNGEN: AN EXPEDITION INTO GENOMICS AND MEDICINE

FinnGen is a research project in genomics and personalized medicine. It is large public-private partnership that has collected and analysed genome and health data from 500,000 Finnish biobank donors to understand the genetic basis of diseases. FinnGen is now expanding into understanding the progression and biological mechanisms of diseases. FinnGen provides a world-class resource for further breakthroughs in disease prevention, diagnosis, and treatment and a outlook into our genetic make-up.

FINNGEN

The final FinnGen cohort consists of over 500 000 individuals

The combined amount of the legacy samples and newly collected samples is 520 0000. The median age of the participants when donating was 53 years and 43% are men, and 57% women.

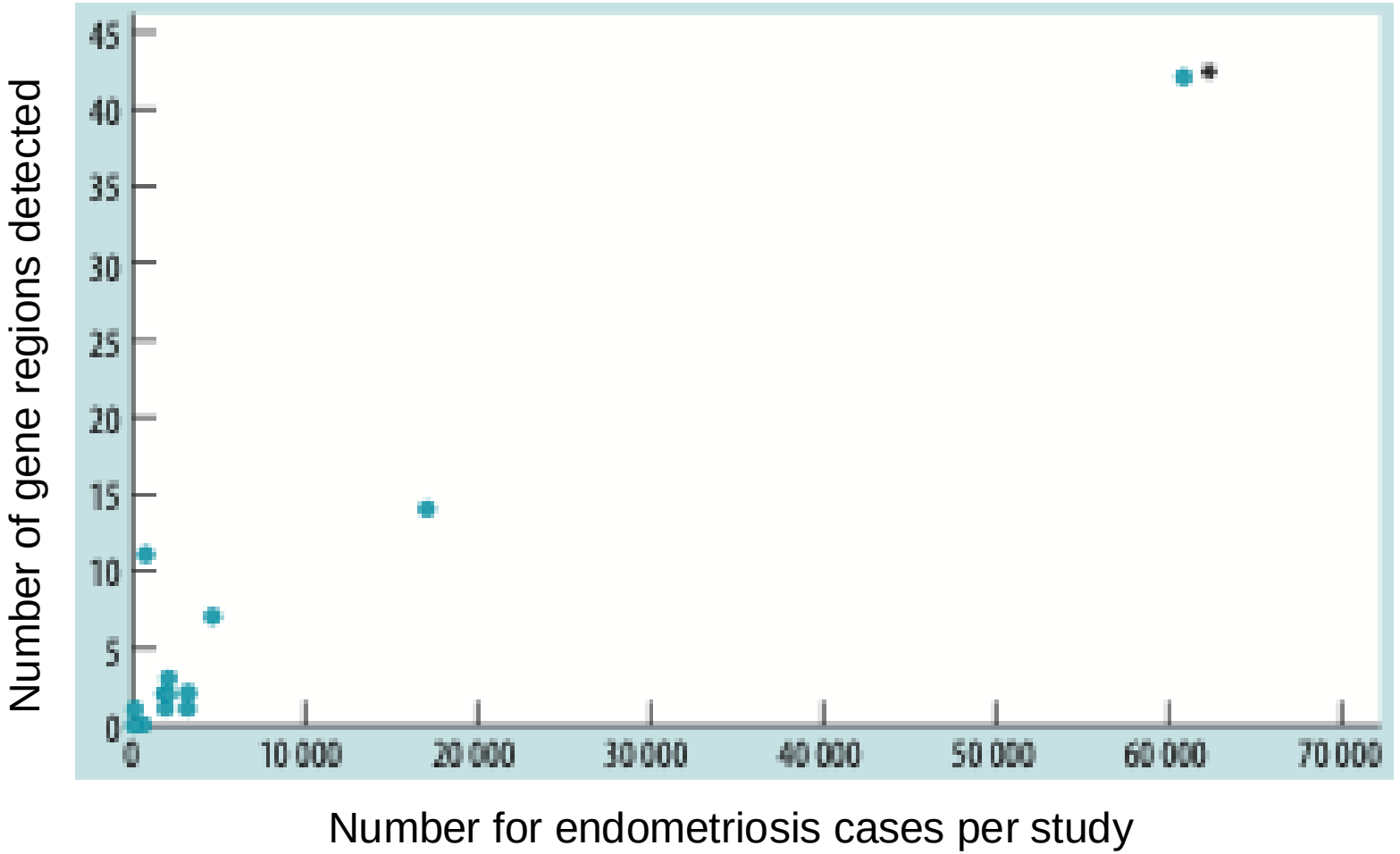


FIGURE 1. Number of endometriosis-susceptible genetic regions found in GWAS studies relative to the sample size of each study. Genome-wide studies require large sample sizes to detect significant associations. To date (as of January 15, 2024), the sample sizes of endometriosis GWAS studies published have been small, with the exception of the most recent study (Rahmioglu et al. Nat Genet 2023).

Uimari, Sliz, Karjalainen. Endometrioosin geneettinen tausta liittyy läheisesti kivun säätelyyn. [The genetic background of endometriosis is closely linked to pain regulation] Duodecim 2024

nature genetics

Article

https://doi.org/10.1038/s41588-023-01323-z

The genetic basis of endometriosis and comorbidity with other pain and inflammatory conditions

Received: 1 December 2021

Accepted: 27 January 2023

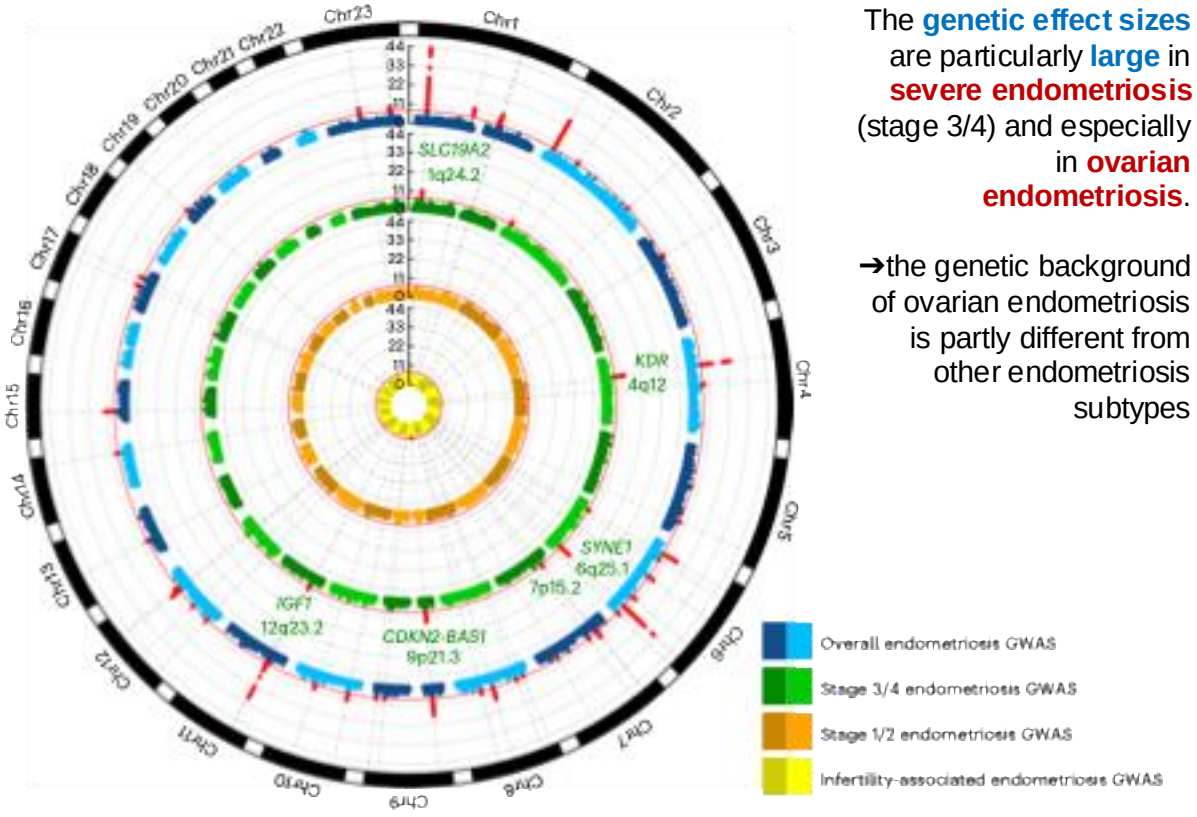
Published online: 13 March 2023

Check for updates

A list of authors and their affiliations appears at the end of the paper

Endometriosis is a common condition associated with debilitating pelvic pain and infertility. A genome-wide association study meta-analysis, including 60,674 cases and 701,926 controls of European and East Asian descent, identified 42 genome-wide significant loci comprising 49 distinct association signals. Effect sizes were largest for stage 3/4 disease, driven by ovarian endometriosis. Identified signals explained up to 5.01% of disease variance and regulated expression or methylation of genes in endometrium and blood, many of which were associated with pain perception/maintenance (*SRP14/BMF*, *GDAP1*, *MLLT10*, *BSN* and *NGF*). We observed significant genetic correlations between endometriosis and 11 pain conditions, including migraine, back and multisite chronic pain (MCP), as well as inflammatory conditions, including asthma and osteoarthritis. Multitrait genetic analyses identified substantial sharing of variants associated with endometriosis and MCP/migraine. Targeted investigations of genetically regulated mechanisms shared between endometriosis and other pain conditions are needed to aid the development of new treatments and facilitate early symptomatic intervention.

42 genome-wide significant loci ($P < 5 \times 10^{-8}$) identified for overall endometriosis, of which 31 novel



The **genetic effect sizes** are particularly **large** in **severe endometriosis** (stage 3/4) and especially in **ovarian endometriosis**.

→the genetic background of ovarian endometriosis is partly different from other endometriosis subtypes

Manhattan plot of GWAS results

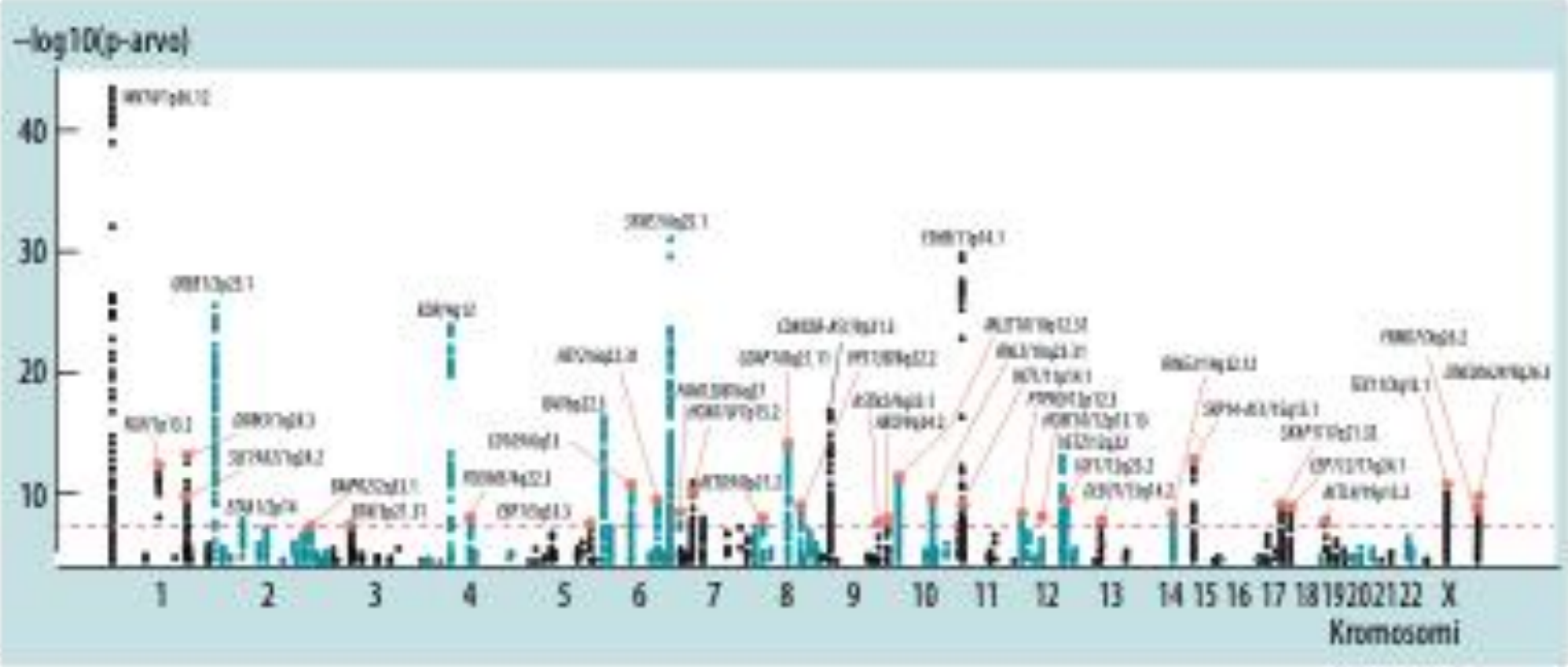
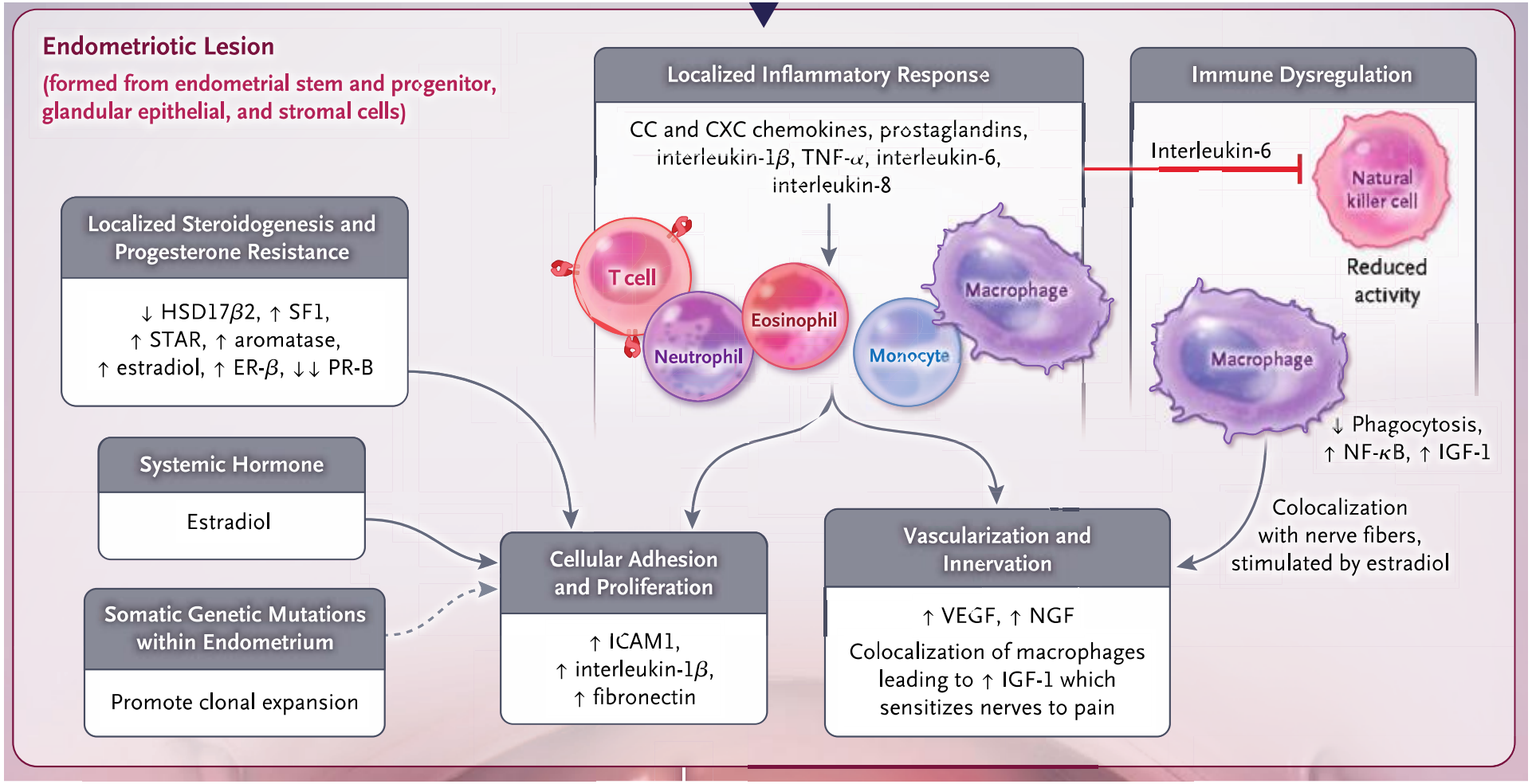


FIGURE 2. Endometriosis-associated loci (38). Data points represent individual variants on 23 chromosomes (x-axis), and the statistical strength of their association with endometriosis is given as the negative logarithm of the p-values (y-axis). Novel endometriosis loci are highlighted in orange.

Uimari, Sliz, Karjalainen. Endometrioosin geneettinen tausta liittyy läheisesti kivun säätelyyn. [The genetic background of endometriosis is closely linked to pain regulation] Duodecim 2024

Analyses of genes closest to the GWAS loci point to biological pathways that have previously been thought to be associated with the development of endometriosis: **Wnt signaling, cell adhesion and proliferation, angiogenesis, inflammation, and hormonal pathways**.



Zondervan et al. NEJM 2020

TABLE. Genetic regions predisposing to endometriosis and pain regulation phenotypes (migraine and multifocal pain). Data are based on multitrait analysis of GWAS (MTAG) (Rahmioglu et al. Nat Genet 2023). Gene and protein function descriptions are taken from https://www.ncbi.nlm.nih.gov/gene/ and https://www.uniprot.org

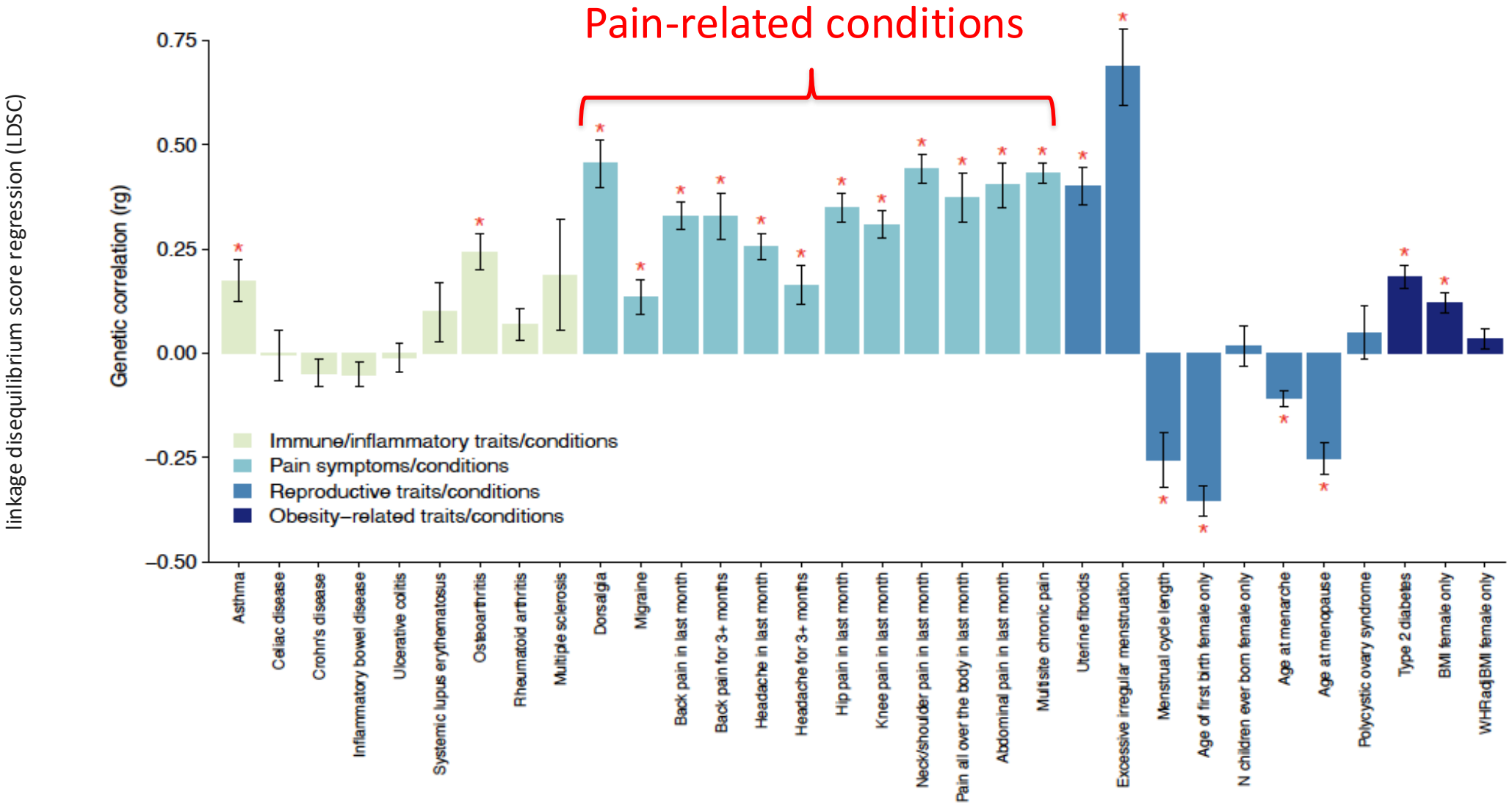
Gene region/gene	Complete gene name and function
1p32.3/*FAF1*	Fas Associated Factor 1: initiation and enhancement of apoptosis, expressed in skeletal muscle and heart
1p13.2/*NGF*	Nerve growth factor: development and maintenance of the sympathetic and sensory nervous system, participates in the regulation of neuronal proliferation, differentiation and survival. Affects pregranulosa cells in the ovaries and participates in the differentiation stages of stem cells in the spinal cord, neurons and brain
1q2	
2q1	
3p2	
5q2	
5q3	
10p	
11p	
12p	
13q14.3/*OLFM4*	Olfactomedin 4: antiapoptotic factor, promotes tumor growth and affects cell adhesion
20q11.21/*NOL4L*	Nucleolar Protein 4 Like: encoded by protein located in the cytosol and nucleoplasm

Support for the HYPOTHESIS:
endometriosis causes pain through both hormonal mechanisms and activation of immune and neuronal cells,
as has been observed in other chronic pain conditions.

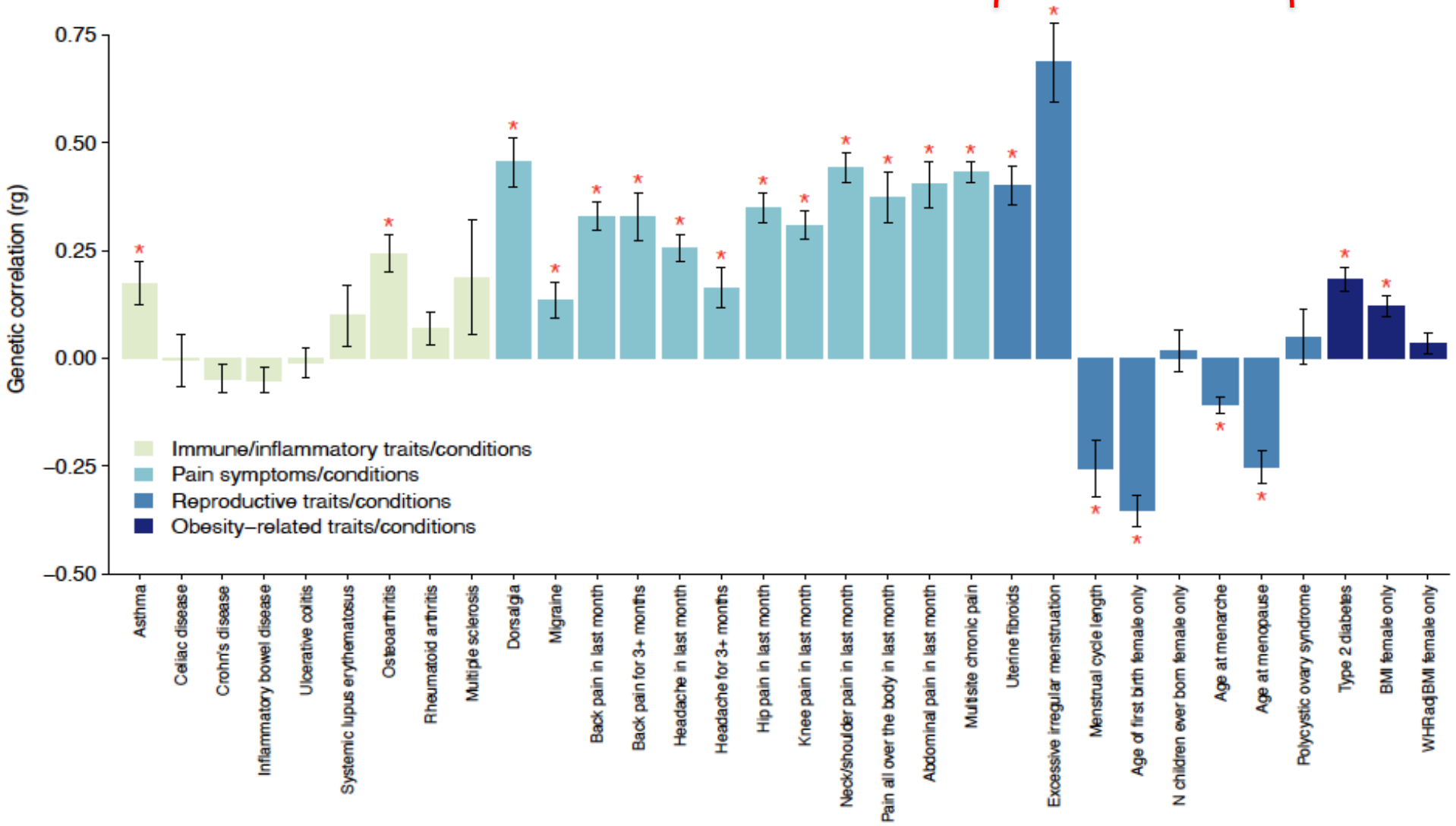
Uimari, Sliz, Karjalainen. Endometrioosin geneettinen tausta liittyy läheisesti kivun säätelyyn. [The genetic background of endometriosis is closely linked to pain regulation] Duodecim 2024

Genetic correlation between endometriosis and various traits

GENETIC CORRELATION – The proportion of variance that two traits share due to genetic causes

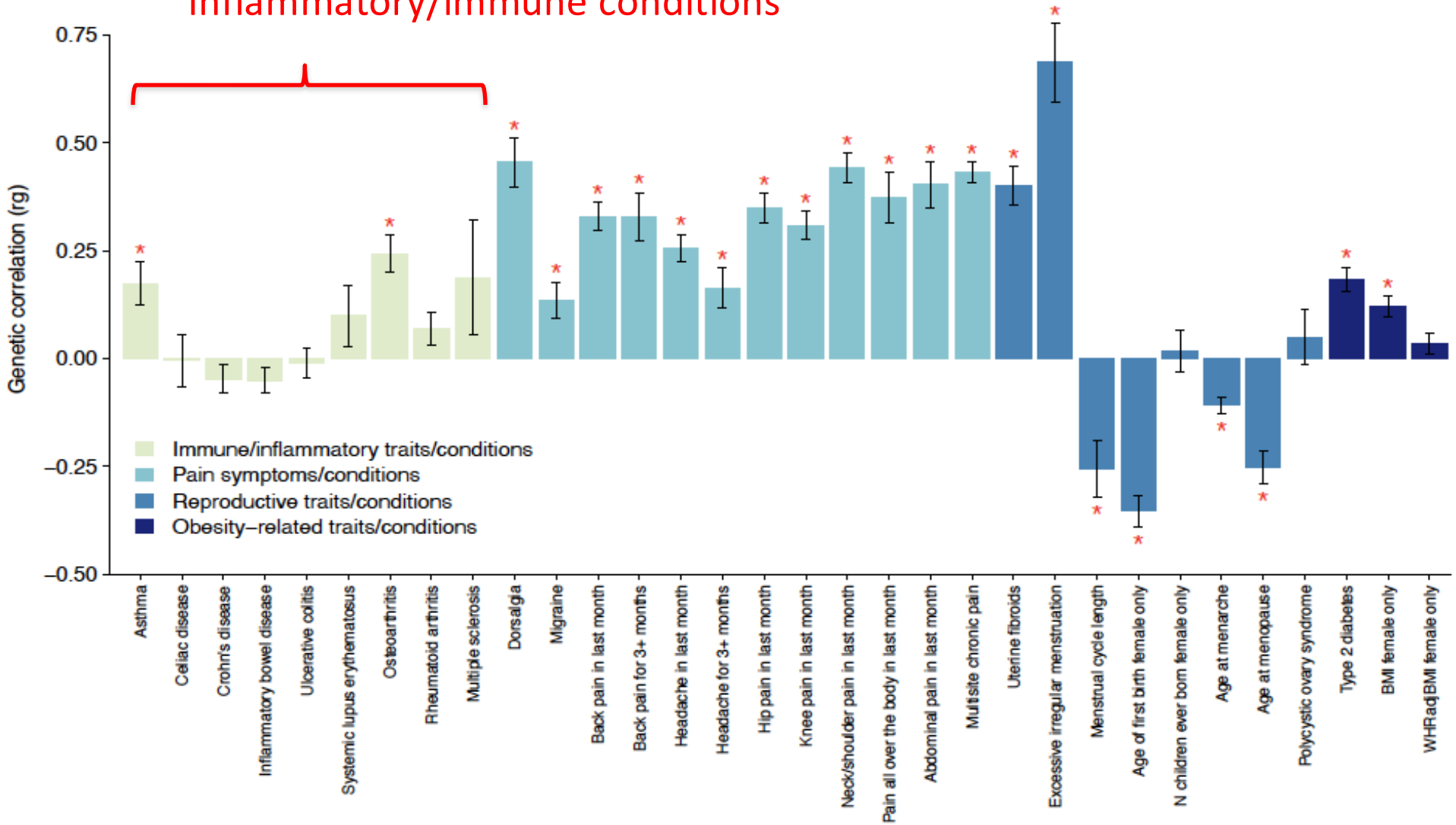


Reproductive traits/conditions



NEGATIVE CORRELATION
when the correlated trait decreases with the original trait increasing

Inflammatory/immune conditions



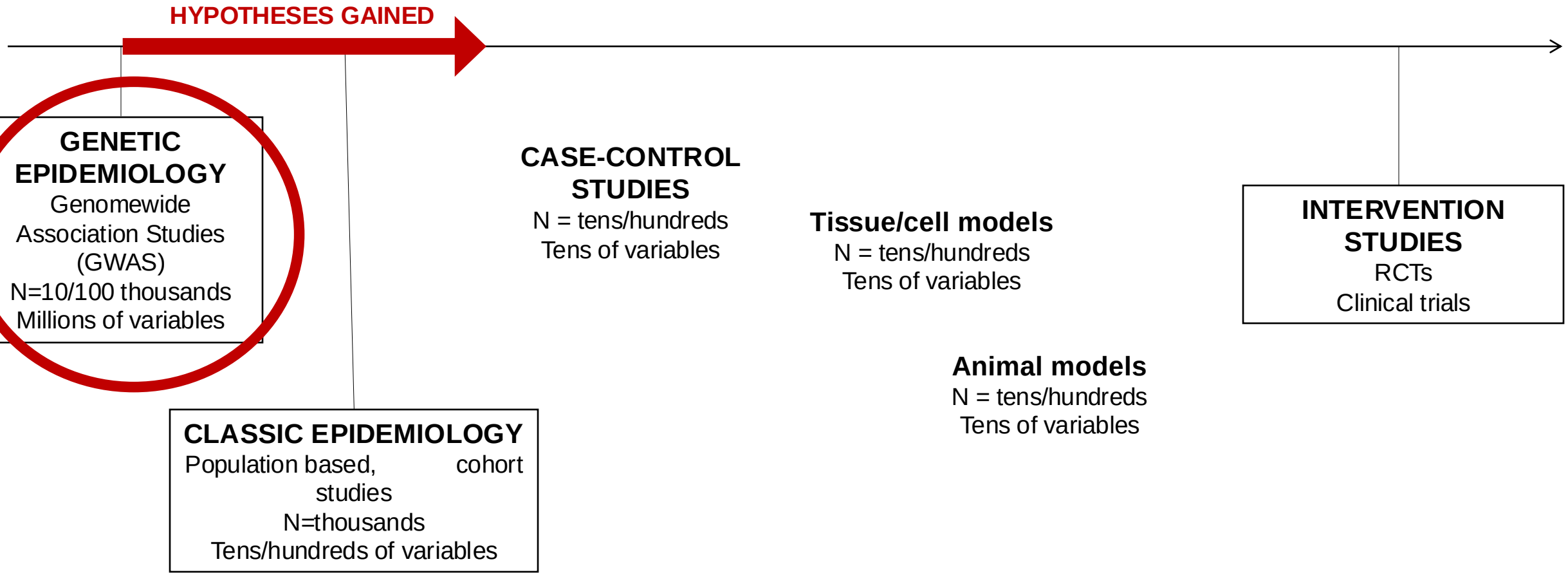
What is the significance of GWAS variants in risk mapping?

- Disease variation of common GWAS variants: only 2.2% (5.6% stage III/IV)
- Combined tools based on family history, genetic variants and other risk factors may in the future provide screening tools for girls/women with a family history of endometriosis
- The validity of such tools in independent cohorts and clinical utility need to be carefully evaluated
- Primary benefit of genetic results: discovery of a new therapeutic target

Research study designs by hypothesis level

Hypothesis free approach

Hypothesis driven approach



KEY MESSAGES

1. Endometriosis is a common chronic pain disease in women, for which nearly 50 low-risk genetic variants have been identified in GWAS studies.
2. Genetic factors predisposing to endometriosis are related to hormonal, immunological and nervous functions, such as pain regulation.
3. Endometriosis partly shares a genetic basis with several pain diseases.
4. The genetic background of ovarian endometriosis appears to be somewhat different from other endometriosis.
5. Family history should be taken into account when investigating chronic pelvic and abdominal pain.

Uimari, Sliz, Karjalainen. Endometrioosin geneettinen tausta liittyy läheisesti kivun säätelyyn. [The genetic background of endometriosis is closely linked to pain regulation] Duodecim 2024

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