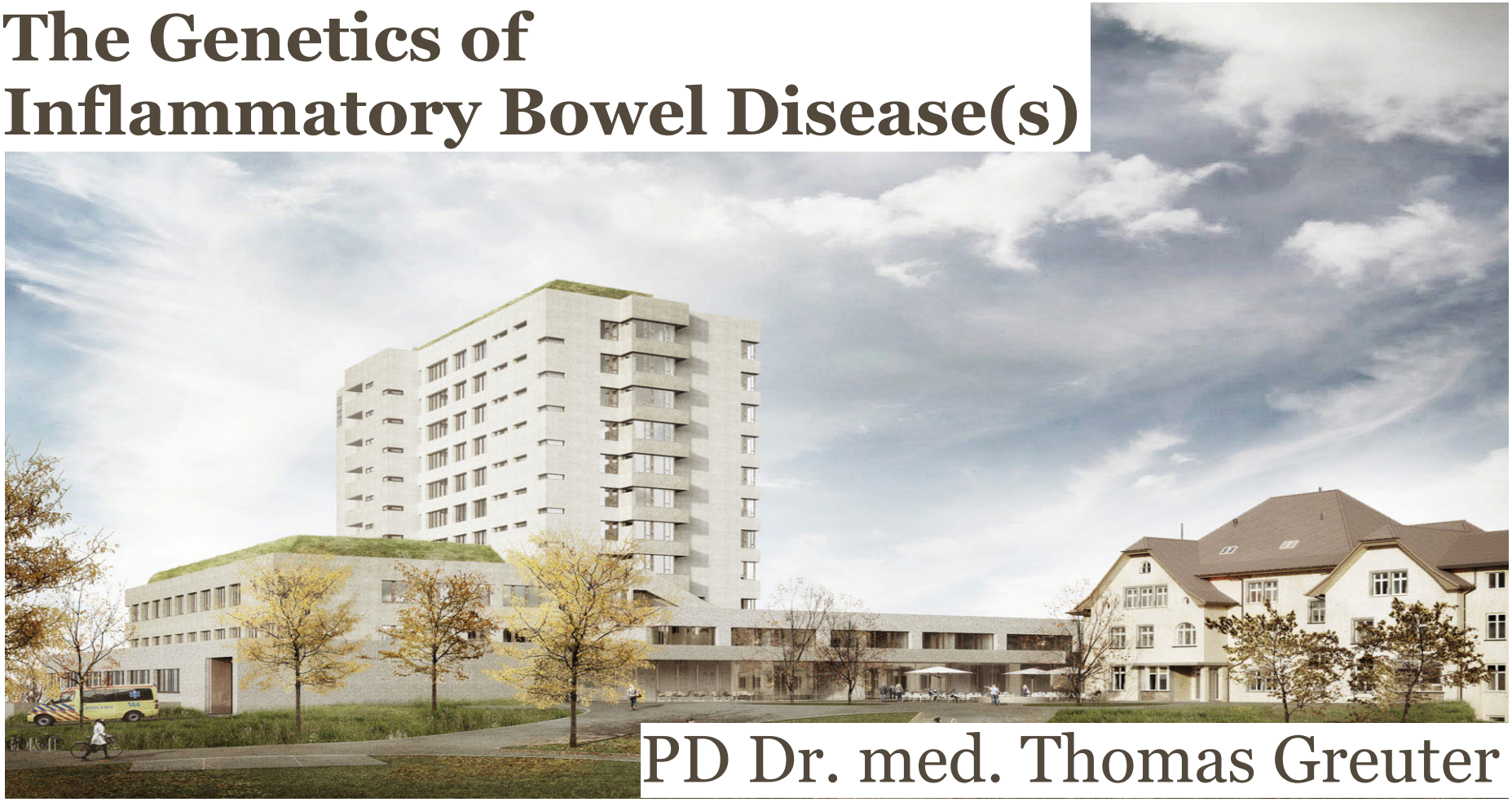
GZO Spital Wetzikon

The Genetics of Inflammatory Bowel Disease(s)



PD Dr. med. Thomas Greuter

GZO Spital Wetzikon

Conflicts of Interest

I herewith declare the following paid or unpaid consultancies, business interests or sources of honoraria payments for the past three years, and anything else which could potentially be viewed as a conflict of interest:

Falk Pharma // Consulting fee, educational + research grant, travel grant
BMS // Consulting fee
Sanofi Aventis // Research grant, consulting fee
Vifor Pharma // Travel grant
Novartis // Unrestricted research grant
Atlantic healthcare // Travel grant
Takeda // Consulting fee
Abbvie // Consulting fee
Janssen // Consulting fee
Pfizer // Consulting fee

Outline

1. Overview of inflammatory bowel disease
2. Genetic aspects of IBD
3. Clinical implications
4. Other “inflammatory bowel diseases”: eosinophilic esophagitis

Take home message

Fascinating, highly innovative and potentially relevant topic that unfortunately has not made it into clinical practice yet (with few exceptions: TPMT)

Overview of inflammatory bowel disease

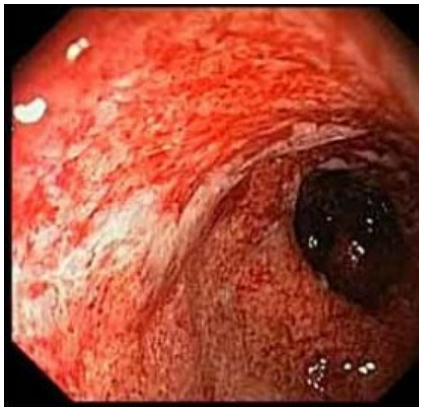
Inflammatory bowel disease – A clinical case

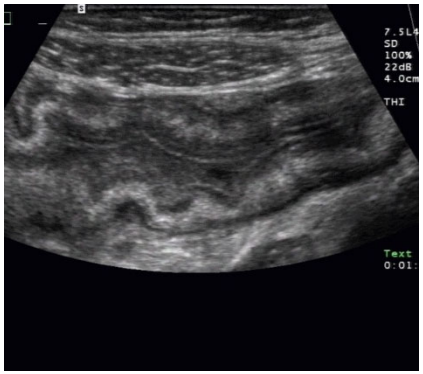
21-year old woman

On-off bloody diarrhea for 2 years, intermittent abdominal pain

Arthralgia

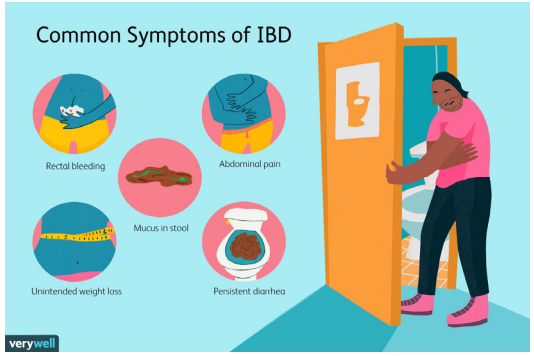
No fever, chills

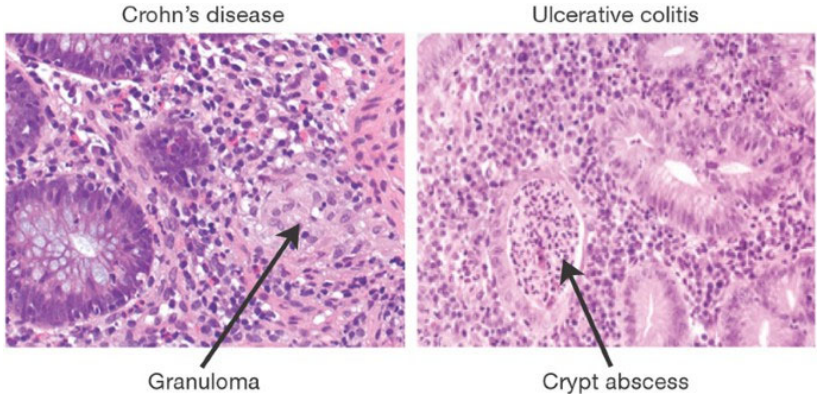


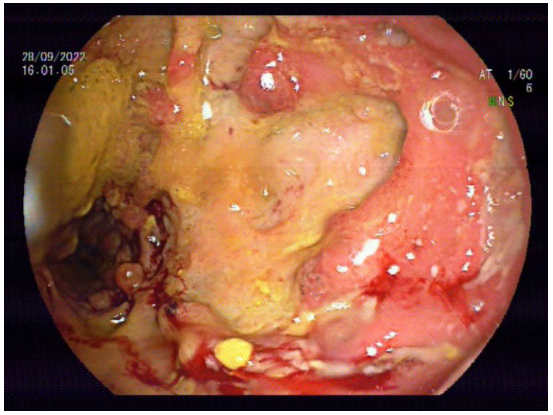


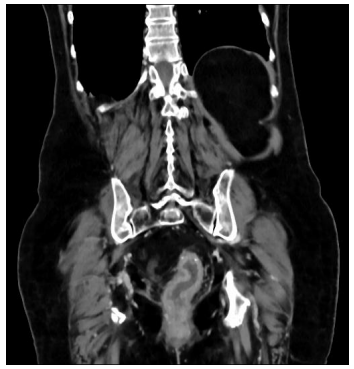
Courtesy of Prof. Stephan Vavricka

IBD – A clinico-endoscopic-histologic-radiological diagnosis







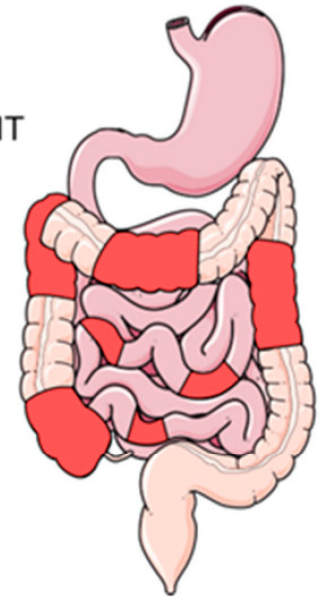


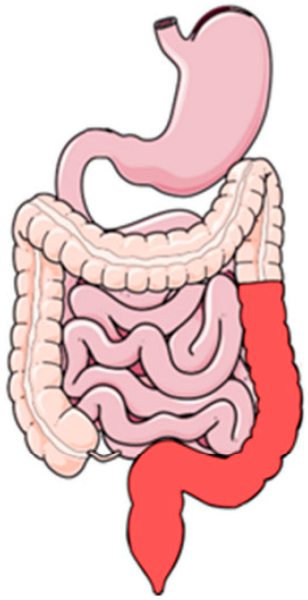
Nature. 2007 Jul 26;448(7152):427-34
https://www.verywellhealth.com/ibd-symptoms-1942663
https://www.walkerfc.com/blog/5-important-benefits-of-routine-bloo

IBD – Crohn's disease vs ulcerative colitis

Crohn's Disease

- May affect any part of the GIT
- Discontinuous patchy inflammation
- Transmural (affects the full thickness of the bowel wall)





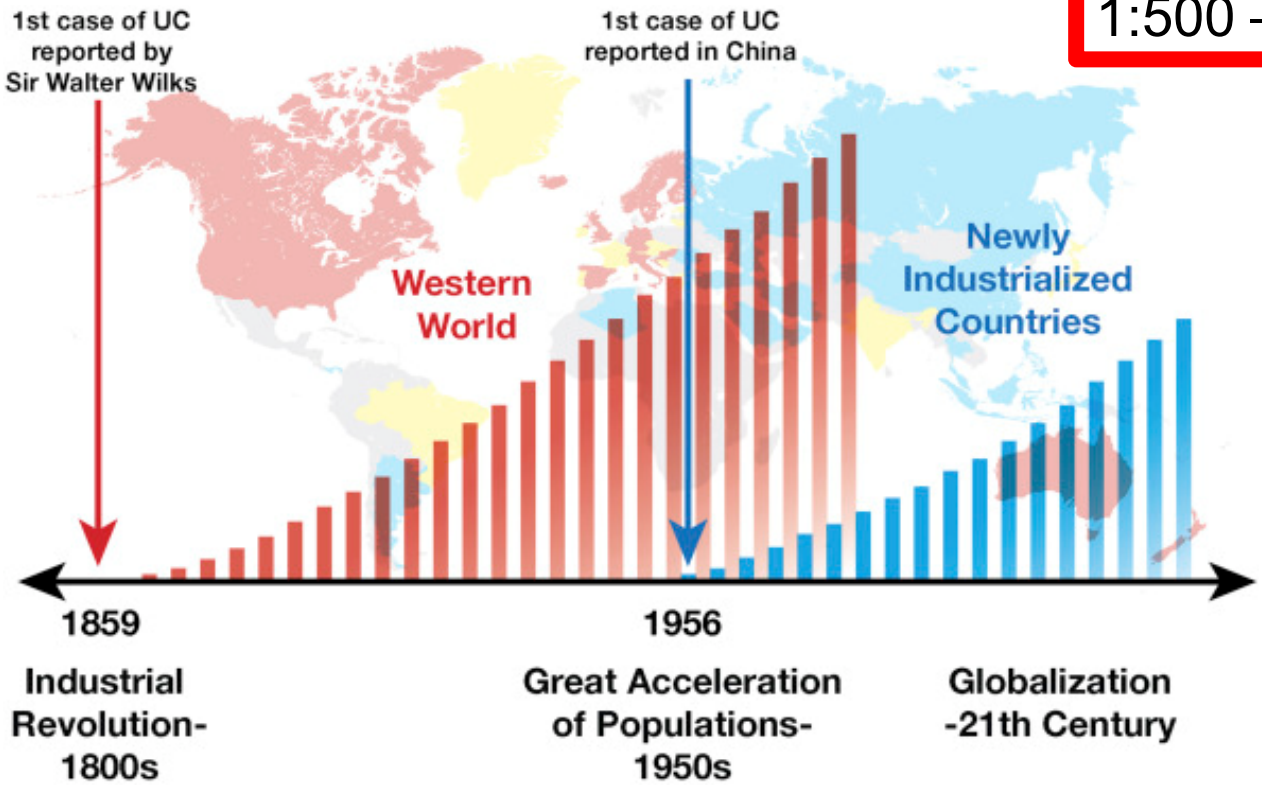
Ulcerative colitis

- Affects only large intestine
- Continuous inflammation
- Mucosal and submucosal layers are affected

Int J Mol Sci. 2019 Oct 26;20(21):5331

IBD – Increasing incidence and prevalence

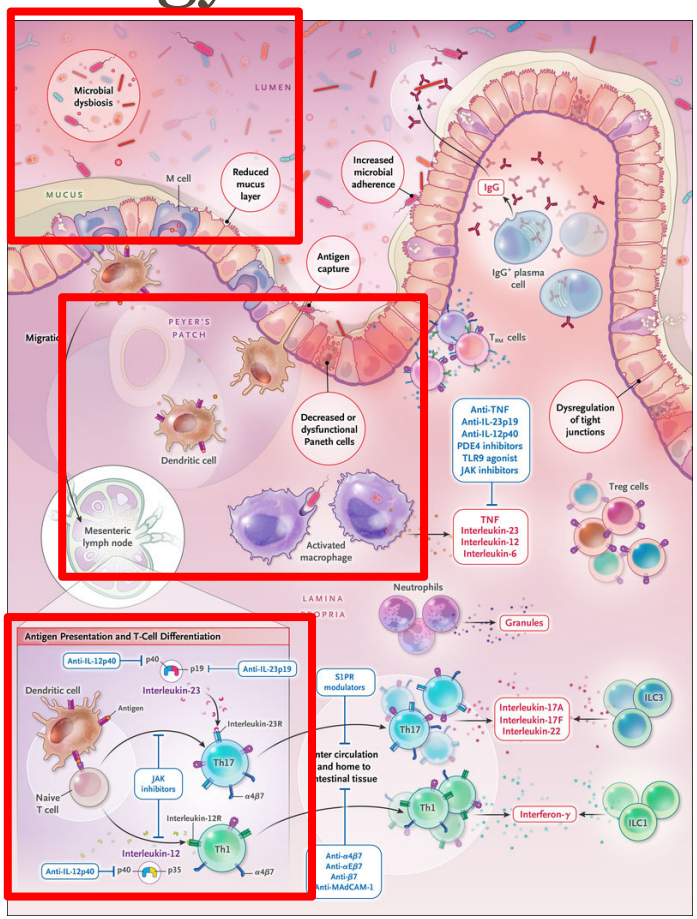
1:500 – 1:200



Gastroenterology. 2017 Feb;152(2):313-321.e2

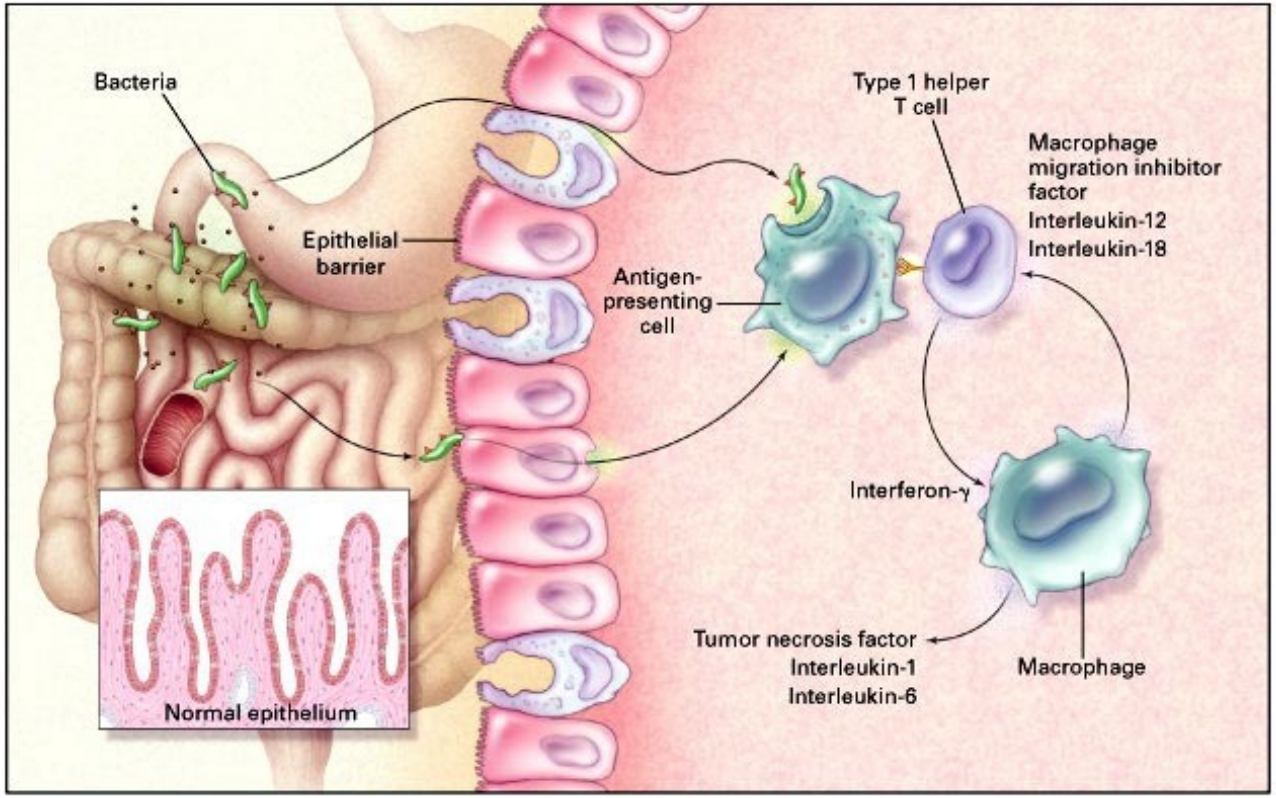
IBD – Pathophysiology

COMPLEX!



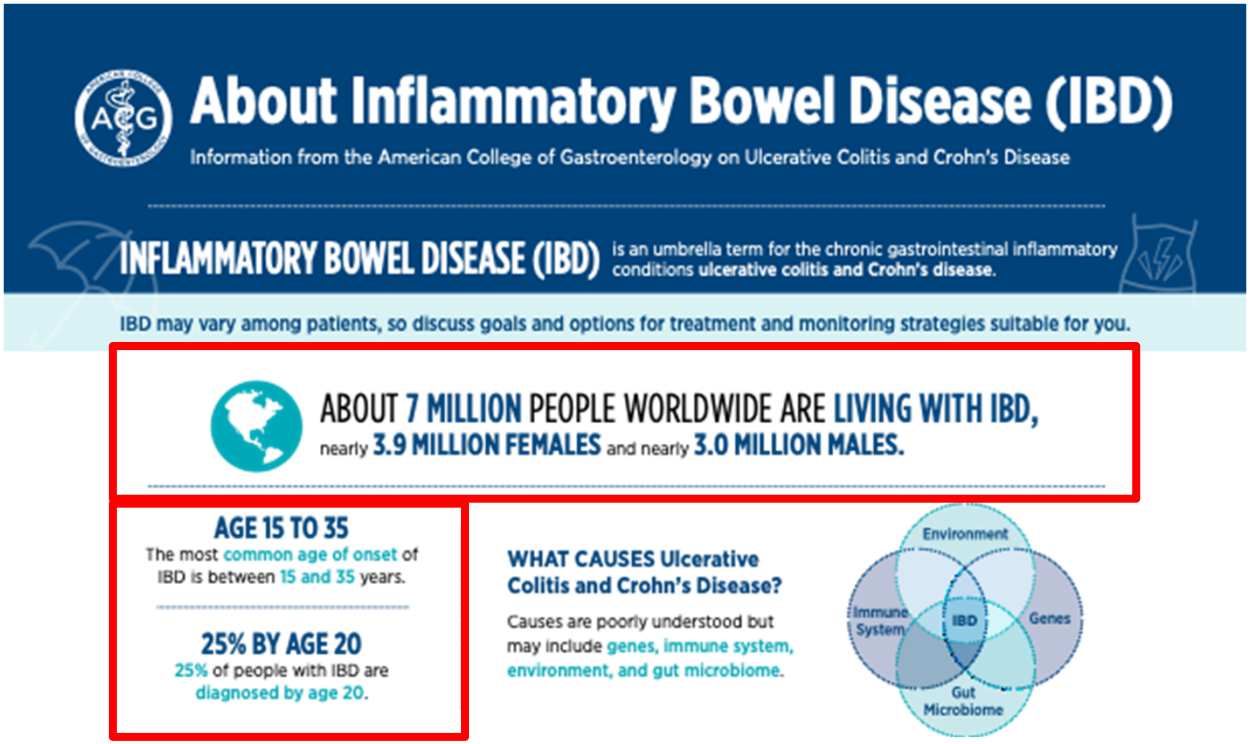
N Engl J Med 2020; 383:2652-2664

IBD – Pathophysiology simplified



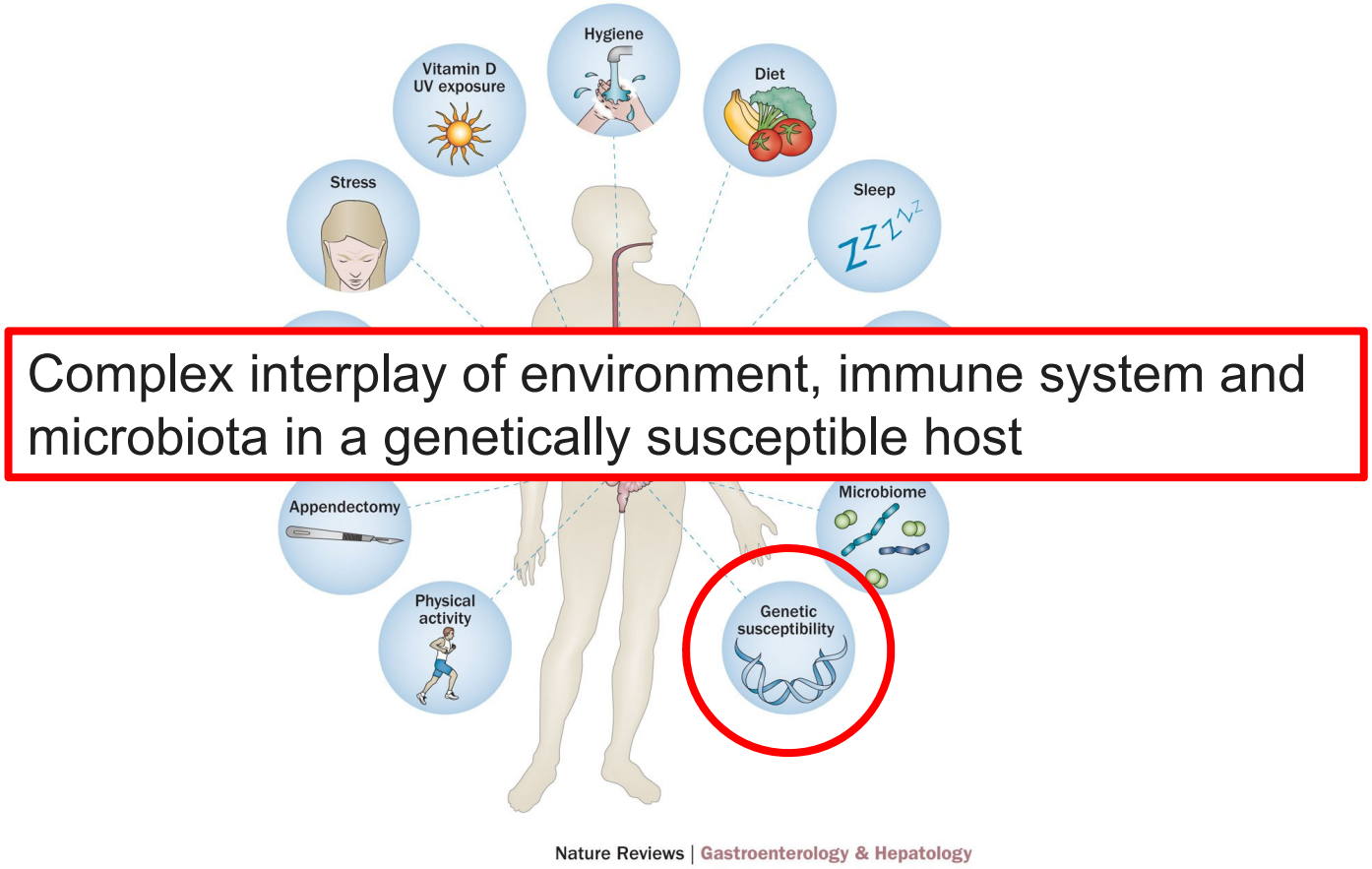
N Engl J Med 2020; 383:2652-2664

IBD – Who are the patients?



https://gi.org/topics/inflammatory-bowel-disease/#tabs4

IBD – Risk factors



Complex interplay of environment, immune system and microbiota in a genetically susceptible host

Nat Rev Gastroenterol Hepatol. 2015 Apr;12(4):205-17

Genetic aspects of IBD

It all started with twin studies…

Table 1 Concordance rates for CD and UC according to three large twin studies

	Monozygotic twins		Dizygotic twins	
	CD	UC	CD	UC
Halfvarsson[7]	50% ($n = 18$)	19% ($n = 16$)	4% ($n = 26$)	0% ($n = 20$)
Orholm[8]	50% ($n = 10$)	14% ($n = 21$)	0% ($n = 27$)	7% ($n = 44$)
Thompson[9]	20% ($n = 25$)	16% ($n = 38$)	7% ($n = 46$)	3% ($n = 34$)

World J Gastroenterol. 2006 Jun 21;12(23):3668-72

The role of genetics

Increased risk for IBD

Increased risk for specific manifestations

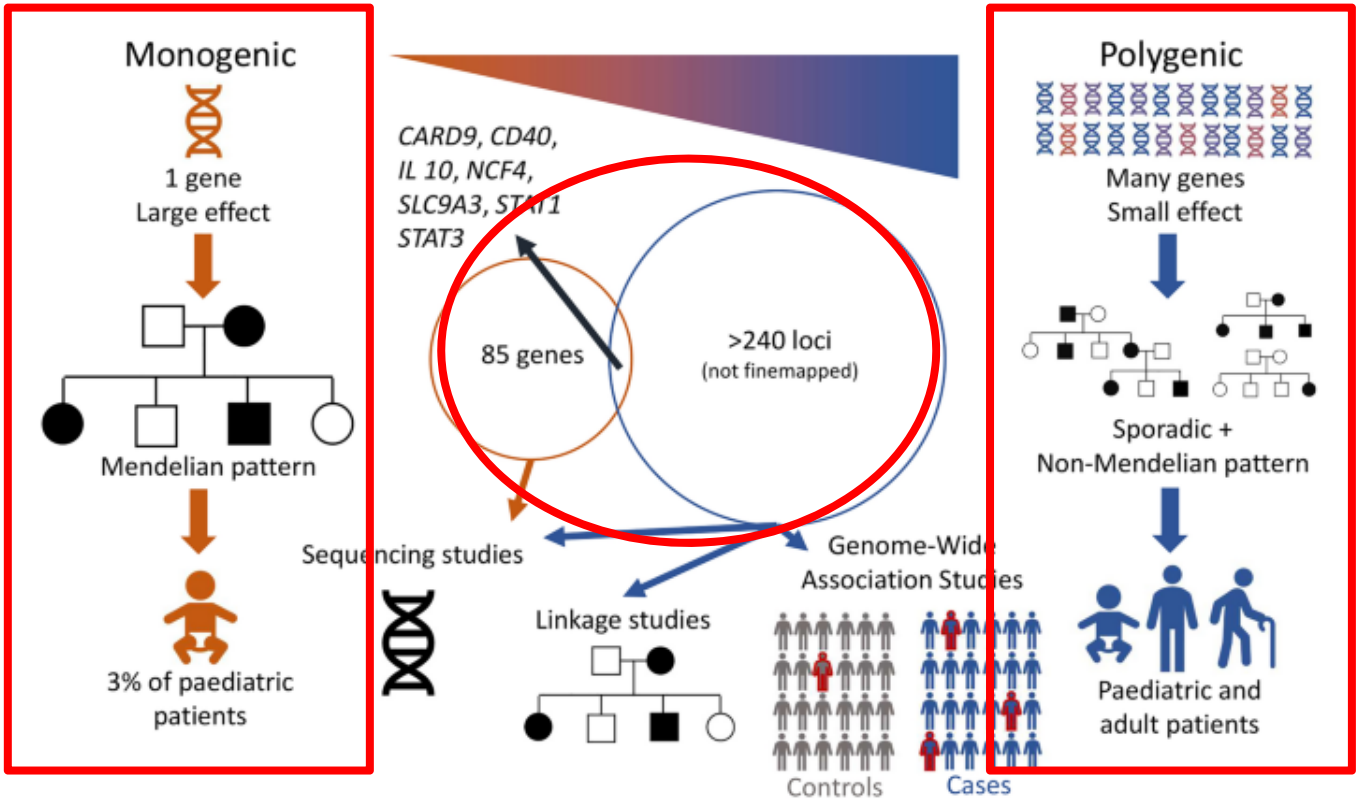
Increased risk for disease progression and disease severity

Therapeutic response

And: from genetics to pathogenic pathways

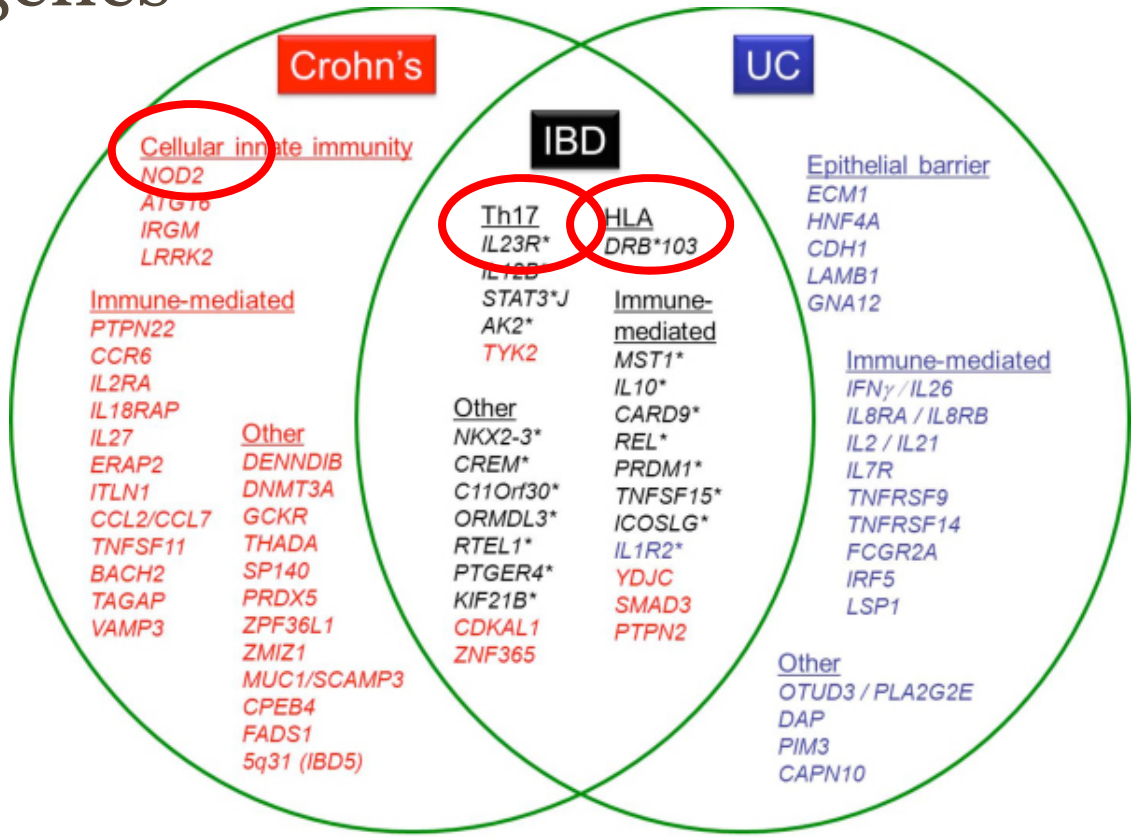
Increased risk for toxicity

IBD is a polygenic disease



Hum Genet. 2023 May;142(5):669-682

IBD risk genes

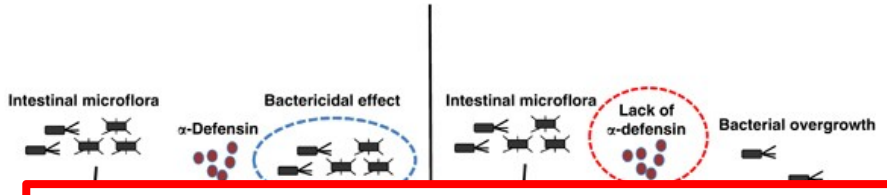


https://www.ibdresearch.co.uk/what-is-inflammatory-bowel-disease-ibd/identifying-the-ibd-genes

NOD2 (=intracellular bacterial sensor)

Disease-related *NOD2* = less active

NOD2 with greatest risk in the development of CD



Mutated *NOD2* alleles occur in 0.5%-2% in healthy individuals

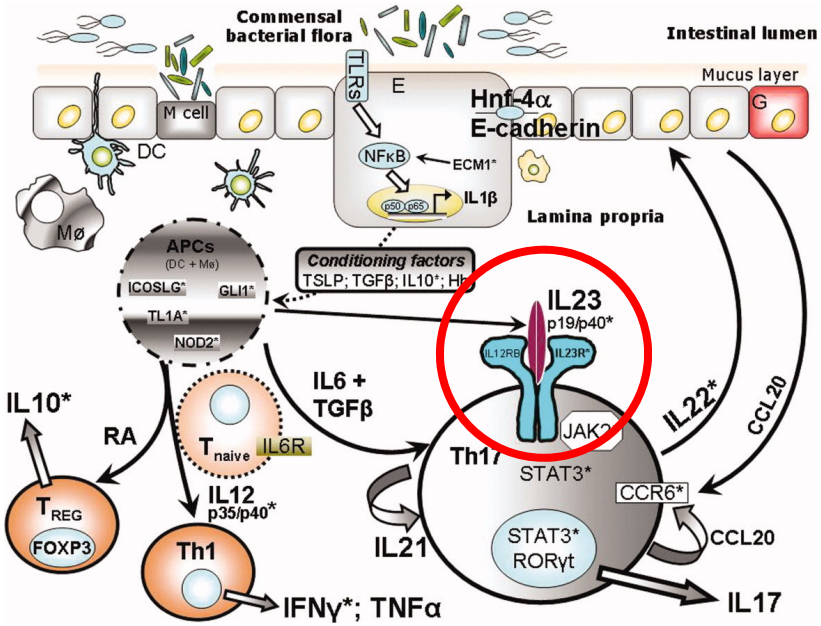
60% of CD patients carry no *NOD2* mutation

-> suggesting synergistic effects of more than one factor in the development of CD

Homozygous or compound heterozygous mutations = 15- to 40-fold increase in CD risk

Mucosal Immunol. 2011 Sep;4(5):484-95

IL23R

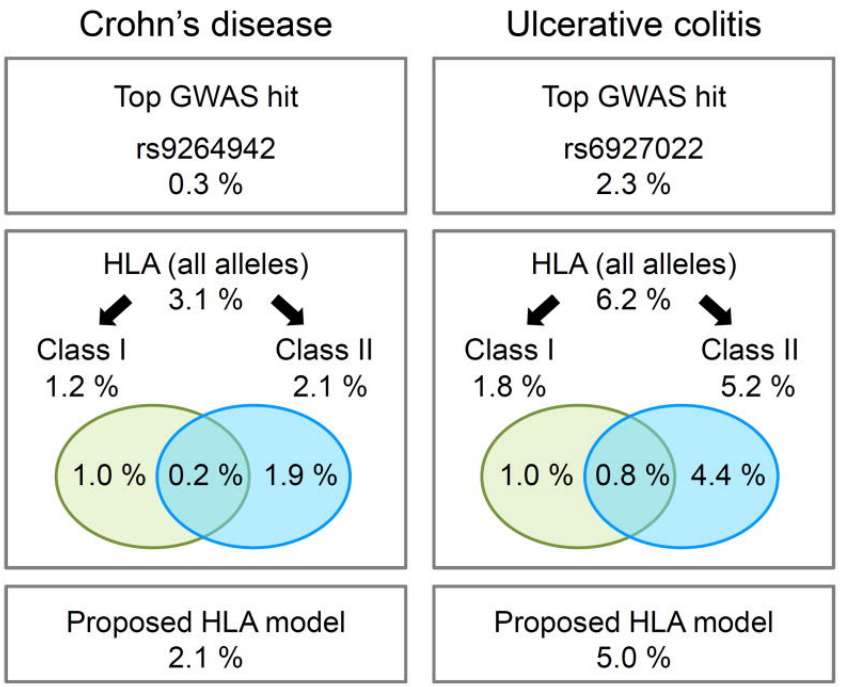


The interleukin-23 receptor *(IL23R)* is located on chromosome *1p31* encoding a subunit of the proinflammatory cytokine IL-23 receptor

Variants associated with a protection against IBD (loss of function)

Inflamm Bowel Dis. 2011 Mar;17(3):831-48

HLA



Most consistent association in IBD with ***HLA-DRB1*** and *HLA-DQB1*

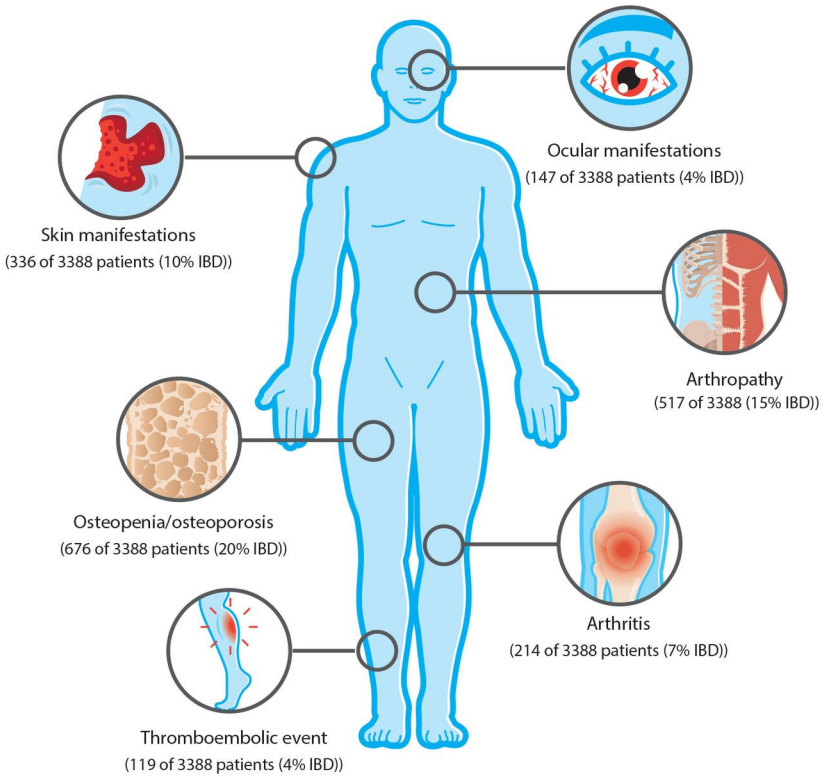
*HLA-DRB1*0103* is strongly associated with both entities, UC and CD

This variant shows particularly strong association in patients with severe, extensive UC and those with colonic CD

Overall, influence of *HLA* has been found to be greater in UC than CD

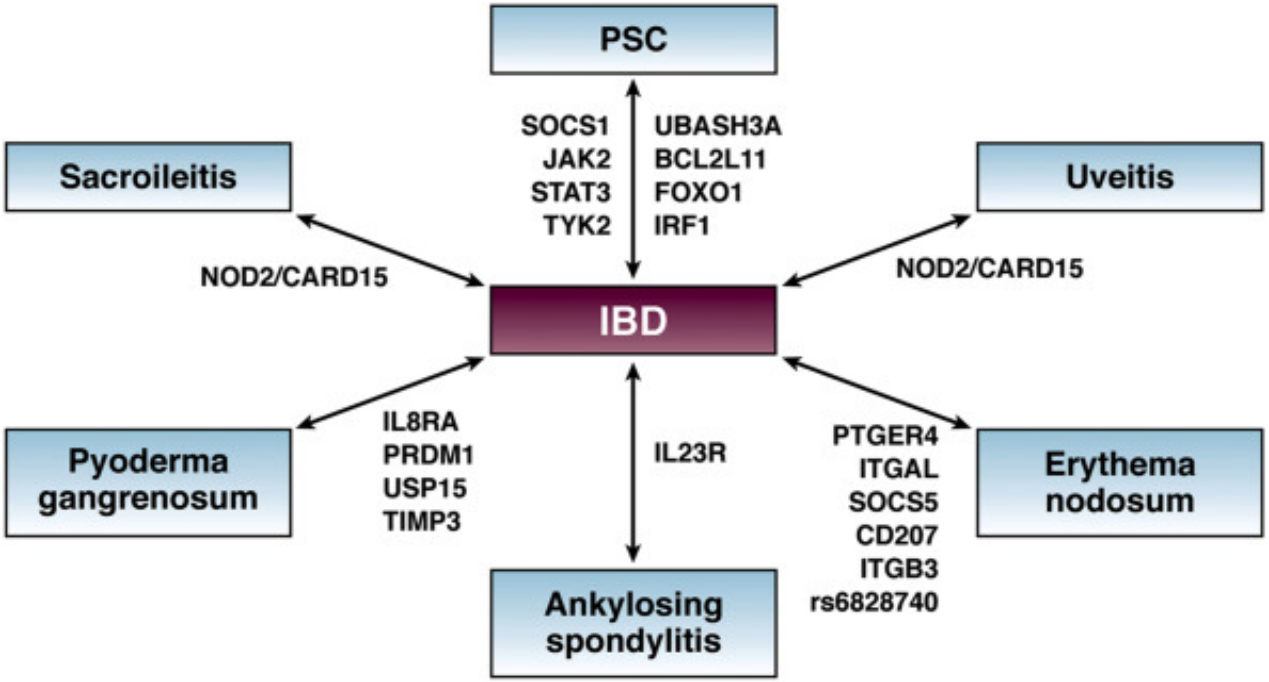
Nat Genet. 2015 Feb;47(2):172-9.
Front Immunol. 2016; 7: 30

Extraintestinal manifestations – IBD as a systemic disease



BMJ Open. 2017 Nov 8;7(11):e016695

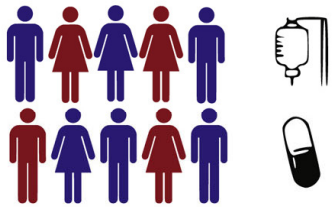
Risk genes for extraintestinal manifestations



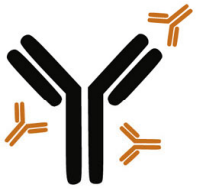
Gastroenterology. 2021 Oct;161(4):1118-1132

Disease course, pharmacogenomics and drug toxicity

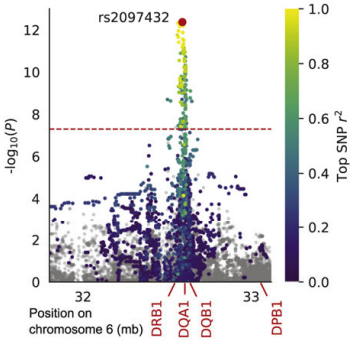
HLA-DQA1*05 Carriage Associated With Development of Anti-Drug Antibodies to Infliximab and Adalimumab in Patients With Crohn's Disease



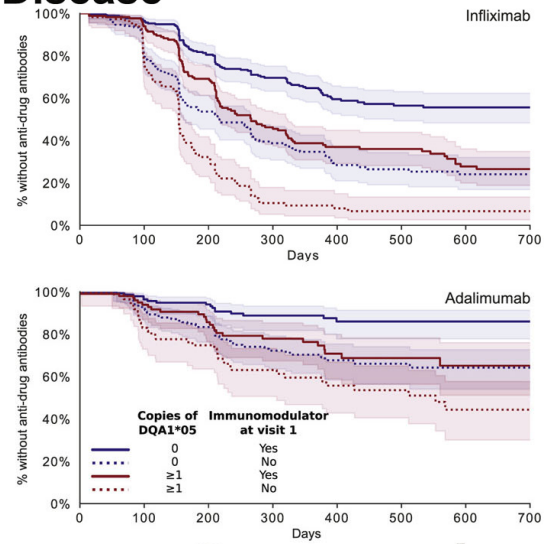
1240 patients with Crohn's disease treated with infliximab or adalimumab ± immunomodulator



Longitudinal measurement of anti-drug antibodies



Genome-wide association study identifies DQA1*05; hazard ratio 1.90 (95%CI 1.60-2.25)

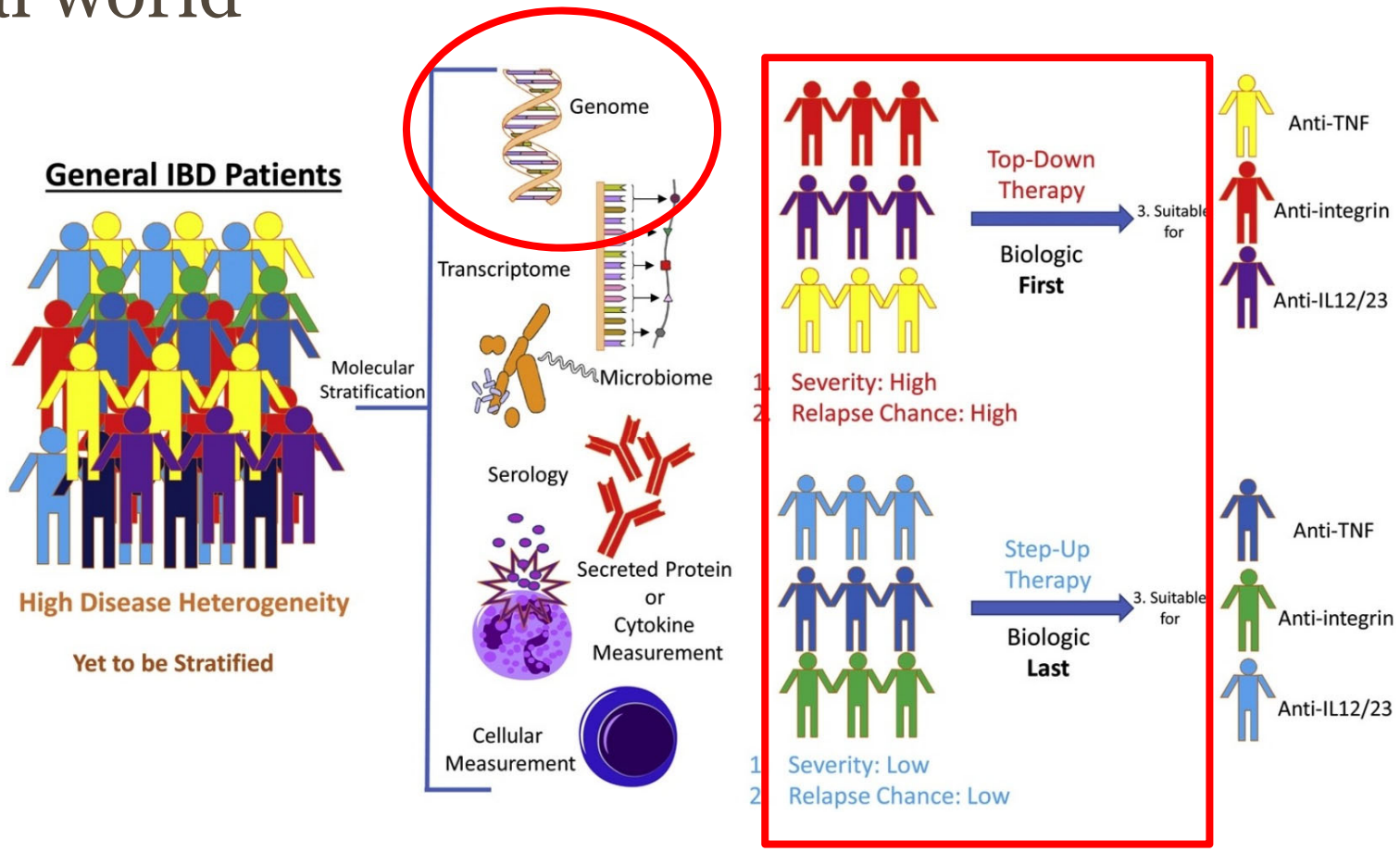


Gastroenterology

Front Med (Lausanne). 2022 Oct 6:9:1025375
Gastroenterology. 2020 Jan;158(1):189-199

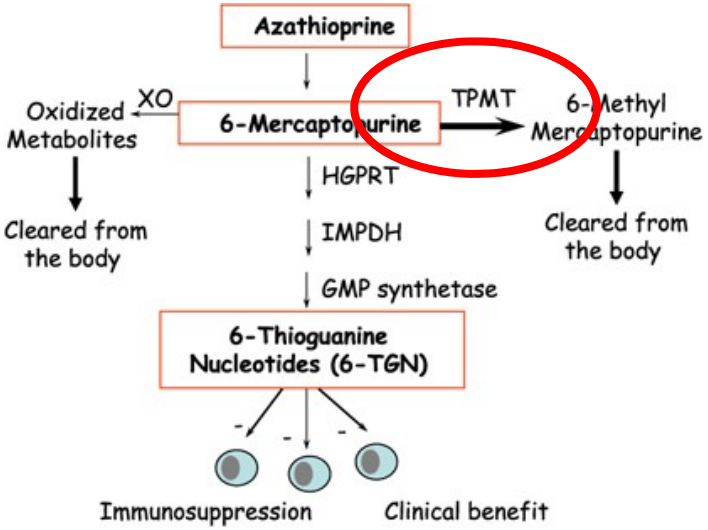
Clinical implications

Ideal world



Pharmacol Res. 2019 Oct:148:104442

Reality



Concordance genotyping / phenotyping: 94.5 %

n=12,663

TPMT genotype	TPMT enzyme activity (U/mL pRBC) n, conditional proportions % (95% CI)		
	High	Intermediate	Low
Wildtype	**10,864** 99.1 (98.9-99.2)	**578** 35.4 (33.0-37.7)	**1** 1.6 (0.0-8.8)
Heterozygous defective	**103** 0.9 (0.8-1.1)	**1,053** 64.4 (62.0-66.7)	**9** 14.8 (7.0-26.2)
Homozygous defective	**0**	**4** 0.2 (0.1-0.6)	**51** 83.6 (71.9-91.8)
Total:	**10,967** (100%)	**1,635** (100%)	**61** (100%)

Eur J Hum Genet. 2009 Aug; 17(8): 991–998
Basic Clin Pharmacol Toxicol. 2021 Jan;128(1):52-65

Take home messages I

Many risk factors

Not a genetic disease

Some predictors for severe disease course

However, only TPMT genotyping has made it into clinical practice

Other “inflammatory bowel diseases”: eosinophilic esophagitis

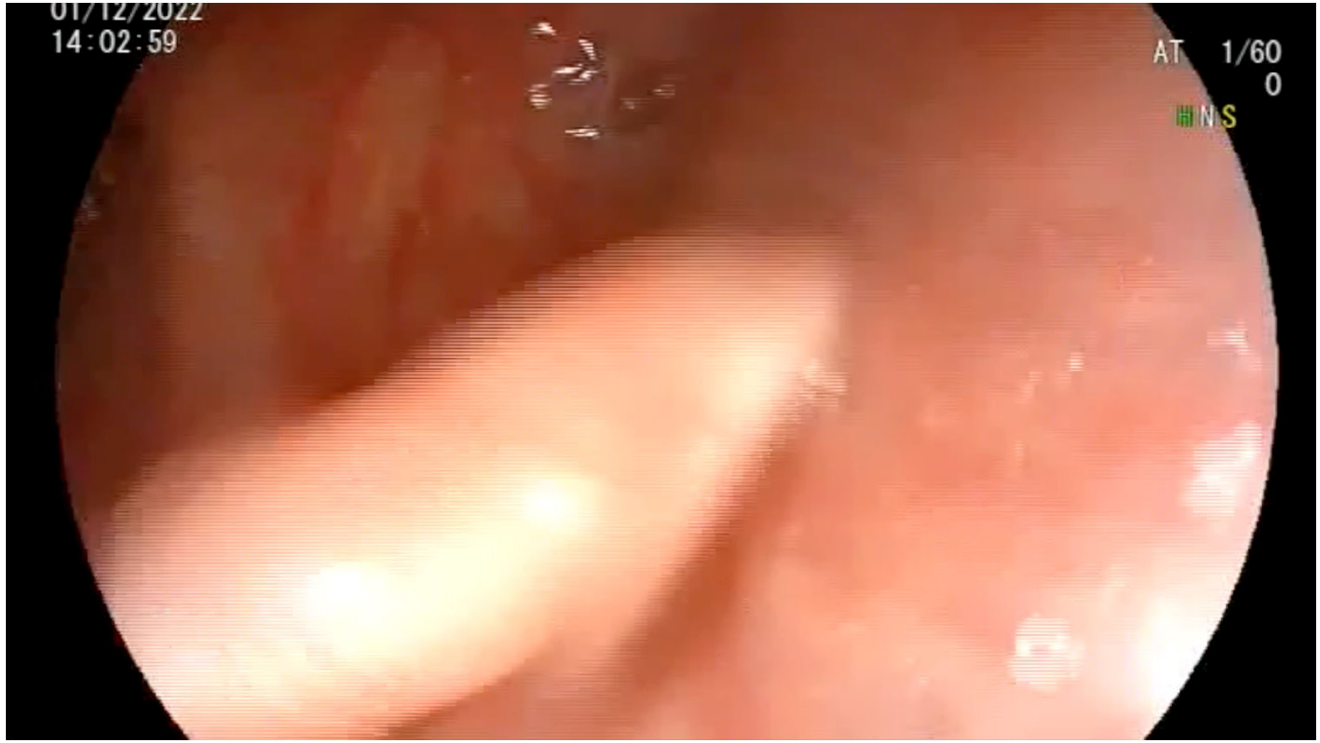
EoE – A clinical case

19 yo patient

Brother with EoE

Food bolus impaction for 24h

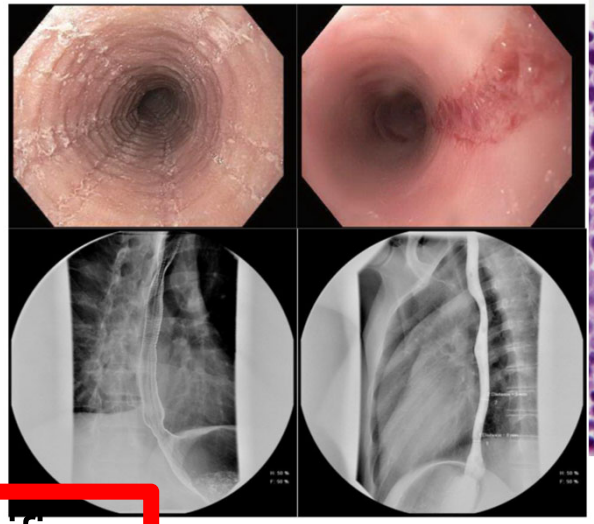
Complete dysphagia



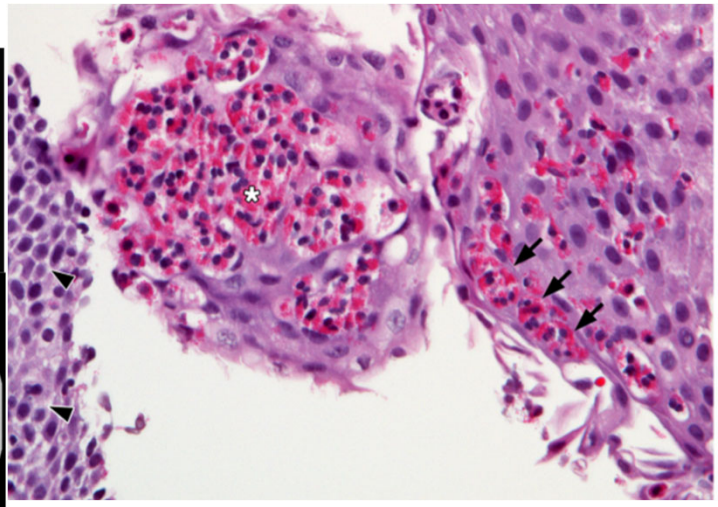
EoE – A clinico-pathological diagnosis

Symptoms

Endoscopy



Histology



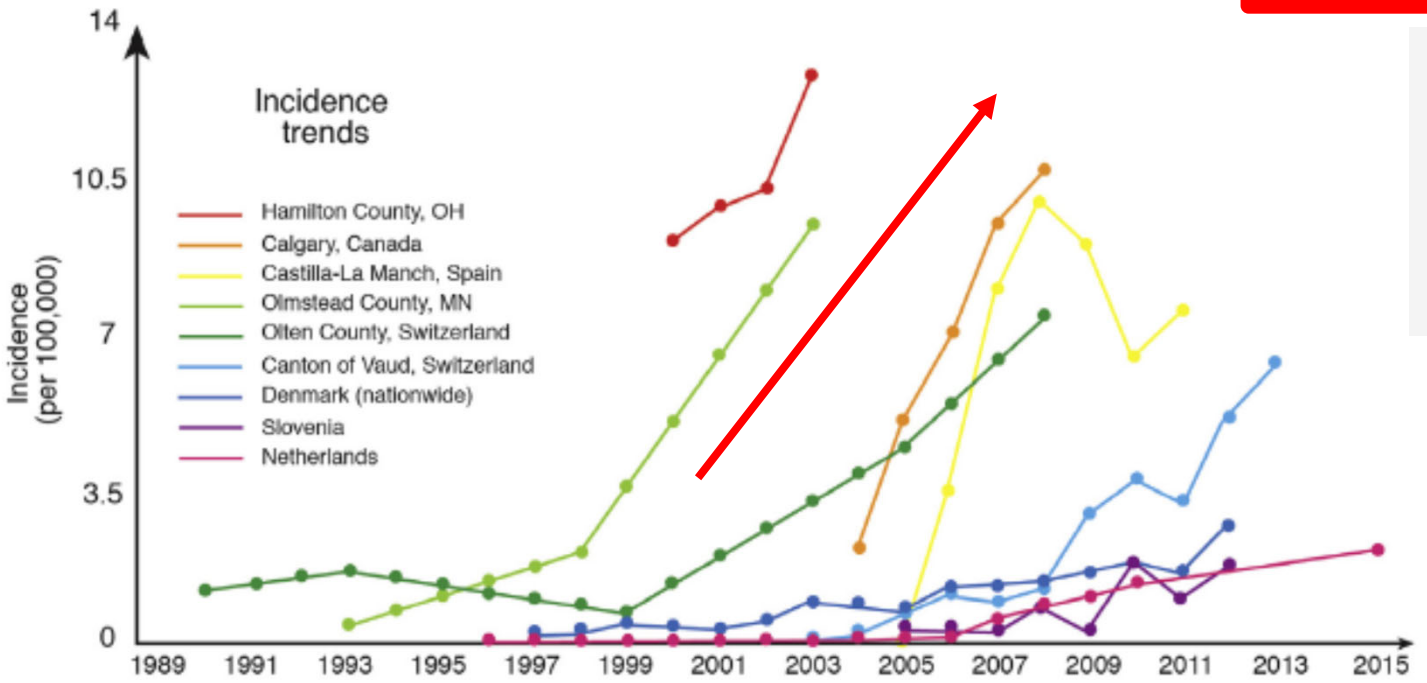
Children with non-specific presentation

15 eosinophils per hpf

N Engl J Med. 2015 Oct 22; 373(17): 1640–1648;
https://www.eoe.de/ueber-eoe/definition-eosinophile-oesophagitis-eo

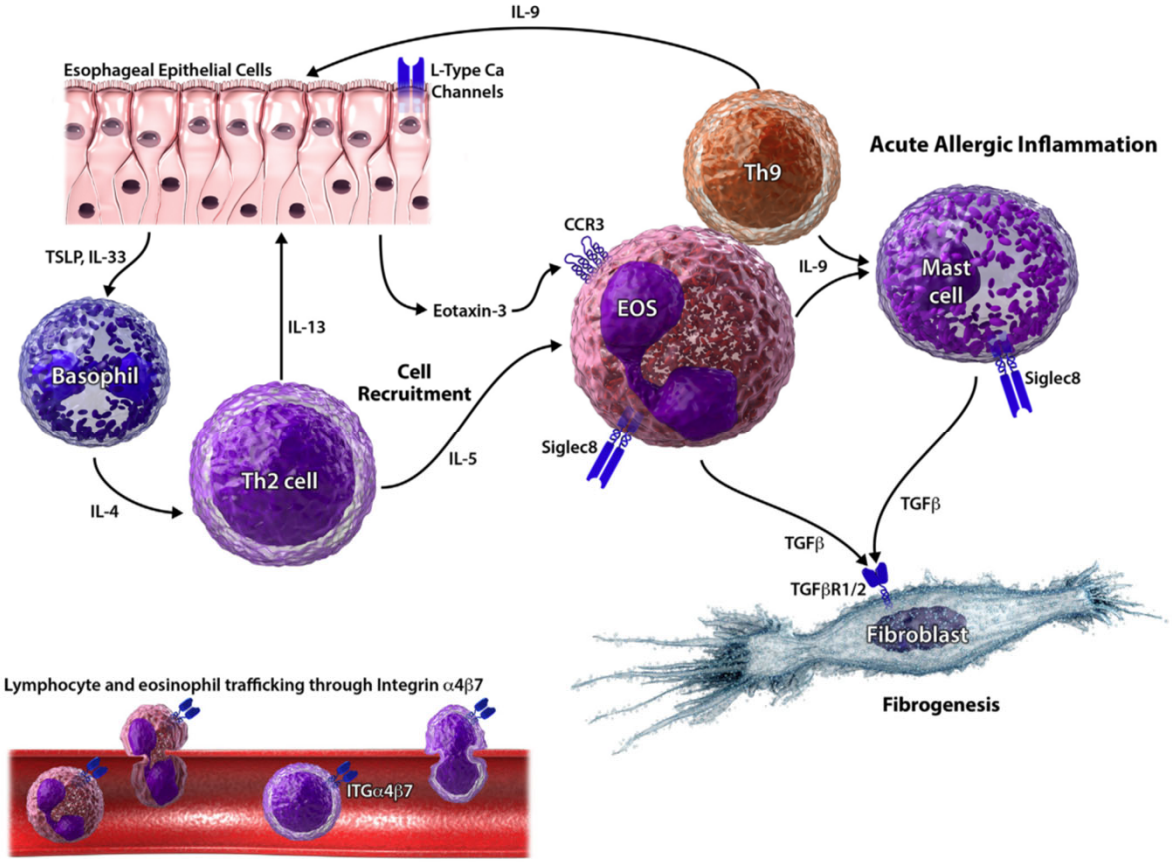
EoE – Increasing incidence and prevalence

1:2000



Dis Esophagus. 2018 Aug 1;31(8):doy015

EoE - Pathophysiology



J Allergy Clin Immunol. 2020 Jan;145(1):38-45

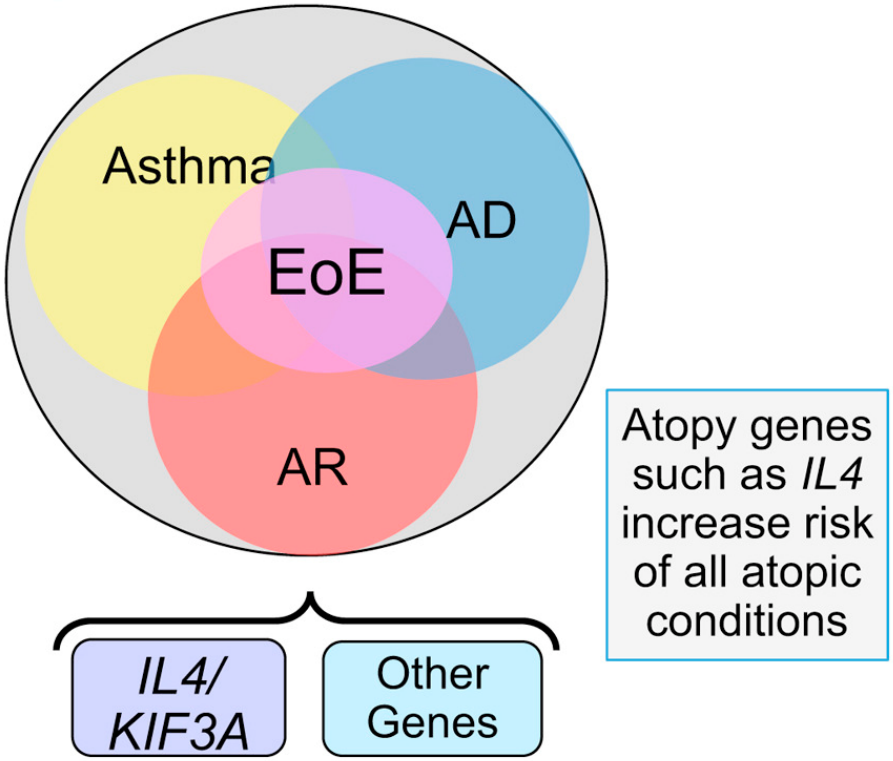
EoE – Who are the patients?

Atopic comorbidities

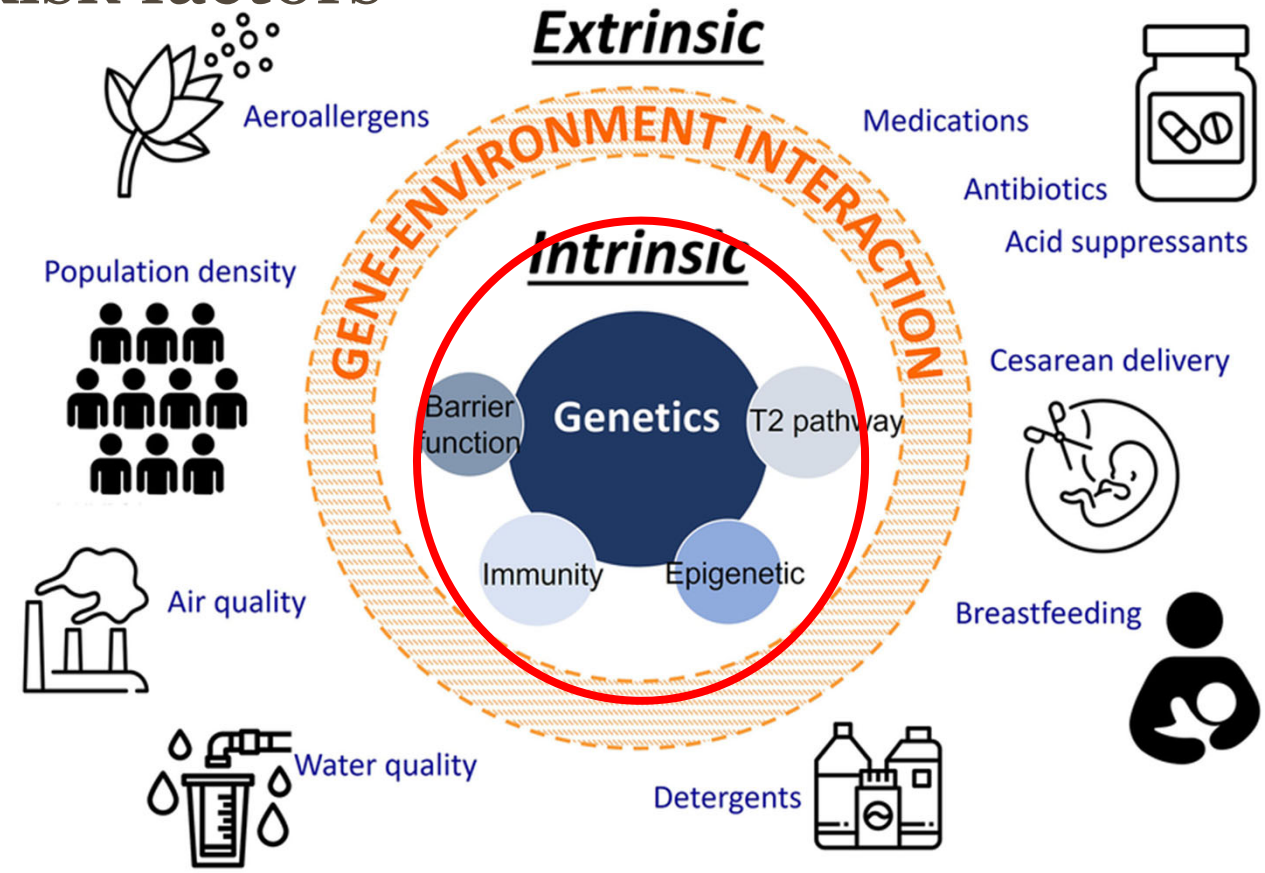
Children and young adults

Male predominance 3:1

Genetic components: TSLP, CAPN14

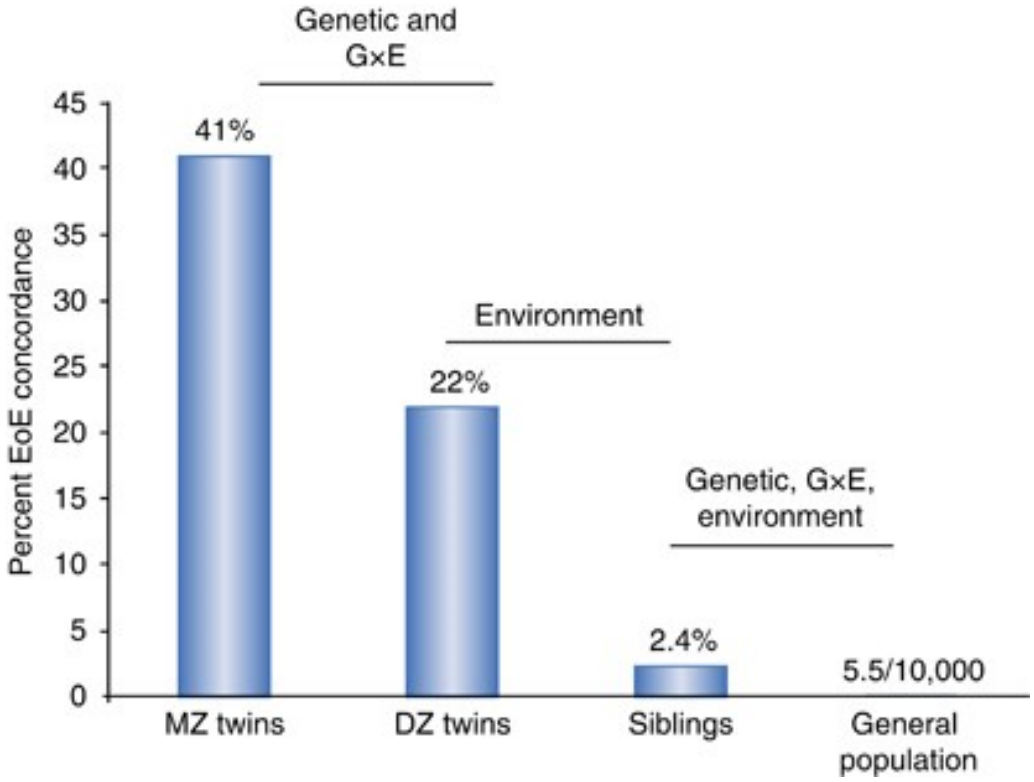


EoE – Risk factors



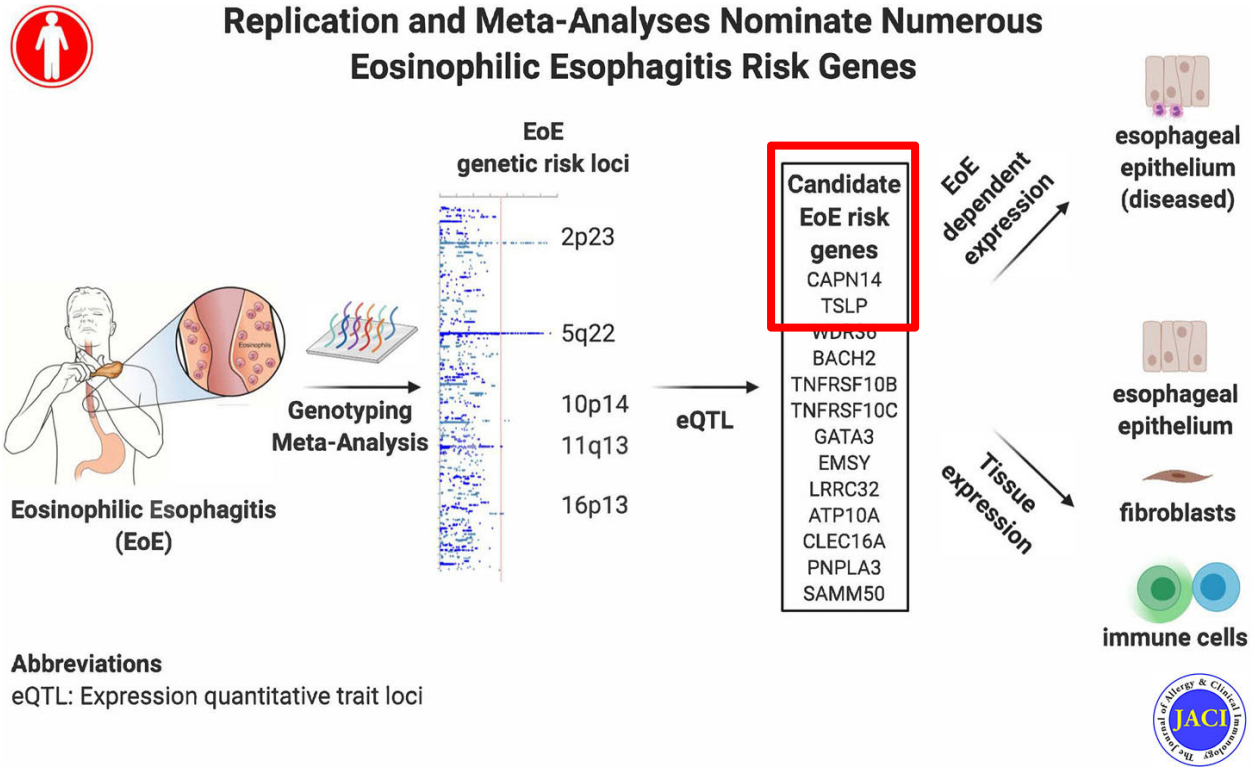
Curr Allergy Asthma Rep. 2022 Dec;22(12):163-170.
https://www.nytimes.com/wirecutter/reviews/best-dish-soap

It all started with twin studies…



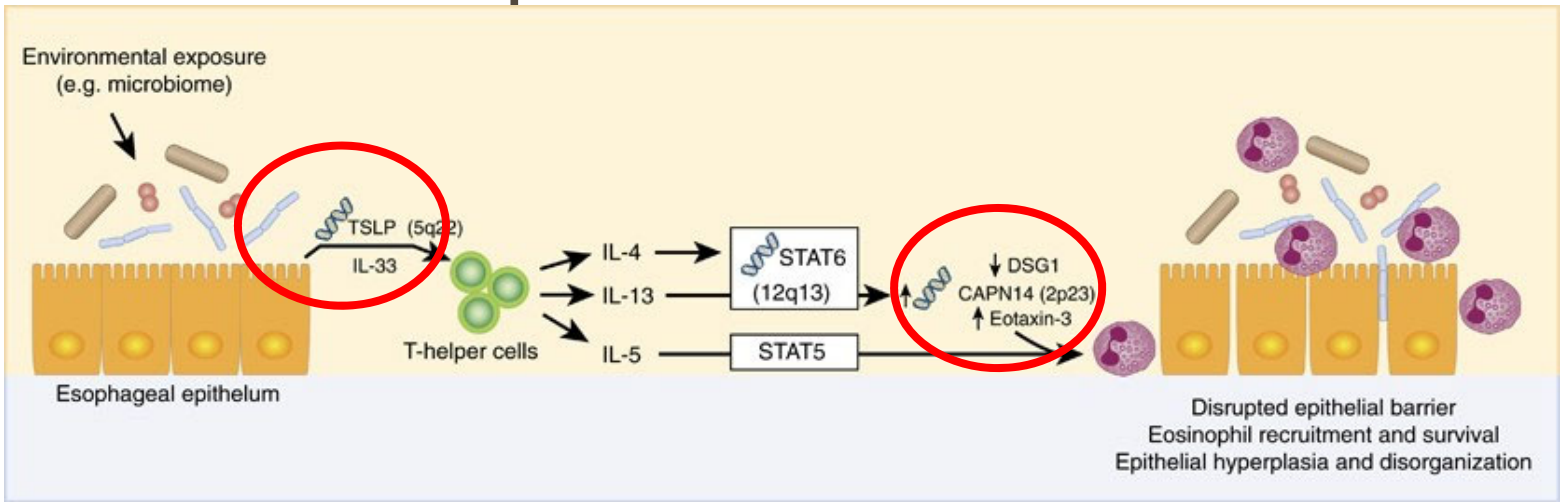
Mucosal Immunol. 2017 May;10(3):580-588

EoE risk genes



J Allergy Clin Immunol. 2021 Jan;147(1):255-26

TSLP and CAPN14

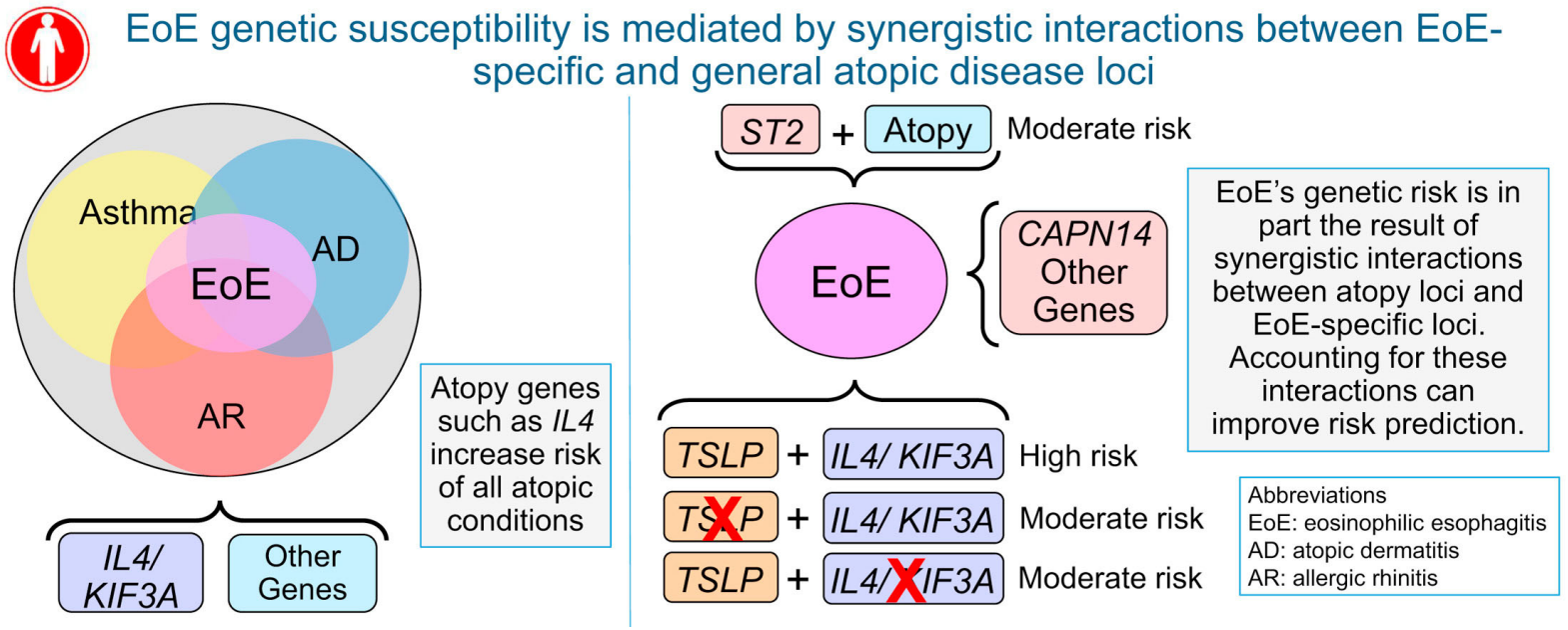


TSLP = most dominant genetic variant associated with EoE, largely independent of allergy

CAPN14 = genetic variants in the promoter region associated with EoE susceptibility

Mucosal Immunol. 2017 May;10(3):580-588

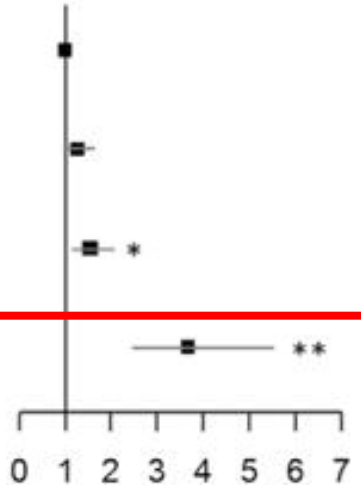
EoE risk genes – EoE as a systemic disease



J Allergy Clin Immunol. 2018 May;141(5):1690-1698

EoE risk genes – EoE as a systemic disease

IL4	*TSLP*	EoE (n) / no EoE (n)	OR (95% CI)
-	-	275/409	1 †
-	+	180/213	1.25 (0.96, 1.62)
+	-	139/131	1.55 (1.15, 2.09) *
+	+	99/48	3.67 (2.48, 5.52) **



J Allergy Clin Immunol. 2018 May;141(5):1690-1698

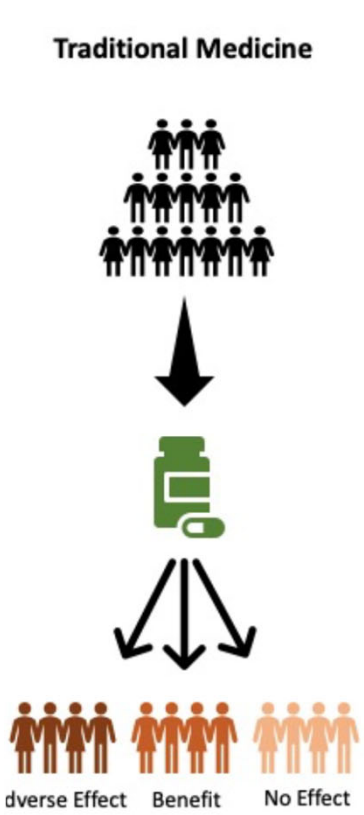
Take home messages II

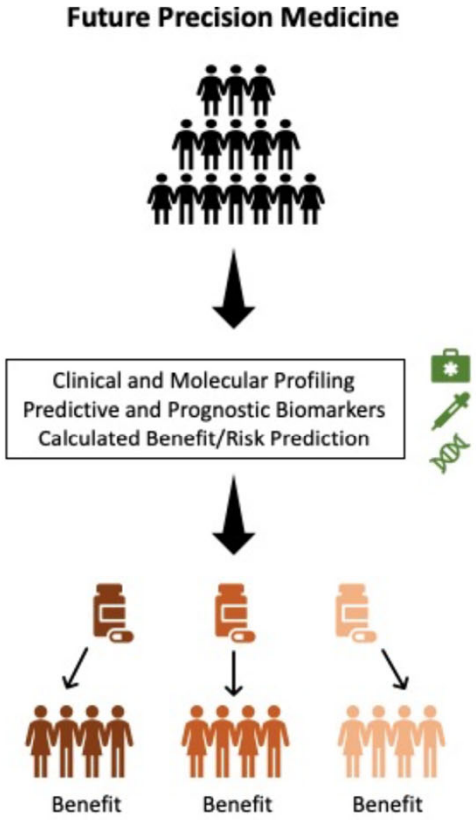
Family history considerably increases the risk for EoE

Risk genes for EoE highlight the pathogenic overlap with other Th2 mediated diseases

However, no clinical implication

Outlook





Mol Diagn Ther. 2024 Jan;28(1):27-35

Thank you for your attention

CEGIR (U54 AI117804) is part of the Rare Disease Clinical Research Network (**RDCRN**), an initiative of the Office of Rare Diseases Research (ORDR), **NCATS**, and is funded through collaboration between **NIAID, NIDDK, and NCATS**. CEGIR is also supported by patient advocacy groups including **APFED, CURED and EFC**

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