

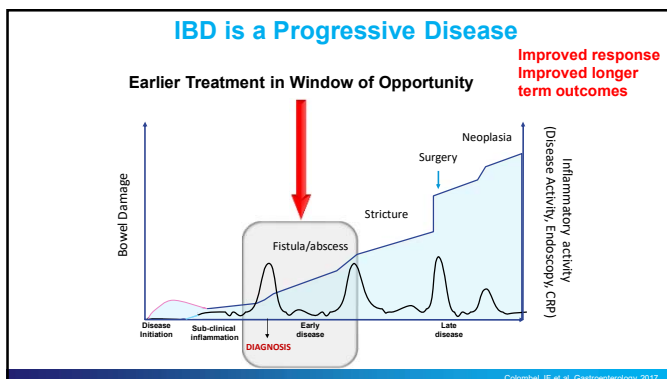


1

Disclosures

- Advisory Board and Consulting
 - AbbVie, Bristol Myers Squibb, Celltrion, Genentech, Janssen, Lilly, Pfizer, Takeda
- Research Funding (past and present)
 - Crohn's and Colitis Foundation
 - AbbVie, Boehringer Ingelheim, Pfizer, Prometheus Laboratories
 - NIH K23 and R03
 - Department of Defense Impact Award and Clinical Trial Award
 - Helmsley Foundation

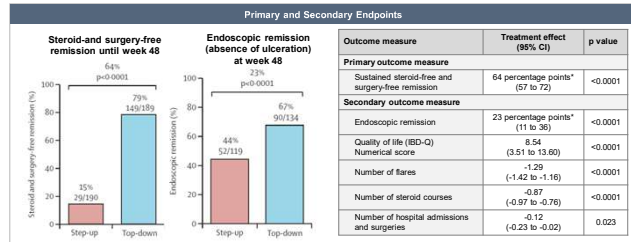
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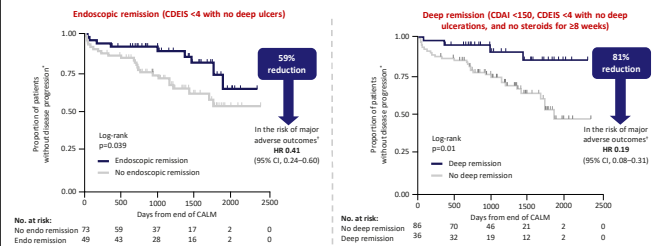
PROFILE Trial: Early Intervention Within Weeks of Diagnosis

Top-down treatment with combination infliximab plus immunomodulator achieved substantially better outcomes at 1 year than accelerated step-up treatment.



4

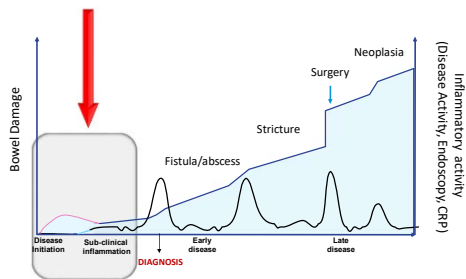
Significantly Lower Risk of Disease Progression in Early CD with Endoscopic or Deep Remission at 48 Weeks



5

Is the Optimal Window of Opportunity Actually Before Diagnosis: Disease Interception and/or Prevention

Best Window of Opportunity?



6

Why do we need to think about IBD prediction and prevention? Need for new paradigms

- Chronic disease affecting young people, no cure
- Current therapies fail in >50% of patients
- High surgery rates, disability, mental health comorbidity, etc.
- Rising incidence in newly industrialized countries (Africa, Asia, and South America) (growing population) – disparity in care
- Rising incidence in children across the world
- Expected prevalence >1% in some areas of the world by 2030
- Total annual IBD related healthcare costs greater than \$8.5 billion (2018, per CDC)



Shaw C, Ng, Lancet 2017, Kaplan G, Winer, JN, NRGH 2020, Agrawal M Gastroenterology 2022, Benichou E Gastroenterology 2022

7

Predicting and Preventing IBD may seem ambitious... ...But it is already being pursued in other immune mediated diseases!

Type 1 Diabetes

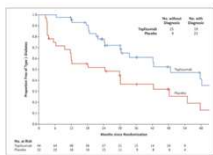


Figure 1. Effects of Teplizumab on Development of Type 1 Diabetes. (Shaw et al, Lancet 2019). Kaplan-Meier estimates of the proportion of participants in whom clinical diabetes was first diagnosed. The overall hazard ratio was 0.48 (95% confidence interval [CI], 0.22 to 1.04, two-sided $P = 0.006$) by adjusted Cox proportional hazards model. The median time to diagnosis of type 1 diabetes was 48.4 months in the teplizumab group and 34.4 months in the placebo group. The number of participants with or without a diagnosis of clinical type 1 diabetes is shown in parentheses at the conclusion of the trial. Tick marks indicate censored data.

Treatment with a single 14-day course of teplizumab (anti-CD3) delayed the time to diagnosis of type 1 diabetes in those at-risk for developing T1DM.

N Engl J Med 2019; 381:603-613

Rheumatoid arthritis

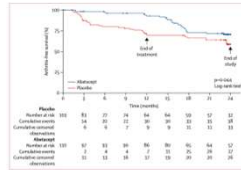


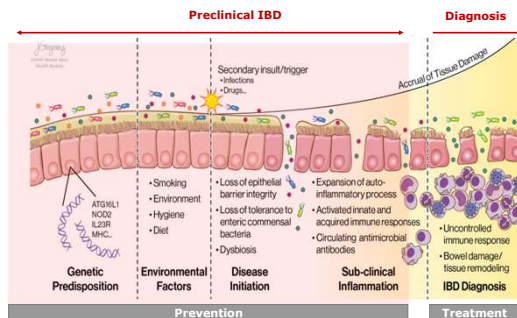
Figure 2. Arthritis-free survival by group.

APPRAS Study: Abatacept (anti-CD80/CD86) for 12 months in RF and anti-CCP + patients with clinical synovitis but not meeting objective RA criteria delayed onset of overt RA

Cope A et al Lancet 2020

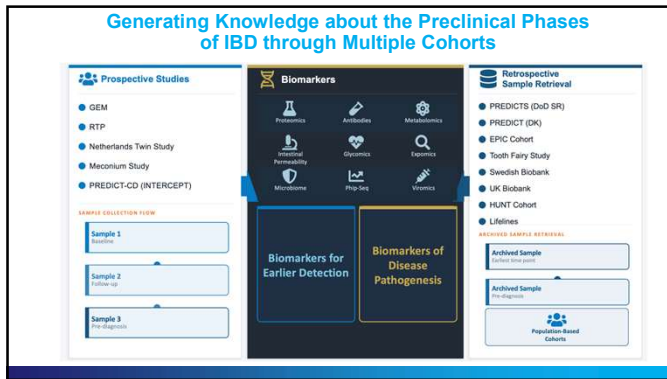
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We Know that IBD Starts Many Years Before Diagnosis

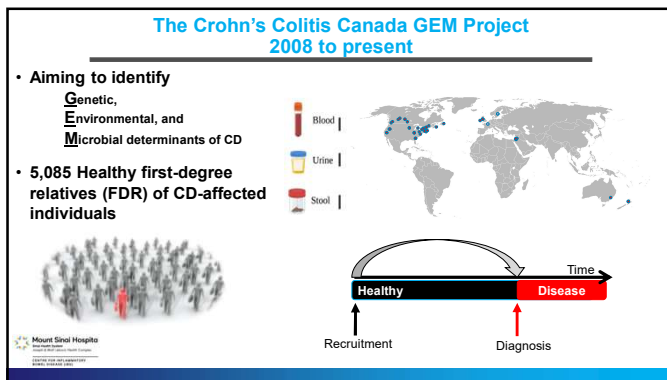


Torres J, et al Gut 2016

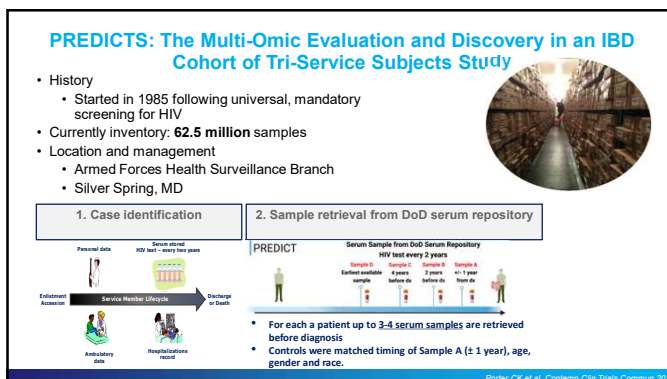
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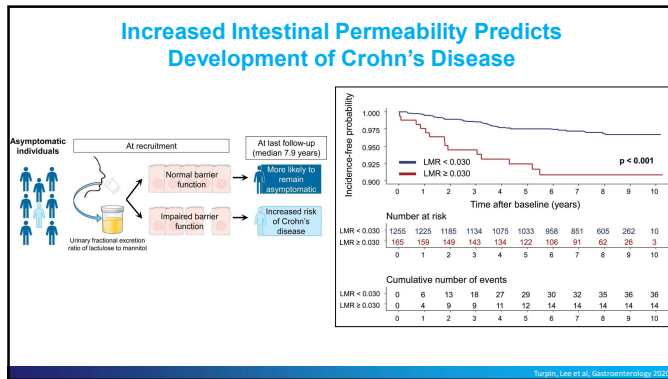
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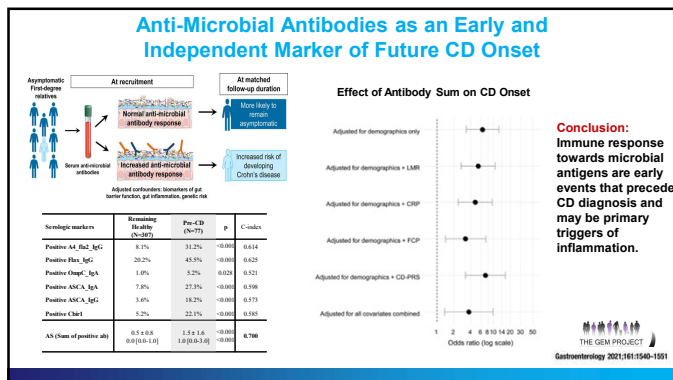
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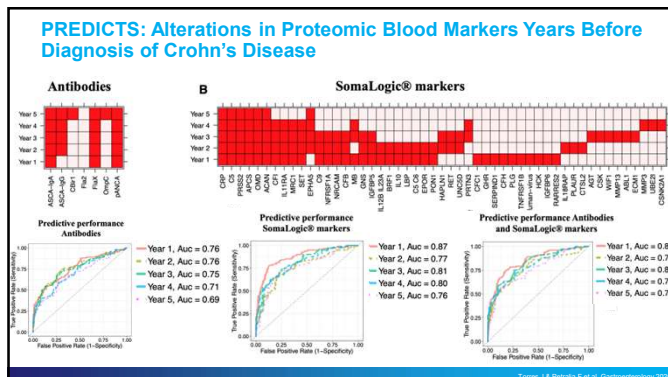
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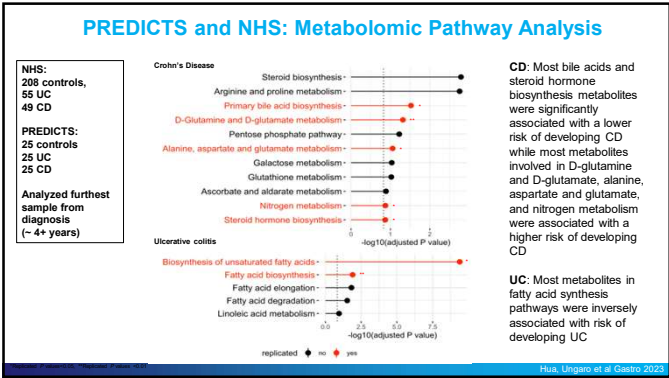
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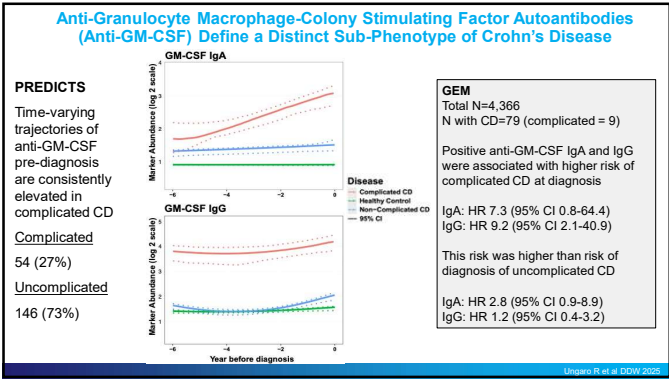
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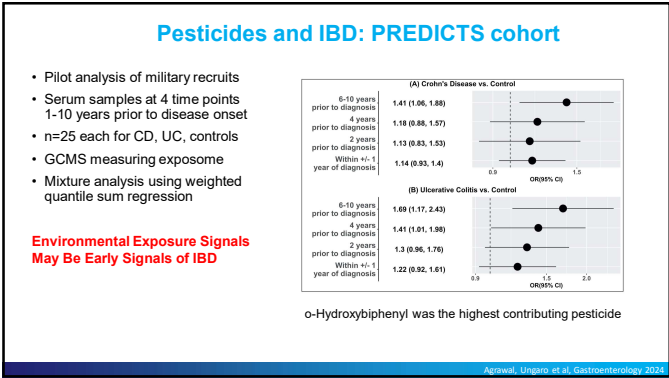
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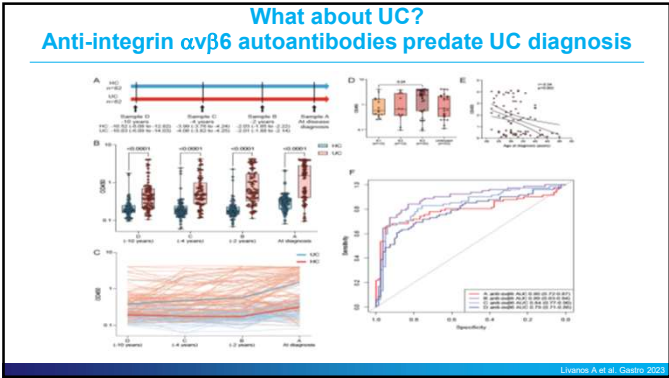
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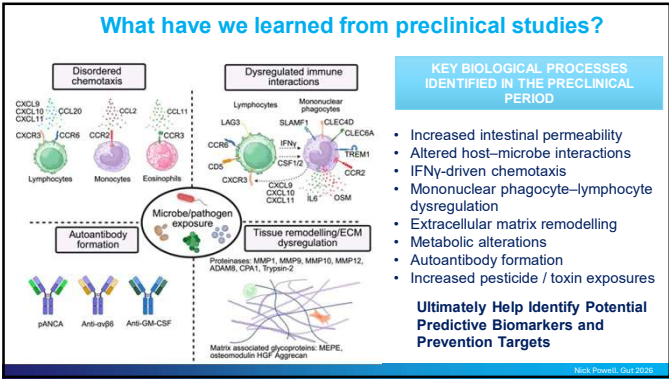
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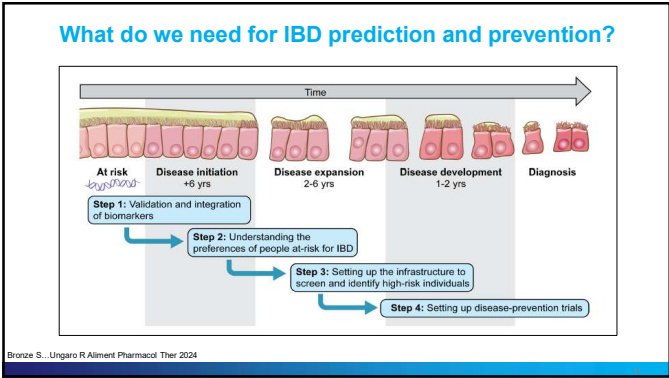
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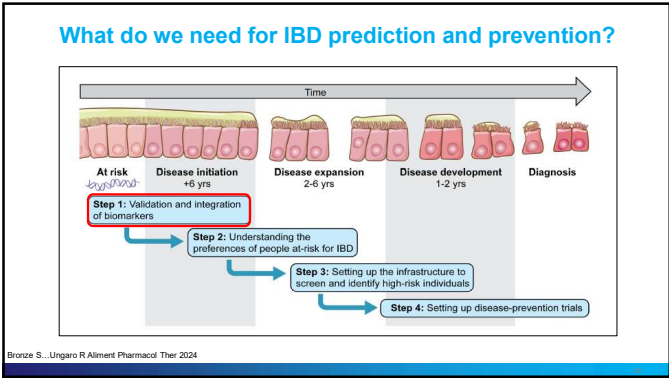
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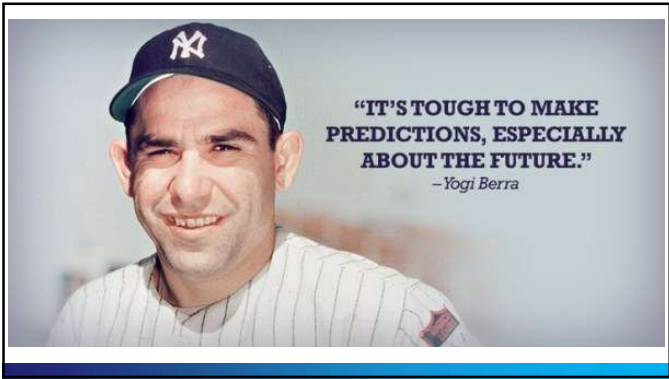
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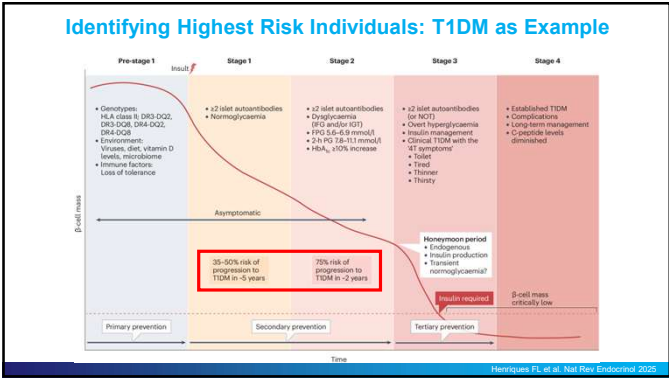
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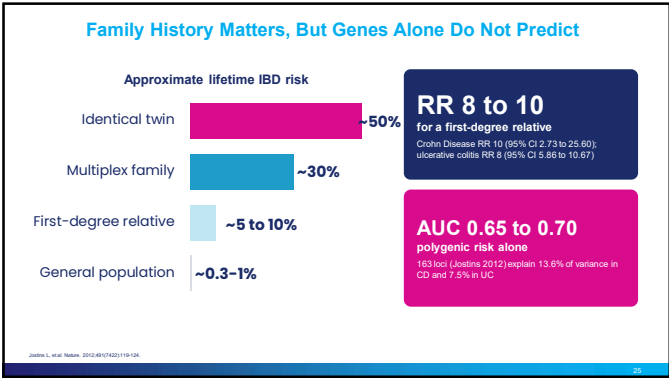
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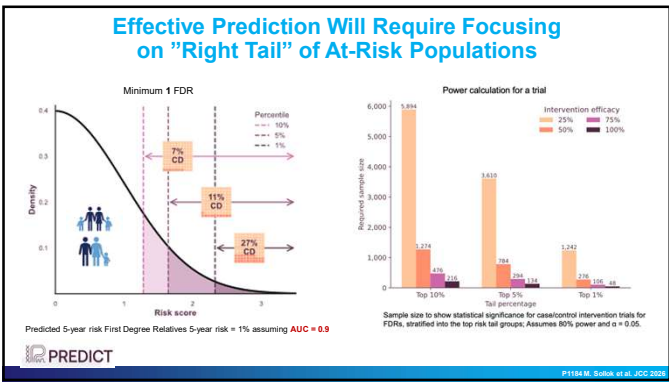
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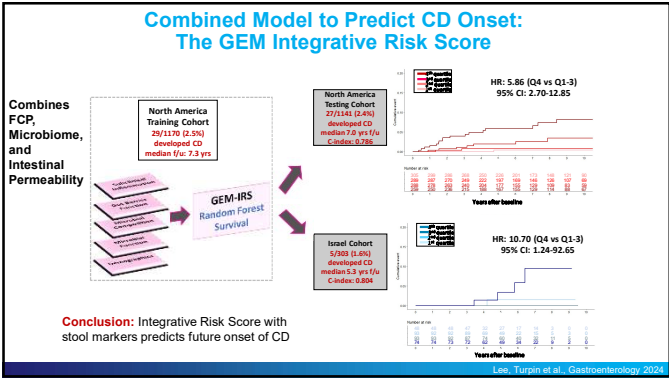
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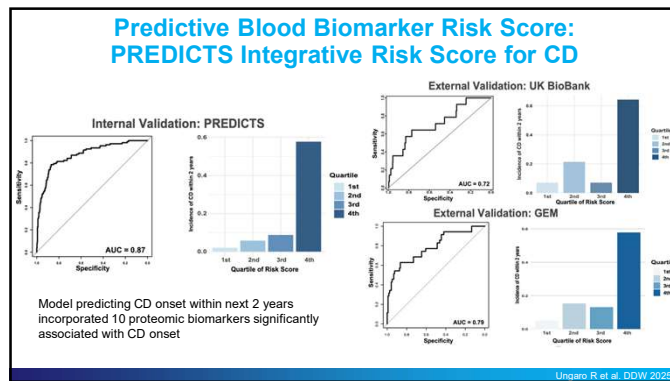


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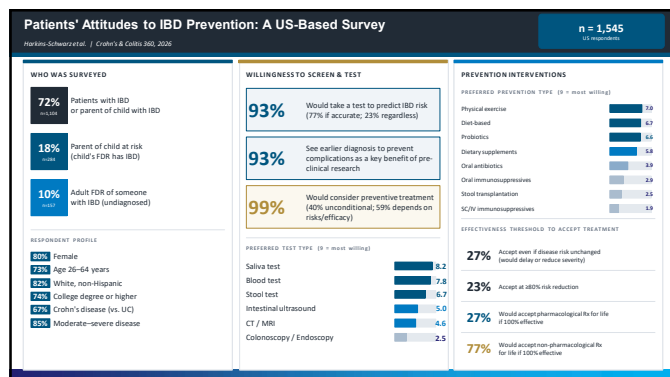
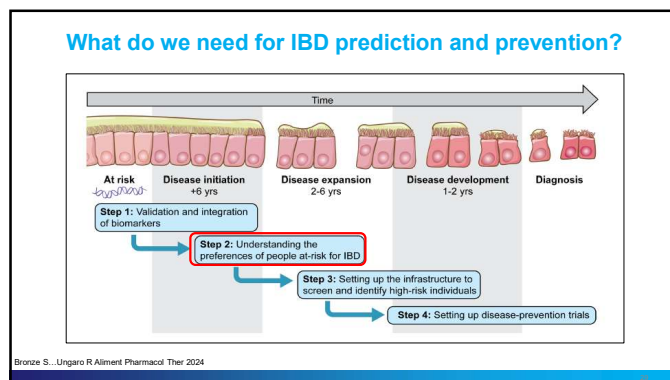


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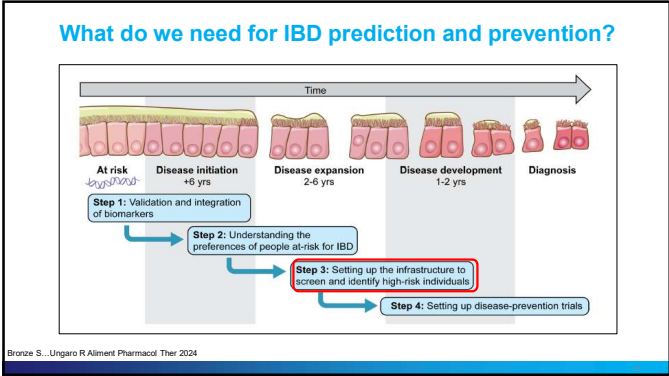
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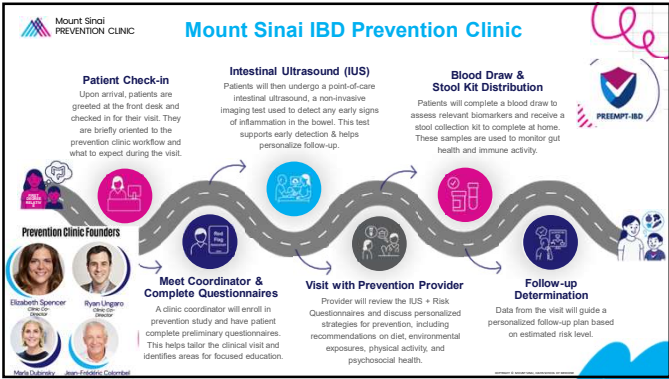
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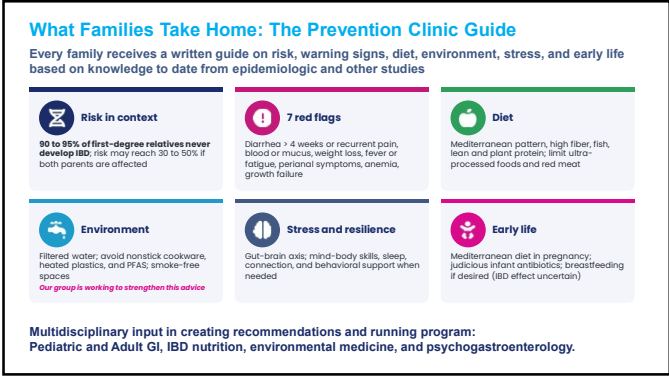
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31

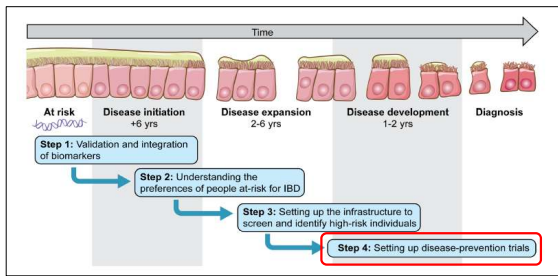


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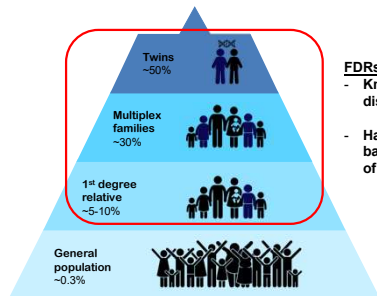
What do we need for IBD prediction and prevention?



Bronze S., Ungaro R Alment Pharmacol Ther 2024

34

First Degree Relatives: Natural First Population

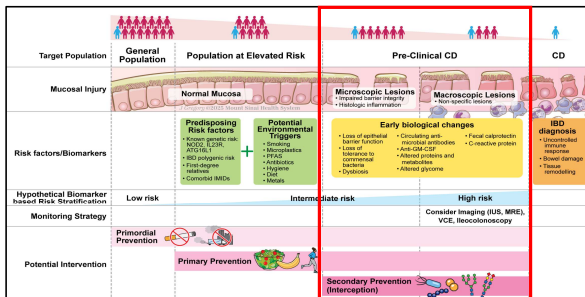


- FDRs**
- Know the impact of the disease
 - Have elevated risk at baseline → improve PPV of risk stratification tools

Jostins L. et al Nature 2012

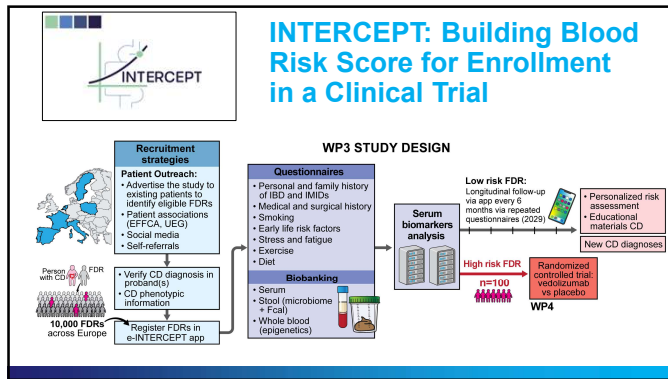
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Prevention may vary according to preclinical stage

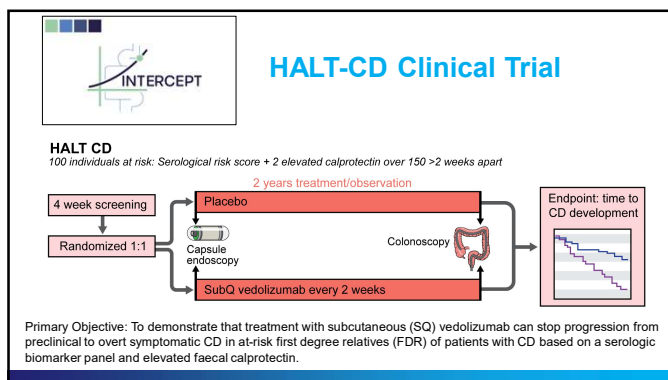


Lee et al. Gastro 2026.

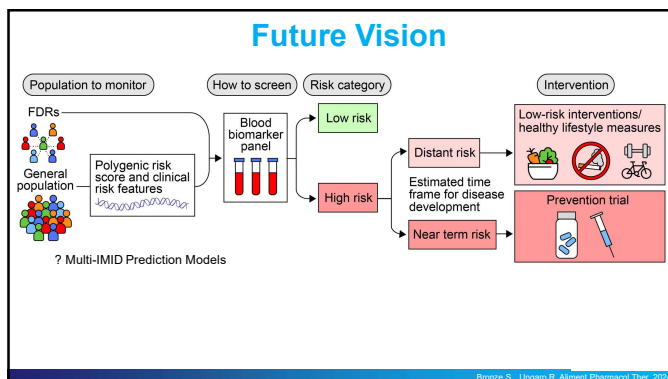
36



40



41



42

Summary

- **CD and UC develop years before diagnosis:** Creates opportunities for earlier detection, monitoring, and intervention.
- **Family history can prompt proactive care:** First-degree relatives can be educated about warning signs, modifiable risk factors, and opportunities for screening and research
 - However, only 5-10% of FDRs will develop IBD
- **Prediction of IBD is advancing:** Emerging blood, stool, microbiome, permeability, and proteomic biomarkers can help identify individuals at highest risk for future IBD.
- **Prevention strategies are entering clinical testing:** Dietary, lifestyle, and biologic interventions are now being evaluated in IBD interception and prevention trials.
- **The future of IBD care may include prevention and early interception programs:** Risk stratification, longitudinal monitoring, and targeted intervention before symptom onset may become part of routine care for high-risk individuals

43

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 • Elisabeth Giselsbrecht



44

Thank You!



45

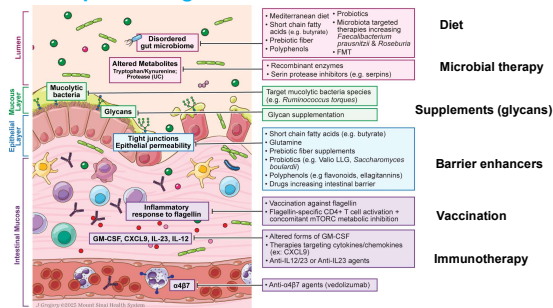
EXTRA SLIDES



46

What Intervention?

Potential Therapeutic Targets based on Preclinical Biomarkers



47

Counseling Family Members of Patients with IBD

ACCURATELY FRAME RISK

5-10%

First-degree relative lifetime risk

90-95%

NEVER DEVELOP IBD

Population risk ≈1%
Higher with multiple affected relatives
Higher with younger age at diagnosis

EDUCATE ON RED FLAGS

GI Symptoms

- Diarrhea >4 weeks
- Recurrent abdominal pain
- Blood or mucus in stool

Systemic

- Weight loss
- Fatigue, fever, anemia

Special situations

- Perianal symptoms
- Growth delay/puberty delay

→ Early GI referral

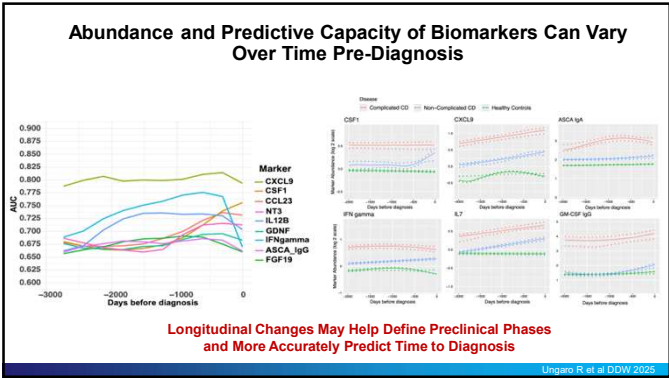
DISCUSS POTENTIALLY MODIFIABLE RISK FACTORS

- ✓ Mediterranean-style diet
- ✓ Fruits, vegetables, legumes, whole grains
- ✓ Fish >2x/week
- ✓ Avoid smoking/vaping
- ✓ Exercise, sleep, stress management
- ✓ Avoid unnecessary antibiotics

Emerging environmental measures:
• Favor whole foods over ultra-processed foods
• Avoid heating food in plastics
• Limit exposures to PFAS "forever chemicals"

Family history should prompt awareness, not alarm.

48



49

Can We Translate This Understanding to Predicting IBD?

- Predict Development of IBD**
 - Identify Biomarkers Associated with IBD Onset
 - Integrate biomarkers to stratify risk among at-risk or asymptomatic individuals
- Define the Stages of Preclinical IBD to Enhance Prediction**

Clarify the continuum from health → subclinical inflammation → early IBD
- "Precision Prediction"**

Enable individualized risk forecasting and precision prevention strategies.

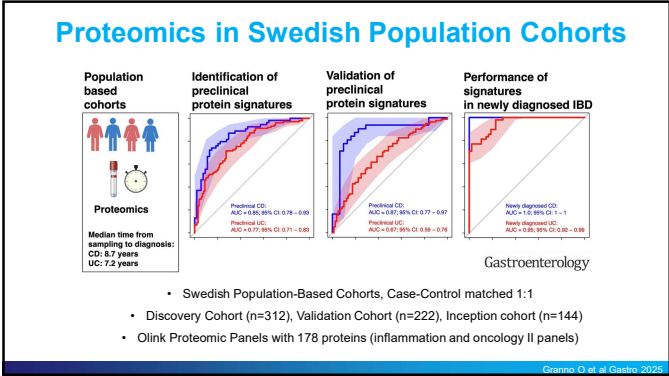
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The PIONIR trial (Preventing IBD ONset in Individuals at Risk)

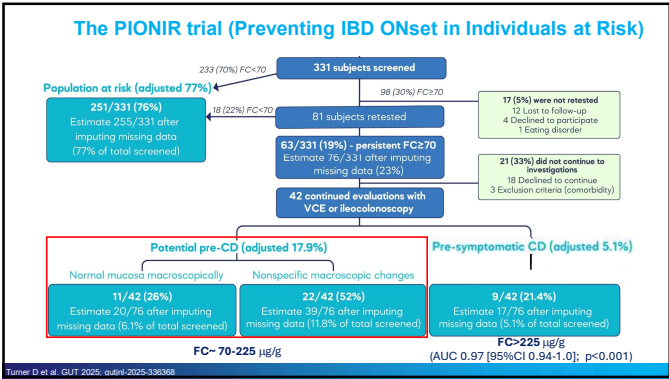
Characteristic	Overall n=29	Habitual diet n=15	Tasty&Healthy n=14	p-value
Sex (Female)	17 (59%)	8 (53%)	9 (64%)	0.71
Age (years)	29.5±7.3	24.7±5.5	26.4±5.1	0.54
<18	4 (14%)	2 (13%)	2 (14%)	0.88
18-25	10 (34%)	6 (40%)	4 (29%)	
>25	15 (52%)	7 (47%)	8 (57%)	
Family Type				0.43
Multiplex	8 (28%)	3 (20%)	5 (36%)	
Simplex	21 (72%)	12 (80%)	9 (64%)	
Proband				0.29
>1 siblings	3 (10%)	0 (0.0%)	3 (21%)	
Parent & Sibling	5 (17%)	3 (20%)	2 (14%)	
Parent	3 (10%)	1 (6.7%)	2 (14%)	
Sibling	18 (62%)	11 (73%)	7 (50%)	
VCE results				0.22
Macroscopic changes	21 (72%)	9 (60%)	12 (86%)	
Normal study	8 (28%)	6 (40%)	2 (14%)	
Week 0 calprotectin (µg/g, median)	205 (97-264)	174 (91-352)	218 (106-264)	0.78

Turner D et al. GIUT 2025; gaitri-2025-330368

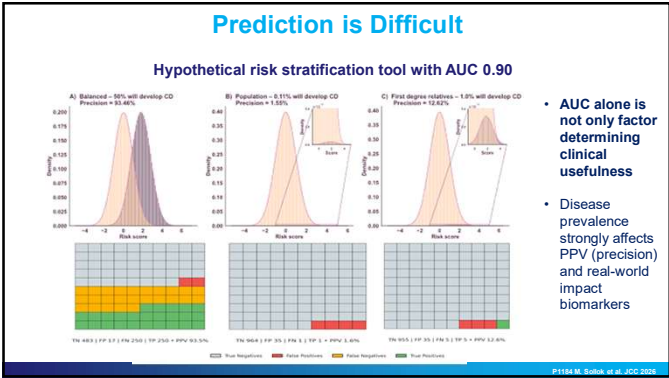
51



52

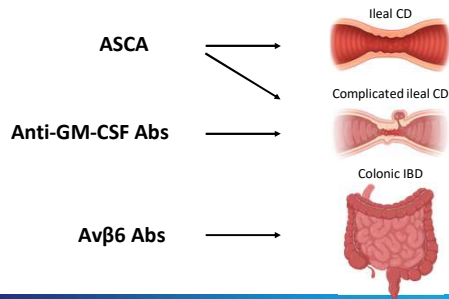


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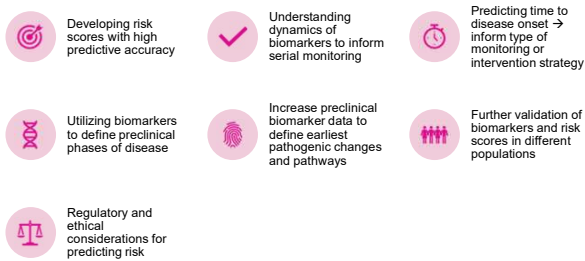
54

Preclinical biomarkers highlight different IBD endotypes and phenotypes at diagnosis



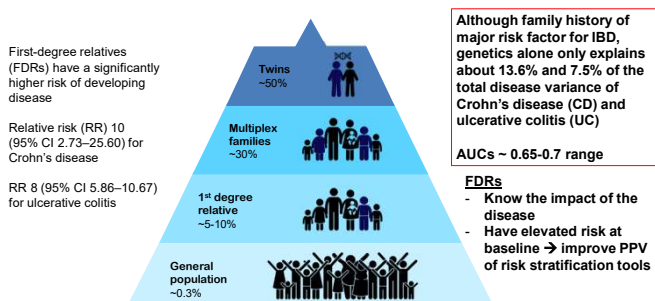
55

Research Needs in IBD Prediction



56

Genetics to Predict IBD?



57