Prevention of IBD: Where We Are and Where We Need to Go

Ryan C. Ungaro, MD MS
Associate Professor of Medicine, Director of Clinical Research
The Henry D. Janowitz Division of Gastroenterology
Icahn School of Medicine at Mount Sinai

Icahn School of Medicine at Mount Sinai

Disclosures

- Advisory Board and Consulting
  - AbbVie, Bristol Myers Squibb, 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

Other Disclosure

I am a Mets fan, which means I can relate to Blue Jays fans.

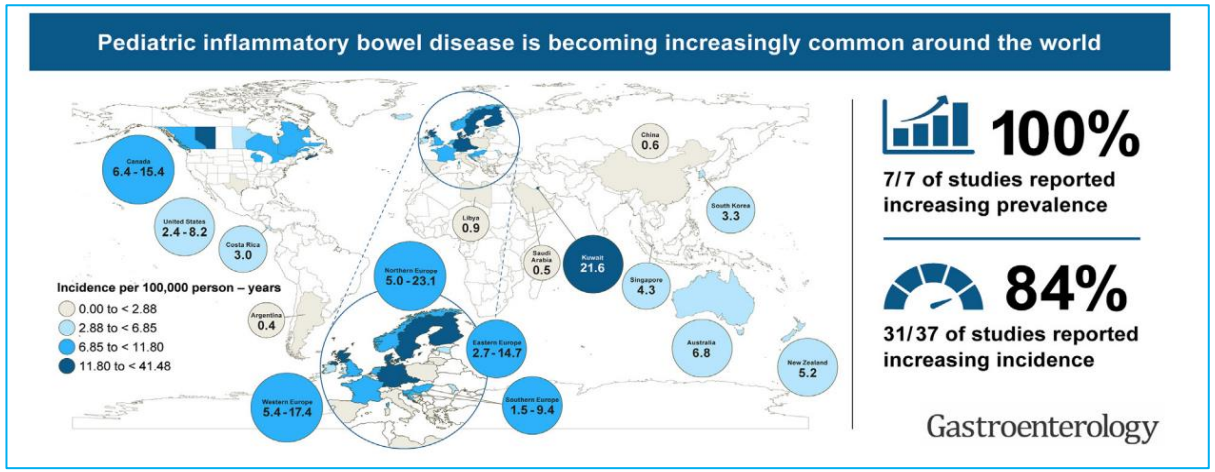
I also dislike both the Yankees and Dodgers…

Objectives

- Review key considerations in the design of inflammatory bowel disease (IBD) prevention trials
- Overview of potential prevention trial therapy targets and interventions
- Discuss ongoing and planned IBD prevention trials

Why do we need to discuss 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.



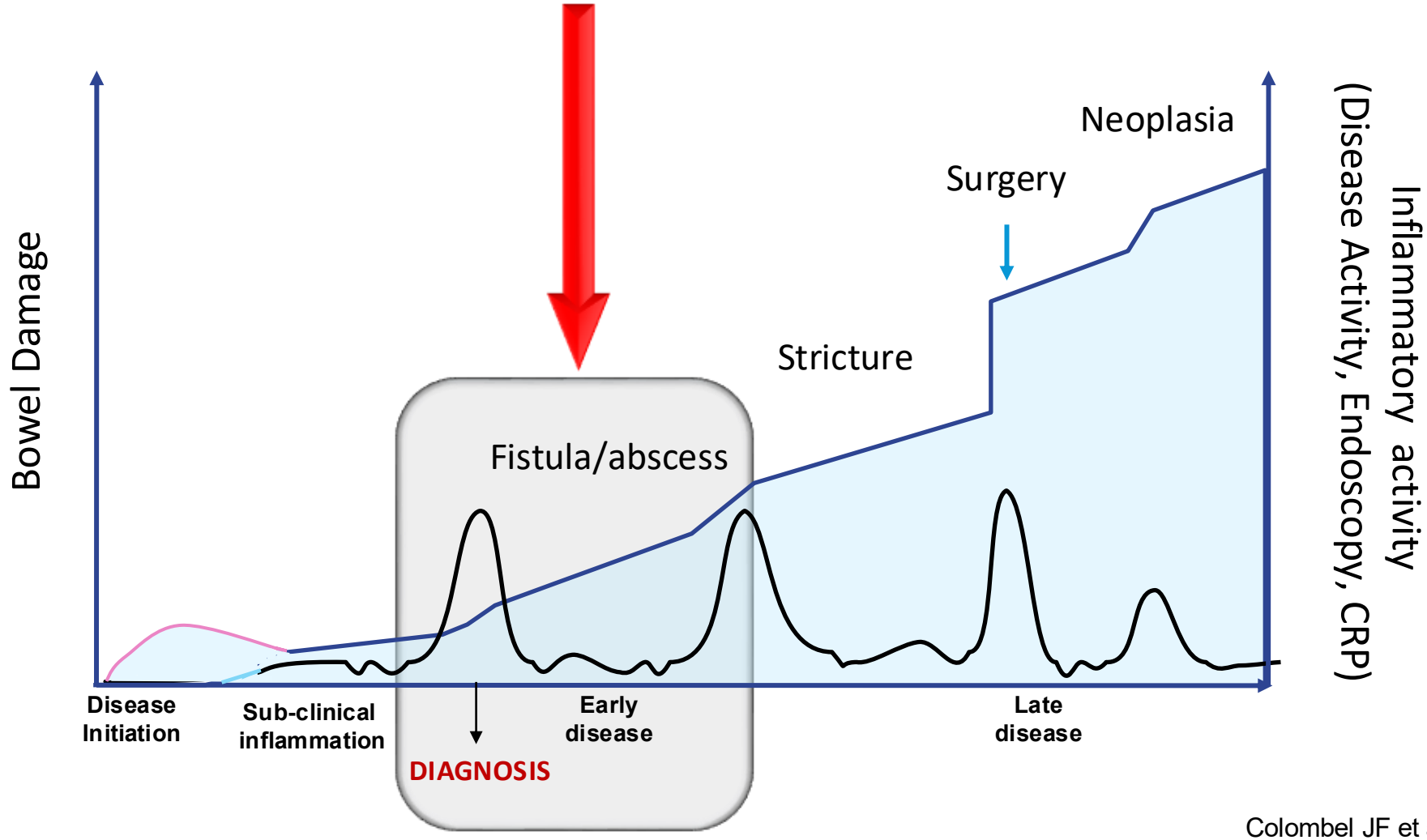
- Rising incidence in newly industrialized countries (Africa, Asia, and South America) (growing population) – disparity in care
- Rising incidence in children across the world
- Expected prevalence **>1%** in some areas of the world by 2030

Siew C Ng Lancet 2017, Kaplan G, Winsor JW. NRGH 2020, Agrawal M Gastroenterology 2022, Benchimol E Gastroenterology 2022

IBD is a Progressive Disease

Improved response
Improved longer term outcomes

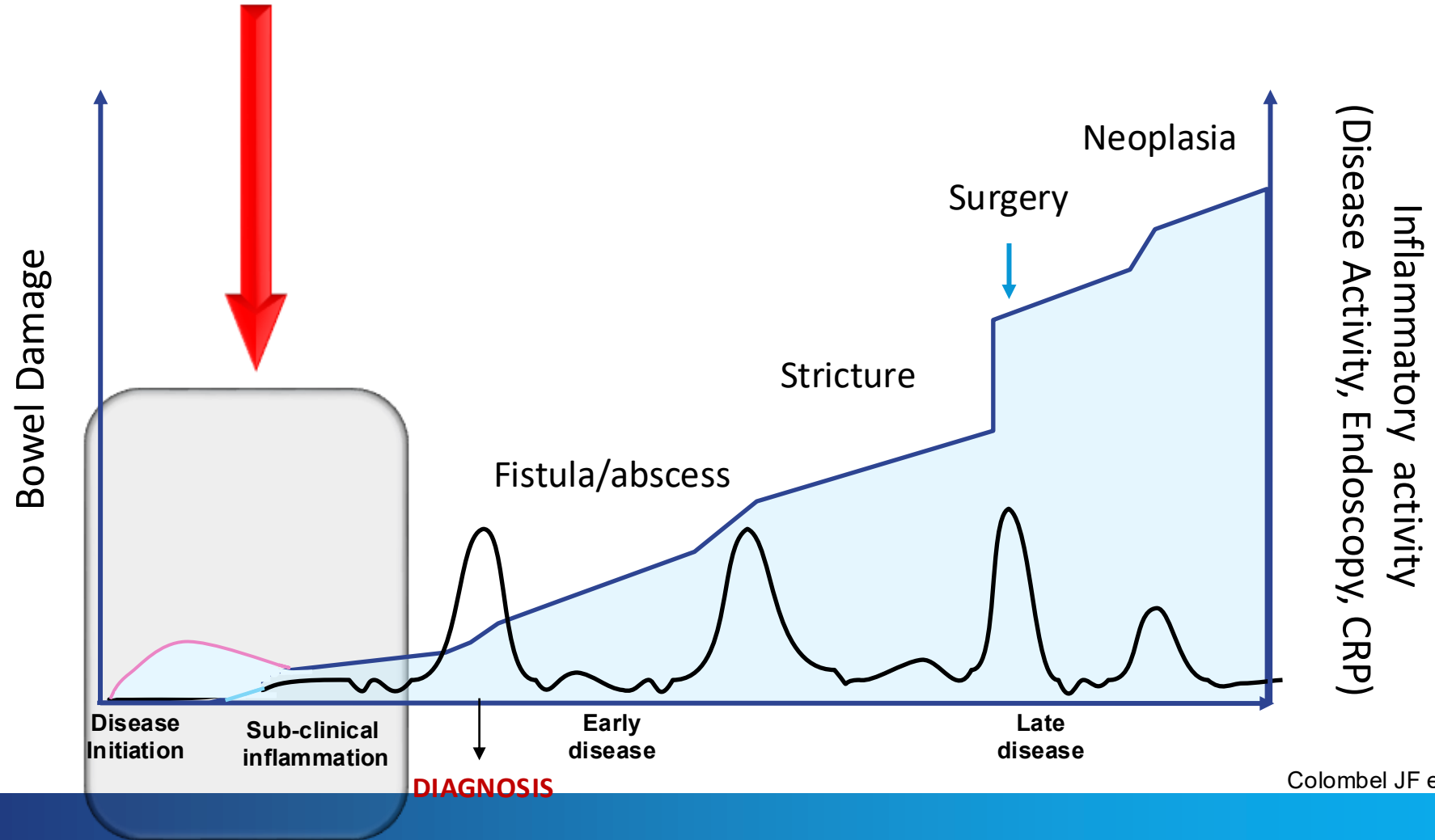
Earlier Treatment in Window of Opportunity



Colombel JF et al. Gastroenterology 2017

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

Best Window of Opportunity?

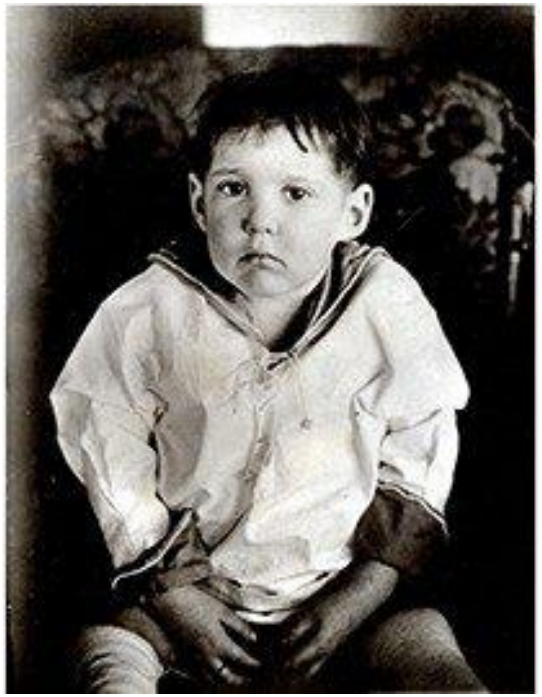


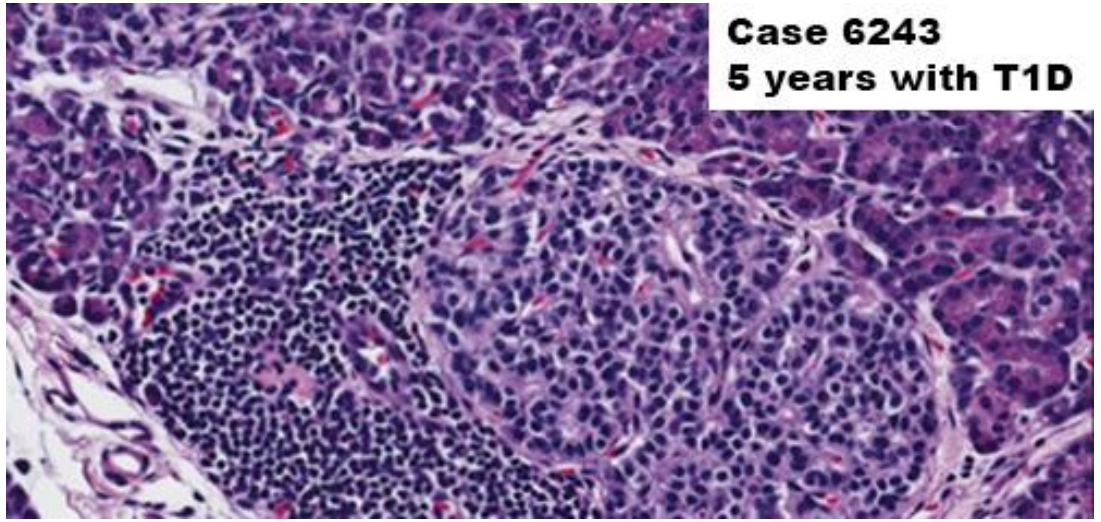
Colombel JF et al. Gastroenterology 2017

Where We Need to Go…

Type 1 diabetes mellitus (T1DM) as the model

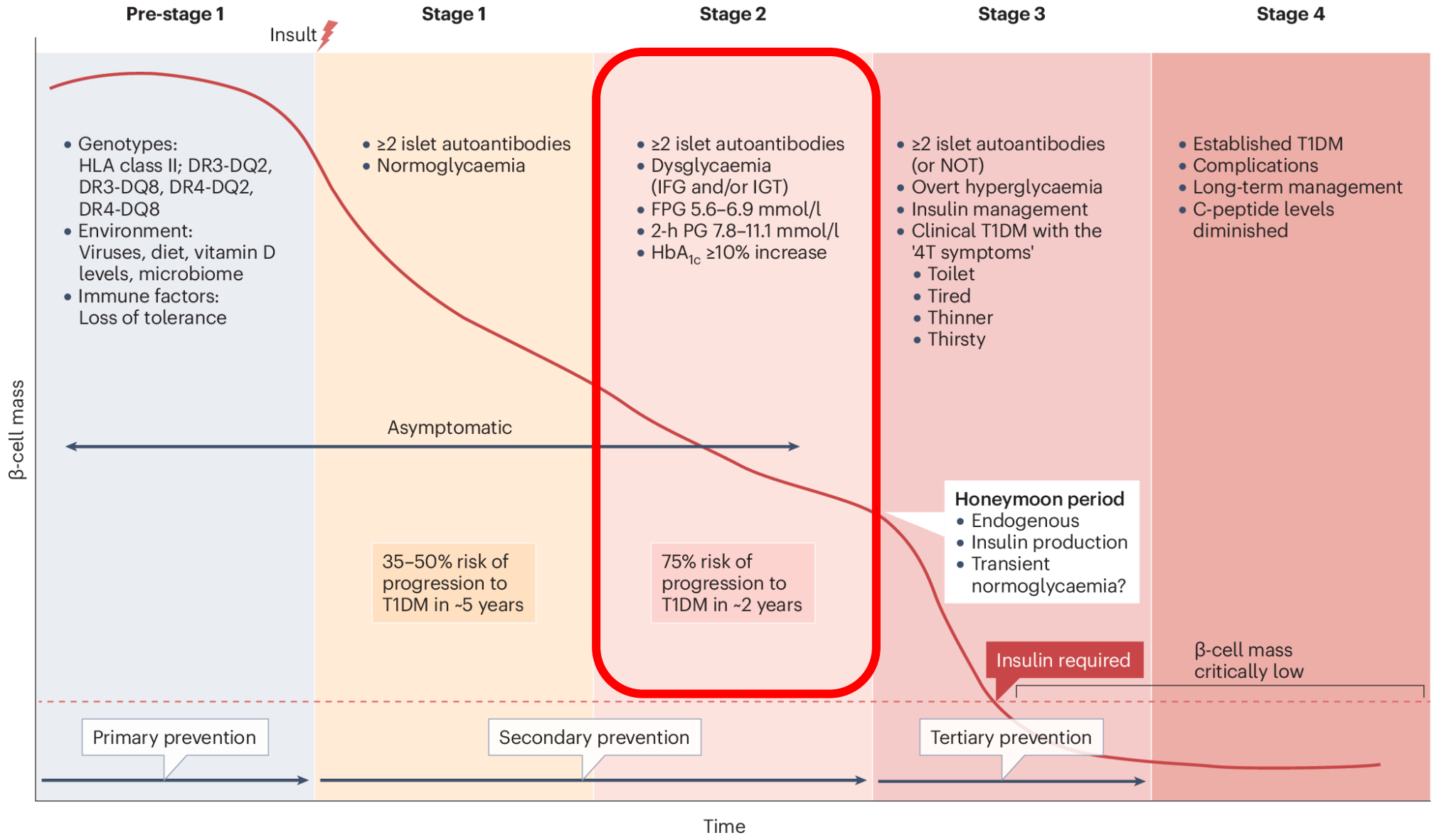
Immune mediated destruction of insulin producing β-cells in the pancreatic islet



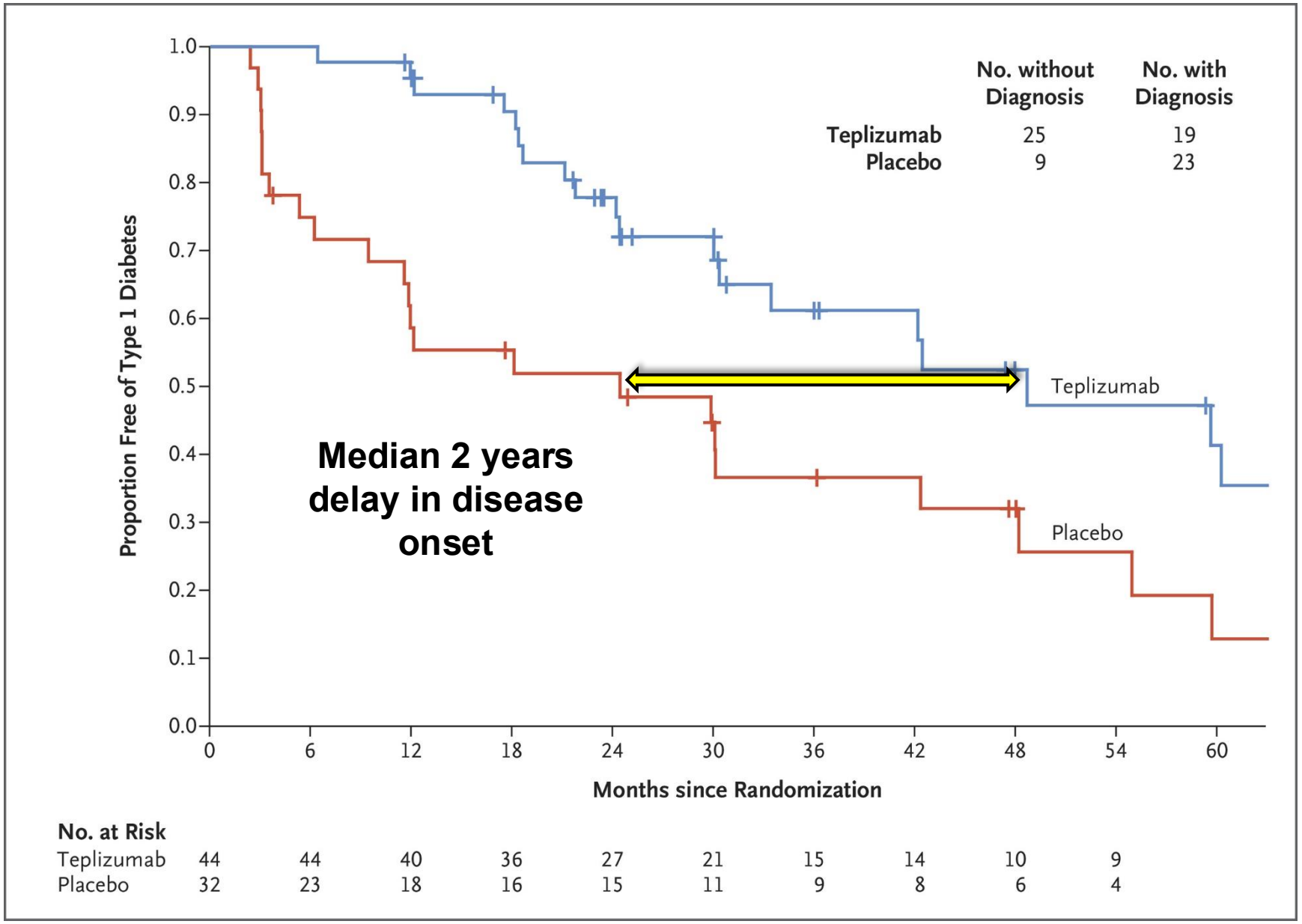


nPOD
Network for Pancreatic Organ Donors with Diabetes

Different stages of T1DM and opportunities for prevention



Teplizumab in relatives at risk of type 1 diabetes



The adjusted cox proportional hazard ratio of teplizumab to placebo was
0.412 (95% CI: 0.216, 0.783)
P=0.006

Herold KC et al. N Engl J Med 2019

F.D.A. Approves Drug That Can Delay the Start of Type 1 Diabetes

By GINA KOLATA

The Food and Drug Administration has approved the first treatment that can delay — possibly for years — the onset of Type 1 diabetes, a disease that often emerges in teenagers.

The new drug, teplizumab, is made by Provention Bio, which will partner with Sanofi to market the drug in the United States under the brand name Tzield. In an investor call on Friday, Provention said the drug would cost $13,850 a vial or $193,900 for the 14-day treatment. The company said teplizumab should be available by the end of the year.

The drug, which the F.D.A. approved on Thursday, does not cure or prevent Type 1 diabetes. Instead, it postpones its onset by an average of two years and, for some lucky patients, much longer — the longest so far is 11 years, said Dr. Kevan Herold of Yale, a principal investigator in trials of the drug.

The only other treatment for the disease — insulin — was discovered 100 years ago and does not affect the course of the disease. It just replaces what is missing.

Teplizumab will be used to treat patients at high risk for Type 1 diabetes who have antibodies that indicate an immune attack on their pancreas and whose glucose tolerance is not normal. Treatment involves a 14-day infusion of the drug, a monoclonal antibody that blocks T cells, preventing them from attacking the insulin-producing cells of the pancreas.

"Talk to anyone who has Type 1 diabetes and any day you are not burdened by measuring blood sugar four times a day and injecting yourself with insulin is a glorious day," said Dr. Mark S. Anderson, director of the diabetes center at the University of California, San Francisco, and a researcher for the pivotal clinical trial that led to the treatment's approval. Dr. Anderson has been a paid consultant for Provention in the past.

Dr. John Buse, a diabetes expert at the University of North Carolina who was not involved in the study, called the approval "really exciting" and said it would "turn the world of Type 1 diabetes on its head."

"There has always been a notion that screening would be a good idea," he said. But medical experts "have never really promoted it to detect Type 1 diabetes."

It will not be easy — no screening test is. But in this case, very few who are screened will have this rare but dire disease, which affects just four in 1,000 in the general population, or 1.4 million Americans.

Type 1 diabetes typically emerges in adolescence when patients suddenly are tired all the time, urinating frequently, drinking copious amounts of water, and losing weight.

With a diabetes diagnosis, their lives are completely changed. They have to measure their blood sugar and take insulin for the rest of their lives. Every time they eat a meal, they have to calculate how much insulin they need. If they take too much, they can pass out or have a seizure or even end up in intensive care.

They also face the specter of complications — eye disease that can lead to blindness, kidney failure, heart disease and stroke. Without good control of blood glucose, complications can set in as early as five years after diagnosis, Dr. Anderson said.

The new treatment, Dr. Anderson said, "opens the door," much in the way that the first immunotherapy for cancer was a breakthrough to a new era of treatment about a decade ago. He expects that as immunotherapy for diabetes improves, the disease may be halted before it can take hold.

In trials, a treatment postponed the onset of the disease by an average of 2 years.

The new drug is not a treatment for the much more common type of diabetes, Type 2, in which the pancreas makes insulin but the body's cells do not respond to it.

The story of the new treatment dates back to the 1980s and involves determined researchers who pursued the idea as company after company — four in total before Provention — got interested but then ended up dropping the drug for a variety of reasons.

Dr. Jeffrey A. Bluestone, an academic until recently who is now chief executive of Sonoma Biotherapeutics, said he and his colleague, Dr. Herold, who has consulted for Provention and other companies, spent 20 years "trying to keep the drug alive."

"Scientists were passionate about it," Dr. Bluestone said. "Guys at companies were really passionate about it." But for reasons unrelated to its potential, it kept being dropped.

Dr. Herold said he vividly remembered trips that he and Dr. Bluestone and a French researcher, Lucienne Chatenoud of Paris Descartes University, made to drug companies "begging them to pick this thing up."

At one point, Dr. Bluestone actually took the antibody, developed at that time by Ortho Pharmaceuticals, and made a clinical batch of the drug in the lab. Dr. Herold tested it in a small study of people who were newly diagnosed with Type 1 diabetes.

The treatment prolonged the period in which they made some insulin, but eventually all got diabetes.

In 2011, Dr. Bluestone and Dr. Herold proposed a different sort of study. They would treat people who were at high risk of diabetes but who had not yet developed it. It was a bold move, Dr. Bluestone noted. "Other than vaccines, there aren't many drugs given before diagnosis," he said.

To find those people, the researchers worked with a group of clinical trial sites, TrialNet, that were supported by the National Institutes of Health. Dr. Herold is now the group's chairman. TrialNet investigators screened 200,000 people who were immediate family members of people with Type 1 diabetes, looking for antibodies indicating an immune attack on the pancreas and abnormal glucose metabolism.

The result was a study, published in The New England Journal of Medicine, that led to Thursday's approval.

Now that the drug is approved, the challenge will be to find people who could benefit. Screening only people with immediate relatives who have diabetes will miss 85 percent of patients.

The JDRF, a nonprofit group that advocates for people with Type 1 diabetes and supports research, which, along with the N.I.H., funded the trial that led to the drug's approval, wants antibody screening tests to become part of routine pediatric care.

"Most families say diagnosis is a bolt out of the blue," said Aaron Kowalski, chief executive of the JDRF. And most patients, he added, are very sick when they first are diagnosed.

The group has conducted blood tests to look for antibodies in Germany and in parts of Colorado. And it has offered an at-home test people can order, underwritten by the foundation. But, Dr. Kowalski said, "we want pediatric offices to do it."

Testing also offers another opportunity, he said. It turns out that antibodies indicating an immune attack often occur when people are as young as 5 or 6 years old, although most do not develop diabetes until they are teenagers.

Now, he said, his hope is to treat people even earlier, as soon as those antibodies emerge. Clinicians and the F.D.A. had previously objected to treating before the disease was clearly underway, asking, "How can you give an immunotherapy if they are normal?" Dr. Kowalski said.

But, he said, the antibodies tell a different story.

"They do have diabetes," he said, although not according to the usual definition of the disease. "It just hasn't unmasked itself yet. We need to help them save their beta cells," the insulin-secreting cells of the pancreas.

Dr. Herold is cautious. If someone has antibodies but their pancreas is not actively being attacked, the treatment may not help.

"It's hard to stop something that isn't happening," he said.

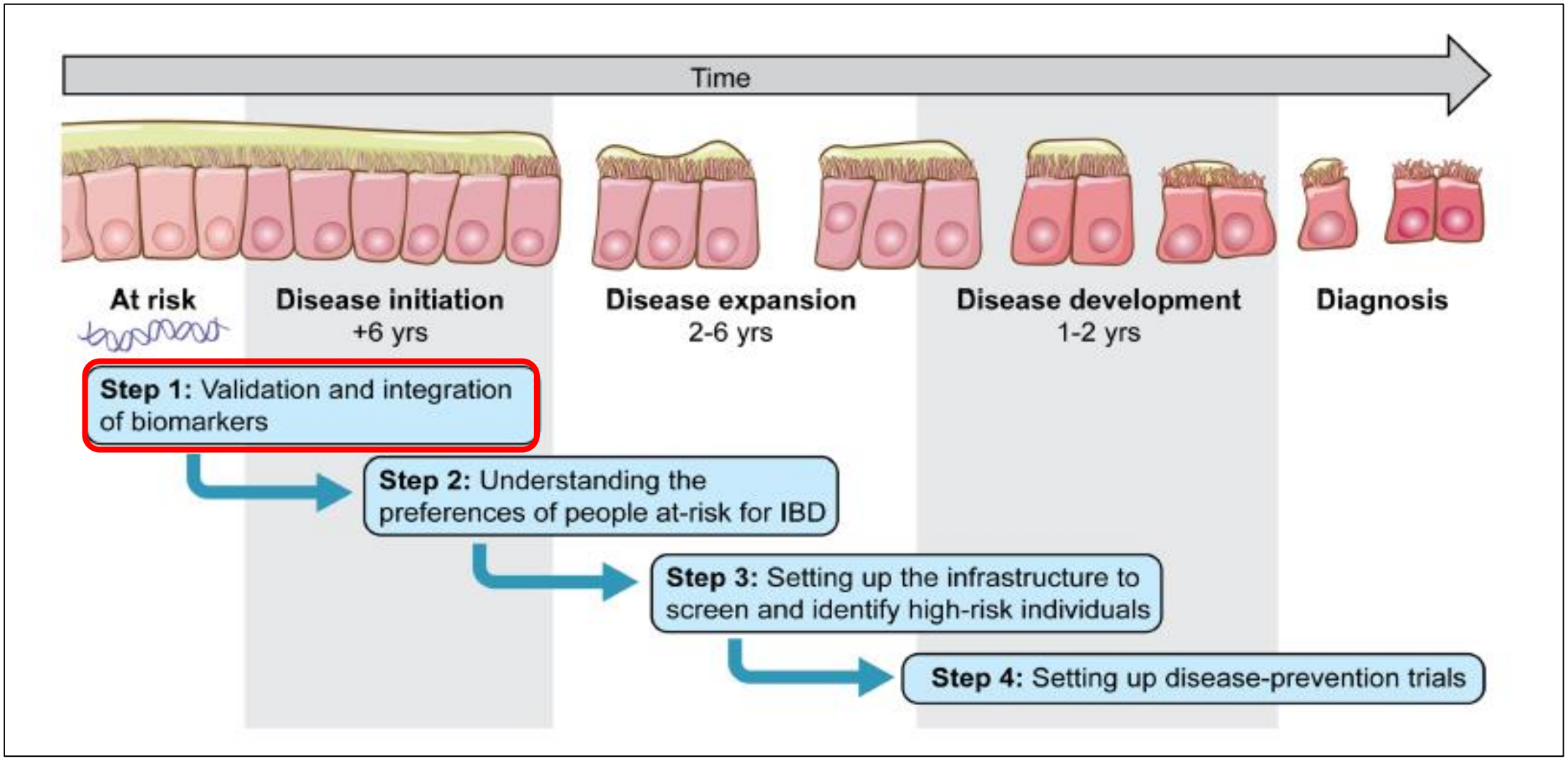
Dr. Bluestone and Dr. Herold wonder if giving a second round of treatment could improve results even further.

For now, Dr. Bluestone would like to see the treatment used to help younger patients than were in the trial. It is approved for patients at least 8 years old. "But the disease affects a lot of patients who are younger than 8," he said.

Although he and others are excited about the possibility of some day preventing the disease entirely, there is an immediate challenge for diabetes experts.

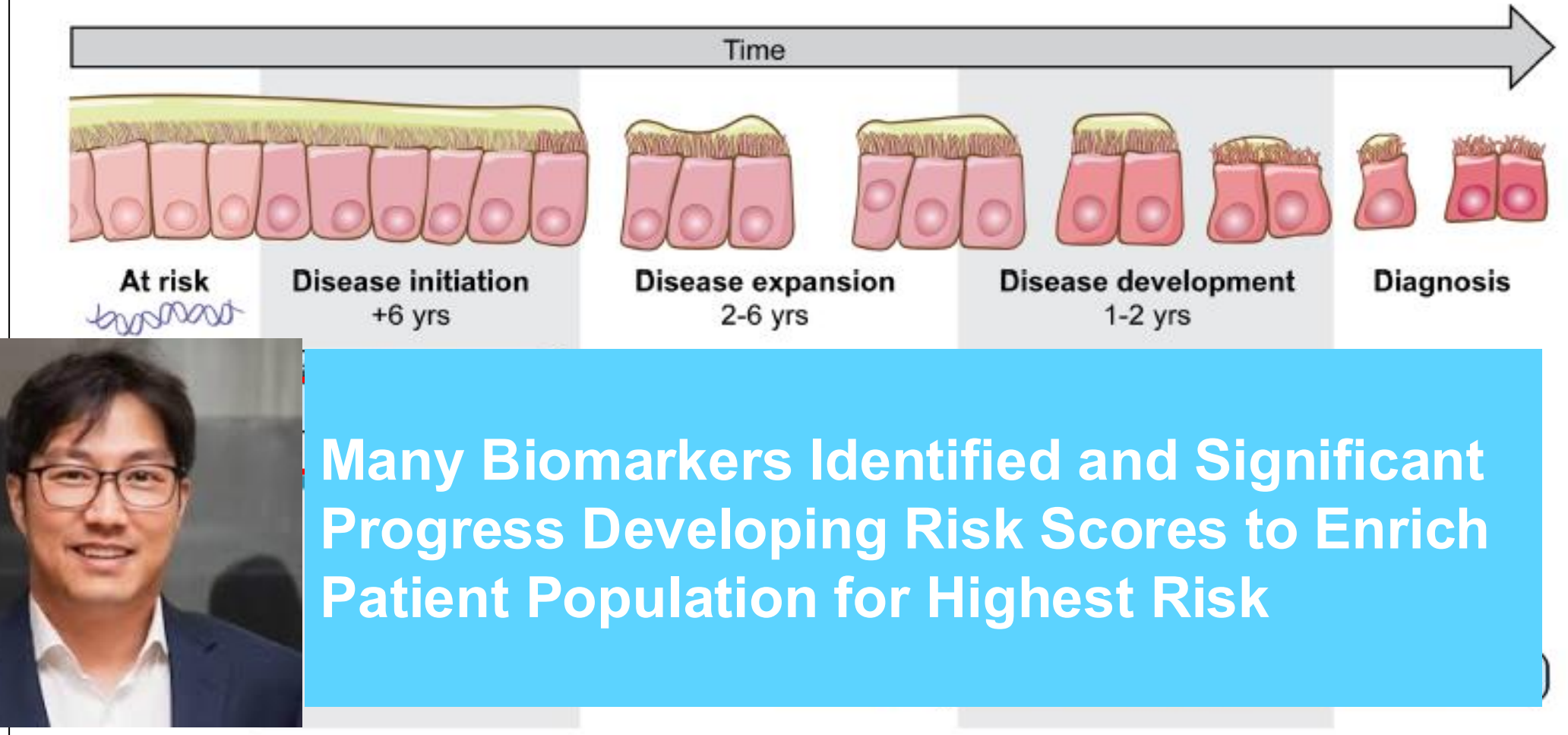
"The most important thing right now is finding the potential patients," Dr. Bluestone said.

Steps towards implementation of IBD prevention



Bronze S…Ungaro R Aliment Pharmacol Ther 2024

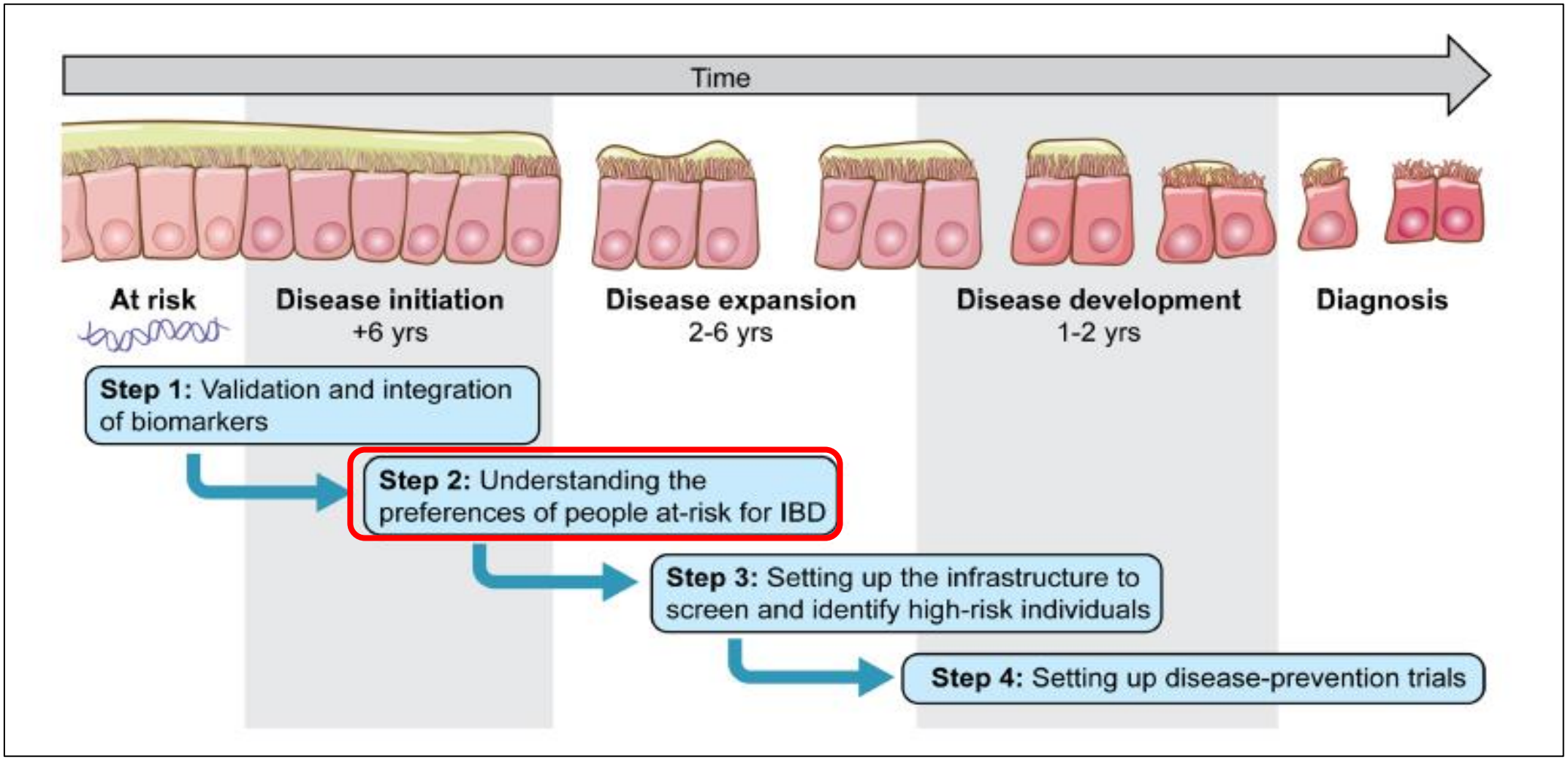
Steps towards implementation of IBD prevention



Many Biomarkers Identified and Significant Progress Developing Risk Scores to Enrich Patient Population for Highest Risk

Bronze S…Ungaro R Aliment Pharmacol Ther 2024

Steps towards implementation of IBD prevention



Bronze S…Ungaro R Aliment Pharmacol Ther 2024

Patients and FDRs are willing to undergo predictive testing and preventive interventions!

n=1327

PREDICTIVE TESTING

85% accepted (for them/their children)

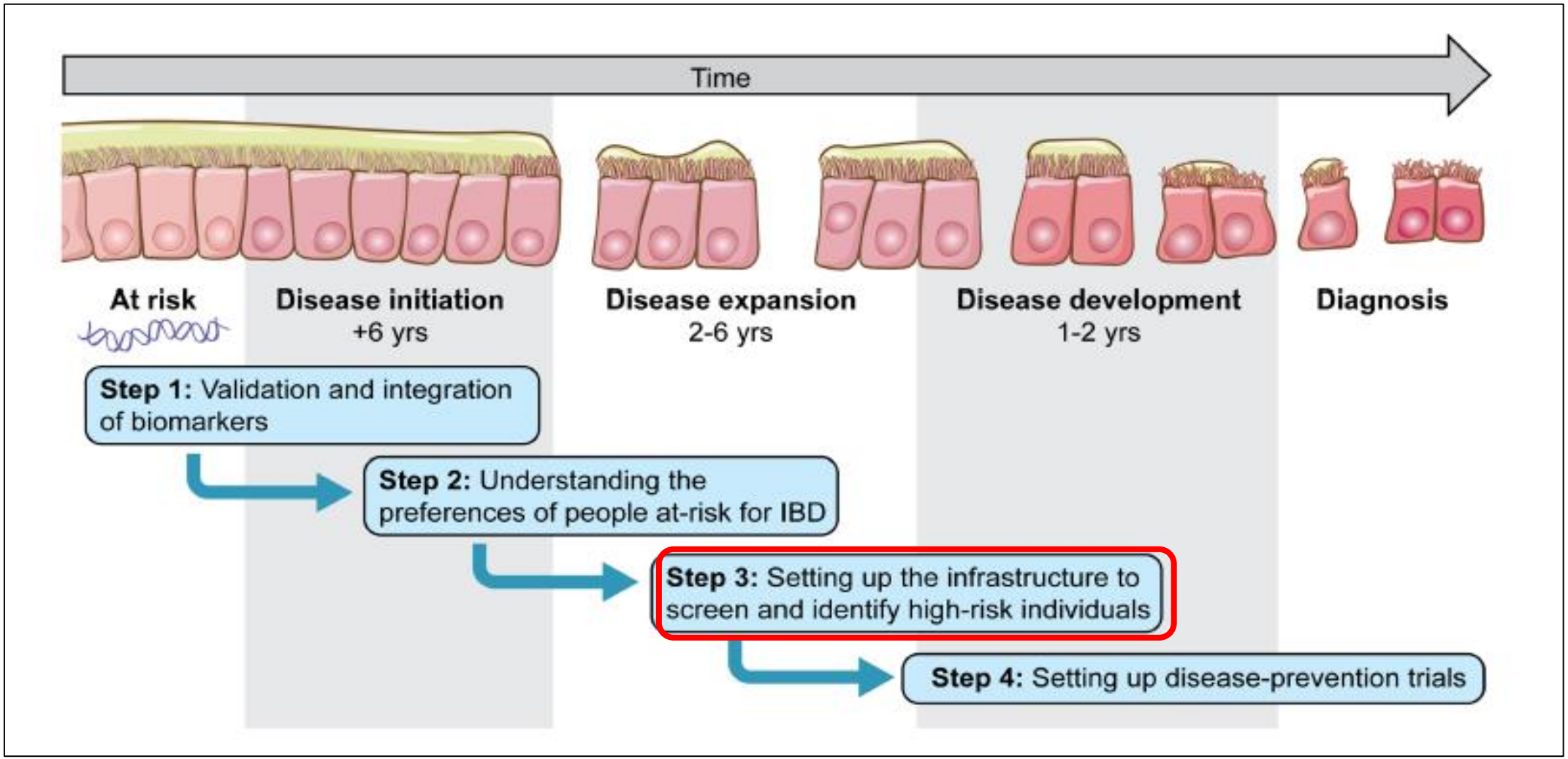
Blood test	**78%** n=1035
Stool test	**76%** n=1012
Saliva test	**67%** n=883
US	**57%** n=761
MRI/CT-scan	**46%/42%** n=604/563
Colonoscopy	**37%** n=490

PREVENTIVE INTERVENTIONS

97% accepted (for them/their children)

Diet modification	**86%** n=1142
Physical exercise	**81%** n=1071
Probiotics	**74%** n=982
Diet supplements	**69%** n=922
Quit smoking	**59%** n=789
Fecal Transplantation	**40%** n=531
Immunosupressive oral drugs	**38%** n=510
Oral antibiotics	**32%** n=430
Immunosupressive IV/SC drugs	**32%** n=423

Steps towards implementation of IBD prevention



Bronze S…Ungaro R Aliment Pharmacol Ther 2024

Imagine a future without type 1 diabetes

TrialNet is an international network of leading academic institutions, endocrinologists, physicians, scientists and healthcare teams at the forefront of type 1 diabetes (T1D) research. We offer risk screening for relatives of people with T1D and innovative clinical studies testing ways to slow down and prevent disease progression. Our goal: a future without T1D!

GET STARTED

Sign up to be screened!

Find a location near me

View upcoming events

Network of 27 sites in North America and Europe

Mount Sinai
PREVENTION CLINIC

MOUNT SINAI IBD PREVENTION CLINIC WORKFLOW

Patient Check-in

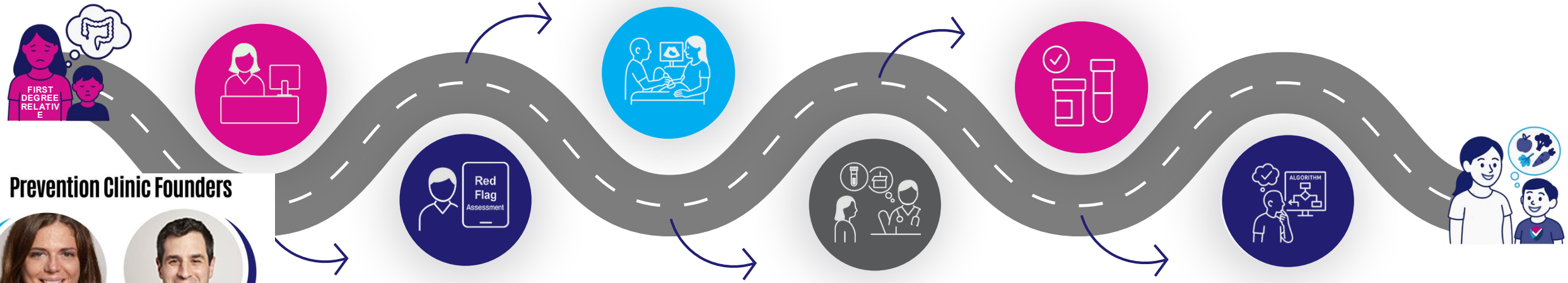
Upon arrival, patients are greeted at the front desk and checked in for their visit. They are briefly oriented to the prevention clinic workflow and what to expect during the visit.

Intestinal Ultrasound (IUS)

Patients will then undergo a point-of-care intestinal ultrasound, a non-invasive imaging test used to detect any early signs of inflammation in the bowel. This test supports early detection & helps personalize follow-up.

Blood Draw & Stool Kit Distribution

Patients will complete a blood draw to assess relevant biomarkers and receive a stool collection kit to complete at home. These samples are used to monitor gut health and immune activity.



Prevention Clinic Founders

Elizabeth Spencer
Clinic Co-Director

Ryan Ungaro
Clinic Co-Director

Marla Dubinsky

Jean-Frédéric Colombel

Meet Coordinator & Complete Questionnaires

A clinic coordinator will enroll in prevention study and have patient complete preliminary questionnaires. This helps tailor the clinical visit and identifies areas for focused education.

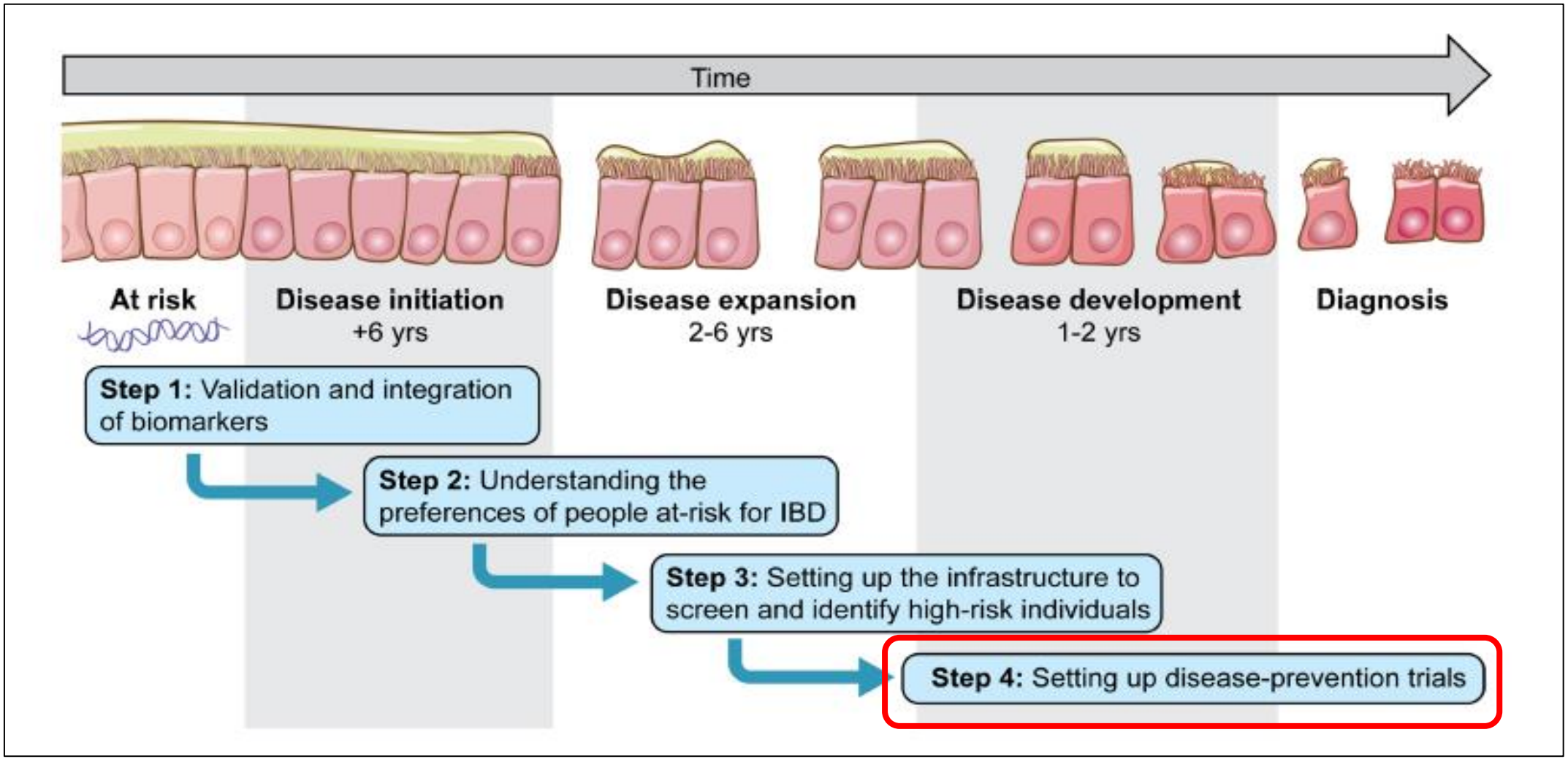
Visit with Prevention Provider

Provider will review the IUS + Risk Questionnaires and discuss personalized strategies for prevention, including recommendations on diet, environmental exposures, physical activity, and psychosocial health.

Follow-up Determination

Data from the visit will guide a personalized follow-up plan based on estimated risk level.

Steps towards implementation of IBD prevention



Bronze S…Ungaro R Aliment Pharmacol Ther 2024

Considerations in Prevention Trial Design

What population to include?

What intervention?

What design?

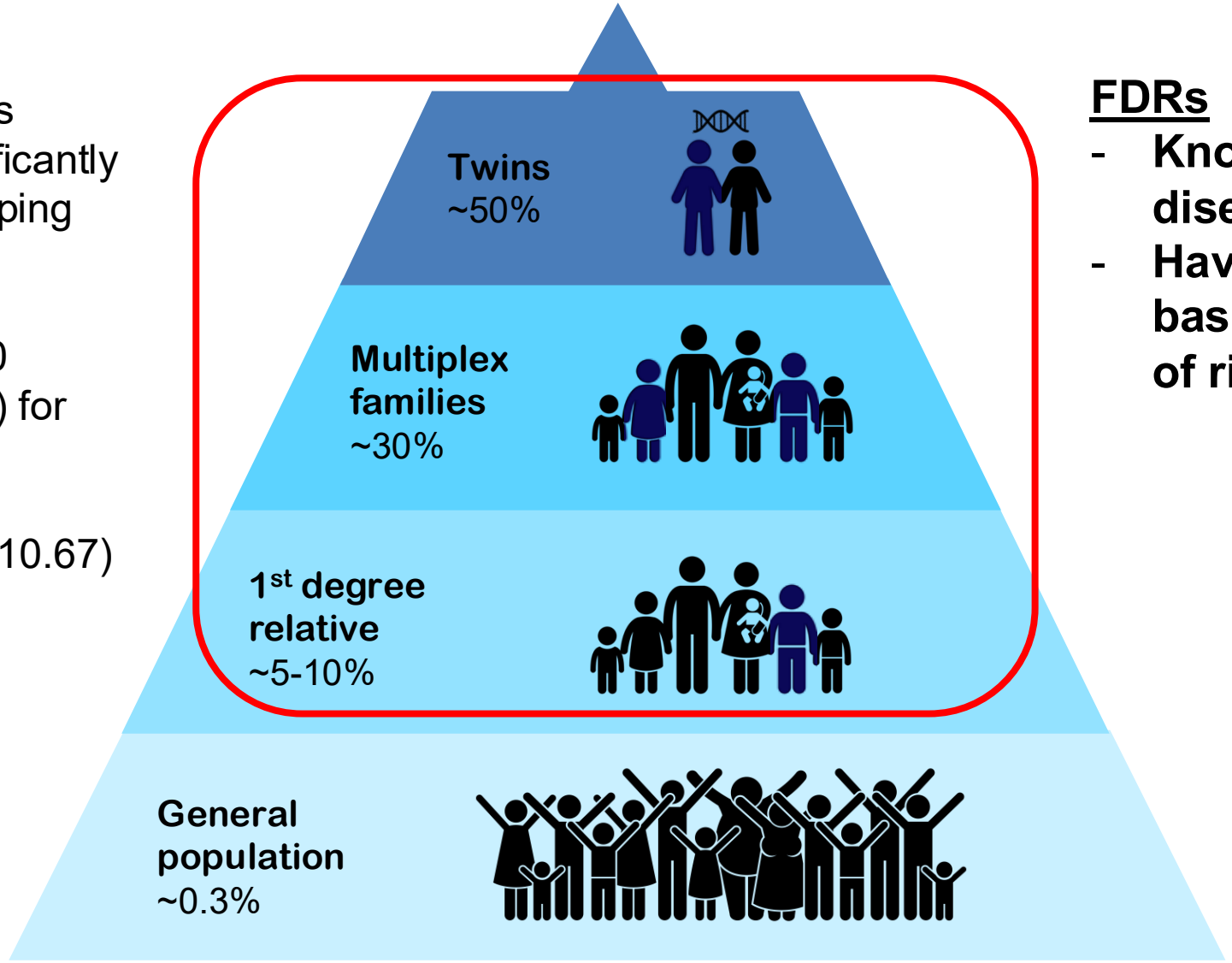
What endpoint?

First Degree Relatives: Natural First Population

First-degree relatives (FDRs) have a significantly higher risk of developing disease

Relative risk (RR) 10 (95% CI 2.73–25.60) for Crohn's disease

RR 8 (95% CI 5.86–10.67) for ulcerative colitis

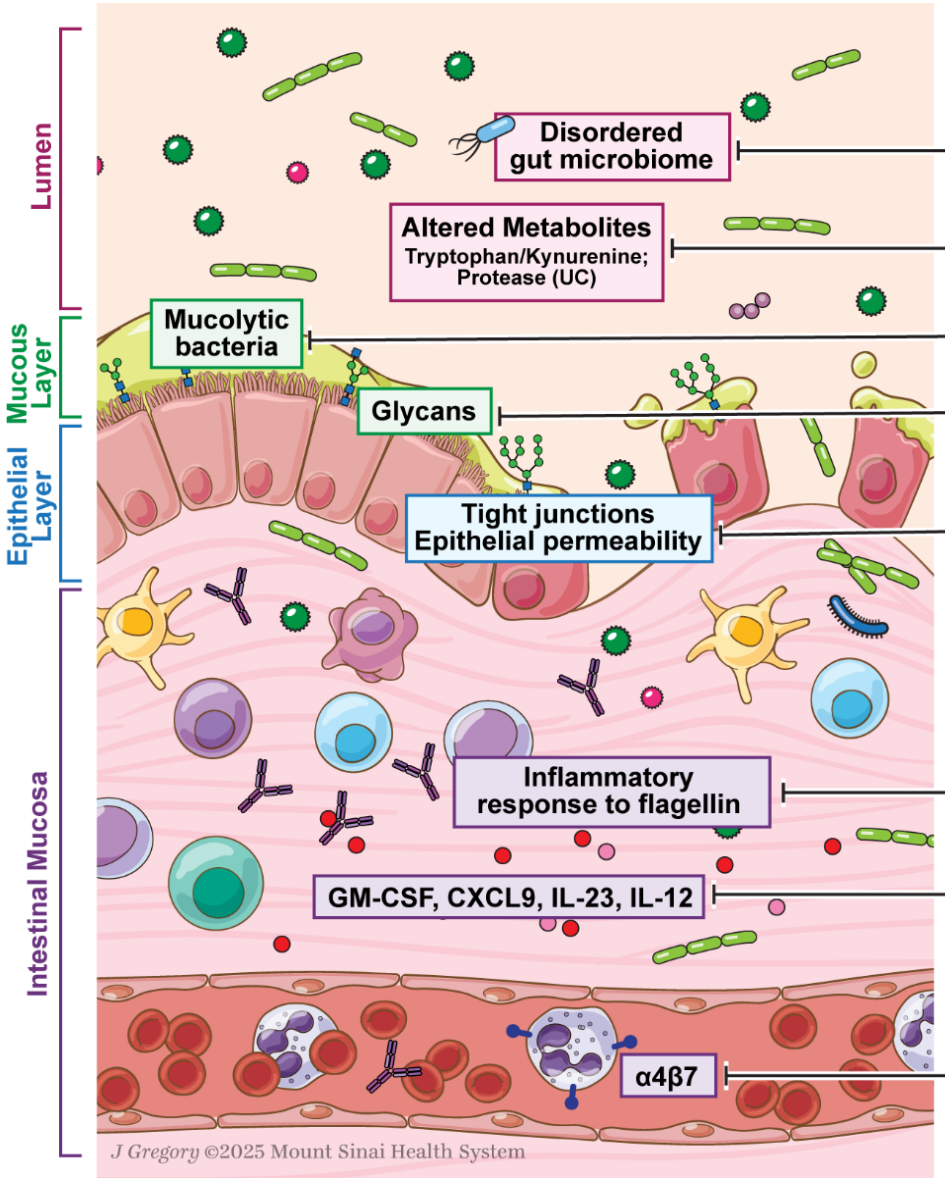


FDRs

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

Jostins L et al Nature 2012

What Intervention?
Potential Therapeutic Targets based on Preclinical Biomarkers



- Mediterranean diet
- Short chain fatty acids (e.g. butyrate)
- Prebiotic fiber
- Polyphenols
- Probiotics
- Microbiota targeted therapies increasing *Faecalibacterium prausnitzii* & *Roseburia*
- FMT

Diet

- Recombinant enzymes
- Serin protease inhibitors (e.g. serpins)

Microbial therapy

Target mucolytic bacteria species (e.g. *Ruminococcus torques*)

Glycan supplementation

Supplements (glycans)

- Short chain fatty acids (e.g. butyrate)
- Glutamine
- Prebiotic fiber supplements
- Probiotics (e.g. Valio LLG, *Saccharomyces boulardii*)
- Polyphenols (e.g flavonoids, ellagitannins)
- Drugs increasing intestinal barrier

Barrier enhancers

- Vaccination against flagellin
- Flagellin-specific CD4+ T cell activation + concomitant mTORC metabolic inhibition

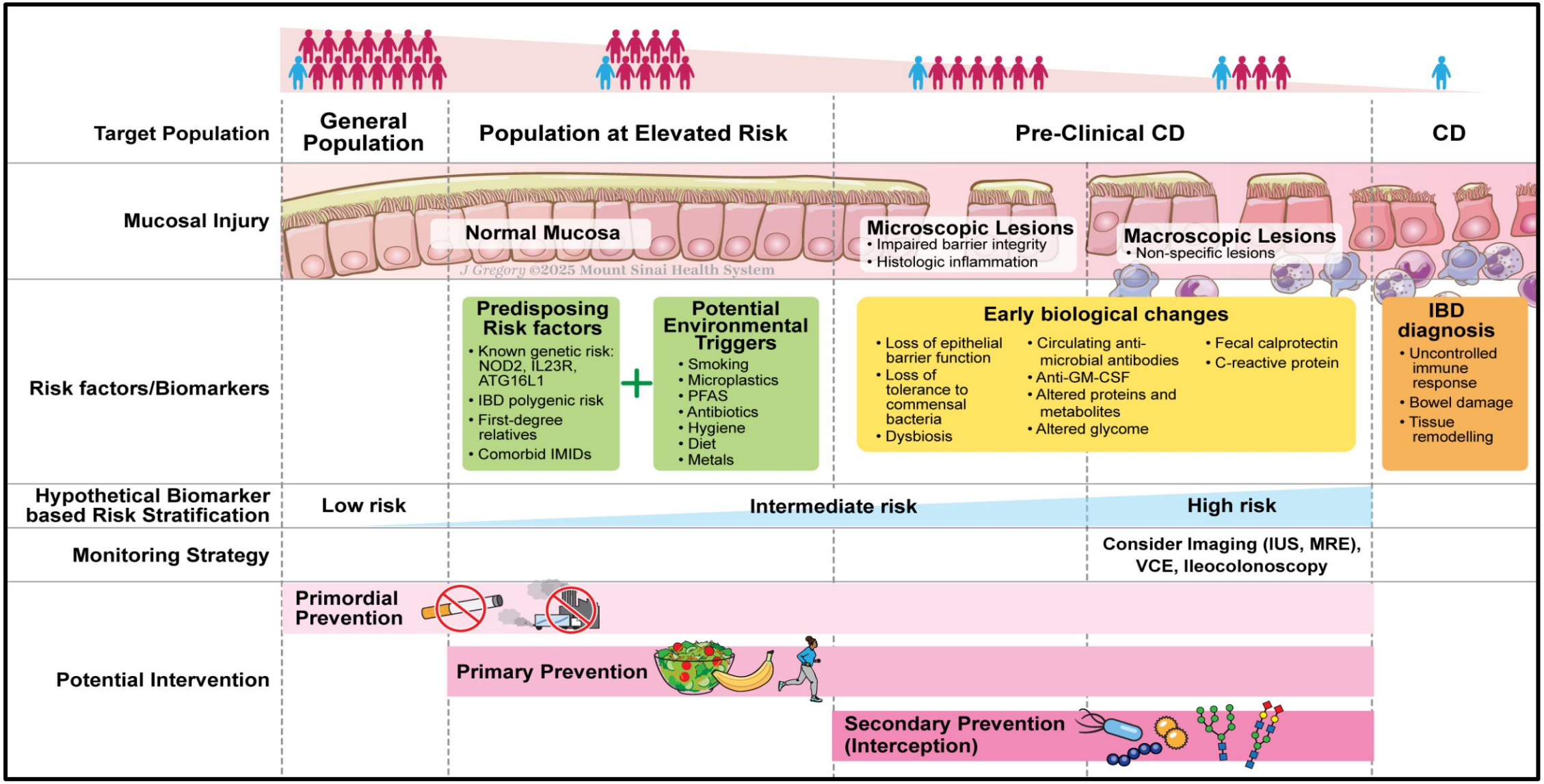
Vaccination

- Altered forms of GM-CSF
- Therapies targeting cytokines/chemokines (ex: CXCL9)
- Anti-IL12/23 or Anti-IL23 agents

Immunotherapy

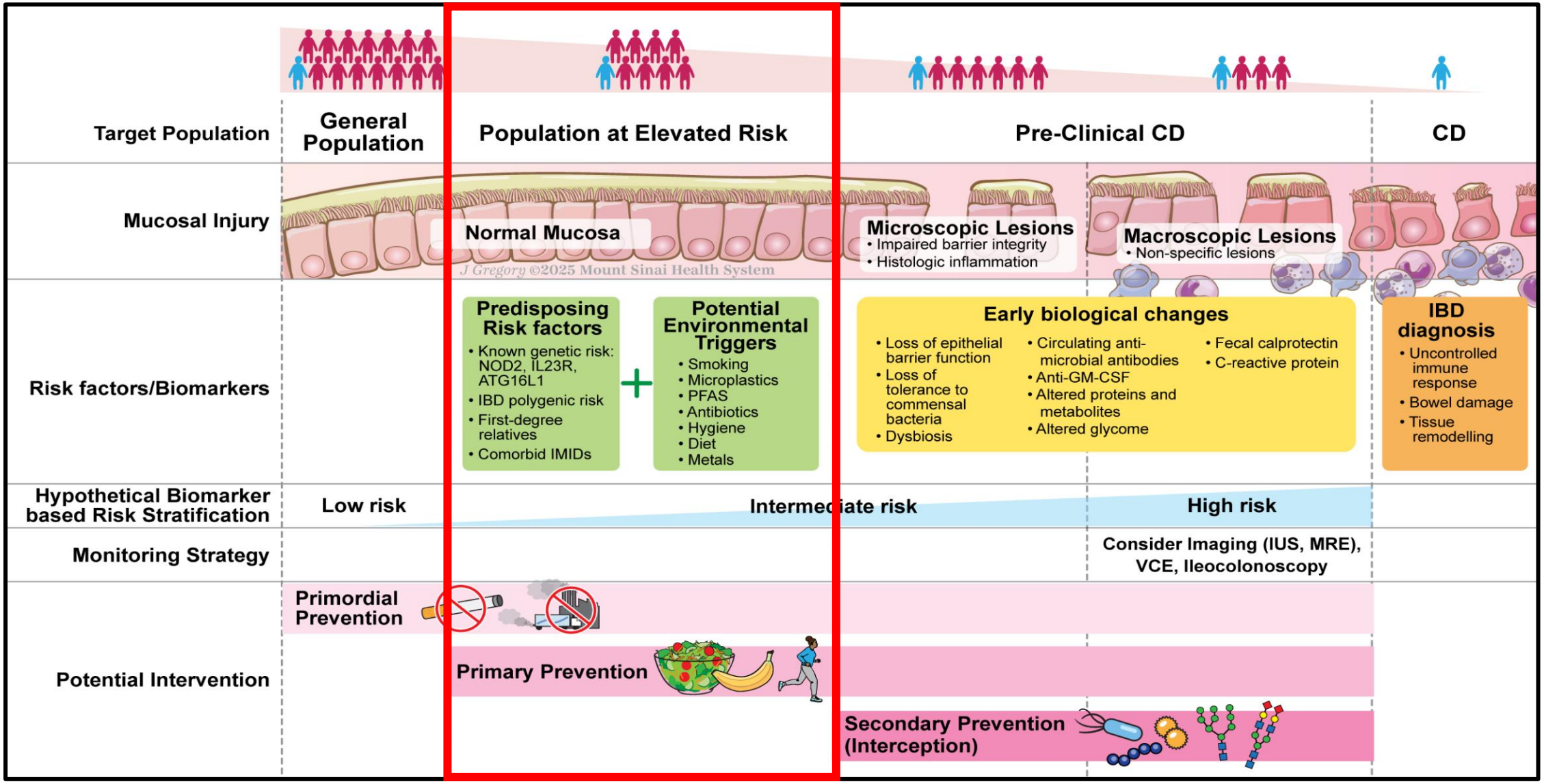
- Anti-α4β7 agents (vedolizumab)

Prevention may vary according to preclinical stage



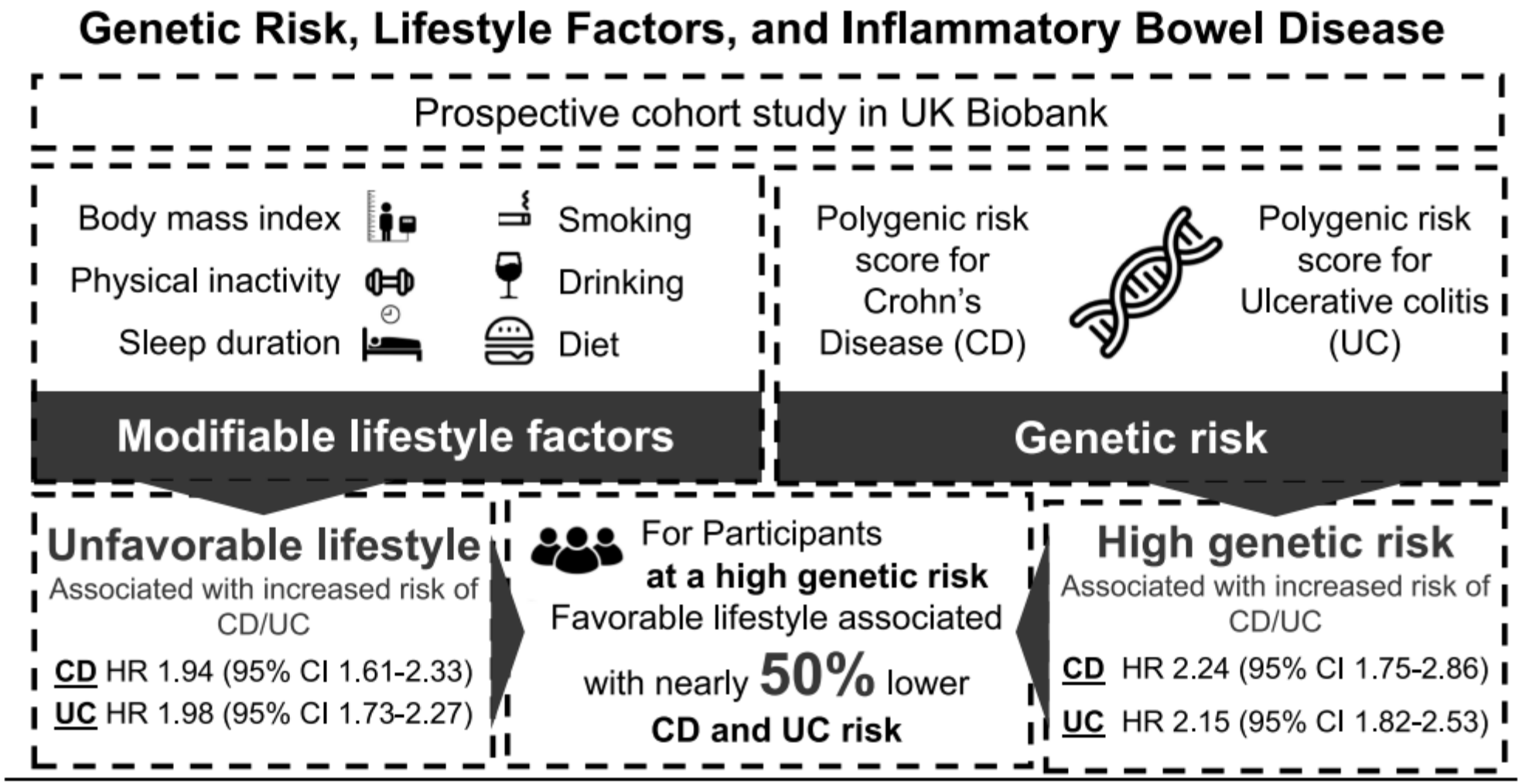
Lee et al. Gastro *In Press*.

Prevention may vary according to preclinical stage

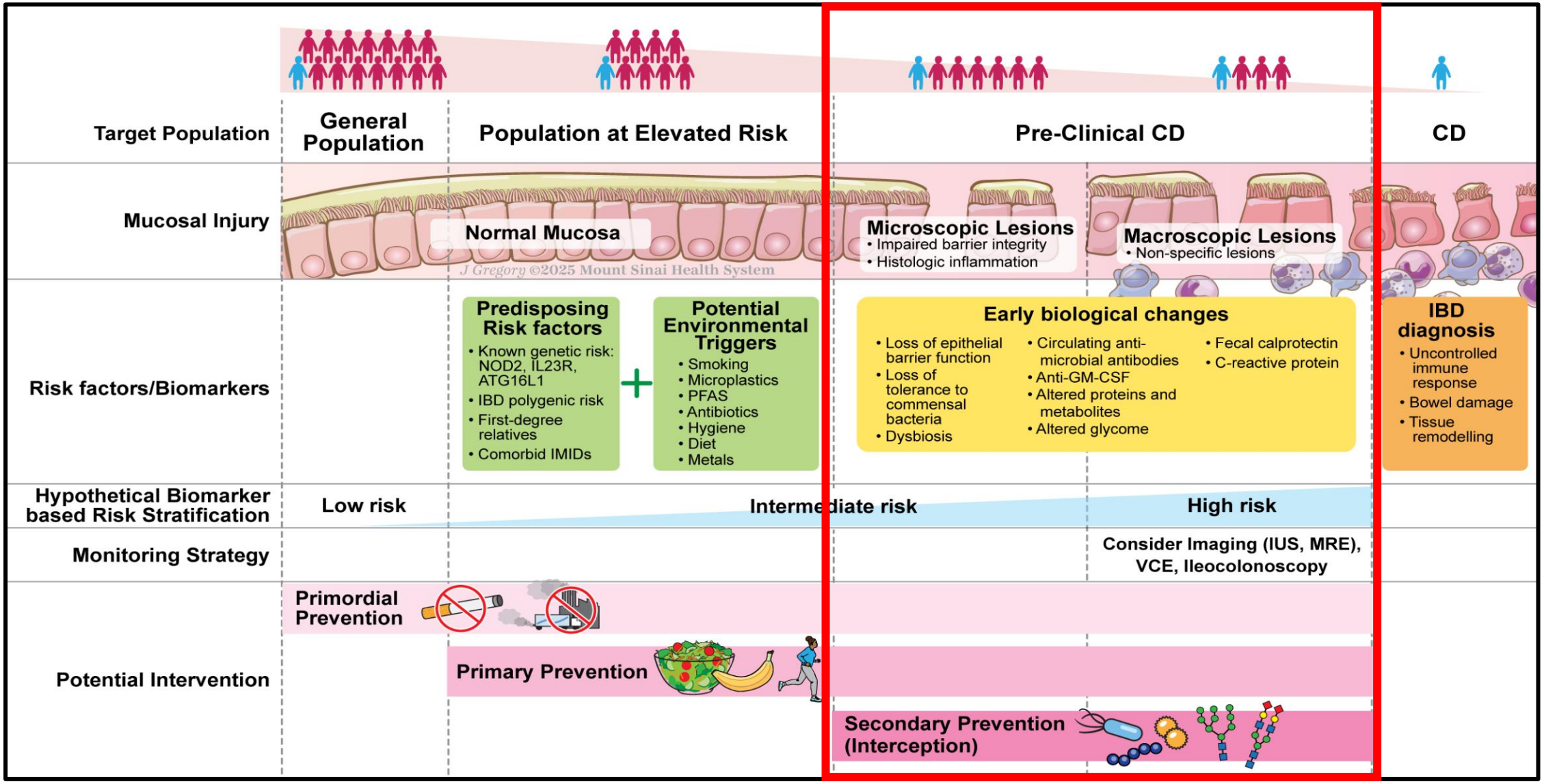


Lee et al. Gastro *In Press*.

Lifestyle modifications can decrease risk even in high genetic burden patients

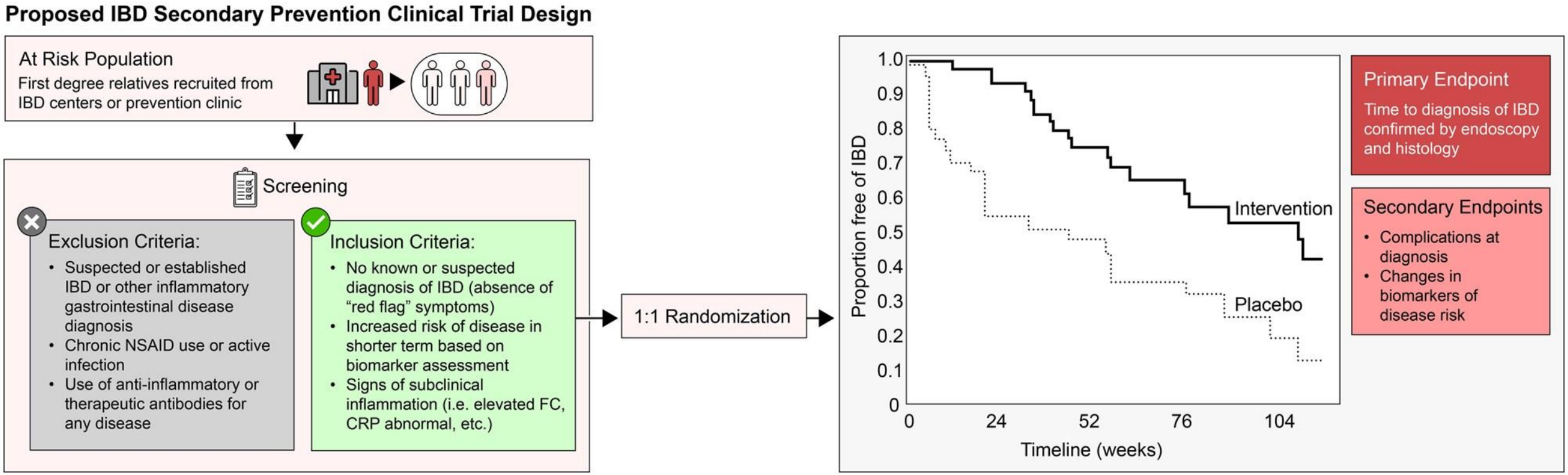


Prevention may vary according to preclinical stage



Lee et al. Gastro *In Press*.

General Secondary Prevention Trial Design Considerations



Goetgebuer RL, Ungaro RC et al IBDJ 2025

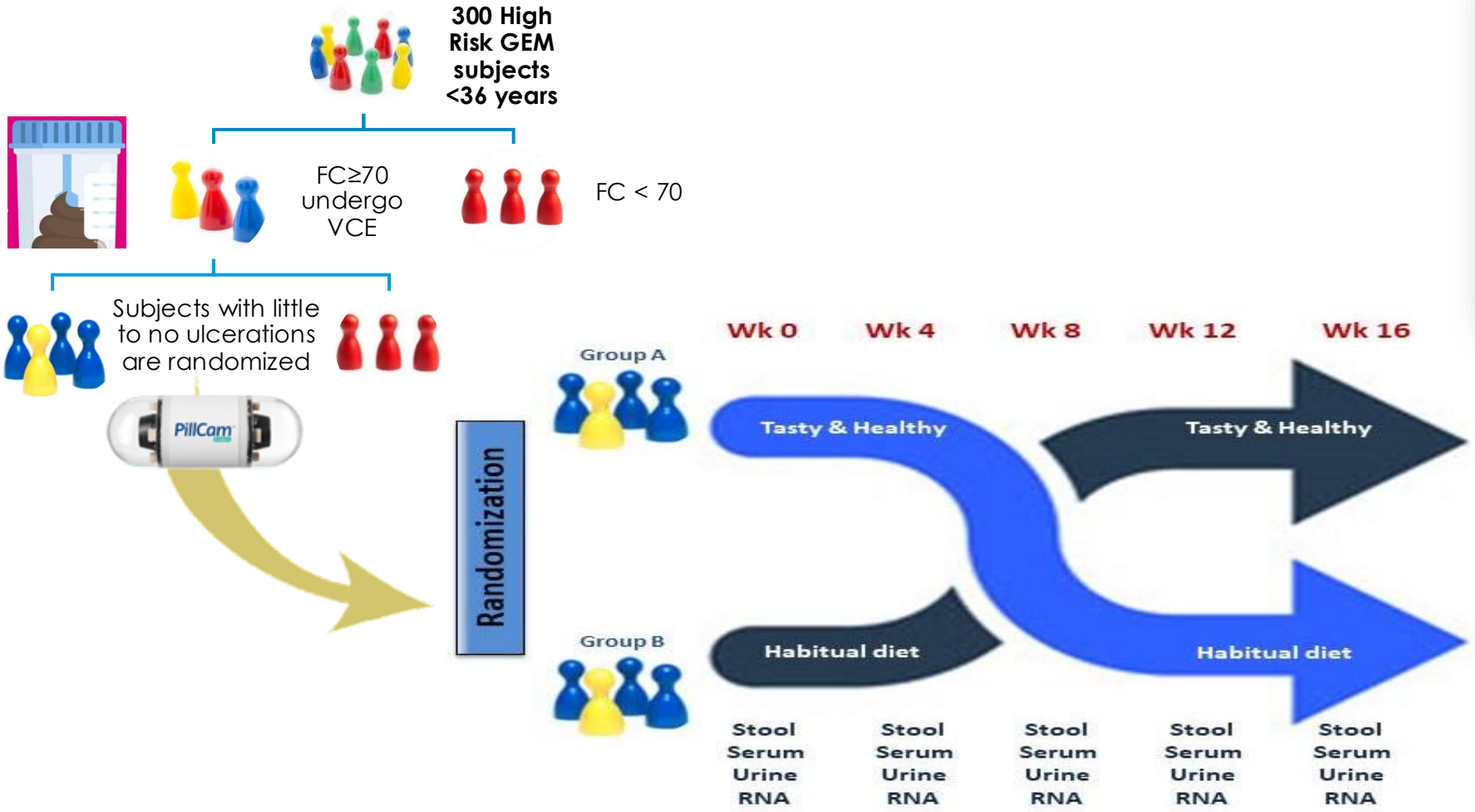
Ongoing Trials in IBD Prevention / Interception

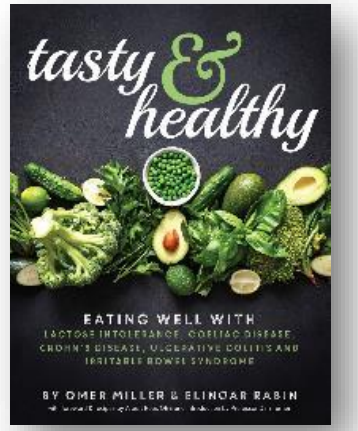
	Disease	Study population	n	Main risk factor	Intervention (individual-level)	Intervention (environment-level)	Trial design	Outcome
Primordial prevention								
VITAL[18]	IMID (including IBD)	Healthy adults	25 871	Vitamin D and omega-3 deficiency	Vitamin D and omega-3 supplementation	None	DB, PC, MC, RCT	Both interventions reduced incident IMIDs: vitamin D better than omega-3
Primary prevention trials								
NCT05566587[19]	Crohn's disease	FDR of patients with Crohn's disease	30	Ultra-processed and pro-inflammatory foods; and dysbiosis	Mediterranean diet	None	OL, MC, RCT	Ongoing
MELODY[20]	Crohn's disease	Pregnant patients with Crohn's disease and healthy offspring as FDR	198	Ultra-processed and pro-inflammatory foods; and dysbiosis	IBD-anti-inflammatory diet	None	OL, MC, NR	Ongoing
PRE-CD[21]	IBD	FDR of patients with IBD	162	Lifestyle and diet	Behavioural intervention for risk factor reduction	None	OL, MC, RCT	Ongoing
NCT03950336[22]	Crohn's disease	FDR of patients with Crohn's disease	33	Ultra-processed and pro-inflammatory foods; and dysbiosis	β-fructans (prebiotic) plus diet with reduced intake of n-6-PUFAs and increased intake of n-3-PUFAs	None	SB, PC, RCT	Ongoing
PIONIR[23]	IBD	FDR of patients with Crohn's disease with increased faecal calprotectin or GEM risk score	30	Ultra-processed and pro-inflammatory foods; and dysbiosis	Tasty&Healthy diet that excludes pro-inflammatory components	None	DB, MC, RCT	Ongoing

There are no secondary prevention (interception) trials. DB=double blind. FDR=first degree relative. GEM=genetic environmental microbiome. IMID=immune-mediated inflammatory diseases. MC=multicentre. NR=non-randomised. OL=open label. PC=placebo controlled. PUFA=polyunsaturated fatty acid. RCT=randomised controlled trial. SB=single blind.

Table 1: **Prevention trials in inflammatory bowel disease**

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





THE LEONA M. AND HARRY B. HELMSLEY CHARITABLE TRUST

Primary Outcome: Likelihood to develop CD measured by the GEM Risk Score

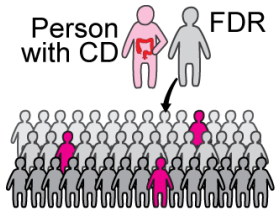
Courtesy of Dan Turner

INTERCEPT: Building Blood Risk Score for Enrollment in Clinical Trial

WP3 STUDY DESIGN

Recruitment strategies

Patient Outreach:
- Advertise the study to existing patients to identify eligible FDRs
- Patient associations (EFFCA, UEG)
- Social media
- Self-referrals



10,000 FDRs across Europe

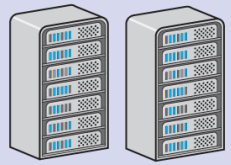
- Verify CD diagnosis in proband(s)
- CD phenotypic information

Register FDRs in e-INTERCEPT app

Questionnaires
- Personal and family history of IBD and IMIDs
- Medical and surgical history
- Smoking
- Early life risk factors
- Stress and fatigue
- Exercise
- Diet

Biobanking
- Serum
- Stool (microbiome + Fcal)
- Whole blood (epigenetics)

Serum biomarkers analysis



Low risk FDR:
Longitudinal follow-up via app every 6 months via repeated questionnaires (2029)

- Personalized risk assessment
- Educational materials CD

New CD diagnoses

High risk FDR

n=100

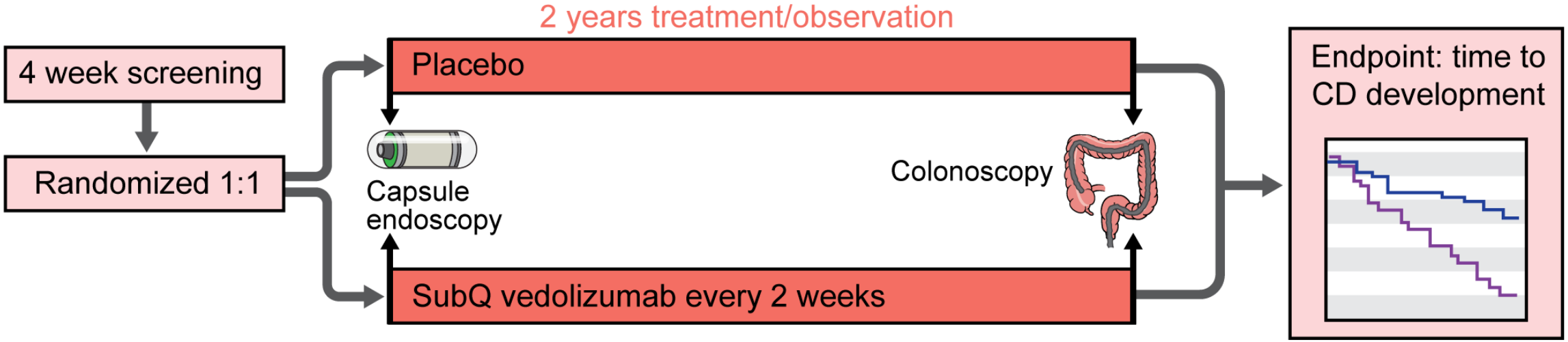
Randomized controlled trial: vedolizumab vs placebo

WP4

INTERCEPT: HALT-CD Clinical Trial

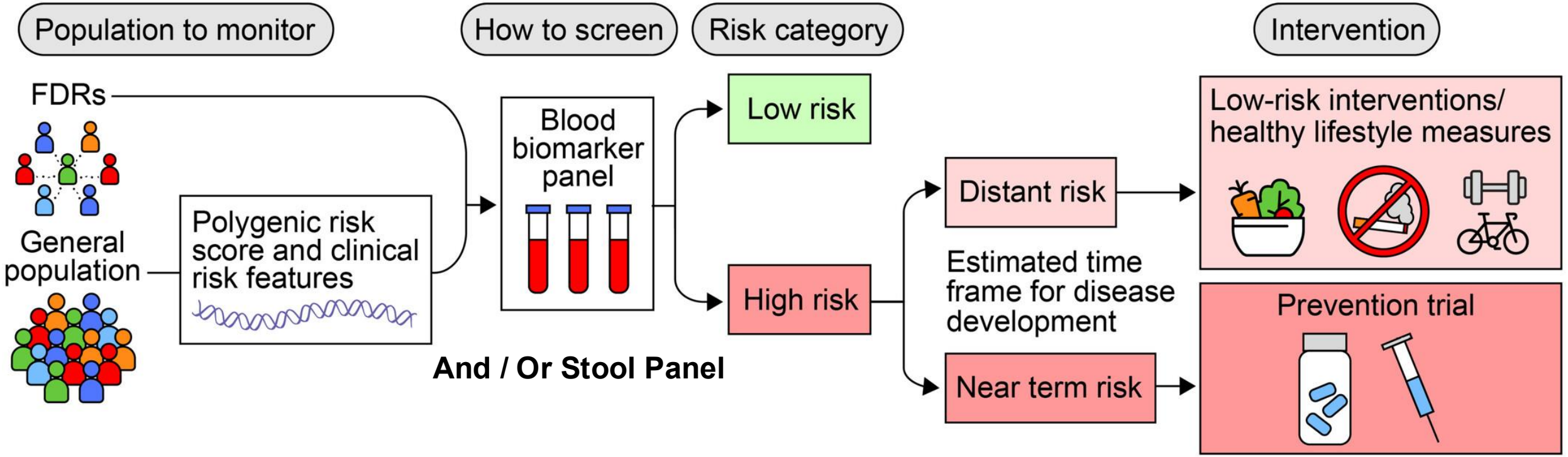
HALT CD

100 individuals at risk: Serological risk score + 2 elevated calprotectin over 150 >2 weeks apart



Primary Objective: To demonstrate that treatment with subcutaneous (SQ) vedolizumab can stop progression from preclinical to overt symptomatic CD in at-risk first degree relatives (FDR) of patients with CD based on a serologic biomarker panel and elevated faecal calprotectin.

Future Approach in IBD Prevention



Prevention in IBD:
A Long Road Ahead but the Future is Bright!

Acknowledgments

Mount Sinai IBD Prevention Group

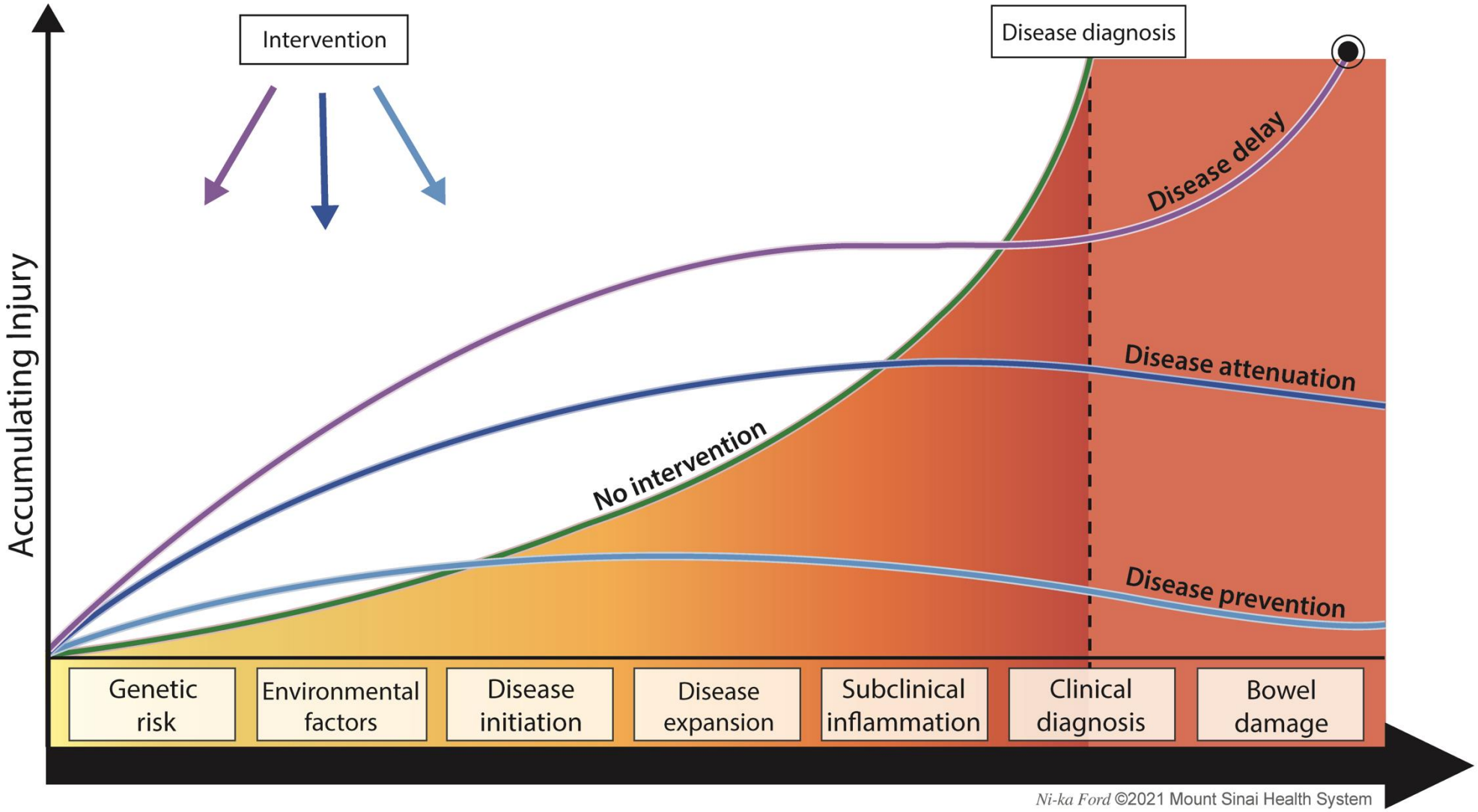
- Jean Frederic Colombel
- Francesca Petralia
- Joana Torres
- Elizabeth Spencer
- Manasi Agrawal
- Alexandra Livanos
- Saurabh Mehandru
- Sacha Gjnatic
- Marla Dubinsky
- Palak Rajauria

Thank You!

Icahn School of Medicine at Mount Sinai

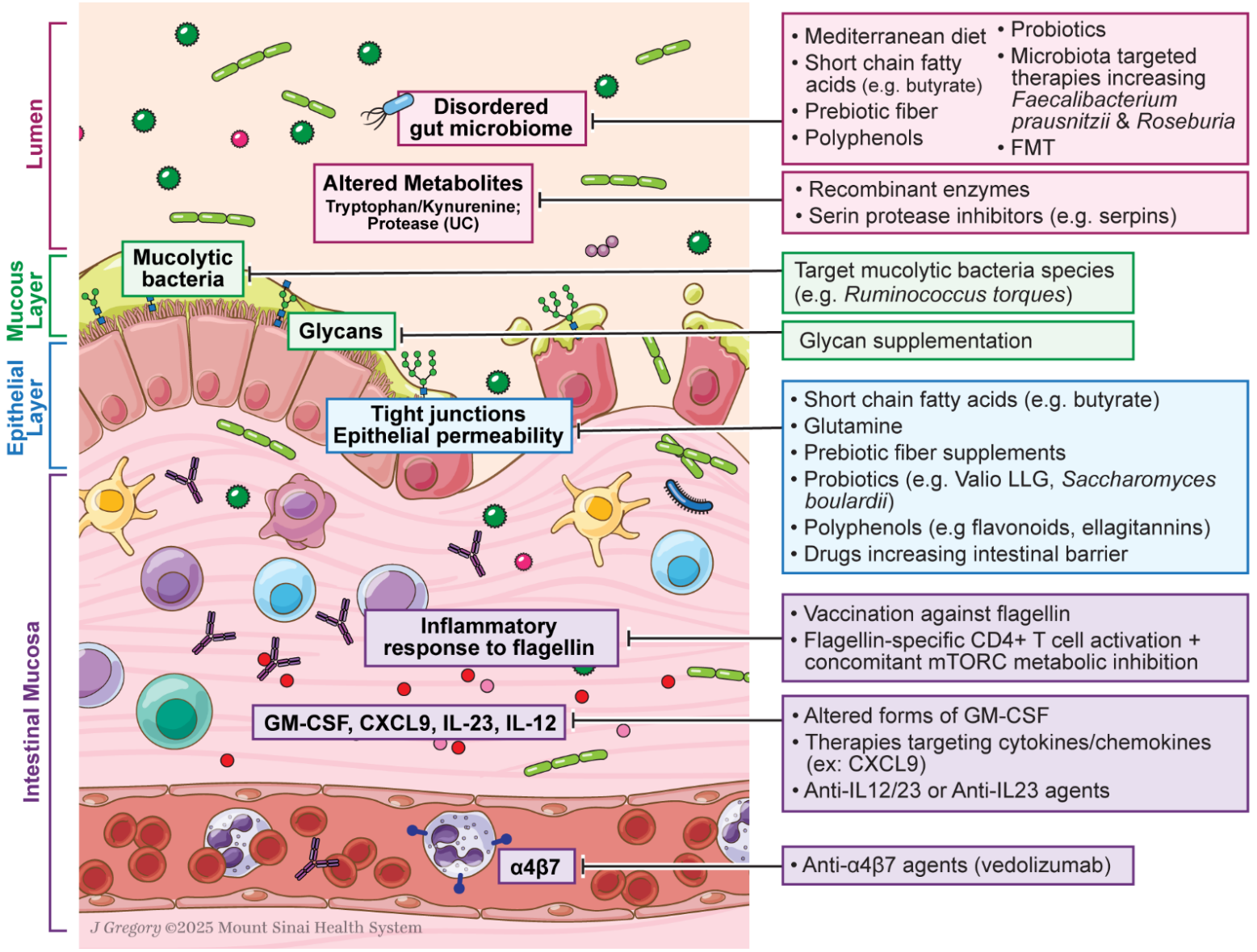
EXTRA SLIDES

What could be the impact and endpoints of an intervention in the preclinical stages of disease?



Potential for Precision IBD Prevention?

Therapeutic targets based on preclinical biomarkers



Lee SH, Lopes E...Ungaro R Inflamm Bowel Dis 2025

MELODY Trial Design

N=198

the MELODY Trial

Crohn's disease + IBD-AID diet

Crohn's disease + no diet

Control + no diet

	Timeline	27-29 w (Baseline)	35 w	37 w	Delivery	14 d	30 d	90 d	6 mo	12 mo
	Samples	Stool Saliva	Stool Saliva	Stool Saliva	Umbilical cord blood	Breast milk			Stool Saliva	Stool Saliva
	Questionnaires (Q)	24HR Basic Info Q Health history/ Reproductive Q		24HR	Delivery/ Postpartum Q			Rome IV	FFQ 24HR Follow-up Q	FFQ 24HR Follow-up Q
		FFQ weekly throughout								
Babies	**Samples**					Stool	Stool	Stool	Stool	Stool
	Questionnaire					IDD	IDD	IDD	IDD 24HR	IDD 24HR

w=gestational weeks; d=days old; mo=months old
FFQ=Food Frequency Questionnaire (online) <30 minutes
24HR=24 Hour Diet Recall (by phone, three separate days) 20-30 minutes
IDD=Infant Diet and Development Questionnaire (online) 10 minutes
Rome IV=Assess functional gastrointestinal disorders in infants (by phone)

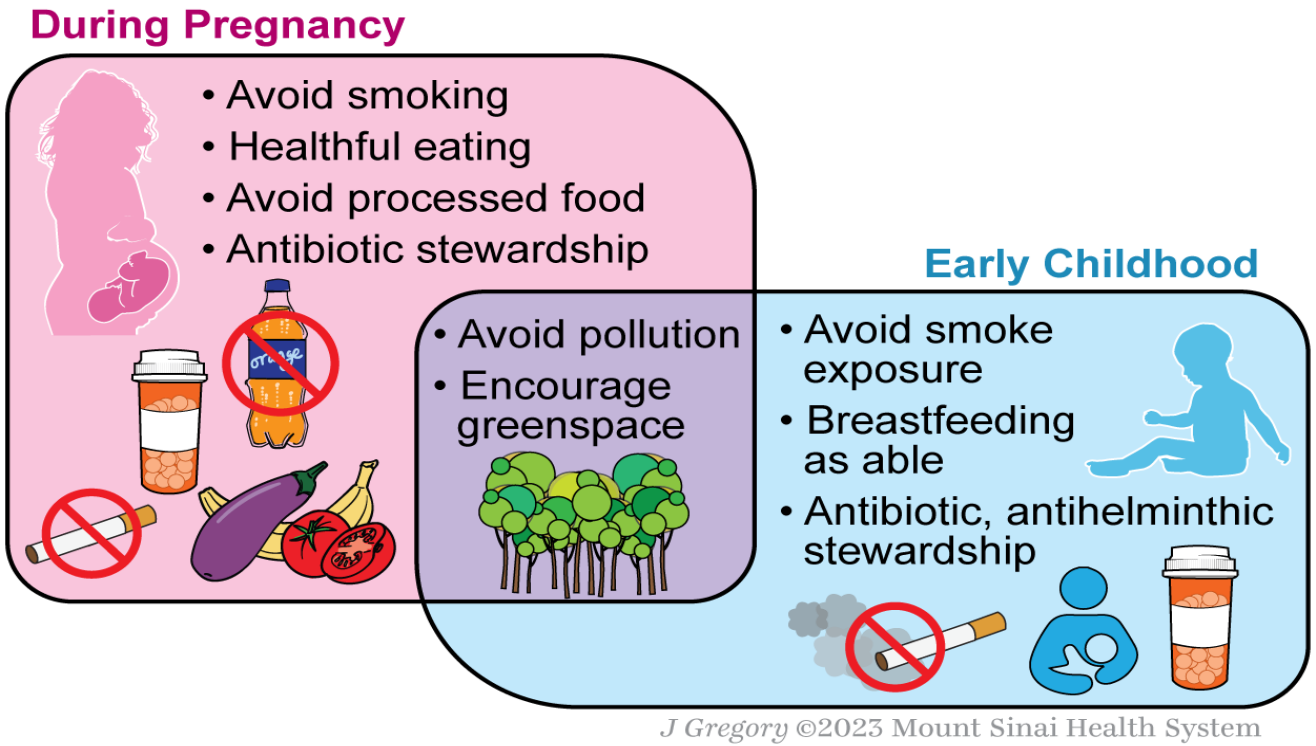
Maternal outcomes

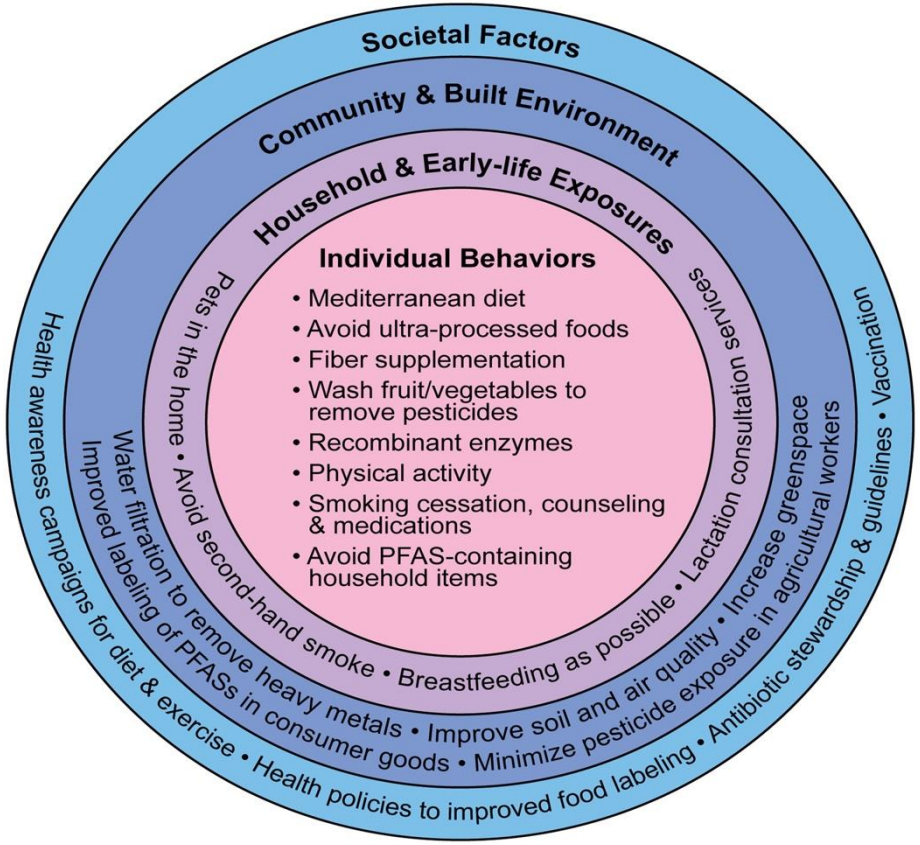
- **Microbiome diversity**
- **Disease activity**

Baby outcomes

- **Colics**
- **Microbiome diversity during first year of life**
- **1-year calprotectin**

Primordial Prevention of Crohn's disease: Exposure Mitigation / Public Health Interventions

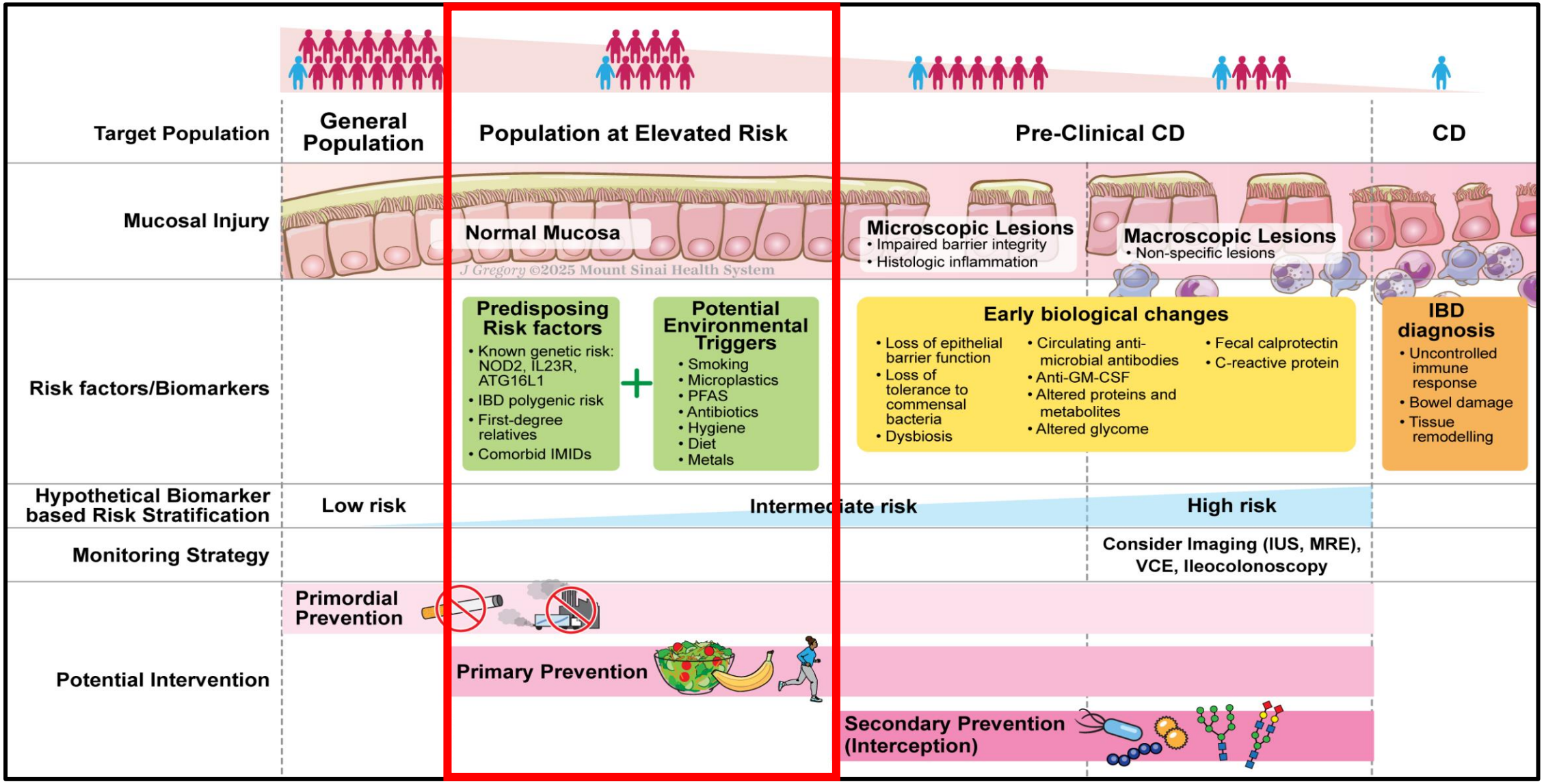




Zhang, Agrawal et al, Gut, 2024

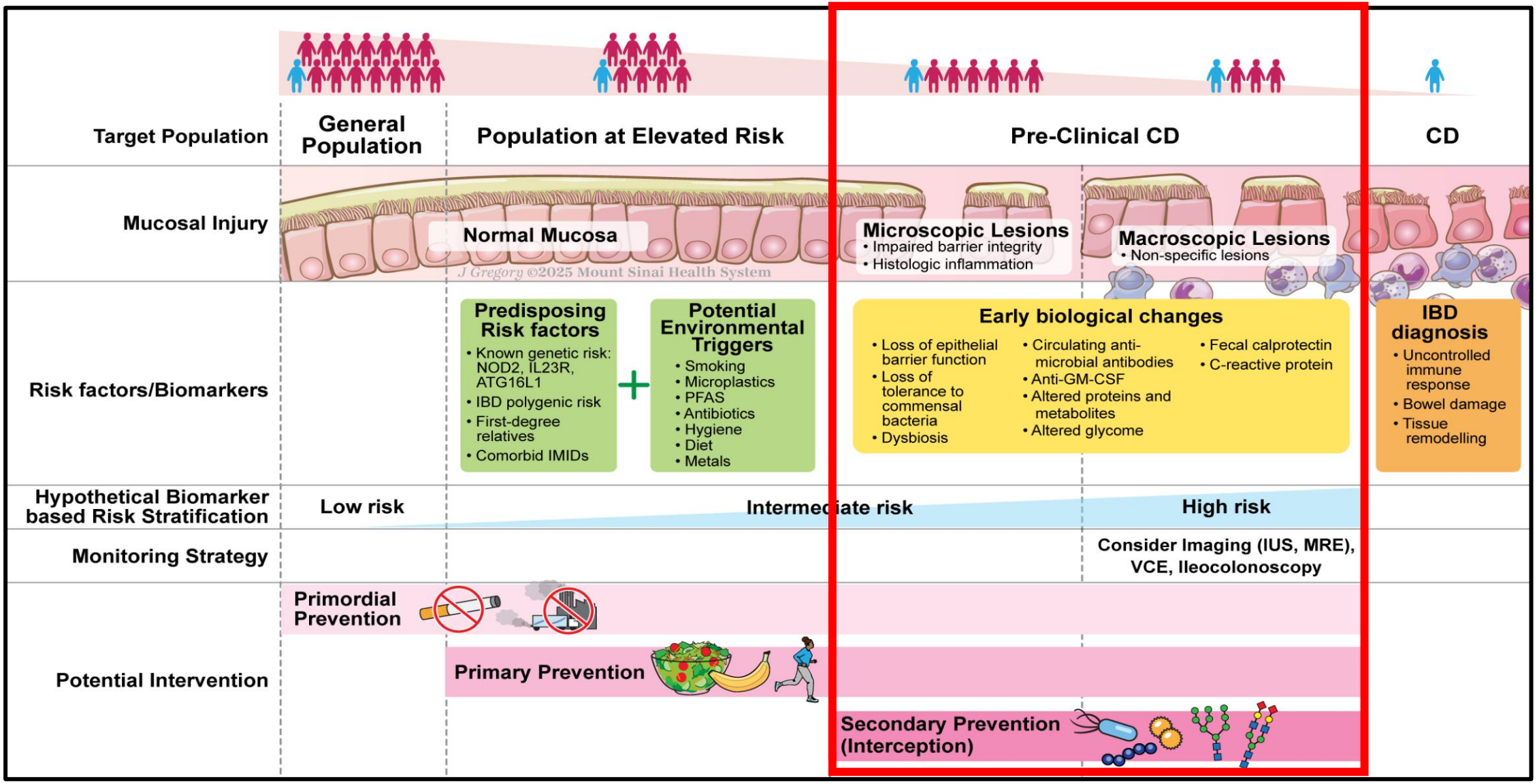
Lee SH, et al. IBD in press.

Prevention may vary according to preclinical stage



Lee et al. Gastro In Press.

Prevention may vary according to preclinical stage



Lee et al. Gastro In Press.

Acknowledgments

PREDICTS Study: A Joint Government Academic & Industry Cooperative Research & Development Agreement

DoD/ Naval Medical Research Center

- Chad K. Porter
- Jared Magee
- Mark S Riddle
- Renee Laird
- Vicky Chapman
- Sandra Isidean
- Karen Mata

Icahn School of Medicine at Mount Sinai

- Jean Frederic Colombel
- Francesca Petralia
- Joana Torres
- Ryan Ungaro
- Manasi Agrawal
- Alexandra Livanos
- Saurabh Mehandru
- Sacha Gjnatic

Prometheus

- Thierry Dervieux

Mayo Clinic

- Rok Seon Choung
- Joseph A. Murray

University of Porto (Por)

- Salome Pinho

University of Toronto (Can)

- Arthur Morta

Harvard Medical School

- Scott B.Snapper
- Anubhab Nandy

Prevention trials: Learning from Others

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 15, 2019 VOL. 381 NO. 7

An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes

Herold KC et al. NEJM 2019

Abatacept in individuals at high risk of rheumatoid arthritis (APIPPRA): a randomised, double-blind, multicentre, parallel, placebo-controlled, phase 2b clinical trial

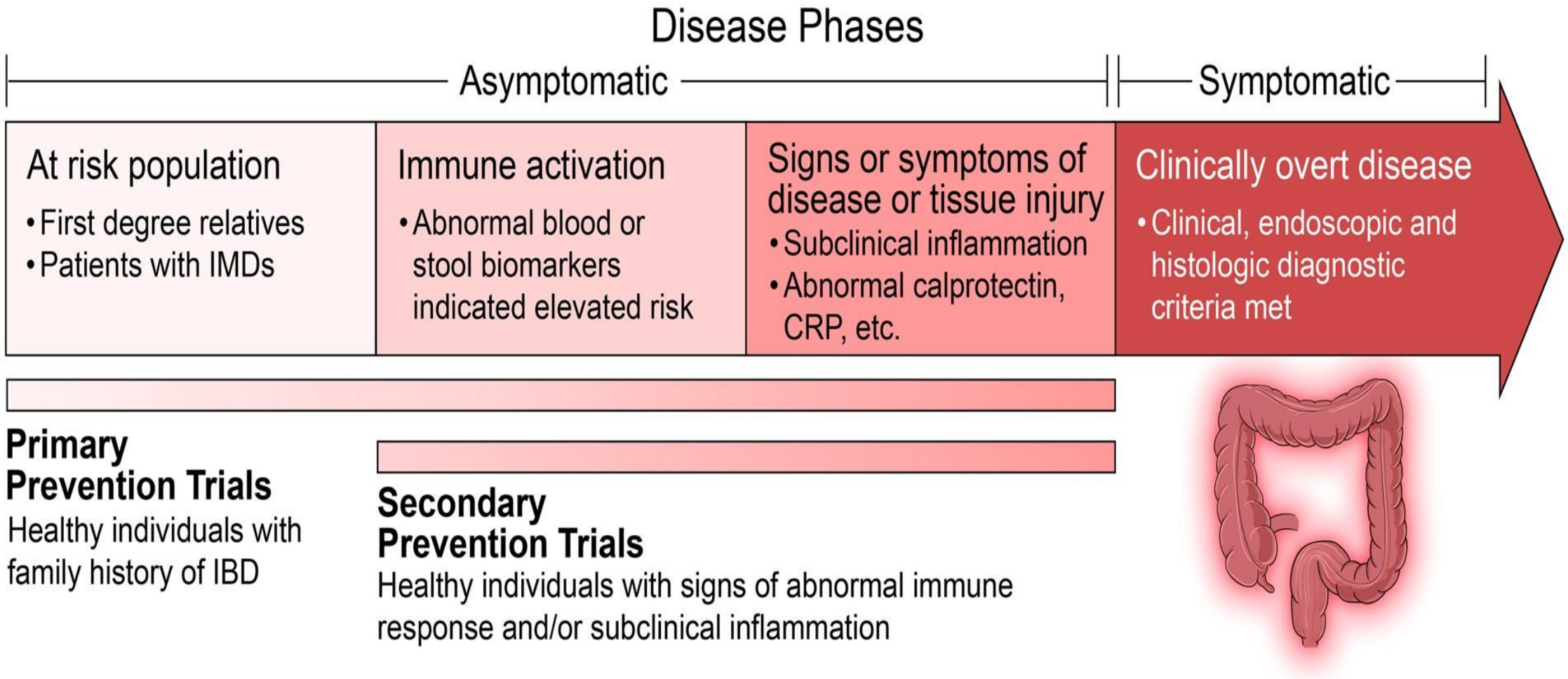
Cope AP et al. Lancet 2024

JAMA Neurology | Original Investigation

Teriflunomide and Time to Clinical Multiple Sclerosis in Patients With Radiologically Isolated Syndrome
The TERIS Randomized Clinical Trial

Lebrun-Frenay C et al. JAMA Neurology 2023

Distinguishing Disease Phases for IBD Prevention Trials

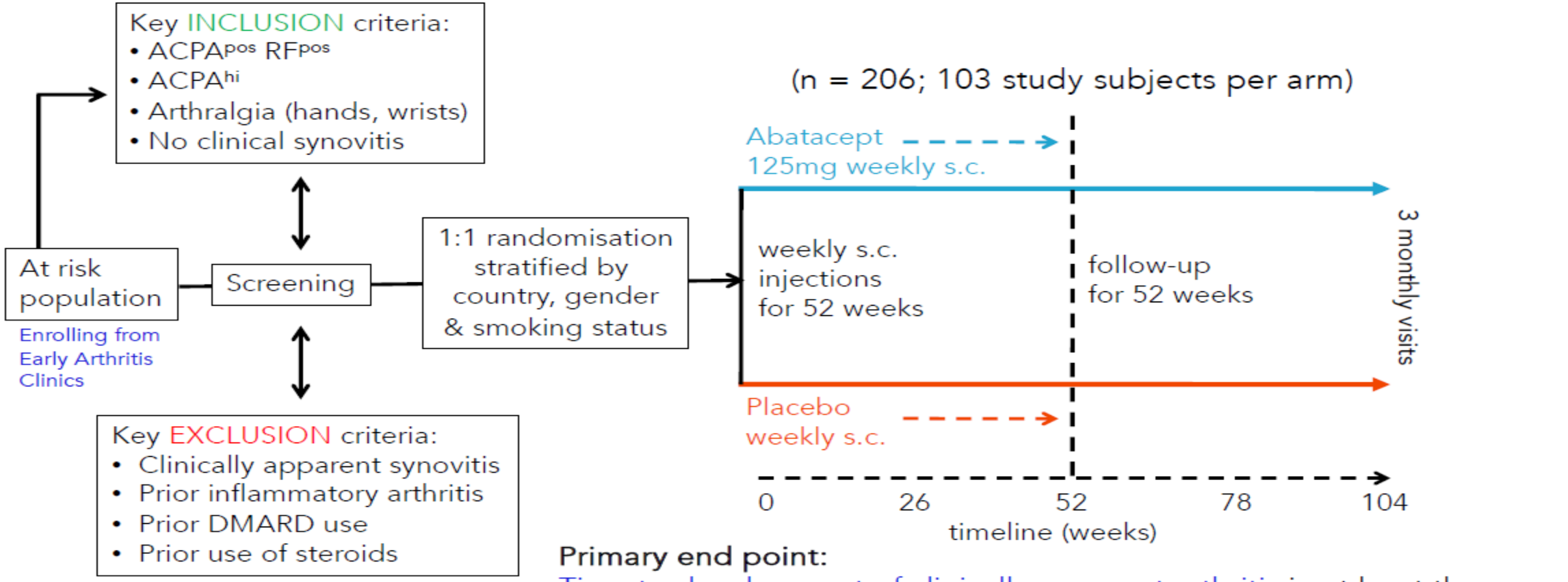


Goetgebuer RL, Ungaro RC et al IBDJ 2025

Pioneering A Future Without Crohn's Disease

https://www.intercept-ihi.eu/

Abatacept in Individuals with High Risk of Rheumatoid Arthritis (APIPPRA)

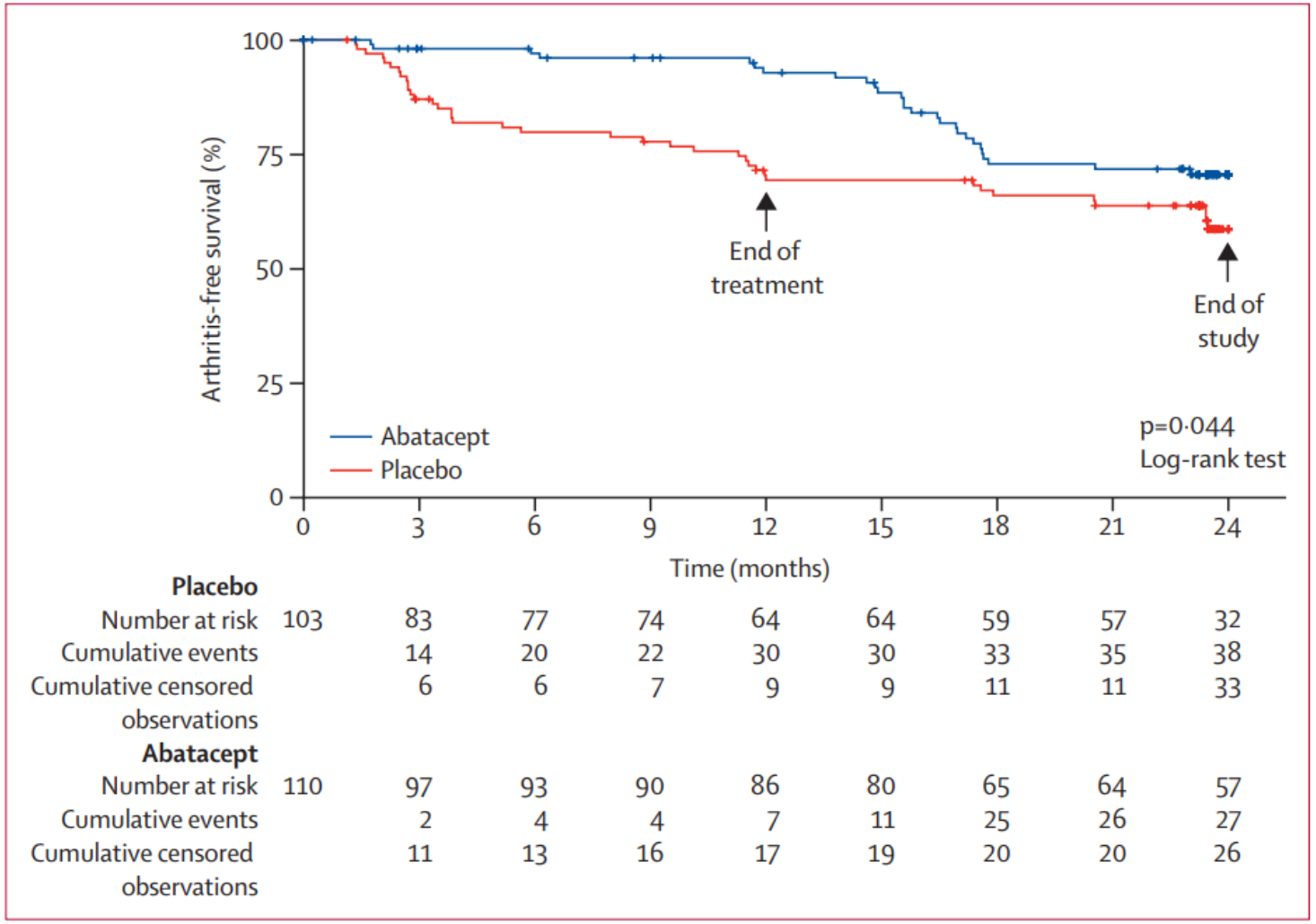


Primary end point:

Time to development of clinically apparent arthritis in at least three joints, or to fulfilment of the ACR/EULAR 2010 criteria for RA, whicheve comes first, during 24 months of follow up. Confirmed by ultrasound.

Al-Laith et al. Trials 2019

Abatacept in Individuals with High Risk of Rheumatoid Arthritis (APIPPRA)



Placebo									
Number at risk	103	83	77	74	64	64	59	57	32
Cumulative events		14	20	22	30	30	33	35	38
Cumulative censored observations		6	6	7	9	9	11	11	33
Abatacept									
Number at risk	110	97	93	90	86	80	65	64	57
Cumulative events		2	4	4	7	11	25	26	27
Cumulative censored observations		11	13	16	17	19	20	20	26

Figure 2: **Arthritis-free survival by group**

Cope AP, et al. Lancet. 2024.

Title and Content, Table Example

Table Headline	Table Headline	Table Headline	Table Headline	Table Headline
Column Heading	Table text, 13pt Arial regular. Lorem ipsum dolor sit amet, consectetur adipiscing elit.	Table text, 13pt Arial regular. Lorem ipsum dolor sit amet, consectetur adipiscing elit.	Table text, 13pt Arial regular. Lorem ipsum dolor sit amet, consectetur adipiscing elit.	Table text, 13pt Arial regular. Lorem ipsum dolor sit amet, consectetur adipiscing elit.
Column Heading	Table text, 13pt Arial regular. Lorem ipsum dolor sit amet, consectetur adipiscing elit.	Table text, 13pt Arial regular. Lorem ipsum dolor sit amet, consectetur adipiscing elit.	Table text, 13pt Arial regular. Lorem ipsum dolor sit amet, consectetur adipiscing elit.	Table text, 13pt Arial regular. Lorem ipsum dolor sit amet, consectetur adipiscing elit.
Column Heading	Table text, 13pt Arial regular. Lorem ipsum dolor sit amet, consectetur adipiscing elit.	Table text, 13pt Arial regular. Lorem ipsum dolor sit amet, consectetur adipiscing elit.	Table text, 13pt Arial regular. Lorem ipsum dolor sit amet, consectetur adipiscing elit.	Table text, 13pt Arial regular. Lorem ipsum dolor sit amet, consectetur adipiscing elit.

Examples of Ongoing Efforts to Advance Prediction and Prevention Research

Mass General Brigham

Sinai Health

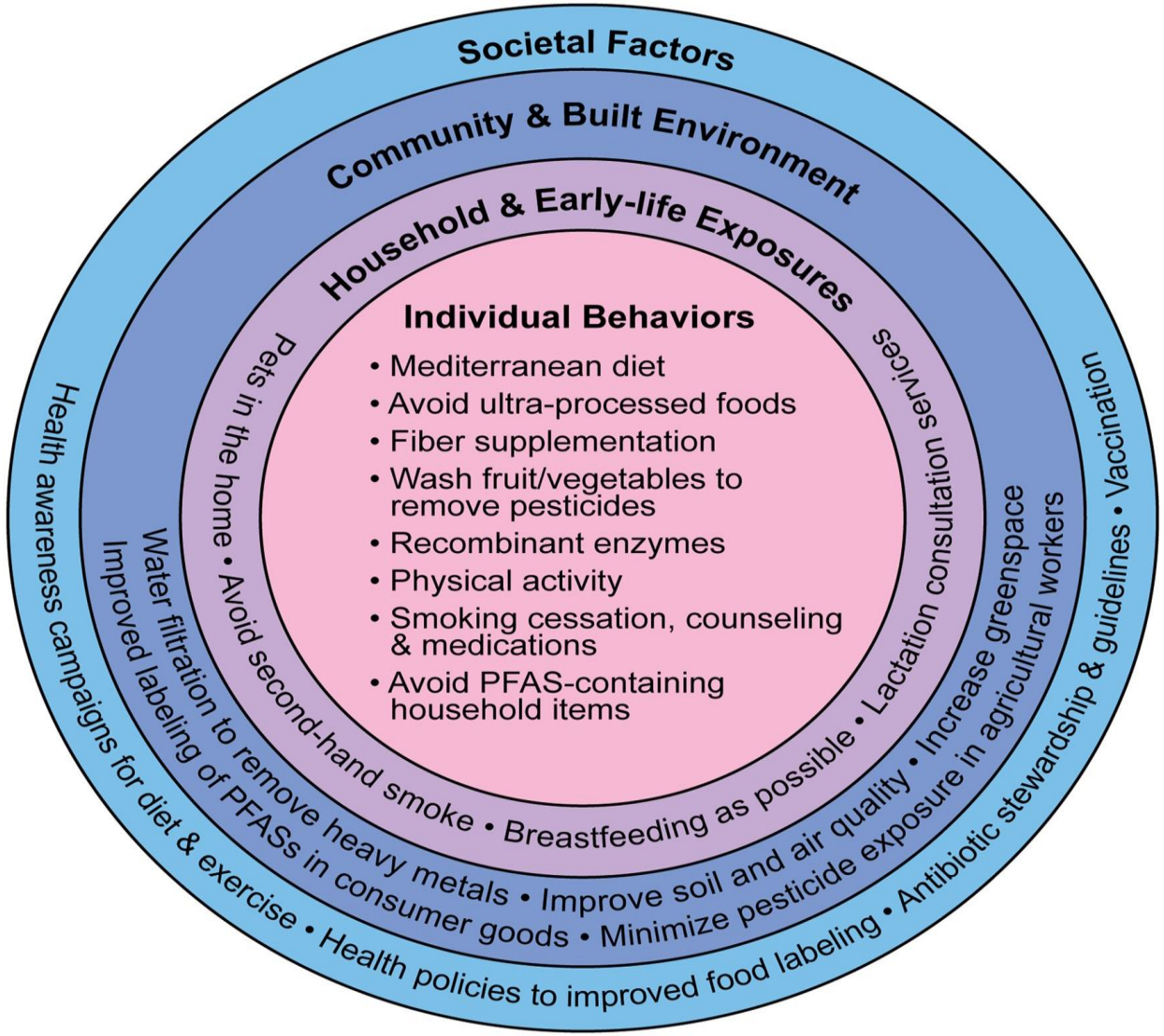
Icahn School of Medicine at Mount Sinai

PROMISE

Defining the Pre-Disease Phase of Crohn's Disease – Predict and Prevent

Funded by
THE LEONA M. AND HARRY B. HELMSLEY CHARITABLE TRUST

Primordial Prevention of Crohn's disease: Exposure Mitigation / Public Health Interventions



Lee SH, et al. IBD in press.

PROMISE Goals

Building an Integrative Signature

- Assess the resulting biomarkers against CD onset.
- Combining the biomarkers that show association with future development of CD.
- Test against different pre-disease cohorts.

Signature validation

- Project the signatures, networks and pathways onto high-risk populations for testing.
- Using the validation cohorts, the MECONIUM Study and Road To Prevention. Two prospective studies of FDRs.

Knowledge development and dissemination

- Understanding the onset of disease in a way that can be target for treatment and mitigation.
- Create protocols and best practices.
- Engage partners for future directions in the prediction and prevention of CD.

Prevention/interception is ambitious but being sought across many therapeutic areas

Abatacept in individuals at high risk of rheumatoid arthritis (APIPPRA): a randomised, double-blind, multicentre, parallel, placebo-controlled, phase 2b clinical trial

*Andrew P Cope, Marianna Jasenecova, Joana C Vasconcelos, Andrew Filer, Karim Raza, Sumera Qureshi, Maria Antonietta D'Agostino, Iain B McInnes, John D Isaacs, Arthur G Pratt, Benjamin A Fisher, Christopher D Buckley, Paul Emery, Pauline Ho, Maya H Buch, Coziana Ciurtin, Dirkjan van Schaardenburg, Thomas Huizinga, René Toes, Evangelos Georgiou, Joanna Kelly, Caroline Murphy, A Toby Prevost, on behalf of the APIPPRA study investigators**

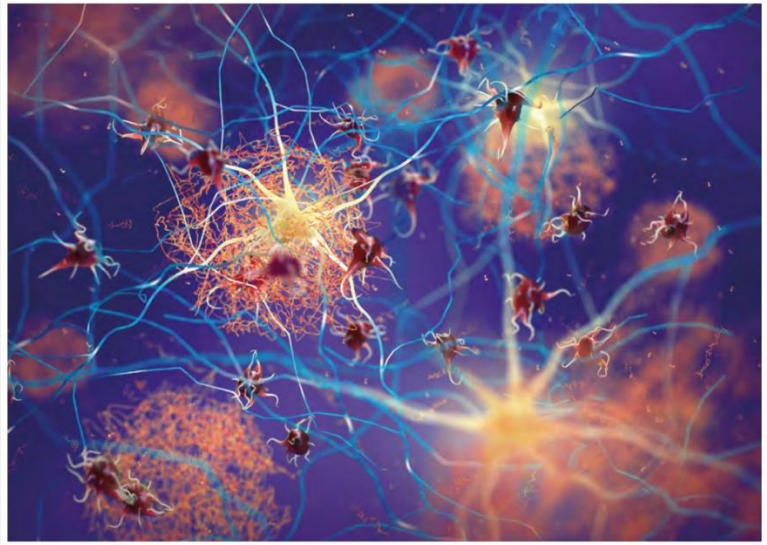
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 15, 2019 VOL. 381 NO. 7

An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes

Kevan C. Herold, M.D., Brian N. Bundy, Ph.D., S. Alice Long, Ph.D., Jeffrey A. Bluestone, Ph.D., Linda A. DiMeglio, M.D., Matthew J. Dufort, Ph.D., Stephen E. Gitelman, M.D., Peter A. Gottlieb, M.D., Jeffrey P. Krischer, Ph.D., Peter S. Linsley, Ph.D., Jennifer B. Marks, M.D., Wayne Moore, M.D., Ph.D., Antoinette Moran, M.D., Henry Rodriguez, M.D., William E. Russell, M.D., Desmond Schatz, M.D., Jay S. Skyler, M.D., Eva Tsalikian, M.D., Diane K. Wherrett, M.D., Anette-Gabriele Ziegler, M.D., and Carla J. Greenbaum, M.D., for the Type 1 Diabetes TrialNet Study Group*

Feature



In Alzheimer's disease, abnormal amounts of amyloid-β proteins clump together to form plaques in the brain.

PREDICTING ALZHEIMER'S WITH A BLOOD TEST

Scientists are closing in on biomarkers that reflect the progression of Alzheimer's disease. **By Alison Abbott**

Like many Alzheimer's researchers, neurologist Randall Bateman is not prone to effusiveness, having endured disappointments in his field. But he and others have found one big reason to be excited lately. In just a few years, he predicts, there will be a simple blood test for your risk of Alzheimer's. "Any family doctor will be able to do it."

Bateman, who is at Washington University in St. Louis, Missouri, has been running clinical trials related to Alzheimer's disease for nearly 20 years. "From all I've seen, this is a very likely scenario," he says. "It'll be just like going to get your blood cholesterol checked and then being given statins if levels are too high."

This extraordinary turnaround in outlook for the disease that affects more than 55 million people worldwide comes down to two things – both of which were thought by many to be nigh on impossible just a decade ago. First, drugs that can slow the disease, if it is caught early enough, are now coming on the market. And second, scientists have developed relatively cheap and highly accurate blood-based biomarkers for Alzheimer's.

These biomarkers – a catch-all term for any biological molecule found in blood or tissue that can indicate someone's medical state – are not treatments. But they are revolutionizing prospects for therapies that might delay or even prevent Alzheimer's. They would do this by catching the disease before symptoms – and brain damage – begin.

That hopeful scenario depends on the further development of drugs that can treat or hold off the disease, when caught early. But even now, biomarkers are already improving clinical trials, allowing researchers to test interventions at much earlier stages than before. And they are transforming how researchers track the course of the disease and learn more about its basic pathology. "The pace of development of these tests is extraordinary," says neurologist Jonathan Schott at University College London. "There is huge excitement."

Markers of success

Alzheimer's disease accounts for around two-thirds of all cases of dementia. The brains of people with Alzheimer's disease have three main characteristics. There are gaps where the tissue has degenerated. The tissue is dotted

Research Gaps in Prediction Biomarkers

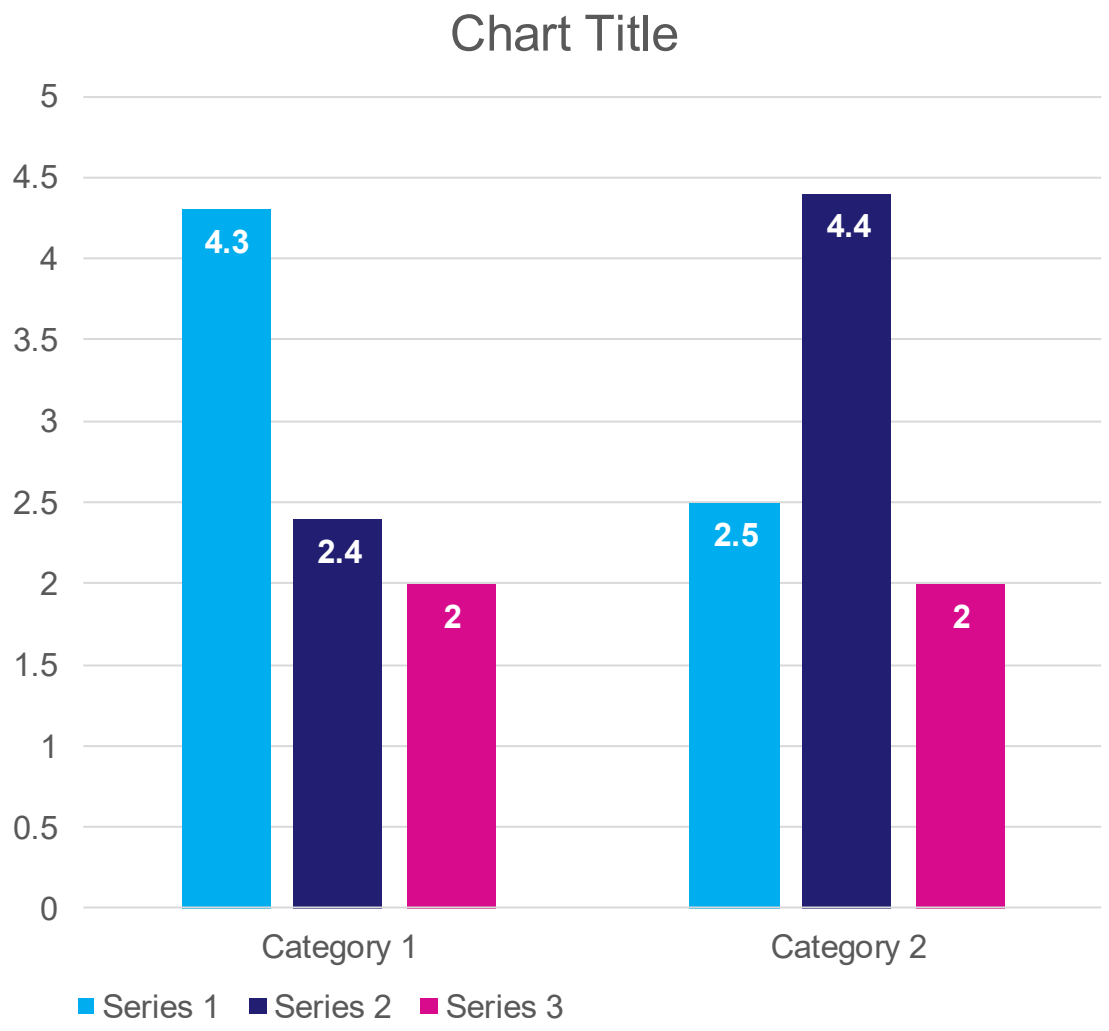
- Developing risk scores with high predictive accuracy
- Understanding dynamics of biomarkers to inform serial monitoring
- Predicting time to disease onset → inform type of monitoring or intervention strategy
- Utilizing biomarkers to define preclinical phases of disease
- Increase preclinical biomarker data to define earliest pathogenic changes and pathways
- Further validation of biomarkers and risk scores in diverse patient populations
- Regulatory and ethical considerations for predicting risk

Title and Two Content, Column Chart Example

First level of text, Arial 18pt

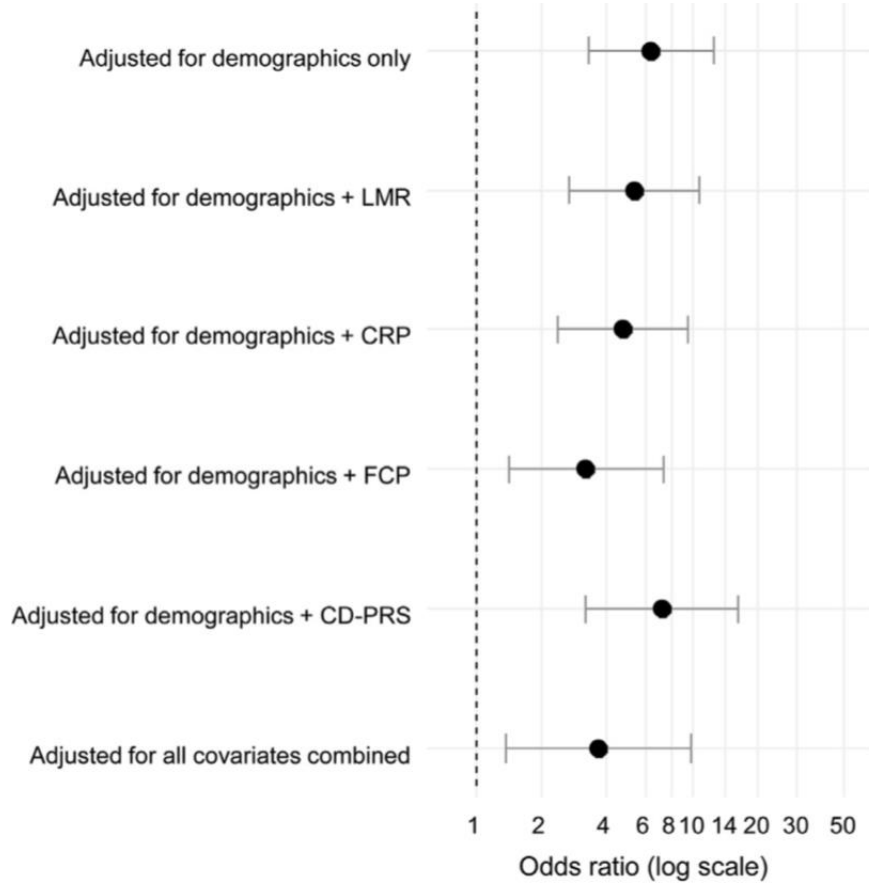
- Second level of text, Bullet, Arial 18pt
  - Third level of text, Sub-bullet, Arial 16pt

Fourth level of text, color, Arial 18pt



Anti-Microbial Antibody Response is Associated with Future Onset of CD Independent of Gut Barrier Function, Subclinical Inflammation, and Genetic Risk

- **77** subjects who later developed CD compared to **307** FDRs remaining healthy
- 6 anti-microbial Abs measured
- Adjustment for Fcal, PRS, IP
- Median f-up time: **2.2 [1.2–4.2] (0.23–9.5) years**



High baseline AS (≥2) (43% of cases, 11% of controls): aOR: 6.36; 95% CI, 3.27–12.37; $p=4.9 \times 10^{-8}$

Sun-Ho Lee & Williams Turpin et al Gastroenterology 2021

CROHN'S & COLITIS FOUNDATION

Anti-GM-CSF Autoantibodies as Marker of Complicated Crohn's Disease

PREDICTS

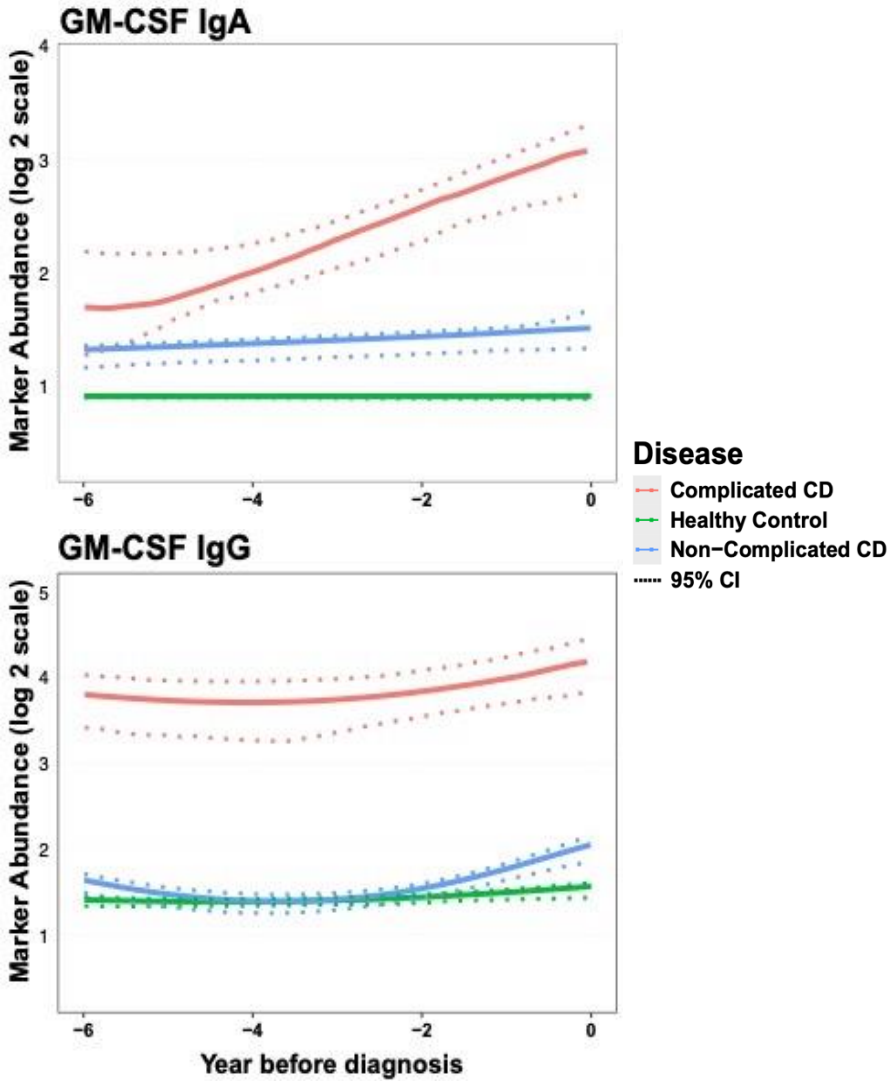
Time-varying trajectories of anti-GM-CSF pre-diagnosis are consistently elevated in complicated CD

<u>Complicated</u>

54 (27%)

<u>Uncomplicated</u>

146 (73%)



GEM

Total N=4,366
N with CD=79 (complicated = 9)

Positive anti-GM-CSF IgA and IgG were associated with higher risk of complicated CD at diagnosis

IgA: HR 7.3 (95% CI 0.8-64.4)
IgG: HR 9.2 (95% CI 2.1-40.9)

This risk was higher than risk of diagnosis of uncomplicated CD

IgA: HR 2.8 (95% CI 0.9-8.9)
IgG: HR 1.2 (95% CI 0.4-3.2)

Summary

Multi-protein panels (Grännö et al., Torres et al., Taylor et al.) provide the highest AUCs (up to 0.87) for predicting future Crohn's disease in preclinical cohorts

Single markers (CXCL9, IL-6, hsCRP, fecal calprotectin) show moderate associations but are less predictive alone.

• Antibody and metabolite signatures, as well as environmental exposures, are emerging as relevant but require further validation for quantitative predictive performance.

- **Multi-protein panels (Gränö et al., Torres et al., Taylor et al.) provide the highest AUCs (up to 0.87) for predicting future Crohn's disease in preclinical cohorts.**
- **Single markers (CXCL9, IL-6, hsCRP, fecal calprotectin) show moderate associations but are less predictive alone.**
- **Antibody and metabolite signatures, as well as environmental exposures, are emerging as relevant but require further validation for quantitative predictive performance.**

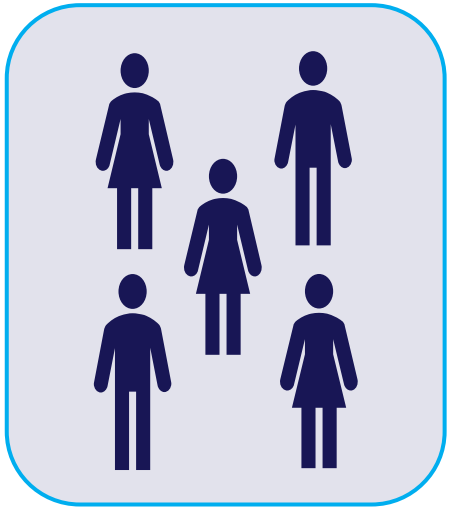
GEM: Mediterranean-like Dietary Pattern Associate With Microbiome and Fecal Calprotectin

Healthy First-Degree Relatives
N=2,289

Dietary Pattern

Effect of Dietary Pattern

Cross-Sectional Analysis



Mediterranean-like Dietary Pattern

vs. Non-Mediterranean -like Dietary Pattern

Altered Microbiome Composition

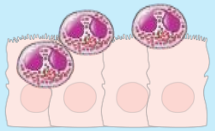
↓ *Ruminococcus*

↓ *Dorea*

↑ *Faecalibacterium*

Subclinical Gut Inflammation

↓ Fecal Calprotectin



Turpin et al. Gastroenterology 2022

PREDICTS Study: A Joint Government Academic & Industry Cooperative Research & Development Agreement

DOD/ Naval Medical Research Center

- Mark S Riddle, PI
- Chad K. Porter
- Renee Laird
- Vicky Chapman
- Sandra Isidean
- Karen Mata
- Jared Magee

Icahn School of Medicine, Mt Sinai

- Jean Frederic Colombel, PI
- Francesca Petralia
- Joana Torres
- Ryan Ungaro
- Manasi Agrawal
- Alexandra Livanos
- Saurabh Mehandru
- Zeynep Gumus
- Berk Turhan
- Robert Klein
- Sacha Gjnatic

Prometheus

- Thierry Dervieux

Mayo Clinic

- Rok Seon Choung
- Joseph A. Murray

University of Porto (Por)

- Salome Pinho

University of Toronto (can)

- Arthur Morta

Harvard Medical School

- Scott B.Snapper
- Anubhab Nandy

Acknowledgments

Janssen Pharmaceutical Companies of Johnson & Johnson

Litwin IBD Pioneers Crohn's & Colitis Foundation

Kenneth Rainin Foundation

IOIBD International Organization for the Study of Inflammatory Bowel Disease

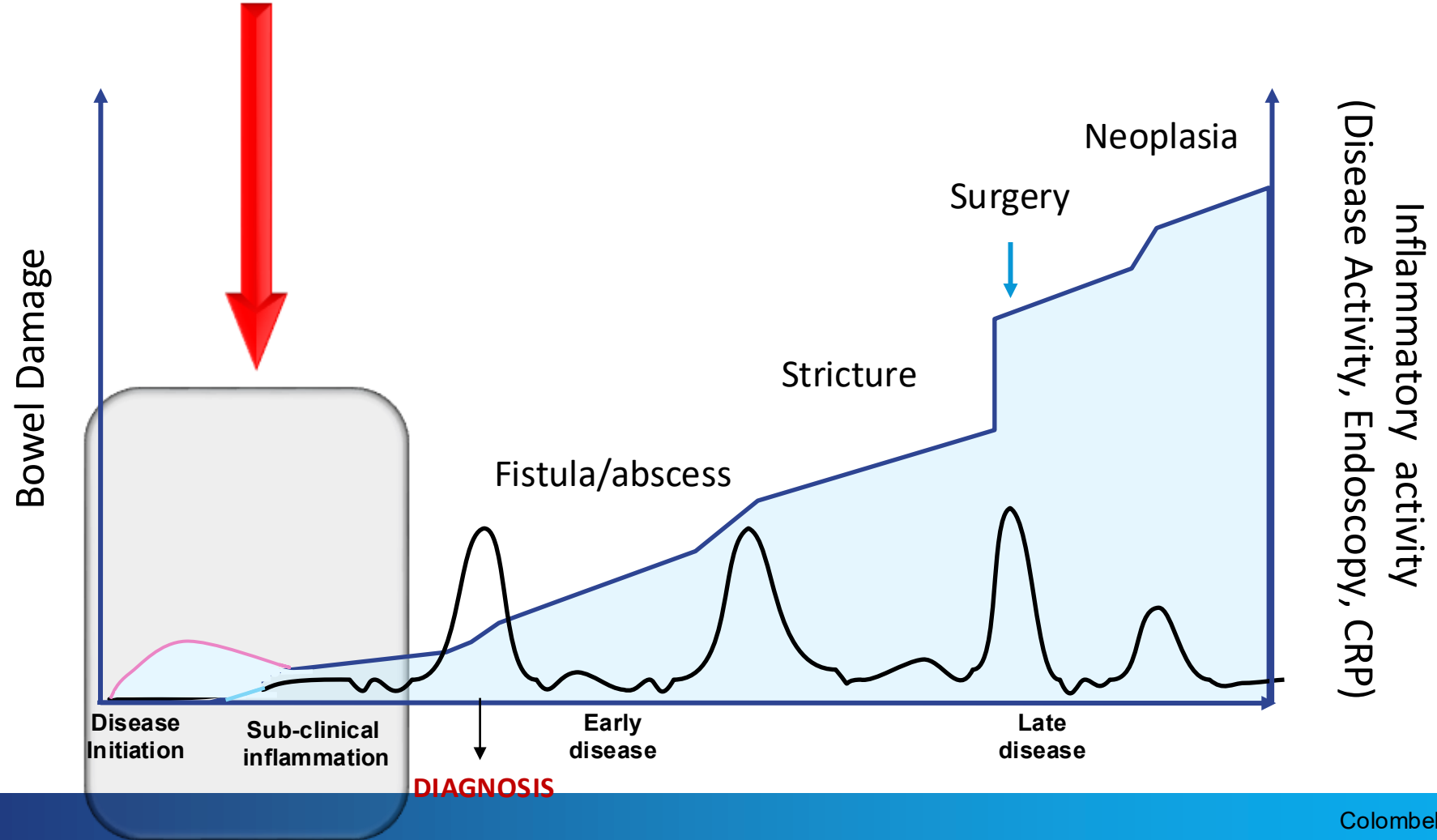
NIH National Institute of Mental Health

The Leona M. and Harry B. Helmsley Charitable Trust

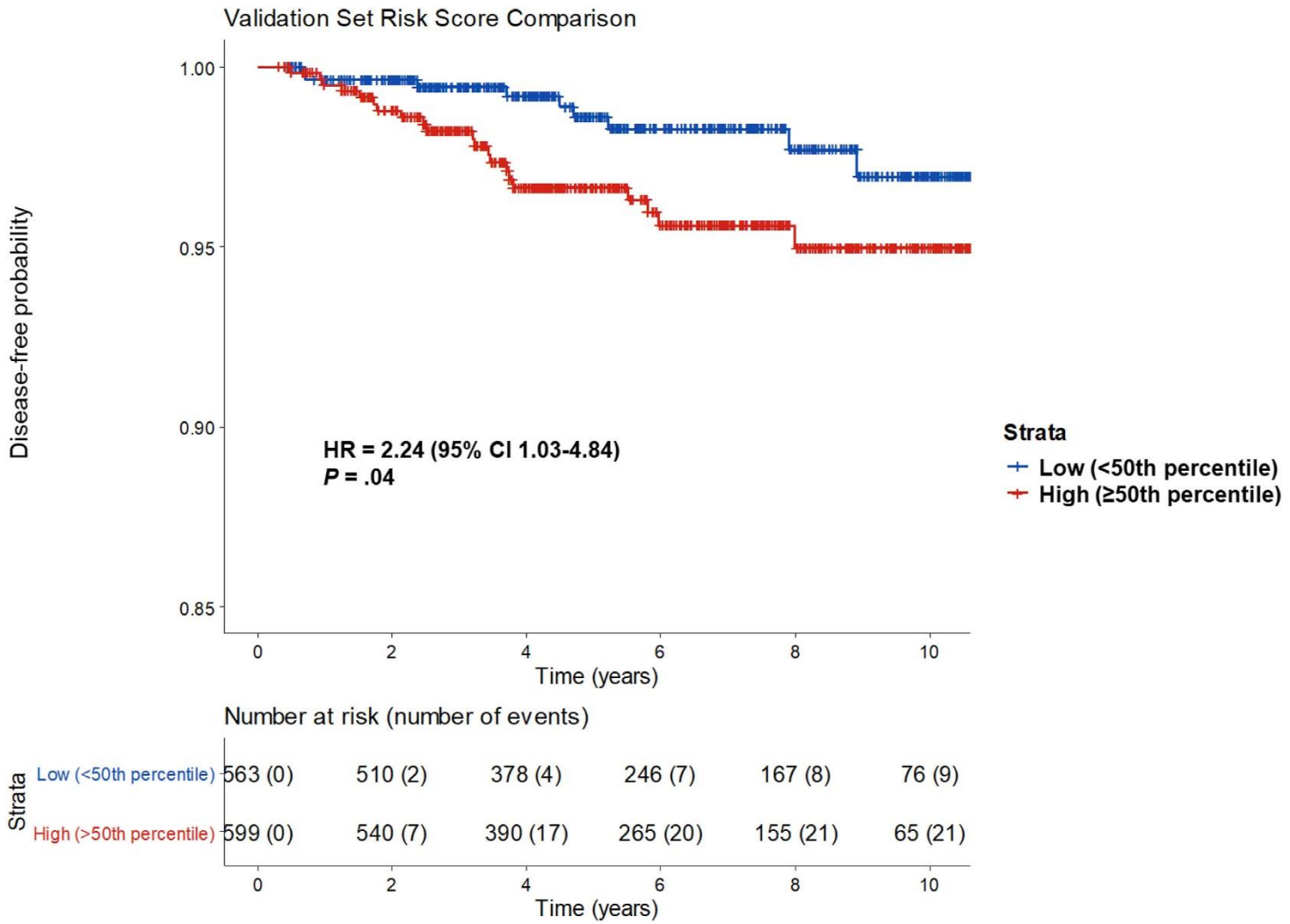
CDMRP Department of War Congressionally Directed Medical Research Programs

Is the Optimal Window of Opportunity Actually Before Diagnosis?

Best Window of Opportunity?

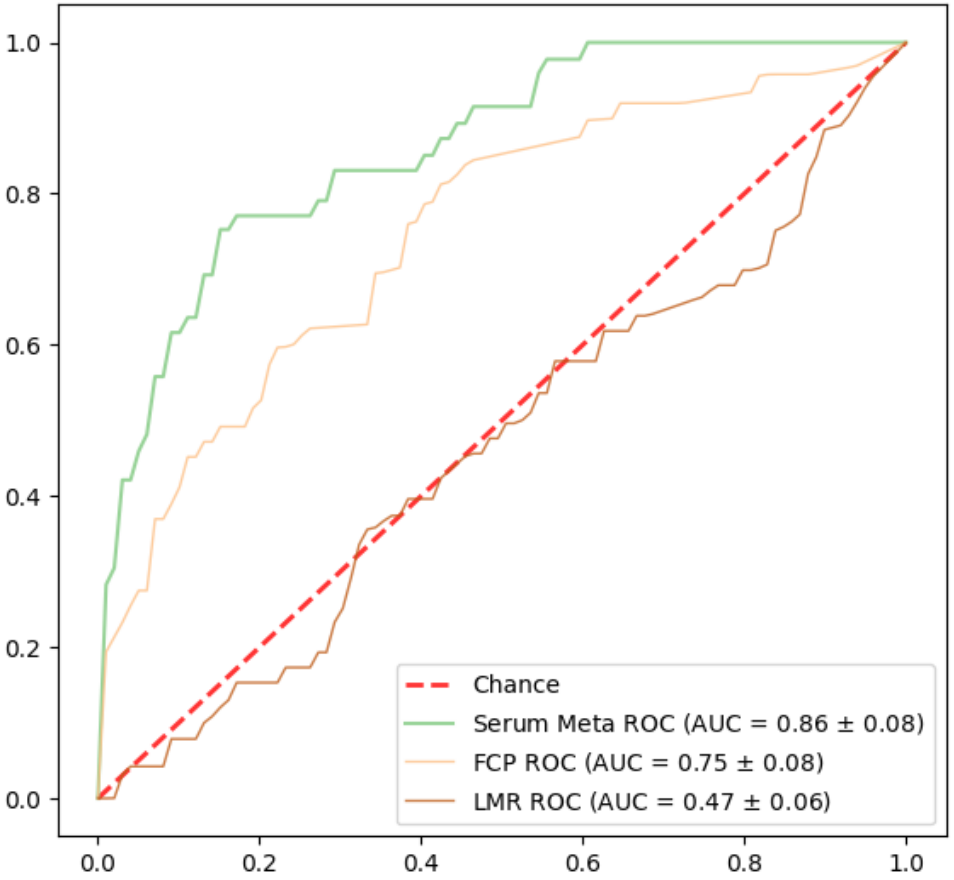


GEM: Machine Learning based Gut Microbiome Risk Score is associated with future risk of Crohn's disease

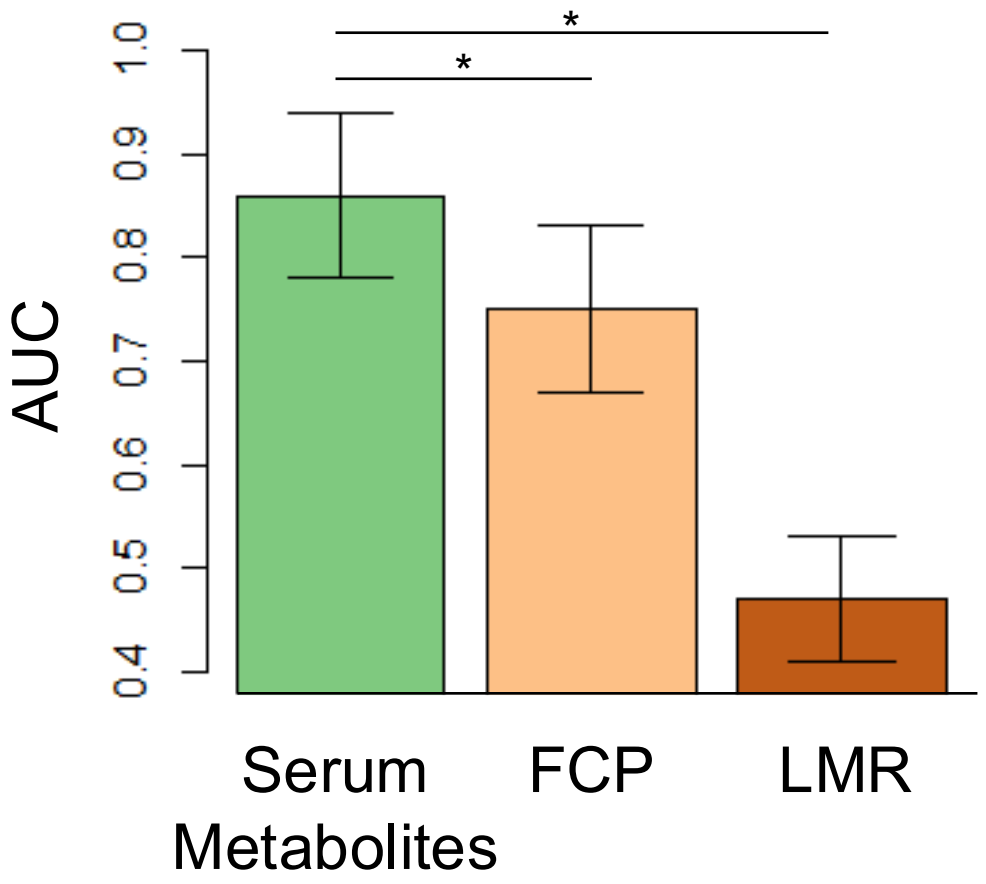


Raygoza Garay*, Turpin*, Lee* et al., Gastroenterology 2023

Serum Metabolomics Profile has Higher Predictive Performance than Fecal Calprotectin or LMR

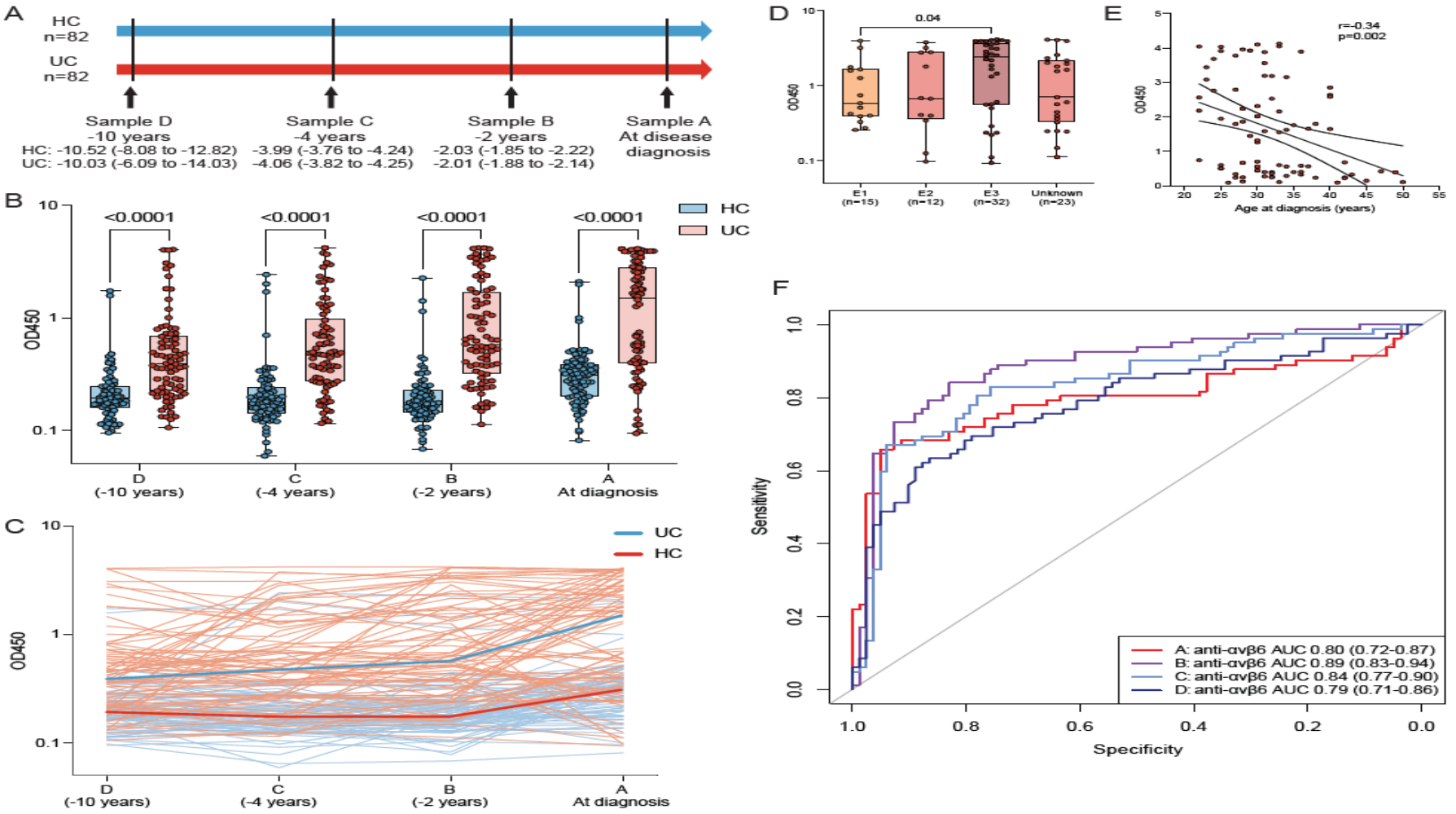


*Random forest (5 cross fold validation)

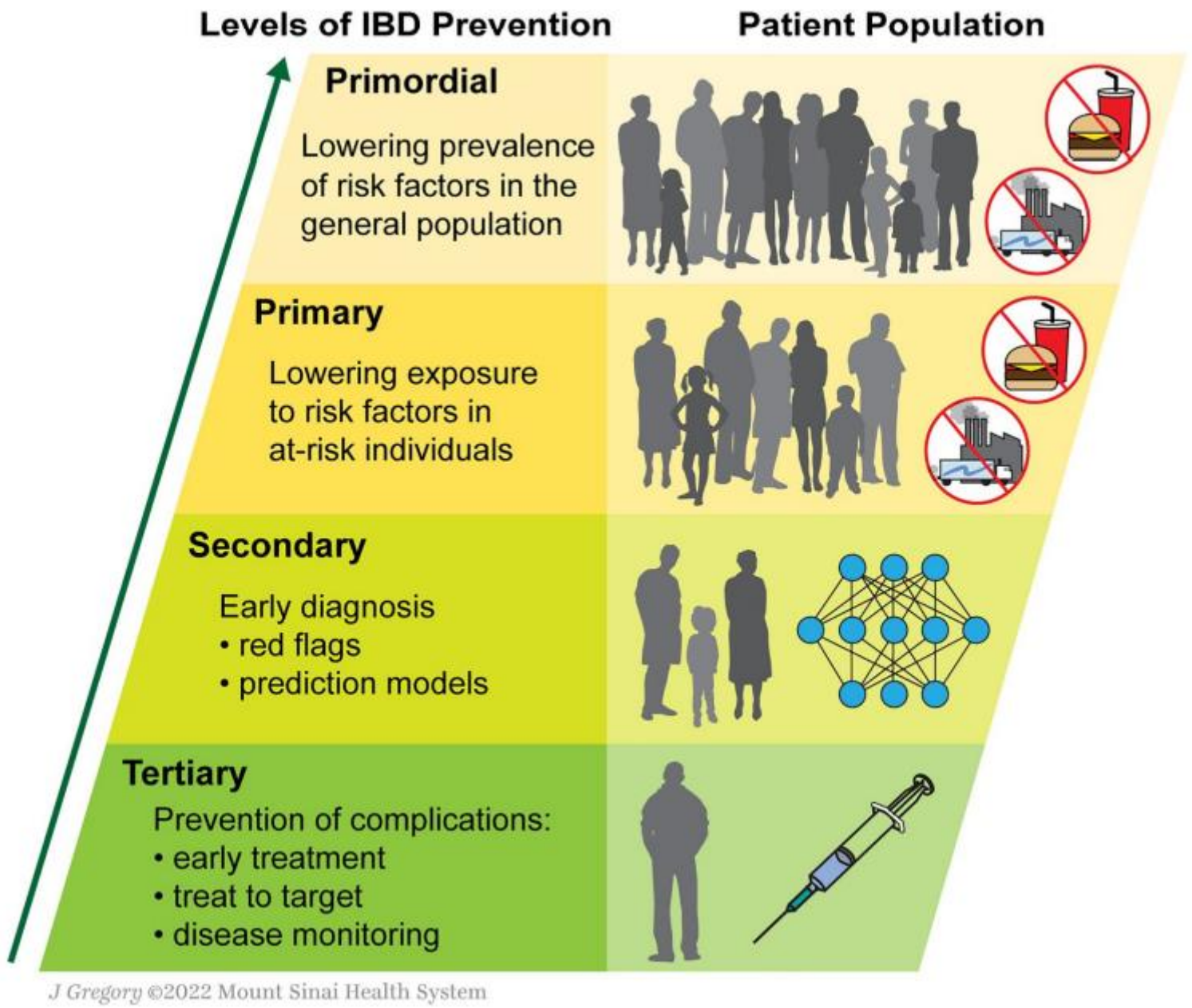


Delong test for AUC, * p<0.001

PREDICTS: Anti-Integrin αvβ6 autoantibodies are present in the blood of patients with UC (and colonic CD) up to 10 years before diagnosis



Livanos AE, et al. Gastroenterology. 2023;164(4):619-629


Levels of IBD Prevention
Patient Population
Primordial
Lowering prevalence of risk factors in the general population
Primary
Lowering exposure to risk factors in at-risk individuals
Secondary
Early diagnosis
• red flags
• prediction models
Tertiary
Prevention of complications:
• early treatment
• treat to target
• disease monitoring
J Gregory ©2022 Mount Sinai Health System

There are multiple predictive biomarkers of Crohn's disease

Blood

- Genomics (PRS)
- Proteomics
- Metabolomics
- Glycomics
- Exposomics
- Serological immune response
  - Antibodies
  - PhipSeq

Stools

- Microbiome
- Calprotectin

Others

- Intestinal permeability
- Imaging (?)

Bronze S et al. Aliment Pharmacol Ther 2024

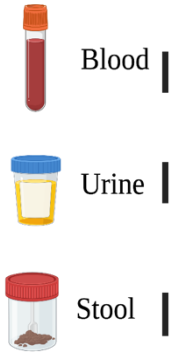
Mount Sinai Hospital
Sinai Health System
Joseph & Wolf Lebovic Health Complex
CENTRE FOR INFLAMMATORY BOWEL DISEASE (IBD)

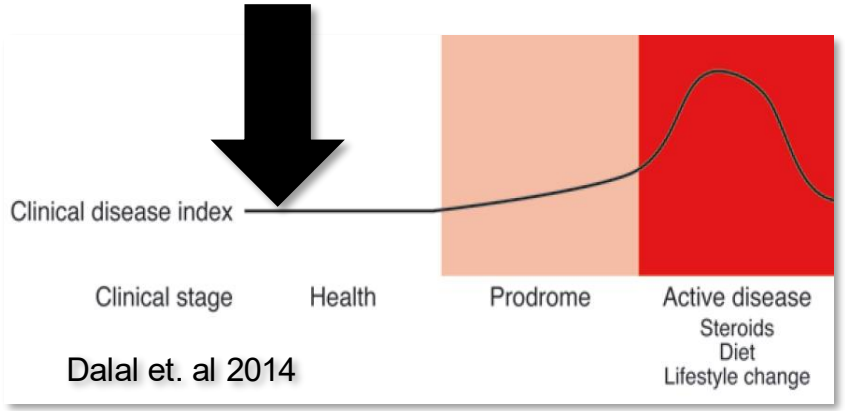
The CCC GEM Project

- Aiming to identify
  - **G**enetic,
  - **E**nvironmental, and
  - **M**icrobial determinants of CD

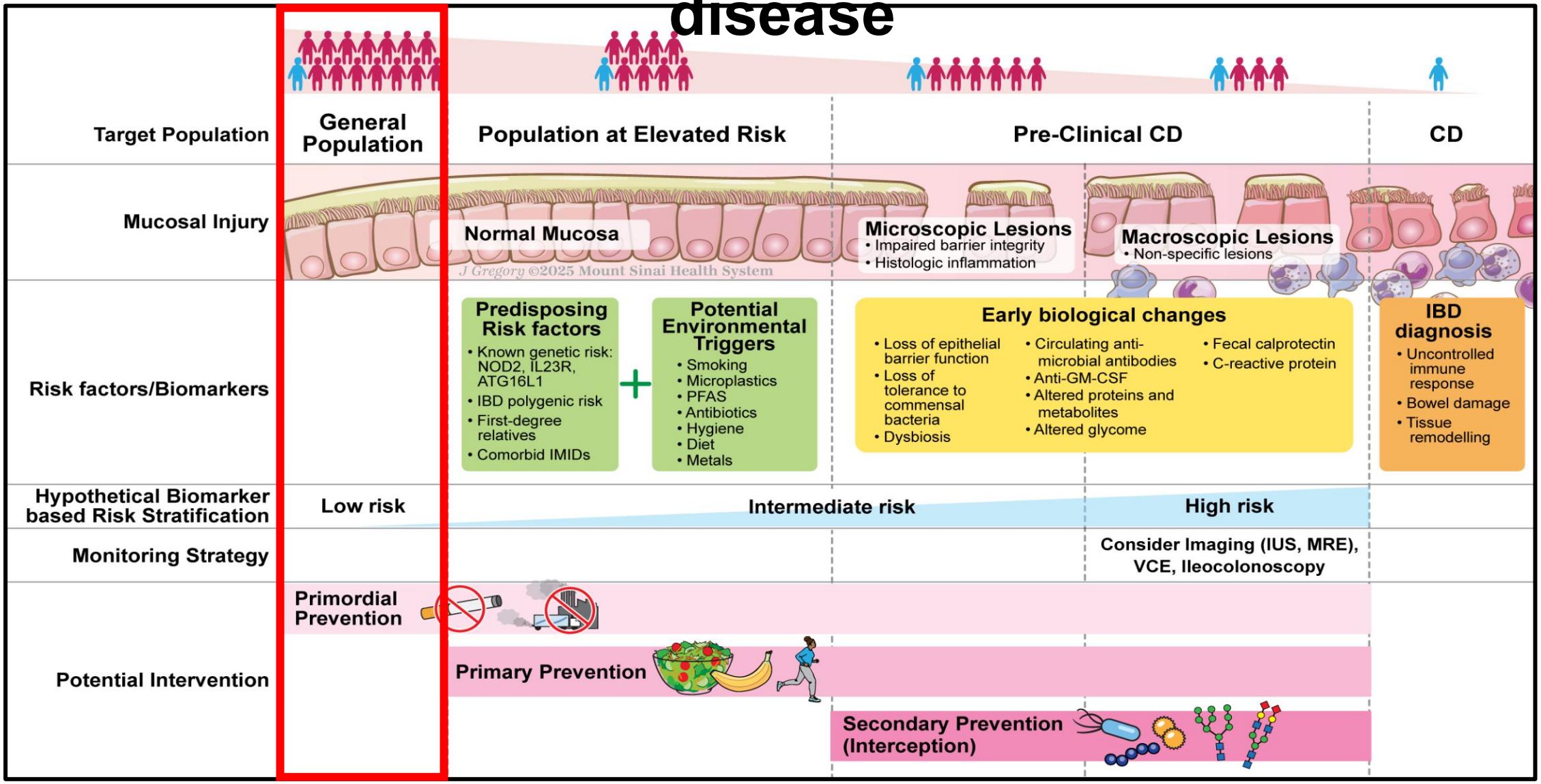
- 5,080 Healthy first-degree relatives (FDR) of CD-affected individuals

THE GEM PROJECT



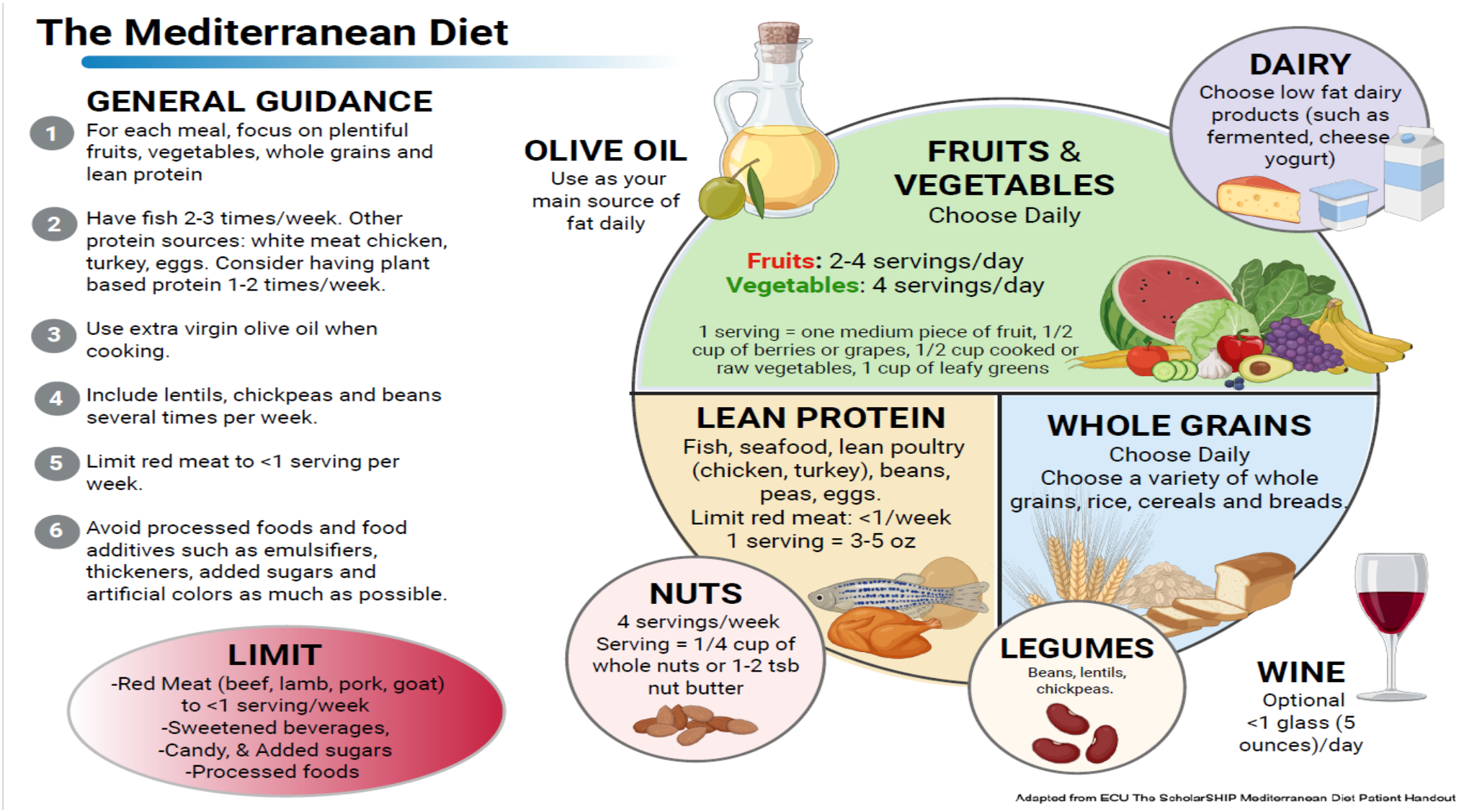


Prevention may vary according to the stages of Crohn's disease

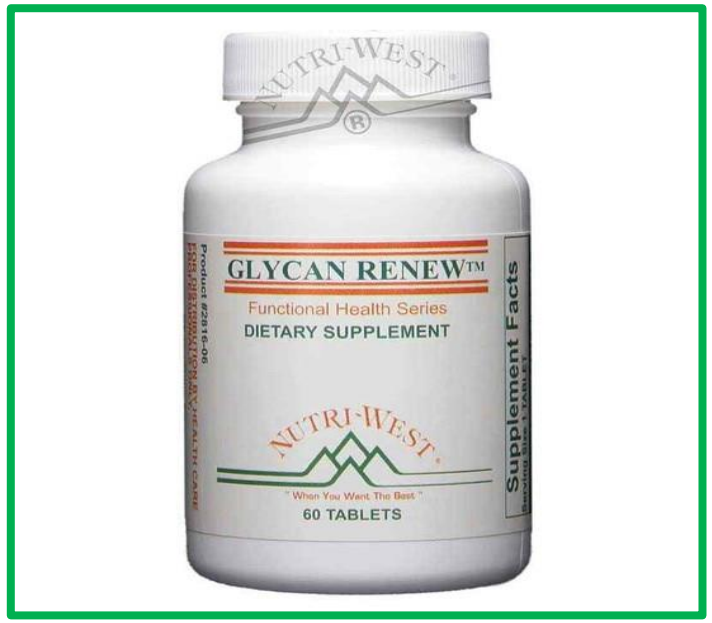


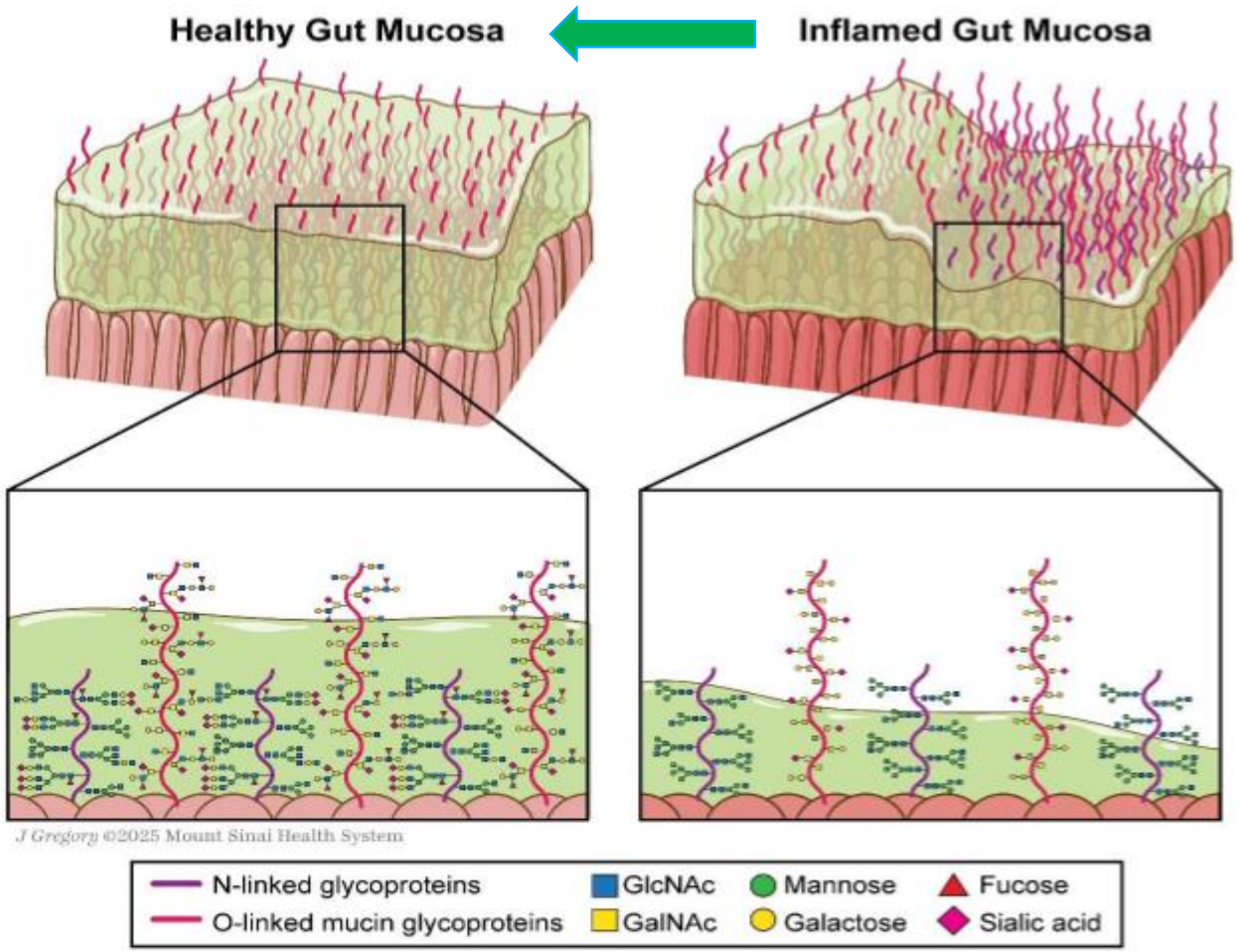
Peter I et al. Gastroenterology, in press.

Primary prevention of Crohn's disease: Dietary interventions



Primary “Sweet” prevention: restoring the gut mucosa glycocalyx with glycan supplements

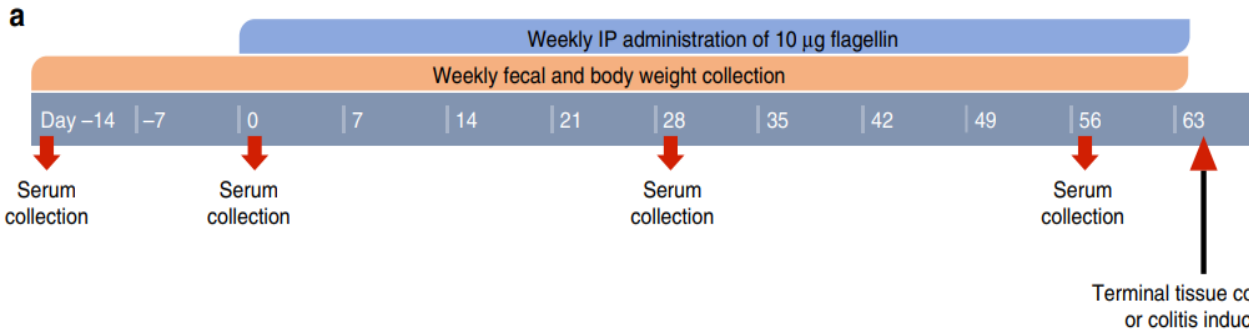




Pinho S, Torres J, Colombel JF. Nat Rev Gastroenterol Hepatol, in press.

Anti-Flagellin Vaccine against Crohn's Disease Onset?

	Serologic markers	Remaining Healthy (N=307)	Pre-CD (N=77)	p	C-index
Anti-Flagellin Ab	Positive A4_fla2_IgG	8.1%	**31.2%**	<0.001	0.614
	Positive Flax_IgG	20.2%	**45.5%**	<0.001	0.625
	Positive Cbir1	5.2%	**22.1%**	<0.001	0.585
Anti-Fungal Ab	Positive ASCA_IgA	7.8%	**27.3%**	<0.001	0.598
	Positive ASCA_IgG	3.6%	**18.2%**	<0.001	0.573
Anti-E.coli Ab	Positive OmpC_IgA	1.0%	**5.2%**	0.028	0.521



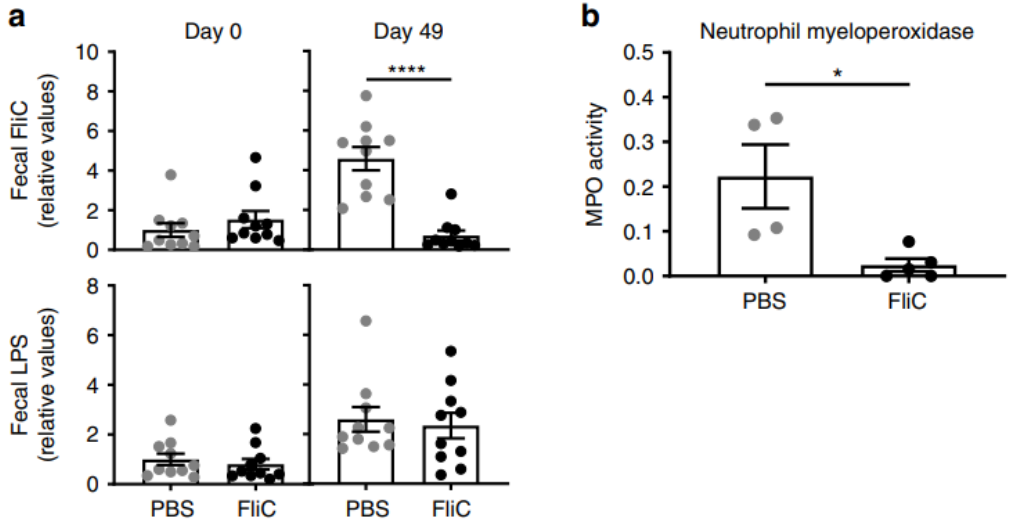
nature COMMUNICATIONS

ARTICLE

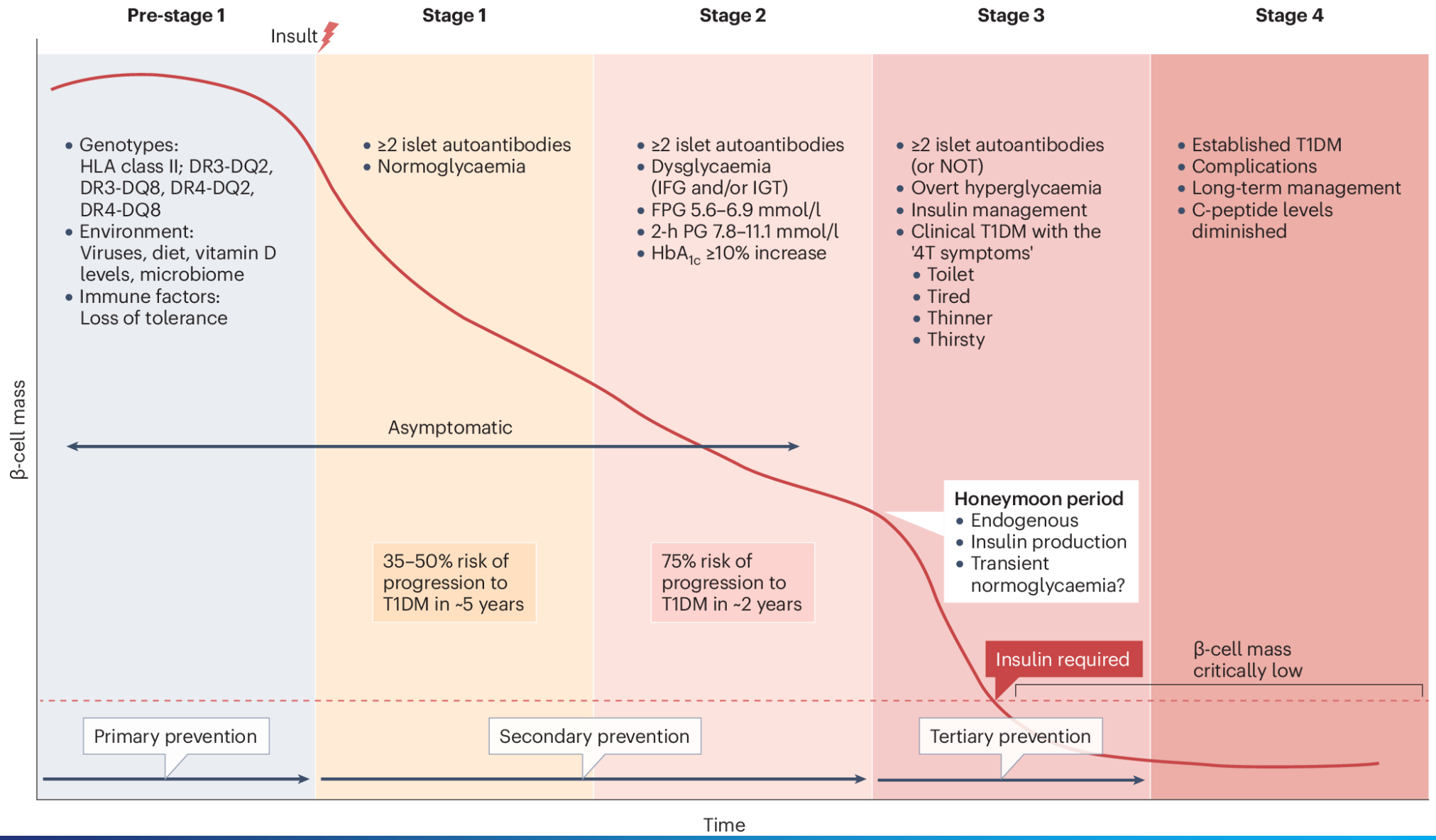
https://doi.org/10.1038/s41467-019-13538-y OPEN

Flagellin-elicited adaptive immunity suppresses flagellated microbiota and vaccinates against chronic inflammatory diseases

Hao Q. Tran[1], Ruth E. Ley[2], Andrew T. Gewirtz[1] & Benoit Chassaing[1,3,4,5*]



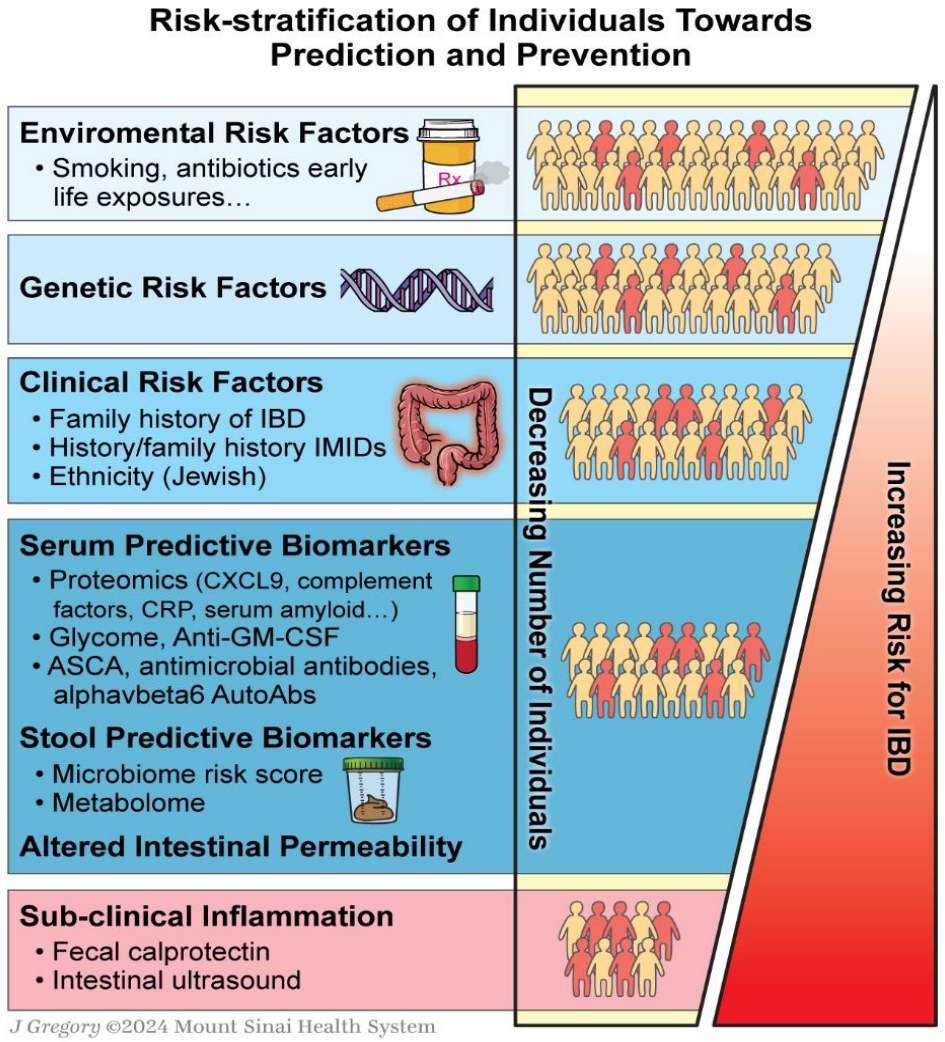
Understanding Preclinical Phases of Disease: T1DM as Example



Henriques FL et al. Nat Rev Endocrinol 2025

Identifying targets for prevention/interception

Prevention of IBD may vary according to age and risk



Population-based measures

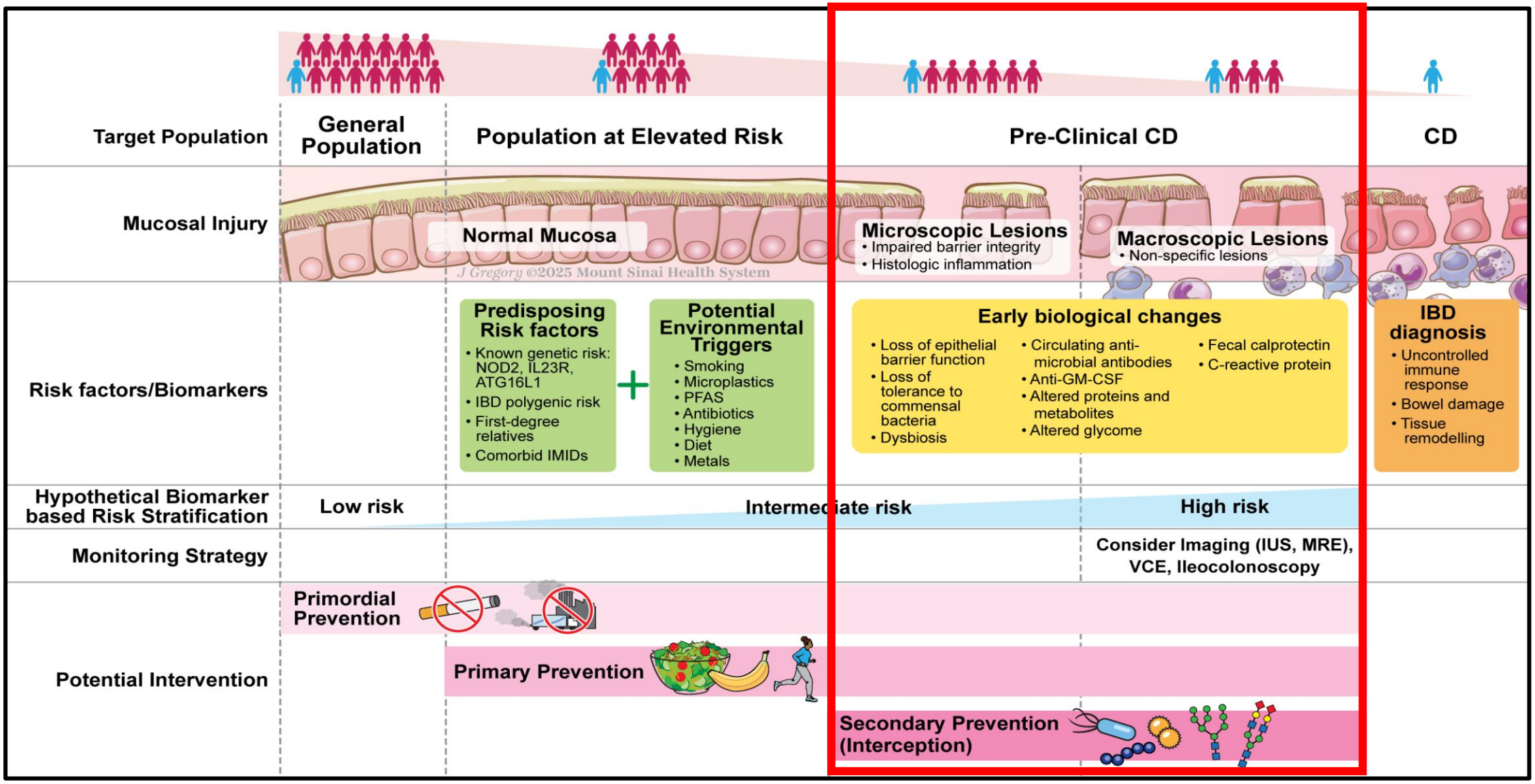
- Diets
- Removal of environmental triggers
- Microbiome modulating strategies

- Improving mucosal barrier
- Oral Drugs
- Immunomodulating drugs

Individual-targeted therapies

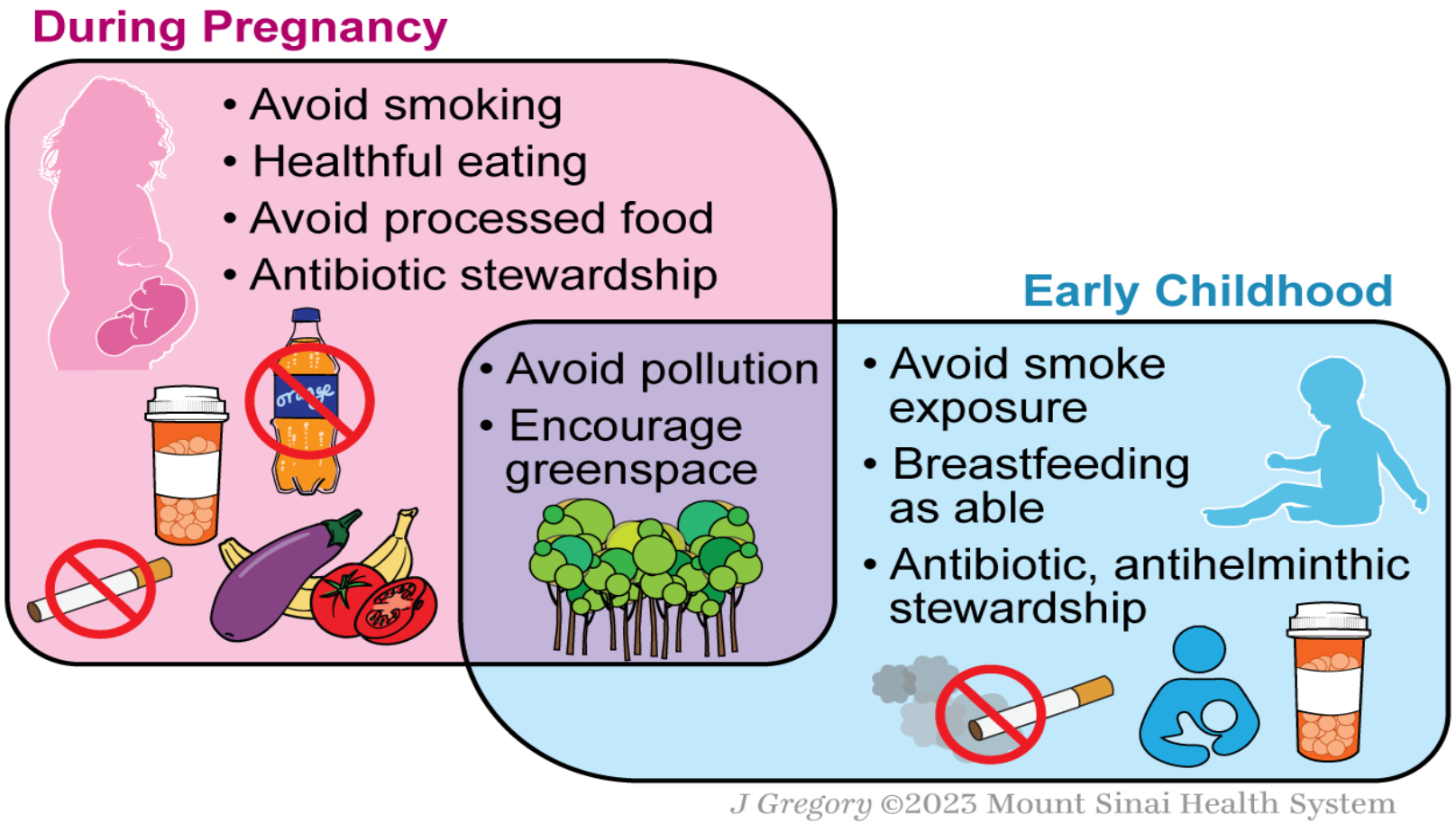
Lopes & Turpins, CGH 2024

Can We Define the Preclinical Phases of CD?



Lee et al. Gastro In Press.

Primordial prevention of Crohn's disease: Exposure mitigation

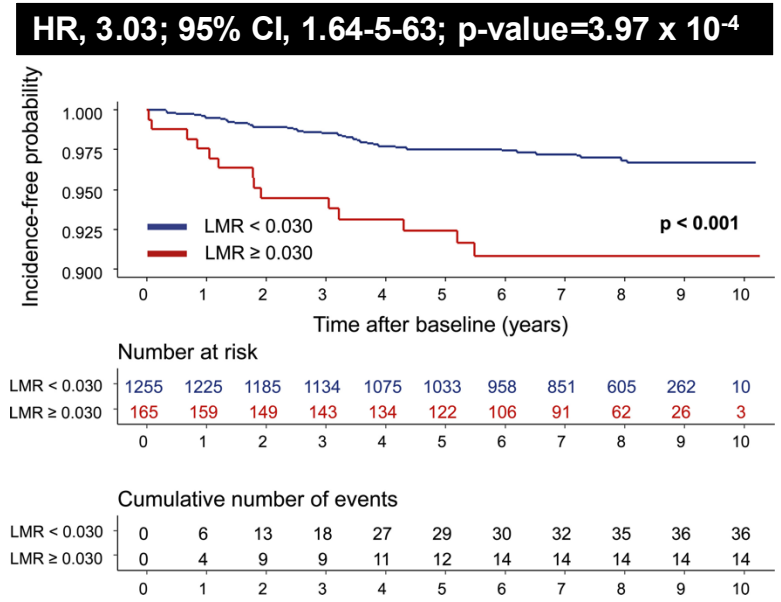


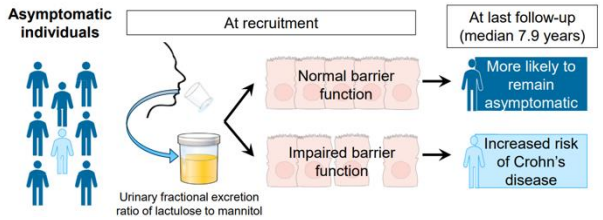
Zhang, Agrawal et al, Gut, 2024

Increased intestinal permeability predicts development of CD

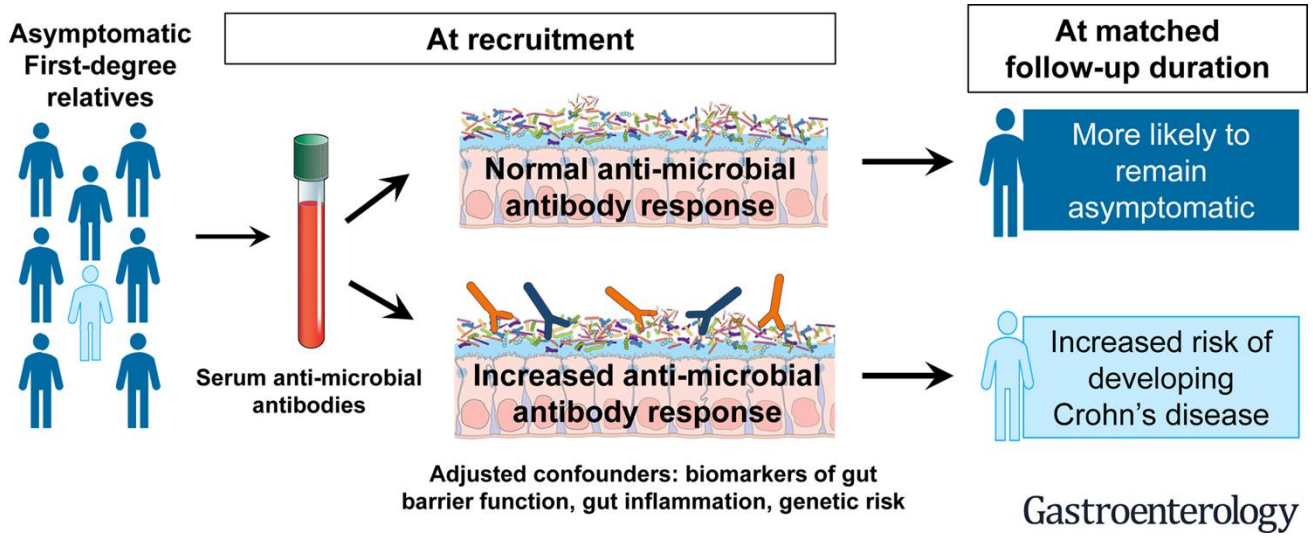
Nested case-control

- 1370 healthy FDRs vs 50 FDRs who developed CD





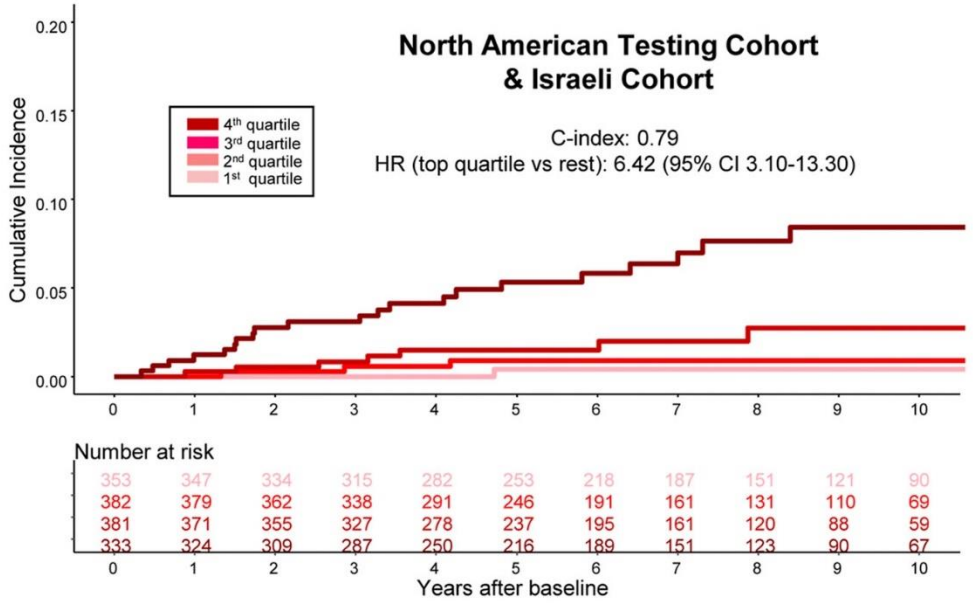
Anti-Microbial Antibody Response is Associated with Future Onset of CD Independent of Gut Barrier Function, Subclinical Inflammation, and Genetic Risk



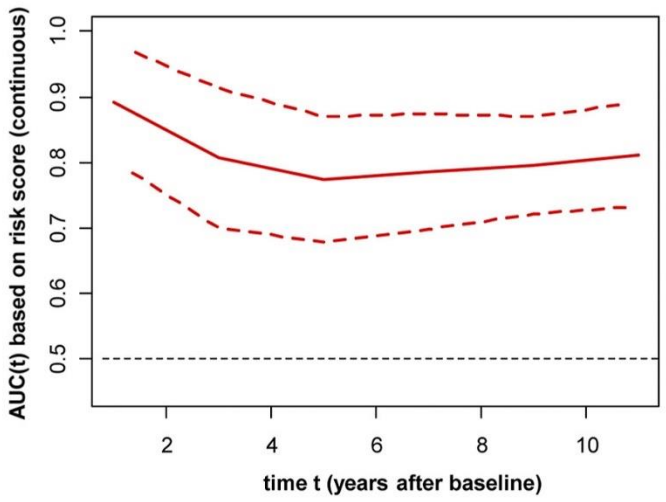
High baseline AS (≥2) (43% of cases, 11% of controls) was associated with higher risk of developing CD (adjusted odds ratio, 6.5; 95% confidence interval, 3.4–12.7; P < .001)

Predictive biomarkers can be combined in a risk score
The GEM Integrative Risk Score in First Degree Relatives (FDRs):
(FCP, Microbiome, and IP)

A



B



C

Cumulative incidence (%) per year based on Integrative Risk Score in the Pooled Testing Cohort

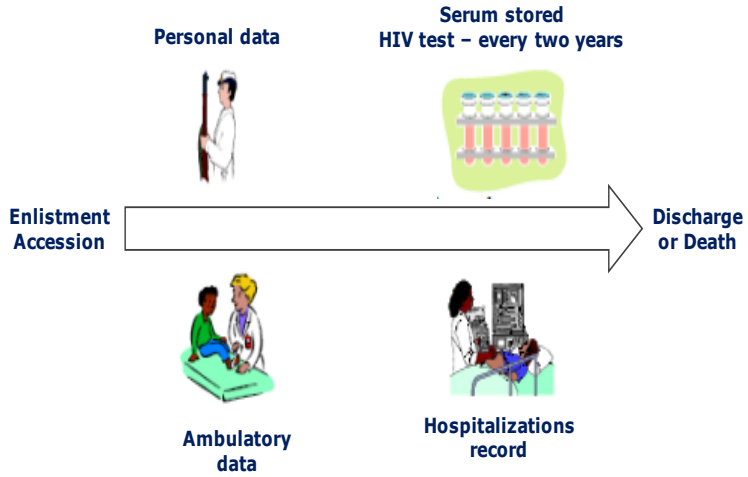
GEM-IRS	At 1 year	At 3 years	At 5 years	At 7 years	At 9 years
Top Decile	1.74	5.26	8.21	11.09	13.77
Top Quartile	1.21	3.08	5.26	6.24	8.55
Median	0.71	1.90	3.35	4.13	5.96
Bottom Quartile	0.46	1.43	2.51	3.09	4.09
Bottom Decile	0.39	1.19	2.18	2.61	3.46

Lee SH et al. Gastroenterology 2024

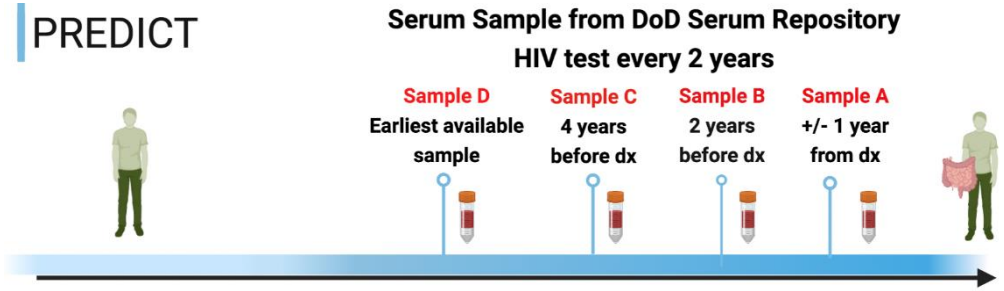
PREDICTS: The Multi-Omic Evaluation and Discovery in an IBD Cohort of Tri-Service Subjects Study

- History
  - Started in 1985 following universal, mandatory screening for HIV
- Currently inventory: **62.5 million** samples
- Location and management
  - Armed Forces Health Surveillance Branch
  - S[illegible] MD

1. Case identification



2. Sample retrieval from DoD serum repository



- For each a patient up to 3-4 serum samples are retrieved before diagnosis
- Controls were matched timing of Sample A (± 1 year), age, gender and race.

Icahn School of Medicine at Mount Sinai

Porter CK et al. Contemp Clin Trials Commun 2019