# Personalization of IBD From Prediction to Prevention

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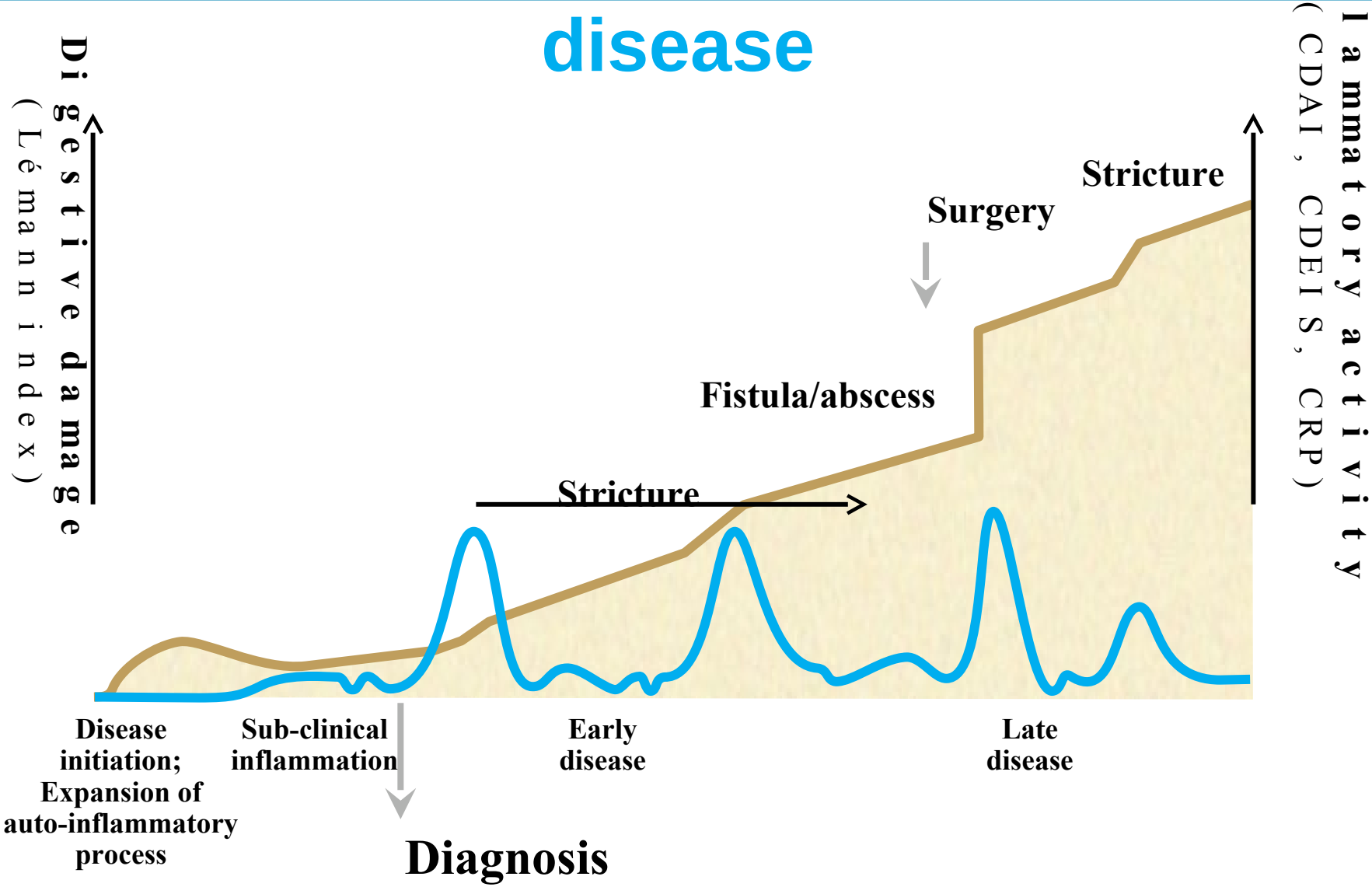
Mount Sinai

# Imagine If…

- We could accurately predict disease course and complications
- Personalize therapy to individual patients
- Closely monitor and tailor medications to ensure optimal, durable response
- **We can then drastically improve quality of life, keep patients well longer, and alter the course of the disease**

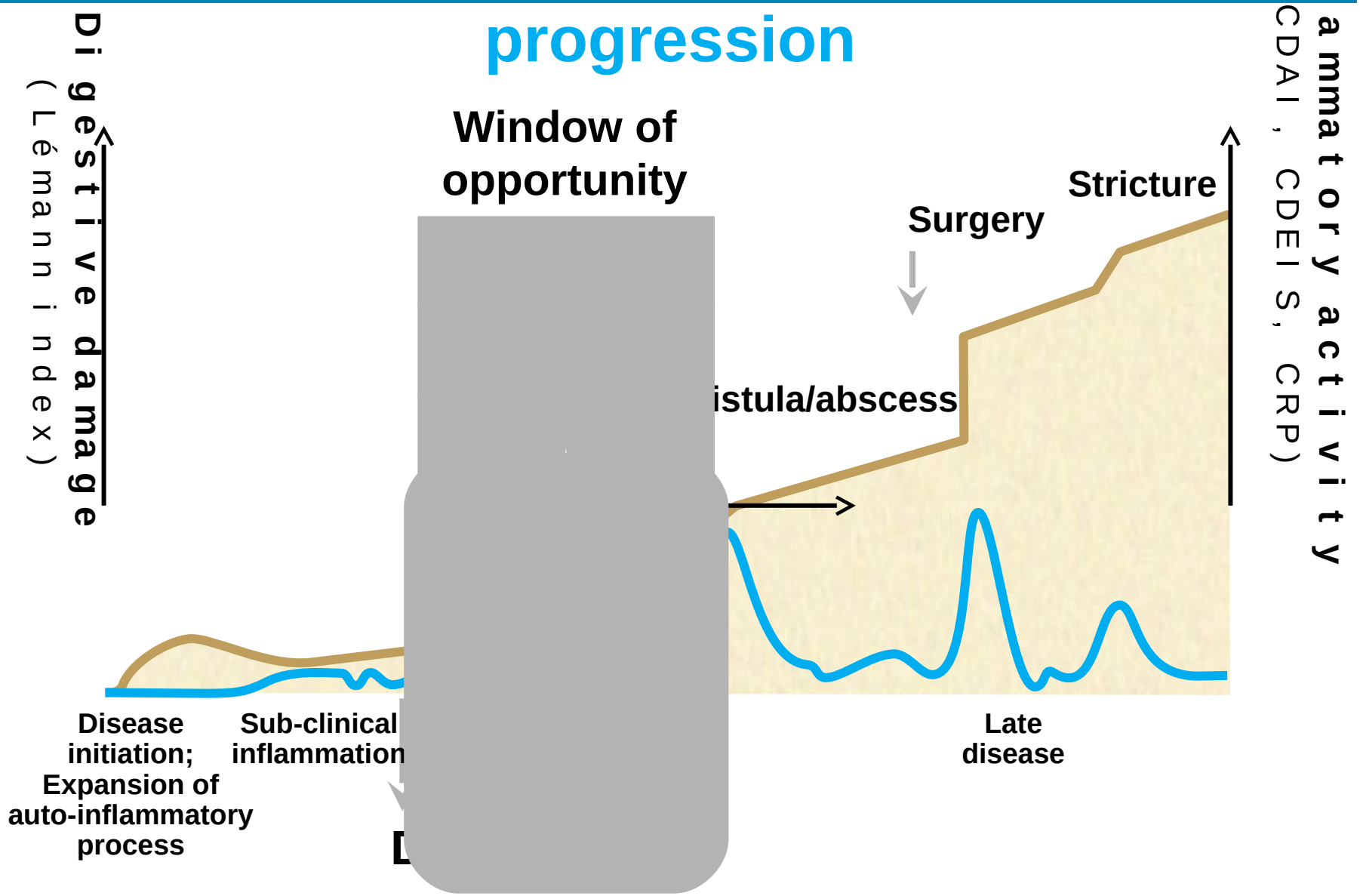
DREAM OR REALITY ?

# Crohn's disease as a progressive disease




*Colombel JF, et al. Gastroenterology, 2017*

# Early intervention is key to prevention of progression




*Colombel JF, et al. Gastroenterology, 2017*

# But not all patients are alike !!!

Assessing prognosis at an early stage is essential for the development of an appropriate management plan

**Indolent** → **Aggressive**

Avoid intensive therapy, immunosuppression, adverse events

Assure early intensive therapy to avoid complications

# Which prognostic risk factors to use?


**Clinical** (age, extent, behaviour, symptoms)

**Endoscopic** (mucosal healing)

**Imaging**

**Genetic** (>200, primarily NOD2/CARD15 and HLA)

**Serological and laboratory markers** (CRP, ASCA, ANCA, OmpC)

**Fecal** (microbiome and calprotectin)

**ANCA: anti-neutrophil cytoplasmic antibodies; ASCA:anti-*Saccharomyces cerevisiae* antibodies; OmpC, outer membrane protein C precursor**

# Crohn's Disease Pattern at Presentation Differ in Serology and Gene Signature: A Pediatric Risk Inception Cohort

| | Stricturing Behavior (B2) | | Penetrating Behavior (B3) | |
|---|---|---|---|---|
| | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value |
| **Age at diagnosis** | 1.07 (0.91-1.27) | 0.42 | 1.45 (0.98-2.14) | 0.0606 |
| **African American race** | 0.30 (0.04-2.47) | 0.27 | 2.31 (0.4-13.27) | 0.35 |
| **Isolated ileal location (L1)** | 1.09 (0.39-2.99) | 0.87 | 1.36 (0.37-4.93) | 0.64 |
| **ASCA IgA positive** | 1.48 (0.58-3.75) | 0.41 | 2.92 (0.81-10.48) | 0.10 |
| **CBir1 positive** | 2.14 (0.84-5.44) | 0.11 | 7.99 (1.89-33.77) | 0.0047 |
| **Extracellular matrix gene signature** | 1.70 (1.12-2.57) | 0.0120 | 1.21 (0.53-2.73) | 0.65 |



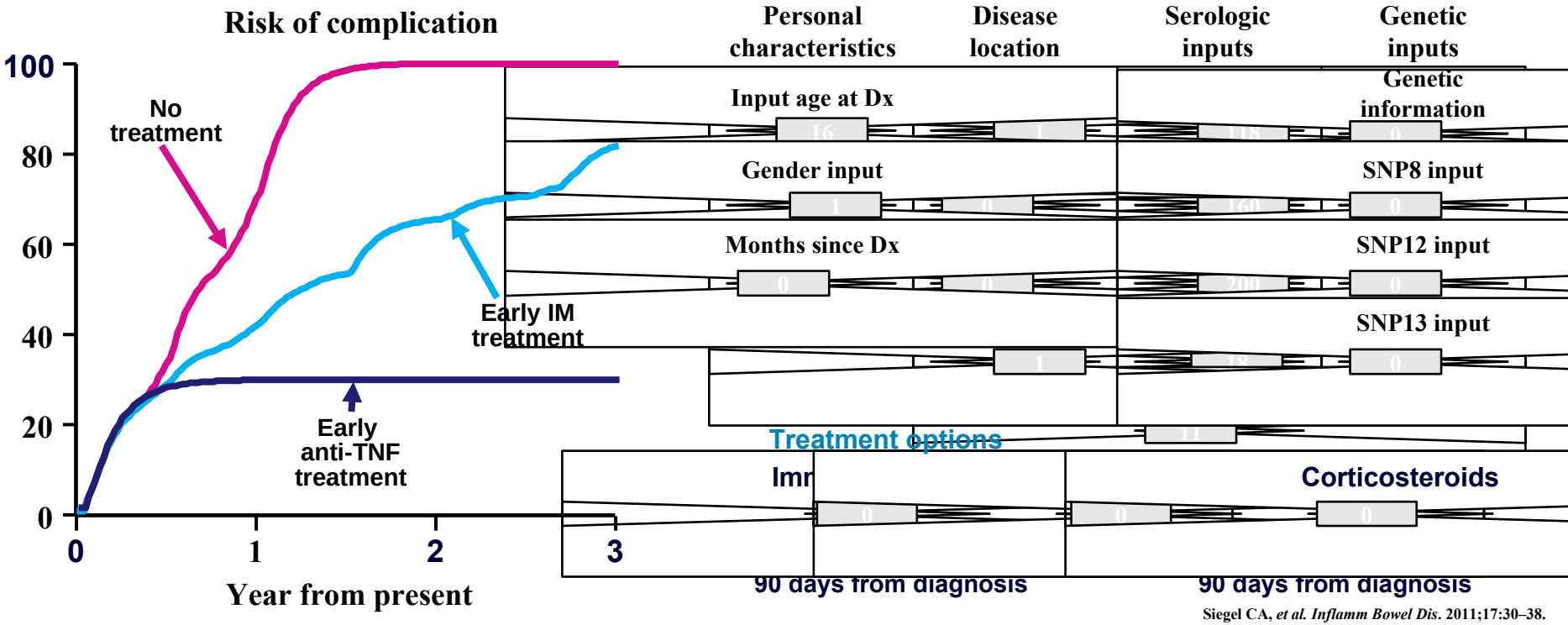
Kugathasan S, *et al. Lancet* 2017; Mar 1]

# Interactive Computer Real Time Display to Predict CD complications

**Allows matching of individual patient characteristics to show the probability of disease complication over 3 years, and how this is modified by different treatments**

**High risk patient: 16-year-old girl, small bowel and perianal disease, QSS group**

**Overall HR: 196.08** **= 4** **Benefits of therapy: 0.18**



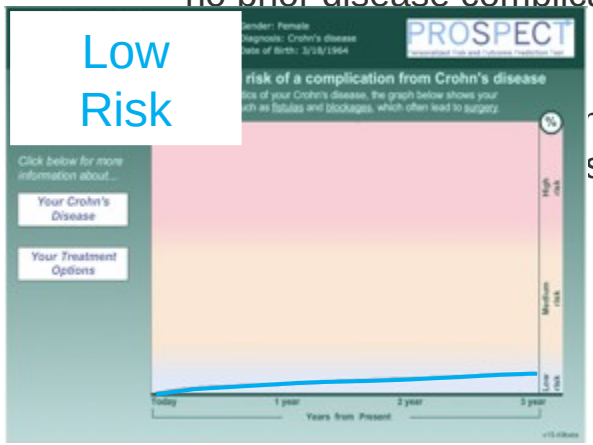

Siegel CA, *et al. Inflamm Bowel Dis*. 2011;17:30–38.

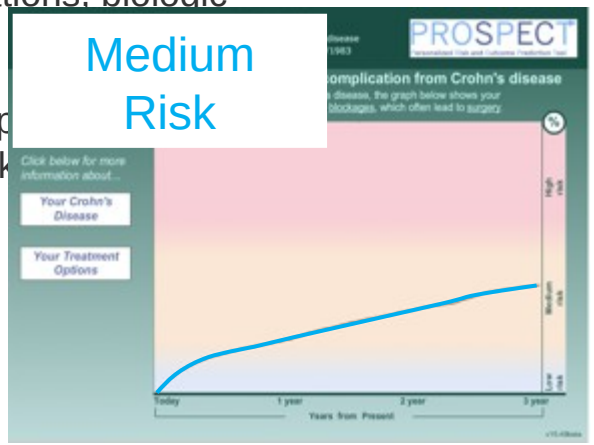
Siegel CA et al. *Inflamm Bowel Dis.* 2011;17:30.

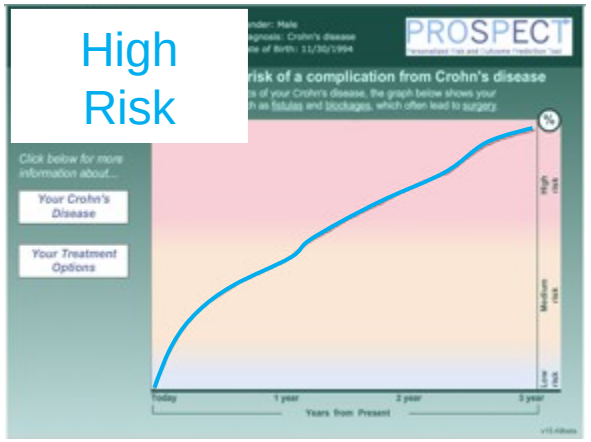
# Crohn's Disease Risk Prediction Model Stratifies Patients' Risk for Disease-Related Complications

- Aim
  - To determine proportion CD patients with complication (penetrating, stricturing, or surgery) in one year according to PROSPECT risk prediction model
- Methods
  - 124 CD pts, within 15 yrs CD diagnosis, no prior disease complications, biologic

| Model Variable | Hazard Ratio, 95% CI |
|---|---|
| Small bowel disease | 2.12, CI 1.05-4.29 |
| Left colonic disease | 0.73, CI 0.49-1.09 |
| Perianal disease | 4.12, CI 1.01-16.88 |
| ASCA | 1.35, CI 1.16-1.58 |
| Cbir1 | 1.29, CI 1.07-1.55 |
| ANCA | 0.77, CI 0.62-0.95 |
| *NOD2* frameshift mutation | 2.13, CI 1.33-3.40 |
| Perianal*ASCA | 0.63, CI 0.42-0.94 |

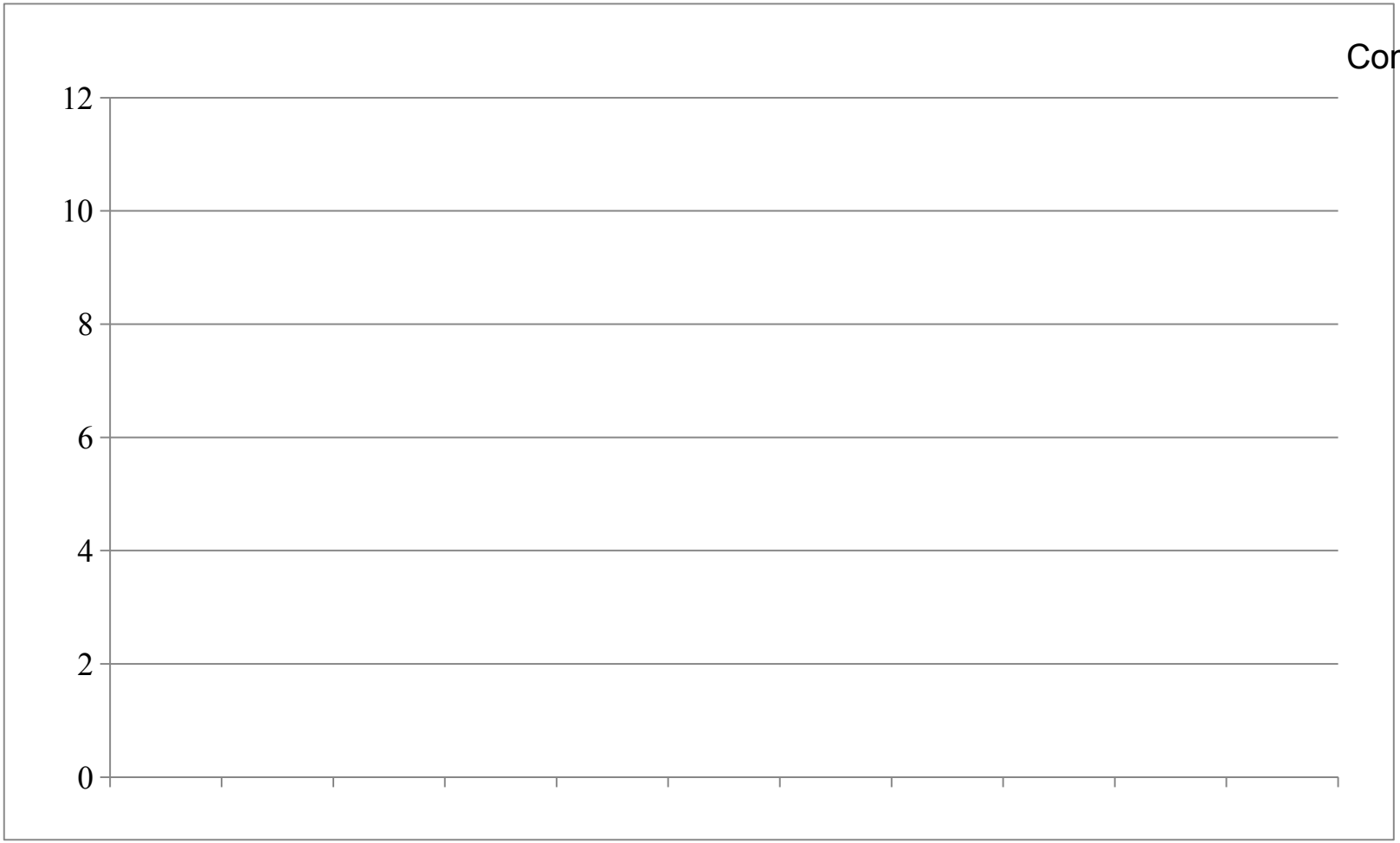



Siegel C Aliment Pharmacol Ther. 2016 Jan;43(2):262-71

# Majority of Complications Occurred in Moderate and High Risk Patients

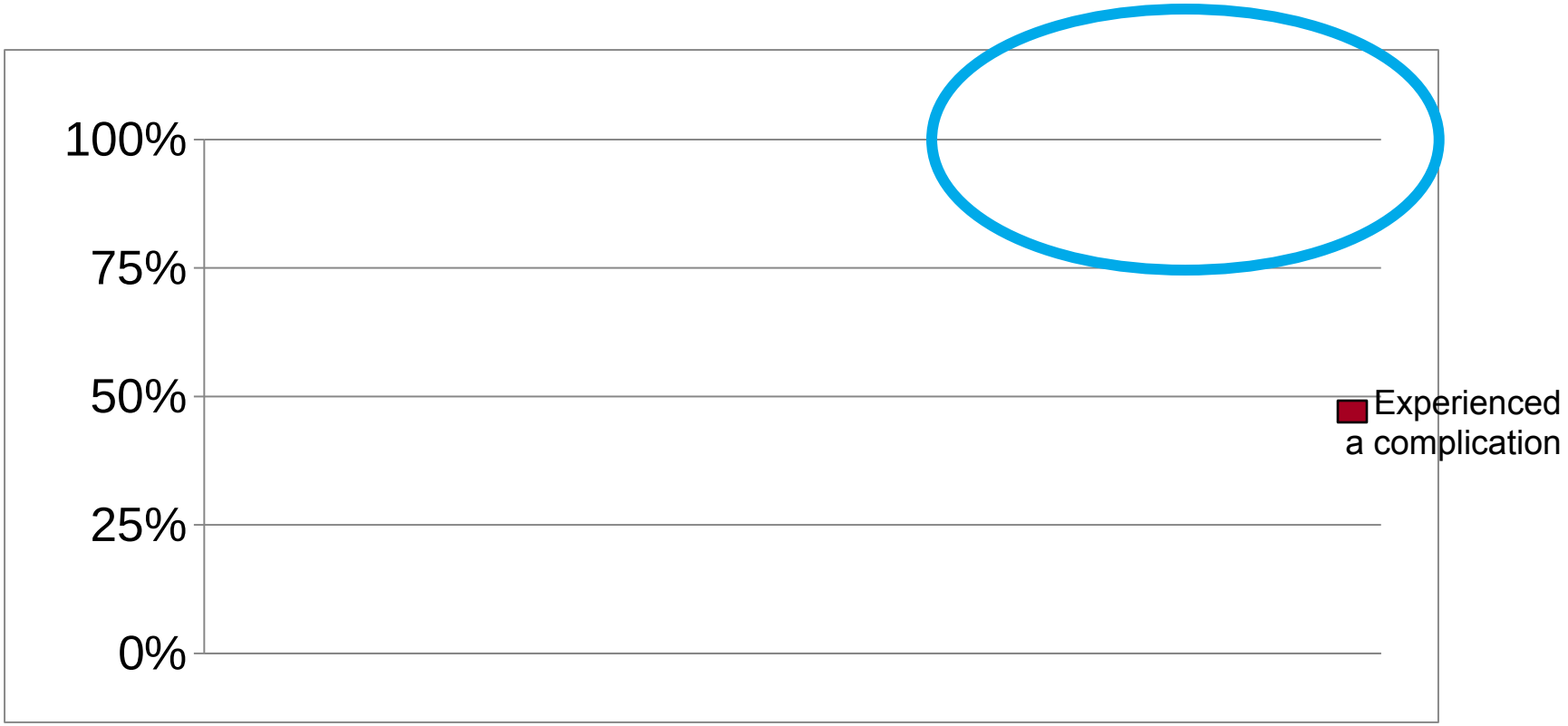



121 CD patients with PROSPECT risk stratification then followed prospectively for 1 year

85% of all complications have been in patients at moderate or high risk

Siegel et al DDW 2017

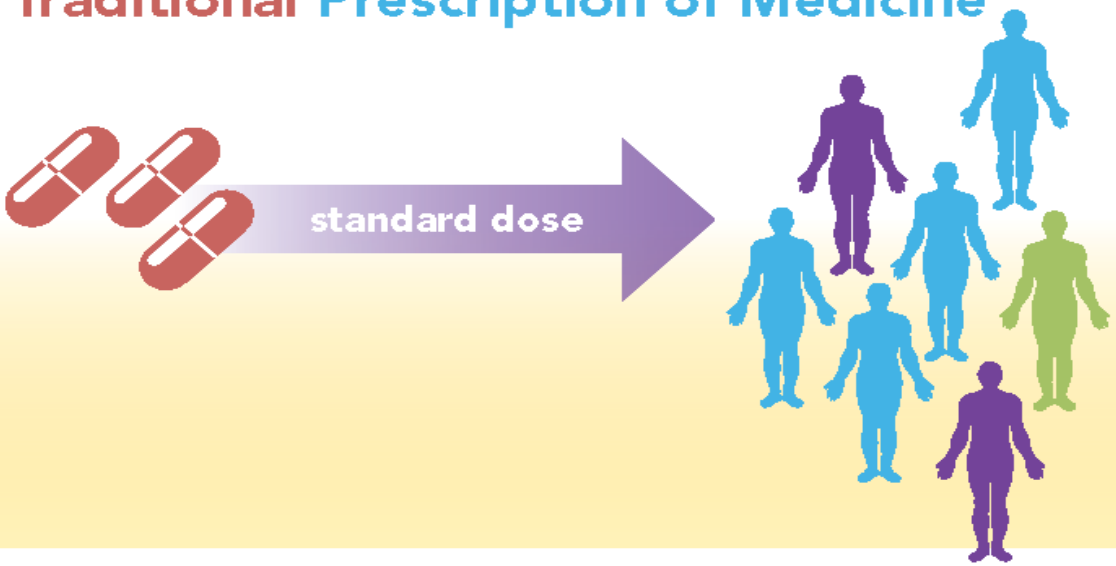
# Proportion of complications in each risk category




Siegel et al DDW 2017

# The Era Of One Drug Fits All Is Over……

## Traditional Prescription of Medicine




This dose works for most patients.

This dose is too high for some patients. So the medicine causes some side effects.

This dose is not enough for some patients. So the medicine doesn't work.

## Prescription of Medicine with Drug-Response Testing


**Drug-Response Testing** tells your doctor how you will respond to medicine.

Then your doctor can prescribe the **best dose.**

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# No association of IL23R in rheumatoid arthritis

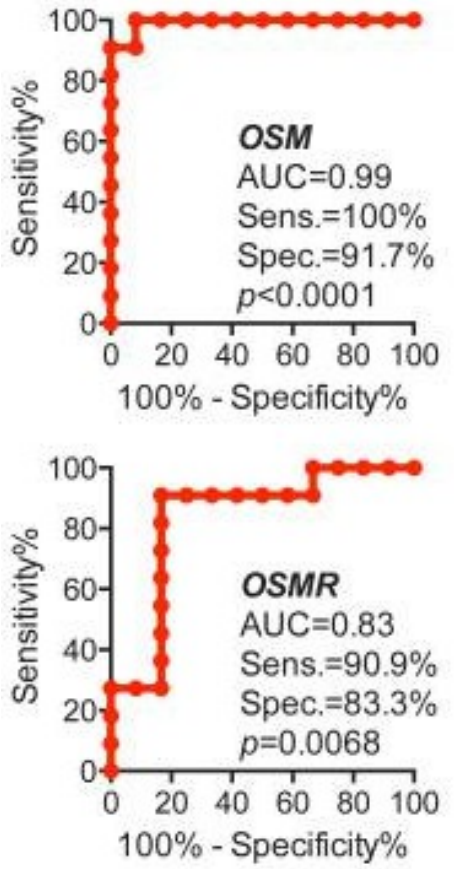
**Table 1 Major genetic association signals across autoimmune diseases**

| | MHC class | IL23R | PTPN22 | CTLA4[a] |
|---|---|---|---|---|
| Type 1 diabetes | Class II | | Arg620**Trp** | Non-coding |
| Juvenile idiopathic arthritis | Class II | | Arg620**Trp** | |
| Autoimmune thyroid disease | Class II | | Arg620**Trp** | Non-coding |
| Rheumatoid arthritis | Class II | | Arg620**Trp** | Non-coding |
| Multiple sclerosis | Class II | | | |
| Celiac disease | Class II | | | Non-coding |
| Systemic lupus erythematosis | Class II | | Arg620**Trp** | |
| Psoriatic arthritis | Class I | Distinct alleles | | |
| Psoriasis | Class I | Arg381**Gln** | | |
| Ankylosing spondylitis | Class I | Arg381**Gln** | | |
| Inflammatory bowel disease | Class II | Arg381**Gln** | **Arg**620Trp | |

Mount Sinai School of Medicine

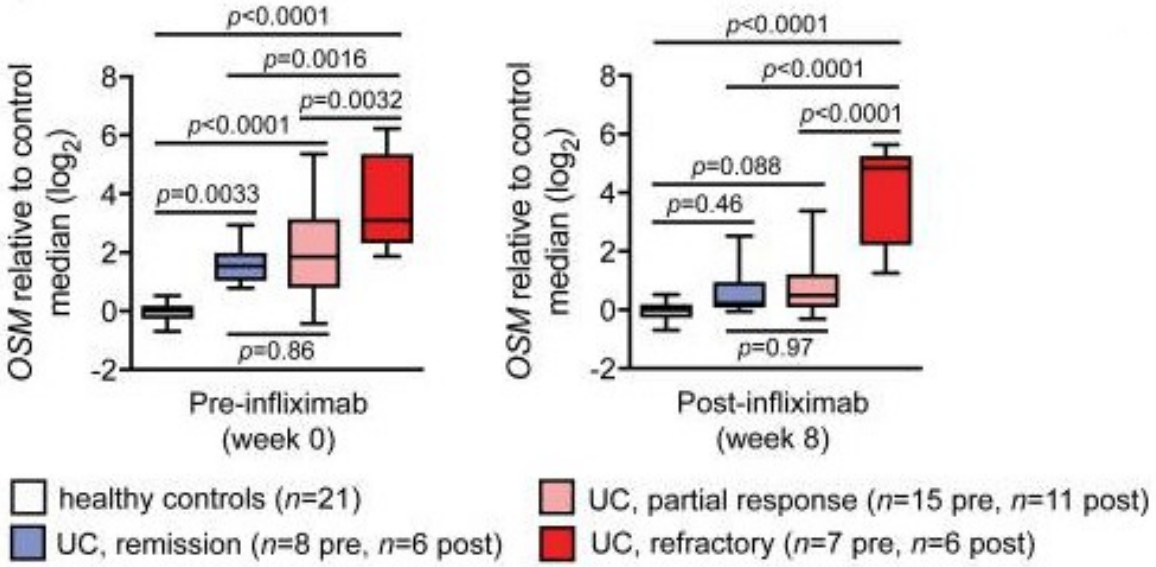
*Cho and Feldmann, Nature Medicine 2015; 730*

# Oncostatin M (OSM) Expression Predicts Response to Anti-TNF in UC Patients




**ROC curves for mucosal healing**

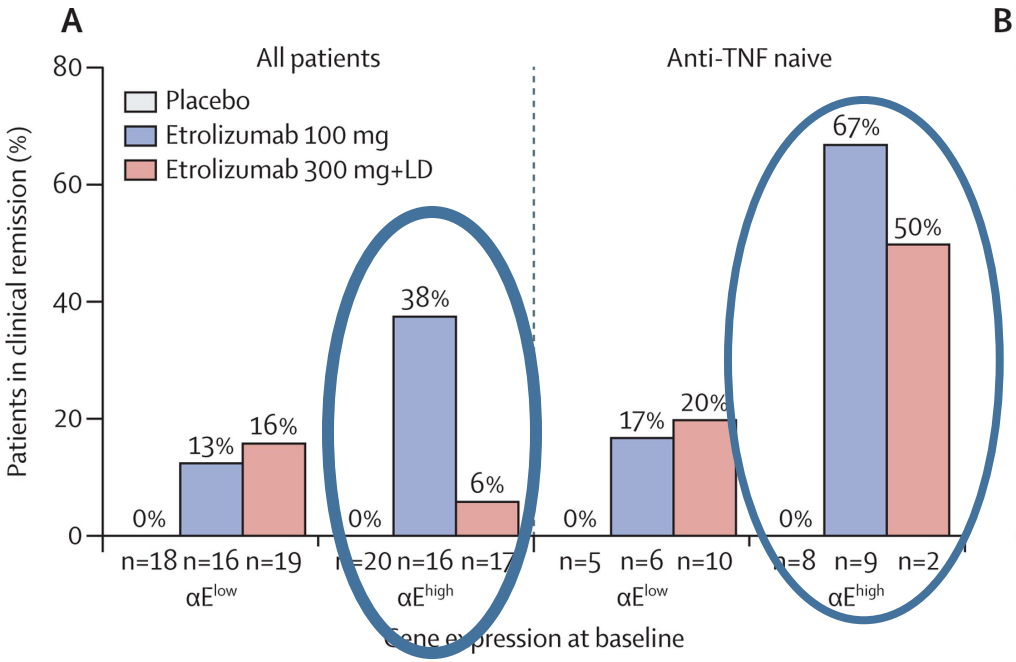
- OSM is cytokine in IL-6 family increased in IBD patients
- OSM and OMS receptor (OSMR) expression increased in colon biopsies of patients who did not respond to anti-TNF
  - Used 5 datasets, overall n =227
  - Combination of endoscopic and clinical

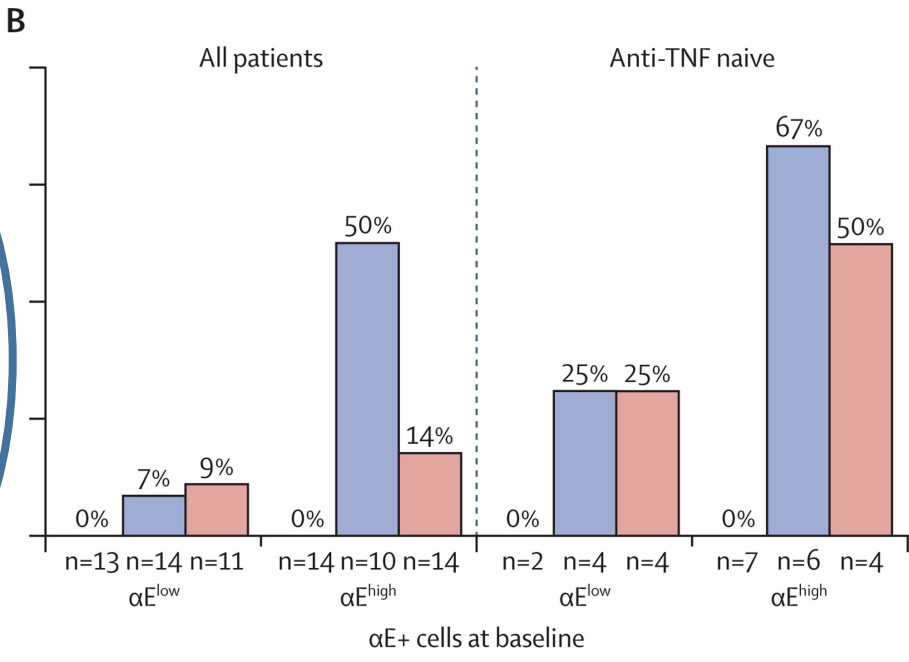



West N et al Nat Med 2017

# Etrolizumab Response and Integrin Expression

- Retrospective analysis of 110 UC patients in phase 2 clinical trial of anti-integrin therapy (etrolizumab) that blocks α4β7 and αEβ7
- Improved rates of remission in patients with **high** αE expression or αE positive cells in baseline colon biopsies

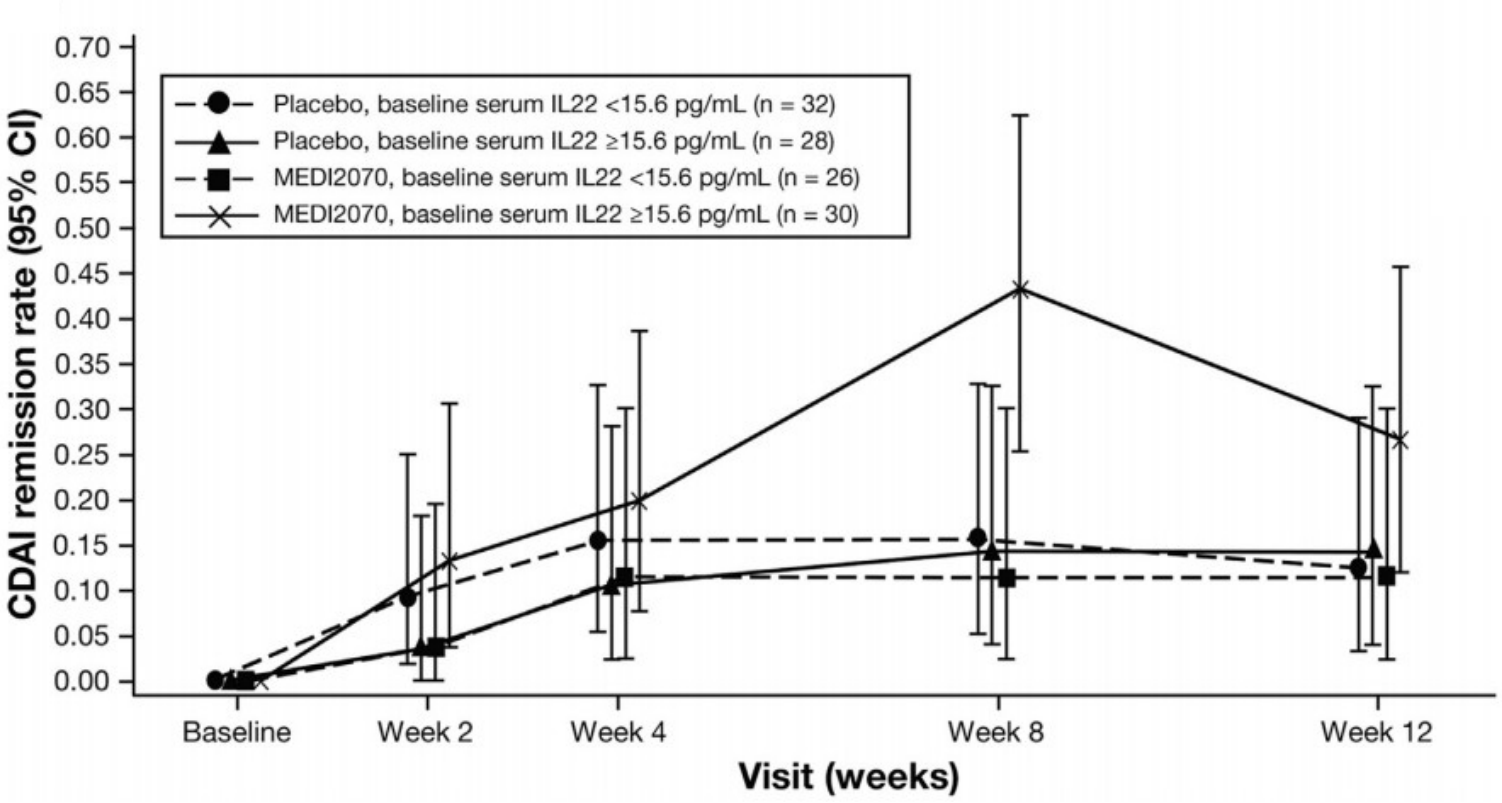



Vermeire S et al Lancet 2014

# IL-22 Levels and Response to Anti- IL-23 (anti p19) Therapy

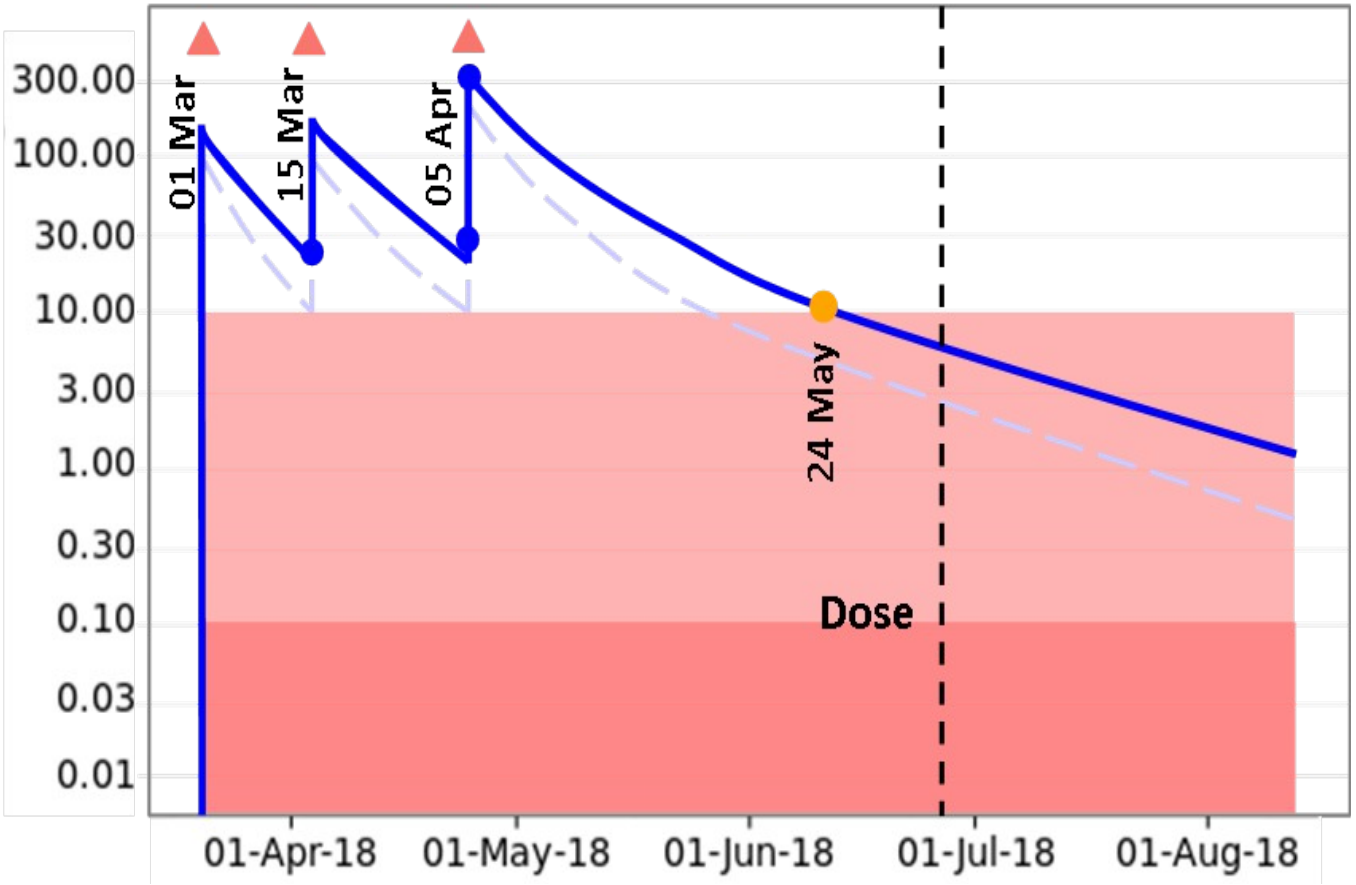
- In phase 2 study of anti-IL23 therapy (MEDI2070) for patients with CD, higher levels of serum IL-22 (> 15.2 pg/ml) were associated with response to drug
  - IL-22 is cytokine whose expression is induced by IL-23




Sands et al Gastroenterology 2017

# *idose*: PK Dashboard Process

ENTER PATIENT → UPDATE INFORMATION → PREDICT TROUGH OUTCOMES → CHOOSE DOSE AND INTERVAL



# STUDY POPULATION

**Patient Population**

114
ENROLLED
& Rec'd 2 Doses

45
IFX 10 MG/KG
Weeks 0

46
IFX 10 MG/KG
Weeks 2

69
IFX 5 MG/KG
Week 0

61Q
IFX 5 MG/KG
Week 2

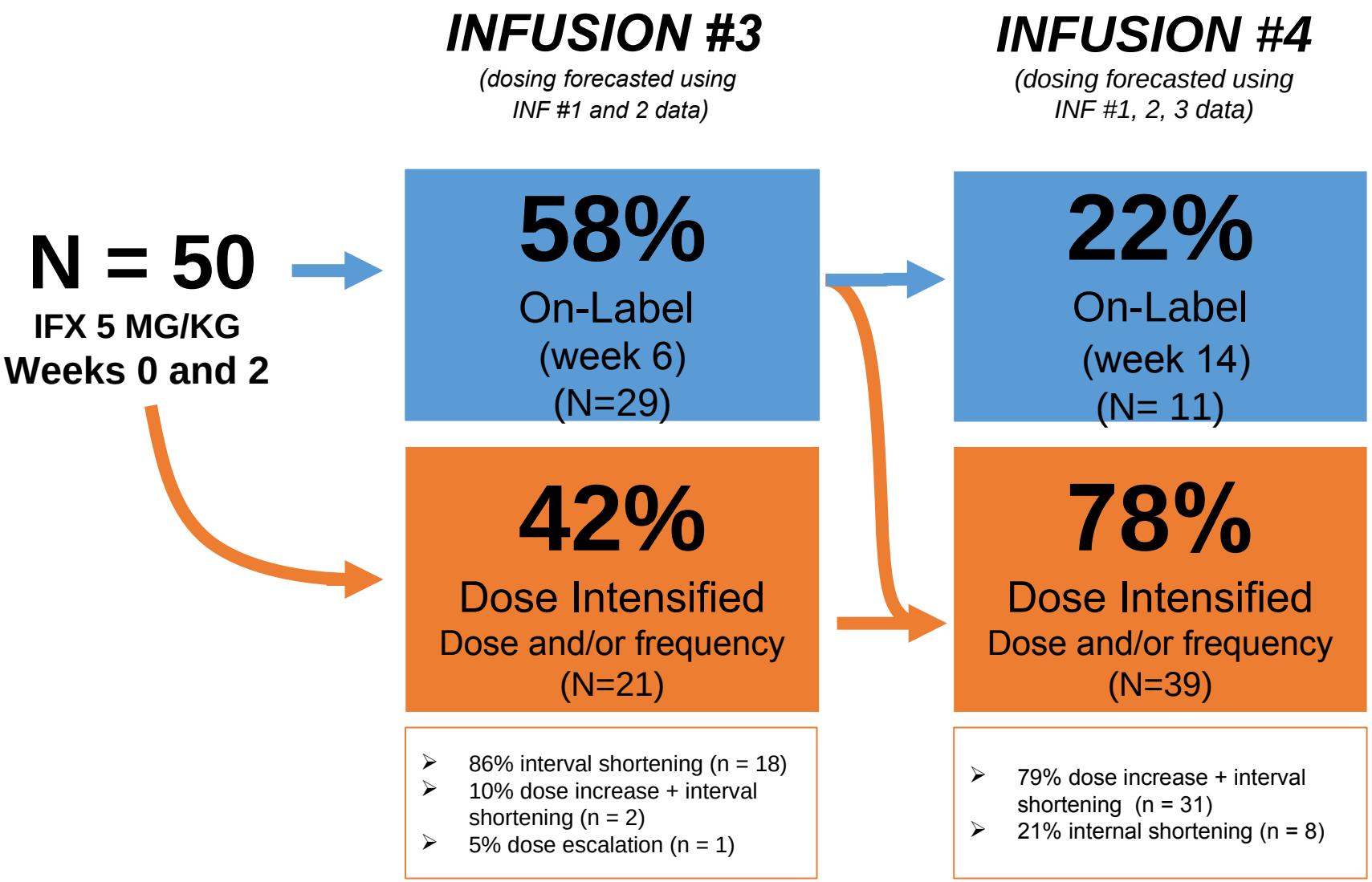
58‡
***INFUSION #3***

**50§**
***INFUSION #4***

**Exclusions:**

Q Protocol Deviations n = 8
Early Termination due to ATI n = 2,
‡ INF #3 Not Yet Completed n = 1
Early Termination due to Non-response n = 1,
Protocol Deviation n = 4,
§ INF#4 Not Yet Completed n = 3

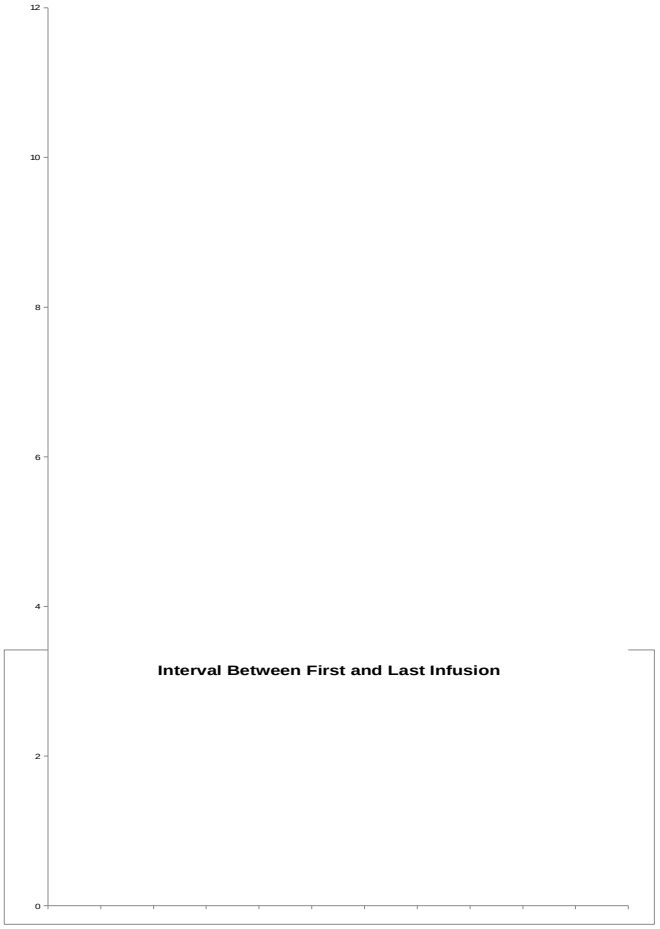
# Results: *i*Dose-Driven Dosing (N=50)




BP updated 22AUG2018

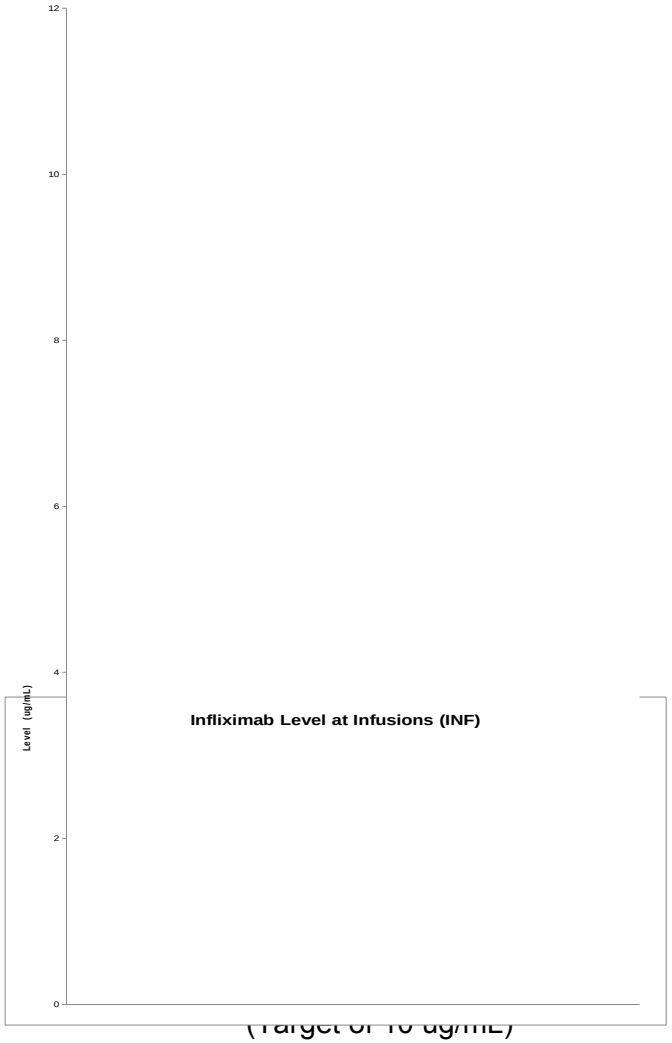
# Results: Median Intervals

**Dosing Intervals for Infusions #3 and #4, N=50**



# Results: Median IFX Levels

**Median IFX Level for INF#3 (n=49) and #4 (n=49)**




(Target of 17 ug/mL)

(Target of 10 ug/mL)

# Infusion 2 Characteristics

## Grouped by SOC vs DI at Infusion #3

| | INFUSION #2 Characteristics | | | |
|---|---|---|---|---|
| | On-Label at Inf#3 (n=29) | | Dose Intensified at Inf#3 (n=21) | |
| | Median | IQR | Median | IQR |
| Albumin (n=48) | 3.90 | 0.58 | 3.70 | 0.50 |
| C-Reactive protein (n=47) | 0.11 | 0.33 | 0.08 | 0.30 |
| Weight | 53.55 | 33.68 | 37.25 | 16.20 |
| Dose (mg/kg) | 5.00 | 0.11 | 5.00 | 0.11 |
| IFX Concentration (n=49) | 50.50 | 18.30 | 23.80 | 9.55 |

# ATI Story

- **Six patients** with ATI in **5 mg/kg Group**
  - Three subjects with ATI Development by Inf#4
  - Three subjects Post Inf#4

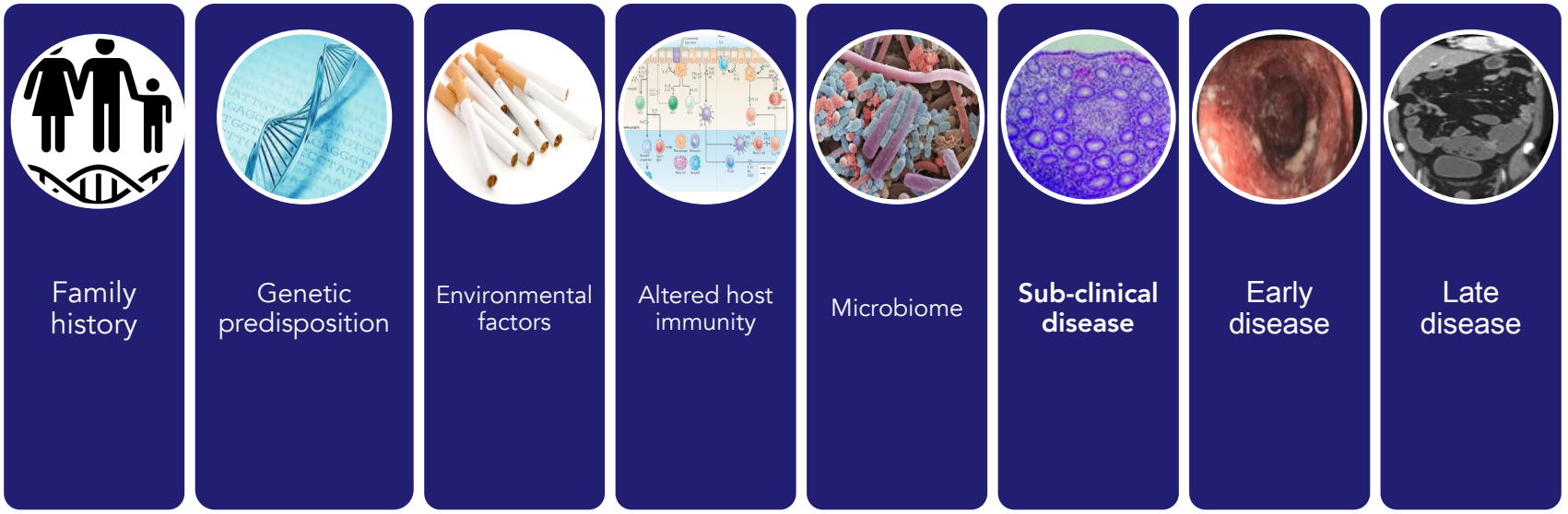
| Subject_ID | INF# w/ ATI | ATI Level | IFX Level | Status |
|---|---|---|---|---|
| IFX-001 | 3<br>4 | 5.4<br>8.3 | 0.0<br>2.3 | --<br>Cleared by Inf#6, On Drug @1yr |
| IFX-010 | 9 | 5.2 | 6.1 | ATI Development/On Drug @1yr |
| IFX-025 | 6 | 13.9 | 0.0 | Early Termination at inf#7/8 |
| IFX-066 | 10<br>11<br>12<br>13 | 4.34<br>6.7<br>4.27<br>5.2 | 0.6<br>5.5<br>8.8<br>8.5 | --<br>--<br>--<br>Sustained, On Drug @1yr |
| IFX-077 | 3 | 5.78 | 2.3 | Cleared by Inf#4, On Drug @1yr |
| IFX-099 | 3 | 3.47 | 5.6 | Cleared by Inf#4, On Drug @1yr |

Median: 5.3 Median: 3.9

# It is time to start thinking out of the box…



# IBD is a chronic life-long disease: Framework of prevention




**Primary prevention**

Prevention in healthy individuals

- Reduction of risk factors

Low risk → High risk

**Secondary prevention**

Early detection in high-risk patients

- Screening and intervention in pre-clinical disease

**Tertiary prevention**

Improved care for patients with established disease

- Early intervention to prevent disease progression
- Prevention of complications,
- Improvement of quality of life

# Insulin Dependent Diabetes Mellitus Studies

- 100% of children who are consistently positive for 2 particular islet autoantibodies will develop diabetes in the next 15 years

- Islet autoantibodies can be detected between 9 months and 2 years of age in genetically high-risk newborns, suggesting that the initiating environmental trigger may occur in utero or early in postnatal life

*Steck AK. Diabetes Care 2015; Barker JM J Clin Endocrinol Metab 2004*

# Prevention trials are already underway in other diseases

## Primary prevention

| Trial | Target population | Intervention |
|---|---|---|
| **The Pre-POINT Randomized Clinical Trial** | Autoantibody–negative children with a family history of type 1 diabetes and HLA-conferred susceptibility to T1DM | Oral insulin |
| **The Nutritional Intervention to Prevent Diabetes (NIP) Study** | Children with a family history of type 1 diabetes and HLA-conferred susceptibility to T1DM | Docosahexaenoic acid |

## Secondary prevention trials

| Trial | Target population | Intervention |
|---|---|---|
| **Diabetes Prevention Trial Type 1 (DPT-1) trial** | Family history of T1DM + autoantibodies | Subcutaneous insulin |
| **Type 1 Diabetes TrialNet** | Family history of T1DM + autoantibodies | Abatacept |
| | Children with family history of T1DM + autoantibodies | GAD65 based, type 1 diabetes vaccine |

# Prior work in preclinical IBD

| Author Year | N patients | Markers studied | Time before diagnosis (Y) | Main findings |
|---|---|---|---|---|
| Israeli 2005 | 32 CD 8 UC | Asca IgA AscA IgG pANCA | CD: 4.9 UC: 5.6 | 31.3% CD patients ASCA+ 25% UC patients pANCA+ |
| Van Schaik 2013 | 77 CD 167 UC | Asca IgA Asca IgG pANCA AntiOmp C AntiCbir1 | CD: 4.4 UC: 4.5 | Combination of multiple markers better predictive accuracy than any marker alone |
| Lochhead 2016 | 83 CD 90 UC | hsCRP, Il6 | CD: 6.6 UC: 6.8 | Median pre-diagnostic hsCRP levels and IL-6 levels higher in pre-patients than in controls |

[redacted]
NS

- Limited number of patients
- One sample per patient
- Not possible to assess the dynamics of changes occurring before diagnosis
- Limited number of markers studied
- Not possible to infer which pathways maybe altered before diagnosis, which may be important if an intervention is to be developed

***Israeli et al Gut 2005, Van Schaik Gut 2013, Lochhead CGH 2016***

THE GEM PROJECT
genetic environmental microbial

**Find 75 healthy subjects who go on to develop disease and compare with healthy subjects**

**75 new cases and 300 controls**

**Risk of Crohn's in FDR = 0.3% per year**

**5000 healthy Sibs**

**and Offspring**

Funders: Crohn's and Colitis Canada / Crohn et Colite Canada
THE LEONA M. AND HARRY B. HELMSLEY CHARITABLE TRUST

www.gemproject.

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Joseph and Wolf Lebovic Health Complex
Bright Minds. Big Hearts. The Best Medicine.

THE GEM PROJECT
genetic environmental microbial

# Nested Cohort

**As of January 23, 2016**

| Nested Cohort New Diagnosis | 54 Diagnoses; 53 Completed Sampling |
|---|---|
| Sibling/Offspring break down | 79% Sibling 21 % Offspring |
| Males: Females | 43%Male  57% Female |
| Average age of CD dx | 19.66 years (Range 10-35) |
| Mean time in study before dx | 2.68 years |

- 1 Subject had their diagnosis changed from CD to UC
- 1 Diagnosis  currently matching controls
- 4 New diagnoses awaiting confirmation
- 37 Controls in the processing of being completed

Funders: Crohn's and Colitis Canada / Crohn et Colite Canada
THE LEONA M. AND HARRY B. HELMSLEY CHARITABLE TRUST



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# Preclinical IBD Cohorts

Studies in the general population (serum repositories)

Study changes in pre-patients individuals who are know to later develop disease

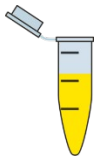
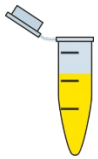
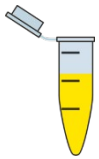
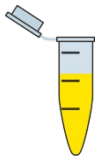
**PREDICTS study**

Studies in at-risk populations (families)

**Meconium Study**
**Multiplex families cohorts**

# The PREDICTS (PRoteomic Evaluation and Discovery in an IBD Cohort of Tri-service Subjects) study

- The PREDICTS study is a cohort study looking at preclinical samples ( 0, -2y, -4y, -6y) obtained from soldiers later diagnosed with CD or UC
- Patients are identified through the Department of Defense Medical Encounter Database, and then linked to the DoD Serum Repository
- Serum is obtained and used for several research projects

| ± -6 years | ± -4 years | ± -2 years | T0:Diagnosis | Clinical info |
|---|---|---|---|---|
|  |  |  |  | · ICD9 codes<br>· CPT codes<br>· (surgery, medication) |

**SEROLOGICAL MARKERS (PROMETHEUS)**
ASCA IgA
ASCA IgG
Anti-OmpC
AntiCBir1
Anti-FlaX
AntiA4-Fla2
ANCA

**SOMALOGICS (JANSSEN)**
**Platform that measures 1129 proteins in serum**

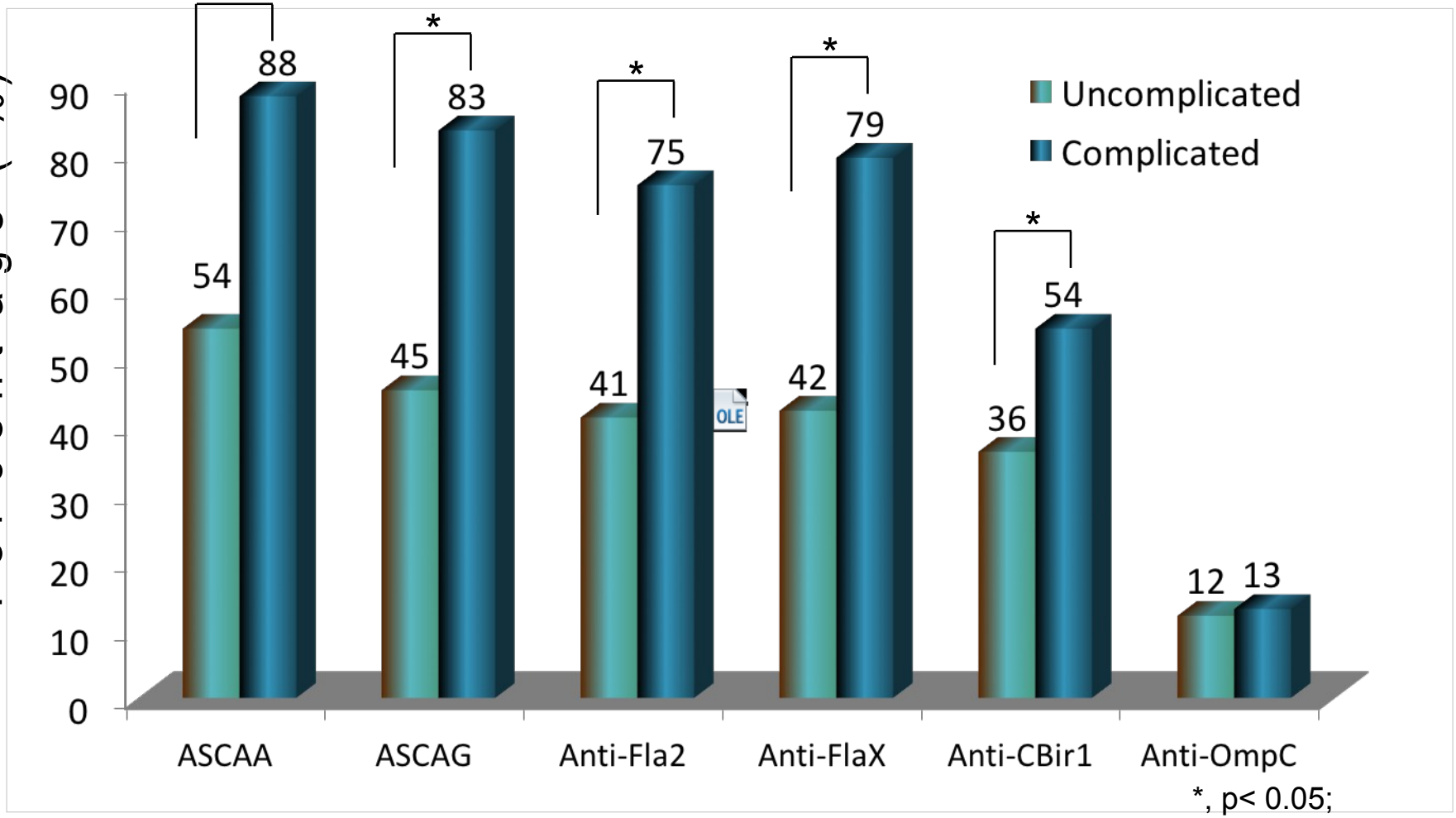
**Anti-GMCSF**
**Miriam Merad Group**
**Mount Sinai**

**Enteric Panel**
**AGAVE and NMRC**

**Microbial microaaray**
**Collaboration with BROAD; Peter Mannon**

**VIROME (VirScan)**
**Collaboration with Scott Snapper and Stephen**

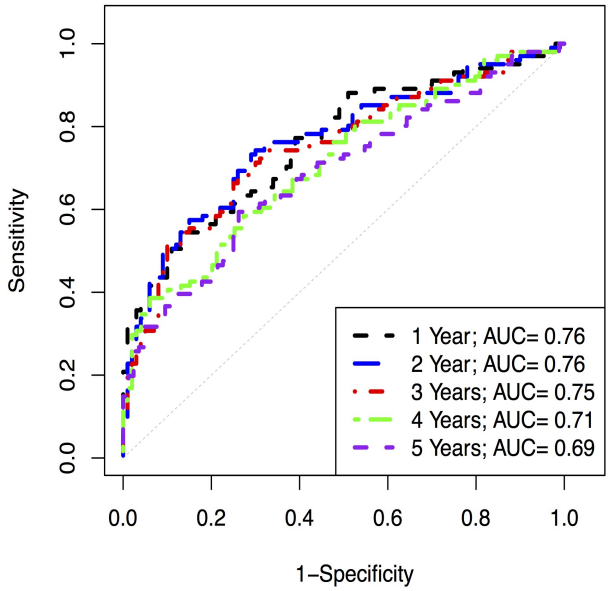
# Preliminary data from PREDICTS: it is possible to predict who will develop complicated disease




*Choung et al. APT 2016*

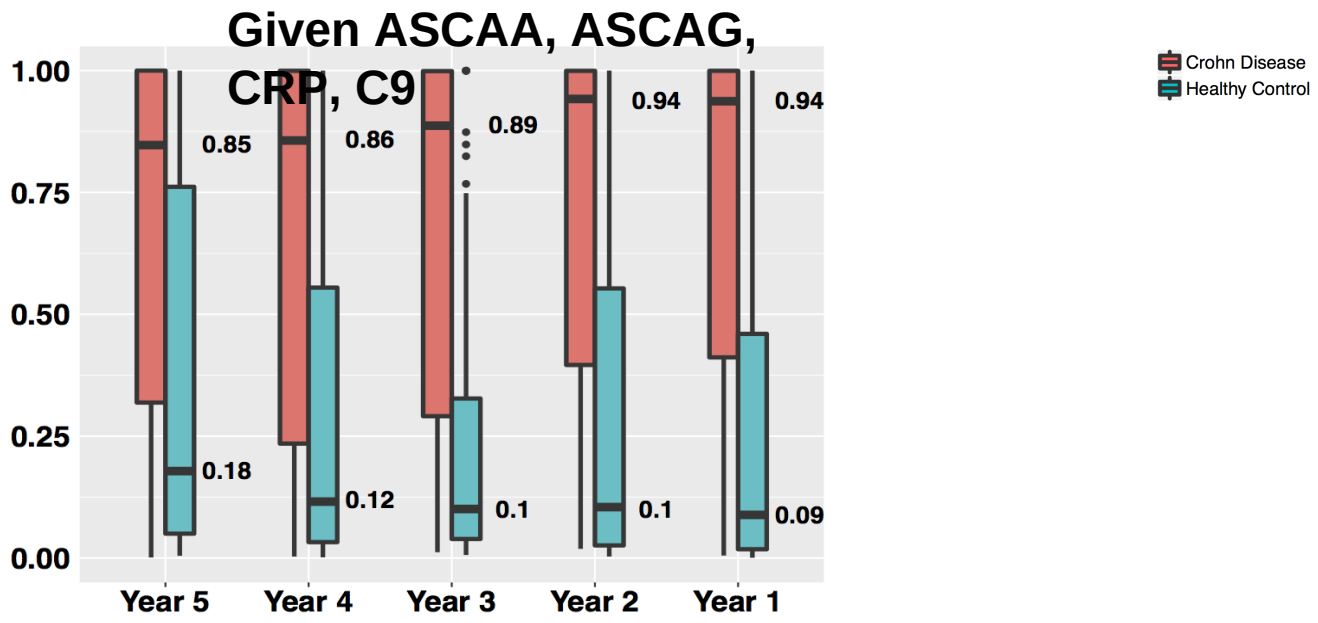
# Predictive accuracy of the serological markers: Multivariate analysis -

| Year | Asca IgA | Asca IgG | Cbir1 | FlaX | Fla2 | OmpC | pANCA |
|---|---|---|---|---|---|---|---|
| - 5 | x | x | x | x | | | x |
| - 4 | x | x | | x | | | x |
| - 3 | x | x | | x | | | x |
| - 2 | x | | | x | | | |
| - 1 | x | x | x | x | | | x |




- **Anti-OmpC and AntiFla2 do not contribute for disease prediction in the multivariate analysis**
- **Given the high correlation between FlaX and Fla2, only one of them (FlaX) was selected by the model**
- **The AUC increases towards the time of diagnosis**

# Probability to develop disease given markers trajectory at a given time



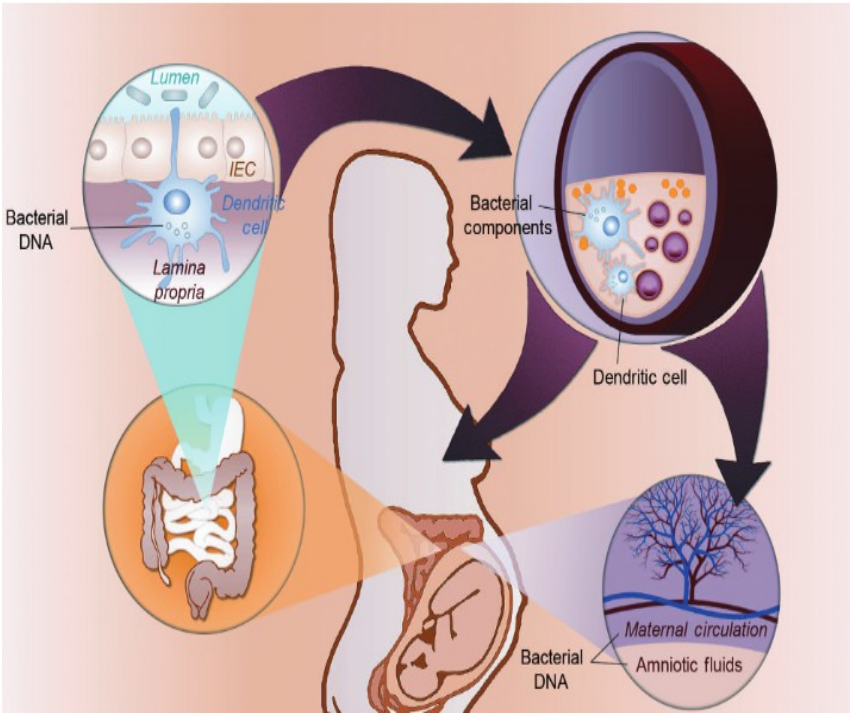

For each patient in the testing data, derive the probability to develop Crohn's **given predicted time-trajectory of markers at a particular time.** Probabilities were derived based on the following formula:

**Prob(CD | Marker,Time) = Prob(Marker | CD,Time) / (Prob(Marker | CD, Time) + Prob(Marker | HC, Time))**

where Prob(Marker|CD) and Prob(Marker|HC) are the likelihood function assuming normal distribution with mean and variance parameters estimated using the training data.

# Initial Microbial Colonization

- The development of the microbiota begins well **before the infant is born**
  - Studies in mice have demonstrated the **transmission** of labeled bacterial strains from a **mother to fetus** during pregnancy
  - Studies in humans have reported different **microbes** in amniotic fluid, **umbilical cord blood**, as well as **placenta** and fetal membranes.
- The initial **intestinal colonization** of the infant gut is believed to play a crucial role in the **priming of the mucosal immune system** and may predispose to the development of immune mediated diseases later in life.



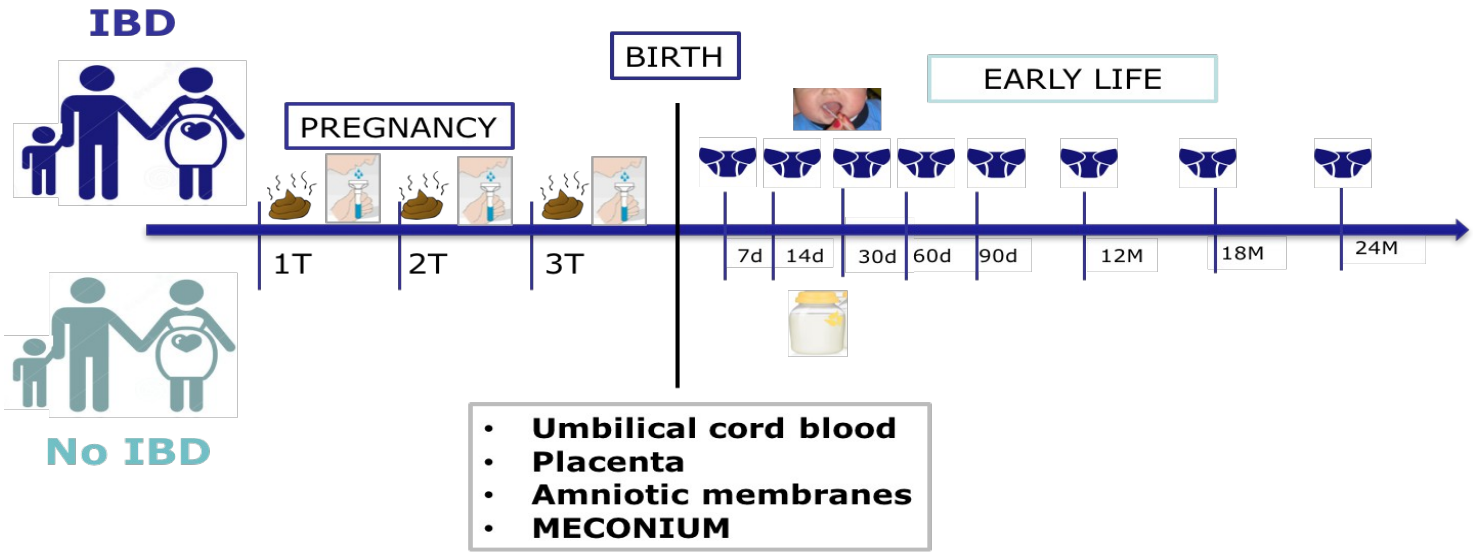

*Aagaard et al., 2014; Ardissone et al., 2014; Funkhouser & Bordenstein, 2013. Oh et al., 2010, Satokari et al., 2009. Hu et al., 2014; Gosalbes et al., 2013*

# The MECONIUM study

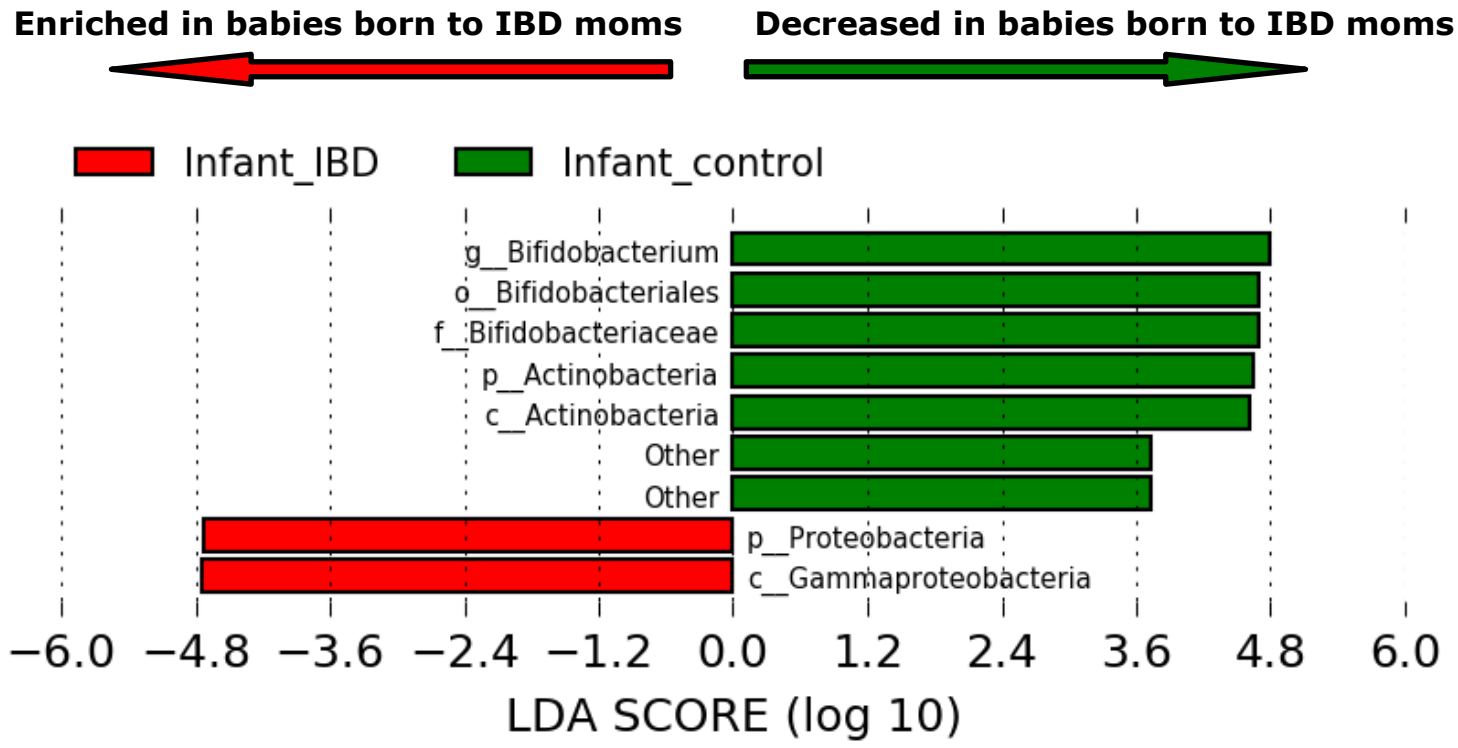
The MECONIUM study

① First colonization of baby starts in utero; some studies show higher transmission rate of disease from mothers with IBD as compared to fathers

② The MECONIUM´s study goal is to explore what role does IBD play in the composition of the maternal and newborn microbiome and whether there are particular bacterial strains that may increase the risk of IBD in offspring that could



# Taxa differentially expressed between infants: follow-up stool



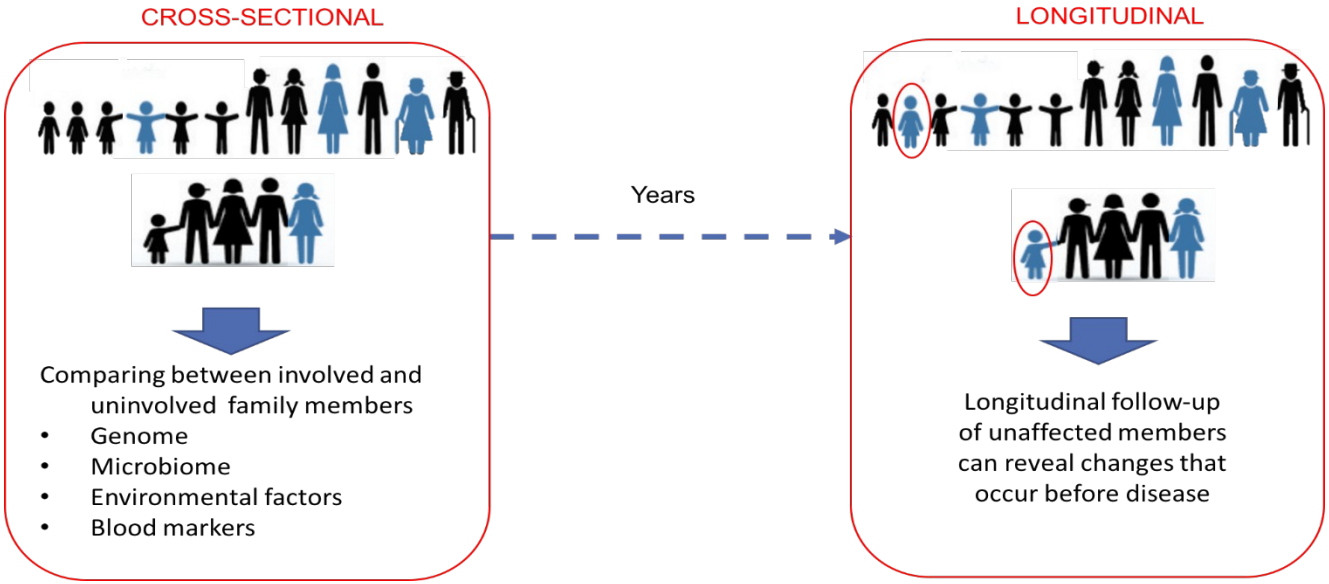

**Adjusted for delivery type**

*Torres J et al. Presented at ECCO*

# The MULTIPLEX Jewish Ancestry family study

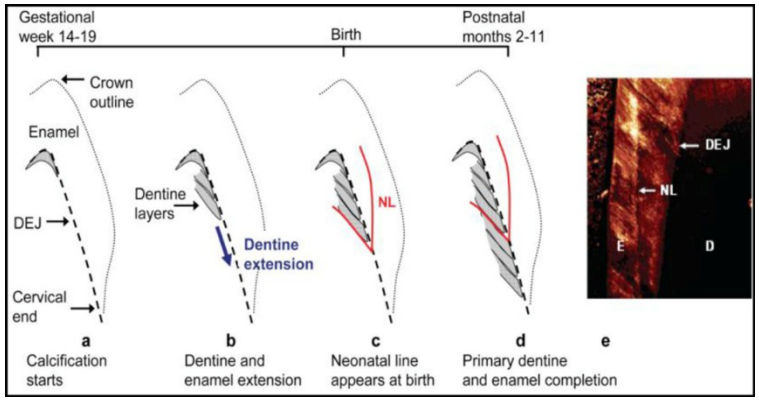
# The MULTIPLEX family study

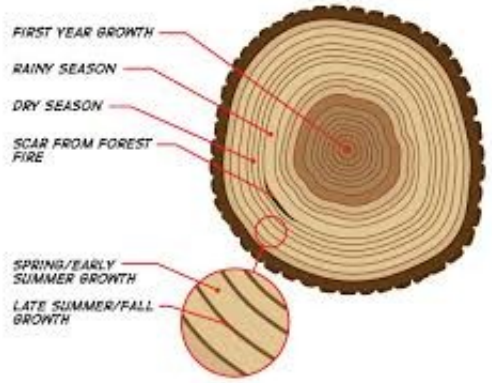
1. Family history is the strongest risk factor for developing IBD; families where multiple individuals are affected bear the highest risk
2. The **MULTIPLEX family study** is a cohort of multiplex families with IBD of Jewish ancestry (very high risk population)
3. **The goals are: 1) to compare microbial, serological and genetic features between affected and unaffected and to follow and serially sample the unaffected FDRs allowing for identification of**



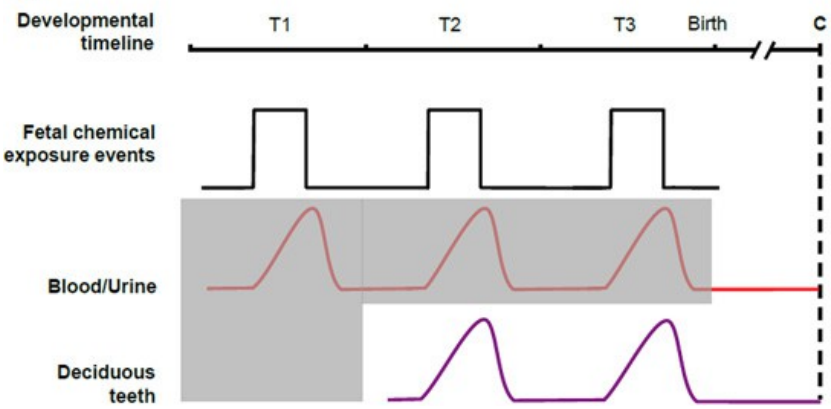
# Deciphering the Environmental Trigger: The Exposome

Assessing accumulated exposures throughout a lifetime




A




B

Scope of prenatal exposure information revealed by biomarkers collected in later life

| Biomarker | Exposure timing | Cumulative exposure | Prenatal exposure source | Limitations of biomarker for low frequency outcomes |
|---|---|---|---|---|
| Blood | No | No | No | Repeated sampling needed. Cost and time burden |
| Urine | No | No | No | Repeated sampling needed. Cost and time burden |
| Deciduous teeth | Yes | Yes | Possible for sources where unique isotopic signature is apparent | No first trimester exposure information. Non-invasive collection is only between 6 to 12 years |

*Andra SS. Environ Int 2015*

# From Prediction to Prevention