Towards Precision Medicine in Inflammatory Bowel Diseases

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Disclaimer

The views expressed here are those of the presenter and do not represent the views of the Crohn’s & Colitis Foundation
Outline

- **Background**: Inflammatory Bowel Diseases (IBD)

- **Current advances** in precision medicine for IBD
  - Biomarkers - Prognosis of disease course
  - Biomarkers - Response to treatment

- **Challenges** to advance precision medicine in IBD

- **IBD Plexus**: the largest research platform to support precision medicine in IBD
Inflammatory Bowel Diseases (IBD)

Chronic inflammation of the gastrointestinal tract

**Crohn’s Disease (CD)**
- Segmental inflammation
- Transmural inflammation of any part of GI tract
- Non-Bloody diarrhea
- Weight loss
- Abdominal pain

**Ulcerative Colitis (UC)**
- Diffuse Inflammation
- Limited to colonic mucosa and rectum
- Bloody diarrhea with pus
- Fecal urgency
- Abdominal cramps
Variable disease course over first 10 years

**IBSEN study:** Norwegian cohort (diagnosis 1990 - 1993) (CD, n=197 / UC, n=423)

- Decrease in symptom severity
  - CD 43%

- Complications (structuring or penetrating) = 53%

- Unremitting continuously active
  - CD 19%

- Recurrent relapsing symptoms
  - CD 32%

Complications in CD: Strictures and Fistulas & Abscesses

Montreal Classification

- Normal (No Event)
- Inflammatory (B1)
  - Inflammation
- Stricturing (B2)
  - Stricture (Fibrosis)
- Penetrating (B3)
  - Fistula

IBD Therapy: Step-Up and Top-Down approaches

**Standard: Step-Up**

- May delay adequate treatment in aggressive disease

**Top-Down**

- May over-treat and expose to cost, and risk of immunosuppression

Problem

Variable Disease Course

Some patients more aggressive disease than others

- Unremitting disease
- Recurrent relapse (flare-ups)
- Need for drug escalation
- Need for surgery

Severe Complications

Difficult to treat once they develop

- Generally require surgery
- Recurrence after surgery
- Dramatically impair quality of life
- In some cases they may be fatal

Variable Response to Treatment

Lack or loss of response

- 30% do not respond to biologicals
- 15% of responders loss response
Unmet need

Early detection, ideally at diagnosis, of

- Patients with potential aggressive disease
- Response to treatment

Decide best treatment options based on patient’s biological and clinical characteristics to deliver:

- Right Drug    Right Dose
- Right Time    Right Patient
Current efforts towards precision medicine in IBD

Prognosis Aggressive Course
- Unremitting
- Complications
- Frequent Relapse
- Treatment Escalation

Response to Treatment
- Biologicals
  - Anti-TNFα
  - Anti-α4β7

Genotype Phenotype
- Clinical
- Molecular
Genotyping and clinical & molecular phenotyping

**Genotype** → **Clinical** → **Molecular** → Genetic risk factors

- Serology markers
- Disease location
- Complications
- Life style

**Phenotype**

- Transcriptomics
- Microbiomics
- Proteomics
- Metabolomics
- Molecular endoscopy
Clinical parameters that correlate with disease severity

- Serology markers
- Disease location
- Complications
- Age & life style

Not enough to predict disease severity and response to treatment for a specific patient at diagnosis
Genotyping

Genotype ➔ Genetic risk factors

Phenotype ➔ Clinical
- Complications
- Life style

Molecular
- Transcriptomics
- Microbiomics
- Proteomics
- Metabolomics
- Molecular endoscopy
GWAS: 240 risk loci associated with IBD susceptibility

Insights into biological processes underlying IBD

1. Epithelial barrier
   - PTPN22, PTGER4, REL, NKX2-3

2. Antimicrobial defense
   - CARD9, NOD2, IRGM, ATG16L1, XBP1, LRRK2

3. Immune regulation
   - JAK2, IRF4, IL23R, STAT3, TNFSF15, TNFSF8, IL12B, IL10, PRDM1, ICOSLG

Modified from https://www.massgeneral.org/csibd/about/mission.aspx
IBD susceptibility genetic variants as prognosis predictors

Limited effect size restricts their use as stand alone biomarkers

<table>
<thead>
<tr>
<th>GENETIC VARIANTS</th>
<th>PROGNOSIS</th>
<th>IBD</th>
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</thead>
<tbody>
<tr>
<td>NOD2/CARD15</td>
<td>Structuring or penetrating (European /North America)</td>
<td>CD</td>
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<tr>
<td>IRGM</td>
<td>Penetrating (Italian patients)</td>
<td>CD</td>
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<tr>
<td>IL23R</td>
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<td>TNFSF15</td>
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Genetic risk score predicts primary nonresponse (PNR) to anti-TNFα in ulcerative colitis

7 SNPs associated With PNR

<table>
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<tr>
<th>Chromosome</th>
<th>SNP</th>
<th>Potential Genes</th>
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<tr>
<td>1</td>
<td>rs6679677</td>
<td>PTPN22, PHTF1</td>
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<td>IFNGR2, IFNAR1, IL10RB</td>
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<tr>
<td>9</td>
<td>rs1330307</td>
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Genetic risk score predicts PNR

ROC 0.8589

Larger prospective studies are required to confirm clinical utility of these SNPs

Summary - Genotyping in IBD for prognostication

Genotyping utility

- Several loci are associated with IBD prognosis and response to treatment
- Their clinical application is still limited
- A composite genetic risk score may provide improved predictive value and effect size
Clinical and molecular phenotyping: transcriptomics

Phenotype

Clinical

Molecular

Genotype

Genetic Risk Score

Disease location

Age at diagnosis

Ethnicity

Serology markers

Transcriptomics

Microbiomics

Proteomics

Metabolomics

Molecular endoscopy
RISK study *

Largest well-characterized inception cohort in pediatric IBD

Inception cohort: patients enrolled at diagnosis and before treatment

AIMS

Identify clinical and biological predictors of complications in Crohn’s disease at diagnosis

Evaluate the effect of early anti-TNFα treatment in reducing risk of complications

* Conceived and Funded by the Crohn’s & Colitis Foundation
RISK Methodology - 3 – 5 years follow up

28 Clinics (USA – Canada)

Data Collection
(1,096 patients)

- Clinical
- Anti-microbial Serology
- Gene Expression
- Microbiome
- Genotyping
- Response to Treatment

Data Analysis
(913 patients)

- Computational Tools
- Bio-statistical Analysis
- 80 million Data Points

Risk Model

- Competing RISK Model (complications prediction)
- Propensity-Score Matching (early anti-TNFα efficacy)

3 years follow up outcomes published in 2017

Principal Investigators: Subra Kugathasan and Denson Lee
RISK 3 years Outcomes
Complications 3 years after diagnosis

Montreal Classification

Inflammatory (B1)

- $n = 913$

Stricturing (B2)

- $n = 54$

Penetrating (B3)

- $n = 24$

Remained inflammatory (B1)

- $n = 835$

10.7% of patients developed complications

3 years follow-up

Penetrating (B3)
Stricturing (B2)
B2 or B3
Transcriptomics: molecular phenotyping at diagnosis
Baseline gene expression profiling of ileal biopsies

Colonoscopy

Biopsy / RNA

Mucosal biopsy

RNA

RNAseq

Extracellular matrix (EMC) and inflammatory (INFL) signatures predict complications at diagnosis

**INFL signature ➔ Penetrating**

**ECM signature ➔ Stricturing**

ECM: Extracellular matrix; INFL: Inflammatory.
Early* anti-TNF-α therapy reduce risk of penetrating (B3) but not fibrotic (B2) complications

* Early anti-TNF therapy

* Early therapy: exposure to anti-TNFα within 90 days of diagnosis
Gene expression prognostic signatures

Complications
- Stricturing (B2)
- Penetrating (B3)

Aggressive disease course
- Continuously active
- Frequent relapse
- Need for treatment escalation

Response to treatment
- Anti-TNFα antibody
- Anti-α4β7 antibody
Blood based gene expression signatures for prediction of aggressive IBD course

**Aggressive disease**

- Unremitting disease
  - Chronically active
  - Frequent relapse

- Need for therapy escalation
  - Oral Immunomodulator
  - Alternative immunomodulators
  - Biologics
  - Surgery

**Indolent disease**

- Sustained remission
- No need for therapy escalation
CD8 T cells gene expression signatures divide CD and UC patients in two distinct groups

**Study Design**
- Active CD n=35
- Active UC n=32
- 58% enrolled at diagnosis
- PBMC (CD8 & CD4)
- Affimetrix arrays & qPCR
- Step-up management of patients

**IBD1** - Elevated gene expression
**IBD2** - Lower gene expression

IBD 1 & 2 signatures predict disease course in CD & UC

**IBD1** – Experienced more aggressive disease than **IBD2**

- More aggressive disease
- More treatment escalation

**IBD2**
- Less aggressive disease
- Less treatment escalation

Utility currently evaluated in the PROFILE study

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Gene expression prognostic signatures

Complications
• Stricturing (B2)
• Penetrating (B3)

Aggressive disease course
• Continuously active
• Frequent relapse
• Need for treatment escalation

Response to treatment
• Anti-TNFα antibody
• Anti-α4β7 antibody
Oncostatin M (OSM) and its receptor (OMSR) are highly expressed in IBD and correlate with disease severity.

- OSM gene is highly expressed in IBD mucosa.
- Histological score

High expression of OSM is associated with no response to anti-TNF therapy

Response to anti-TNF
Endpoint: Clinical remission (Mayo score)

Prognostic utility of gene expression signatures

Gene expression

ECM
INFL
IBD1
IBD2
OSM

Early prognosis

Complications (ECM ; INFL)
- Stricturing behavior (B2)
- Penetrating behavior (B3)

Aggressive disease (IBD1/2)
- Continuously active
- Frequent relapse
- Need for treatment escalation

Response to treatment

OSM, ECM, INFL

Decide early, best personalized treatment options
Clinical and molecular phenotyping: microbiomics

- **Genotype**
- **Clinical**
  - Disease location
  - Age
  - Ethnicity
- **Molecular**
  - Transcriptomics
  - Proteomics
  - Metabolomics
  - Molecular endoscopy
- **Microbiomics**
  - Serology markers

Phenotype

Genetic Risk Score
Bacterial taxa associated with Crohn’s disease complications

4 taxa are associated with Complications *

* These microbial signatures were not included in the RISK model. Further validation is required.
Baseline and longitudinal microbial abundance and function predicts response to anti-integrin antibody treatment

Baseline (pre-treatment)

2 taxa increased in remitters

- **Burkholderiales**
  - Relative abundance (%) in remission vs. non-remission

- **Roseburia inulinivorans**
  - Relative abundance (%) in remission vs. non-remission

13 pathways upregulated in CD remitters

Longitudinal (week 14)

5 taxa decreased in remitters

17 pathways downregulated in CD remitters
Neural network algorithm predicts response to treatment: clinical and microbial phenotype integration

Increased predictive value of network training (clinical and microbial signatures integration)

Neural network analysis (clinical + microbial signatures)

AUC 0.87
Gene expression and microbiome prognostic signatures

Complications
- Stricturing (B2)
- Penetrating (B3)

Aggressive disease course
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Response to treatment
- Anti-TNFα antibody
- Anti-α4β7 antibody
Clinical phenotyping is just the tip of the iceberg in IBD prognosis and treatment

Multi-omics data integration is key for precision medicine in IBD

Multi-Omics Data integration
Challenges in precision medicine for IBD

• Data collection and integration
  - Harmonized data and sample collection
  - Multi-omics data integration
  - Integration of EHR and multi-omics data
  - Development of bioinformatics and AI tools

• Validation of candidate biomarkers
  - Longitudinal prospective cohorts
  - Inception cohorts
  - Ethnically diverse cohort

• Clinical utility of biomarkers
  - Rigorous testing in RCT
  - Demonstrate Improvement in patient outcomes
  - Demonstrate cost-effective care
IBD Plexus: research platform to advance precision medicine in IBD

* CROHN'S & COLITIS FOUNDATION

Largest repository of IBD biosamples & patient data
4 patient cohorts (40,000 patients)

* Supported by The Helmsley Charitable Trust
IBD Plexus Cohorts: resources for biomarker identification & validation

Four diverse cohorts for IBD research

- IBD Qorus: Quality of Care Program
- RISK: Pediatric Risk Stratification Study
- IBD Partners: Online Patient Survey Study
- SPARC IBD: Adult Prospective Research Study
IBD Plexus Cohorts: SPARC IBD

SPARC IBD
- **7,000 adult** IBD patients at 19 sites by 2020
- Longitudinal & prospective
- Clinical data biosamples

IBD Qorus
Quality of Care Program

RISK
Pediatric Risk Stratification Study

IBD Partners
Online Patient Survey Study

SPARC IBD
Adult Prospective Research Study
**RISK**

- 1075 CD pediatric patients
  - Inception cohort, 5th year follow-up; 28 sites
  - Clinical data & biosamples

**IBD Qorus**
Quality of Care Program

**SPARC IBD**
Adult Prospective Research Study

**RISK**
Pediatric Risk Stratification Study

**IBD Partners**
Online Patient Survey Study
Conclusions

Advances have been made in the last decade to integrate genotyping and deep clinical and molecular phenotyping for IBD prognosis.

Complications
- Stricturing (B2)
- Penetrating (B3)

Aggressive disease course
- Continuously active
- Frequent relapse
- Need for treatment escalation

Response to treatment
- Anti-TNFα antibody
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Paving the path towards precision medicine in IBD
Thank you