Companion Diagnostics in Autoimmune Disorders: Improving Outcomes Through Personalized Medicine

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**Immune-Mediated Diseases**

- Rheumatoid Arthritis
- Lupus
- Crohn’s Disease
- Ulcerative Colitis
- Psoriasis

- Despite advancement of therapeutic options over the past 2 decades, including a range of biologics, only 10-20 percent of patient suffering with known immune inflammatory disorders today are effectively treated.
What contributes to the variability in response?

- Waxing and waning
- Complex phenotypes
- Composite Outcome Measures
  - CDAI
  - SLEDAI
  - ACR
  - DAS
  - SES-CD
  - PASI
  - ...

**Characteristics**

**External Triggers**
- bacteria
- viruses
- chemicals
- diet
- stress
- pollution

**Autoimmune Diseases**

**Genetic susceptibility**

**Unknown factors**

**Gender**

**Immune Status**
Personalized Medicine in Immune Diseases: Promise not achieved
Root cause of failure?

Expectation vs Perception vs Reality:
- Reality: In IBD for example response rates of 40% even lower for remission rates
- Perception by Individual Physicians: Response Rates of 60-70%
- Expectation of Predictive Test: 80% or better positive prediction

Phenotype
- Registrational endpoints are not adequate measures of response and non-response to allow for molecular prediction... too subjective
- Population results vs individual response

Redefine the disease phenotype and understand the immune heterogeneity
- Clinical Symptoms are not enough: Molecular Phenotype Defines Heterogeneity
Inflammatory Bowel Disease

- Chronic inflammation of the GI tract
  - Abdominal pain, chronic diarrhea, bloody stool, weight loss, perianal disease, extraintestinal manifestations

- Ulcerative colitis
  - Homogenous inflammation in rectum/colon
  - Inflammation confined to the tissue

- Crohn’s disease
  - Patchy inflammation throughout GI
  - Systemic inflammation and symptoms

- Etiology unknown but thought to be related to inappropriate inflammatory response to intestinal microbiota
  - Contributing factors: genetic susceptibility, environmental triggers, gut microbiome, immune response
Response Definitions in Ulcerative Colitis

- **Clinical response** is defined as a decrease from baseline in the Mayo* score by ≥ 30% and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1 (baseline required Mayo of 6 to 12).

- **Clinical remission** is defined as a Mayo score ≤ 2 points, with no individual subscore > 1.

- **Mucosal Healing** defined as an endoscopy subscore of 0 or 1 out of a scale of 3 (baseline required endoscopy of >2).
  - Standard practice was local endoscopy reader
  - Moving towards standard of central readers

*Mayo – composite index of patient and physician reported measures and endoscopic score
IBD: Is Mucosal Healing a Stable Endpoint?

Central Read
17% (n=16)
R
9% (n=9)
R
13% (n=13)
NR
61% (n=59)
NR
Wk 6
Wk 30
Total # of subjects = 96

Local Read
25% (n=24)
R
15.6% (n=15)
R
17.7% (n=17)
NR
41.7% (n=40)
NR
Wk 6
Wk 30
Total # of subjects = 96

• Endoscopy scores are highly variable
  • 50% difference in endoscopy score calls between readers in PROgECT
    - Variability in calls between 1 and 2 significantly impacts prediction accuracy

NR = non-response or discontinued
## Prediction is possible – Identifying primary non-responders

- Utilized colon tissue biopsies at baseline
- Generated gene expression based signature to predict response to anti-TNF
- Tested in multiple cohorts

<table>
<thead>
<tr>
<th>Test Population*</th>
<th>AUC</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT I / T37 (N=23)</td>
<td>N/A</td>
<td>0.92</td>
<td>1.00</td>
<td>0.92</td>
<td>1.00</td>
</tr>
<tr>
<td>PURSUIT/T17 (N=58)</td>
<td>0.77 [0.75-0.79]</td>
<td>0.90 [0.83-0.96]</td>
<td>0.63 [0.58-0.67]</td>
<td>0.87 [0.81-0.94]</td>
<td>0.68 [0.66-0.70]</td>
</tr>
<tr>
<td>PROgECT, central reads (N=97)</td>
<td>0.67 [0.60, 0.74]</td>
<td>1.00 [0.98, 1.00]</td>
<td>0.22 [0.16, 0.29]</td>
<td>1.00 [0.98, 1.00]</td>
<td>0.31 [0.24, 0.39]</td>
</tr>
<tr>
<td>Ph. 2 Simponi Japan (N=22)</td>
<td>0.74 [0.57, 0.86]</td>
<td>0.88 [0.74, 0.96]</td>
<td>0.46 [0.30, 0.62]</td>
<td>0.85 [0.70, 0.94]</td>
<td>0.53 [0.37, 0.69]</td>
</tr>
</tbody>
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*13-gene signature applied to all cohorts except for T37 (applied the 109 transcript panel) to predict mucosal healing
Common emerging theme: Prediction of Non-responders (NR)

Genetic Markers Predict Primary Nonresponse and Durable Response to Anti–Tumor Necrosis Factor Therapy in Ulcerative Colitis

Kristin E Burke, MD, Hamed Khalili, MD, MPH, John J Garber, MD, Talin Haritunians, PhD, Dermot P B McGovern, MD, PhD, Ramnik J Xavier, MD, PhD, Ashwin N Ananthakrishnan, MD, MPH

In Inflammatory Bowel Diseases, Volume 24, Issue 8, 12 July 2018, Pages 1840–1848,

Higher expression of TNFα-induced genes in the synovium of patients with early rheumatoid arthritis correlates with disease activity, and predicts absence of response to first line therapy

Aurélie De Groof¹, Julie Ducreux¹, Frances Humby², Adrien Nzeusseu Toukap¹,³, Valérie Badot⁴, Costantino Pitzalis⁵, Frédéric A. Houssiau¹,³, Patrick Durez¹,³ and Bernard R. Lauwers¹,³

Identifying primary NR is beneficial but likely only accounts for <50% of NR population
Where do go from here?

- Deconvolution of the Non-Responder Population
  - What is the driving biology in this subtype?
  - Does this subtype evolve or is it truly a different patient population?
  - What can be done to treat this non-responsive population?
    - Combination therapy?
    - Alternative mechanisms beyond the anti-inflammatory spectrum

- Reducing subjectivity in outcomes will increase accuracy of prediction...are expectations achievable?
  - Molecular definitions of disease and response may reduce variability
  - Combined clinical and molecular decision making may pave path towards personalized medicine
Where do we go from here...
Immune Diseases Are “Multiscale” Problems

- Immune diseases involve **molecular dysregulation** driving **tissue damage** and **organ dysfunction** leading to **clinical symptoms**

- Inherent genetic and environmental factors can influence ability to respond

- Decision-making should include assessment of **multi-scale therapeutic effects**
Current use of data for decision making

- Proteomics
- Transcript-omics
- Flow
- Single cell
- Histology
- Endoscopy
- PROs
- Symptoms
Development of Molecular “Endpoints”

- Utilizing extremes of response (“truth”) to define molecular surrogates to objectively measure response
  - ACR 50 (responder) vs ACR 40 (non-responder) – are these really different? How many times would the assessments reproduce this?
  - <ACR20 response vs >ACR70 response – reproducibly different

- Depending on the disease start at the source of the disease (gut, joint, etc.) and derive molecular endpoints and then move to least invasive method for obtaining the same information
  - e.g. Gut biopsies gene expression → serum proteins
Example: Tissue gene expression and Clinical Phenotypes in Crohn’s Disease

- Co-expression modules (WGCNA) generated
  - Groups of genes that are tightly correlated
  - “Units” of biology from transcriptomics datasets

- Analyzed the association between co-expression modules and clinical parameters
  - Generic way to estimate the strength of association between transcriptomics and metadata

- Results summary
  - Histology: strong
    - Histology scoring: D’Haens et al., Gastroenterology, 1998
  - Endoscopy (not shown): moderate
  - CDAI (registrational endpoint): weak
Transcriptomics Data Exhibited Ability to Predict Histology Scores

- Separated data into 1 training set and 3 testing sets

- Train model with multiple machine learning algorithms
  - Including cross validation

- Test on external sets

![Training](R^2 = 0.85)

![Testing](R^2 = 0.32)

![Testing](R^2 = 0.54)

![Testing](R^2 = 0.56)
Utility of Molecular Endpoints

- Supportive decision making in early trials
  - Efficient study designs

- Proving divergence from pbo response allows for opportunity to reduce/eliminate pbo arms in early trials

- Stabilizing response definition can lead to identification of enrichment (population) or predictive markers (individual)
What else can be done to reveal the variability in response to therapies?

- Moving from static assessments to functional assessments of immune “fitness” may illuminate the differences in response not related to alternate disease drivers.
Future State: “Multiscale” Approach to Personalized Medicine for Immune Diseases

- Proteomics
- Transcriptomics
- Immune perturbation
- Flow/Single cell
- Histology
- Endoscopy
- PROs
- Symptoms
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