What is Personalized Medicine?

- **Personalized medicine:**
  - Use of patient’s own information (genetic or other molecular biomarker information) to improve the safety, effectiveness and health outcomes via more efficiently targeted risk stratification, prevention and tailored treatment management approaches

- **Examples:**
  - HER2/neu: Herceptin - Herceptin, Tamoxifen, hormonal therapies
  - PGx Predict: warfarin dosing

- **Examples in IBD:** TPMT: azathioprine dosing
Examples of Uses for Personalized Medicine

- 1) Risk stratification
  - Patient MORE or LESS likely to develop disease/condition?

- 2) Inform treatment selection
  - Is it safe?
  - Is it effective?

- 3) Inform dosage
  - Rapid / Slow metabolizers

- 4) Prognostic testing
  - How likely is the patient to respond to standard treatments?

- 5) Treatment monitoring
  - Is it working?
  - Should we switch therapies or treatment strategies?

- 6) Improve or optimize clinical treatment pathways

Why do we need to personalize IBD therapy?
Heterogeneity in IBD

- **Patient examples:**
  - A) 25 yo male with new diagnosis and 10 stools per day. He has wt loss, and deep ileal ulcers on scope
  - B) 42 yo male with new diagnosis, 4 stools per day and mild patchy colitis on scope

- **Differences in**
  - Patient presentation
  - Disease behavior
  - Disease genetics and immune response
  - Development of complications
  - Response to therapy
  - Complications of therapy

Effectiveness of Step-up Treatment

[Diagram showing different treatments for Crohn's disease and cumulative need for first surgery]
Personalizing therapy

Can We Predict Disease Course?
Factors significantly associated with disabling Crohn's disease within 5 years of diagnosis (n=1123)

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid use</td>
<td>3.1</td>
<td>2.2 – 4.4</td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>2.1</td>
<td>1.3 – 3.6</td>
</tr>
<tr>
<td>Perianal disease</td>
<td>1.8</td>
<td>1.23 – 2.8</td>
</tr>
</tbody>
</table>

Positive Predictive Value

<table>
<thead>
<tr>
<th># Factors</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>61</td>
</tr>
<tr>
<td>1</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>91</td>
</tr>
<tr>
<td>3</td>
<td>93</td>
</tr>
</tbody>
</table>

CI = confidence interval
OR = odds ratio

Beaugerie et al. Gastroenterology. 2006; 130:650-6
Predictors of Rapid Progression to Surgery

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoker</td>
<td>3.1 (1.5–6.5)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1.8 (1.1–3.2)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>2.1 (1.0–4.1)</td>
</tr>
<tr>
<td>Ileal localization only</td>
<td>2.2 (1.3–3.8)</td>
</tr>
<tr>
<td>Oral steroid use in 1st 6months</td>
<td>3.8 (1.9–7.6)</td>
</tr>
</tbody>
</table>

Sands et al., Am J Gastroenterol. 2003

Prognosis of CD Patients with Severe Ulcerations

- Retrospective study, 102 patients with active CD
- Severe endoscopic lesions (SEL) defined as deep ulcerations >10% of mucosal area with at least one colonic segment
- Risk of colectomy associated with SELs, high CDAI, absence of immunosuppression

Ulcerative colitis - predictors

- Factors significantly associated colectomy within 10 years of diagnosis for pts with UC (n=519):
  - Age > 50 years – 0.28 (95% CI 0.12 – 0.65)
  - Extensive colitis – 2.98 (95% CI 1.25 – 7.08)
  - ESR ≥ 30 mm – 2.94 (95% CI 1.58 – 5.46)

Solberg et al. Scand J Gastro 2009

Antibodies and NOD2 Genotype Associated with Specific Crohn’s Disease Phenotypes

<table>
<thead>
<tr>
<th></th>
<th>Small bowel disease</th>
<th>Fibrostenosis</th>
<th>Internal Perforating</th>
<th>Small Bowel Surgery</th>
<th>UC-like disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-I2</td>
<td>-</td>
<td>P&lt;0.027</td>
<td>-</td>
<td>P=0.01</td>
<td>-</td>
</tr>
<tr>
<td>Anti-OmpC</td>
<td>-</td>
<td>-</td>
<td>P&lt;0.006</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ASCA</td>
<td>P=0.023</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001a</td>
</tr>
<tr>
<td>pANCA</td>
<td>P&lt;0.013a</td>
<td>P&lt;0.002a</td>
<td>-</td>
<td>P&lt;0.001</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>NOD2</td>
<td>P&lt;0.003</td>
<td>P&lt;0.002</td>
<td>-</td>
<td>P&lt;0.001</td>
<td>P&lt;0.008a</td>
</tr>
<tr>
<td>Anti-CBir1</td>
<td>P&lt;0.018</td>
<td>P=0.05</td>
<td>P=0.008</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Complications Increase with Number of Positive Serologies

Dubinsky et al., Am J Gastro 2006
Dubinsky et al., Clin Gastro Hep, 2008

NOD2/CARD15 Gene Status and Need for Surgery

Presence of NOD2/CARD15 variants was associated with:

- More frequent surgery for stricture
- Earlier requirement of surgery
- More frequent surgical recurrence
- Earlier requirement for reoperation

Serology and Genetics Predictors of Disease Severity

Logistic Regression Model: Higher QSS is Associated with a Greater Risk of Complications

NOD2 Positive Patients have a Higher Risk of Complications than NOD2 Negative Patients with the same QSS

Lichtenstein et al., Inflamm Bowel Dis. 2011
ANCA Predicts Chance of Relapse in UC

Relapse Rate

N = 432


42%

Precolectomy pANCA Reactivity and Postoperative Risk of Pouchitis

42%

17%

25%

20%

11%

9%

Weighing The Value of Top-Down Therapy

**Pros**
- Maintenance of remission
- Improved function and QOL
- Early promotion of mucosal healing to prevent complications

**Cons**
- Side effects
- Cost
- Majority of patients may not require more potent treatments initially
- Under-treatment of most severe patients with episodic strategy?

Lichtenstein et al. Inflamm Bowel Dis. 2004; 10:S2-S10

Can We Predict Response to Therapy?
Infliximab in Children Study (REACH) (ie-Shorter Disease Duration)

Median disease duration 2 years

- Patients (%)
  - Week 10: n=99, Response 88% Remission 59%
  - Week 54 q8: n=33, Response 64% Remission 56%
  - Week 54 q12: n=17, Response 33% Remission 24%

Overall number of subjects n=112


Higher Remission Rates with ADA and CZP with Shorter Disease Duration Post-hoc Analyses

- Placebo vs All ADA
  - <2 years: 17%, 2 to <5 years: 25%, 5 years: 14%

- Placebo vs All CZP
  - <1 year: 37.1%, 1 - <2 years: 36.4%, 2 - <5 years: 29.1%, ≥5 years: 23.5%

*p=0.002; **p=0.001; †p=0.014; ‡p=0.001; all vs placebo

TPMT Testing

6-TG Levels and Clinical Response

Dubinsky et al, Gastroenterology 2000
Clinical Characteristics as Predictors of Response to Biologic Therapy

- **Positive**
  - Younger age
  - Shorter disease duration
  - Inflammatory phenotype
  - Isolated colonic disease

- **Negative**
  - Smoking
  - Isolated ileitis
  - Presence of intestinal stricture

- **No effect**
  - Gender and race
  - Albumin levels and platelet counts
  - Serology

Arnott et al, Aliment Pharmacol Ther. 2003; 17:1451-7
Vermeire et al, Am J Gastroenterol. 2002; 97:2357-63
Schnitzler et al, Gut. 2005; 56:492-500

Biomarkers and Likelihood of Response

- Data is mixed. Pts can still respond to Biologic Treatment if not elevated but likelihood is reduced.

Reinisch et al. APT 2012
High Infliximab Levels are Associated with Mucosal Healing in Crohn’s Disease

Serum samples in 210 CD patients undergoing treatment with infliximab were collected.

Infliximab trough levels were correlated with endoscopic healing (complete, partial or none).

Van Moerkercke W. et al. DDW 2010. Abs #405b

SONIC: Clinical Remission Without Corticosteroids

By Trough IFX Concentration at Week 26

Primary Endpoint

Clinical Utility of Measuring Infliximab and HACA Levels in Patients with IBD

Clinical Outcomes in Patients with Detectable HACA (N=35)*

Clinical Outcomes in Patients with Subtherapeutic Concentrations (N=69)*


ADA Levels and Anti-Adalimumab Antibodies (ATA) and Outcomes

- 66 patients: 27% with detectable ATA
  - 59 (89%) CD, 7 (11%) UC
- ADA level ≥ 5 µg/ml is associated with lower CRP
- Conclusions:
  - ADA level ≥5 µg/mL correlates with lower CRP and mucosal healing;

Anti-Drug Antibodies Associated With Treatment Failure

The development of anti-drug antibodies are associated with poor treatment prognosis


Assessing Response to Treatment
Efficacy Endpoints

- **Clinical response**
  - CDAI decrease 70-100 points

- **Clinical remission**
  - CDAI <150

- **Decrease in CRP, stool calprotectin**

- **Mucosal healing**
  - Absence of mucosal ulceration on colonoscopy

- **“Deep remission”**
  - Clinical remission plus mucosal healing


Using Biomarkers to Assess Response to Therapy (Calprotectin and CRP)

N=64

Bjorkesten et al. *Scand J Gastro*
Symptomatic recurrence stratified according to endoscopic lesions:


Endoscopic healing and reduced hospitalizations and surgeries: Infliximab maintenance for Crohn’s disease:

Mucosal Healing Predicts Sustained Clinical Remission in Early CD


Identifying Patients at Increased Risk Of Adverse Events
### Long-Term Safety: Association Between Use of Specific Medications and Odds for Opportunistic Infection in IBD

<table>
<thead>
<tr>
<th>Medication</th>
<th>OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No medication</td>
<td>1.0 (reference)</td>
<td>1.0</td>
</tr>
<tr>
<td>Mesalamine</td>
<td>1.0 (0.6-1.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>3.3 (1.8-6.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>AZA/6MP</td>
<td>3.8 (2.0-7.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Anti-TNF agent</td>
<td>4.4 (1.1-17)</td>
<td>.03</td>
</tr>
</tbody>
</table>

# of Immunosuppressants

<table>
<thead>
<tr>
<th>None</th>
<th>1.0 (reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.9 (1.5-5.3)</td>
</tr>
<tr>
<td>2 or 3</td>
<td>14.5 (4.9-43)</td>
</tr>
</tbody>
</table>

1 Odds ratio and 95% confidence intervals assessed by multiple variable conditional logistic regression.

2 P value using conditional logistic regression.


### Elderly IBD At Increased Risk For Severe Infection/Mortality with Anti-TNF Therapy

95 patients (37 U.C., 58 CD) over 65 of an IBD database of 2475 pts. given IFX.

<table>
<thead>
<tr>
<th>%</th>
<th>S.I. %</th>
<th>Neo %</th>
<th>Mort.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly</td>
<td>11</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Younger</td>
<td>0.5</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Cottone et al., Clin Gastro Hep 2011
**Risk of lymphoma**

<table>
<thead>
<tr>
<th>Rate of Lymphoma per 1000</th>
<th>Baseline US population*</th>
<th>Immunosuppressant-treated1</th>
<th>Anti-TNF + Immunosuppressant-treated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.9</td>
<td>3.6</td>
<td>6.1</td>
</tr>
<tr>
<td>Relative risk of anti-TNF + immunosuppressant therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compared to baseline: SIR 3.25 (95% CI 1.5–6.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compared to immunosuppressant alone: SIR 1.7 (95% CI 0.5–7.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sieg et al., Gastro Hep 2009

**HSTCL**

<table>
<thead>
<tr>
<th>Number</th>
<th>AZA/IFX + anti-TNF</th>
<th>AZA/IFX alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of CM</td>
<td>47 (67.6%), 9 (12.8%)</td>
<td>24 (35.3%), 16 (22.5%)</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>27 (range 11–58)</td>
<td>24.2 (range 15–58)</td>
</tr>
<tr>
<td>Median age, y</td>
<td>23</td>
<td>22.5</td>
</tr>
<tr>
<td>Sex</td>
<td>Male: 23 (95%), Female: 1 (5%)</td>
<td>Male: 10 (62.5%), Female: 1 (6.25%)</td>
</tr>
<tr>
<td>Median duration of thiopurine exposure (P = .03)</td>
<td>5.6 y (range 1-13.5 y)</td>
<td>6 y (range 3-17 y)</td>
</tr>
<tr>
<td>Outcome</td>
<td>Died: 16 (80%), Unknown: 4 (20%)</td>
<td>Died: 11 (68.8%), Alive: 4 (25%), Unknown: 1 (6.25%)</td>
</tr>
</tbody>
</table>

Risk in men younger than 35 years

1 in 45,000

**AZA**

1 in 7,404

1 in 3,534

**AZA/IFX**

Thai et al., J Crohn’s colitis 2010

Current Stratification of Natalizumab-Associated PML Risk

<table>
<thead>
<tr>
<th>Anti-JCV Antibody Status</th>
<th>Negative</th>
<th>Positive</th>
<th>Prior IS Use</th>
<th>Natalizumab Exposure</th>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1/1,000</td>
<td>95% CI 0.3–0.38</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Note: Low body mass has recently been identified as an additional potential risk factor for the development of PML.

IS = immunosuppressant; CI = confidence interval.

Conclusion
Where We are Now with Personalized Medicine in IBD

1) Risk stratification
   - yes = Clinical, serologic and genetic factors

2) Inform treatment selection
   - Just Beginning: clinical factors but not much for genetics, etc

3) Inform dosage
   - Evolving (TPMT for immunomods, Nothing yet for initial TNF dosage)

4) Prognostic testing
   - Evolving: Clinical factors, biomarkers, genetics (too early to use)

5) Treatment monitoring
   - Evolving: Endoscopy (yes), TNF levels (+/-), Biomarkers (+/-)

6) Improve or optimize clinical treatment pathways
   - Evolving: Drug and metabolite levels