PERSONALIZED MEDICINE: A NECESSITY OR AN OPPORTUNITY

The gastroenterology perspective

Massimo C Fantini MD, PhD
Dep of Systems Medicine
University of Rome «Tor Vergata»
Personalized medicine: a necessity or an opportunity

PERSONALIZED MEDICINE

Is this a relevant problem in IBD?
New therapeutic targets to hit!

OLD TARGETS

- Clinical response
- Steroid sparing
- Clinical remission

NEW TARGETS

- Mucosal healing
- Histological healing
- Tight control
- Deep remission
- Change of disease natural history
- Patient's reported outcomes (PRO)
Looking for new therapeutic strategies to reach ambitious targets

Step-up vs Top-down

...10 years later

- % of Pts with no Disease flare
- % of Pts with no Hospitalization
- % of Pts with no Surgery
- % of Pts with no Rescue treatment

D’Haens G et al Lancet 2008

Hoekman DR et al J Crohns Colitis 2018
Exploring new strategies I

TAXIT study

REACT trial
Exploring new strategies II

The CALM study

Primary Endpoint at 48 Weeks After Randomization

CDEIS < 4 AND NO DEEP ULCERATIONS

*CDAI>220 AND one of the following: steroid therapy > 4 weeks and best to taper per investigator assessment, intolerant/contraindication for steroid therapy, best interest of the patient per investigator assessment.

** CDAI > 300 for 2 consecutive visits 7 days apart or per investigator discretion (elevated CRP/FC, ulceration taken into consideration); moved to T2T group.

Colombel JF et al Lancet 2017
More drugs with different mode of action (MOA) to position

Phosphodiesterase-4-inhibitors
Apremilast

Anti-IL23p19
Risankuzumab
Brazikumab, MEDI2072
Guselkumab
Mirikizumab

Anti-Integrins
Vedolizumab

S1PR agonists
Ozanimod
Etrasimod

Anti-TNFs
Infliximab
Adalimumab
Golimumab
Certolizumab

JAKs inhibitors
Tofacitinib
Upadacitinib
Filgotinib
Peficitinib

Anti-MadCAM1
PF-00547659

Anti-IL12/IL23p40
Ustekinumab

1st line
(Its cheaper!!)

2st line

WE HAVE A PROBLEM.

Its cheaper!!

Shit! It cost a lot!....but it works and it's safe!!

Thanks GOD!

I deserved more!
Limited efficacy of the new drugs

**Ozanimod**

**TOUCHSTONE**

- Placebo (N=65)
- Ozanimod 0.5 mg (N=65)
- Ozanimod 1 mg (N=67)

**Ustekinumab**

**UNITI-1**: antiTNF failure

- Placebo 130 mg
- ~6 mg/kg

**UNITI-2**: Conv therapy failure

- Placebo 130 mg
- ~6 mg/kg

**Tofacitinib**

**OCTAVE 1**

- Placebo
- Tofacitinib 10 mg BID

**OCTAVE 2**

- Placebo
- Tofacitinib 10 mg BID
From a generalistic approach to personalized medicine

One-size-fits-all approach

Population of patients with given disease:
or or nearly all respond to different drugs

Proportion of patients who respond to drug

Patients receiving drug

Personalized medicine

Population of patients with given disease
Where are we?.........The present
How to approach the problem

Response to therapies can be seen as a biologic phenomenon governed by the same mechanisms determining diseases.
Pharmacogenomic to select the right drug

*Point mutations and allele variants to predict response to therapy and side effects*

**Response to steroids:**

- SNPs of **multidrug resistance protein 1 (MDR1)** coding gene are not association with steroid resistance in IBD while SNP at position -308 of the **TNFα** gene has been associated with an increased rate of both steroid resistance and requirment for surgery in pts with CD.  
  

- SNPs in the **Glucocorticoid Receptor (GCR)** gene have been shown to decrease GCR protein level resulting in a drop of steroid potency, but no assocation with IBD pts not responding to steroid has been demonstrated.

  Koyano S et al J Pharmacol Exp Ther 2003

**Response to methotrexate:**

In patients with IBD, the homozygous **MTHFR 1298C** variant was found to be associated with toxicity to Methotrexate (MTX) whereas the 677T variant was not.

  Herrlinger KR et al Pharmacogenet Genomics 2005
Carriage of the risk allele (HLA region) is associated with a 3-fold increased risk of renal injury after 5-ASA administration.

These data were not replicated in a validation cohort.

The high frequency of this SNP and the low frequency of the adverse event limits its clinical utility.

Genetic testing could not be recommended in guiding treatment choice or monitoring intervals.
Pharmacogenomic to avoid side effects: Thiopurines

Allele variants of the **Thiopurine S-Methyltransferase (TPMT)** affect the conversion rate of 6-MP to 6-MMP

A single point mutation leading to loss of catalytic activity in human thiopurine S-methyltransferase

Eugene Y. Krynetski, John D. Schuetz, Amy J. Galpin, Ching-Hon Pui, Mary V. Relling, and William E. Evans*

Pharmaceutical Department, St. Jude Children’s Research Hospital, and Center for Pediatric Pharmacokinetics and Therapeutics, Departments of Clinical Pharmacy and Pediatrics, University of Tennessee, Memphis, TN 38105

Communicated by Gertrude B. Elion, Burroughs Wellcome Co., Research Triangle Park, NC, November 1, 1994 (received for review October 6, 1994)

[TPMT]  

Thiopurine S-Methyltransferase Deficiency: Two Nucleotide Transitions Define the Most Prevalent Mutant Allele Associated with Loss of Catalytic Activity in Caucasians


Department of Pharmaceutical Sciences, St. Jude Children’s Research Hospital; and Center for Pediatric Pharmacokinetics and Therapeutics, Departments of Clinical Pharmacy, Pharmaceutics, and Pediatrics, University of Tennessee, Memphis

[Diagram of metabolic pathways involving Thiopurine S-Methyltransferase (TPMT) and its variants, Azathioprine, 6-MP, 6-MMP, 6-ThioU, 6-TIMP, 6-TGN, and HPRT.]

Proc. Natl. Acad. Sci. USA  

Medical Sciences


6-TGN

Mielosuppression
Pharmacogenomic to avoid side effects: the TOPIC trial

**Intervention**

- IBD patients initiating thiopurine therapy
  - TPMT*2, TPMT*3A, and TPMT*3C genotyping
    - WT: 100% dose
    - Heterozygous: 50% dose
    - Homozygous: 0-10% dose

**Control**

- Regular therapy
  - (2–2.5 mg/kg/day azathioprine or 1–1.5 mg/kg/day 6-MP)
  - TPMT genotyping

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Coenen MJH. Gastroenterology 2015
Pharmacogenomic to avoid side effects: TOPIC trial results

- Similar therapeutic efficacy
- 200 patients need to be genotyped to avoid 1 episode of hematologic ADR (7.4% vs 7.9%; i.e. 0.5% risk difference)
- Genetic testing should be considered as a cost-effective addition to hematological monitoring
- 1 patient of 11 with low enzyme activity TPMT variant developed leukopenia: no all cases of leukopenia can be explained by the known TPMT known variants!

Coenen MJH. Gastroenterology 2015
NUDT15 genetic variants are associated with thiopurine-related toxicity

Yang SK. Nat Genet 2014
Genomic predictors of response to anti-TNF therapy

**Single gene-association studies**

SNPs of *tnfrsf1a, tnfrsf1b, tnfip3* and *fasl* have been associated with response to anti-TNF therapy.

- Matsukura H et al Aliment Pharmacol Ther 2008
- Magdelaine-Beuzelin C et al Pharmacogenet Genomics J 2013
- Prieto-Pérez R et al Pharmacogenomics J 2013
- Prajapati R et al Pharmacogenomics 2011
- Steenholdt C et al Aliment Pharmacol Ther 2012

**FCGR3A-158V/V polymorphism**

A sub-analysis of the ACCENT I trial showed no association between FCGR3A variants and clinical response but showed a trend towards a greater decrease in C-reactive protein after IFX.

- Louis EJ et al Pharmacogenet Genomics 2006

**FCGR3A-158 polymorphism** influences the biological response to IFX in CD by affecting ADCC.

- Moroi R et al Immunogenetics 2013

No associations was found between response to IFX and genetic variants of *NOD2/CARD15, TNFα and TNFαR* genes

- Niess JH et al Dig Dis Sci 2012

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**The low frequency of single allele variants associated with IFX failure hamper their use in clinical practice**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Biologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNFRSF (TNF receptor superfamily 1A and 1B)</td>
<td>Infliximab</td>
</tr>
<tr>
<td>TNFAIP3 (TNFα-induced protein 3 gene)</td>
<td>Infliximab</td>
</tr>
<tr>
<td>FCGR3A (Fcγ receptor)</td>
<td>Infliximab</td>
</tr>
<tr>
<td>IL-23 (interleukin 23)</td>
<td>Infliximab</td>
</tr>
<tr>
<td>FASLG (Fas ligand)</td>
<td>Infliximab</td>
</tr>
<tr>
<td>IGHG1 (IgG1 heavy chain-coding gene)</td>
<td>Infliximab</td>
</tr>
<tr>
<td>NOD2 (nucleotide-binding oligodimerization domain-containing protein 2)</td>
<td>Infliximab</td>
</tr>
<tr>
<td>IL-10 (interleukin 10)</td>
<td>Adalimumab</td>
</tr>
</tbody>
</table>
Wide scale polymorphism association studies to predict response to IFX in CD

Illumina Immunochip-v1: genotyping platform containing 196 524 polymorphisms (718 small insertion deletions, 195 806 SNPs), with dense coverage of known major immune and inflammatory disease loci.

**Primary Non-Response**

Multivariable analysis of predictors of PNR to anti-TNF therapy in CD

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>1.01</td>
<td>0.97–1.06</td>
<td>0.65</td>
</tr>
<tr>
<td>Disease duration</td>
<td>1.04</td>
<td>1.00–1.09</td>
<td>0.073</td>
</tr>
<tr>
<td>Disease location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileal</td>
<td>1.00</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Colonic</td>
<td>1.05</td>
<td>0.28–4.00</td>
<td>0.94</td>
</tr>
<tr>
<td>Ileocolonic</td>
<td>0.30</td>
<td>0.08–1.18</td>
<td>0.85</td>
</tr>
<tr>
<td>History of smoking</td>
<td>2.12</td>
<td>0.75–6.34</td>
<td>0.15</td>
</tr>
<tr>
<td>GRS (per 1 unit increase)</td>
<td>2.65</td>
<td>1.95–3.61</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Durable Response**

Multivariable analysis of predictors of DR to anti-TNF therapy in CD

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ileal (reference)</td>
<td>1.00</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Colonic</td>
<td>1.89</td>
<td>0.60–5.97</td>
<td>0.28</td>
</tr>
<tr>
<td>Ileocolonic</td>
<td>1.50</td>
<td>0.63–3.57</td>
<td>0.36</td>
</tr>
<tr>
<td>Disease behavior</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory (reference)</td>
<td>1.00</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>Strictureing</td>
<td>1.15</td>
<td>0.45–2.92</td>
<td>0.77</td>
</tr>
<tr>
<td>Penetrating</td>
<td>1.39</td>
<td>0.58–3.34</td>
<td>0.46</td>
</tr>
<tr>
<td>Immunomodulator</td>
<td>1.90</td>
<td>0.94–3.83</td>
<td>0.07</td>
</tr>
<tr>
<td>Prior resection</td>
<td>0.38</td>
<td>0.18–0.83</td>
<td>0.02</td>
</tr>
<tr>
<td>History of smoking</td>
<td>0.73</td>
<td>0.38–1.51</td>
<td>0.39</td>
</tr>
<tr>
<td>GRS (per 1 unit increase)</td>
<td>1.60</td>
<td>1.41–1.83</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Anti-TNF, anti-tumor necrosis factor therapy; CD, Crohn’s disease; CI, confidence interval; GRS, genetic risk score; OR, odds ratio; PNR, primary non-response.

Genetic risk score (GRS) for PNR could not predict DR (p=0.71) and vice versa (p=0.72; p0.02), suggesting that the mechanisms underlining the genetic predisposition to PNR and DR might be distinct.

Barber GE et al Am J Gastroenterol 2016
Wide scale polymorphism association studies to predict response to IFX in UC

**Primary Non-Response**

Multivariable analysis of predictors of PNR to anti-TNF therapy in UC

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>0.980</td>
<td>0.940-1.019</td>
<td>0.319</td>
</tr>
<tr>
<td>Disease duration</td>
<td>0.959</td>
<td>0.887-1.026</td>
<td>0.249</td>
</tr>
<tr>
<td>Sex</td>
<td>1.055</td>
<td>0.383-2.888</td>
<td>0.916</td>
</tr>
<tr>
<td>Disease extent (pancolitis vs not)</td>
<td>0.680</td>
<td>0.236-1.935</td>
<td>0.467</td>
</tr>
<tr>
<td>Active tobacco use</td>
<td>0.135</td>
<td>0.002-2.316</td>
<td>0.784</td>
</tr>
<tr>
<td>Genetic risk score (per 1-unit increase)</td>
<td>3.419</td>
<td>2.294-5.562</td>
<td>3.87 x 10^{-1}</td>
</tr>
</tbody>
</table>

**Durable Response**

Multivariable analysis of predictors of DR to anti-TNF therapy in CD

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>0.978</td>
<td>0.952-1.005</td>
<td>0.116</td>
</tr>
<tr>
<td>Disease duration</td>
<td>0.997</td>
<td>0.956-1.039</td>
<td>0.873</td>
</tr>
<tr>
<td>Sex</td>
<td>1.132</td>
<td>0.603-2.125</td>
<td>0.700</td>
</tr>
<tr>
<td>Disease extent</td>
<td>1.195</td>
<td>0.636-2.244</td>
<td>0.580</td>
</tr>
<tr>
<td>Active tobacco use</td>
<td>1.817</td>
<td>0.428-7.712</td>
<td>0.418</td>
</tr>
<tr>
<td>Genetic risk score (per 1-unit increase)</td>
<td>2.799</td>
<td>2.060-3.803</td>
<td>4.74 x 10^{-2}</td>
</tr>
</tbody>
</table>

Predictors of PNR and DR were again mutually exclusive

No association between genetic risk score for DR and anti-IFX antibodies

Burke K et al Inflamm Bowel Dis 2018
From genes to their expression: the TRANSCRIPTOMICS
Gene-expression screening to predict response to IFX

CDc cohort

UC cohort

4 overlapping genes:
- IL13Rα2
- IL-11
- IL-6
- TNFAIP6

Arijs I et al Inflamm Bowel Dis 2010
Gene-expression screening to predict response to IFX

Gene expression profile

Predication of cell subsets variation

Adjusting samples for cell subset variation unmasks upregulated pathways in biopsies of anti-TNF non-responders.

Gaujoux R et al GUT 2018

AUC=94%
Gene expression profiling of CD8+ T cells predicts prognosis in patients with Crohn’s disease and ulcerative colitis

End point: treatment escalation

Lee JC. J Clin Invest 2011
The **Proteome** is defined as the full complement of proteins encoded by a genome.

- Allelic variants predisposing to disease are generally present in the general population thus limiting their use as diagnostic tool.
- The effect size of associations of genetic factors with clinical phenotypes is often small.
- Biological and functional output of cells is governed primarily by proteins.
Proteomics to predict response to IFX

Fifteen proteins corresponding to 240 spots were identified (more than one spot correspond to the same protein)

Gazouli M et al J Crohn Colitis 2013
Proteomic approach for the identification of disease markers

Targeted Analysis of Serum Proteins Encoded at Known Inflammatory Bowel Disease Risk Loci

Drobin K et al J Crohn Colitis 2018

IBD risk loci

Candicate proteins

Proteomic analysis

Serum markers identification

LOO-hit rate 0.83 p<0.0001

LOO-hit rate 0.76 p<0.0001

Sparse PLS (sPLS) discriminant analysis

LAC1

IL2RA

LNPEP
Profiling based on the drug specific mechanism of action

*The candidate target approach*
The expression of α4β7 and α4β1 integrin expression predict response to Vedolizumab

**Vedolizumab (VDZ) mechanism of action**

- **α4β1**
- **αEβ7**

**Peripheral blood**

**Intestinal mucosa**

- **MCS: 1**
- **MCS: 5**

*Fuchs F et al Front Immunol 2017*

*Fuchs F et al Front Immunol 2017*

*Fuchs F et al Front Immunol 2018*

*Fuchs F et al Front Immunol 2018*
The expression of $\alpha E$ integrin predicts response to Etrolizumab

Colonic biopsies

$\alpha E$ gene expression

$\alpha E$ protein expression

Paramsothy S et al Mucosal Immunol 2018

Vermeire S et al Lancet 2014
Novel imaging modalities for immune cell monitoring in the intestine

**Fluorescein-aided endomicroscopy**

**2005**

- Kiesslich R et al. Gastroenterology 2007

**2014**

- Neumann H et al. Gastroenterology 2010

- Ralf Kiesslich

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**Table:**

<table>
<thead>
<tr>
<th>Type</th>
<th>Peptide</th>
<th>Antibody</th>
<th>Activatable probe</th>
<th>Nanoparticle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages</td>
<td>Easy delivery to target structure</td>
<td>Low immunogenicity</td>
<td>Specific activation</td>
<td>Loading with multiple proteins for multivalent targeting</td>
</tr>
<tr>
<td></td>
<td>Low cost</td>
<td>High specificity</td>
<td>Optimized signal-to-noise ratio</td>
<td>Strong fluorescence</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Variable affinity</td>
<td>Potential immunogenicity</td>
<td>Internalization frequency required for activation</td>
<td>Potential toxicity of non-biodegradable core</td>
</tr>
</tbody>
</table>

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**Images:**

- A: Confocal imaging window
- B: Objective lens
- C: Light guide
- D: Biopsy channel
- E: Air/water nozzles
- F: Auxiliary water jet channel

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**References:**

- Kiesslich R et al. Gastroenterology 2007
- Neumann H et al. Gastroenterology 2010
Mucosal expression of mTNF as predictor of response to ADA

Enhanced confocal

Confocal

IF

Fluorescein (FITC)-labeled ADA

High-resolution endoscopy
Molecular imaging in vivo

High mTNF

Low mTNF

High-resolution endoscopy
Molecular imaging in vivo

Mean mTNF-positive cells

Clinical response (%)

No response
Response

All patients
Low mTNF
High mTNF

13/25
2/13
11/12

*
Vedolizumab *in vivo* mucosal staining as predictor of response

5 anti-TNF refractory CD patients with active mucosal inflammation underwent high definition endoscopy and evaluated for VDZ labeling by confocal endomicroscopy.

2 of the five Pts who showed pericryptal FITC-VDZ *in vivo* staining responded to VDZ therapy.
Predicting response to anti-(IL23)p19

Exposure to IL-23 is needed for the development of inflammatory Th17 cells producing high levels of IL-17, IL-22, IFNγ, and TNF.

In the absence of IL-23, Th17 cells differentiate into non-pathogenic IL-17+ and IL-10+ cells.

Week 8

Primary endpoint: Clinical remission (CDAI<150) or clinical response (CR-100)

Difference: 32.4% of the patients responded to MEDI2070.

Clinical Response

Clinical Remission

- IL22 serum level decreases after exposure to MEDI2070.
- Pretreatment serum IL22 above 15.6 pg/ml is associated with higher rate of clinical response and remission.
Combining different Mode of Action (MOA)
Combining different Mode of Action (MOA)

Gene expression in intestinal mucosa at week 0 and week 14 after VDZ therapy

Might these patients benefit from an anti-integrin plus an anti-TNF combined therapy?

Upstream regulators associated with Non-Response

**Baseline characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Remitters</th>
<th>Non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>2/3</td>
<td>2/3</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59 ± 16</td>
<td>67 ± 16</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>3 ± 0.5</td>
<td>7 ± 4.2</td>
</tr>
<tr>
<td>Prior anti-TNF treatment</td>
<td>2/3</td>
<td>1/1</td>
</tr>
<tr>
<td>Concomitant medication</td>
<td>1/1</td>
<td>1/1</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>2/3</td>
<td>1/1</td>
</tr>
<tr>
<td>Immunosuppressants only</td>
<td>2/3</td>
<td>1/1</td>
</tr>
<tr>
<td>No glucocorticoids and immunosuppressants</td>
<td>2/1</td>
<td>1/1</td>
</tr>
</tbody>
</table>

**Upstream regulators**

<table>
<thead>
<tr>
<th>Upstream regulator</th>
<th>p-value of overlap</th>
<th>Activation Z-Score</th>
<th>Predicated Activation</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF</td>
<td>4.81E-20</td>
<td>4.374</td>
<td>Activated</td>
</tr>
<tr>
<td>TGFB1</td>
<td>1.43E-17</td>
<td>4.357</td>
<td>Activated</td>
</tr>
</tbody>
</table>

Rath T et al Front Immunol 2018
Combining different MOA

Combining Anti-TNF-α and Vedolizumab in the Treatment of Inflammatory Bowel Disease: A Case Series

Lydia C.T. Buer MD, Marte L. Haavik MD, PhD, David J. Warren MD, Asle W. Medhus MD, PhD and Bjørn A. Moum MD, PhD

NO SAFETY ISSUES WERE REPORTED

Safety, efficacy and pharmacokinetics of vedolizumab in patients with simultaneous exposure to an anti-tumour necrosis factor

S. Ben-Horin¹² | B. Ungar¹ | U. Kopylov¹ | A. Lahat¹ | M. Yavzori¹ | E. Fudim¹ | O. Picard¹ | Y. Peled³ | R. Eliakim¹ | E. Del Tesesco⁴ | S. Paul³

Ben-Horin S et al Aliment Pharmacol Ther 2018

Long-term Combination Therapy with Anti-TNF plus Vedolizumab Induces and Maintains Remission in Therapy-refractory Ulcerative Colitis

Sarah Fischer, MD¹, Timo Rath, MD¹, Carol-Immanuel Geppert, MD², Bernhard Manger, MD³, Georg Schett, MD³, Markus E. Neurath, MD¹ and Raja Atreya, MD¹

Fischer S et al An J Gastroentorol 2017
Microbiota and personalized medicine: does it play a role?
Role of microbiome in anti PD-1 response
Role of microbiome in predicting response to VDZ

VedoNet (a neural network algorithm) incorporates microbiome and clinical data.

VedoNet containing 40 microbiome variables provided the highest classifying power (AUC=0.872), >80% true positive discovery rate and <25% false negative discovery rate.

Ananthakrishnan AN et al. Cell Host & Microbe 2017
The long way to success

The infancy of personalized medicine in IBD

Signals from the future

Thanks for your attention