Transition of microbiota analysis from research tool to clinical utility

6TH MICROBIOME R&D & BUSINESS COLLABORATION FORUM
Rotterdam, The Netherlands

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Genetic Analysis AS

- Genetic Analysis is a Norwegian diagnostic company focused on developing the GA-map® technology for mapping microbiota.

- GA-map® is based on many years of research at the Norwegian University of Life Science by Prof. Knut Rudi and co-workers.

- Currently 20 employees, and growing. In addition with a large network of key opinion leaders and consultants.

- Products on the market in EU and US.

- Complete in-house value chain, combined with strong global partnerships.

BIO-RAD  Luminex®  BIOHIT HealthCare
Business model

Partners

• Sales of reagent kits to major laboratories
• Marketed through international partners, global and regional

In house laboratory

• Sales of lab services to the research and clinical market.
• Generating value through the use of our extensive database linking microbiota profiles to clinical outcomes
The GA-map® Dysbiosis Test Lx is intended to be used as a gut microbiota DNA analysis tool to identify and characterize dysbiosis.

- A **standardized, documented and CE marked faecal IVD test** to easily profile the microbiome
- Simple to perform in any molecular laboratory
- Fast and easy to use and interpret
GA-map® platform

- Two peer-reviewed publications on methodology
- Several independent publications on use of method
- Six patent families

Reagent kit
- GA-map® Dysbiosis Test (CE-marked)
- ISO 13485 certified production facility

GA-map® platform

gDNA extraction

Probe labelling

Detection
Two types of probes:
1) Specific probes – selected based on literature and KOLs feedback
2) Dysbiosis group probes – selected based on ability to separate normobiosis from dysbiosis

Example of 7 group probes represented by different colors. Each object represents one bacterial clone. The objects are clustered based on 16S rRNA gene phylogeny.
Technical performance

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeatability</td>
<td>2.6% CV, DI = 3.2 ± 0.04</td>
</tr>
<tr>
<td>Reproducibility</td>
<td>4.2% CV, DI = 3.2 ± 0.07</td>
</tr>
</tbody>
</table>

- Actinobacteria
- Bacteroidetes
- Firmicutes/Clostridia
- Firmicutes/Bacilli
- Firmicutes/Erysipelo-trichia & Negativicutes
- Proteobacteria
- Tenericutes
- Verrucomicrobia (A. muciniphila)
Based on a Normal Reference Range

Normobiotic reference based on approximately 300 samples from:
- Norway
- Sweden
- Denmark
- Germany
- Italy
- Spain

Clinical validation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IBD (%)</th>
<th>IBS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysbiotic</td>
<td>73%</td>
<td>69%</td>
</tr>
<tr>
<td>Normobiotic</td>
<td>27%</td>
<td>31%</td>
</tr>
</tbody>
</table>

GA-map® shows good separation of normal from diseased

- T2-Qres plot showing the cut-off line between a pre-defined normobiotic and dysbiotic state
- One point is one sample, and the points are coloured according to donor
Result output
Result output – for clinical research
Strong scientific foundation

Extensive network

Expanding scientific and clinical recognition
Prediction of responsiveness to low FODMAP diet

Motivation:
Not all IBS patients respond to the low FODMAP diet
Low FODMAP diet*

- Restricted intake of foods containing FODMAPs.
- Avoid food rich in fructans and galactooligosaccharides (wheat, barley and rye, onion and certain legumes)
- Avoid lactose-containing products and foods with fructose in excess of glucose (apples, pears, asparagus, watermelon and honey)
- Avoid food items rich in mannitol, maltitol, sorbitol and xylitol (peaches, apricots and artificially sweetened products)

Traditional IBS diet*

- Portion control and frequency. Eat three meals and three snacks during the day and to do so in a relaxed manner, chewing thoroughly and to a comfortable degree of fullness.
- Fibres were advised to be eaten distributed evenly over the day
- Reduce spicy and fatty foods, alcohol, coffee, onions, cabbage and beans.
- Avoid soft drinks, carbonated beverages and sweeteners that end with –ol (frequently found in chewing gums)

Prediction of responsiveness to low FODMAP diet

Figure 1  CONSORT flow diagram. Flow chart depicting patient numbers during the different phases of the study. FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides and polyols.
Prediction of responsiveness to low FODMAP diet

Orthogonal partial least squares discriminant analysis (OPLS-DA) scatter plots
R² – goodness of fit, R²>0.5 is acceptable for biological data
Q² – predictive robustness, Q²>0.4 is acceptable for biological data

Conclusion
Low FODMAP responders could be discriminated from non-responders before the intervention based on faecal bacterial profiles.
Motivation
Anti-tumour necrosis factor [TNF] therapy is used in patients with ulcerative colitis [UC], but not all patients respond to treatment
Anti-TNF Therapy response in UC patients

Conclusion
Anti-TNF therapy responders and non-responders display distinctly separate gut microbiota profile before treatment start.

Stool samples for microbiota analysis were obtained from 7 patients at baseline prior to 14 weeks intervention.

Treatment response was defined as a decrease in total Mayo score with ≥ 3 compared with baseline. Non-responders showed no improvement of the Mayo score.

OPLS-DA of Anti-TNF therapy responders and non-responders differ at baseline with respect to their fecal microbiota composition. Fecal samples were obtained at baseline [responders \( n = 4 \) and non-responders \( n = 3 \)] and analysed by the GA-map™ Dysbiosis Test. OPLS-DA scatter plot [A]
Disease course in IBD (UC) patients

Motivation
The clinical disease course of ulcerative colitis (UC) varies substantially between individuals and can currently not be reliably predicted.
Disease course in IBD (UC) patients

Stool samples were obtained from 18 therapy-naive newly diagnosed patients with UC.

Patients were defined to have mild or moderate/severe disease course assessed by disease activity during the 3 years follow-up.

Conclusion:
In patients with newly diagnosed UC, fecal microbiota composition are linked to disease course.
Thank you!

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