Personalised Nutrition: Therapeutic Potential & Regulatory Challenges

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Personalised nutrition for better health - targeting the microbiome
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What next?

- Nutrition & ‘Healthy Consumer-Patient’ Continuum
- Personalised Nutrition
  - Untapped, targeted potential for health and disease management
- Gut Microbiome
  - Complex, not a fad, a partner re: healthcare solutions
- Regulatory Considerations
  - Innovation & investment ‘friendly’, with the consumer & patient in mind
- Future of Personalised Nutrition
  - Already here // still plenty to do & more future to come
How much can Nutrition do for Health & Disease? To what extent can we personalise nutrition? is the regulatory framework fit-for-purpose?

Challenges & Paradigms Shifts in Health & Healthcare

- Societal issues: aging population / overweight / rare & chronic diseases & malnutrition / costs

Health & Therapeutic Solution Potential ➔ encompasses Microbiome, Nutrition & Diagnostics

- New science (incl. microbiome) & technology («omics», IVD, apps …) ➔ faster; increased complexity
- Nutrition potential for health / as disease prevention / disease-related malnutrition / dietary disease management/ even (symptomatic) «therapy»
- Personalisation («targeted») ➔ none of us is in the «average» // yet no «over-personalization» either

Ways Forward – Balanced Evidence & Multistakeholder Dialogue ➔ Efficient Healthcare «Logistics»

- Regulatory Framework interpreted/enforced ‘fit for purpose’ ➔ ROI; acceptable «uncertainty»
  1. Product development: reduce unnecessary technological barriers ➔
     Nutrients: quality/safety, not disease based (CMC: analytics, GMP, stability, …; global harmonization)
  2. Broad based evidence (RCTs, RWE, «citizen research»…), post-marketing shift when possible
  3. Balance precautionary approach vs. innovation benefits

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Healthy Consumer ⇔ Patient Continuum

- **I.V. Nutrition**
  - FSMP (Tube Feeds)
    - «Dietary Disease Management ...»
    - Food for Special Medical Purposes (FSMP) (ONS)
- **Diet**
  - Genes
  - Lifestyle

- **Health - Disease**
- **Disease - Health**

- **General Food**
  - (incl. Food Supplements; «Functional Food», Health Claims)

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PERSONALISED NUTRITION
Who benefits from Targeted/Personalised Nutrition?

- Physiological needs of an individual may differ from group needs
- Personalisation requires to meet measured individual nutrient needs
- Personalised nutrition with a demonstrated potential to improve health, wellbeing, patient care.
Personalisation everywhere?

- Personalised & customised approaches are big trends, a potential “tool” for increased customer loyalty & engagement

- Personalised (or “targeted”) Nutrition: Reality or Fiction?
  - Selected micronutrients adjusted per individual, eating habits, differentiation by gender, age/life situation (pregnancy, kids, 50+), gut microbiome/ genome/ biomarker analysis-based nutrient cocktails
  - Healthcare professionals adapt nutrition care to their patient needs

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The Future for Medical Foods *(S.Bigelow, 2013)*

Genomic scientific findings on genetic polymorphisms related to disposition of dietary components/nutrients have been shown to have an effect on the risk, progression and clinical outcome for many diseases. For each of the diseases listed below, medical foods can be developed to address the biological effects of each nutrient-related human polymorphism.

- **Vitamin D receptor.** Vitamin D can be viewed as a master hormone that exerts its metabolic action via a cellular receptor located in most human tissues. While most dietary sources of vitamin D may be found in dairy products, certain populations may not obtain adequate vitamin D to meet their nutritional requirements (Norman and Henry 2012). Its classical nutrition-related actions involve calcium mobilization, whereas more recent findings involve skeletal muscle and immune system development and maintenance (Girgis et al. 2013, Prietl et al. 2013). Human polymorphisms of the vitamin D receptor affect the ability of vitamin D to exert its biological action, which has been found to be associated with the risk, progression and/or clinical outcome of several diseases including diabetes, rheumatoid arthritis, polycystic ovarian syndrome (PCOS), and ovarian and oral cavity cancers (Gezen-Ak et al. 2012, Hitchon et al. 2012, Larcombe et al. 2012, Levin et al. 2012, Milner 2012, Yokoyama et al. 2012).

- **Folate MTHFR.** Two relatively common human polymorphisms related to dietary folate (vitamin B9) disposition have been characterized for the methylene-tetrahydrofolate reductase (MTHFR) and methionine synthase reductase (MFRR) genes, designated as C677T and A2756G, respectively, which can result in elevated blood levels of homocysteine, a known risk factor for hypertension and vascular disease (Bailey and Caudill 2012). Associations have been characterized between human MTHFR polymorphisms and the risk, progression and/or clinical outcomes for numerous diseases including depression, mild cognitive impairment, heart disease including myocardial infarctions, and spina bifida (Ma et al. 1996, Morita et al. 1997, Schwartz et al. 1997, Lucock et al. 2000, Yates and Lucock 2003, Milner 2012, Smith et al. 2010, Wilson et al. 2013).

- **Dietary fatty acid utilization.** Human polymorphisms affecting energy utilization of dietary polyunsaturated and saturated fatty acids include the genes that code for CALPAIN-10 (Ca-mediated protease), PPAR receptor (peroxisome proliferator-activated receptor), INK4 (a tumor suppressor), lipoprotein lipase, fatty acid desaturase-1 and -2, and endothelial nitric oxide synthase. These human polymorphisms are associated with the progression to metabolic syndrome (a condition that often leads to diabetes and obesity), elevated blood cholesterol levels and asthma (Bendlova et al. 2008, Perez-Rodriguez et al. 2011, Joffe et al. 2012, López-Alarcón et al. 2012, Thompson et al. 2012, Ahmed et al. 2013, Gillingham et al. 2013).

- **Human microbiome.** The microbiome is defined as the total community of microbes that inhabit the human gastrointestinal (GI) tract, of which the microbial community is responsible for aiding the digestive process. The human microbiome has been characterized by the NIH Human Microbiome Consortium in 2012 (Huttenhower et al. 2012). The genetic disposition of human microbiome has been found to be associated with the risk, progression and/or clinical outcome of many diseases including obesity, type 1 diabetes, inflammatory bowel disease, rheumatoid arthritis, muscular dystrophy, multiple sclerosis, fibromyalgia and some cancers (Aomatsu et al. 2012, Clemens 2012, Huttenhower et al. 2012). There is the potential that genetic variations in the members of the microbiome or its human host may have an effect on their interactions in respect to human disease state. Dietary probiotics in the form of cultured dairy products and prebiotic supplements provide positive effects the nature and activity of the human microbiome in respect to digestive process, immunity and perhaps obesity.
Some companies are on the market or are fundraising right now.

Personalisation starts with Measuring.
Complexity of Personalising Micronutrients?

Cofactor – Protein Interactions

Cofactor interactions

Nestedness index

0
More

Mg
Vit A
Fe
Mg
Vit A
Fe

Enzymes

Ez 1
Ez 2
Ez 3

Diabetes
Obesity

Databases
EBI CoFactor
UniProt
Expasy
Metal Macle

OMIM
GWAS

Diseases
Science Approach towards Targeted Nutrition

- **Nutrition & Health Interactions**
  - Socio-economics
  - Lifestyle
  - Dietary habits
  - Environmental exposures
  - Health status
  - Medical conditions (drugs)
  - Age, gender
  - Genetics (incl. microbiota)

- **Metabolic Phenotypes & Biomarkers**

- **Dietary assessment & Nutritional status**

- **System Nutrient Profiling**
  - Amino acids, fatty acids, micronutrients

- **Personalized Nutrient Requirements**
  - Proven causality between nutrient deficiency with health and disease status

- **Targeted Nutrition**
  - IVD & Nutrition
  - Nutritional efficacy monitoring

- **Health Maintenance**
  - Healthy aging & Preventive medicine

- **Medical Food / FSMPs**
  - Dietary management of disease specific nutrient requirements

**Science Approach towards Targeted Nutrition**

- **Nutrition Molecular Epidemiology**
  - Risk factors & prevalence of nutrition-related disease

- **Personalized Nutrition Healthcare**
  - Nutritional patient stratification

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### Nutrition as Disease-related Malnutrition Management

<table>
<thead>
<tr>
<th>Disease / Medical Condition</th>
<th>Clinical Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short Bowel Syndrome; Stroke</td>
<td>Lifesaving Intervention</td>
</tr>
<tr>
<td>COPD</td>
<td>Increased Ventilatory Capacity</td>
</tr>
<tr>
<td>Surgical Patients</td>
<td>Less Complications</td>
</tr>
<tr>
<td>Older patients</td>
<td>More Active, Better quality of Life, Decreased Mortality</td>
</tr>
</tbody>
</table>

### Nutrition as Disease Management («Therapy»)

<table>
<thead>
<tr>
<th>Disease / Medical Condition</th>
<th>Clinical Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crohn’s Disease</td>
<td>Induction of Remission</td>
</tr>
<tr>
<td>Cow’s Milk Allergy</td>
<td>Reduced Symptoms, Catch-up Growth</td>
</tr>
<tr>
<td>IEMs: PKU, MSUD, FAOD, GSD</td>
<td>Normal Growth &amp; Development</td>
</tr>
<tr>
<td>Intractable Epilepsy</td>
<td>Less Seizures; Normal Growth &amp; Development</td>
</tr>
</tbody>
</table>

The PKU story
For Inborn Errors of Metabolism (IEM)

Disease / patient need
- Inborn error of metabolism

Two siblings with PKU. Only the sister had been diagnosed and treated since birth

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Nutritional solution
- Nutritional therapy is the gold standard
- Vitaflo’s portfolio offers “diet for life” solutions
Intractable Epilepsy & the Value of formulated Ketogenic Diet Products* as Nutritional Therapy

Ketogenic Diet: The Basics

- Traditionally started gradually in the hospital over 2-3 days, after a 24 hour fast
  - Families educated daily
- Ratio (fat: carbs and protein)
  - 4:1 more strict
  - 3:1 for infants and adolescents
- Calories and fluids measured
- Solid foods and/or formula

Case Study: 17 year old female

- 1 week: No change in seizures, likes the fat foods but misses rice and pasta
- 1 month: Seizures reduced 90%! (but not driving...)

*Adapted from Prof. Eric Kossoff (RAPS Convergence, Sept 2017; Regulatory Focus journal, Oct. 2017)
Personalized Nutrition – A Gut Feeling

- Nutrition is crucial in health & disease management
  - Microbiome part of the solution
    - Nutrition is safe, physiologic, nourishes (!), can be a sole or additional solution to disease prevention, related malnutrition, dietary disease management, symptomatic disease therapy
    - Use untapped nutrition potential in an adapted, «modern» way*

- Regulatory framework tested by a real world scenario
  - Aging society, NCDs, healthcare costs, patient empowerment
  - Increased complexity: blurring lines between established food, drug, devices categories (FSMP, nutritional therapy, ‘apps’ ...)

• We must interpret/enforce regulations in an innovation & consumer/patient friendly way
  - Eliminate unnecessary technological hurdles (CMC; global)
  - Opportunities will be lost if no investment (ROI)*
  - Accept a ‘certain’ uncertainty (IT/Big data ...)

*Europe invests 97% in treatment, i.e. drugs & devices, 3% in prevention

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Innovation Engine – Critical to long-term Success

Partnering in GI Health

Networking with Academia

Partnering in Food Allergy

Partnering in Brain Health / Devices

Leveraging Venture Funds
A broad Role of Microbiome

Microbiome

- Oncology
  - Which particular cancers?
  - Chemo-radiotherapy

- CNS
  - Alzheimer, Parkinsons, others?

- GI
  - Gut Health, IBD, NFLD/NASH, Celiac Disease

- Derm
  - Psoriasis, Eczema, Acne, others?

- Infectious Disease
  - cDiff, others?
**Critical Path to Microbiome Modulation & Deployment in Multiple Indications**

*We can influence by…*  

<table>
<thead>
<tr>
<th>#</th>
<th>Task</th>
<th>Description</th>
<th>Using Differentiating Technologies</th>
</tr>
</thead>
</table>
| 1 | Diagnosing the microbiome | *How do we measure microbiota status in health & disease* | - Metagenomic ‘footprint’ of microbiota in health & disease  
- MetaHIT database (10 million bacterial genes)  
- De-risking CTs & development plans across indication areas |
| 2 | Replacing the Microbiome | *Restore a healthy microbiome* | - Bacterial cultivation & spore technology  
- Access to unique bioinformatic tools to generate new Ecobiotics: defined live bacterial engraftments |
| 3 | Feed the healthy microbiome | *Develop nutrients/molecules enhancing healthy microbiome* | - Developing nutrients/natural derived ingredients to modulate the microbiome (eg AAs, oligosaccharides, prebiotics, probiotics, lipids) |
| 4 | Kill the unhealthy microbiome | *Develop targeted solutions & prevent colonisation of pathogens* | - Nutrients or bacteria derived small molecules  
- Antagonise attachment / metabolic activity of non-beneficial bacteria |
| 5 | Use bacteria as delivery system | *Select & develop live bacteria as benefit delivery system* | - Unique delivery system (*eg. L. lactis*) for biologics & small molecules  
- Specific probiotics |

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Mastering the Microbiome… a New Health Frontier

- Anxiety
- Gastrointestinal Health
- Allergy, Obesity/Diabetes

Probiotics (BL 999) in Anxiety Management

Ecobiotics in the Microbiome

IBD  IBS
Crohn’s Disease
Ulcerative Colitis

Targeted Bacteria in Inflammation & Immunity-related Diseases

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Brussels 2017

IBD = Inflammatory Bowel Disease  IBS = Irritable Bowel Syndrome
Building Leadership in the Microbiome Field
Strategic investment and partnership with Seres

- Microbiome is a fast developing and new health frontier
- Exclusive agreement outside North America for Seres’ novel class of microbiome therapeutics
  - Clostridium difficile infections (CDI): SER-109, SER-262
  - Inflammatory bowel disease (IBD): SER-287, SER-301
- Complementary relationship to support future commercialization
- Seres: leader in the microbiome space with most advanced pipeline
- Nestlé Health Science: global footprint; strong category expertise in Acute Care & GI; opportunities for co-therapeutic approaches (Dx-Rx-Nx)
Gut Microbiome – Healthcare Potential
- Need to address basic development issues

Baseline Thoughts
- Patient or Microbiome? Symbiosis? Dysbiosis? «Healthy» Microbiome?
- Health & disease impact? define gaps

Transformative Science
- Dynamics of gut microbiome: mechanism of action, physiologically relevant endpoints, individual metabolism, e.g. nutrition phenotyping to quantify “DNR” (nutritional needs)

Quality, Safety, Efficacy
- Regulate what: Safety 1st (pathogen free)?
- Large scale production; batch consistency?
- Classify non-gut systemic microbiome effect

Gold Standard, Precedent, Analogy, Learning?
- Pro-, Pre-, Symbiotics / Antibiotics
- 1st 1000 days, functional variability
- Access: patients’, payers’ views?

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Microbiome - A Gut Feeling

- Microbiome is a complex adaptive system ➔ not a fad, a ‘quasi organ’ not to be viewed in isolation ➔ a variable in every aspect of host health ➔ the diet has a strong effect on gut microbial composition

- Blurred lines ➔ view in context, good vs. bad over-simplified ➔ only few strains seem important, 1 bacteria present in a certain host environment & a genetic susceptibility can influence health or disease

- Don’t oversell ➔ targeting the microbiome will not affect or cure all GI diseases
REGULATORY CONSIDERATIONS
«Modify* the Gut Microbiome for the ...

<table>
<thead>
<tr>
<th>Biological Drug</th>
<th>• ... prevention, treatment, cure of IBD / ... C.diff. »</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSMP/Medical Food (tube feeds or ONS)</td>
<td>• ... dietary management of IBD»</td>
</tr>
<tr>
<td>Food Health Claim (EU NHCR Art.14; US)</td>
<td>• ... risk (factor) reduction of IBD» (~«Disease Prevention»)</td>
</tr>
<tr>
<td>Food Health, S/F Claim (EU NHCR Art.13; US S/F)</td>
<td>• ... normal bowel function/ increase in faecal bulk»</td>
</tr>
</tbody>
</table>

* incl. e.g. FMT from healthy to sick individuals

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Regulatory framework for personalised nutrition in health & disease

- Current rules & advice based on average requirements & limits (EAR, DRI, UL, …), health, age or gender related ➔ personal needs, safety, claims may deviate ➔ healthy people (homeostasis) vs. disease

- Measuring tests & devices (e.g. IVD, LDTs, apps, wearables) must be validated to ascertain quality & reliable nutritional advice
**POLICY FORUM**

**SCIENCE AND REGULATION**

**Food and microbiota in the FDA regulatory framework**

How should microbiota-directed foods be regulated?

By Jonathan M. Griffin,* Michael J. Murray,** Michael Kohn,*** Jeffrey L. Gordon†

- Understanding of how our gastrointestinal microbiota regulate our health has expanded rapidly over the past several decades due to the advances in our understanding of the human microbiome. The gut microbiota has been shown to play a critical role in the development and maintenance of health and disease, and its dysregulation is associated with various conditions, including obesity, diabetes, inflammatory bowel disease, and other chronic diseases.

- The FDA has recognized the importance of the gut microbiota in health and disease, and has taken steps to develop regulatory frameworks to ensure the safety and efficacy of products that may affect the gut microbiota. A key issue is how to define and regulate such products.

- The FDA has introduced the concept of microbial functional foods (MFFs), which are defined as foods that have beneficial effects on health, and to regulate these products based on their potential to modulate the gut microbiota. However, defining and categorizing MFFs is challenging, as the effects of these products on the gut microbiota can vary widely, and the regulatory framework needs to balance the need for safety and efficacy with the need for innovation and flexibility.

- The FDA has established a working group to develop a regulatory framework for MFFs, and has published guidance documents to provide industry with information about the regulatory process and to help ensure that products are safe and effective. However, there is still a need for further research and development to better understand the effects of MFFs on the gut microbiota and to develop effective regulatory strategies.

**POTENTIAL CLASSIFICATIONS**

If an MFF is designed primarily to provide dietary fiber, a key issue is whether such products should be classified as a "functional" food. The FDA (U.S. Food and Drug Administration) has developed criteria for classifying foods as "functional" foods, and these criteria are based on the product's claimed health benefits and the evidence supporting these claims. However, the criteria for classifying products as "functional" foods can be complex, and there is a need for further research and development to better understand the effects of these products on the gut microbiota.

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**OECD (2017)**

**THE MICROBIOME, DIET AND HEALTH**

**TOWARDS A SCIENCE AND INNOVATION AGENDA**

**OECD SCIENCE, TECHNOLOGY AND INNOVATION POLICY PAPERS**

September 2017 No. 43

- The OECD is a forum for governments to work together to address shared concerns, tackle collective challenges, and create policies that deliver sustainable, efficient, and equitable results. The OECD has been at the forefront of scientific and technological innovation, and has been instrumental in shaping the global economy.

- The OECD has published a series of policy papers on the topic of the microbiome, diet, and health, which cover a range of issues, including the role of the microbiome in health and disease, the impact of dietary interventions on the microbiome, and the development of new technologies and products to support healthy eating and lifestyle choices.

- The OECD has also been active in promoting research and innovation in the field of the microbiome, diet, and health, and has supported initiatives to increase collaboration and knowledge sharing among researchers, policymakers, and practitioners.

- The OECD has been instrumental in developing policies and guidelines to support healthy eating and lifestyle choices, and has been active in promoting the integration of science and technology into public policy making.
References


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Ruthsatz M & Morck T, “Medical Food/Food for Special Medical Purposes: Global Regulatory Challenges and Opportunities”, Regulatory Focus, August 2016, RAPS


Schneeman BO (2017) Guest Editorial: Does Nutrition Have a Role in Disease Management? Regulatory Focus, October 2017, Regulatory Affairs Professionals Society (RAPS)

US Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease (SKumanyika & MP Oria, Eds.; NASEM …) (2017 pre-publication)
Increase Flexibility between Food & Drug Frames for Innovative Solution-Focused Dietary Disease Management

**Regulatory Design & Gaps**

Geographical Destination & Food or Drug «Intended use»: Design @ very start of development:

‘ Changing horses midstream? ’ ➔

~Start from scratch to meet compliance requirements

«Disruptive innovations» in dietary disease management:
Difficult to meet all category requirements when switching frames

- Nutrition vs. drug CMC (monographs; analytics; G(X)P; ...); clinical (disease) endpoints
- Nutrient «cocktails» not adapted to (mono-)dose-response drug requirements
- Health vs. disease dosage continuum: nutritional ➔ pharmacologic ➔ toxic
- Patho-mechanism of action («DNR») proof for medical food, yet not drugs
Why citizen-driven research strategies

20th century
- Cure
- Religion of the Average
- “We take good care of you”
- You are either sick or healthy
- Reductionist
- Knowledge imperative
- Certainty / uncertainty

21st century
- Prevention
- Uniqueness of the individual
- “I take good care of myself”
- Focus on resilience
- Appreciative of complexity
- Learning imperative
- Curiosity

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Personalised Nutrition’s Future?

- Science is crucial to develop effective regulation & policy, but may not provide answers to all aspects

- Incentives for the development of nutrition solutions is of public interest ➔ Accelerate current thinking & approaches ➔ Prepare for unexpected “disruptive”, cost-efficient solutions (“omics”, IT/Big data, diagnostics)

- Nutrition approach still largely driven by averaging needs (EAR, DRI, UL …). Personalisation is a general, non-stoppable trend. Personalised Nutrition is already amongst us. Both approaches can co-exist together.

- No «over-personalising» (homeostasis vs. disease)

- Demonstrated, perceived & sustained benefit for consumers, patients, health care systems is key ➔ Need for a continued multi-stakeholder dialogue.

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Personalised Nutrition - Making a Difference

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