Nutrigenomics: Understanding Nutrition from Table to Gene

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Nutrigenomics: Understanding Nutrition from Table to Gene

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Definitions

- **Nutrigenomics**: The study of the effects of specific nutrients on gene expression
- **Nutrigenetics**: The study of variations in dietary responses due to genetic predispositions
- **Phenotype**: The observable characteristics of an individual
- **Genotype**: The entire set of genes in an individual
- **Polymorphism**: inter-individual, heritable, differences in DNA sequence
History of Nutrigenomics

1945: First reports describing an interaction between genes (strains) and diet
1953: Watson & Crick and their double helix
1975: The term nutrigenomics appeared
1980s: Technical capacity to interrogate specific genes and identify variants
1997: Nutrigenomic companies first appear
2003: Human genome project completed
2005-2015: ‘-Omics’ technologies widely accessible; GWAS studies
Nutrigenomics: Potential Applications

- Provides proof of principle for product differentiation
- Estate maintenance for health claims and patents
- Move toward Personalized Nutrition
Personalized Nutrition: The 4 P’s

- The 4P paradigm empowers consumers looking to proactively manage their health or to physicians whose clinical assessment of a patient may suggest that more aggressive dietary management is in order.
  - Predictive
  - Preemptive
  - Personal
  - Participatory
Achieving Personalized Nutrition: The 4 Ps

- The Approach
- Nutrigenomic Toolbox
  - Transcriptomic Profiling
  - Transcription factor profiling
  - Lipidomics
  - Toxicogenomics
  - Genotyping
- The Future
The Approach

Example: New Product Development

- Leveraging nutrigenomics as part of the product life-cycle management process: a novel omega-3 fatty acid-enriched oil (NewHarvest™ (NH), DuPont).
- Similar approaches have been used to examine the beneficial effects of pistachios, walnuts, peanuts, soy protein, spices.*

*Publication list available upon request (jackvh@psu.edu)
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Transcriptomics

- Measurement of mRNA or miRNA
- Individual transcripts can be examined and quantified using RT-PCR
  - From tissue samples as part of clinical study
  - Following treatment of cells in culture with product of interest
  - Sensitive and accurate tools (can specifically measure expression in a single cell)
Transcriptomics

- Comprehensive analysis can be performed with microarrays or sequencing
  - Sensitive and validated biomarkers
  - Mechanistic information
  - Product differentiation
Transcriptomics

B.

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<th>Function</th>
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<th>#</th>
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- The Future
Transcription factor profiling

- Measurement of activity of a transcription factor that is affected by a complex mixture or individual compound
- Utilizes genetically-altered cells or *in vitro* systems
- Provides mechanistic information that can be used for product differentiation or strengthening health claims
- Can be used for bioactive molecular discovery
Transcription factor profiling

- Nuclear receptors (NRs) are drug targets as well as important nutrient sensors.

- High-throughput sensitive assays utilizing Luciferase as a reporter gene have been developed for many transcription factors including NRs.
Transcription factor profiling

A.

- PPARα
- PPARγ
- RXRβ
- ERα
- ERβ
- LXRα
- LXRβ
- VDR
- TRα
- FXR
- CAR3
- RARγ
- PPARβ

B.

![Graph showing relative luciferase activity vs. log(dose) for different receptors.]

C.

<table>
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<th>Curve Fitting</th>
<th>PPARα</th>
<th>PPARβ/δ</th>
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<th>RXRα</th>
<th>FXR</th>
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<td>2.2</td>
<td>9.9</td>
<td>2.0</td>
<td>6.9</td>
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Achieving Personalized Nutrition: The 4 Ps

- The Approach
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  - Lipidomics
  - Genotyping
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Lipidomics

- In the evaluation of a novel oil, lipidomics is the metabolomic platform of choice
- Omega-3 index or SCD index indicate potential cardiovascular disease benefit
- Similarly lipoprotein particle number, size and subclasses are markers of disease risk and are affected by diet and supplements
- Bioactive molecules present in diet (i.e. β-sitosterol) are measured in many lipidomic profiles
Lipidomics

<table>
<thead>
<tr>
<th>Fatty Acid Profiling</th>
<th>Product Profiling</th>
<th>Human Response Profiling</th>
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<td>Regulatory Filings</td>
<td>Index Fatty Acids, e.g. EPA, EPA/AA</td>
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<td></td>
<td>Patent protection</td>
<td>Omega Score™</td>
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<td>Quality assurance</td>
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<table>
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<table>
<thead>
<tr>
<th>Apo A1 Family</th>
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<td>HDL₁</td>
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<tr>
<td>Phospholipids</td>
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<tr>
<td>Cholesteryl Esters</td>
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## Lipidomics

### Serum lipids from individuals given fatty acid supplements for 6 weeks

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<th>Lipid&lt;sup&gt;1&lt;/sup&gt;</th>
<th>O.O.</th>
<th>EPA Oil (Low)</th>
<th>EPA Oil (High)</th>
<th>DHA</th>
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<td></td>
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<td>Post</td>
<td>p-value&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Pre</td>
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<tr>
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<td>5.67</td>
<td>5.63</td>
<td>0.84</td>
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<td>AA/(EPA)</td>
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<tr>
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<td>0.57</td>
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<td>0.85</td>
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<td>DHA</td>
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<td>3.57</td>
<td>0.93</td>
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<td>0.01</td>
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</table>

Data shown as means ± standard error of 26 individuals. All concentrations are expressed as mg/dl.

<sup>1</sup>Abbreviations used: Omega3, total DHA plus EPA; AA, arachidonic acid; SCD18,
Achieving Personalized Nutrition: The 4 Ps

• The Approach
• Nutrigenomic Toolbox
  • Transcriptomic profiling
  • Transcription factor profiling
  • Lipidomics
  • Genotyping
• The Future
Genotyping

- Much like transcript profiling, genotyping can examine a specific gene(s) (i.e. TaqMan SNP assays) or be more comprehensive (i.e. arrays, NextGen Sequencing)
- Several consumer choices for genotyping services
- Consumer surveys suggest that 78% of Americans are favorably disposed to using genetic information to optimize their personal nutrition
Genotyping

- Can categorize subjects
  - Statistical assistance
  - "Get to know" your study population
- Explain outliers
- Coupled with mechanism of action studies
- Study size may limit type of SNPs examined
Genotyping

- Known genetic polymorphisms in the omega-3 biosynthetic pathway, notably in fatty acid desaturase 1 and fatty acid desaturase 2 and in the nuclear receptors that are activated by omega-3 fatty acids such as PPARα

- Hypothesis testing
  - Population associations
  - Personalized nutrition
SNPs in *SCD1*-modified cardiometabolic risk factors pre and post *n*-3 PUFA supplementation: triglyceride (*rs508384, p = 0.0086*), IL6 (*rs3071, p = 0.0485*), C-reactive protein (*rs3829160, p = 0.0489*), and SCD18 indices (*rs2234970, p = 0.0337*).
**Variation Summary:**

<table>
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<td>Total rare variations (GAF &lt;1%):</td>
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<table>
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<th>Variations by Gene Impact:</th>
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<td>Intron</td>
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</table>

**Gene Summary:**

| Total number of genes in reference genome: | 34,948        |
| Genes with protein-coding variation:       | 3,244         |
| Genes with more than one protein-coding variation: | 2,263        |
| Genes with rare protein-coding variation:  | 363           |
| Genes with more than one rare protein-coding variation: | 323           |
| Genes with low exon call coverage (<80%):  | 27,197        |
**Genotyping**

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**rs1801282**, also known as Pro12Ala, is a common SNP in the peroxisome proliferator-activated receptor **PPARG gene**. May be associated with metabolic syndrome.

**rs1800206**, also known as PPARA L162V polymorphism. Plasma TG and apoC-III concentrations depends on the dietary PUFA, with a high intake triggering lower TG in carriers of the 162V allele.
The Future

- Nutrigenomic tool kit
  - Transcriptomic profiling
  - Nuclear receptor profiling
  - Lipidomics
  - Toxicogenomics
  - Genotyping

- Multi-level, multi-media, science-driven networking to engage thought-leaders and empowered consumers

- Research provides critical “Proof of Principle” underpinning product differentiation and patent estate to protect return on investment

- Re-invent product in “4P” paradigm of “Personal Nutrition”

- Decline
The Future

- The future of nutrition and health can be framed as “4P” nutrition that is “predictive, preemptive, personal, and participatory.”
- Empower consumers to proactively manage their health.
- Provide physicians and dietitians with individualized dietary management approaches.
- Overcoming regulatory hurdles such as direct-to-consumer marketing of genetic tests and ethical considerations (problematic at the moment, but likely resolvable in time).
- The curse of so much data with so little knowledge.
Thank You!

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Professor and Founding Director  
New Jersey Institute for Food, Nutrition and Health  
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director@ifnh.rutgers.edu
Nutrigenomics: The 21st Century Diet?

- Consumer media
- Research projects
- Food industry programs
- Genetic testing
- Resources

We all respond differently to the things we eat. Our physical traits, our lifestyles and our genetic make-up all differ. How can we use our understanding of food and our genes to design a better, healthier and more individualized diet?
What are Consumers Reading?
Prevention: Eat for a Cure

- Alzheimer’s Disease
  - “Eat more vegan meals”
- Obesity
  - “Eat more calcium-rich foods to shrink belly fat”
- Macular Degeneration
  - “Eat more fish and lutein- and zeaxanthin-rich foods”
- Heart Disease
  - “Eat a diet rich in fruits, vegetables, whole grains and nuts”
- Colon Cancer
  - “Eat a Mediterranean-style diet low in omega-6 fats”

“Certain nutrients are so powerful they can turn off genes related to specific diseases. Use these edible Rx’s to counteract your family history and control your destiny.”

December 2014 Prevention.com
Food4me: One Size Does Not Fit All

- EU-funded project founded in 2011 investigating the opportunities and challenges for personalised nutrition.
  - Compile current scientific knowledge and consumer understanding, including best practice communication strategies and ethical boundaries.
- Consortium of 25 partners from 12 European countries in the fields of biological sciences, consumer studies, marketing, business development, IT and technology, ethical and legal industry, and communication.
- 4-year grant; final project conference held in Brussels 2/26/2015
Nestlé: Personalised Nutrition

• Created Nestlé Health Sciences and Nestlé Institute of Health Sciences in 2010 to pioneer a new industry between food and pharma.

• Find efficient and cost-effective ways to prevent and treat many of today’s acute and chronic diseases.
  o Targeted at specific needs
  o Understanding of genetic and environmental interactions with food
Nutrigenomix®: Eat According to Your Genes

- University of Toronto start-up biotech company.
- Saliva sample DNA test to tell you if your body responds better or worse to 7 different nutrients; NGx-Gluten™ test in HLA gene region.
- Based on peer-reviewed studies and approved by Nutrigenomix International Science Advisory Board.
- DNA-based dietary advice shown to be more actionable than general population-based recommendations.¹
- Launched in 2012 to RDs in Canada, Australia and the U.S.
- Available in 1,500 clinics in 22 countries; only available through dietitians. Takes 2-4 weeks and costs $300-$400.

Dieting to Fit Your Genes

The answer may be in your genes

In 480 BC, Hippocrates noted that "positive health requires knowledge of man’s primary constitution". This was just an ancient way of saying that we cannot achieve optimum health without knowing about our genes. We now know that specific variations in our genes can explain how we will respond to the foods, beverages and supplements we consume.

Learn how your genes affect how you respond to...

- Sodium and risk of high blood pressure
- Folate and risk of low blood levels of folic acid
- Omega-3 Fat and risk of elevated triglyceride levels
- Saturated Fat and risk of developing obesity
- Vitamin C and risk of low blood levels of vitamin C
- Whole Grains and risk of type 2 diabetes
- Caffeine and risk of heart disease
“It is the position of the Academy of Nutrition and Dietetics that nutritional genomics provides insight into how diet and genotype interactions affect phenotype.

The practical application of nutritional genomics for complex chronic disease is an emerging science and the use of nutrigenetic testing to provide dietary advice is not ready for routine dietetics practice.

Registered dietitian nutritionists need basic competency in genetics as a foundation for understanding nutritional genomics; proficiency requires advanced knowledge and skills.”

“Whether or not the knowledge gained from nutritional genomics can be integrated into the everyday lives of consumers is yet unknown.”
What’s Next?

- Is it effective?
- What do consumers think about personalised nutrition?
- What are the social, legal and ethical implications?
- How do you translate individual health data into dietary recommendations?
- What is the effectiveness of various types of personalised nutrition advice?
- What is the best business model to use for marketing and distribution and which technical devices are needed to make personalised nutrition a reality?
What Now?

- Personalized nutrition already exists at different levels—but is not yet evidence-based on nutrigenomics.
- Functional foods with proven benefits exist—including fruits and vegetables—but are not yet based on nutrigenomic efficacy.
- Today's power of nutrigenomics lies in improving our understanding of diet-gene interactions. Tomorrow, these tools may become integral to consumer assessment and dietary advice.
Resources

- International Society of Nutrigenetics/Nutrigenomics (ISNN) http://www.nutritionandgenetics.org/
  - Increase the understanding of the role of genetic variation and individual dietary response, and the role of nutrients in gene expression generally
  - 9th Congress of the ISSN will be held in Chapel Hill, NC, on May 17-19, 2015.

- CDC’s Office of Public Health Genomics (OPHG) http://www.cdc.gov/genomics/
  - Nearly 2 million Americans are at increased risk for early-onset cancer or heart disease because they have one of three genetic conditions: BRCA-associated hereditary breast and ovarian cancer, Lynch syndrome, and familial hypercholesterolemia.

- Nutrition Dimension Magazine, Spring 2015
  - Free CE course on Nutrigenetics http://www.nutritiondimension.com/archive/
“We’ve started to better appreciate the fact that it’s not just the diet and it’s not just the genetic factors but it is an interaction of the two that permits a metabolic change that gets translated in a complex disease over time.”

--Kenneth Kornman, InterLeukin Genetics
Thank You!

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