Vetting Personalized and Genomically-Guided Nutrition: Issues and Strategies

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(TGen, Phoenix AZ; UCSD, JCVI, La Jolla, CA)

1. Leveraging Trends in Biomedical Science in Nutrition-Based Health Care
2. Identifying, Verifying and Vetting Nutrition Strategies for Individuals
3. N-of-1, Aggregated N-of-1, Personal Threshold-Based, etc. Trials
Food and Nutrition Board Member 2003-2007

Nutrigenomics and Beyond: Informing the Future
June 1-2, 2006
National Academy of Sciences Auditorium
2100 C Street, NW
Washington, DC 20037

Ann L. Yaktine and Robert Pool, Rapporteurs
(Copyright 2007; National Academy of Sciences)
1. Leveraging Trends in Biomedical Science in Nutrition-Based Health Care
Four Trends in Contemporary Biomedical Science

“Garbage in, Garbage out” concerns, so need objective trials

**Big Nutritional Science Question:**
How to optimally develop and deploy nutritional interventions when data clearly suggest that factors influencing response(s) exhibit great inter-individual variation? Need insights from:

- Early Intervention Development
- Early Studies on *Humans*
- Clinical Vetting and Proof
- Deployment Efficiencies

**Big Economics/Social Question:**
How does one define ‘optimal?’

- Individual Outcomes?
- Quality of Life?
- Cost-Savings for Society?
Revamped US FDA: Facilitating Use of New Techs

21\textsuperscript{st} Century Cures Act: An act to accelerate the discovery, development, and delivery of 21st century cures
(Signed as law by Obama on 12/13/2016)

Scott Gottlieb

- Among many other things, intended to expedite the process by which new techs and devices are approved
- Eases requirements put on drug companies looking for FDA approval on new products or new indications on existing drugs
- Under certain conditions, allows companies to provide "data summaries" and "real world evidence" such as observational studies, insurance claims data, patient input, and anecdotal data rather than full clinical trial results.
2. Identifying, Verifying and Vetting Nutrition Strategies for Individuals
Personalized Nutrition: *What* is Being Tailored to *What*?

Genetics -> Gross Diet

Complex Profile -> Nutrients, Supplements, Etc.

- Genetics
- Gross Diet
- Complex Profile
- Nutrients, Supplements, Etc.
Conceptualizing Traditional, Stratified, Precision and Personalized Nutrition

1. Collect data that could impact nutritional response on N patients:
   - History on medications
   - Genomic profile
   - Biomarker profile
   - Pathology analysis

2. Form an N x N similarity matrix from the response profiles:

   |   | 1  | 2  | 3  | 4  | ... | N   |
---|---|---|---|---|-----|-----|
1  | 1.00| 0.75| 0.50| 0.25| 0.50 |
2  | 0.75| 1.00| 0.25| 0.40| 0.80 |
3  | 0.50| 0.25| 1.00| 0.50| 0.10 |
4  | 0.25| 0.40| 0.50| 1.00| 0.35 |
N  | 0.05| 0.80| 0.10| 0.35| 1.00 |

3. Cluster patients using the similarity matrix and find treatment rules

Questions: What level works best? How does one define ‘best’ (e.g., economics, patient benefit, scientific understanding)? How does one prove that one or another approach is best?
Personalized Nutrition by Prediction of Glycemic Responses

One week profiling (26 participants)

Dietitian prescribed meals

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<tr>
<td>Breakfast</td>
<td>B₁</td>
<td>B₂</td>
<td>B₃</td>
<td>B₄</td>
<td>B₅</td>
<td>B₆</td>
</tr>
<tr>
<td>Lunch</td>
<td>L₁</td>
<td>L₂</td>
<td>L₃</td>
<td>L₄</td>
<td>L₅</td>
<td>L₆</td>
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<tr>
<td>Snack</td>
<td>S₁</td>
<td>S₂</td>
<td>S₃</td>
<td>S₄</td>
<td>S₅</td>
<td>S₆</td>
</tr>
<tr>
<td>Dinner</td>
<td>D₁</td>
<td>D₂</td>
<td>D₃</td>
<td>D₄</td>
<td>D₅</td>
<td>D₆</td>
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</table>

Choose meals for dietary intervention weeks

Expert-based

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<th>L₂</th>
<th>S₅</th>
<th>D₂</th>
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<tbody>
<tr>
<td>'Good' diet</td>
<td>B₆</td>
<td>L₅</td>
<td>S₆</td>
<td>D₃</td>
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'Bad' diet

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<th>S₁</th>
<th>D₁</th>
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<tr>
<td>'Good' diet</td>
<td>B₂</td>
<td>L₄</td>
<td>S₂</td>
<td>D₂</td>
</tr>
</tbody>
</table>

'Bad' diet

|  | B₃ | L₆ | S₂ | D₅ |

Personal features

<table>
<thead>
<tr>
<th>16S</th>
<th>MG</th>
<th>B</th>
<th>Q</th>
<th>A</th>
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</thead>
<tbody>
<tr>
<td>Color-coded response (blue: low; yellow: high)</td>
<td></td>
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</tbody>
</table>

Text meal identifier

Measure and analyze intervention weeks

Glucose (mg/dl)

A. Participant E7

B. Participant P3

Blood

Anth.

16S RNA

Metagenomics

KEGG Pathways

KEGG Modules

Glucose

Bread

Bread & butter

Fructose

Color Scale

N: Negative association

P: Positive association

P-values:

P < 0.001

P < 0.01

P < 0.05

P = n.s.
Implementing personalized cancer genomics in clinical trials

Richard Simon and Sameek Roychowdhury

- Insights or ‘Rules’ Relating tumor genomic alterations to specific therapeutic agents are building up

- The evidence for the matching (or repurposing) of drugs to alterations comes from different sources

- Only a subset of patients is likely to have the alteration

- Too many (focused/small) trials need to verify each match? How to accommodate?

- What constitutes evidence for a clinically-useful match?
## Conceptual Scheme Behind a ‘Basket’ Trial

### Table

| Patient | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10...
<table>
<thead>
<tr>
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<td>CRC</td>
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<td>CRC</td>
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<td>Mut 1</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mut 2</td>
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<td>X</td>
<td></td>
<td>X</td>
<td></td>
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<tr>
<td>Mut 3</td>
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<td>Mut 4</td>
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<td>X</td>
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<td>X</td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>Mut X</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

### Diagram

**A PRIORI DEFINED SCHEME FOR MATCHING PATIENTS TO DRUGS**

**THIS (I.E., A MATCHING STRATEGY) IS WHAT IS BEING TESTED!**

### GOAL

Assess outcomes compared to individuals treated **without matching scheme**

### ISSUES

*What is the scheme (algorithm) based on? What about multiple genetic perturbations? What about alternative treatments to any one? What about combination treatments? Why not adapt the scheme as data is accrued (i.e., adaptive designs)?*
Issues Testing Algorithms vs. Drugs
(FDA visit and discussion: June 8, 2015)

- **Combinations** of drugs are an issue? (ICU? Non-cancer chronic disease?)
- **Real time nature** of the **trials** = complex adaptive designs
- **Real time nature** of the **disease** = algorithms with temporal component
- **Insights external to the trial data need to be accommodated**
- What does the **algorithm include**? (e.g., sequencing technologies, tumorgrafts, cell lines, etc.?)
- What if, e.g., a tumor board decides **not to go with the algorithm’s drug**?
- **Randomization**: when or at all? i.e., When is there sufficient biological, as opposed to trial, evidence to **forego randomization/equipoise**
- **Poor Outcomes** (e.g., SHIVA): algorithm’s fault or drug’s fault, or both?
- The **time it takes** to do the assays is an issue; how to incorporate?
- Accommodating crossover to **competitors’ drugs**? Who pays?
- **Resources** for conducting many smaller trials? Med-C or ASCO?
- Best for **Repurposing** drugs or new drugs, combinations of old and new?
- **Biomarker-based responses**, how much vetting for individual drugs?
Maybe not, but a company or group that is so incurious about, or simply not confident in, their technology that they do not want to see if and how it works should be approached with major caution...
3. N-of-1, Aggregated N-of-1, Personal Threshold-Based, etc. Trials
A greater focus on the **science of response** should emerge from and **guide** clinical trials.

Most large phase III trials don’t generate enough data on any one person to determine if they are **unequivocal responders/non-responders** to an intervention.

Focus: objectively assess **patient’s condition/well being**, not necessarily the intervention...
Equipoise and Single Subject or ‘N-of-1’ Clinical Trials

Basic Goal: Make objective claims about the utility of an intervention for an individual. (Most trials focus on population effects; do not have data to identify unequivocal responders)

Standard design and statistical methods can be leveraged: randomization, blinding, washout periods, sequential and adaptive designs, multivariate outcomes, etc. Causality can be inferred via temporal data (Lillie EO, ..., Schork NJ. Per Med. 2011 Mar;8(2):161-173. PMID:21695041; Magnuson V, Wang Y, Schork NJ. F1000 2016 Feb. 3. PMID:28781744)
Although many studies leverage, e.g., blinding, multiple crossovers, etc. they are not very sophisticated in terms of measurements or data analysis (Med Care 2011; 49:761-768): **Design Optimization is Possible!**

Wireless Medical Data Collection Devices: Primary or Surrogate Endpoint Monitoring

Patient Experience

Mood, anxiety, etc.

Microbiome

Tissue Biomarkers

Weight

Pulse Oximeter

Glucometer

Blood Pressure

Sleep

Patients/Individuals

Actigraphy

ECG

Senses

(Taste, Eyesight, Touch)

Motion

(solos in shoes)

Wireless Medical Data Collection Devices:
Primary or Surrogate Endpoint Monitoring

"You can't list your iPhone as your primary-care physician."

The New Yorker, 5/25/15
Single-Subject Studies in Translational Nutrition Research

Nicholas J. Schork1,2,3 and Laura H. Goetz2,4,5

Patrick J. Stover
Editor
Annual Review of Nutrition

Response Profile Similarity Analysis: Use N-of-1 Studies to ‘Bring Out a Phenotype*’

*Consider Monitoring Post Nutritional Challenge (e.g., OGTT) to Bring Out a Phenotype*
**Single Subject Microbiome Studies: Impact of Diet**

*Genome Biology 2014, 15:R89*

*Host lifestyle affects human microbiota on daily timescales*

Lawrence A. David, Arne C. Matern, Jonathan Friedman, Maria I. Campos-Baptista, Matthew C. Blackburn, Allison Perrotta, Susan E. Erdman and Eric J. Alm

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**Table 1: Significant correlations between Subject A’s metadata and microbiota**

<table>
<thead>
<tr>
<th>Body site</th>
<th>Lag (days)</th>
<th>Host factor</th>
<th>Representative OTUs (n)</th>
<th>p</th>
<th>P value</th>
<th>Abun. (%)</th>
<th>Cluster ID</th>
<th>Total OTUs</th>
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<td><strong>Subject A Gut</strong></td>
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<td>Eggerthella/Glodositrum (11)</td>
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<td>1.0E-06</td>
<td>0.2144</td>
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<tr>
<td></td>
<td>0</td>
<td>Stock: Time Of Day</td>
<td>Eggerthella/Clostridium (11)</td>
<td>0.27</td>
<td>7.4E-06</td>
<td>0.2144</td>
<td>10</td>
<td>23</td>
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<tr>
<td></td>
<td>1</td>
<td>Nutrition: Fiber</td>
<td>Clostridium (6)</td>
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<td>7.4E-06</td>
<td>0.0442</td>
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<td>Ruminococcaceae/F. prausnitzii (4)</td>
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<td>Ruminococcus/R. gravis/Clostridium (5)</td>
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<td>3.8E-10</td>
<td>0.3495</td>
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<td>Blautia (3)</td>
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<td>0.0346</td>
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<td><strong>Subject A Saliva</strong></td>
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Example N-of-1 Trial: The ‘1HAT’ Antihypertensive Trial

(https://clinicaltrials.gov/ct2/show/NCT012587)

• N-of-1, double blind, crossover trial with washout periods
• Lisinopril (10 mg oral/d; ACE inhibitor) vs. Hydrochlorothiazide (25 mg oral/d; Diuretic)
• Pharmacy provided pills with same presentation/packaging
• BP measurements daily (at least 4 times) with covariates collected (e.g., weight)
• One of the patient’s experience detailed below:

Mean SBP

Weight

• Could not attribute BP drop to the drug; patient became much more health conscious
Example N-of-1 Trial: Genetically-Mediated Sleep Disorder

Patient Background

- 60 year-old female, treated for anxiety, depression and genetic sleep phase disorder (Seasonal Affective Disorder)
- **Polypharmacy** an issue: antidepressants impact sleep; sleep aids impact mood...
- Different drugs tested in combination:
  - Cymbalta (CYM): treat depression, anxiety
  - Temazepam (TEM): treat insomnia, anxiety
  - Melatonin (MEL): treat sleep-phase disorder
- Measurements and outcomes:
  - Zeo: sleep time, sleep phases
  - PAM-RL: restless legs
  - Fitbit: activity, sleep
  - Equivital belt: vital signs (e.g., HR)
  - Sleep image device: sleep apnea
- No blinding; washouts = no medications

Results

- Cymbalta exacerbated sleep disturbances
- Drug removal unmasked sleep apnea condition (data not shown)
- Personalized trials for complicated, multi-faceted conditions are necessary
**Population vs. Personal Thresholds**

<table>
<thead>
<tr>
<th>Biomarker (e.g., Cholesterol or DNA Damage Level, etc.)</th>
<th>Personal Average</th>
<th>Personal Threshold</th>
<th>Population Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25</td>
<td>But do the historical values for an individual reflect “health?”</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Ex Vivo Assessment of Nutrient-Mediated DNA Damage

Am J Clin Nutr 2010;91(suppl):1438S–54S.
Dietary reference values of individual micronutrients and nutriomes for genome damage prevention: current status and a road map to the future

Michael F. Fenech

TABLE 1
Strengths and weaknesses of best-validated DNA damage assays for nutritional studies in humans

<table>
<thead>
<tr>
<th>DNA damage assays</th>
<th>DNA damage events measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBMN Cyt</td>
<td>Red blood cell</td>
</tr>
<tr>
<td>DNA breaks</td>
<td>Yes</td>
</tr>
<tr>
<td>Mispair of DNA breaks</td>
<td>Yes</td>
</tr>
<tr>
<td>Oxidized DNA bases</td>
<td>No</td>
</tr>
<tr>
<td>Chromosomal malsegregation</td>
<td>Yes^2</td>
</tr>
<tr>
<td>Chromosomal deletions</td>
<td>Yes^2</td>
</tr>
<tr>
<td>Dicentric chromosome or telomere-end fission</td>
<td>Yes^3</td>
</tr>
<tr>
<td>Telomere length</td>
<td>No</td>
</tr>
<tr>
<td>Hypermethylation of DNA</td>
<td>No</td>
</tr>
<tr>
<td>DNA damage</td>
<td>No</td>
</tr>
<tr>
<td>mtDNA damage</td>
<td>No</td>
</tr>
<tr>
<td>Other features</td>
<td></td>
</tr>
<tr>
<td>Distinguishes DNA damage in viable cells from cell death</td>
<td>Yes</td>
</tr>
<tr>
<td>Suitability for in vitro studies</td>
<td>Yes</td>
</tr>
<tr>
<td>Cell type in which assay is performed</td>
<td>PBLs</td>
</tr>
</tbody>
</table>

^2 If used in combination with glycolytic enzymes that remove oxidized bases.
^3 By measuring nucleosomes with/without centromere staining.
^4 If at a lower version of the assay is used.
^5 The inability to distinguish between DNA damage from dead or viable cells may confound DNA damage results.

Consider in vitro/ex vivo cellular challenge-induced phenotypes as indicators of in vivo changes
The Schork Group

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