The Underlying Biological Processes for Special Nutritional Requirements

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Vice Chancellor and Dean for Agriculture and Life Sciences
<table>
<thead>
<tr>
<th>AFFILIATION/FINANCIAL INTERESTS (prior 12 months)</th>
<th>ORGANIZATION</th>
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<tbody>
<tr>
<td>Grants/Research Support:</td>
<td>NIH:</td>
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<td>T32-DK007158</td>
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<td>Scientific Advisory Board/Consultant:</td>
<td>Nestle Health Sci, Biofortis, Marabou</td>
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<td>Foundation, National Academy of Sciences</td>
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<td>Chronic Disease Endpoints Committee</td>
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<tr>
<td>Speakers Bureau:</td>
<td>None</td>
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<tr>
<td>Stock Shareholder:</td>
<td>TIAA</td>
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<tr>
<td>Owner</td>
<td>MetabolicSolutions LLC</td>
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Engineering the Food Supply:

- Diet diversification
- Fortification (Chem/Bio)
- Supplements, etc

Dietary and Nutrient Recommendations:

- Adequate for what?
  - Nutritional Status/Avoid Deficiency?
  - Metabolic Function/Other Function?
  - Chronic Disease Prevention?
  - Disease Management?
How the DGA can better prevent chronic disease, ensure nutritional sufficiency for all Americans, and accommodate a range of individual factors, including age, gender, and metabolic health.
Chronic Diseases are complex traits
- age, diet, genetics, epigenetics, environment

Few chronic diseases are affected by:
- single nutrients
- single pathways

Consider systems/networks over pathways

Establish system readouts as biomarkers (integrative biomarkers)

Understand biomarkers of aging – system decay

“GRADE” standards of evidence
### Modifiers of Nutrient & Food Needs

<table>
<thead>
<tr>
<th>Physiological Processes</th>
<th>Modifiers and Sensitizers</th>
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<tbody>
<tr>
<td>Absorption</td>
<td>Disease/Health</td>
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<tr>
<td>Catabolism</td>
<td>Epigenetics</td>
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<td>Excretion</td>
<td>Food Matrix</td>
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<tr>
<td>Metabolism</td>
<td>Genetics</td>
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<td>Stability</td>
<td>Nutrient-Nutrient Interactions</td>
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<tr>
<td>Transport</td>
<td>Pharmaceuticals/Toxins</td>
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<td>Bioactivation</td>
<td>Microbiome</td>
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<tr>
<td>Energetic State</td>
<td>Age/Physiological Decay</td>
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<td>Nutrient Storage</td>
<td>Sex/Pregnancy/Lactation</td>
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50% of the US adult population suffers from a chronic disease

Adequate for whom?
- Clinical populations or individuals?

Adequate for what?
- Address disease-induced changes in nutritional needs

Special Nutritional Requirements are different from drugs
- Drugs: cure, mitigation, treatment of primary disease but
- Drugs can alter nutrient requirements – lead to secondary disease

Are they safe?
- Special nutrition requirements are meant for clinical populations
A folic acid–enalapril combination was more effective than enalapril alone in the secondary prevention of renal function decline among Chinese adults with hypertension across a spectrum of mild to moderate chronic kidney disease (CKD).


Enalapril treatment alone in the absence of supplemental folic acid increased serum folate by 5.1 ng/mL, with a modest decrease in serum homocysteine (0.2 μM).

While the mechanisms for this interaction are unknown and should be explored, this drug-nutrient interaction may underlie the secondary prevention of renal function decline observed in this study.
Drugs Can Alter Nutrition Needs

*Pharmaceutics 2018, 10: 36*

- **NSAIDS/Aspirin**
  - Vitamin C, Iron
- **Hypoglycemics (Metformin)**
  - Vitamin B12, calcium, vitamin D
- **Acid-Suppressing Drugs Proton Pump Inhibitors**
  - Vitamin B12, Vitamin C, Iron, Calcium, Magnesium, Zinc
**Special Nutrient Needs are Not Treating a Primary Disease**

*Is the nutrient intervention having a physiological or “drug’ (off target) effect?*

Special Nutritional Needs act through evolutionary-derived physiological mechanisms (as opposed to “off-target” effects) to restore nutritional adequacy and physiological function and thereby manage a specific disease state.

*For example*: pharmacological doses (10X DRI) of niacin, but not nicotinamide, improves lipid profiles and reduces coronary events and total mortality in patients at high risk for coronary heart disease.  
http://lpi.oregonstate.edu/mic/vitamins/niacin
Considerations for Proposed Standards
Special Nutritional Needs

– Establish Robust Biological Premise
  • How and why are nutrient needs different?
  • What are the relevant biomarkers of altered nutrient needs?

– Efficacy
  • Does increased or decreased intake address diseased-induced changes in nutrient needs?
    – nutritional status and/or function
    – acute and chronic
  • Does altered intake improve clinical outcome(s)?
    – Symptoms of primary disease outcome and/or co-morbidities?

– Classify clinical subgroups with Special Nutrient Requirements.
  • Can you identify those with altered needs (biomarkers)? Heterogeneity?
Disease influences whole-body nutrient status and/or specific tissue nutrient status
Disease-related etiology:
- Inflammation
- Genetic predisposition
- Autoimmunity
- Mitochondrial dysfunction
- Pharmaceuticals
- Trauma

Physiological impact on nutrients & function:
- Gut absorption
- Brain/Nerve Barriers
- Degradation/turnover
- Excretion
- Metabolism
- Redistribution

Impact on human nutrition:
- Whole-body deficiencies
- Tissue-specific deficiencies
- Conditionally essential nutrients
- Nutrient toxicities

Impact on biomarkers:
- Function & Status
- Whole-body (serum)
- Tissue-specific (CSF, tissue)
- Predictive biomarkers
- Cells & Stem cells

Examples of factors that affect nutrient status and/or biomarkers of status

- Increased rates of catabolism
  - Acquired Arginine Deficiency Syndrome  
    Arginase is elevated in sickle cell disease, malaria, acute asthma, cystic fibrosis, pulmonary hypertension, cardiovascular disease, certain cancers, trauma, infection, and gastrointestinal disorders
  - Inflammation (vitamin B6, vitamin D, others)  

- Tissue redistribution and/or excretion
  - Infection (iron)  
  - Inflammation (vitamin B6, vitamin D)  

- Decreased rates of uptake (gut and blood-brain barrier transport)
  - Genetics, inflammation, drug use, autoimmunity, mitochondrial depletion, others
Stem Cell Nutrition and Tissue Regeneration

Serine is an essential amino acid for muscle myoblast proliferation.

Neurogenesis is influenced by: curcumin, resveratrol, blueberry polyphenols, sulforaphane, salvionic acid, polyunsaturated fatty acids (PUFAs).


*Nutrients* 2018, 10(2), 186

*BBRC* 1976 70: 1085
Inborn Errors of Metabolism (IEM) inform Special Nutritional Requirements in Disease

Genetics as proof-of-principle

Biological premise: Nutrition compensating for loss-of-function

IEM

Medical Food

Nutrition Compensating for Functional Deficits Caused by Genetics

Chronic Disease

Nutrition Compensating for Functional Deficits Caused by Disease
Disease-related Alterations in Nutrition Needs

**Physiological Change**
- Impaired Nutrient Transport
- Nutrient Depletion (Renal Excretion)
- Toxic Nutrient Accumulation
- Conditionally Essential Nutrient

**Special Nutritional Requirement**
- Overcome Barrier (Energetic or Physical)
- Provide more input
- Provide Less Input
- Provide New Input

**IEM Example**
- FRα Mutation in BBB (Folate)
- Falconi Syndrome (Electrolytes, Vit D)
- PKU (phenylalanine restriction)
- FA Oxidation Defects (Carnitine)

**Disease**
- Loss of BBB Function (Autoantibodies/Mitochondrial depletion)
- Loop Diuretics (Thiamine)
- Hemochromatosis (Iron Restriction)
- Trauma/Surgery (Arginine)
## Comparison of Dietary Reference Intakes and Special Nutritional Needs

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<thead>
<tr>
<th></th>
<th>DRI</th>
<th>Special Nutritional Needs</th>
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<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Healthy Populations</td>
<td>Clinical Populations</td>
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<tr>
<td></td>
<td>Sex, Age, Pregnancy, Lactation</td>
<td>Classifiable Condition/Disease</td>
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<tr>
<td><strong>Intervention</strong></td>
<td>Diet, Dietary Supplement</td>
<td>Needs may not be met by “diet” alone</td>
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<tr>
<td><strong>Comparisons</strong></td>
<td>Dose-Response</td>
<td>Dose-Response</td>
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<tr>
<td><strong>Outcomes</strong></td>
<td>Avoid Nutrient Deficiency, Support Physiological Processes, and/or Chronic Disease Prevention</td>
<td>Avoid Disease-Induced Nutrient Deficiency, Support Compromised Physiological Processes in Disease, and/or Support Tissue Regeneration <em>(Dietary Management of Disease)</em></td>
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American Society for Nutrition Nutrition Research Priorities

Variability in Responses to Diet & Food
Achieving personalized nutrition with dietary recommendations tailored to each person’s needs.

Healthy Growth, Development and Reproduction
Understanding how nutrition during critical, early periods of development (including pregnancy) impacts future health.

Health Maintenance
Improving health with noncommunicable disease prevention and weight maintenance.

Medical Management
Slowing disease progression through nutrition with improved responses to therapy and survival rates.

Nutrition-Related Behaviors
Understanding how the human brain influences food choice and nutrition-related behaviors.

Food Supply & Environment
Realizing the potential of the food environment to improve diet and lifestyle choices.

## Question 1: How can we better understand and define eating patterns to improve and sustain health?

<table>
<thead>
<tr>
<th>Question 1 Topic 1 (Q1T1):</th>
<th>How do we enhance our understanding of the role of nutrition in health promotion and disease prevention and treatment?</th>
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<tbody>
<tr>
<td>Question 1 Topic 2 (Q1T2):</td>
<td>How do we enhance our understanding of individual differences in nutritional status and variability in response to diet?</td>
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<tr>
<td>Question 1 Topic 3 (Q1T3):</td>
<td>How do we enhance population-level food- and nutrition-related health monitoring systems and their integration with other data systems to increase our ability to evaluate change in nutritional and health status, as well as in the food supply, composition, and consumption?</td>
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[https://www.google.ch/?gfe_rd=cr&ei=Og8SWOLrLcHCaNn8gOAN#q=national+nutrition+roadmap](https://www.google.ch/?gfe_rd=cr&ei=Og8SWOLrLcHCaNn8gOAN#q=national+nutrition+roadmap)
Precision Nutrition

What patients will need to know

1. Classification of Subgroups for Nutrient Intakes?
2. Snap Shot versus Progression
3. Real Time Personalized Readouts of Health/Disease and Nutrition/Physiology

- Data will be readily accessible!
- What guidance will we (or the cell phone) give?