Dietary Reference Intakes Around Distinct Nutritional Needs

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Disclosures

AFFILIATION/FINANCIAL INTERESTS (prior 12 months)	ORGANIZATION
Grants/Research Support:	NIH: T32-DK007158 R37DK58144; ODS Supplement HD059120
Scientific Advisory Board/Consultant:	NHSc-Pamlab; Biofortis, Marabou Foundation, ASN Board; National Academy of Sciences Chronic Disease Endpoints Committee
Speakers Bureau:	None
Stock Shareholder:	TIAA
Owner	MetabolicSolutions LLC



What should we expect from the food supply?

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

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CONSENSUS STUDY REPORT



GUIDING PRINCIPLES FOR

Developing Dietary Reference Intakes Based on Chronic Disease

Chronic Disease Endpoints - Challenges -

- 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)
- Consider DRIs as ranges in lieu of point estimates
- Understand biomarkers of aging system decay
- "GRADE" standards of evidence

Neural Tube Defects (NTDs)

- Common congenital abnormality at birth in US (1-2 in 1000 births).
 - 2,500 affected births in the US/year
- Rate is 5-10/1000 in developing countries.
- Recurrence rate is 1-5/100.





1960s

Present

Clin Observations \rightarrow Clinical Trials \rightarrow Recommendations \rightarrow Food Policy \rightarrow Evaluation

Mother exhibited: Formiminoglutamate in urine Lower RBC folate Elevated Homocysteine



1960s

Present

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1991 MRC NTD Recurrence Trail The Lancet, 1991 **338**, 131.

1992 Occurrence Trail

72% reduction in NTD frequency in folic acid supplemented group



1960s

Present

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US Fortification of the Food Supply with Folic Acid

In January 1998, the FDA mandated that enriched flour and grain products include folic acid at levels from 0.095-0.308 mg folic acid/100 g product.



Clin Observations \rightarrow Clinical Trials \rightarrow Recommendations \rightarrow Food Policy \rightarrow Evaluation

Public Health Success Story

Neural Tube Defect Prevention



Folic acid fortification worldwide



http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5931a2.htm

Why don't all Countries Fortify the Food Supply with Folic Acid?

Field & Stover, Ann N Y Acad Sci. 2018 1414(1):59

- First fortification initiative that sought a medicinal purpose: prevent a "rare" disorder
 - Disease Endpoint for a Nutrient Exposure Level
- There are no established risks of folic acid fortification, but:
 - Exposes everyone, but targets a small population subgroup (who benefits, who accrues risk?)
 - Mechanism of folate-NTD relationship unknown; Mechanism of folate-cancer relationship unknown
 - Observational studies of risk with high folate and low B12 status
 - Biological activity of unmetabolized folic acid

• Exacerbate common concerns of unintended consequences

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Improving Metabolic Health through Precision Dietetics in Mice

Genetics 2018: 208(1):399





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.



Medical Management

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



Healthy Growth, Development and Reproduction

Understanding how nutrition during critical, early periods of development (including pregnancy) impacts future health.



Nutrition-Related Behaviors

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



Health Maintenance

Improving health with noncommunicable disease prevention and weight maintenance.



Food Supply & Environment

Realizing the potential of the food environment to improve diet and lifestyle choices.

Olhorst et. al. (2013) Am J Clin Nutr doi: 10.3945/ajcn.113.067744.

National Nutrition Research Roadmap 2016–2021 USA Interagency Committee on Human Nutrition Research

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

Question 1 Topic 1 (Q1T1): How do we enhance our understanding of the role of nutrition in health promotion and disease prevention and treatment?

Question 1 Topic 2 (Q1T2): How do we enhance our understanding of individual differences in nutritional status and variability in response to diet?

Question 1 Topic 3 (Q1T3): How do we enhance population-level food- and nutritionrelated 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? The National Academies of SCIENCES • ENGINEERING • MEDICINE

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- Food as Medicine

Maternal Nutrition and Child Development When Does Chronic Disease Risk Initiate?



Risk for chronic disease can initiate at the earliest stages of life and progress throughout life

For many chronic diseases, nutrition may modify the course, but may not "prevent"

Developmental Origins of Disease

Fetal environmental exposures, especially nutrition, act in early life to program risk for adult health outcomes



Stem Cells Sense → Adapt -Irreversible programming



Choline plays a key role in fetal development



RCT

Supplementing the maternal diet with extra choline may ease baby's stress by changing production of the stress hormone, cortisol



Supplementing the diet with extra choline



Effect of maternal choline intake (930 vs. 480 mg/d) on maternal and fetal cortisol.



Xinyin Jiang et al. FASEB J 2012;26:3563-3574

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This lower production of cortisol in "choline" babies may reduce risk of stress-related diseases



FASEB J. 2012 Aug;26(8):3563-74.

Maternal choline supplementation improves infant information processing speed FASEB J. 2018 Jan 5 [Epub ahead of print]

Maternal consumption of twice the recommended amount of choline during the last trimester improves infant information processing speed

.. there was a significant linear effect of exposure duration, suggesting that even modest increases in maternal choline intake during pregnancy may produce cognitive benefits for offspring.

The Epigenetic Landscape Decays with Age



Nutrient Needs in Chronic Disease

Activity

Examining Special Nutritional Requirements in Disease States: A Workshop

Туре:	Stand Alone Workshop		
Topics:	Diseases, Food and Nutrition		
Board:	Food and Nutrition Board		

Activity Description

An ad hoc committee will plan a two-day public workshop exploring the evidence for special nutritional requirements in disease states and medical conditions that cannot be met with a normal diet and the workshop will explore how these requirements may apply to the management of chronic or acute conditions or diseases that include inborn errors of metabolism, burns or surgical trauma, cancer, inflammatory bowel disease, traumatic brain injury, and other non-communicable diseases or medical conditions. The workshop will explore the currently available evidence used to determined potential nutritional requirements that are not encompassed within normal population variation, and how nutritional interventions affect the overall clinical management of diseases in terms of patient safety, efficacy and access. The workshop discussions will encompass the strengths and limitations of different types of evidence (e.g. clinical, non-clinical) in establishing whether special nutritional requirements exist for a given disease or medical conditions and invite speakers and discussants, and moderate the discussions. A summary of the presentations and discussions at the workshop will be prepared by a designated rapporteur in accordance with institutional guidelines.

As of March 2016, the Health and Medicine Division continues the consensus studies and convening activities previously undertaken by the Institute of Medicine (IOM).

Planning Committee Members

- Barbara Schneeman, Chair
- + View Full Planning Committee Roster

Staff

- Maria Oria, Study Director
- + View Full Study Staff Roster

Sponsors

- National Institute of Diabetes and Digestive and Kidney Diseases
- Health Canada
- Office of Dietary Supplements National Institutes of Health
- American Society for Nutrition
- Academy of Nutrition and Dietetics
- U.S. Food and Drug Administration
- Crohn's and Colitis Foundation
- National Institutes of Health/National Cancer Institute

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

Inspired by: *Aust N Z J Med* **2**, 69-77 (1972).

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

Increased rates of catabolism

- Acquired Arginine Deficiency Syndrome Nutr Clin Pract. 2017 Apr;32(1_suppl):30S-47S 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) Ueland et al., (2015) Ann. Rev. Nutr.; Reid et a. (2011) AJCN
- Tissue redistribution and/or excretion
 - > Infection (iron) Lang & Lang, (2015) Semin Cell Dev Biol
 - Find the second second
- Decreased rates of uptake (gut and blood-brain barrier transport)
 - Genetics, Inflammation, Drug use, Autoimmunity, others

Decreased rates of synthesis

Serine is essential for muscle myoblast proliferation *BBRC 1976 70: 1085*

Considerations for Proposed Standards Special Nutritional Needs



- Establish Robust Biological Premise

- How and why are nutrient needs different?
- What are the relevant biomarkers of nutritional deficiency?
- Is the nutrient intervention having a physiological or "drug' (off target) effect?

- Efficacy

- Does increased intake address the nutritional deficiency?
- Does increased intake improve clinical outcome(s)?
 - Primary disease outcome and/or co-morbidities

Classify clinical subgroups with Distinctive Nutrient Needs.

• Can you identify responders versus non responders?

Classifying and Evaluating Human Nutrient Needs

Groups		Health	Disease Prevention Primary - Secondary – Tertiary	Disease Management Acute - Chronic
Indicators	<	V	Vhole Body Nutritional Statu lormal Physiological Functio — Clinical Outcomes — • Predictive Biomarkers - T	s on Tissue Specific Nutritional Status Restoration of Function Tissue Regeneration
		Dietary Reference Intakes (DRIs)	s Disting	ct Nutritional Requirements

50% of the US adult population suffers from a chronic disease Prev. Chronic. Dis. 2014, 11, E62

Precision Nutrition



What consumers will need to know

- 1. Classification of Subgroups for Diets/Nutrient Intakes?
- 2. Real Time Personalized Readouts of Health/Disease and Nutrition/Physiology
 - > Data will be readily accessible!
 - > What guidance will we (or the cell phone) give?
 - Can Systems/Network Biology be applied?

SCIENTIFIC REPORTS

OPEN A hybrid stochastic model of folate-mediated one-carbon





Stochastic Model/Simulation – Infrastructure

- Entire One-Carbon Metabolism Network
 - compartmentalization
- Known Expression Ranges of all Enzymes
- Ranges for all Nutrient "Inputs"
- System/Network Level Biomarkers as "readouts"

Current Analyses

- Sensitivity Analyses for all Changes in Enzyme Levels
- Dynamic Range of Nutrient Inputs Required under Different Network States to Maintain Network Outputs.

Tolate cycle

Misselbeck, K., Marchetti, L., Field, M.S., Scotti, M., Priami, C., and Stover, P.J. (2017) Sci. Rep., 7: 797.

AEGEAN CONFERENCES

International Conference on Precision Nutrition and Metabolism in Public Health and Medicine

Chania Crete Greece

September 2I-26 2018 Organizers

Martha Field, Ph.D.

Cornell University Biochemistry and Bioinformatics, 315 Savage Hall Ithaca New York 14853 USA

Karsten Hiller, Ph.D.

University of Braunschweig Biochemistry and Bioinformatics Rebenring 56 Braunschweig Niedersachsen 38106 Germany

Christian Metallo, Ph.D.

University of California, San Diego Metabolic Systems Biology 9500 Gilman Drive, MC-0412 La Jolla California 92093 USA

Patrick Stover, Ph.D.

Cornell University Division of Nutritional Sciences 127 Savage Hall

When: 21/09/2018 - 26/09/2018

Where: Chania, Crete, Greece

Conference Center: Avra Imperial Hotel

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Linking the international scientific community Bringing the humanity scholars together

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WW. aegeanconterences.org

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Nutrient Needs are Complex Traits

Physiological Processes	Modifiers and Sensitizers
Absorption	Disease
Catabolism	Epigenetics
Excretion	Food Matrix
Metabolism	Genetics
Stability	Nutrient-Nutrient Interactions
Transport	Pharmaceuticals
Bioactivation	Toxins
Energetic State	Age/Physiological Decay
Nutrient Storage	Microbiome/Pregnancy/Sex