John W. Finley *
USDA-ARS

* Views expressed herein are those of J. Finley and do not necessarily represent those of the USDA or any other government agency
USDA–ARS PROGRAM IN HUMAN NUTRITION:

Spanning the Divide from Basic Research to Healthy Outcomes
Research Capability

Total budget: $85 m
~ 200 scientists
Diet and Genetics


Metabolomics


Analytical Methodology

IOF position statement: vitamin D recommendations for older adults

B. Dawson-Hughes • J.-P. Bonjour • S. Boonen • P. Burchhardt • G. E.-H. Fuleihan • R. G. Josse • P. Lips • J. Morales-Torres • N. Yoshimura

- Consumption of WHOLE FOODS not nutrients
  - Variability of foods
  - Dietary interactions
- The preeminence of DIET over Individual Foods
USDA-ARS: Integrating Human Nutrition with the Food Supply


Research outside of the Human Nutrition Program

Lee J, Finn CE.
Anthocyanins and other polyphenolics in American elderberry (Sambucus canadensis) and European elderberry (S. nigra) cultivars. J Sci Food Agric. 2007 Nov;87(14):2665-75.
Percent of Obese (BMI $\geq 30$) in U.S. Adults

APPLIED RESEARCH DIRECTED TOWARD DEVELOPING HEALTHIER PEOPLE

- Obesity – A National Epidemic
- A major focus of USDA-ARS
Percent of Obese (BMI \geq 30) in U.S. Adults
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• Obesity – Nutrition + Lifestyle Interventions


…… Helping HAND, a 6-month intervention, targeted children with body mass index 85-99% tile and their parents. Intervention group attended monthly sessions and self-selected child behaviours and parenting practices to change.


…… behavioral science guided the design of a serious video game health messages of how to prevent Type 2 diabetes and obesity among youth. Video game designers and behavioral scientists worked together to create a highly focused serious video game that entertains while promoting behavior change.
• Obesity – The intersection of many factors beyond genomics and diet

Body size, body composition, and metabolic profile explain higher energy expenditure in overweight children. [J Nutr. 2007 Dec;137(12):2660-7.]

Numerous factors associated with obesity and energy intake including net mechanical energetic efficiency, sex, Tanner stage, fat free mass, fat mass (FM), fasting serum nonesterified fatty acids, leptin, free thyroxine, triiodothyronine, and 24-h urinary norepinephrine and epinephrine.
• Obesity – The intersection of many factors beyond genomics and diet


Work that shows that the microbiota in the pig’s intestinal tract is changed by presence of a parasite, Trichuris suis, and that this resulted in large changes in metabolism

What Role do Grapes and Grape Products Play in Good Nutrition?

Research Needs and Gaps
Health benefits of grapes

Grapes are rich in polyphenolic ...resveratrol. Resveratrol ... plays protective function against cancers, coronary heart disease (CHD), degenerative nerve disease, Alzheimer's disease and viral/fungal infections.

Resveratrol reduces stroke risk

Anthocyanins are another class of polyphenolic anti-oxidants .... have been found to have anti-allergic, anti-inflammatory, anti-microbial, as well as anti-cancer activities.

Catechins, a type of flavonoid tannin group of anti-oxidants found in white/green varieties has also shown to have these health protecting functions.

In addition, the berries are very low in calories. 100 g fresh grapes just provide 69 calories but zero cholesterol levels.

Grapes are rich source of micronutrient minerals like copper, iron and manganese. Copper and manganese are an essential co-factor of antioxidant enzyme, superoxide dismutase. Iron is specially concentrated more in raisins. In addition 100 g of fresh grapes contain about 191 mg of health benefiting electrolyte, potassium.

They are also good source of vitamin-C, vitamin A, vitamin K, carotenes, B-complex vitamins such as pyridoxine, riboflavin, and thiamin.
Consider the reality of former Nutritional Superstars

Health Claims About Grapes
Selenium: A trace mineral with antioxidant properties, selenium may be useful in preventing arthritis and other conditions, including age-related blindness, cancers, cardiovascular disease, cataracts and kidney disease. You’ll get selenium from whole-grain wheat products and shellfish, such
SELENIUM AND CANCER – THE GREAT NUTRITIONAL STAR

**PUBMED:**

- Selenium & Cancer  = > 3,500 hits – most showing positive benefit
- Selenium & Cancer & Epidemiology ~ 400 hits, most positive benefit
- Selenium & Cancer & Clinical Trial ~ 600 hits, most positive benefit
THE NUTRITIONAL PREVENTION OF CANCER (NPC) TRIAL

- 1312 participants; mean age = 63
- Intervention – 200 ug Se/d as Se-enriched yeast or placebo
- Primary endpoint = skin cancer
RESULTS

• Slight increase in benign skin cancer

• BUT secondary analysis =
  • 50% decrease in all cancer mortality
  • 70% decrease in prostate cancer
  • Significant reduction in lung and colo-rectal cancer

FDA Qualified Health Claim:
"Selenium may reduce the risk of certain cancers. Some scientific evidence suggests that consumption of selenium may reduce the risk of certain forms of cancer. However, FDA has determined that this evidence is limited and not conclusive."
THE SELECT TRIAL

- Largest prostate cancer trial ever funded by NIH
- 35,000 participants
- 200 ug Se/d (as selenomethionine) or vitamin E (400 I.U./d as D,L alpha-tocopherol) or placebo
- Planned for 12 years, but stopped at interim:
THE SELECT TRIAL

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- 200 ug Se/d (as selenomethionine) or vitamin E (400 I.U./d as D,L alpha-tocopherol) or placebo
- Planned for 12 years, but stopped at interim:
  - NO benefit to cancer
  - Slightly elevated (non-significant) diabetes risk from Se
  - SIGNIFICANT INCREASE in prostate cancer from vitamin E
THE SELECT TRIAL

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FDA amended Health Claim:

“Two weak studies suggest that selenium intake may reduce the risk of prostate cancer. However, four stronger studies and three weak studies showed no reduction in risk. Based on these studies, FDA concludes that it is highly unlikely that selenium supplements reduce the risk of prostate cancer.”
Selenium: Ongoing trials to reverse negative press and boost sagging sales?

According to new data from SPINS, sales of supplements with selenium as the principle ingredient were $4.7 million for the current 52-week period ending May 2011 from $5.5 million versus the prior period.

Paul Willis, CEO and president from Cypress Systems, a Fresno-based biotechnology company and producer of high selenium yeast, said that decline is due “in large part to the negative press created by the 2008 termination of the SELECT trial by the National Cancer Institute (NCI)”. 
ATBC trial: \( \beta \)-carotene supplementation = 18\% INCREASE in lung cancer (29,000 male smokers)

PNAS report of Ristow et al: Antioxidants prevent health-promoting effects of physical exercise in humans

JAMA meta analysis: Treatment with beta carotene, vitamin A, and vitamin E may increase mortality.
The U.S. Food and Drug Administration's evidence-based review for qualified health claims: tomatoes, lycopene, and cancer. Kavanaugh CJ, Trumbo PR, Ellwood KC.

The FDA found no credible evidence to support an association between lycopene intake and a reduced risk of prostate, lung, colorectal, gastric, breast, ovarian, endometrial, or pancreatic cancer. The FDA also found no credible evidence for an association between tomato consumption and a reduced risk of lung, colorectal, breast, cervical, or endometrial cancer. The FDA found very limited evidence to support an association between tomato consumption and reduced risks of prostate, ovarian, gastric, and pancreatic cancers.
EFSA mass rejects probiotics and antioxidants as article 13.1 batch two published

By Shane Starling, 25-Feb-2010; Beverage Daily.com

The European Food Safety Authority (EFSA) has issued negative opinions to ‘most’ of 416 health claim dossiers including submissions linking health benefits to vitamin D, probiotics, green tea, black tea, lutein, beta glucans, meso-zeaxanthin, alpha-lipoic acid and melatonin.
Dear Mr. Yates:

This is to advise you that the Food and Drug Administration (FDA) reviewed your websites at the Internet addresses http://www.Nestle-Nutrition.com, www.NestleNutritionStore.com, and http://www.kidessentials.com in November 2009. Your BOOST Kid Essentials Nutritionally Complete Drink (Vanilla, Chocolate, and Strawberry flavors) is promoted on your websites as a "medical food," and the labeling claims on your websites represent the product as a medical food.
SO HOW CAN WE AVOID THESE POTHOLES IN THE ROAD?????

The need for Evidenced-Based nutrition
Evidence-based medicine (EBM)
(from Wikipedia)

- Applies the best available evidence gained from the scientific method to medical decision making.
- Assesses the quality of evidence of the risks and benefits of treatments (including lack of treatment).
- EBM seeks .....to apply these methods to ensure the best prediction of outcomes in medical treatment.
1. Predicted (no evidence); Organic food is more nutritious?
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2. Chemistry; e.g. ORAC
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4. Animal studies
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But all the above only generate HYPOTHESES

Evidence requires human studies
Valid biomarkers

Many common biomarkers NOT acceptable to FDA

- Cancer
  - PSA
  - COMET assay and similar
  - Gene activation
  - Enzyme activity
  - Circulating cytokines
Valid biomarker

Accurate estimate of intake
- Validated Food Frequency Questionnaire
  - Secondary measures help validate:
    - Urinary nitrogen $\sim$ protein intake
    - Doubly labeled water $\sim$ energy intake
- Surrogate markers of intake
  - Serum conc., enzyme activity, etc.
Epidemiologic evidence
Judging study value:

- Valid biomarker
- Accurate estimate of intake
- Relevant/Adequate survey population
- Valid baseline or comparative group
  - DRUGS cure ill health,
  - FOOD maintains good health
  - Use Healthy subjects
**Epidemiologic evidence**

**Judging study value:**

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**Lack of ‘bias’**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Most often encountered</th>
<th>Solution</th>
</tr>
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<tbody>
<tr>
<td>Selection</td>
<td>Case/control/RPC</td>
<td>Care in selection/none</td>
</tr>
<tr>
<td>Recall</td>
<td>Retrospective</td>
<td>Care/statistics</td>
</tr>
<tr>
<td>Attrition</td>
<td>Prospective/RPC</td>
<td>None/statistics</td>
</tr>
<tr>
<td>Detection</td>
<td>All</td>
<td>Validate all measures</td>
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<tr>
<td>Expectation</td>
<td>All</td>
<td>Objective measures</td>
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<tr>
<td>Compliance</td>
<td>RPC</td>
<td>Control measures</td>
</tr>
<tr>
<td>Confounding</td>
<td>All/esp. Epideme</td>
<td>Statistics</td>
</tr>
</tbody>
</table>
Epidemiologic evidence
Judging study value:

- Valid biomarker
- Accurate estimate of intake
- Relevant/Adequate survey population
- Valid baseline or comparative group
- Lack of ‘bias’

- Adequate statistics
  - Sample size (Power analysis)
  - Randomization
  - Sequence effects (e.g. day length)
  - Proper design
    - Controls
    - Validated measures
Epidemiologic evidence
Judging study value:

- Valid biomarker
- Accurate estimate of intake
- Relevant/Adequate survey population
- Valid baseline or comparative group
- Lack of ‘bias’
- Adequate statistics

Are conclusions justified?
- Do data support conclusions?
- Where are conclusions published?
- Are they relevant to the target population?
- Do they fit known chemistry/metabolism?
Intervention studies - Food, NOT drugs
1. Conceptualization/need
   - Purpose of study
   - Background/history

Exploratory research?
Data for label/claims/advertising?
Toxicity?
GRAS?
1. Conceptualization/need
2. Design - Statistical
   - Involve a statistician at BEGINNING!
   - Make only valid/necessary measures
     - Remember “p=0.05” means chance alone accounts for 5/100 sig. differences
     - Make contrasts a priori
     - Avoid ‘data mining’
   - Design
     - Repeated measures?
       - Adequate washout?
     - Simple randomized block?
     - Have you adjusted for: gender, age, menopause, smoking, general health, screening clinicals, day length, physical activity, baseline diet, supplement use?
1. Conceptualization/need
2. Design – Statistical
3. Use the correct population

What is the objective?
Top questions for Grape/Wine

1. What do you want to do?
   a. Sell more product
      a. Which products?
      b. Are you willing to treat products differently (e.g. raisins vs table grapes vs grape seed extract vs wine)?
   b. Ascertain health benefits

2. What is the state of the nutritional data?
   a. A critical analysis
   b. How would FDA/IOM view the evidence?
   c. How universal are results?
   d. What are the gaps (see question 1)?

3. How much do you have to spend (a discount clinical trial may not be worth the money)

4. Who should be approached for collaboration?