Nutrigenetics and Nutrigenomics in Clinical Research and Practice

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Outline

NGx lessons for clinical research

Analyzing study data

Optimizing study design

Applications for clinical practice

Utility in practice

Some genotype-nutrient interactions

Nutrition guidance
Application in Clinical Research
Analyzing study data

Jacob et al., J Nutr 1994
Application in clinical research

Analyzing study data

Jacob et al., J Nutr 1994
Application in clinical research

Statistical analysis

\[ t = \frac{\bar{x}_1 - \bar{x}_2}{\sqrt{\frac{S_1^2}{N_1} + \frac{S_2^2}{N_2}} / \sqrt{n}} \]
Design and analysis

Controlled feeding trial of 126 adults for 4 months at four folate intake levels

% change of Hcys levels

µg DFE Intakes

226 282 660 814

-35 -30 -25 -20 -15 -10 -5 0

CC CT TT

MTHFR Genotypes

Ashfield-Watt et al., Am J Clin Nutr 2002
Optimizing study design

SUBJECTS AND METHODS

Study population

Healthy adults between the ages of 18 and 65 y of age were recruited between September and October 2008 by public advertisement from the University of Toronto community. During an initial screening visit in the Clinical Investigation Unit at The Hospital for Sick Children, individuals provided a venous blood sample to confirm normal red blood cell (RBC) folate concentrations and determine their 5,10-methylenetetrahydrofolate reductase (MTHFR) 677C>T genotype. Individuals shown to be homozygous for the T allele were excluded from participating in the study to minimize potential intersubject differences in the way folate was metabolized. Blood samples were also analyzed in the Core Laboratory Facilities at The Hospital for Sick

TT prevalence is 10-30%

Lakoff et al., Am J Clin Nutr 2015
Optimizing study design

FOLATE ABSORPTION ACROSS THE COLON

Lakoff et al., Am J Clin Nutr 2015
Optimizing study design

It might have been better to select participants with the same PCFT rs2239907 genotype (minor allele frequency 0.33) since blood was the targeted compartment.
Design and analysis

Public Health Nutrition: 18(8), 1514–1521

Review Article

The effect of folate fortification on folic acid-based homocysteine-lowering intervention and stroke risk: a meta-analysis

Key point:
Once a genetically heterogeneous response has been credibly observed, from then on it cannot be ignored.
Applications for Clinical Practice
Evaluation of genetic information

Before a genetic test can be generally accepted in clinical practice, data must be collected to demonstrate the benefits and risks that accrue from both positive and negative results.

Final Report of the Task Force on Genetic Testing:
*Promoting Safe and Effective Genetic Testing in the United States*
National Institutes of Health-Department of Energy Working Group on Ethical, Legal and Social Implications of Human Genome Research, September 2007
Evaluation of genetic information

• Analytical validity (is the result correct)
• Clinical validity (sensitivity/specificity)
• Clinical utility (is it worth it)

Foundation for Blood Research/CDC, 2004
Clinical utility of genetic information

• Clinical utility takes into account the impact and usefulness of the test results to the individual, the family, and society.
• The benefits and risks to be considered include the psychological, social, and economic consequences of testing as well as the implications for health outcomes.

Secretary’s Advisory Committee on Genetic Testing, 2008
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Clinical utility = “net benefit”
Utility of genetic information

In how many cases is the outcome better with the information than without it?

Outcome is the balance of

- benefits
- and
- harms
A brief digression about nutrigenetic harms

Such harms are mostly related to

- Expenditures and opportunity costs
- Misguided use of risky therapies
- Psychological and social burdens
- Insurance and employment risks
Evaluation of genetic information

How to reduce harms

By eliminating exposure to genetic information

benefits and harms
How to reduce harms

By eliminating exposure to genetic information

Patients and clients need nutrition guidance, not DNA sequence data!
Evaluation of genetic information

How to reduce harms

By protecting sensitive genetic information

In many cases it is best not to record genetic information in patient files because privacy cannot be ensured.
Practice-ready Examples
Case Study: Folate intake and homocysteine

- **MTHFR 677TT**
- **MTHFR 677CC**

<table>
<thead>
<tr>
<th>Homocysteine (µmol/L)</th>
<th>Dietary Folate Equivalents (µg/day)</th>
<th>Δ Hcys</th>
<th>Δ MI risk</th>
<th>stroke risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.04 µmol/L</td>
<td>RDA</td>
<td>-15 %</td>
<td>-24 %</td>
<td></td>
</tr>
<tr>
<td>0.64 µmol/L</td>
<td>2xRDA</td>
<td>-3 %</td>
<td>-5 %</td>
<td></td>
</tr>
</tbody>
</table>

- **677CT**
- **677CC**
- **677TT**

Practice-ready examples
Case Study: Folate intake and homocysteine

What you want to do in practice:
Guide individuals with two MTHFR 677 T alleles (rs1801133 TT) to get at least 600 µg dietary folate equivalents.
Case Study: Folic acid and breast cancer

52% increase in breast cancer risk
5% decrease in breast cancer risk

Based on data from Xu et al. AJCN 2007;85:1098-1102
Case Study: Folic acid and breast cancer

What you want to do in practice:
Guide women with a DHFR 19 bp del allele to get generous amounts of folate from plant sources and avoid supplements and fortified foods with folic acid.
Case Study: Coffee and myocardial infarction

Data from Cordelis et al. JAMA 2006;295:1135-1141

Prevention potential: Screen 2200 middle-aged men, adapt recommendation for 1000, to prevent 2-4 MI per year. Additional benefits are possible.
Case Study: Coffee and myocardial infarction

What you want to do in practice:
Guide men with a CYP1A2*1F allele (rs762551 C) to caffeine intakes of less than 200 mg/day
Case Study: Saturated fat and obesity

BMI difference of 2.1

Prevention potential:
Screen 1,000 people, adapt recommendation for 150, prevent 12-14 pounds weight gain in more than half of them.

Case Study: Saturated fat and obesity

What you want to do in practice:
Guide carriers of two APOA2 alleles C (rs5082 CC) to limit their saturated fat intake to less than 12 g/day
Nutrition Guidance
Nutrition guidance

Assessment → Targets → Planning
Nutrition guidance

Assessment
- Age
- Gender
- Weight
- Height
- Exercise Conditions
- Medications
- Genetics

Targets
- Diet patterns
- Food groups
- Macronutrients
- Fats
- Minerals
- Micronutrients
- Bioactives

Planning
- Behavioral Change (limit snacking)
- General guidelines (eat more vegetables)
- Specific directions (limit to 1 cup of coffee)
- Meal plans and tips
- Dietary supplements (300 IU Vitamin E)
Do you know where your genetic data go?
Dangerous information

What if it was sent to you on a postcard?

Dear Alec,
Glad you’re having fun.

<table>
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<tr>
<th>SOD2</th>
<th>rs2758331</th>
<th>AA</th>
</tr>
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<tr>
<td>SOD2</td>
<td>rs2855262</td>
<td>CC</td>
</tr>
<tr>
<td>SOD2 A18V</td>
<td>rs4880</td>
<td>GG</td>
</tr>
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Sincerely yours
Genetic data is quite public

Where else does it go?
- Spouse, family, friends
- Medical files
- Insurer files
- Employer files
- Legal files
- Research files
- Corporate files
Anonymized use of genetic data

- The lab may not know the client’s identity and user-linked genetic information cannot be leaked.

- The client receives personalized nutrition information without exposure to raw genetic data.
What is the need?

Setting the individual targets is hard enough

<table>
<thead>
<tr>
<th>Nutrition Item</th>
<th>My Targets</th>
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<tr>
<td>Calories</td>
<td>1616 kcal</td>
</tr>
<tr>
<td>Protein</td>
<td>40 g</td>
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<tr>
<td>Saturated Fat</td>
<td>&lt;= 9 g</td>
</tr>
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<td>Cholesterol</td>
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<td>Folate</td>
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<td>Iron</td>
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<tr>
<td>Sodium</td>
<td>&lt;= 1096 mg</td>
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<tr>
<td>Magnesium</td>
<td>&gt; 334 mg</td>
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<td>Red Meat</td>
<td>&lt;= 104 g</td>
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<tr>
<td>Fruits/Veggies</td>
<td>&gt; 626 g</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>2436 IU</td>
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<tr>
<td>Preformed Vit. A</td>
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<td>Beta-Carotene</td>
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Now the really difficult part: making food choices

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What is the need?

Client

Foods should match the targets

Professional
Personal Online Nutrition Guidance

Gluten-free
Lactose-free
Genotype-specific

Vegetarian
Vegan
Low-Carb
Users can enter data describing their individual characteristics and lifestyle, review estimated intake targets, and develop their own meal plans.

The minimal required input is age and gender. All additional data entries are at the user’s discretion.

Target estimates are recalculated every time the user enters additional or changed information.
Users can view meal plans that meet their individual needs and dietary preferences.

The user gets help with understanding how well the displayed meal plan meets targets. Alternative food items and recipes can be viewed that match the user’s needs and preferences.
11th Congress of the International Society of Nutrigenetics and Nutrigenomics
Los Angeles, CA  September 16-19, 2017

REGISTRATION NOW OPEN!!!

September 16-19, 2017
Los Angeles, CA, USA

https://isnn2017.org
Questions?