



Realizing the Health Benefits of Genomics

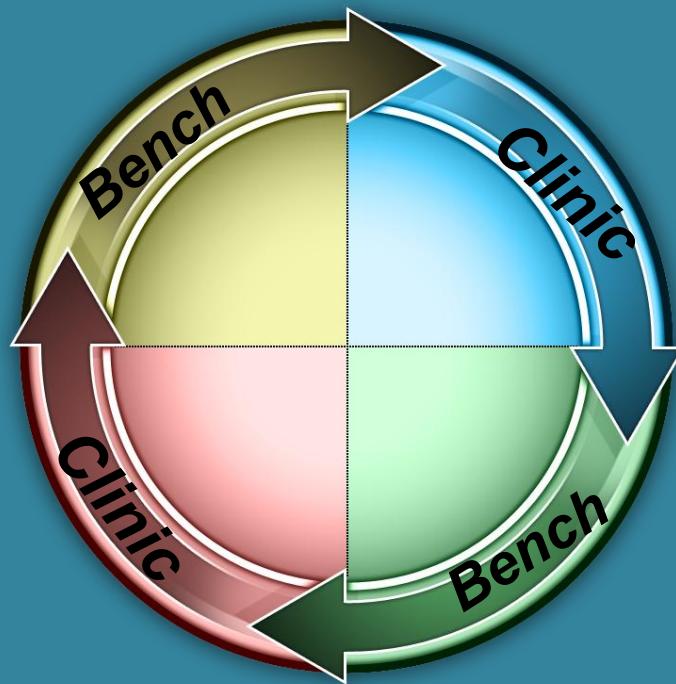
Which way for translational research?

**Colleen M. McBride, Ph.D.
Social & Behavioral Research Branch
Public Health Genomics Seminar**

Assumptions/Questions to Consider

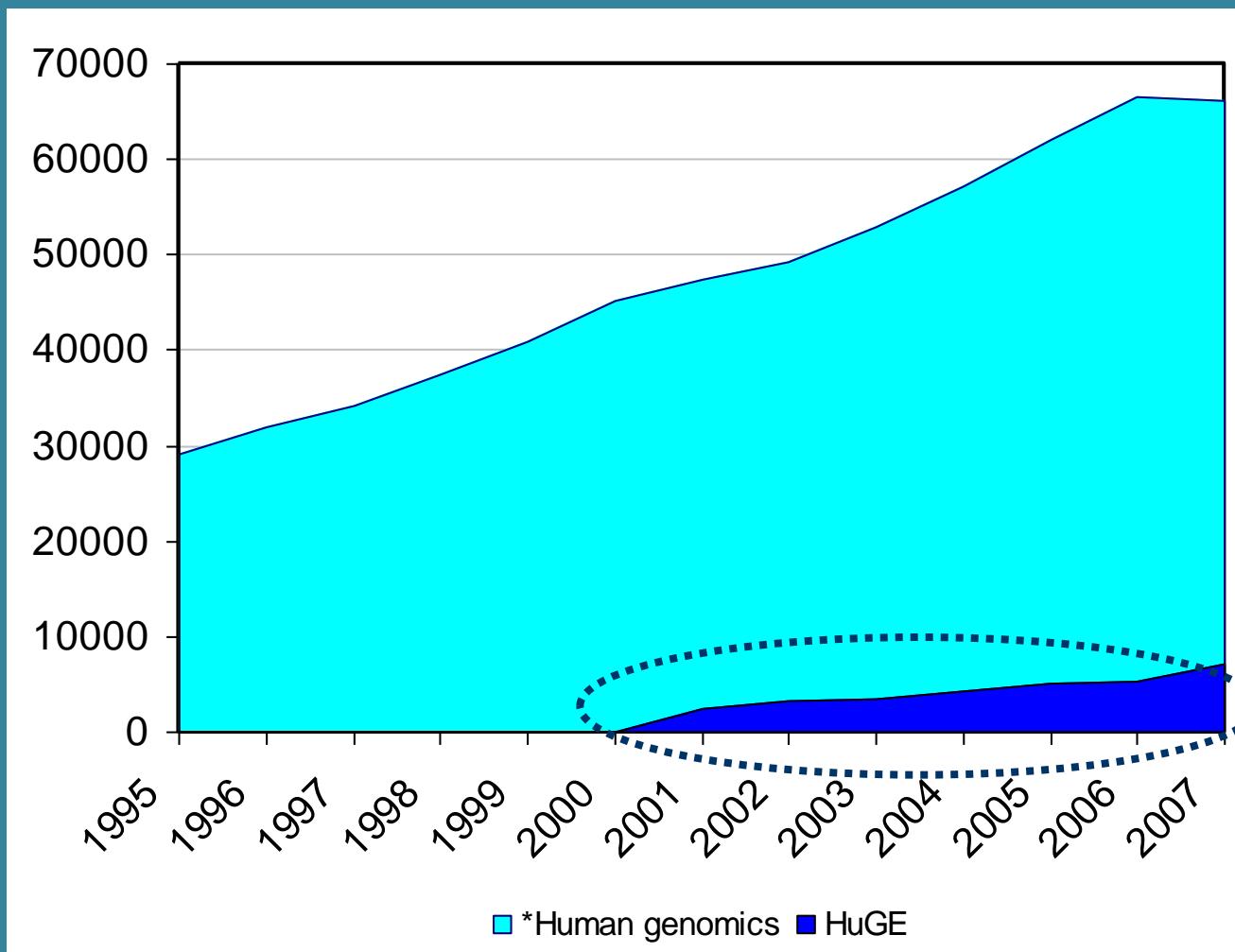
- **Amidst rapid discovery, when is the “right” time to start translational research?**
 - E.G. Do we have wait for established clinical validity before starting TR?
- **What could we learn now that would help us understand in what instances genomic products could be useful?**
 - E.G. Will having precise risk estimates make any difference in applying genomics to improve health outcomes?

NIH Roadmap Defines Translational: “translate new knowledge to the clinic – and back again to the bench”



When is the “right” time to start translational research?

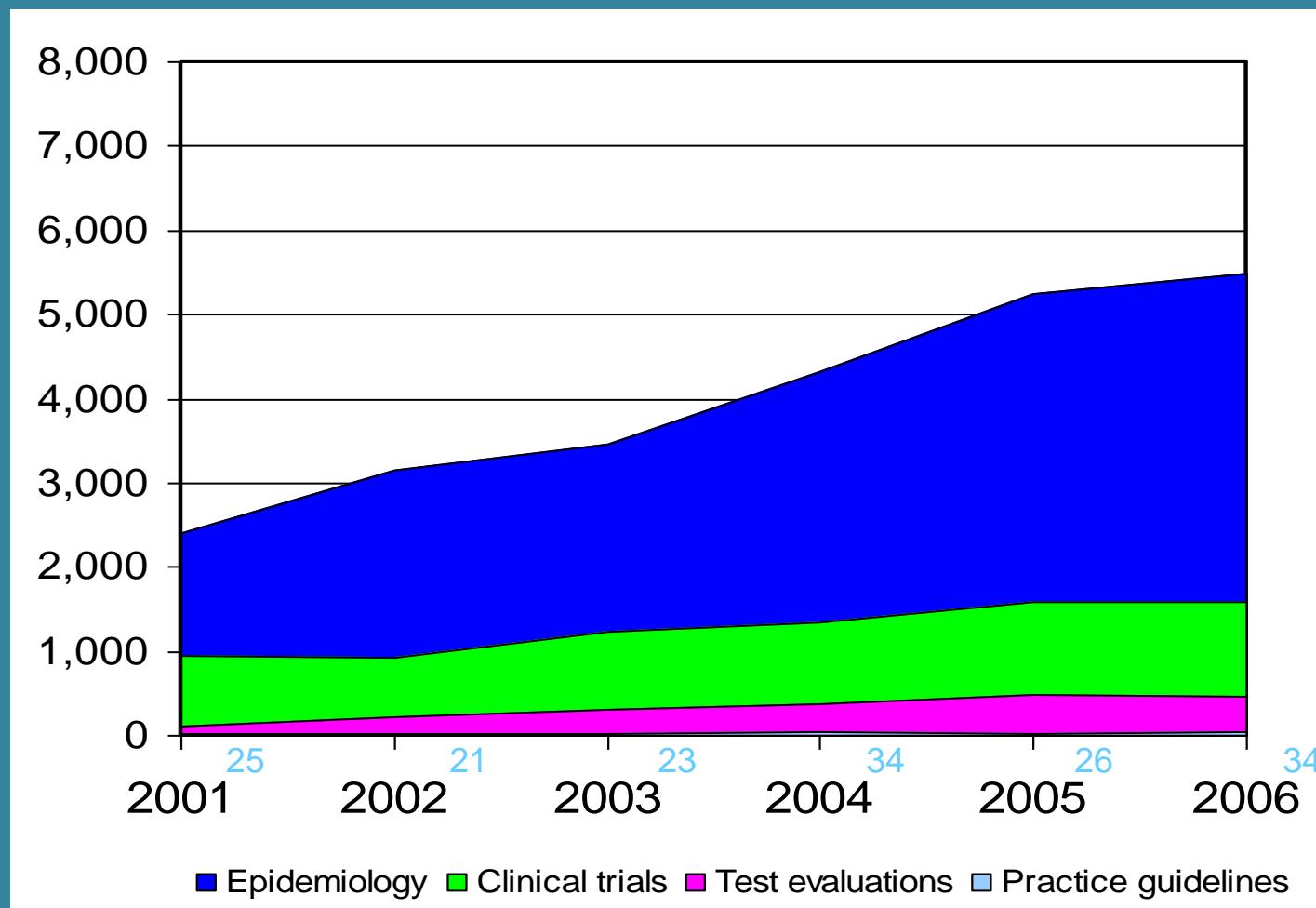
Publications related to human genetics/genomics, PubMed, 2001-2007*



NOPHG, CDC --*based on PubMed, HuGE Navigator, Aug 2008

HUMAN GENOME RESEARCH INSTITUTE
Division of Intramural Research

Numbers of publications related to human genetics and genomics, 2001-2006*

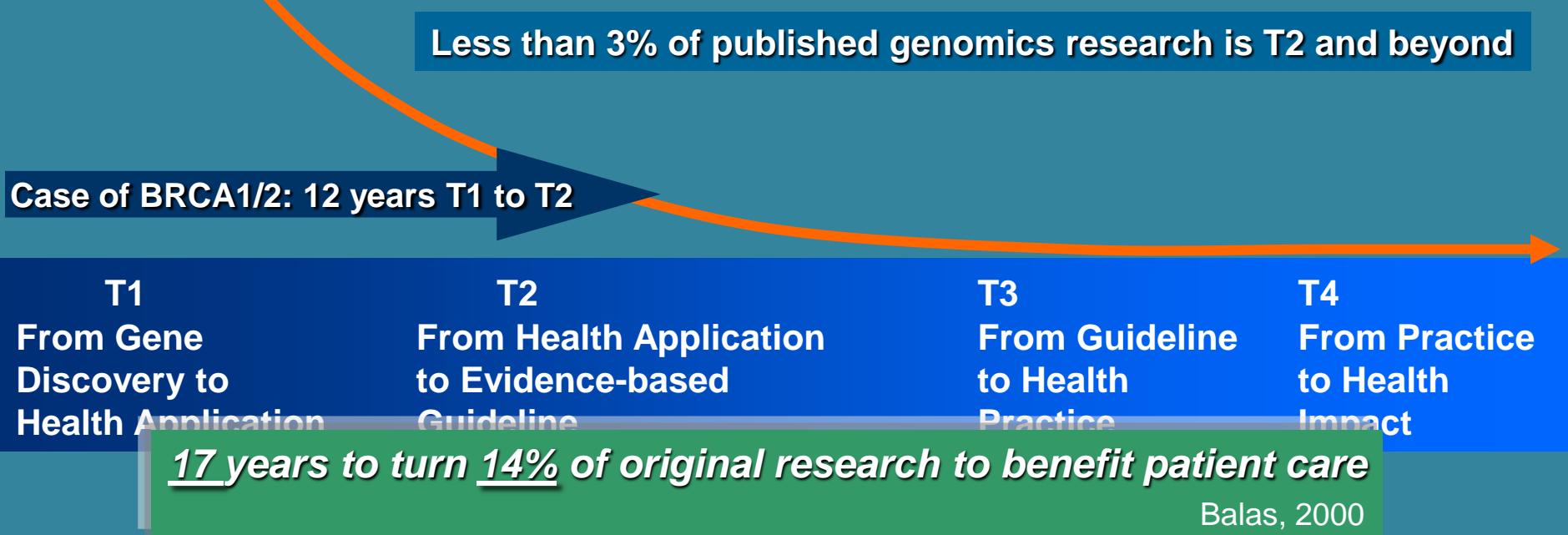


*Gwinn et al., from PubMed -- HuGE Navigator

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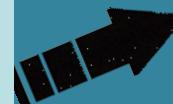
The Translation Continuum from Gene Discovery to Population Health



Bridging the Research-Application Gap:

Goal: To develop an evidence-based practice to maximize Impact, adoption, reach

Science “Push”:
Documenting, improving, &
communicating the knowledge
for broad population use



Delivery capacity

Building the capacity of
relevant systems to apply
the knowledge



Market “pull” & demand

Building a market &
demand for the

The screenshot shows the Navigenics website with a dark header containing the logo and navigation links for About, Leadership, Policies, and Contact. Below the header is a main banner featuring a man's face and the text "My Genes. My Health. My Life. My Guide." A sidebar on the right is titled "The Navigenics advantage" and includes text about being at the forefront of genetics revolution and a list of bullet points. At the bottom, there are sections for "Video Not Available" and "Your genes offer a road map to optimal health".

Trailblazing a research agenda

Optimal application

Translation Research

Lost in translation



Premature translation

The Navigenics website homepage features a dark header with the company logo and navigation links for About, Leadership, Policies, and Contact. Below the header is a large image of a man sitting on a couch. To his right, a blue box contains the text "My Genes. My Health. My Life. My Guide.". Below the image, a message states "Video Not Available" and provides instructions for viewing. At the bottom, a red link reads "Your genes offer a road map to optimal health".

challenge Assumed Path of Scientific Development

Trailblazing

- **Stage 5: Consider existing health challenges/unmet needs**
- **Stage 5: Anticipate how discovery could address challenges**
- **Stage 1: Basic Research**
- **Stage 2: “Treatment” Development**
- **Stage 3/4: Efficacy/Effectiveness**

T1 From Gene Discovery to Health Application	T2 From Health Application to Evidence-based Guideline	T3 From Guideline to Health Practice	T4 From Practice to Health Impact
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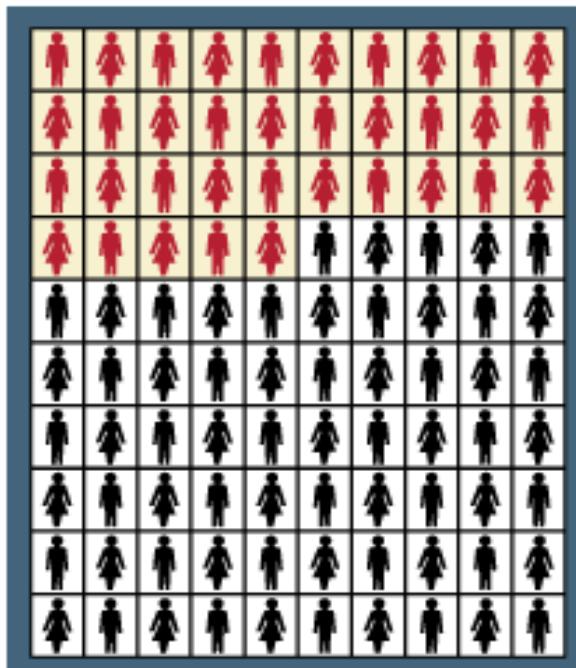
What could we learn now that would help establish potential utility of genomic products?

What is someone's chance of getting diabetes in their lifetime if they have any KCNJ11 risk versions?

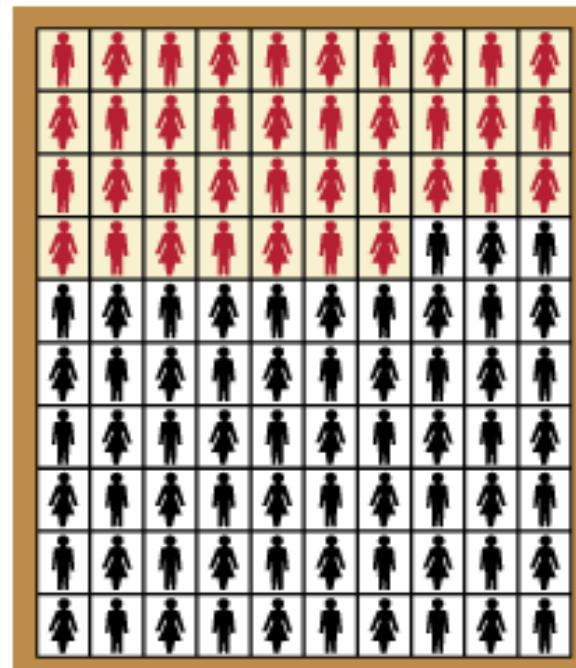
- People who have **no risk versions** of KCNJ11 will have, on average, a 35 in 100 chance of getting diabetes.
- People who have **1 risk version** of KCNJ11 will have, on average, a 37 in 100 chance of getting diabetes.
- People who have **2 risk versions** of KCNJ11 will have, on average, a 43 in 100 chance of getting diabetes.

Chance of getting diabetes based on the number of risk versions of KCNJ11
(Out of 100 people. People with diabetes are shown in red.)

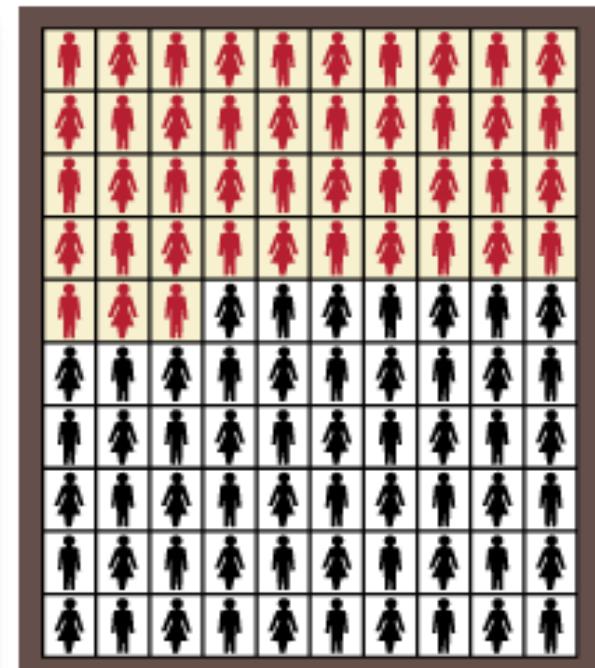
0 Risk Versions



1 Risk Version



2 Risk Versions



1990's Clinical Trials: Genetic feedback effects on smoking cessation

Percent not
smoking

CYP2D6

N=426

40
20
0

14 16 16

2 months

Cessation co

Lerman et al., 1997; Audrain

Percent not
smoking

GSTM1
N=308

40
20
0

23

17

6 months

15 18

12 months

12 12

Continuous

Missing Present

McBride, Bepler et al., 2002

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Welcome to the FAMILY RISK AND LUNG CANCER STUDY

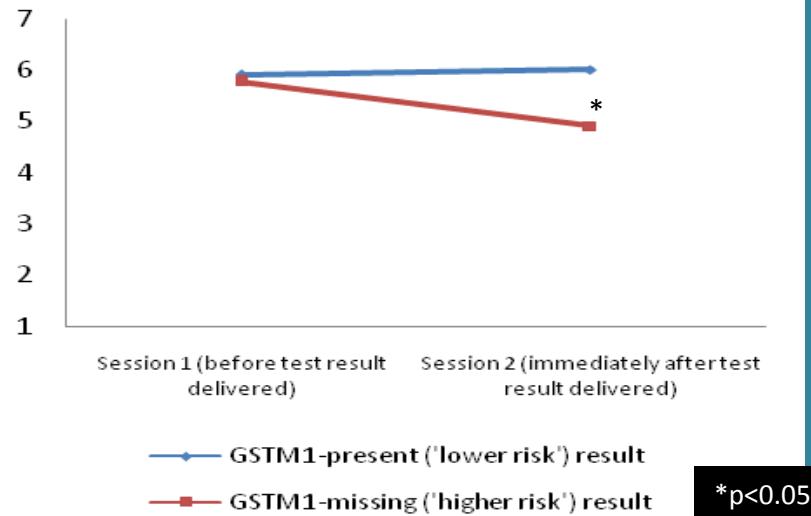
Thank you for Participating!



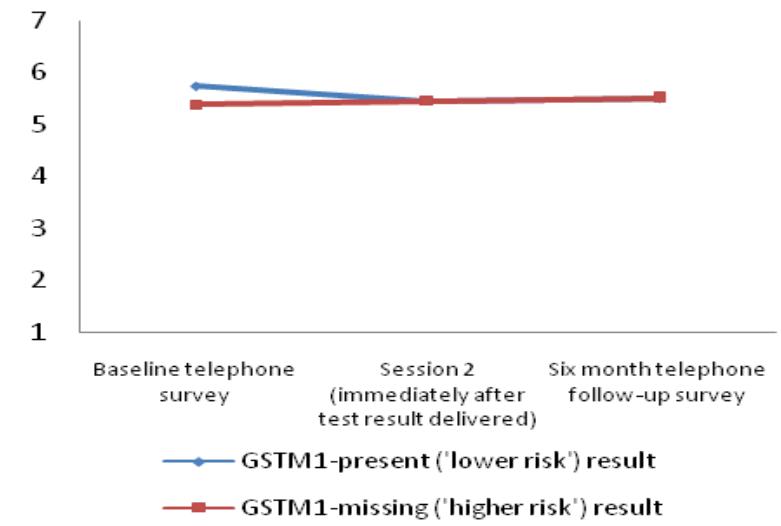
NEXT

Response to test results

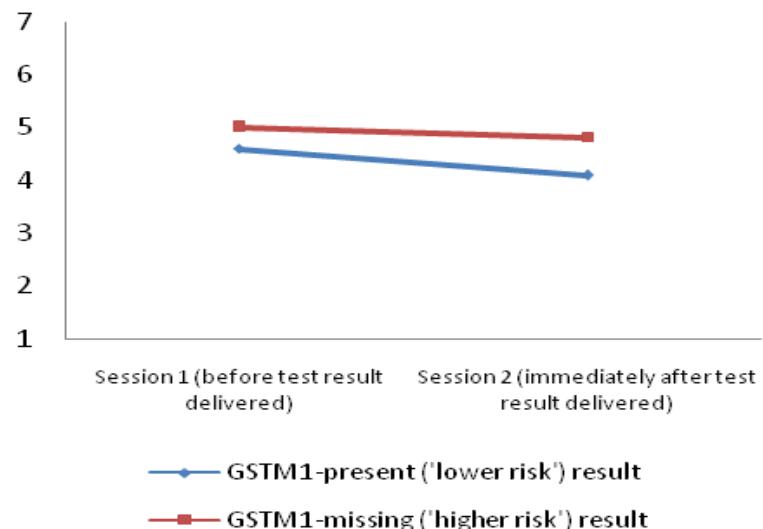
Perceived response-efficacy



Perceived risk



Perceived self-efficacy



Sanderson et al, CEBP in press

The Multiplex Initiative



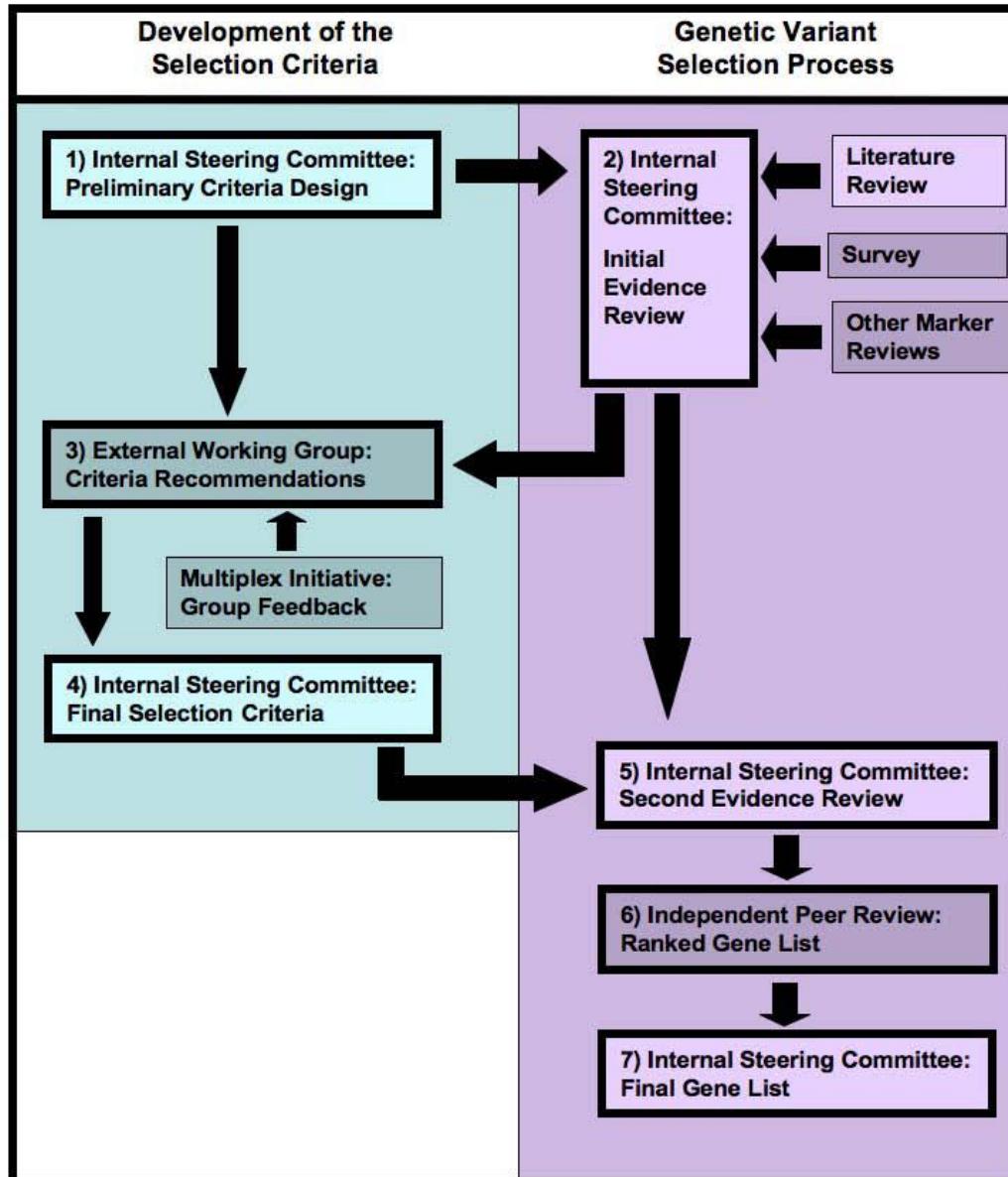
New Participants

Returning Participants

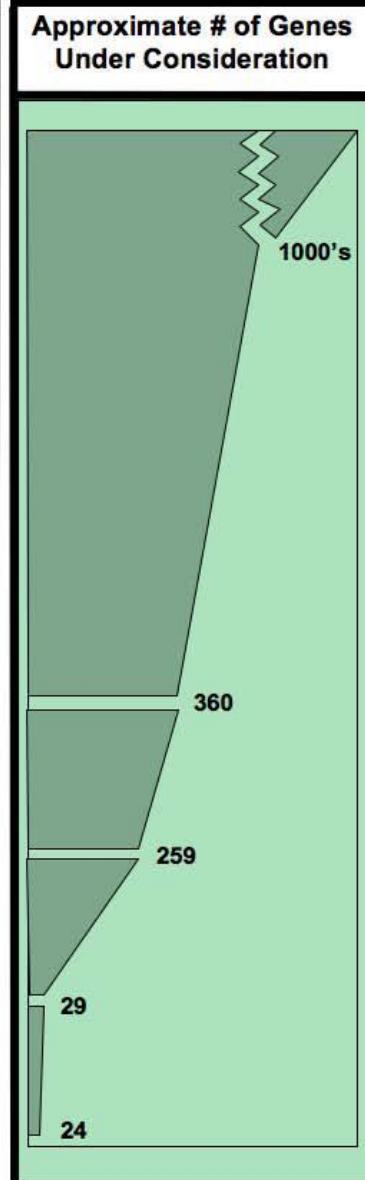
Health Care Providers | Researchers

Genetic Markers: Selection Process

A)



B)



From: Wade, McBride, Kardia, Brody, under review

Multiplex Prototype Test

8 health conditions & 15 genes

Diabetes

- KCNJ11
- CAPN10
- PPARg
- TCF7L2

Heart Disease

- APOB
- NOS3
- CETP

High Cholesterol

- LIPC

Hypertension

- AGT

- Lung cancer
 - MPO
- Colon Cancer
 - MTHFR
- Skin Cancer
 - MC1R
- Osteoporosis
 - ESR1
 - IL6
 - COL1A1

Study Population

➤ Cancer Research Network (NCI-funded)

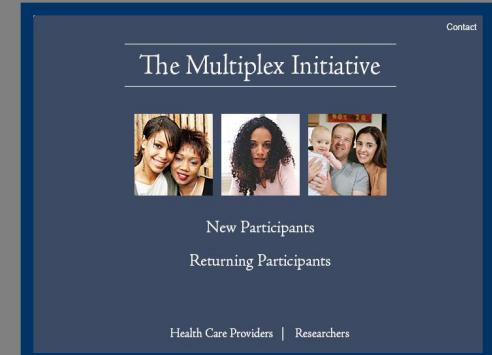
- Henry Ford Health System clinical recruitment site
 - Group Health Cooperative Survey coordination

➤ Sample:

- 5000+ touched ~ 500 tested

➤ Healthy adults

- Ages 25-40
- Without diseases on test battery



New Horizons in Personalization

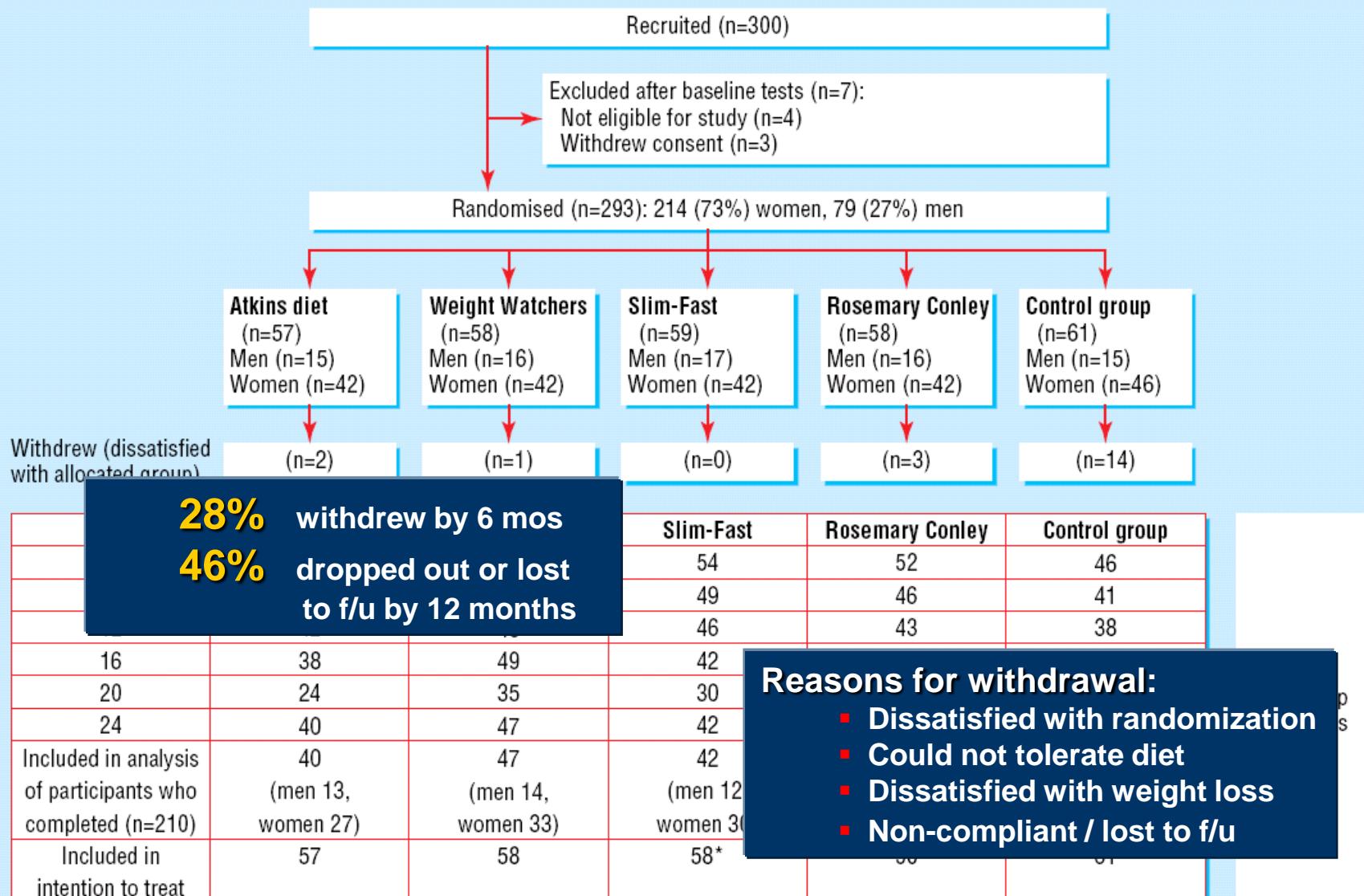
	<u>Marker</u>	<u>Function</u>
Type 2 Diabetes	PPAR gamma KCNJ11 TCF7L2	Fat cell development Stronger risk messages
Myeloid leukemia	CYP1A1 CYP1B1	Phase I enzymes activating environmental carcinogens

> 400 genes involved in obesity

- Adipocyte growth & differentiation
- Energy expenditure
- Individual response to caloric restriction
- Appetite control

Enabling interventions to be individualized to specific behavioral phenotypes

Randomized controlled trial of four commercial weight loss programmes in the UK



*1 excluded because of pregnancy

PAPER

Difficulty in losing weight by behavioral intervention for women with Trp64Arg polymorphism of the β_3 -adrenergic receptor gene

K Shiwaku^{1*}, A Nogi¹, E Anuurad¹, K Kitajima¹, B Enkhmaa¹, K Shimono¹ and Y Yamane¹

¹Department of Environmental Medicine, Shimane Medical University, Izumo City, Shimane, Japan

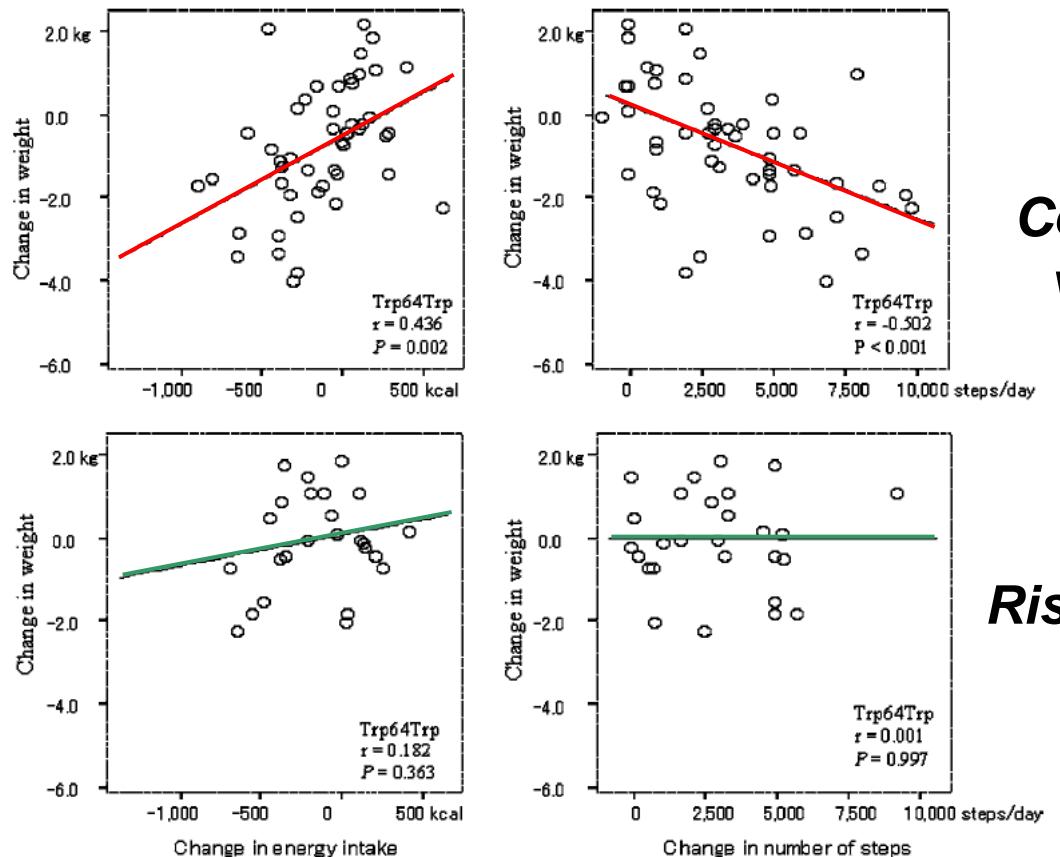


Figure 1 Correlation between weight loss and changes in energy intake or number of steps Pearson's correlation coefficients associated with weight loss and P values were expressed.

A Transdisciplinary Model Integrating Genetic, Physiological, and Psychological Correlates of Voluntary Exercise

Bryan, Hutchison, Seals, Allen, 2007

CORRELATES OF VOLUNTARY EXERCISE

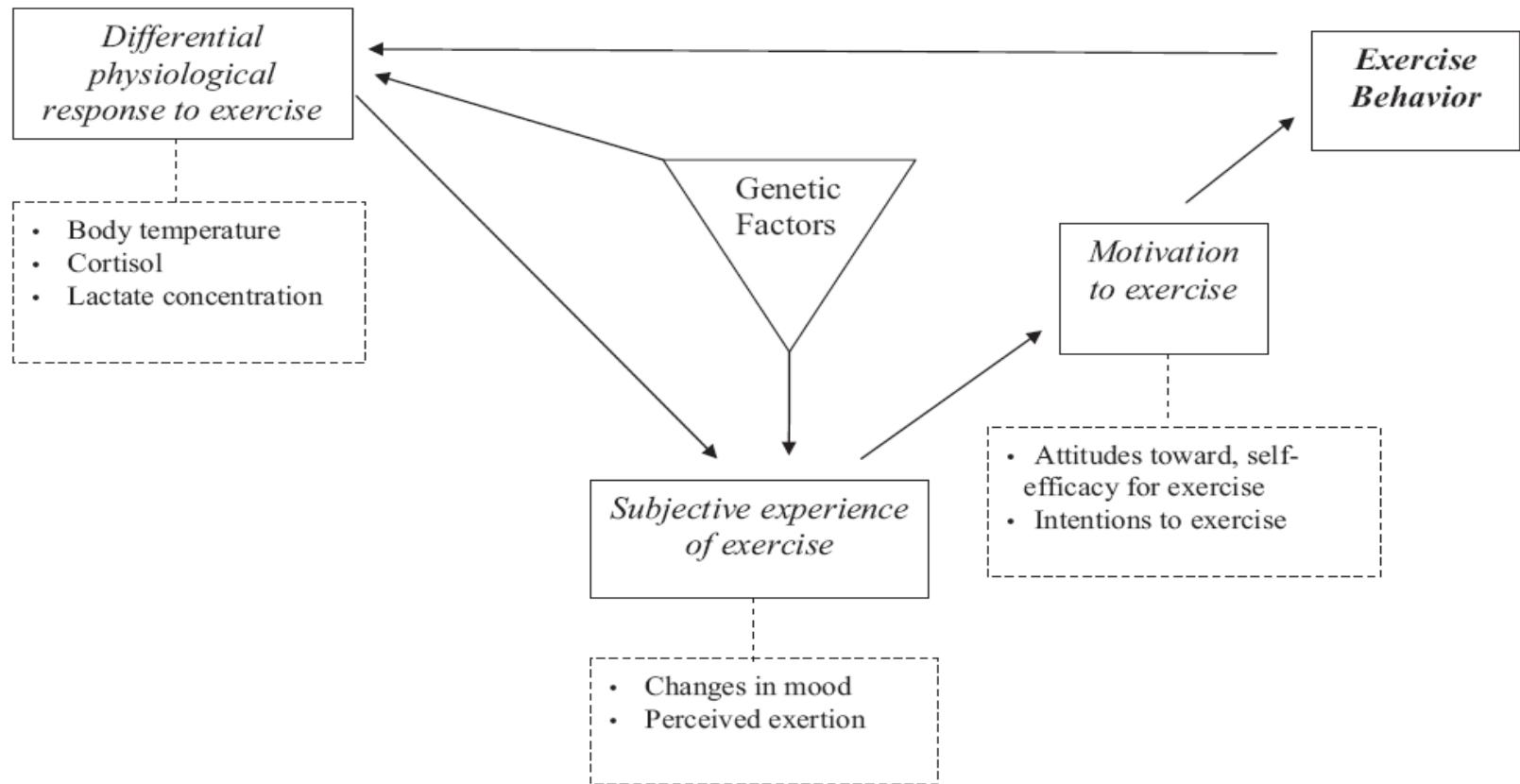
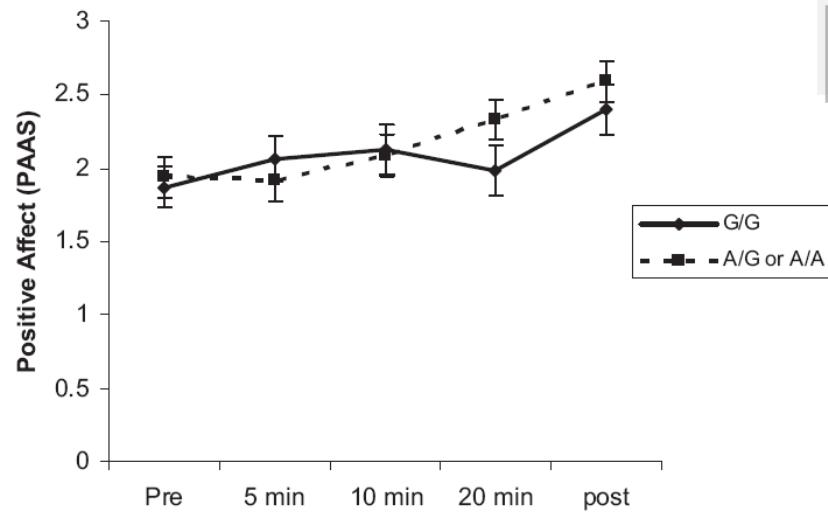
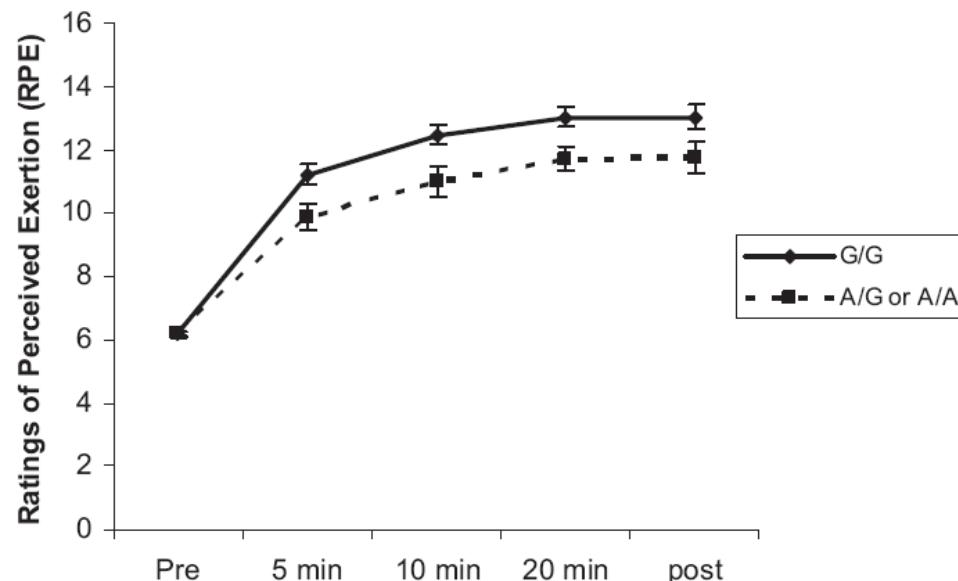


Figure 1. Transdisciplinary model of exercise behavior.

CORRELATES OF VOLUNTARY EXERCISE



Positive Affect

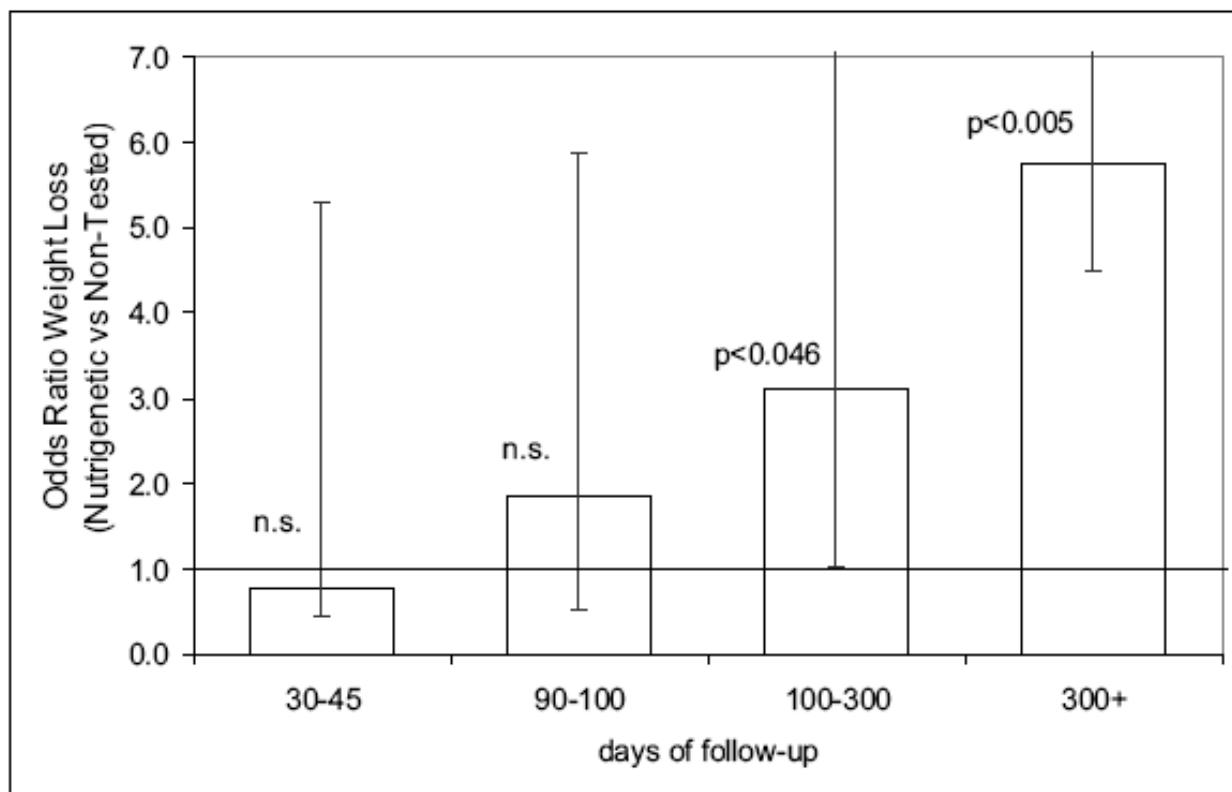


Perceived Exertion

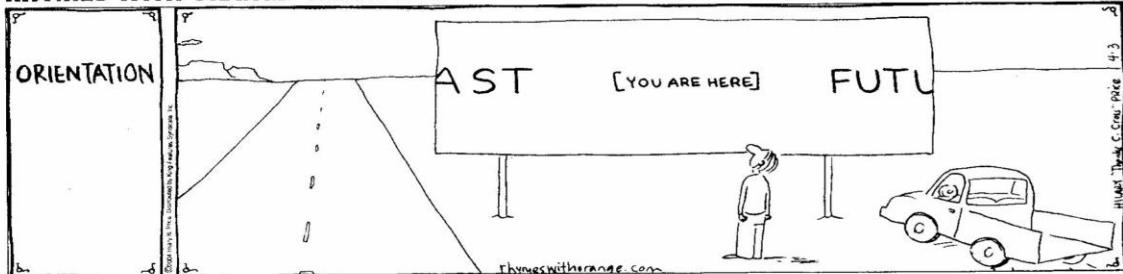
Research

Improved weight management by personalizing a calorie-controlled dietIoannis Arkadianos¹, Ana Rosalynn D Gill⁴ and Keith

- **Patients with hx of failed wt loss**
- **50 patients
43 controls**
- **19 genes
7 categories
amenable to intervention**
- **Personal & specific advice based on genotype**

**Figure I**

Odds ratio of losing weight (adjusted for age and gender) for individuals in the nutrigenetic test group compared to the control groups. age and sex adjusted odds ratio for weight loss > 0 between the nutrigenetic test group and the non-tested group.



Where do we go from here....

- **Set priorities for translational research**
 - Apply models like REAIM to develop phased research plan
 - Public health & conceptually based research questions
- **Anticipate direction of genomic discovery**
 - Move beyond psychological effects of genetic risk communication
- **“Deconstruct” behavioral phenotypes**
 - Measure intermediate pathways of influence that might affect behavioral adherence
 - Move to a bi-directional influence models (e.g., systems thinking)