



Realizing the Health Benefits of Genomics

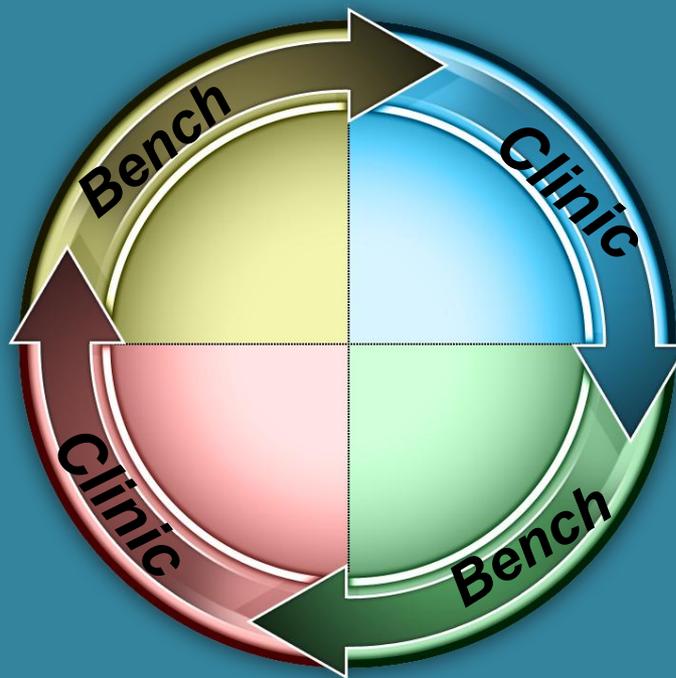
Which way for translational research?

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

Assumptions/Questions to Consider

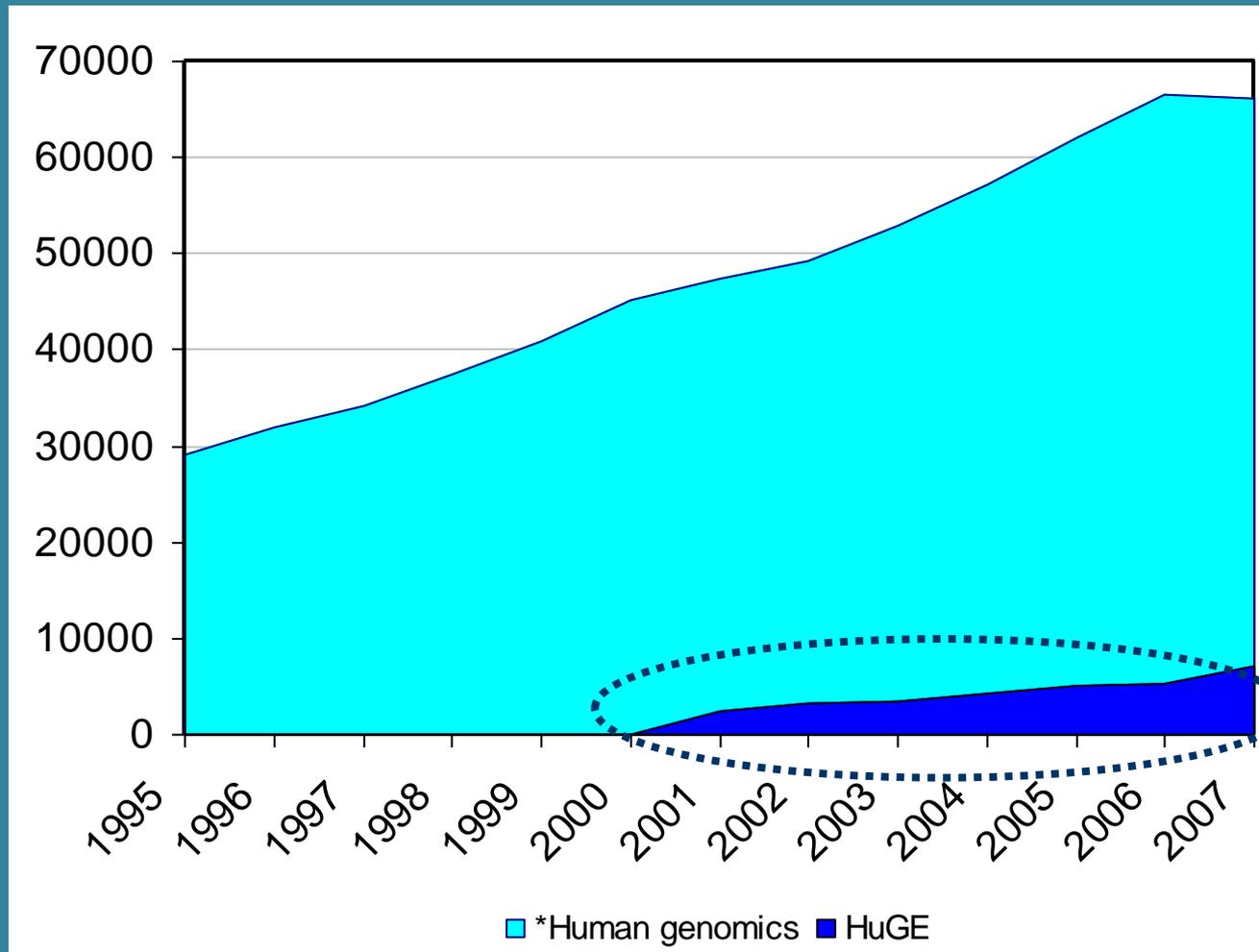
- **Amidst rapid discovery, when is the “right” time to start translational research?**
 - E.G. Do we have wait for established clinical validity before starting TR?
- **What could we learn now that would help us understand in what instances genomic products could be useful?**
 - E.G. Will having precise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



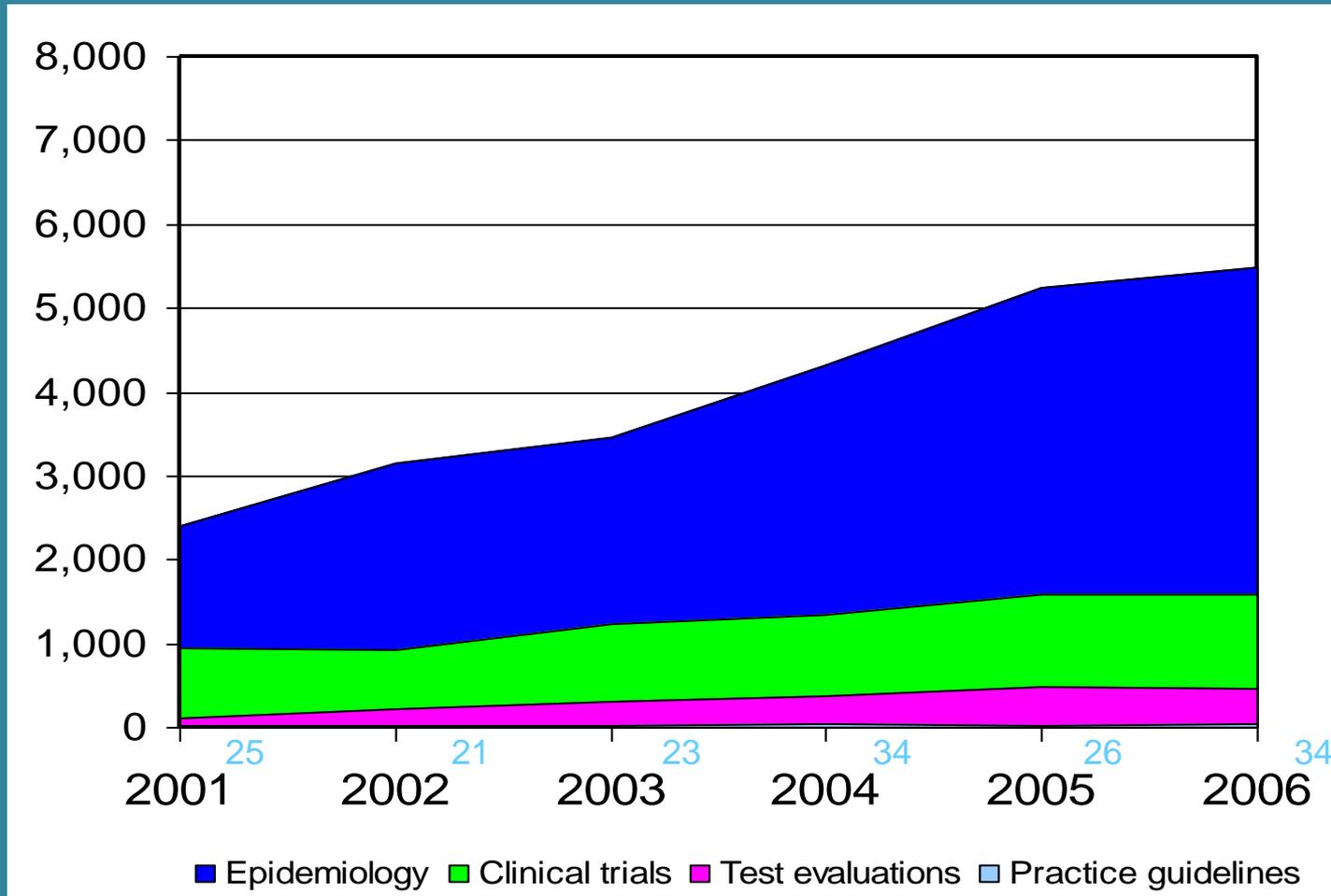
When is the “right” time to start translational research?

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



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

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

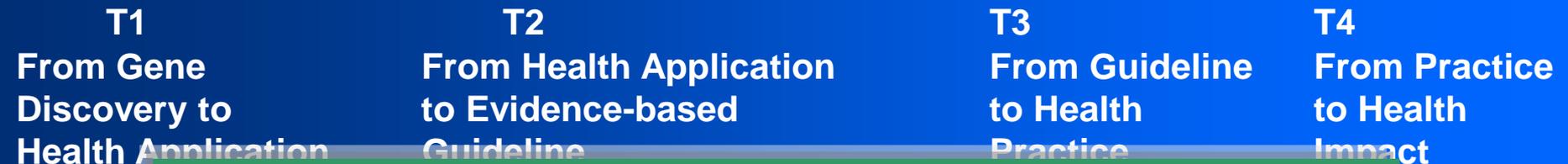


*Gwinn et al., from PubMed -- HuGE Navigator

The Translation Continuum from Gene Discovery to Population Health

Less than 3% of published genomics research is T2 and beyond

Case of BRCA1/2: 12 years T1 to T2



17 years to turn 14% of original research to benefit patient care

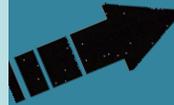
Balas, 2000

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

Navigenics

About Leadership Policies Contact

**My Genes.
My Health.
My Life.
My Guide.**

The Navigenics advantage

Write in the midst of the genomics revolution, discovering new connections between your DNA, your environment and your personal health and wellness. You can feel confident choosing Navigenics to help you harness this information, because:

- Our team of leading **scientific and clinical advisors** provides expert review of our service.
- Our lab is certified under CLIA, the law covering accuracy and timeliness of test results.
- Our genetic counselors, available by phone, help you interpret your results.
- Our **medical partnerships** help inform and guide your next steps on the way to optimal health.
- Our practices are consistent with HIPAA standards for privacy and protection of your personal data.

Your genes offer a road map to optimal health

Trailblazing a research agenda

Optimal application

Translation Research

Lost in translation

Premature translation



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

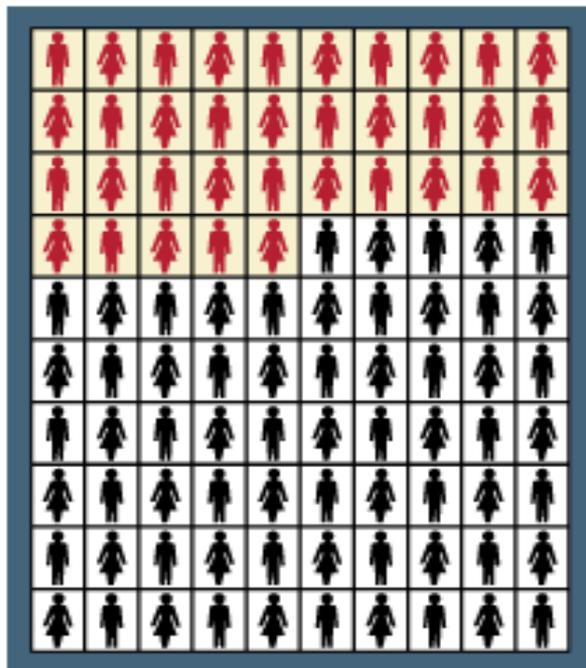
What could we learn now that would help establish potential utility of genomic products?

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

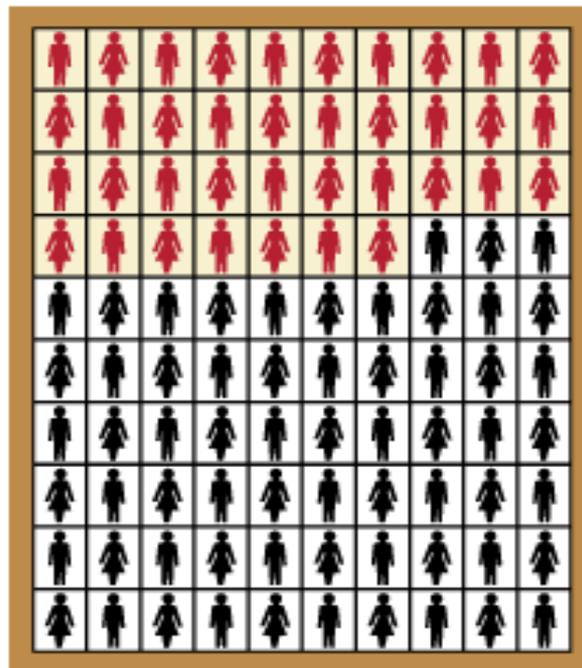
- People who have **no risk versions** of KCNJ11 will have, on average, a 35 in 100 chance of getting diabetes.
- People who have **1 risk version** of KCNJ11 will have, on average, a 37 in 100 chance of getting diabetes.
- People who have **2 risk versions** of KCNJ11 will have, on average, a 43 in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

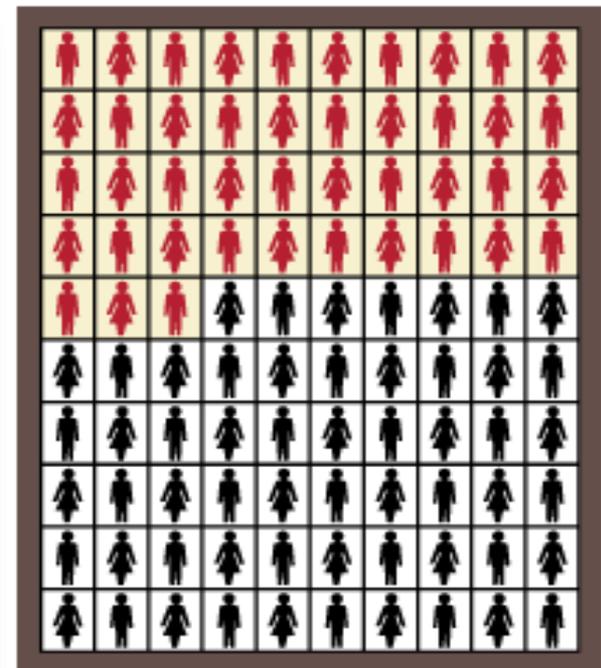
0 Risk Versions



1 Risk Version

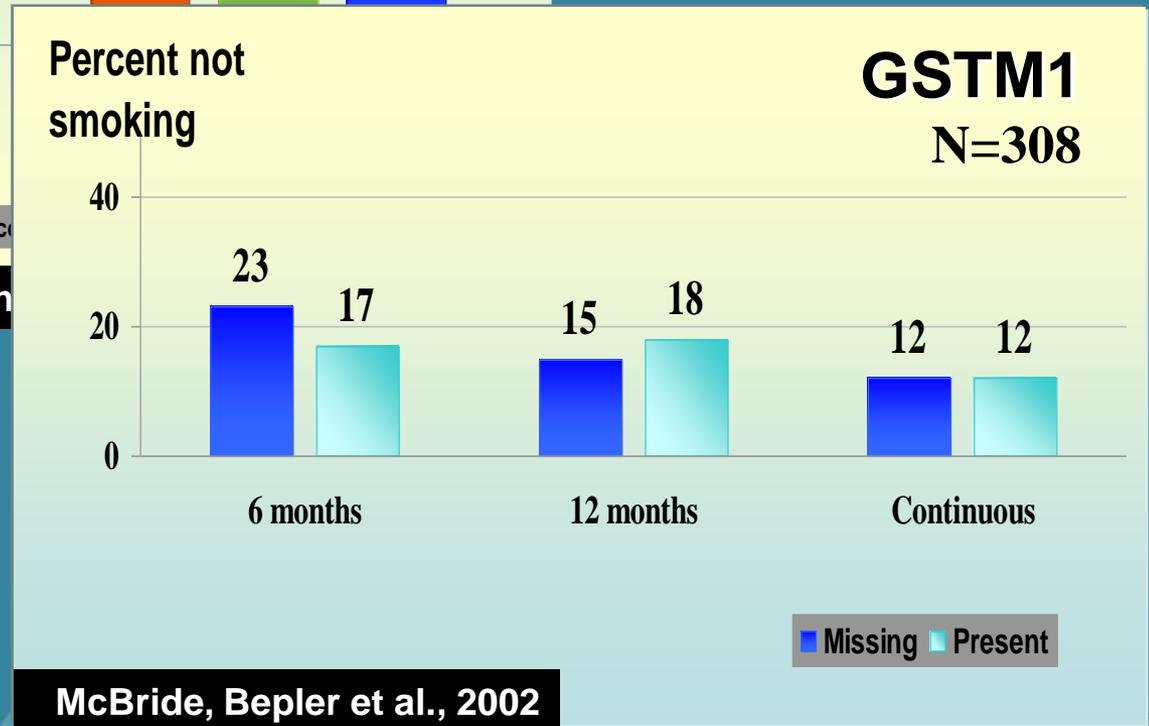
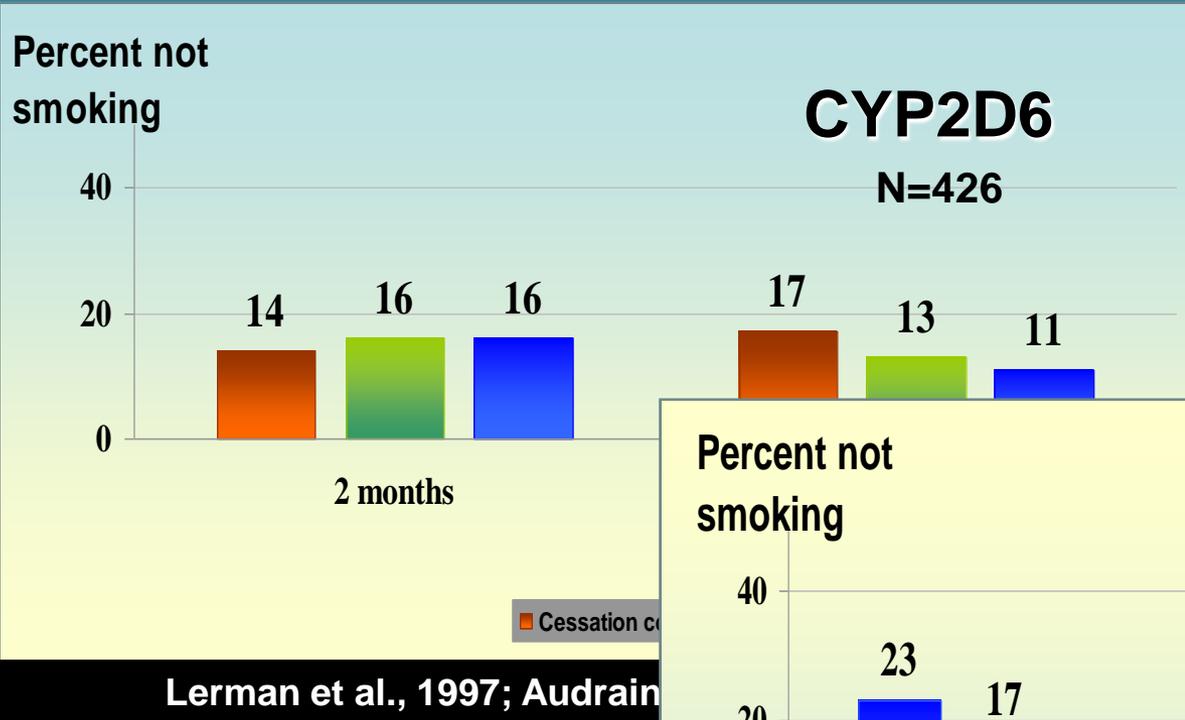


2 Risk Versions



1990's Clinical Trials:

Genetic feedback effects on smoking cessation



Welcome to the FAMILY RISK AND LUNG CANCER STUDY

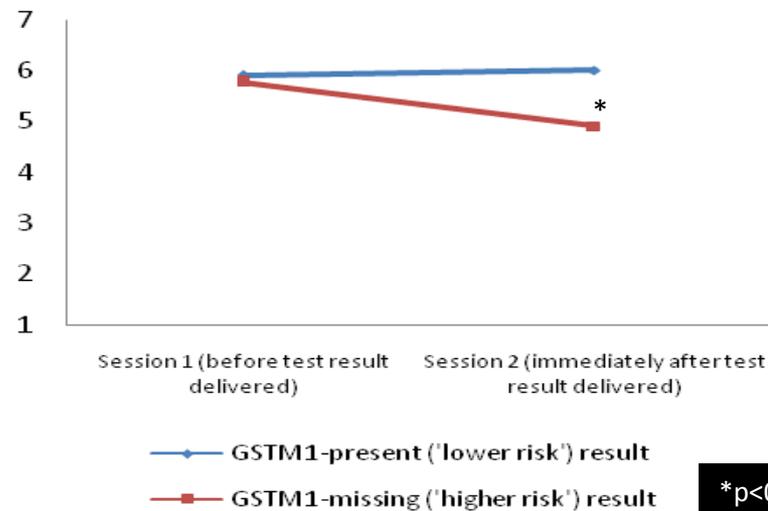
Thank you for Participating!



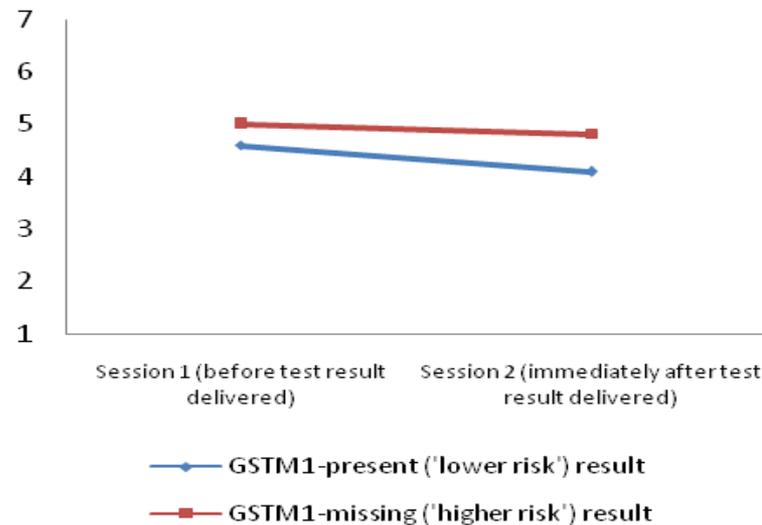
NEXT

Response to test results

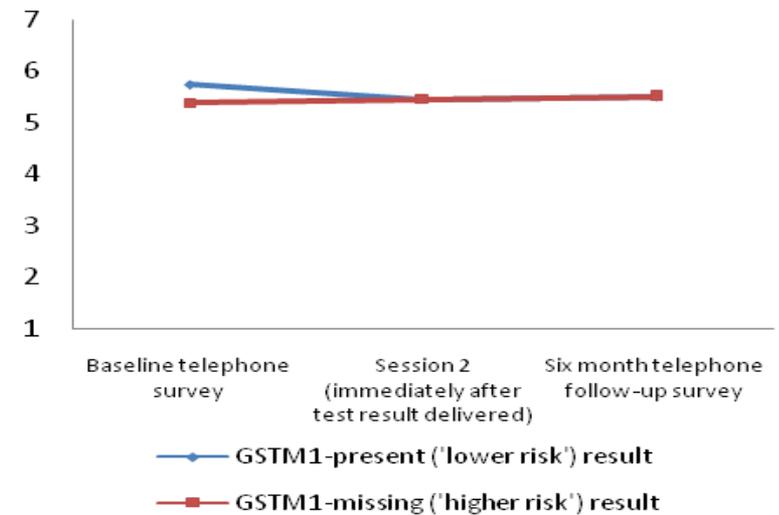
Perceived response-efficacy



Perceived self-efficacy



Perceived risk



Sanderson et al, CEBP in press

The Multiplex Initiative



New Participants

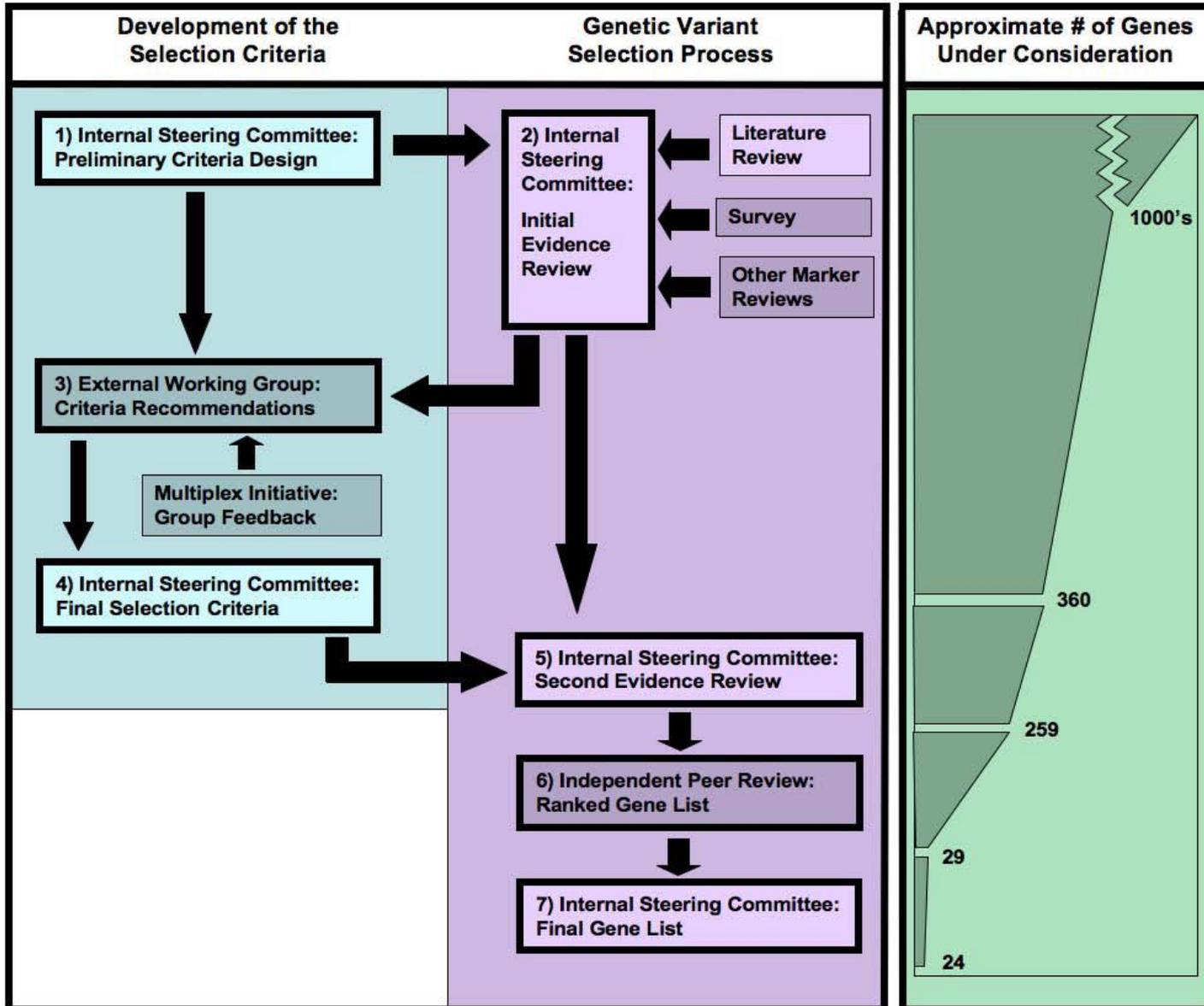
Returning Participants

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

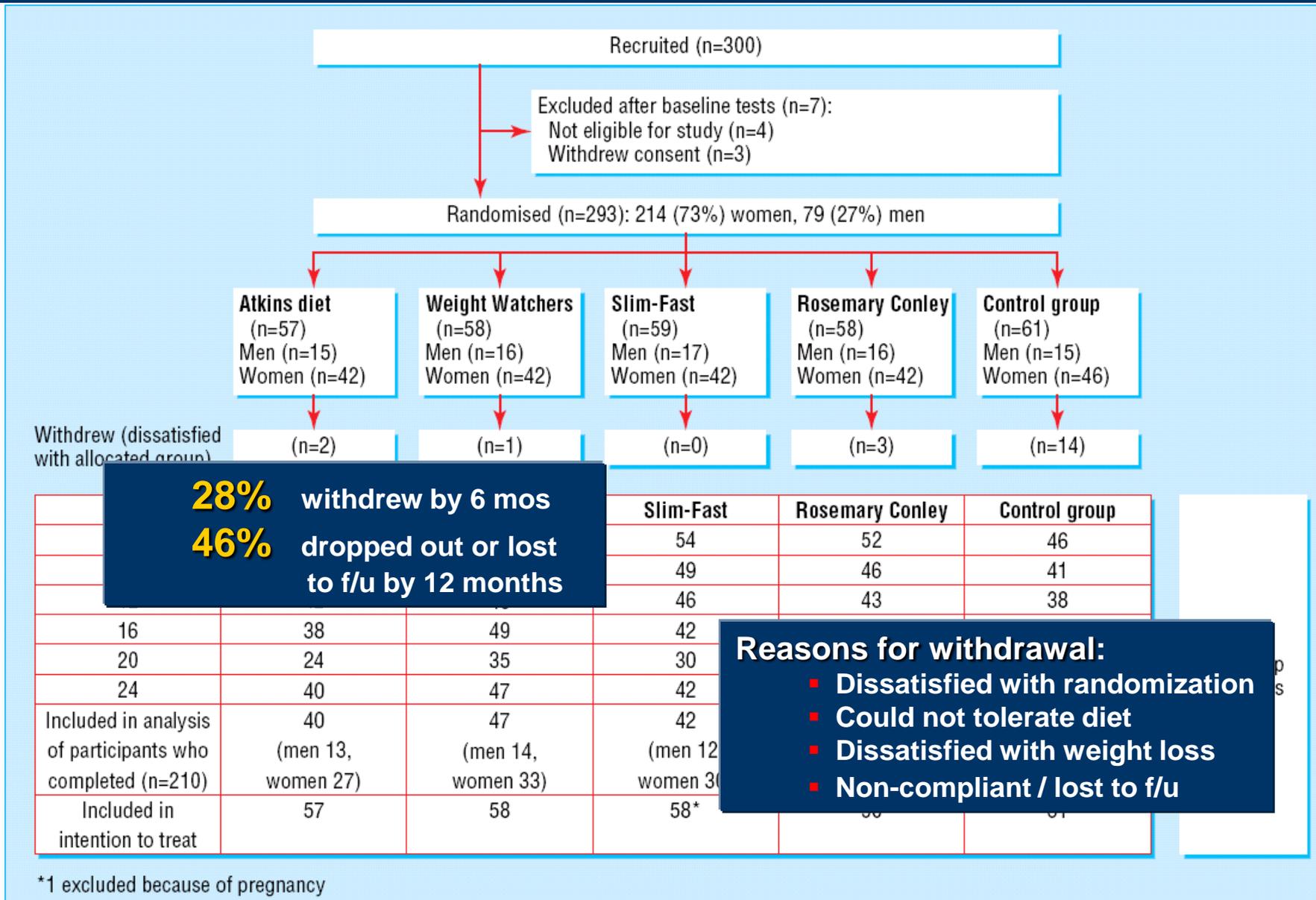


Fig 1 Flow of participants through the BBC diet trials

PAPER

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

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

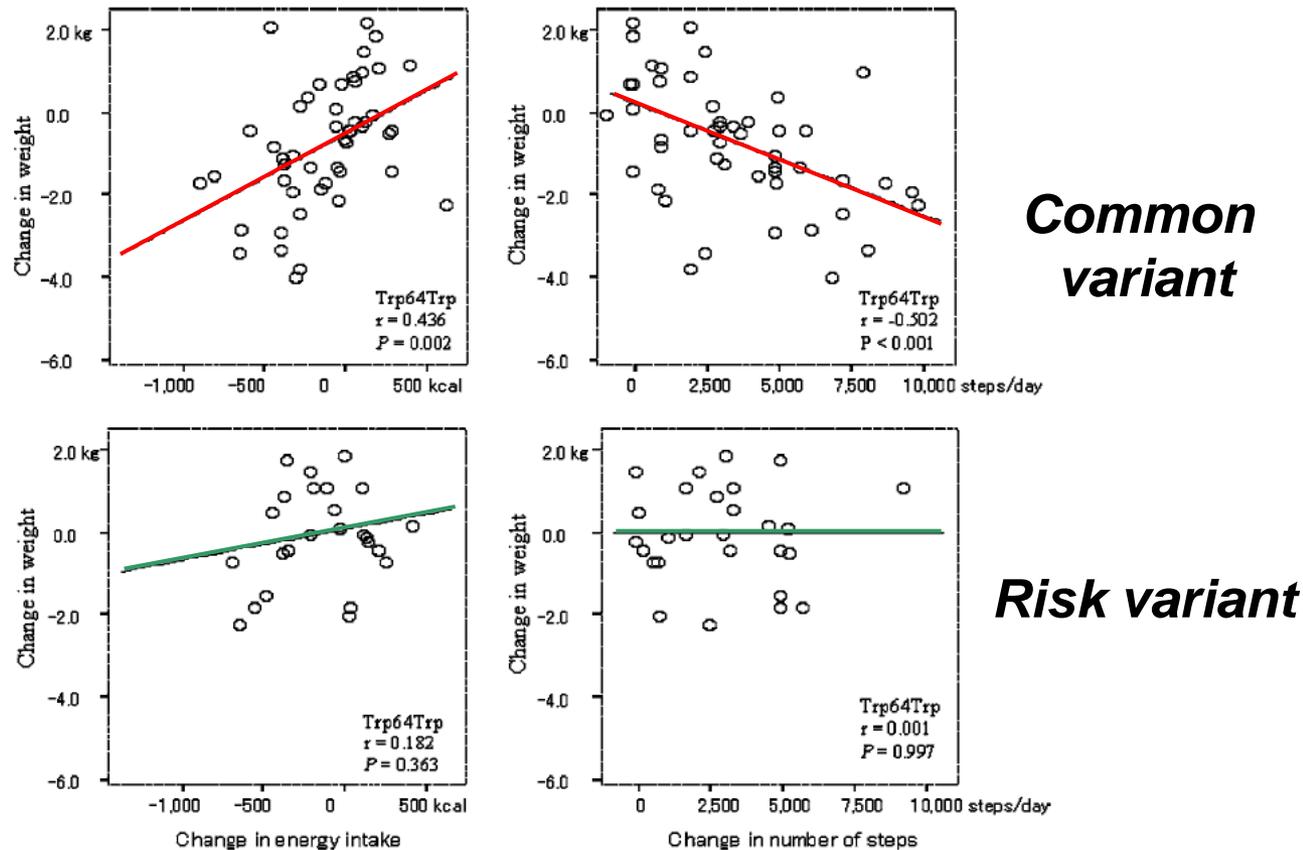


Figure 1 Correlation between weight loss and changes in energy intake or number of steps Pearson's correlation coefficients associated with weight loss and P values were expressed.

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

Bryan, Hutchison, Seals, Allen, 2007

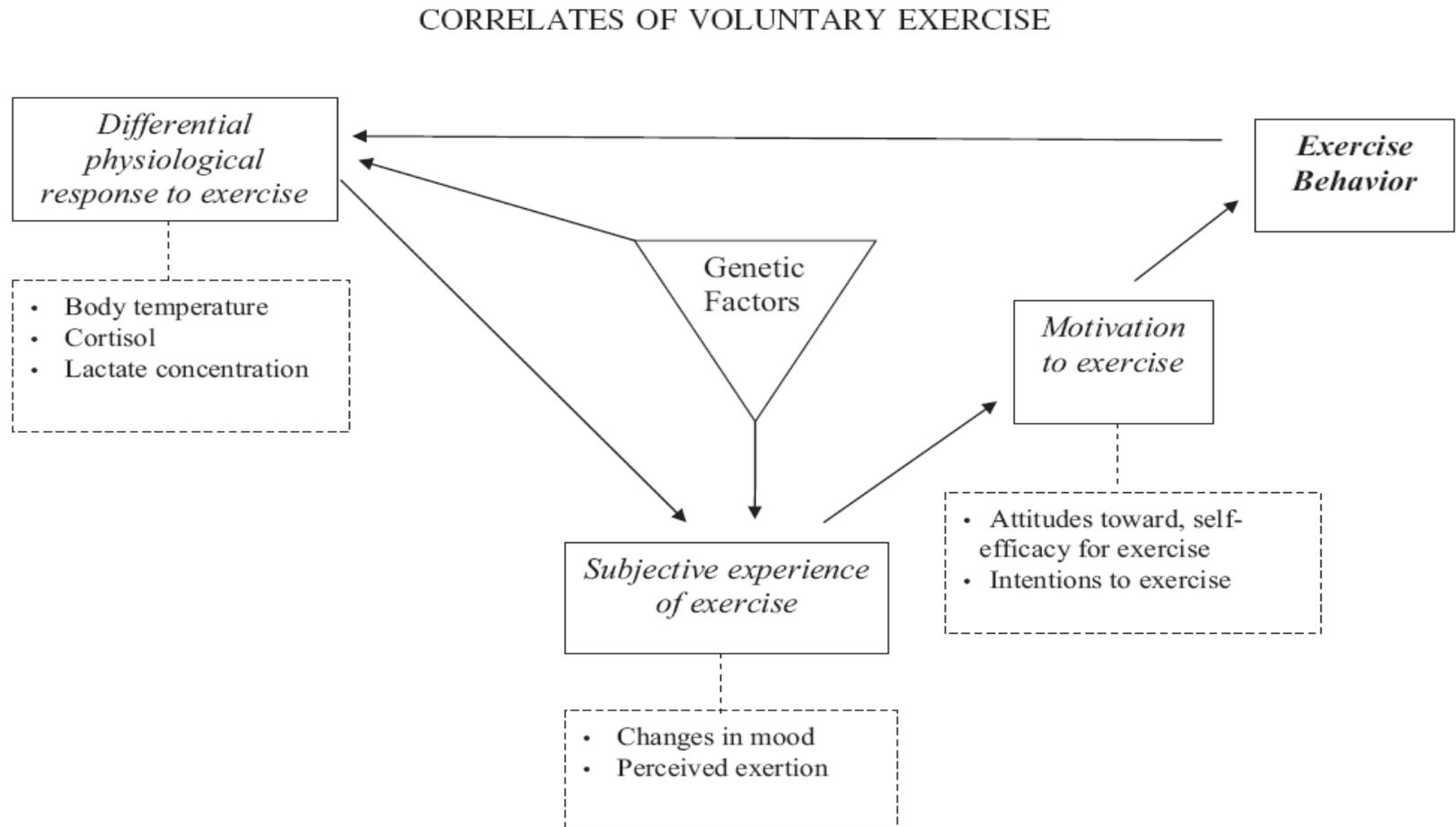
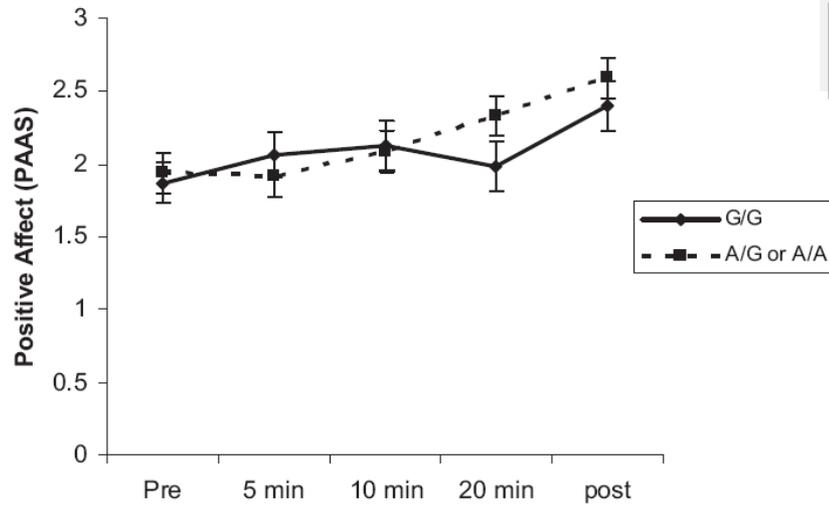


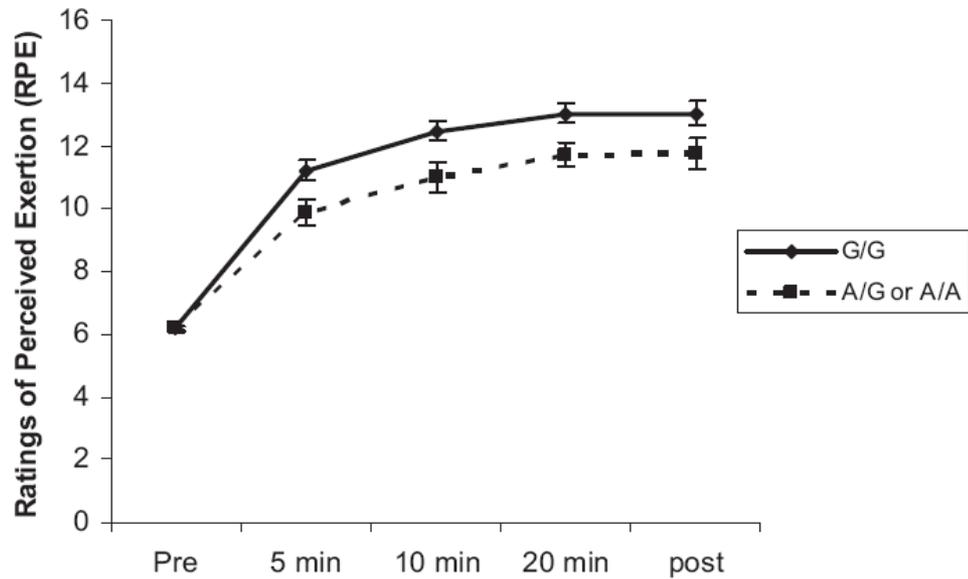
Figure 1. Transdisciplinary model of exercise behavior.

CORRELATES OF VOLUNTARY EXERCISE



Positive Affect

Perceived Exertion



Research

Improved weight management by personalizing a calorie count

Ioannis 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

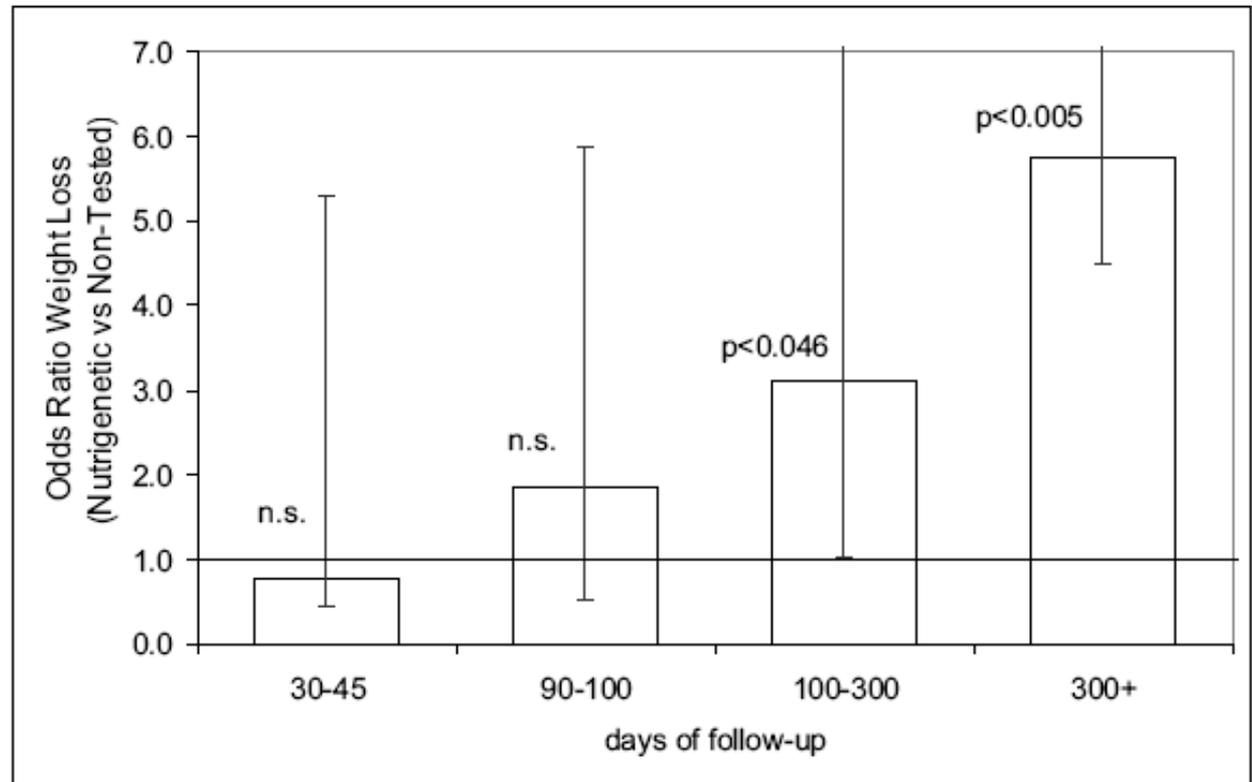
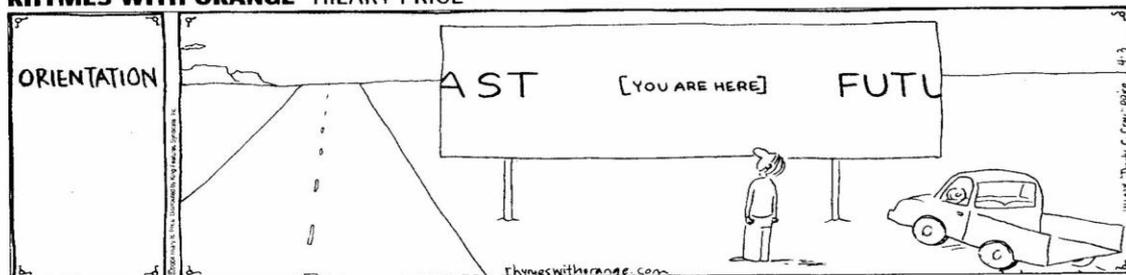


Figure 1

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)