DETERMINANTS AND CHALLENGES OF PERSONALIZED OBESITY TREATMENTS

ACCUMULATING DATA TO OPTIMALLY PREDICT OBESITY TREATMENT

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No conflicts to disclose.

Funding Support

- NIH R01 DK038088 (exercise and weight regain)
- NIH P01 HD038129 (obesity and lactation)
- NIH P50 HD073063 (menopause and weight regain)
- NIH R01 CA164166 (obesity and breast cancer)
- Colorado Obesity Research Initiative
- Colorado Nutrition Obesity Research Center
- Colorado Comprehensive Cancer Center
The Problem of Obesity

- **High Incidence**
  - Over 2/3 of adults are overweight or obese
  - Does not discriminate by sex/race

- **Numerous Co-Morbidities**
  - $100-$150 billion/yr health care cost

- **Numerous Consequences**
  - Social stigmatization
  - Discrimination
  - Reduced quality of life

Medical Complications of Obesity

- Pulmonary disease: abnormal function, obstructive sleep apnea, hypoventilation syndrome
- Nonalcoholic fatty liver disease: steatosis, steatohepatitis, cirrhosis
- Coronary heart disease
- Diabetes
- Dyslipidemia
- Hypertension
- Gynecologic abnormalities: abnormal menses, infertility, polycystic ovarian syndrome
- Osteoarthritis
- Skin
- Gall bladder disease
- Cancer: breast, uterus, cervix, colon, esophagus, pancreas, kidney, prostate
- Phlebitis: venous stasis
- Gout
- Medical Complications: idiopathic intracranial hypertension, stroke, cataracts, severe pancreatitis
Propensity to Regain Weight After Weight Loss

Meta-Analysis of US Weight Loss Studies

% of Lost Weight Regained

# of Studies with Data Available

<table>
<thead>
<tr>
<th>Years after Weight Loss</th>
<th># of Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
</tr>
</tbody>
</table>

Adapted from Anderson et al, AJCN 2001
Why Do We Regain?

FACTORS THAT HAVE BEEN LINKED TO WEIGHT REGAIN

Elfhag and Rössner, 2005; Weiss et al., 2007; MacLean et al 2011

- Elevated Hunger
- Binge Eating
- Sedentary Lifestyle
- Poor Coping Strategies
- Family History/Bad Genes
- Suppressed Metabolism
- Disinhibited eating
- History of Weight Cycling
- Readily Available Foods
- Race/Cultural Impact
- Lack of Social Support
- Lack of Self Confidence
- Amount of Lost Weight
- Eating Out
- TV Viewing
- Reduced Fat Oxidation
- Computers/Video Games
Overview

• Pressures affecting body weight

• Barriers and challenges to weight loss and weight loss maintenance

• ADOPT Core Measures Project
  – One effort to pursue a personalized or targeted approach to obesity therapeutics
NIH Working Group - 2014
Innovative Research for Weight Loss Maintenance

• Multiple Institutes Involved
  – NHLBI, NCI, NIDDK, NICHD
  – Led by Rena Wing and Paul MacLean

• Broad Range of Expertise
  – Behavioral psychologists, physiologists, neuroscientists, dietician/nutrition experts, epidemiologists, mathematical modelers, basic/clinical researchers
  – Terry Davidson, Leonard Epstein, Bret Goodpaster, Kevin Hall, Barry Levin, Michael Perri, Barbara Rolls, Michael Rosenbaum, Alexander Rothman, Donna Ryan
Framing the Discussion

Pressures Affecting Body Weight

Biology
- genetic and epigenetic predisposition
- metabolic homeostasis

Environment
- food composition and availability
- need for exercise
- promotion of activity
- comfortable technology
- climate and weather
- social and cultural expectations

Behavior
- fast food vs gardening
- stairs vs elevator
- TV vs outside play
- daily run vs daily nap
- car vs bike
- choice of friends and activities
Framing the Discussion

Pressures Affecting Body Weight

Biology

Environment

Behavior

Steady-State Weight

Psychobiology

Psychosocial
BARRIER 1
Biological Drive to Regain Weight

- Complex, strong, redundant
  - Coordination of several tissues and regulatory nodes.
  - Extends to hedonic aspects of food intake.
  - May extend to the motivation to be physically active.

- Persistent
  - Does not resolve with time.
  - May even strengthen with time.

MacLean et al, AJP 2011; MacLean, Wing et al Obesity 2015.
BARRIER 2
Persistence of the Obesogenic Environment
(food and physical activity)

- Food Availability and Security
- Socio-Economic Status
- Cultural Demands/Expectations
- Built Environment
- Home, Neighborhood, Work

BARRIER 3
Decline in Adherence to Behavioral Programs

• Between 6 – 9 months of a weight loss program
  • Coincides with weight plateau
  • Both dietary and exercise prescriptions

• Gradual, intermittent
  • Very difficult to study
  • Complex, multi-factorial

WHY?

Psychosocial + Psychobiological

• Weight loss strategies are viewed as transient endeavors
• Perceived cost / benefit ratio changes
• Boredom/aversion to dietary/exercise regimen
• Return of entrenched eating/inactivity habits
• A strengthening biological drive to overeat

Challenges to Developing Better Strategies

Individual Variability

- **BIOLOGY**
  - Genetic and epigenetic variability

- **BEHAVIOR**
  - Psychological aspects of behavior change

- **ENVIRONMENT**
  - Diverse, and changing across the lifespan

Manifestations of Individual Variability

- Predisposition for obesity
- Biological adaptations to weight loss
- Motivations behind behavior change/failure
- Food/Activity environmental pressures
- Response to diet, exercise, drug, surgery, and other behavioral interventions

When individual weight loss is displayed, it looks like this:

- **Lifestyle Modifications Alone (n=557)**
- **PHEN/TPM ER 7.5/46 (n=338)**
- **PHEN/TPM ER 15/92 (n=625)**

Each vertical bar represents a single subject experience in subjects completing 56 weeks on study drug.

*McCullough PA et al, Poster AANP 2013.*

*Courtesy of Donna Ryan, Pennington BRC.*
Mean and Individual Weight Loss Response with Low-carbohydrate Ketogenic Diet or Orlistat with Low-fat, Reduced-calorie Diet

Variability in response, regardless of the treatment.

Yancy W, et al
Arch Intern Med 2010.
Advancing the Science

One next step in this effort

• Pursue the individual variability in the effectiveness of obesity treatments.
  – Acknowledge the “responder/non-responder” phenomenon.
  – Targeting specific treatment(s) to “responders” to give individual the best chance for success.

• Long Range Goal:

  Targeted or personalized treatments in obesity medicine.
Demand for This Effort

- Patients are asking for it.
  - Too many programs, too much misinformation
- Clinicians are asking for it.
  - Trial and error is frustrating and expensive
- Many clinicians are already doing it.
  - Based upon personal experience
- The scientific community is already pursuing it.
  - Studies that are too limited in scope or size
  - Not gauging all domains in the effort to find predictors, moderators, and mediators of treatment response
NIH Working Group
May 26-27, 2016

• Organized by NIH in December of 2015

• Leadership Team
  – Co-Chairs:
    • Alex Rothman and Paul MacLean
  – NIH Program Staff:
    • Catherine Loria, Holly Nicastro, Tanya Agurs-Collins, Susan Czajkowski, Elise Rice, Katrina Serrano

ADOPT Core Measures Project
( Accumulating Data to Optimally Predict obesity Treatment )
Focus on Adult Obesity
Long Term Vision

- Predictive Algorithms
- Personalized and/or Targeted Strategies

Biology
- Genetics
- Energy Homeostasis
- Learning/Memory/Reward
- Cognitive Function
- Intervention Effects/Response

Behavior
- Food Eating
- Physical Activity
- Sleep
- Adherence/Compliance

Psychosocial
- Personality Traits
- Affect/Mood/Stress
- Executive Function/Self-Regulation
- Intervention Effects/Response

Environment
- Social
- Eating/Food
- Activity Levels
- Neighborhood/SES

Relevant Measures

Predictive Algorithms

Personalized and/or Targeted Strategies
Short Term Objectives

**Core set of high-priority measures** that when consistently used in studies will identify constructs and parameters that predict or moderate treatment response.
Recruiting the Panel

Affiliations of 43 Panel Members

19 Universities

Banner Alzheimer’s Institute
Brown University
Columbia University College of Physicians & Surgeons
Florida State University College of Medicine
Johns Hopkins University
Pennington Biomedical Research Center
Sheffield Hallam University
University of California, San Diego
University of California, San Francisco

University of Illinois at Chicago
University of Colorado School of Medicine
University of Connecticut
University of North Carolina, Chapel Hill
University of Pittsburgh Medical Center
University of Minnesota
University of Texas at Austin
University of Washington
Tufts University
Yale Medical School

5 NIH Centers/Institutes

National Heart, Lung, & Blood Institute (NHLBI)
National Cancer Institute (NCI)
National Institute on Aging (NIA)
National Institute of Diabetes, Digestive & Kidney Diseases (NIDDK)
Office of Behavioral and Social Sciences Research (OBSSR)
Biological Domain

Subdomain Experts
- Molly Bray
- Michael Rosenbaum
- Dana Small
- Cary Savage
- Mark Hopkins
- Susan Roberts

Genetics
- Energy Homeostasis
- Learning/Memory/Reward
- Cognitive Function
- Exercise Response/Variability
- Diet Response/Variability

NIH Co-Leads
- Tanya Agurs-Collins
- Aynur Unalp-Arida
- Luke Stoeckel
- Maren Laughlin
- Padma Maruvada
Psychosocial Domain

Subdomain Experts
- Angelina Sutin
- David Williams
- Elissa Epel
- Kerri Boutelle

NIH Co-Leads
- Lis Nielson
- Christine Hunter
- Paige Green
- Deborah Young-Hyman
Perspectives, Input on All Domains

Added Perspectives

Daniel Bessesen

Anita Courcoulas

Donna Ryan

Kevin Hall

Pharmacotherapy
Variability in Response

Surgery/Devices
Variability in Response

Behavioral Interventions
Variability in Response

Complex Data Modeling
Charge to Panel Members

• Prioritize the “BEST” constructs that could be predictors or moderators of treatment responses.

• Prioritize the “BEST” measure for those constructs that could be used in weight loss trials.
Criteria for “BEST” Constructs and Measures

• Strength and Source of the evidence
  – Relevance to obesity, weight loss
• Quality of measure (validity, reliability)
• Feasibility of measure
  – Researcher cost/expertise
  – Study size
• Subject burden
Expected Products

- Core set of high priority list of constructs/measures
  - Based on the current state of the science
  - Modifiable with advancements in the science
  - With input from the scientific community
- Online accessible database of measure protocols
  - To facilitate consistency in obesity research
- Identification of Gaps in Knowledge or Process
  - Better constructs, measures, or measurement schedules
  - More helpful study designs
- Roadmap for future efforts and applications
Publically Available

4 Workspaces/Measures
- Biology – 29
- Behavior – 46
- Psychosocial – 129
- Environment - 34

<table>
<thead>
<tr>
<th>Construct</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormones: Long-Term Regulators</td>
<td>Insulin, Leptin, Glucagon, Amylin (ELISA)</td>
</tr>
<tr>
<td>Hormones: Long-Term Regulators</td>
<td>Thyroid Hormone Panel (T3, fT3, T3/T4)</td>
</tr>
<tr>
<td>Biological Affectors of Energy Balance</td>
<td>Metabolite Panel (Glucose; NEFA, TG; Colorimetric)</td>
</tr>
<tr>
<td>Genetic Markers</td>
<td>SNPs (DRB3, FTO, GNPDA2, LYPLA, MTCH2, MTIF3, NEGR1, PLIN, RANK)</td>
</tr>
<tr>
<td>Body Composition: Fat Mass/Fat Free Mass</td>
<td>Dual Energy X-ray Absorptiometry (DXA)</td>
</tr>
<tr>
<td>Energy Intake</td>
<td>Model Calculated Energy Intake</td>
</tr>
<tr>
<td>Expended Energy: REE, TEF</td>
<td>Metabolic Cart (Indirect Calorimetry)</td>
</tr>
<tr>
<td>Fuel Utilization: Respiratory Exchange Ratio</td>
<td>Metabolic Cart (Indirect Calorimetry)</td>
</tr>
<tr>
<td>Metabolic Function: Diabetes Status</td>
<td>Fasting Glucose, HBA1c, HOMA</td>
</tr>
<tr>
<td>Metabolic Response to Fast/Feed Challenge</td>
<td>Hunger/Satiety Hormone Panel (Ghrelin, GLP1, GIP, PYY)</td>
</tr>
<tr>
<td>Biobanking Tissues (-omics)</td>
<td>Whole Blood and Saliva</td>
</tr>
<tr>
<td>Construct</td>
<td>Measure</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>--------------------------------------------------------------</td>
</tr>
<tr>
<td>Total Dietary Intake</td>
<td>Interview-administered 24hr recall</td>
</tr>
<tr>
<td>Eating Away from Home</td>
<td>EARLY Eating Away from Home Questionnaire</td>
</tr>
<tr>
<td>Sugar-sweetened beverage (SSB) consumption</td>
<td>EARLY SSB Consumption Questionnaire</td>
</tr>
<tr>
<td>Food hedonics and Preference</td>
<td>Leeds Food Preference</td>
</tr>
<tr>
<td>Appetite Sensations</td>
<td>Appetite (Visual analogue scale)</td>
</tr>
<tr>
<td>Overall Physical Activity</td>
<td>Global Physical Activity Questionnaire</td>
</tr>
<tr>
<td>Moderately Vigorous Physical Activity</td>
<td>Paffenbarger Questionnaire</td>
</tr>
<tr>
<td><strong>(1) Physical Activity/ (2) Sleep Duration</strong></td>
<td><strong>Actigraphy (wrist-worn)</strong></td>
</tr>
<tr>
<td>Sleep Disorders</td>
<td>Berlin Questionnaire for Sleep Apnea</td>
</tr>
<tr>
<td>Sleep Timing</td>
<td>Munich Chronotype Questionnaire</td>
</tr>
<tr>
<td>Self-Weighing Behavior</td>
<td>EARLY Self-weighing Questionnaire</td>
</tr>
</tbody>
</table>

**ADOPT Working Group: Behavioral Domain Initial Draft of High Priority Measures**

*Good Constructs*
*OK Measures*
*Good Predictive Potential*
*Needed Work*
*Food Intake Feasibility/Burden*

Working Draft
# ADOPT Working Group: Psychosocial Domain

**Initial Draft of High Priority Measures**

<table>
<thead>
<tr>
<th>Construct</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affect (Trait/State)</td>
<td>Positive and Negative Affect Scale/ EMA Daily Diary</td>
</tr>
<tr>
<td>Restraint/Inhibition/Hunger</td>
<td>Three Factor Eating Questionnaire</td>
</tr>
<tr>
<td>Eating Behaviors: Stress and Emotion</td>
<td>Palatable Eating Motives: Coping Subscale</td>
</tr>
<tr>
<td>Eating Behaviors: Food Craving</td>
<td>Food Craving Questionnaire ( Trait, Reduced)</td>
</tr>
<tr>
<td>Personality: Big Five Factors</td>
<td>Mini-international Personality Item Pool (Short form)/ Big Five Inventory (Long form)</td>
</tr>
<tr>
<td>Behavioral Intention</td>
<td>Behavioral Intention Scale(s)</td>
</tr>
<tr>
<td>Self-Efficacy</td>
<td>Self-Efficacy Scale(s)</td>
</tr>
<tr>
<td>Executive Function</td>
<td>Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A)</td>
</tr>
</tbody>
</table>

*Working Draft*
## ADOPT Working Group: Environmental Domain Initial Draft of High Priority Measures

<table>
<thead>
<tr>
<th>Construct</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geographic Location</td>
<td>Home address(es)</td>
</tr>
<tr>
<td><strong>Neighborhood Food Accessibility</strong></td>
<td>(1) Supermarkets, (2) Fast food restaurants, convenience stores</td>
</tr>
<tr>
<td>Neighborhood Food Accessibility</td>
<td>NEWS walking proximity (1) Supermarkets, (2) Fast food restaurants, convenience stores</td>
</tr>
<tr>
<td>Neighborhood Food Availability</td>
<td>MESA Neighborhood Healthy Food Availability</td>
</tr>
<tr>
<td>Neighborhood Socioeconomic Deprivation</td>
<td>Neighborhood Deprivation Index (Diez Roux; Lian)</td>
</tr>
<tr>
<td>Neighborhood Socioeconomic Deprivation</td>
<td>Neighborhood Socioeconomic Position Index</td>
</tr>
<tr>
<td>Neighborhood Socioeconomic Deprivation</td>
<td>Neighborhood Police-Reported Crime</td>
</tr>
<tr>
<td>Neighborhood Socioeconomic Deprivation</td>
<td>Perceived Neighborhood Safety</td>
</tr>
<tr>
<td><strong>Neighborhood Physical Activity</strong></td>
<td>Block Group Level Walkability</td>
</tr>
<tr>
<td>Perceived Land Use Mix Access</td>
<td>NEWS Land Use Mix Access Subscale</td>
</tr>
<tr>
<td>Autonomy Support</td>
<td>Perceived Autonomy Support Scale</td>
</tr>
</tbody>
</table>

*Working Draft*
Follow-Up Workshop  
February 8-9, 2017

- Final curation of the core measure lists
  - Hone and merge the lists
  - Develop the GEM website resource
  - Assess feasibility/cost of application in weight loss trials
  - Identify gaps and problems

- Dissemination plan
  - Publication
    - Overview + 4 domain papers in 2017
  - Integration with other NIH and professional initiatives
  - Plans and steps for the future
Perspectives

- This is challenging, complicated, and difficult.
- The need to fill this gap in knowledge is great.
- The pay off for obesity therapeutics could be substantial.
  - We won’t know, unless we try.