Study Designs for Translational Research

Maureen Smith, MD PhD MPH
ICTR Short Course
University of Wisconsin - Madison
Types of Research

- **Basic research - 60% of NIH funds**
  - involves laboratory studies that provide the foundation for clinical research (ACS)
  - Research performed to understand nature and its laws without thought of practical ends (NSF)

- **Clinical research – 30% of NIH funds**
  - Patient-oriented research – direct interaction
  - Epidemiology, behavioral, outcomes, health services research

* Debated – appears to include preclinical animal models
What is translational research?

• Old definition (from cancer literature)
  – Spanning different types of research
  – Spanning disciplines within a type of research
• Implies work at the INTERSECTION

• NIH Clinical and Translational Science Awards
  – T1: apply lab and preclinical studies to clinical trials
  – T2: enhance adoption of best practice in the community
• Implies MOVEMENT on a continuum
## Continuum of Translational Research

<table>
<thead>
<tr>
<th>Type 1 Translational Research</th>
<th>Type 2 Translational Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH Type 1</td>
<td>NIH Type 2</td>
</tr>
<tr>
<td>&quot;Bench to bedside&quot;</td>
<td>&quot;Bedside to community&quot;</td>
</tr>
</tbody>
</table>

### Key Stages

1. **Basic Research**
2. **Methods Development**
3. **Efficacy Trials**
4. **Effectiveness Research**
5. **Implementation Research**
6. **Policy Research**

### Research Goals
- **NIH Type 1 Translational Research**: Focuses on translating basic research findings into clinical applications.
- **NIH Type 2 Translational Research**: Involves scaling up and implementing effective clinical practices into community settings.

### Methodologies
- **NIH Type 1**: "Bench to bedside" - Moves from laboratory to patient settings.
- **NIH Type 2**: "Bedside to community" - Extends clinical applications to broader community settings.

---

**UW ICTR**
Challenges

• Very different study designs for lab, clinical, and population based studies

• Argued that needed to include basic research in sciences related to populations
  – Causes of disease (epidemiology)
  – Causes of behavior (behavioral sciences)
    • Psychology
    • Economics
    • Sociology
Circle of translational research
Association for Clinical Research Training

- Patient-oriented research
- Basic research
- Population-based research
- T1
- T2
- T3
T1 expedites the movement between basic research and patient-oriented research that leads to new or improved scientific understanding or standards of care.
Circle of translational research
Association for Clinical Research Training

T2 expedites the movement between patient-oriented and population research that leads to better patient outcomes, implementing best practices, & better health
T3 promotes interaction between basic research and population research to stimulate a robust scientific understanding of human health and disease.
Presentations today

• Three presenters
  – T1: Jim Gern
  – T2: Maureen Smith
  – T3: Steve Waring

• Each presentation
  – Two examples of research
  – Questions for consideration
    • How to develop the research question?
    • How to design the study?
    • How to collect the data?
Study Designs for Type 1 Translational Research

James E. Gern, M.D.
Professor of Pediatrics and Medicine
University of Wisconsin-Madison
Basic Science

\[ \uparrow \downarrow \]

Patient-Oriented Research
Steps in Translational Research

- Find an area of interest
- Develop a research question (hypothesis)
- Design a study to test the question
  - Data collection procedures
  - Sample analysis
- Analyze the data
Global Epidemiology Of Wheezing in Childhood

ISAAC Survey: 13-14 y/o Wheezing in the Past 12 Mo.

Rural Lifestyle and Reduced Allergy and Asthma

- 9082 school children ages 12-19 yr
- Survey:
  - 802 children raised on a farm
  - 397 non-farming controls
- Allergy/Asthma evaluation
  - Skin tests
  - Spirometry
  - Methacholine reactivity

### Rural Lifestyle and Reduced Allergy and Asthma

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Odds Ratio*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheeze</td>
<td>0.72 (0.56 – 0.99)</td>
</tr>
<tr>
<td>AHR</td>
<td>0.80 (0.56 – 0.87)</td>
</tr>
<tr>
<td>Asthma</td>
<td>0.71 (0.37 – 0.98)</td>
</tr>
<tr>
<td>+ Skin tests</td>
<td>0.62 (0.48 – 0.80)</td>
</tr>
</tbody>
</table>

*Adjusted for gender, current smoking, and # siblings

*Ernst AJRCCM 2000*
Rural Lifestyle: Potential Protective Factors

- Contact with animals
  - Stable
  - Pigs
  - Cats and dogs
- ↑ Endotoxin exposure
  - Activates innate immune responses (IL-10, IFN-γ)
  - May promote immune development in infancy
- Fermented beverages
  - Early exposure to bacteria
The Hygiene Hypothesis

Birth

**Immature immune responses**

Day Care
Older sibs
Farm

*Infections (Th1) microbes animals*

**Allergen exposure**

Only child
Few infections “sterile” environment

**Tolerance**
Healthy

**Th2**
Allergies Asthma
Research Question

What are the immunologic changes associated with pet ownership?

Hypothesis

Pets alter immune development in early life to reduce rates of allergic diseases.
Prospective birth cohort study of immune development and VRI in children (n=287) at increased risk (+FH) for allergies and asthma.
Pet Exposure in the Home

Gern et al JACI 113:307-314, 2004
What is the relationship between pet exposure at birth and subsequent atopic disease?
Dog Exposure at Birth and Atopic Dermatitis

**Age 1**

- No Dog: AD (% active) = 40
- Dog: AD (% active) = 10

p<0.001

**Age 3**

- No Dog: AD (% active) = 30
- Dog: AD (% active) = 20

p=0.004
Dog Exposure at Birth and Allergen Specific IgE

Age 1

No Dog

Dog

p = 0.02

Age 3

No Dog

Dog

p = 0.14
Dog Exposure at Birth and Wheezing

- **Age 1**: No Dog (Wheezing %) vs. Dog (Wheezing %)
  - p = 0.16

- **Age 3**: No Dog (Wheezing %) vs. Dog (Wheezing %)
  - p = 0.005
Research Question

Is there a relationship between environmental exposures and immune development?

Hypothesis

Exposure to dogs (endotoxin) in infancy promotes development of cytokines (IL-10, IFN-g) that reduce the risk of allergic diseases.
Developmental Changes in PHA-induced Cytokine Responses

**IL-5 (pg/ml)**

- **CORD**
- **YEAR 1**
- **YEAR 3**

**p < 0.001**

**IL-10 (pg/ml)**

- **CORD**
- **YEAR 1**
- **YEAR 3**

**p < 0.001**
Study Design

- House dust samples were collected from the bedrooms of a subset of 101 children at age 3 years.
  - *Can f1* and *Fel d1*
    - Dr. Peyton Eggleston, Johns Hopkins University
  - Endotoxin
    - Dr. Andrew Liu, National Jewish Clin Res Ctr
Can f1 and Cytokine Responses

### IL-10 Age 1

- Rs = 0.33
- p = 0.001

### IL-10 Age 3

- Rs = 0.072
- p = 0.5
Can f1 and Th2 Cytokine Responses

IL-5 Age 1

Can f1 (µg/ml)

IL-5 (pg/ml)

Rs = 0.34
p = 0.001

IL-5 Age 3

Can f1 (µg/ml)

IL-5 (pg/ml)

Rs = 0.23
p = 0.03
Other Findings

- Effects of dog exposure on cytokine responses were independent of endotoxin
- No associations between cat or Fel d1 exposure and clinical outcomes or cytokine responses
- Rates of dog allergy were similar in homes with or without dogs (11% vs 12%, p=ns)
Summary: Pet Exposure in a High Risk Birth Cohort

Birth

Age 1

Age 3

↑ IL-10

↑ IL-5, IL-13

↓ RAST (+)

↓ Atopic Dermatitis

(\textit{CD}14 -159 TT)

↓ Atopic Dermatitis

↓ Wheezing

↑ IL-5, IL-13

(weaker)
Why Dogs and not Cats?
Potential Mechanisms…
Study Designs for Type 2 Translational Research

Maureen A. Smith, MD, PhD, MPH
Associate Professor of Population Health Sciences, Family Medicine, and Surgery
T2 Translational Research

Patient-oriented Research

Patient-oriented Research

↓↑

Population-based Research

Patient-oriented Research

↓↑

Population-based Research
Authoritative Parenting: Can it reduce teen weight?

ICTR Type 2 Pilot

PI: Susan K. Riesch PhD RN FAAN
Professor, School of Nursing
“The Clinic says we should eat breakfast. So, I get up, clear the table, and I make breakfast; he wouldn’t eat it. On the way to school he says he is really hungry, can we stop at McDonald’s, just this once, please? So I stopped for fast food. That was pretty appalling. I just can’t follow through.”
How would you develop the Research Question?
Authoritative Parenting: Can it reduce teen weight?

Problem Definition

– According to NHANES 2007-2008:
  • 12.5% of youth aged 12 through 19 years were at or above the 97th percentile BMI-for-age growth charts,
  • 18.1% were at or above the 95th percentile, and
  • 34.2% were at or above the 85th percentile.
Significance

– dramatic secular increase in overweight youth highlight the importance of environment;
– Look to the family environment, where children are socialized in nutrition, physical activity, and behavior;
– Parenting style associated with numerous youth health and developmental outcomes.
Aims of the project:

• Translate the extensive theory and evidence about authoritative parenting into an intervention for parents of overweight/obese adolescents

• Document the acceptability of such an intervention with parents of adolescents and adolescents who are overweight/obese
How would you develop the intervention?
Authoritative Parenting: Can it reduce teen weight?

Goal of the intervention
A behavioral intervention that is part of a comprehensive treatment plan.
It is the 3rd leg of the treatment stool – diet, physical activity, behavior.
Targeted to adults with responsibility for high BMI youth.
Tailored to those who are non-authoritative.
Steps in the intervention development process:

– Literature review
– Theory
– Survey and Focus groups
– Intervention
  • Consultation
  • Scenarios to raise awareness of parenting style
  • A step-by-step training program to build skills
– Focus groups for acceptability of the scenarios, program, and instruments to assess outcomes.

Authoritative Parenting: Can it reduce teen weight?
Authoritative Parenting: Can it reduce teen weight?

Proposed Intervention

Stage 1: Raise awareness of parenting styles
- 15 Baumrind Constructs
- iPod scenarios, no stigma
- Avoid battlefield of diet and physical activity; Include both parents
Construct I: Expect vs. Do not expect participation in household chores

“Parents require participation in household tasks and it is an important part of parents’ views on child rearing.” Vs. “Parents do not require any regular tasks and they offer little help in tasks.”
A family is having company over for the night. It seems like whenever people come over to their house, the mom goes on the war path trying to get the house clean. The teen does not really understand why it is so important to get the house “spic and span” before the company comes over because the house is always a mess by the time they leave. The teen is busy in her room, working on her homework and listening to music. She can hear her mom coming up the stairs. She knows her mom is not going to be happy that she hasn’t gotten the laundry done like she had asked a few hours ago. How would an authoritative parent best handle this situation?
Authoritative Parenting: Can it reduce teen weight?

• **A.** Why have you not gotten the laundry done? I asked you over two hours ago to finish it. It does not even look like you started? Is that the case?

• **B.** Wow… it looks like you are really busy doing your homework. How is your homework going?

• **C.** Ohhh great!!! Yet again you don’t listen to me. Do whatever you want. I do not care anymore.

• **D.** If you do not get the laundry done like I asked over two hours ago you will be sorry!
How would you implement the intervention?
Authoritative Parenting: Can it reduce teen weight?

Proposed Intervention

• Stage 2: Skill building (or Parenting 101)
  – 10 sessions, 2 hours per session, Internet-based using the Wellbe.me platform
  – Parents only
  – Based on 3 theory & evidence based programs:
    • Parenting Through Change (Forgatch & Gerwitz, 2009),
    • Mission Possible: Parents and Kids Who Listen (Riesch et al., 2006), and
    • Parental Agency Targeting Children’s Health (Golan, 2006).
How would you collect data to document the acceptability of the intervention (Aim 2)?
Focus Groups
- 8 parents found scenarios informative, technology;
- Thought they already used skills;
- 9 youth would appreciate being approached in the manner taught, would resist or push back though.
Colorectal Cancer Screening

ICTR Type 2 Pilot
PI: Jen Weiss, MD
Fellow, Division of Gastroenterology
Developing the Research Question
Background

• Colorectal cancer (CRC) is the third leading cause of cancer-related death in the US for both men and women
  – ~147,000 new diagnoses in 2009
  – ~50,000 deaths from CRC in 2009

• National Health Interview Survey (2000)
  – 43% of adults age 50 or older reported having FOBT within the preceding year or optical colonoscopy within the past 10 years
Background

• 2006 → 17 health systems in Wisconsin voluntarily reported CRC screening measures

• Wisconsin Collaborative for Healthcare Quality

• UW Health ranked 11 out of 17

• Considerable variation seen across the state
  – Range: 57% to 69%
CRC Screening by Primary Care Clinic

Dashed line = UW Health overall average CRC screening rate (64.96%)
Size of bubble corresponds to the size of the eligible patient population
Aims

• What explains the wide variation within a single health system for CRC screening rates?
  – Use information gained to develop interventions that target identified barriers
Designing the Study
Collecting the Data
Survey of Primary Care Providers

• Sample:
  • UW primary care providers: MDs/DOs/NPs/PAs
  • N = 322 (70% response rate)

• Administered February 2010 – March 2010

• Modified version of the National Cancer Institute Survey on Primary Care Physician Colorectal Cancer Screening Practices
<table>
<thead>
<tr>
<th>Patient concern about tolerating prep</th>
<th>81%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient fear of invasive tests</td>
<td>74%</td>
</tr>
<tr>
<td>Patient embarrassment or anxiety</td>
<td>68%</td>
</tr>
<tr>
<td>Cost or insurance doesn’t cover</td>
<td>52%</td>
</tr>
<tr>
<td>Shortage of trained providers</td>
<td>40%</td>
</tr>
<tr>
<td>Long wait times between order &amp; test</td>
<td>35%</td>
</tr>
<tr>
<td>Lack systematic way to id patients</td>
<td>19%</td>
</tr>
<tr>
<td>PCPs don’t actively recommend</td>
<td>15%</td>
</tr>
<tr>
<td>Patient fear of cancer</td>
<td>14%</td>
</tr>
<tr>
<td>Not enough time in visit</td>
<td>14%</td>
</tr>
<tr>
<td>Patient belief screening not effective</td>
<td>5%</td>
</tr>
</tbody>
</table>
### Intervention Targets

- Patient concern about tolerating prep: 81%
- Patient fear of invasive tests: 74%
- Patient embarrassment or anxiety: 68%
- Cost or insurance doesn’t cover: 52%
- Shortage of trained providers: 40%
- Long wait times between order & test: 35%
- Lack systematic way to id patients: 19%
- PCPs don’t actively recommend: 15%
- Patient fear of cancer: 14%
- Not enough time in visit: 14%
- Patient belief screening not effective: 5%
Stay Tuned

Subsequent grant will track impact of interventions on rates of CRC screening
Study Designs for Type 3 Translational Research

Steven Waring, PhD DVM
Research Scientist
Marshfield Clinic Research Foundation
T3 Translational Research

Basic Science

Community/Population-based Research
T3 Translational Research

• T3 research promotes interaction between basic research and population research to stimulate a robust scientific understanding of human health and disease

• Examples
  – Molecular and genetic epidemiology in population-based genomics, metabolomics, proteomics
  – Research in populations informing hypothesis to be tested in basic science
  – Biomarkers from laboratory studies translating into population-based screening tools
Childhood diabetes risk and insulin resistance

“There is currently no practical mechanism to measure and track IR in school or community settings other than rudimentary assessment of weight and body mass index.”

“A valid, cost-effective, and feasible field-based tool for diabetes risk assessment in children is needed to assist practitioners, schools, and communities in identifying children at risk of developing T2DM in the future.”
Insulin-resistance and diabetes risk: a field-based tool for assessment in children

Developing the research question
Insulin-resistance and diabetes risk: a field-based tool for assessment in children

Definition of problem

• Insulin Resistance (IR) is an independent predictor for the development of hypertension, coronary heart disease, stroke, cancer, and T2DM
• IR is thought to be an early initial step in the pathogenesis of T2DM. IR and T2DM are increasing in childhood and adolescence
• A number of factors contribute to IR, including body composition, cardiovascular fitness (CVF), and genetic predisposition
  – childhood obesity is also a powerful predictor of IR later in life
  – increased CVF in children improved insulin sensitivity, independent of any change in BMI
Insulin-resistance and diabetes risk: a field-based tool for assessment in children

Significance

• Efforts to improve fitness levels and decrease childhood IR are critical, given the epidemic rise in T2DM, obesity, and cardiovascular disease

• A valid, cost-effective, and feasible field-based tool for diabetes risk assessment in children is needed to assist practitioners, schools, and communities in identifying children at risk of developing T2DM
Insulin-resistance and diabetes risk: a field-based tool for assessment in children

Preliminary studies

- Cross-sectional assessment of intervention (PACER) and association with fitness and insulin resistance
- Needs validation in ‘at risk’ (overweight) children and further refinement to develop a tool to assess diabetes risk
Insulin-resistance and diabetes risk: a field-based tool for assessment in children

Specific Aims

• To develop and validate a cost-effective and feasible field-based tool for diabetes risk assessment in children
Insulin-resistance and diabetes risk: a field-based tool for assessment in children

Designing the study
Defining the study population

- Source – UW Pediatric Fitness Clinic and Wisconsin Partnership for Childhood Fitness (WPCF)
- 36 children from each of 5 middle schools in the state
- Sample size: 180 children
Insulin-resistance and diabetes risk: a field-based tool for assessment in children

Data/sample acquisition

• Progressive Aerobic Cardiovascular Endurance Run (PACER) conducted by trained school PE teachers
• Body composition measurements, demographics, family history
• blood samples for IR

Analyzing the data

• Biostatistician support
• Analytic plan
• Statistical significance vs clinical significance
Implementing the study

Insulin-resistance and diabetes risk: a field-based tool for assessment in children
Insulin-resistance and diabetes risk: a field-based tool for assessment in children

Development of the tool for risk assessment

• Step 1
  – determine predictive value of various field-based tests for IR

• Step 2
  – develop this field-based measurement of IR into a valid tool for diabetes risk assessment in children
Insulin-resistance and diabetes risk: a field-based tool for assessment in children

Implications
Insulin-resistance and diabetes risk: a field-based tool for assessment in children

*Translational nature of study*

- research performed in exercise physiology lab will be translated to the community (classroom) by transforming risk factors for type 2 diabetes (T2DM) into a tool to determine risk for later development of T2DM
- expected to provide critical information that can be used at many levels – to guide public policy, target community resources, evaluate interventions, and assist individual children and families
- project also engages schools, children, and parents as partners in the research process
“Is there a biological marker associated with the biological onset (pre-clinical) of colon cancer that could be used as a screening tool in the general or at-risk population?”
Biomarkers for colon cancer: is there a reliable test for screening

Developing the research question
Biomarkers for colon cancer: is there a reliable test for screening

**Definition of problem**

- Spectrum of colonic neoplastic pathways exist
- Current methods for early detection of colon cancer (colonoscopy, fecal occult blood test, fecal DNA markers) are highly sensitive but lack satisfactory specificity
- Need to develop markers that can identify the subset of early tumors with highest potential to develop adenocarcinoma
Biomarkers for colon cancer: is there a reliable test for screening

**Significance**

- Validation of a blood-borne biomarker or suite of biomarkers to detect early colon cancer and distinguish adenomas with high potential to grow versus those that will remain benign
- A cost-effective blood test would improve the chances of screening patients at risk but reluctant or unwilling to undergo colonscopic examination
Biomarkers for colon cancer: is there a reliable test for screening

**Specific Aims**

- To identify candidate marker proteins and peptides in patient plasma before and after polypectomy
- To assay ... plasma levels of candidate plasma proteins (coronin, procollagen Type 1alpha, Wnt-inhibitory factor, insulin-like factor binding protein, cryptidin, tumor-necrosis factor receptor, clusterin)
- To assess the sensitivity, specificity, and positive predictive value of candidate markers, singly and in combination
Biomarkers for colon cancer: is there a reliable test for screening

Designing the study
Biomarkers for colon cancer: is there a reliable test for screening

**Defining the study population**

- **Cases:** patients undergoing colonoscopy with polypectomy
- **Controls:** healthy individuals undergoing screening colonoscopy
- **Source:**
  - Cases – 100 of the 1,200 patients undergoing Computed Tomographic Colonography (CTC) at UW
  - Controls – 100 of the over 4,000 individuals undergoing colonoscopy at Marshfield Clinic (MC) without polypectomy
- **Timespan for recruitment:** 1 year
Biomarkers for colon cancer: is there a reliable test for screening

**Defining the study population**

- **Inclusion Criteria**
  - Male and female patients ≥ 50 years of age
  - Undergoing a diagnostic or screening colonoscopy for purposes of detection of colon cancer

- **Exclusion Criteria**
  - Acute lower GI bleeding as the reason for colonoscopy
  - Biopsy of normal appearing colonic mucosa tissue
  - Personal or family history of colon cancer
  - History of colon polyps
  - History of ulcerative colitis
  - Complete examination of the colon not possible due to inadequate preparation
Biomarkers for colon cancer: is there a reliable test for screening

Data/sample acquisition
- Subjects screened and consented prior to colonoscopy
- Heparinized blood samples drawn pre- and post- polypectomy (cases) or colonoscopy (controls)
- Laboratory methods - Mass spectrometry, AQUA analysis

Analyzing the data
- Biostatistician support
- Analytic plan
- Statistical significance vs clinical significance
Biomarkers for colon cancer: is there a reliable test for screening

Implementing the study
Biomarkers for colon cancer: is there a reliable test for screening

**Project initiation**
- Finalize study protocol/manual of procedures
- IRB approvals
- Training

**Recruitment and progress**
- Screening and consent
- Monthly meetings to track progress and identify problems/issues
- Plasma sample archiving and tracking
Biomarkers for colon cancer: is there a reliable test for screening

Implications
Biomarkers for colon cancer: is there a reliable test for screening

Translational nature of study

- laboratory evidence will be translated to community-based populations to develop and validate a biomarker test (single or suite) for early detection of colon cancer
- expected to provide critical information to inform policy, evaluate interventions, and assist individual patients and their families