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What is Translational Research?

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What is Translational Research?

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May 20, 2011

DISCLOSURE

I have no actual or potential conflict of interest in relation to this program or presentation.

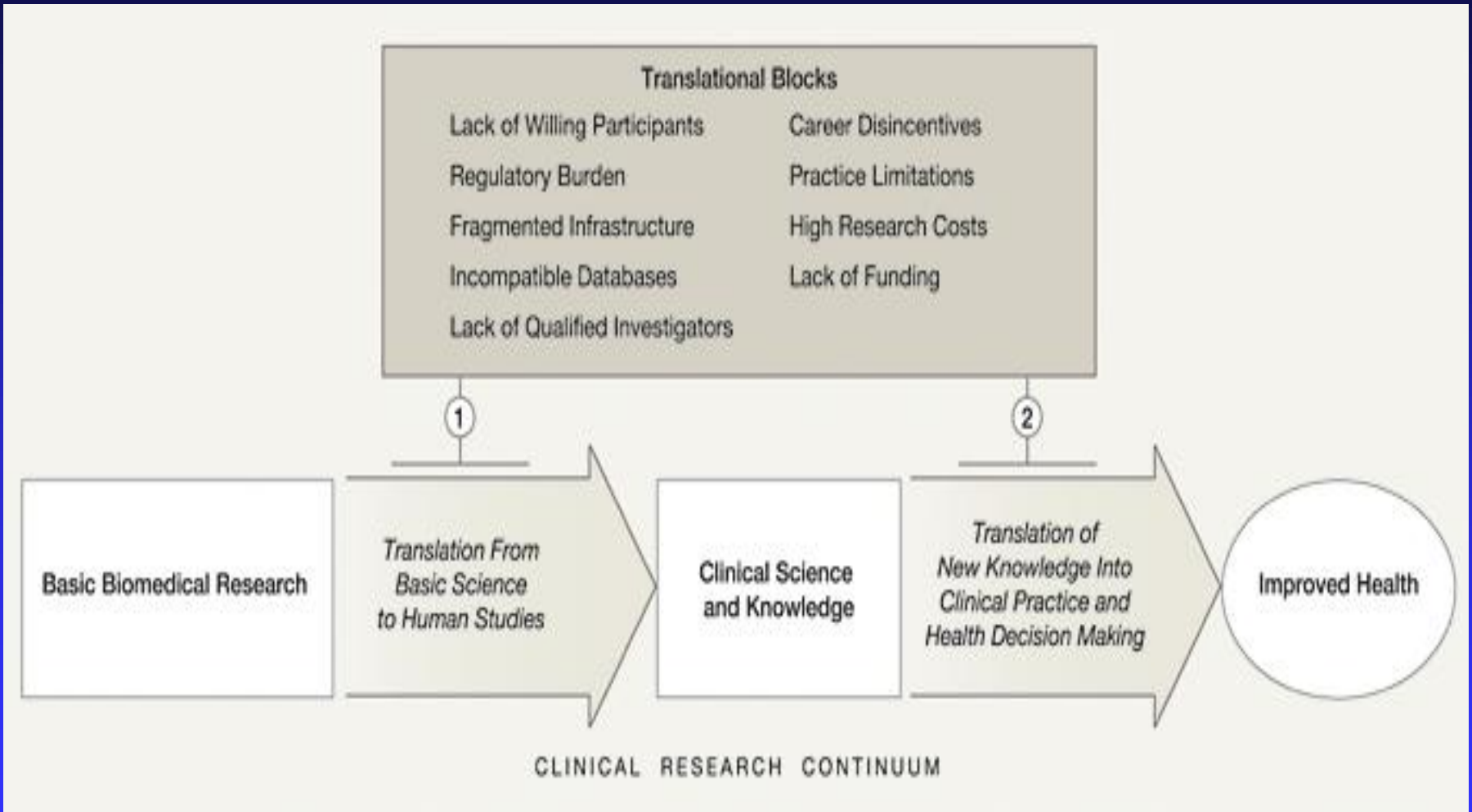
Overview

- Translational Science
 - Why?
 - What?
 - The translational spectrum: a changing nomenclature
- “Bench to bedside”: a limited paradigm
 - Wrong endpoint (bedside)
 - Wrong direction: what about “bedside” to bench?
- Charge for the day

Why Translational Science?

- Median time from description of a new discovery in a basic science journal to publication of use of this discovery in a highly cited article in the medical literature: 24 years
 - Contopoulos-Ioannidis, *Science*, Sept 2008
- Mean time to implement a new clinical research finding into practice: 17 years
 - Balas, Boren, *Yearbook Medical Informatics*, 2000

Translational Blocks in the Clinical Research Continuum



Sung, N. S. et al. JAMA 2003;289:1278-1287.

Translational Research in US

▶ Introduced as part of NIH Roadmap

- *Zerhouni . The NIH Roadmap. Science 2003 (302:63-72)*

▶ NIH Definitions used in CTSA funding (e.g. [RFA-RM-10-020](#))

- Clinical research comprises studies and trials in human subjects
- Translational research includes two areas of translation:
 - Applying findings from laboratory research and preclinical studies to the development of trials and studies in humans
 - Enhancing the adoption of best practices in the community

Translational Research in Europe

- UK Cooksey Report:
 - Process of taking the findings of either basic or clinical research to produce innovations in health care settings
Cooksey 2006. The Stationery Office. London
- The European Advanced Translational Research Infrastructure in Medicine (EATRIS)
Becker and vanDongen. J Cardiovasc Trans Res 2011
 - Funded in part by European Union, to be established through both public and private funds
 - “Maintain Europe's competitiveness in biomedical research and health industry”

The Continuum of Clinical and Translational Science

T1

First in Human
Phase I-II Trials
Proof of Concept

T2

Phase III Trials
Clinical Efficacy
Clinical Guidelines

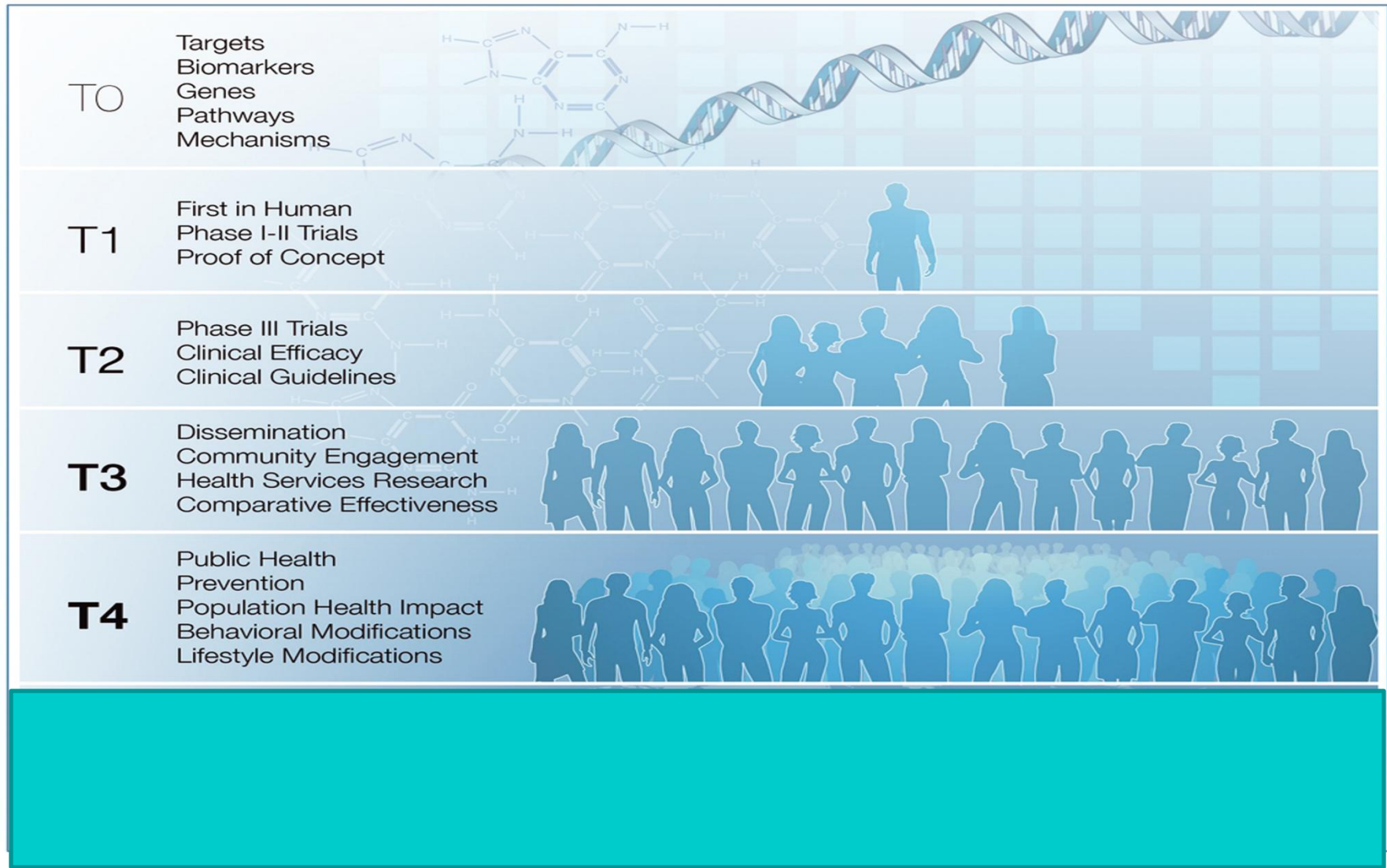
T3

Dissemination
Community Engagement
Health Services Research
Comparative Effectiveness

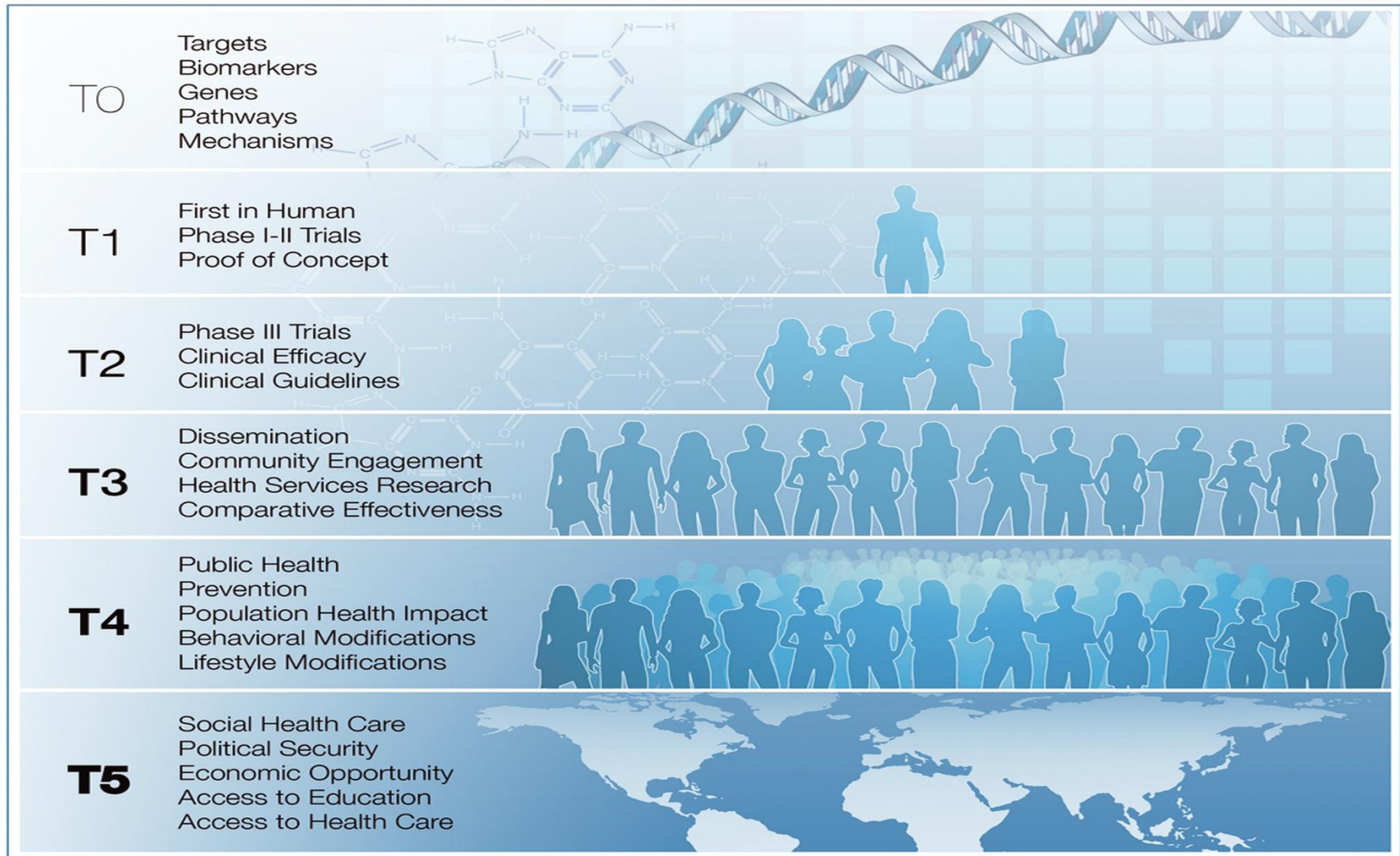
T4

Public Health
Prevention
Population Health Impact
Behavioral Modifications
Lifestyle Modifications

The Continuum of Clinical and Translational Science



The Continuum of Clinical and Translational Science



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The Broad Spectrum of Biomedical Research: Genomics

Khoury et al. *Genet Med* 2007;9(10):665-74

- T0: Genome
- T1: Moves genome-based discovery into candidate health application (eg genetic tests)
- T2: Assesses value of application for health practice, leads to evidence-based guidelines
- T3: Moves guidelines/evidence into practice
- T4: Evaluates “real world” health outcomes of genomic applications
- T5: Studies genomics in the context of the social determinants of health
- **<3% of genomic research focuses on T2 – T5**

T1 vs. T2+: Changing Boundaries

- Initially, translational research required “whole humans” or human population groups as study units. Evolving nomenclature:
- T1 research takes knowledge from the bench (“wet lab”) to clinical knowledge
 - Initially: Phase 1-3 clinical trial (including RCTs)
 - **Recently: also “T0”, mice, even cells...**
- T2+ research takes clinical knowledge into realized human benefit
 - E.g. Group-randomized implementation trials
 - **Recently: also phase 3 clinical trials**

T1 versus T2+ Research

- T2+ defining elements:
 - “dry lab” research that uses statistics and epidemiology as its basic tools
 - The study units may be individual humans, groups of humans (populations), or health systems
- T1 defining elements:
 - May also use “wet lab” tools but **used to** involve “whole humans”
 - Study unit **now** from lab animal to individual patient
- Cultural innovations for both:
 - Transdisciplinary, team science
 - Bidirectionality as emerging concept

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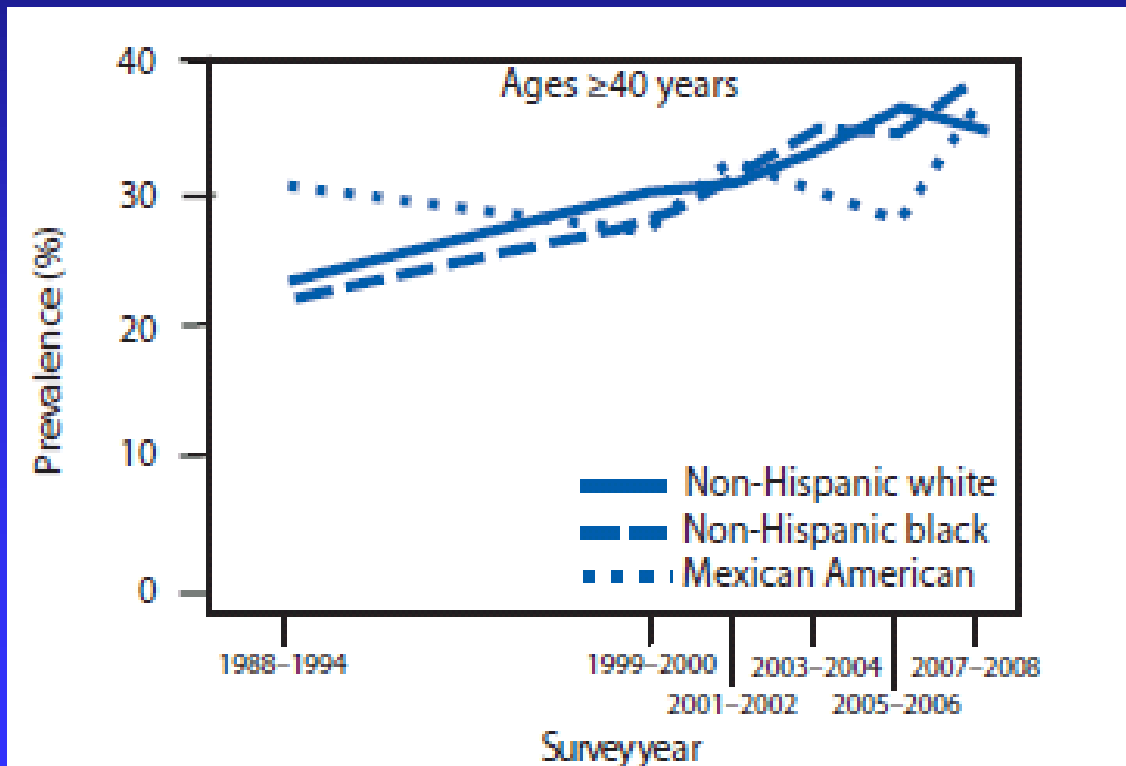
Example : Type 2 Diabetes Prevention

- Chronic hyperglycemia causes severe end-organ damage through fairly well understood pathophysiology (T0, T1)
- T0-T1 research has resulted in multiple medications that control hyperglycemia
- Solid clinical research links Type 2 diabetes to overweight/obesity (T2 - T3): the diabetes epidemic

Why T2+ Research?

- The diabetes epidemic

Prevalence of obesity among men in the US



With a parallel rise in the incidence of diabetes

Important Translational Question

- Weight loss and other lifestyle modifications improve glucose control in patients with diabetes
- Can lifestyle modification and weight reduction PREVENT diabetes?

Diabetes Prevention Program (DPP)

- RCT : 3,234 persons at 27 centers, followed for 10 years *Knowler, NEJM 2002; Knowler, Lancet 2009*
- Cumulative incidence of DM2 lowest in lifestyle group:
 - 58% lower incidence at 1 year
 - 34% lower incidence at 10 years
- Classical efficacy study (T1 –T2)
 - Oral GTT as the screening tool
 - Very intensive, expensive one-on-one intervention
 - Educated population, all literate
 - Overweight/obesity assumed important mediator

Why Research Beyond the “classical” RCT?

- DPP efficacy study notwithstanding, diabetes epidemic marches on
- Lawrence Latino “DPP” (LLDPP)
 - community-based effectiveness study – “real world”
 - 252 at risk pts randomized
 - Group-based less intensive intervention
 - Inexpensive
 - **30** % of population illiterate in Spanish and English

DPP vs. LLDPP outcomes at 1 year *

Improvements in Outcomes at 1 year *		
	DPP	LDPPP
Weight (lbs)	17	3.1
HgbA1c (%)	0.1	0.1

* Numbers approximate; personal communication from I Ockene

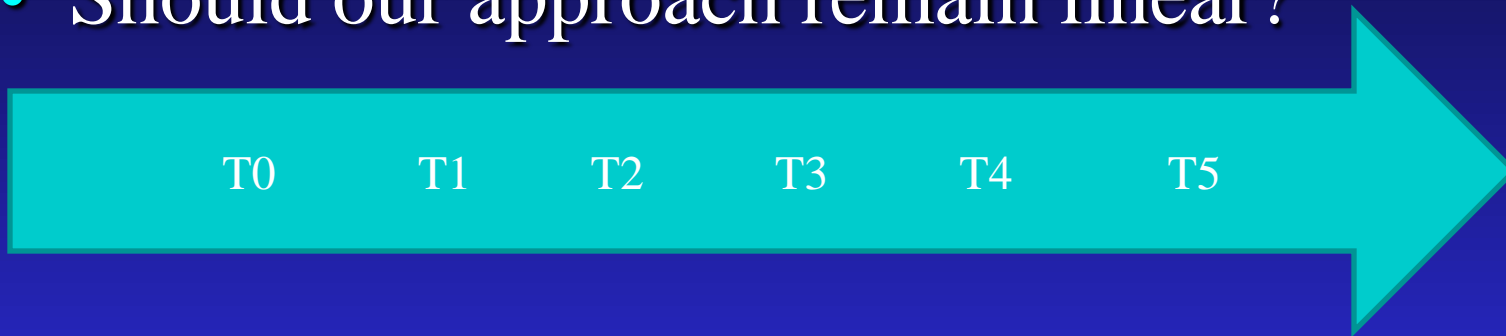
Why similar effect of intervention on hyperglycemia, yet much weaker effect on weight????

Why different effects LLDDP vs. DPP?

- Efficacy vs. effectiveness study?
 - But effect on HgbA1c was similar
- Different populations?
 - Some Latino groups, Native Americans know to be exquisitely sensitive to weight gain re diabetes incidence
 - Are we seeing reverse effect here?
- Need to investigate mechanism that underlies these differences: genetics ?

Bidirectionality

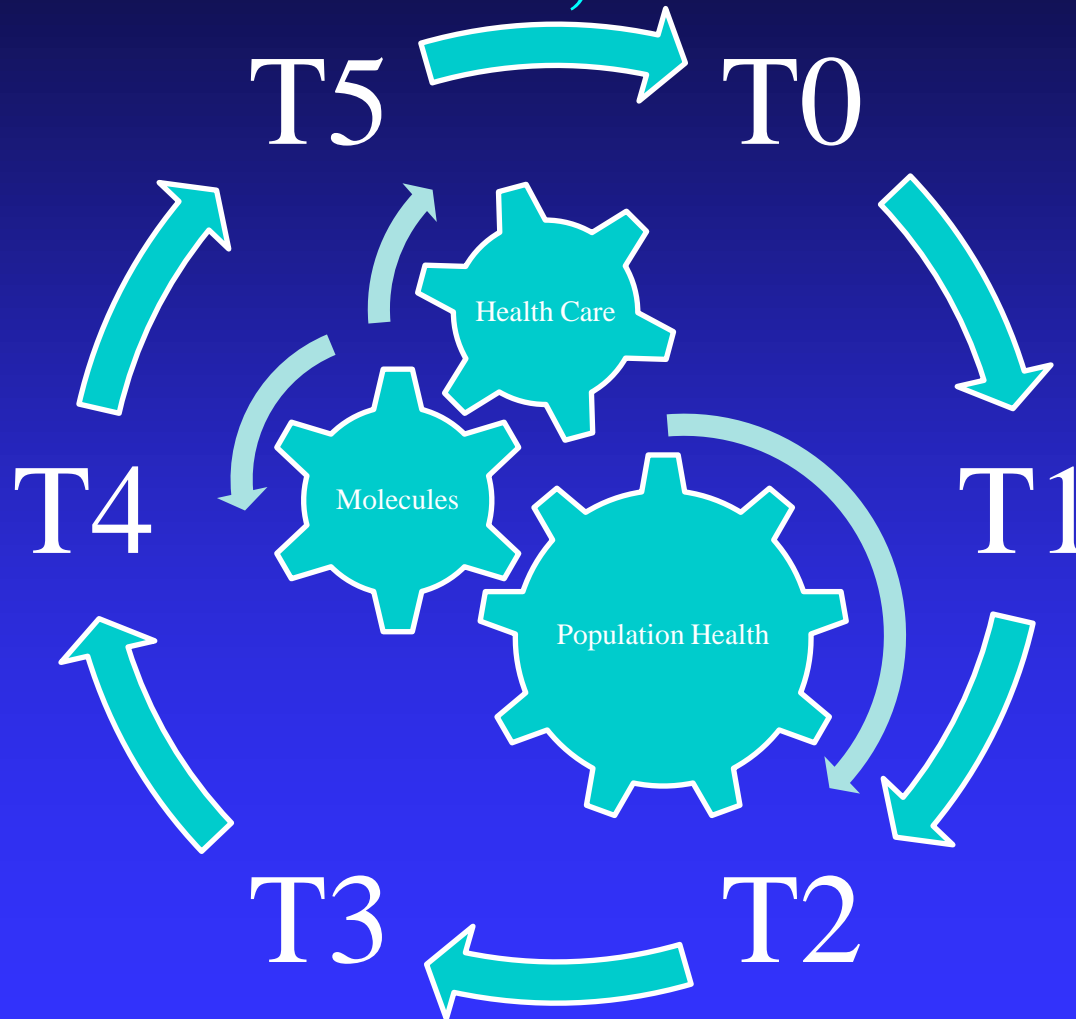
- Should our approach remain linear?



OR

- Should transdisciplinary teams implement true bidirectionality?

Team Science, Bidirectionality



3 Historical Examples of Bidirectionality

Rutter and Plomin, Psychol Med 2009

- Tobacco and lung cancer
 - First: Epidemiologic studies *Doll and Hill, BMJ 1950 and 1954*
 - Later: clinical and animal studies, then gene expression studies *Wen, Mod Path 2011*
- Lipids and heart disease
 - Initial rabbit studies ignored (1913)
 - Epidemiologic evidence in 1956
 - Basic lab research in '70s: model of how LDL causes atherosclerotic lesions
 - LRC trial in the 80s, large statin RCTs in 90's
- Fetal alcohol syndrome
 - Clinical observations define syndrome *Kl Jones, Lancet 1973*
 - Mice studies confirm

SUMMARY

- Translational research is
 - Transdisciplinary
 - Bidirectional
 - Driven by the need to move from knowledge for the sake of knowledge to realized human benefit
 - Reminds us that
 - “Science without conscience is the soul’s perdition” *Rabelais, Pantagruel, 1572*

QUESTIONS?????

Charge for the Day

- Look for bidirectionality
 - Keynote lecture
 - Mini-symposia
 - Posters
- Think transdisciplinary teams
 - Next presentation, lunch, coffee breaks
- Tell us how to do better
 - Fill-out evaluations
- HAVE FUN
 - All day long and evening reception with posters
 - 5 prizes for best posters at evening reception