NASEM SCESCDCR
Webinar: 7/10/2025

Introduction to Types of Evidence

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1. Why is Evidence Needed?
2. How is Evidence Generated?
3. What's Next for Evidence Generation?

10 minutes

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Disclosures and Primary Funding

Seraphina Therapeutics

net.bio

actio BIOSCIENCES

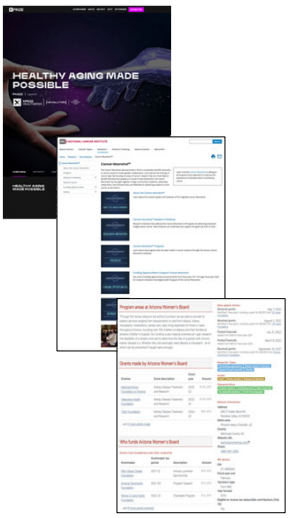
JUMPCODE GENOMICS

Click Therapeutics

Phenomics HEALTH

abbvie

Consultant on the design of the trial(s)



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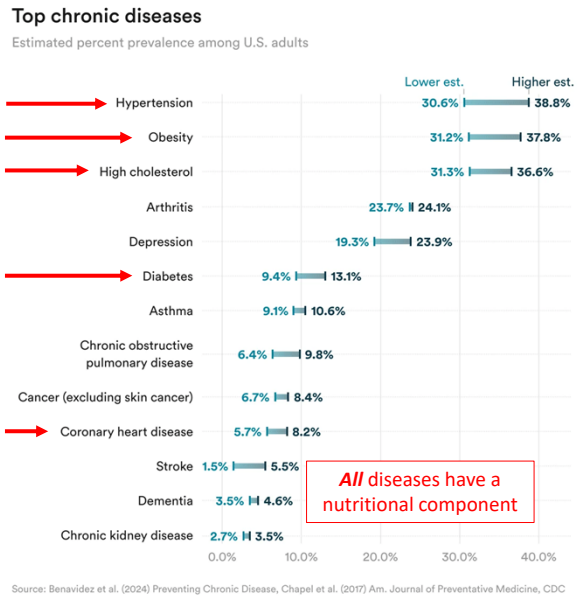
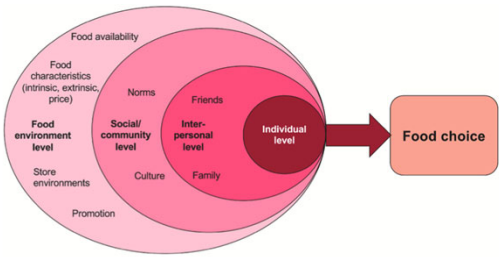
Chronic Disease in the United States



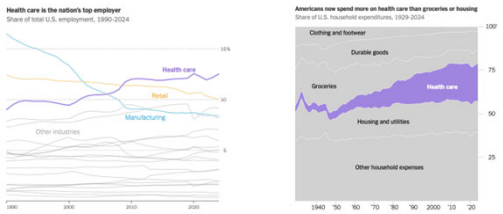
All diseases have a nutritional component

What motivates food choices?



Fernqvist et al. *Heliyon* (2024) PMID: 38952383

Where does scientific evidence fit in?



New York Times, July 3, 2025

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Scientific Evidence and Motivation for Adopting Dietary Practices

Three Important Questions:

1. What evidence would compel the *average person* to make changes to their diet so that they could remain or become healthy?
   - Personal experience? A friend? A podcaster? A government official? The scientific literature? What do these sources base *their* claims on?
2. What evidence would compel *a scientist or physician* to promote a specific diet or nutrient as having health benefits?
   - A large epidemiological association study? A clinical trial exploiting, e.g., randomization? A highly contrived study involving model organisms or cellular constructs?
3. What evidence would compel *a regulatory agency or advisory group* to advocate for the health benefits of a specific diet or nutrient?
   - A review of the literature? Expert opinion? The conduct of studies organized by them for the express purpose of determining health benefits?

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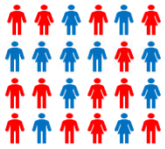
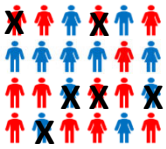
Three Broad Strategies for Generating Evidence for Health Benefits of Food

Population-Based Observational Studies



Test associations with outcomes



Randomized Clinical Trails

Randomize to Tx Groups

Test to see who exhibits an outcome

Non-human and cell/tissue construct studies

Develop Construct

Provide intervention

Deep phenotyping

Explore outcomes and associations

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Many Have Reconsidered Evidence for Dietary Health Claims and Guidance

- Are observational studies compelling? Can they capture cause and effect?
- Are controlled clinical trials powerful? What designs are appropriate?
- Are, e.g., mouse and cell models good surrogates for *in vivo* human biology?

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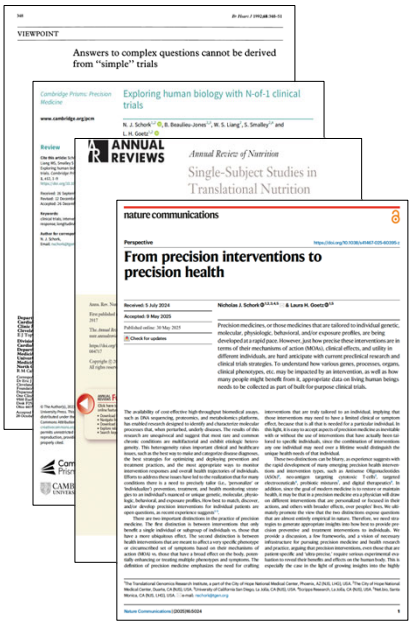
Mega and *Mini* Trials Have Complementary Motivations



Mega vs. Mini Trials

Mega-trials "can provide definitive evidence about the mortality *(or morbidity)* reduction afforded by a class of [intervention] so that broad changes in [health practices] can be justified."

Mini-trials "can explain why [an intervention] is effective to allow development of more effective approaches attacking the identified mechanisms."

Further complementarity: the mechanistic and comprehensive "rationale for mega-trials and the 'fine-tuning' of minor adjustments in [intervention] will be the task of the mini-trials."

Design and motivation for mini-trials are crucial!

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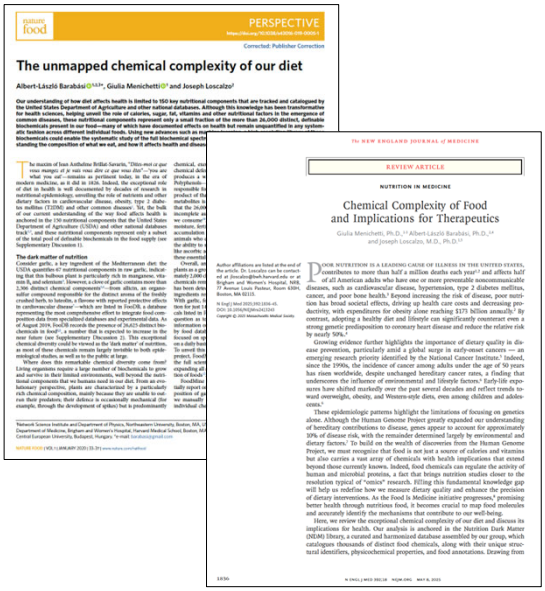
How Many Studies Are Necessary?

The Chemical Complexity of Food

- >139,000 molecules in food, known as "nutrition dark matter (NDM)," hold therapeutic potential
- These food molecules affect ~half the human proteome and can modulate biologic processes
- ~2000 food molecules are used as drugs, highlighting their pharmaceutical relevance
- What would the financial and logistical burden be for conducting appropriate studies?



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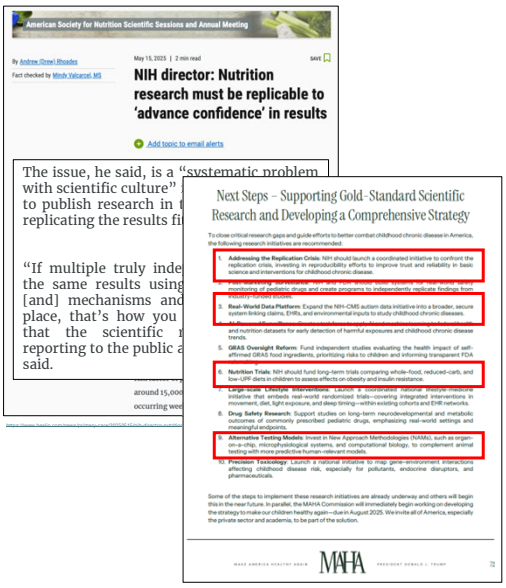
The Importance of *Replicating* Findings: Once is Not Enough?



- Many scientific findings have not been replicated = replication crisis?
- What about inter-individual variability in response? Variability in response among subgroups of individuals?
- Completely independent replication is costly, and budget cuts won't help with this!
- So… data integration and study result 'triangulation' may be key! AI/LLMs?

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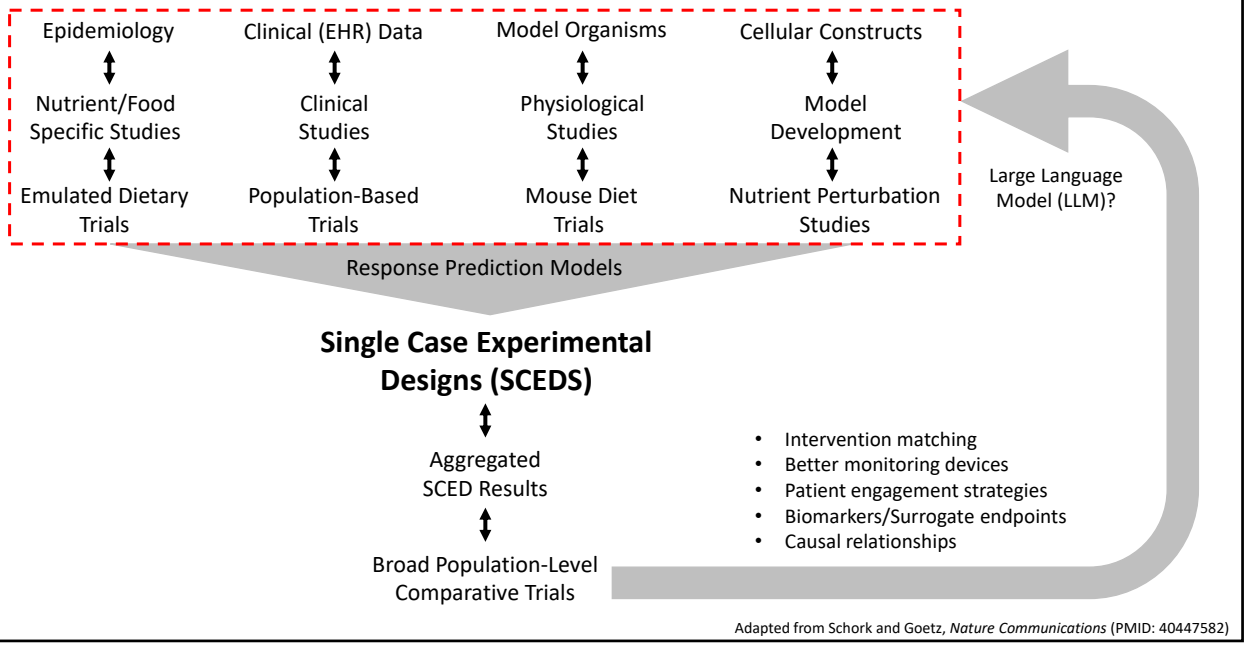
Integrating Different Approaches Via a Learning System



Adapted from Schork and Goetz, *Nature Communications* (PMID: 40447582)

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Some Key Questions or Things to Keep in Mind

- What are the principles behind ways of generating evidence?
- What are good examples of different ways of generating evidence?
- How practical are different ways of generating evidence?
- What can be done to ensure appropriate evidence is being generated?
- Can different methods for generating evidence be combined?
- How easily understood are the different ways of generating evidence?
- How can/should evidence in favor of a diet/nutrient be communicated to the public?
- How can we train next generation researchers to reveal appropriate evidence?
- *The devil is in the details… so pay attention and keep an open mind*

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