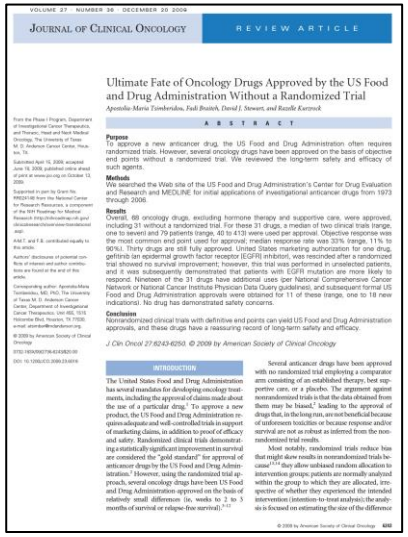
Emerging Clinical Trials Designs in Precision Nutrition and Medicine

- Re-evaluation of the foundations of the traditional RCT
- Bucket/umbrella trials: biomarker-based guidance
- N-of-1 trials: strict focus on individual response
- Adaptive, real-time 'individual policy' identification
- Vetting intervention-individual profile matching algorithms



USA FDA Organized Meeting, ASCPT 2012

Alternatives to prospective RCTs? Mediation analysis (e.g., Mendelian Randomization); General causal analysis (especially longitudinal data); Non-randomized trials; Matching via propensity scores and analysis; Triangulation and 'evidence synthesis' of disparate study type data

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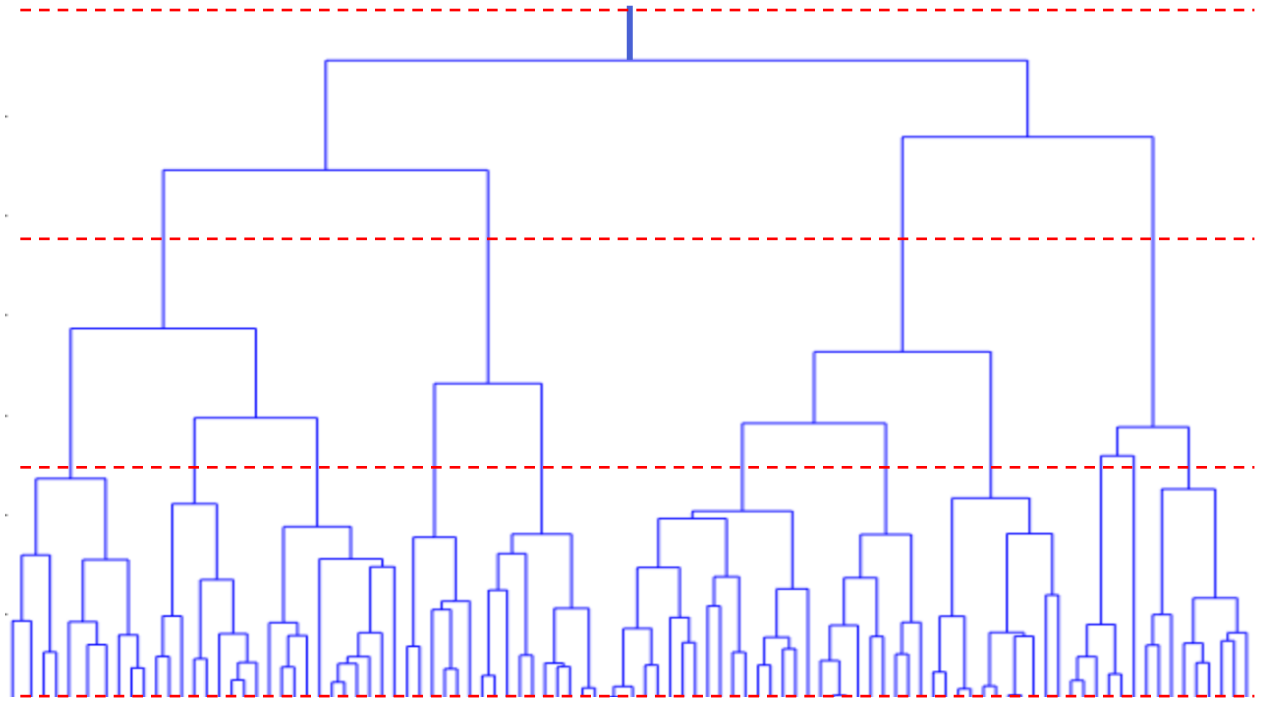
Similarity of individuals based on measures associated with a phenotype
(e.g., microbiome and nutritional deficiencies)



Traditional Nutrition/Medicine ('One Size Fits All')	Standard RCT
Stratified Nutrition/Medicine (Few Biomarkers; e.g., Sex, Ancestry)	Multi-arm trial Bucket/umbrella trials
Precision Nutrition/Medicine (Many Biomarkers; e.g., SNP Profile)	Biomarker-guided trials Bucket/umbrella trials Trials vetting matching strategies
Individualized or Personalized Nutrition/Medicine (Everyone is Unique)	N-of-1 and aggregated N-of-1 trials Adaptive individual policy trials Trials vetting matching strategies

- Need better biomarkers to **identify subgroups** and ways of vetting those biomarkers
- Need better ways of monitoring response, including **surrogate** and meaningful **intermediate endpoints**
- Need to understand **how similarity can be defi**ned? assays may capture one aspect relevant similarity
- Need to appreciate **trait (e.g., genetic)/state (e.g., metabolome) dichotomy** in assessing categories

Therapeutic Drug Monitoring Studies
- Leverage indicators of activity
- Leverage surrogate endpoint
- Better monitoring (e.g., wireless)

Schork NJ, Goetz LH, Lowey J, Trent J.Clin Pharmacol Ther. 2020 Sep;108(3):542-552..PMID: 32535886

Statistical Rapid Learning Systems (RLS): Building-up Insights in Real Time

Patients → DATA → $Outcome = y + b_1x_1 + e$ → Test the Predictions with New Data

+/-	Prediction +	Prediction -
Outcome +	TP	FN
Outcome -	FP	TN

New patients → DATA → $Outcome = y + b_1x_1 + e$ → Test the Predictions with New Data

+/-	Prediction +	Prediction -
Outcome +	TP	FN
Outcome -	FP	TN

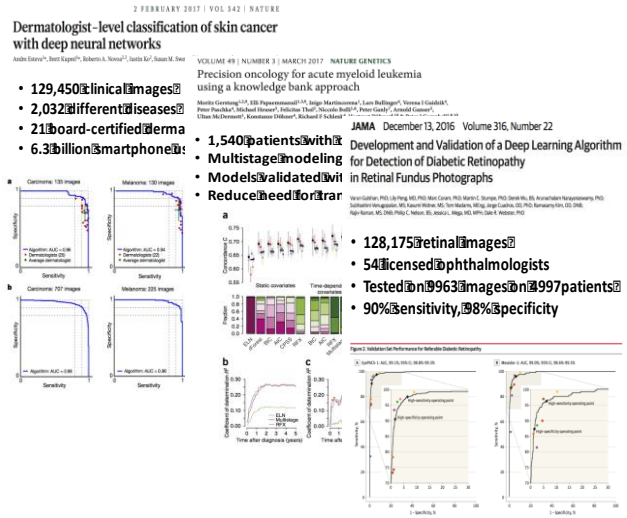
→ DATA DATA → New predictor and expanded prediction model → $Outcome = y + b_1x_1 + b_2x_2 + e$ → Test the Predictions with New Data

+/-	Prediction +	Prediction -
Outcome +	TP	FN
Outcome -	FP	TN

→ DATA DATA → $Outcome = y + b_1x_1 + b_2x_2 + e$ → Test the Predictions with New Data

+/-	Prediction +	Prediction -
Outcome +	TP	FN
Outcome -	FP	TN

→ In Perpetuity → ...



HEALTH AFFAIRS 26 January 2007

A Rapid-Learning Health System

What would a rapid-learning health system look like, and how might we get there?

by Lynn M. Etheredge

J Clin Oncol 34:756-763. © 2016

Building a Rapid Learning Health Care System for Oncology: Why CancerLinQ Collects Identifiable Health Information to Achieve Its Vision

Alaap Shah, Andrew K. Stewart, Andrej Kolacevski, Dina Michels, and Robert Miller

Nat. Rev. Clin. Oncol. **11**, 109–118 (2014);

Rapid learning for precision oncology

Jeff Shrager and Jay M. Tenenbaum

Note: need a mechanism to collect data and a large database to house, query, and analyze them

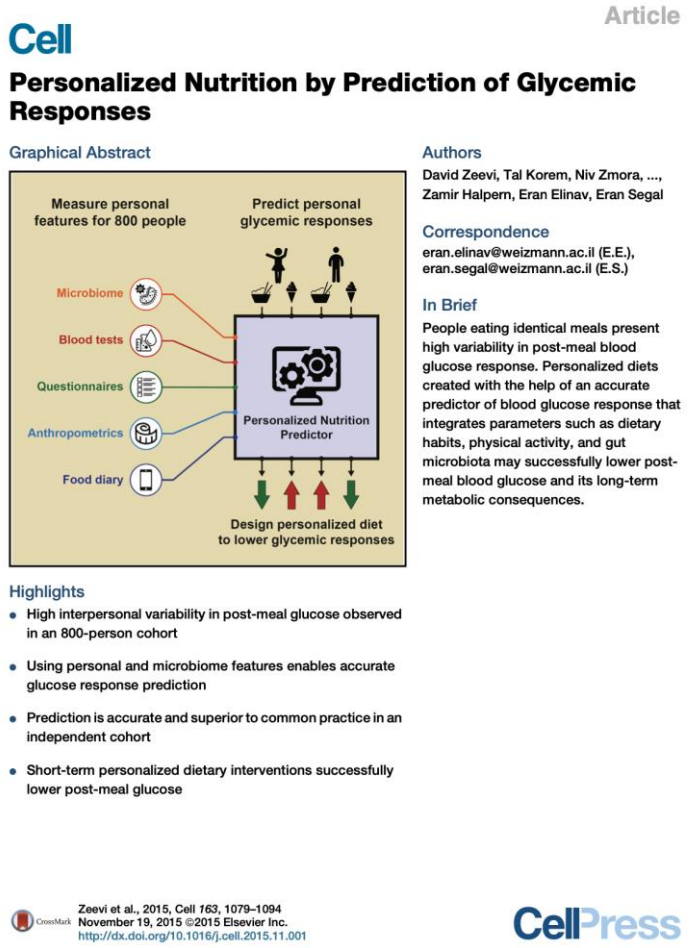
Matching Individual Profiles to a Particular Diet or Medicine(s)

Table 1 Cancer interventions that assume strategies for matching interventions to patient characteristics

Technology/strategy	Example reference	Description
Tumor perturbation rules	Simon and Roychowdhury (2013)[69]	Rules for choosing specific Rx based on patient profile
Combination drug rules	Lazar *et al.* (2015)[70]	Rules to pick out > 1 Rx based on patient profile
Connectivity map	Lamb *et al.* (2006)[8]	Choose drugs "reversing" disease GEx signature
Network analysis	Barabasi *et al.* (2011)[71]	Find best drug targets from interaction maps
Sequential administration	Koopman *et al.* (2011)[72]	Provide drugs in sequence (via biomarkers?)
Multitarget therapies	Galloway *et al.* (2015)[73]	Single compounds known to hit > 1 target
Immunotherapeutics	Kreiter *et al.* (2015)[5]	Neo-antigen targeting via cytotoxic T cell therapy
RNAi/Antisense therapies	Haussecker *et al.* (2015)[74]	Repress GEx via constructs that bind to DNA
In Vivo tumor implants	Jonas *et al.* (2015)[75]	Test drug effects on tumor *in vivo*
Tumorgraft models	Stebbing *et al.* (2014)[76]	Test drug effects on tumor engrafted mice
In Vitro/*Ex Vivo* assays	Crystal *et al.* (2014)[77]	Test tumor drug sensitivity *in vitro*
Engineered cell replacement	Golchin and Farahany (2019)[78]	Modify patient-unique defects in replacement cells
Dosing via biomarkers	Schuck *et al.* (2016)[79]	Set treatment dose per (e.g., patient genotype)
Delivery schedule via biomarkers	Innominato *et al.* (2014)[80]	Time of drug administration is based on diurnal patterns
Physician intuition	–	Decisions based on physician training and experience
Physician-assisted choice	–	Decision support by external data and publications

GEx, Gene expression signature; Rx, prescription.

Schork NJ, Goetz LH, Lowey J, Trent J.Clin Pharmacol Ther. 2020 Sep;108(3):542-552. dPMID: 32535886

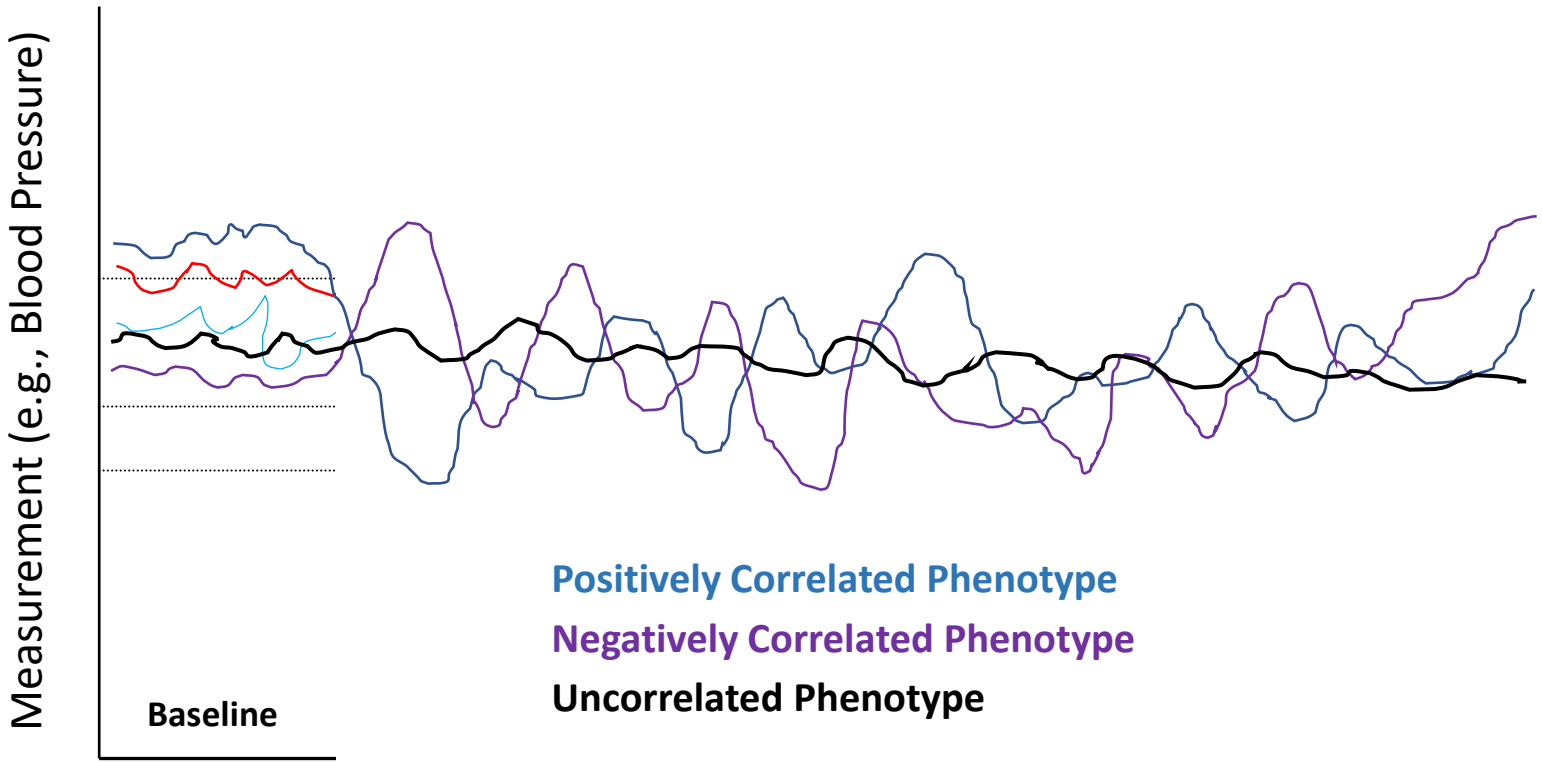


Important Points:

- The algorithms themselves need vetting (diets determined by algorithms vs. those determined by something else?)
- Should one compare two (or more) algorithms in the way, e.g., Lipitor and Simvastain, have been compared?
- Could one use N-of-1 trials on exploring patient responses to an algorithm-determined diet and then aggregate results?

Equipoise, Personalized Nutrition/Medicine and ‘N-of-1’ Clinical Trials

Basic Goal: Make objective claims about the utility of an intervention for an *individual* (note: most trials focus on population effects and likely do not collect enough data to identify *unequivocal* responders vs. non-responders)



Many familiar statistical strategies can be used in their design to achieve greater scientific rigor:

- Randomization
- Blinding
- Multiple crossovers
- Washout periods
- Accommodating covariates
- Multivariate analyses
- Aggregation and meta-analyses

USA FDA Organized Meeting, ASCPT 2012

Schork NJ and Goetz LH. Annual Review of Nutrition. 2017; 37: 395-422; Lillie EO, Patay B, Diamant J, Issell B, Topol EJ, Per Med. 2011 Mar;8(2):161-173.