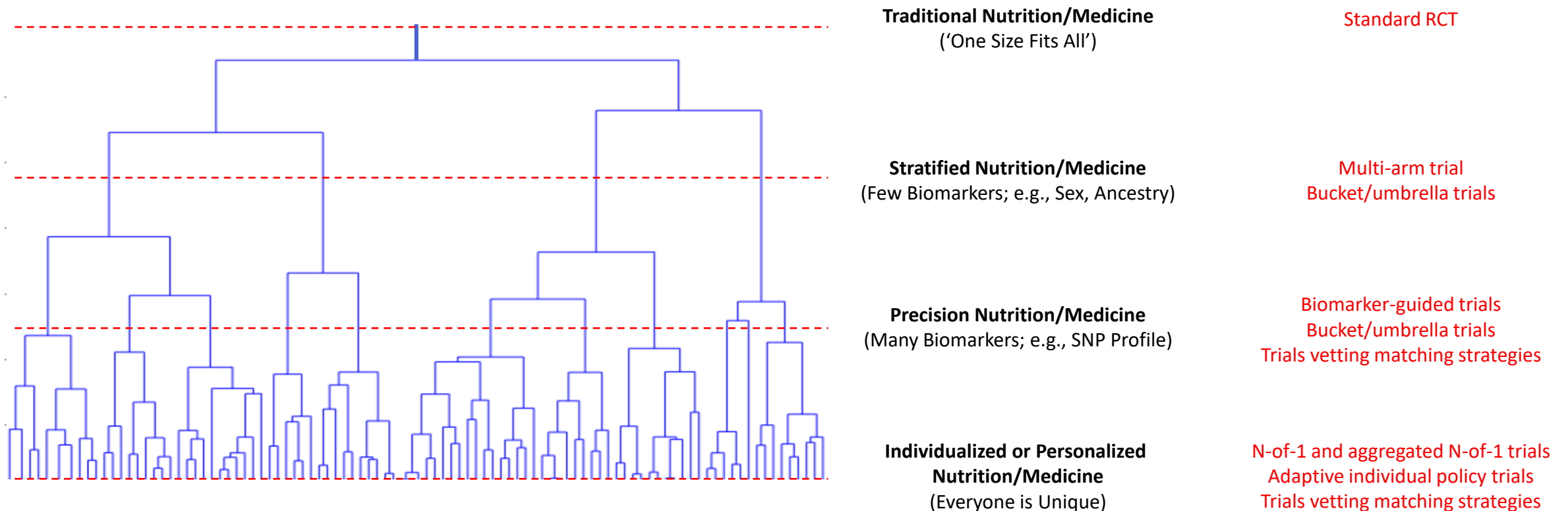


Emerging Clinical Trials Designs in Precision Nutrition and Medicine

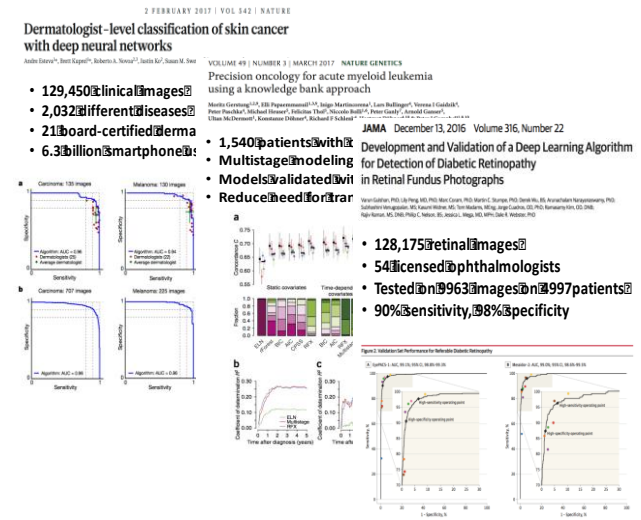
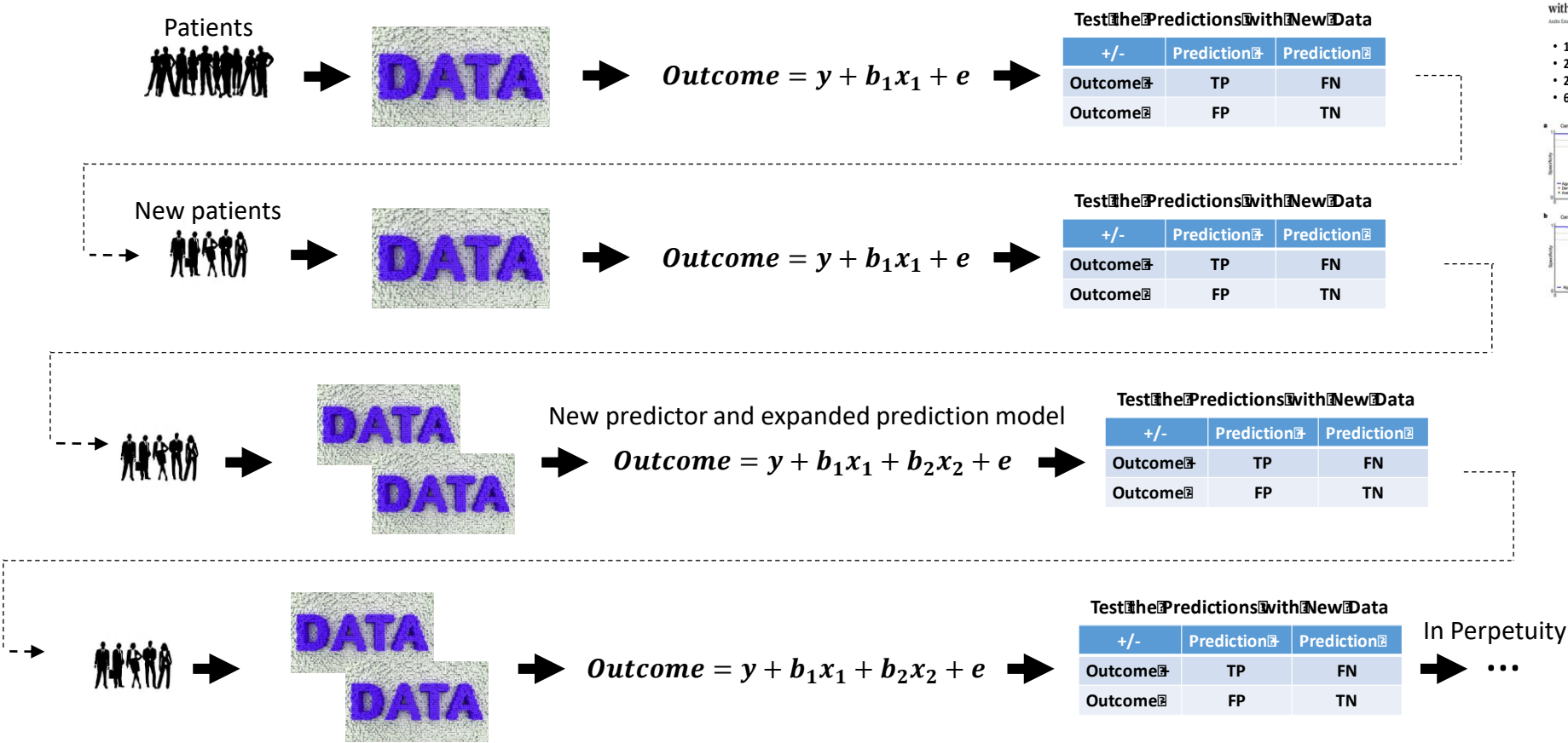
Similarity of individuals based on measures associated with a phenotype
(e.g., microbiome and nutritional deficiencies)



- 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 defined?** 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)

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



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 Kolacovski, Dina Michels, and Robert Miller

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

Rapid learning for precision oncology

Jeff Shrager and Jay M. Tenenbaum

ONLINE RULES FOR CONTROL OF FALSE DISCOVERY RATE AND FALSE DISCOVERY EXCEEDANCE

BY ADEL JAVANMARD¹ AND ANDREA MONTANARI²

University of Southern California and Stanford University

Multiple hypothesis testing is a core problem in statistical inference and arises in almost every scientific field. Given a set of null hypotheses $H_0 = (H_1, \dots, H_n)$, Benjamini and Hochberg [J. R. Stat. Soc. Ser. B, Stat. Methodol. 57 (1995) 289–300] introduced the false discovery rate (FDR), which is the expected proportion of false positives among rejected null hypotheses, and proposed a testing procedure that controls FDR below a pre-assigned significance level. Nowadays FDR is the criterion of choice for large-scale multiple hypothesis testing.

In this paper we consider the problem of controlling FDR in an online manner. Concretely, we consider an ordered—possibly infinite—sequence of null hypotheses $H = (H_1, H_2, H_3, \dots)$, where, at each step i , the statistician must decide whether to reject hypothesis H_i having access only to the previous decisions. This model was introduced by Foster and Stine [J. R. Stat. Soc. Ser. B, Stat. Methodol. 70 (2008) 429–444].

We study a class of generalized alpha investing procedures, first introduced by Aharoni and Rosset [J. R. Stat. Soc. Ser. B, Stat. Methodol. 76 (2014) 771–794]. We prove that any rule in this class controls online FDR, provided p -values corresponding to true nulls are independent from the other p -values. Earlier work only established an FDR control. Next, we obtain conditions under which generalized alpha investing controls FDR in the presence of general p -value dependencies. We also develop a modified set of procedures that allow to control the false discovery exceedance (the tail of the proportion of false discoveries). Finally, we evaluate the performance of online procedures on both synthetic and real data, comparing them with offline approaches, such as adaptive Benjamini–Hochberg.

1. Introduction. The common practice in claiming a scientific discovery is to support such claim with a p -value as a measure of statistical significance. Hypotheses with p -values below a significance level α , typically 0.05, are considered to be statistically significant. While this ritual controls type I errors for single testing problems, in case of testing multiple hypotheses it leads to a large number

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²Supported in part by NSF Grants CCF-1319979 and DMS-1106627, and the AFOSR Grant F49620-13-1-0036.
MSC2010 subject classifications. Primary 62F03, 62F05; secondary 62L99.
Key words and phrases. Hypothesis testing, false discovery rate (FDR), false discovery exceedance (FDE), online decision making.

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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 <i>et al.</i> (2015) ⁷⁰	Rules to pick out > 1 Rx based on patient profile
Connectivity map	Lamb <i>et al.</i> (2006) ⁸	Choose drugs "reversing" disease GEx signature
Network analysis	Barabasi <i>et al.</i> (2011) ⁷¹	Find best drug targets from interaction maps
Sequential administration	Koopman <i>et al.</i> (2011) ⁷²	Provide drugs in sequence (via biomarkers?)
Multitarget therapies	Galloway <i>et al.</i> (2015) ⁷³	Single compounds known to hit > 1 target
Immunotherapeutics	Kreiter <i>et al.</i> (2015) ⁵	Neo-antigen targeting via cytotoxic T cell therapy
RNAi/Antisense therapies	Haussecker <i>et al.</i> (2015) ⁷⁴	Repress GEx via constructs that bind to DNA
<i>In Vivo</i> tumor implants	Jonas <i>et al.</i> (2015) ⁷⁵	Test drug effects on tumor <i>in vivo</i>
Tumorgraft models	Stebbing <i>et al.</i> (2014) ⁷⁶	Test drug effects on tumor engrafted mice
<i>In Vitro/Ex Vivo</i> assays	Crystal <i>et al.</i> (2014) ⁷⁷	Test tumor drug sensitivity <i>in vitro</i>
Engineered cell replacement	Golchin and Farahany (2019) ⁷⁸	Modify patient-unique defects in replacement cells
Dosing via biomarkers	Schuck <i>et al.</i> (2016) ⁷⁹	Set treatment dose per (e.g., patient genotype)
Delivery schedule via biomarkers	Innominato <i>et al.</i> (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

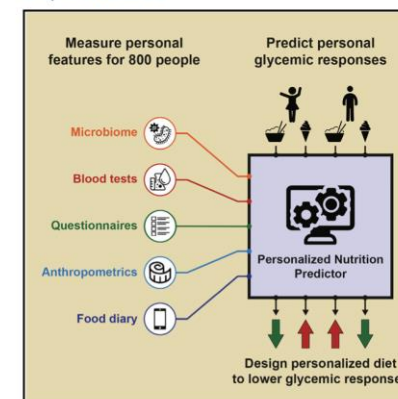
Important Points:

- 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 Simvastatin, have been compared?
- Could one use N-of-1 trials on exploring patient responses to an algorithm-determined diet and then aggregate results?

Cell

Personalized Nutrition by Prediction of Glycemic Responses

Graphical Abstract



Authors

David Zeevi, Tal Korem, Niv Zmora, ..., Zamir Halpern, Eran Elinav, Eran Segal

Correspondence

eran.elinav@weizmann.ac.il (E.E.), eran.segal@weizmann.ac.il (E.S.)

In Brief

People eating identical meals present high variability in post-meal blood glucose response. Personalized diets created with the help of an accurate predictor of blood glucose response that integrates parameters such as dietary habits, physical activity, and gut microbiota may successfully lower post-meal blood glucose and its long-term metabolic consequences.

Highlights

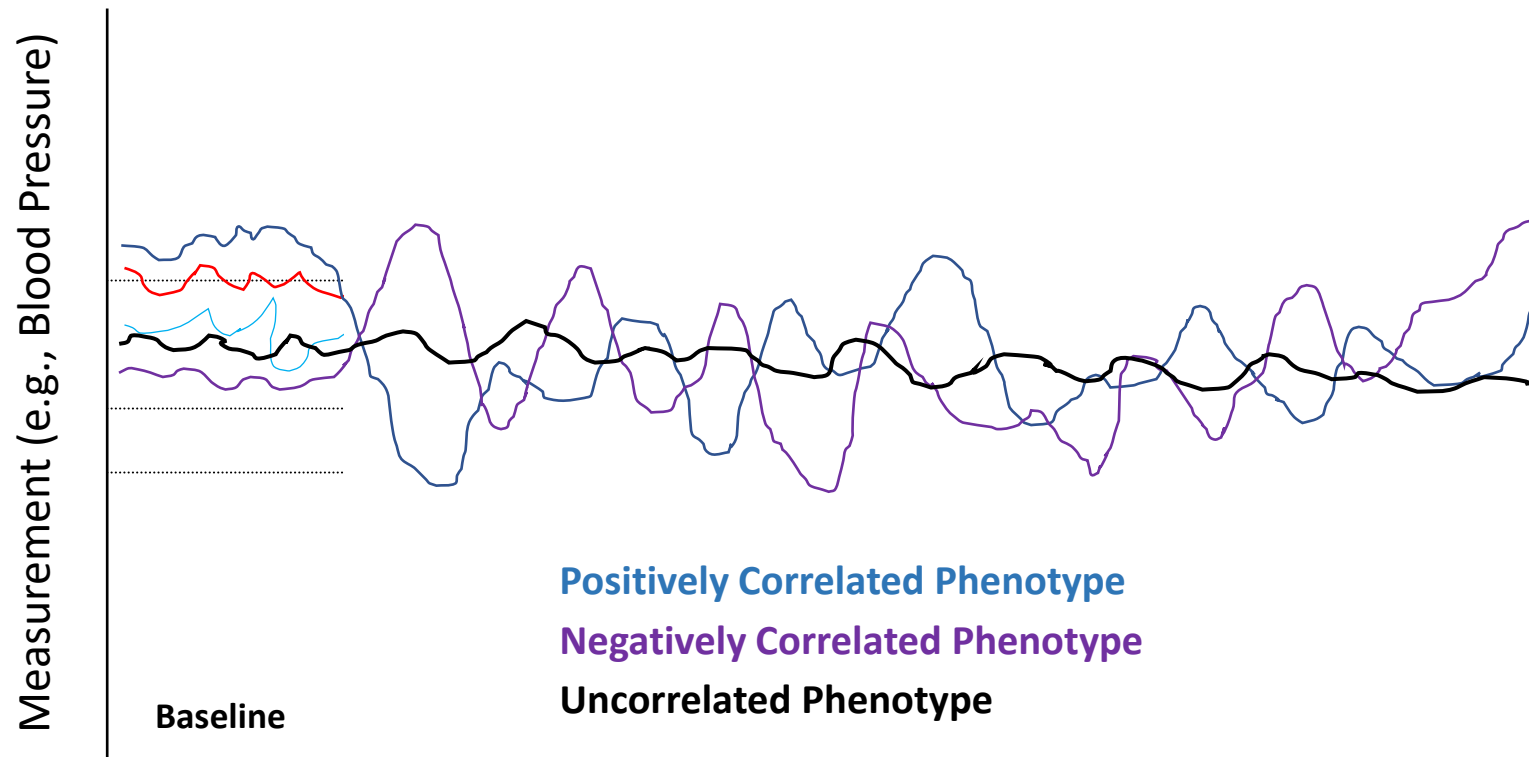
- High interpersonal variability in post-meal glucose observed in an 800-person cohort
- Using personal and microbiome features enables accurate glucose response prediction
- Prediction is accurate and superior to common practice in an independent cohort
- Short-term personalized dietary interventions successfully lower post-meal glucose

Zeevi *et al.*, 2015, Cell 163, 1079–1094
November 19, 2015 ©2015 Elsevier Inc.
<http://dx.doi.org/10.1016/j.cell.2015.11.001>

CellPress

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

