Vetting Personalized and Genomically-Guided Nutrition: Issues and Strategies

Nicholas J. Schork, Ph.D.
(TGen, Phoenix AZ; UCSD, JCVI, La Jolla, CA)

1. Leveraging Trends in Biomedical Science in Nutrition-Based Health Care

2. Identifying, Verifying and Vetting Nutrition *Strategies* for Individuals

3. N-of-1, Aggregated N-of-1, Personal Threshold-Based, etc. Trials

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2003-2007

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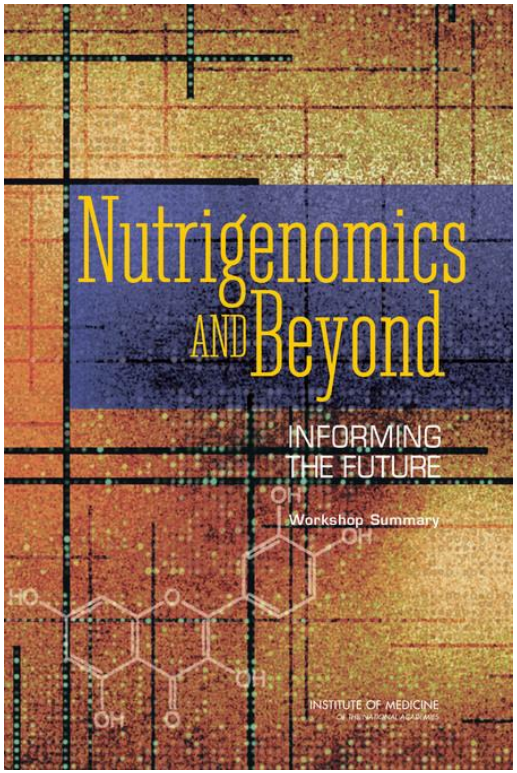

Ann L. Yaktine and Robert Pool, Rapporteurs

Nutrigenomics and Beyond: Informing the Future
June 1-2, 2006
National Academy of Sciences Auditorium
2100 C Street, NW
Washington, DC 20037

PLANNING COMMITTEE FOR THE WORKSHOP ON INFORMING NUTRITION RESEARCH THROUGH NUTRIGENOMICS AND NUTRIGENETICS

NICHOLAS J. SCHORK (*Chair*), Director of Research, Scripps Genomic Medicine and Professor, Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, CA

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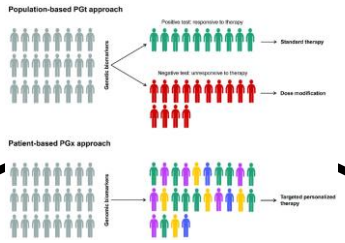
1. Leveraging Trends in Biomedical Science in Nutrition-Based Health Care

Four Trends in Contemporary Biomedical Science

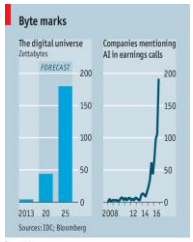


Personalized Health Care

Artificial Intelligence

Emerging Technologies

Big Data and Information Technology



"Garbage in, Garbage out" concerns, so need objective **trials**

Big Nutritional Science Question: How to optimally develop and deploy nutritional interventions when data clearly suggest that factors influencing response(s) exhibit great inter-individual variation? Need insights from:

- Early Intervention Development
- Early Studies on *Humans*
- Clinical Vetting and Proof
- Deployment Efficiencies

Big Economics/Social Question: How does one define 'optimal?'

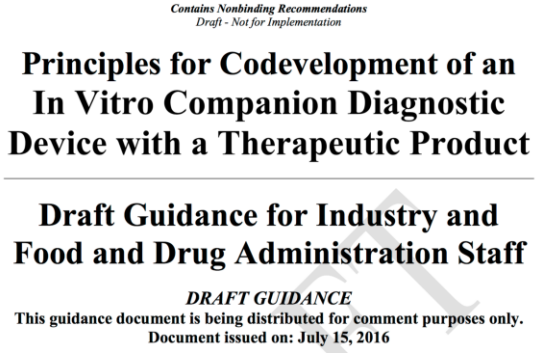
- Individual Outcomes?
- Quality of Life?
- Cost-Savings for Society?

Revamped US FDA: Facilitating Use of New Techs

Scott Gottlieb

21st Century Cures Act: An act to accelerate the discovery, development, and delivery of 21st century cures
(Signed as law by Obama on 12/13/2016)

- Among many other things, intended to expedite the process by which new techs and devices are approved
- Eases requirements put on drug companies looking for FDA approval on new products or new indications on existing drugs
- Under certain conditions, allows companies to provide "**data summaries**" and "**real world evidence**" such as observational studies, insurance claims data, patient input, and anecdotal data rather than full clinical trial results.

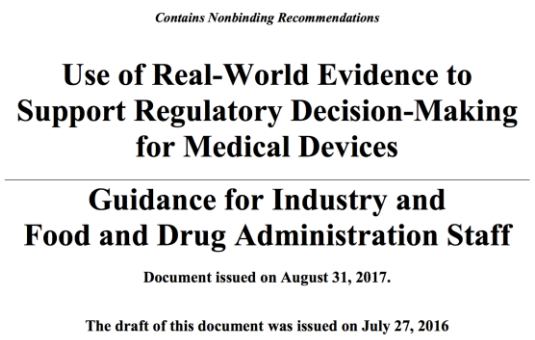


Contains Nonbinding Recommendations
Draft - Not for Implementation

Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE
This guidance document is being distributed for comment purposes only.
Document issued on: July 15, 2016



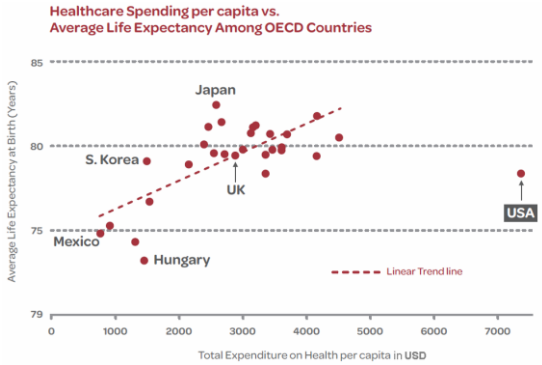
Contains Nonbinding Recommendations

Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff

Document issued on August 31, 2017.

The draft of this document was issued on July 27, 2016



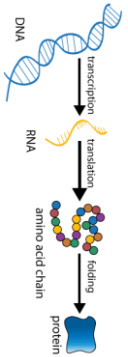
2. Identifying, Verifying and Vetting Nutrition Strategies for Individuals

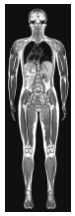
Personalized Nutrition: *What* is Being Tailored to *What*?

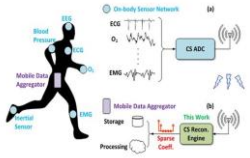
Genetics -> Gross Diet

?

Complex Profile -> Nutrients, Supplements, Etc.







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Conceptualizing Traditional, Stratified, Precision and Personalized Nutrition

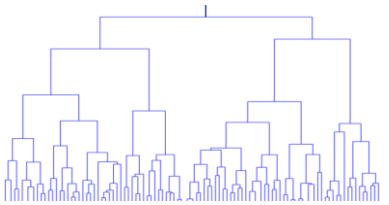
1. Collect data that could impact nutritional response on N patients:

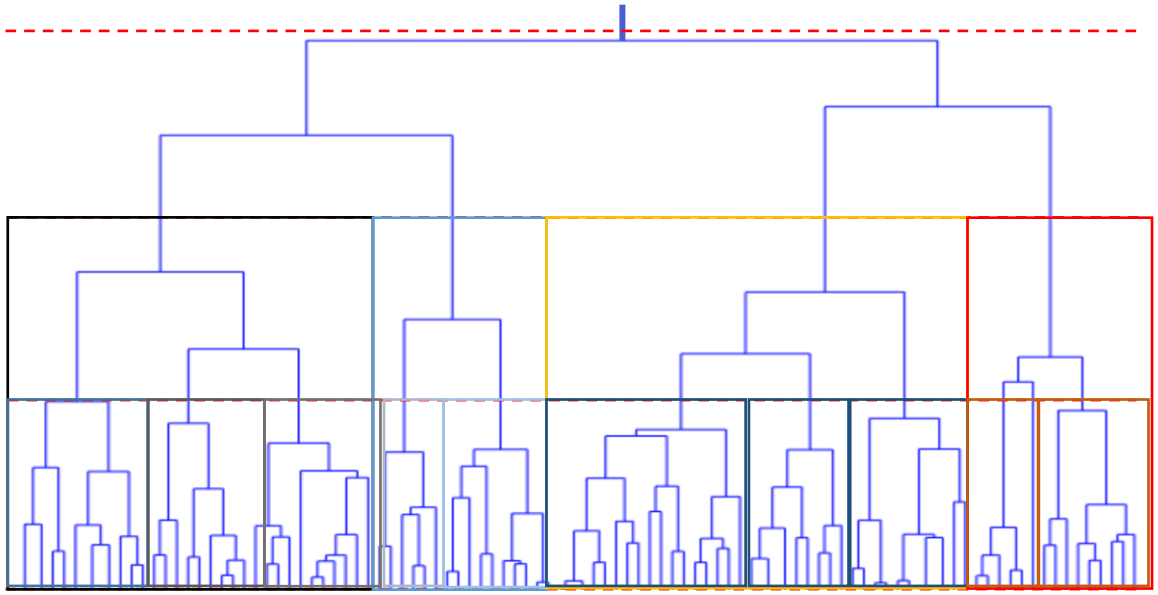
- History on medications
- Genomic profile
- Biomarker profile
- Pathology analysis

2. Form an N x N similarity matrix from the response profiles:

	1	2	3	4	…	N
1	1.00	0.75	0.50	0.25		0.50
2	0.75	1.00	0.25	0.40		0.80
3	0.50	0.25	1.00	0.50		0.10
4	0.25	0.40	0.50	1.00		0.35
□					…	
N	0.05	0.80	0.10	0.35		1.00

3. Cluster patients using the similarity matrix and find treatment rules





Traditional 'One Size Fits All' Nutrition

Stratified Nutrition (e.g., Sex x Race)

Precision Nutrition (e.g., Multiple Biomarkers)

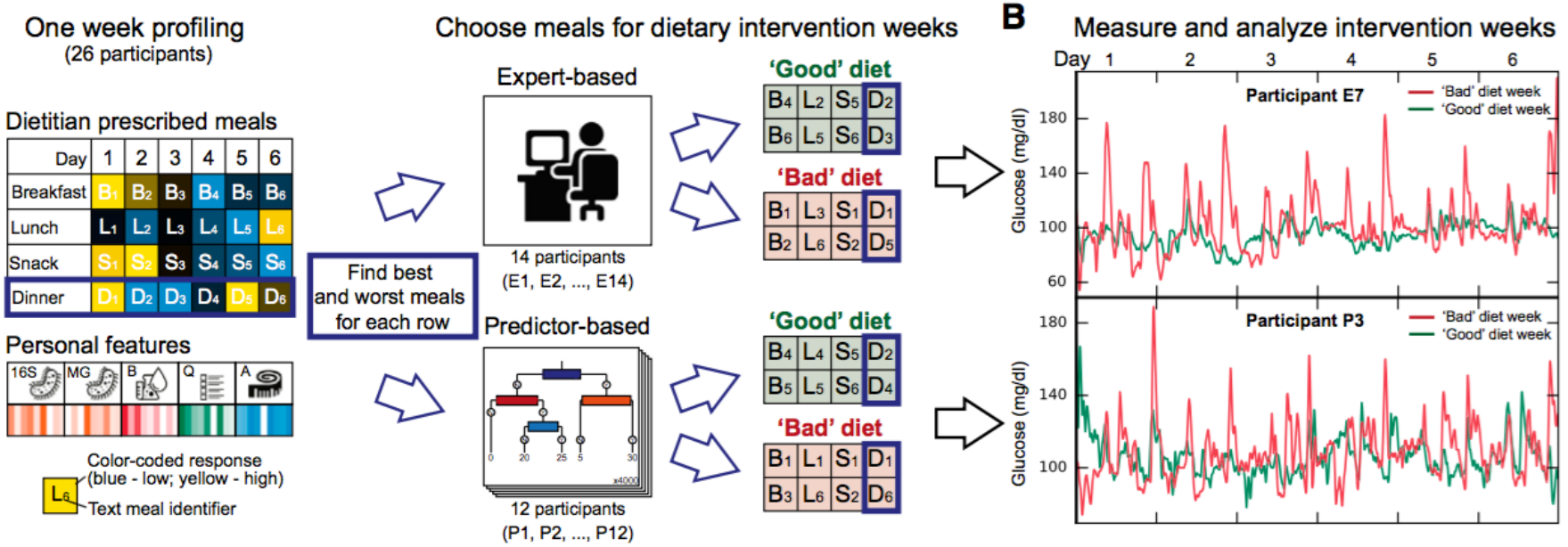
Individualized or Personalized Nutrition

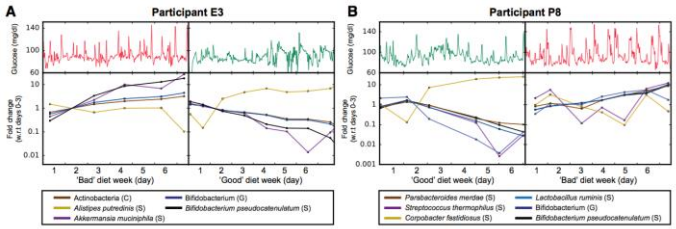
Questions: What level works best? How does one define 'best' (e.g., economics, patient benefit, scientific understanding)? How does one prove that one or another approach is best?

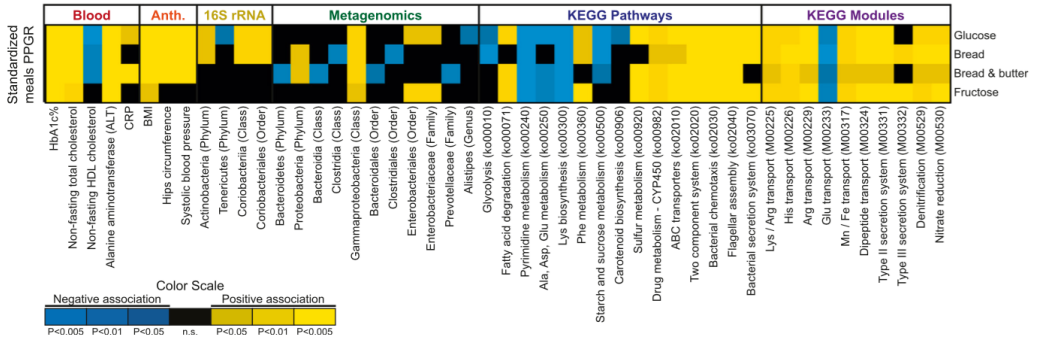
Cell *163*, 1079–1094, November 19, 2015

Personalized Nutrition by Prediction of Glycemic Responses

David Zeevi,[1,2,8] Tal Korem,[1,2,8] Niv Zmora,[3,4,5,8] David Israeli,[6,8] Daphna Rothschild,[1,2] Adina Weinberger,[1,2] Orly Ben-Yacov,[1,2] Dar Lador,[1,2] Tali Avnit-Sagi,[1,2] Maya Lotan-Pompan,[1,2] Jotham Suez,[3] Jemal Ali Mahdi,[3] Elad Matot,[1,2] Gal Malka,[1,2] Noa Kosower,[1,2] Michal Rein,[1,2] Gili Zilberman-Schapira,[3] Lenka Dohnalová,[3] Meirav Pevsner-Fischer,[3] Rony Bikovsky,[1,2] Zamir Halpern,[5,7] Eran Elinav,[3,9,*] and Eran Segal[1,2,9,*]







NATURE REVIEWS | DRUG DISCOVERY
INNOVATION

Implementing personalized cancer genomics in clinical trials

Richard Simon and Sameek Roychowdhury

- Insights or **'Rules'** Relating tumor genomic alterations to specific therapeutic agents are building up

- The evidence for the matching (**or repurposing**) of drugs to alterations comes from different sources

- Only a **subset** of patients is likely to have the alteration

- **Too many (focused/small) trials need to verify each match? How to accommodate?**

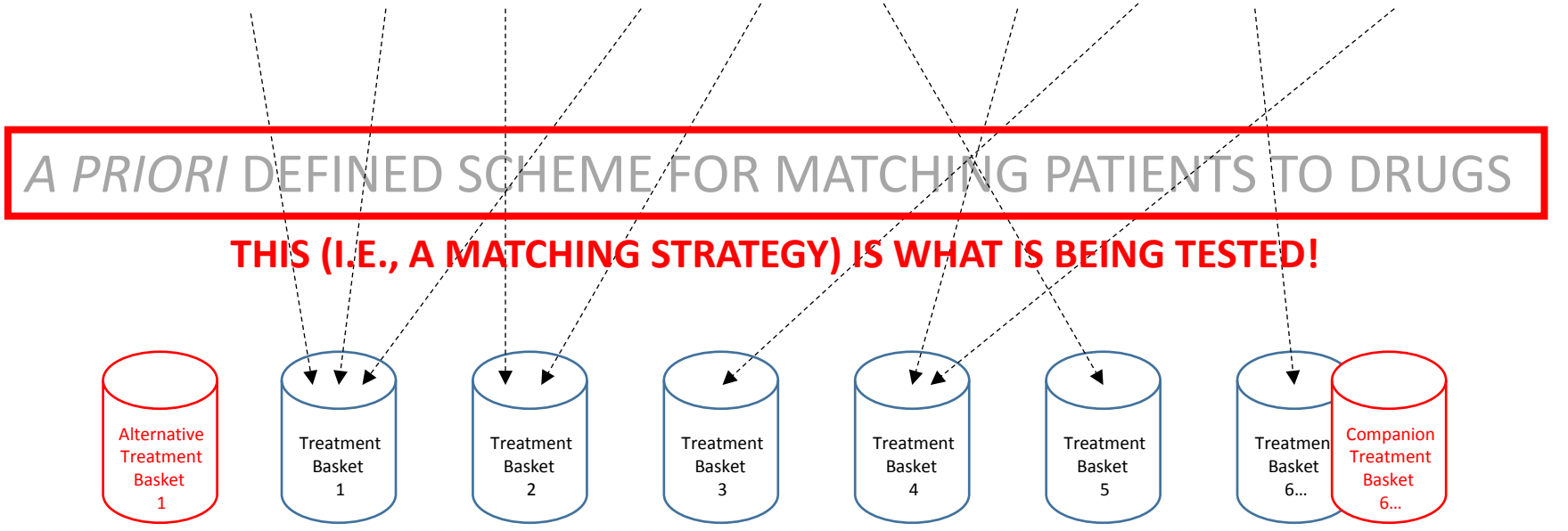
- **What constitutes evidence for a clinically-useful match?**

Table 1 | **Genomic alterations as putative predictive biomarkers for cancer therapy**

Genes	Pathways	Aberration type	Disease examples	Putative or proven drugs
PIK3CA[51,52], *PIK3R1* (REF. 53), *PIK3R2*, *AKT1*, *AKT2* and *AKT3* (REFS 54,55)	Phosphoinositide 3-kinase (PI3K)	Mutation or amplification	Breast, colorectal and endometrial cancer	• PI3K inhibitors • AKT inhibitors
PTEN[56]	PI3K	Deletion	Numerous cancers	• PI3K inhibitors
MTOR[57], *TSC1*[58] and *TSC2* (REF. 59)	mTOR	Mutation	Tuberous sclerosis and Bladder cancer	• mTOR inhibitors
RAS family (*HRAS*, *NRAS*, *KRAS*), *BRAF*[60] and *MEK1*	RAS–MEK	Mutation, rearrangement or amplification	Numerous cancers, including melanoma and prostate cancer	• RAF inhibitors • MEK inhibitors • PI3K inhibitors
Fibroblast growth factor receptor 1 (*FGFR1*), *FGFR2*, *FGFR3*, *FGFR4* (REF. 36)	FGFR	Mutation, amplification or rearrangement	Myeloma, sarcoma and bladder, breast, ovarian, lung, endometrial and myeloid cancers	• FGFR inhibitors • FGFR antibodies
Epidermal growth factor receptor (*EGFR*)	EGFR	Mutation, deletion or amplification	Lung and gastrointestinal cancer	• EGFR inhibitors • EGFR antibodies
ERBB2 (REF. 61)	ERBB2	Amplification or mutation	Breast, bladder, gastric and lung cancer	• ERBB2 inhibitors • ERBB2 antibodies
SMO[62,63] and *PTCH1* (REF. 64)	Hedgehog	Mutation	Basal cell carcinoma	• Hedgehog inhibitor
MET[65]	MET	Amplification or mutation	Bladder, gastric and renal cancer	• MET inhibitors • MET antibodies
JAK1, *JAK2*, *JAK3* (REF. 66), *STAT1*, *STAT3*	JAK–STAT	Mutation or rearrangement	Leukaemia and lymphoma	• JAK–STAT inhibitors • STAT decoys
Discoidin domain-containing receptor 2 (*DDR2*)	RTK	Mutation	Lung cancer	• Some tyrosine kinase inhibitors
Erythropoietin receptor (*EPOR*)	JAK–STAT	Rearrangement	Leukaemia	• JAK–STAT inhibitors
Interleukin-7 receptor (*IL7R*)	JAK–STAT	Mutation	Leukaemia	• JAK–STAT inhibitors
Cyclin-dependent kinases (*CDKs*;[67] *CDK4*, *CDK6*, *CDK8*), *CDKN2A* and cyclin D1 (*CCND1*)	CDK	Amplification, mutation, deletion or rearrangement	Sarcoma, colorectal cancer, melanoma and lymphoma	• CDK inhibitors
ABL1	ABL	Rearrangement	Leukaemia	• ABL inhibitors
Retinoic acid receptor-α (*RARA*)	RARα	Rearrangement	Leukaemia	• All-trans retinoic acid
Aurora kinase A (*AURKA*)[68]	Aurora kinases	Amplification	Prostate cancer and breast cancer	• Aurora kinase inhibitors
Androgen receptor (*AR*)[69]	Androgen	Mutation, amplification or splice variant	Prostate cancer	• Androgen synthesis inhibitors • Androgen receptor inhibitors
FLT3[70]	FLT3	Mutation or deletion	Leukaemia	• FLT3 inhibitors
MET	MET–HGF	Mutation or amplification	Lung cancer and gastric cancer	• MET inhibitors
Myeloproliferative leukaemia (*MPL*)	THPO, JAK–STAT	Mutation	Myeloproliferative neoplasms	• JAK–STAT inhibitors
MDM2 (REF. 71)	MDM2	Amplification	Sarcoma and adrenal carcinoma	• MDM2 antagonist
KIT[72]	KIT	Mutation	GIST, mastocytosis, leukaemia	• KIT inhibitors
PDGFRA and *PDGFRB*	PDGFR	Deletion, rearrangement or amplification	Haematological cancer, GIST, sarcoma and brain cancer	• PDGFR inhibitors
Anaplastic lymphoma kinase (*ALK*)[9,37,73,74]	ALK	Rearrangement or mutation	Lung cancer and neuroblastoma	• ALK inhibitors
RET	RET	Rearrangement or mutation	Lung cancer and thyroid cancer	• RET inhibitors
ROS1 (REF. 75)	ROS1	Rearrangement	Lung cancer and cholangiocarcinoma	• ROS1 inhibitors
NOTCH1 and *NOTCH2*	Notch	Rearrangement or mutation	Leukaemia and breast cancer	• Notch signalling pathway inhibitors

Conceptual Scheme Behind a 'Basket' Trial

Patient	1	2	3	4	5	6	7	8	9	10…
Tumor	Mel	Mel	Breast	CRC	Breast	CRC	Lung	Mel	CRC	Lung
Mut 1						X			X	
Mut 2	X	X		X						
Mut 3			X	X	X					
Mut 4							X			X
Mut 5		X				X				
…										
Mut X								X		



GOAL: Assess outcomes compared to individuals treated *without matching scheme*

ISSUES: *What is the scheme (algorithm) based on?* What about multiple genetic perturbations? What about alternative treatments to any one? What about combination treatments? Why not adapt the scheme as data is accrued (i.e., adaptive designs)?

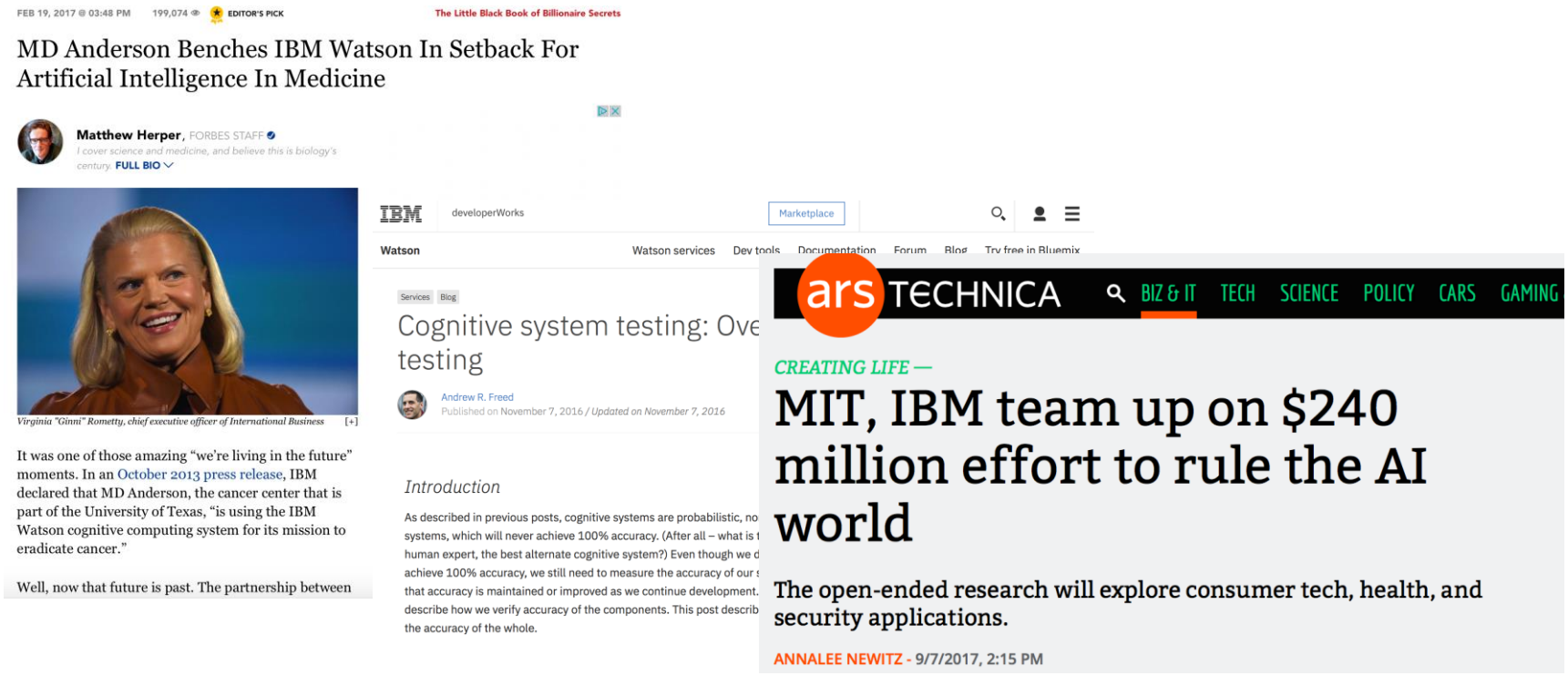
Sean Khozin

Issues Testing Algorithms vs. Drugs

(FDA visit and discussion: June 8, 2015)

- **Combinations** of drugs are an issue? (ICU? Non-cancer chronic disease?)
- **Real time nature** of the **trials** = complex adaptive designs
- **Real time nature** of the **disease** = algorithms with temporal component
- **Insights external to the trial data need to be accommodated**
- What does the **algorithm include**? (e.g., sequencing technologies, tumorgrafts, cell lines, etc.?)
- What if, e.g., a tumor board decides **not to go with the algorithm's drug**?
- **Randomization**: when or at all? i.e., When is there sufficient biological, as opposed to trial, evidence to **forego randomization/equipoise**
- **Poor Outcomes (e.g., SHIVA): algorithm's fault or drug's fault, or both?**
- The **time it takes** to do the assays is an issue; how to incorporate?
- Accommodating crossover to **competitors' drugs**? Who pays?
- **Resources** for conducting many smaller trials? Med-C or ASCO?
- Best for **Repurposing** drugs or new drugs, combinations of old and new?
- **Biomarker-based responses**, how much vetting for individual drugs?

Should There Be *Regulated* Vetting of Algorithms?



FEB 19, 2017 @ 03:48 PM 199,074 EDITOR'S PICK

The Little Black Book of Billionaire Secrets

MD Anderson Benches IBM Watson In Setback For Artificial Intelligence In Medicine

Matthew Herper, FORBES STAFF

I cover science and medicine, and believe this is biology's century. FULL BIO

Virginia "Ginni" Rometty, chief executive officer of International Business [+]

It was one of those amazing "we're living in the future" moments. In an October 2013 press release, IBM declared that MD Anderson, the cancer center that is part of the University of Texas, "is using the IBM Watson cognitive computing system for its mission to eradicate cancer."

Well, now that future is past. The partnership between

IBM developerWorks Marketplace

Watson Watson services Dev tools Documentation Forum Blog Try free in Bluemix

Services Blog

Cognitive system testing: Ove testing

Andrew R. Freed

Published on November 7, 2016 / *Updated on November 7, 2016*

Introduction

As described in previous posts, cognitive systems are probabilistic, no systems, which will never achieve 100% accuracy. (After all – what is t human expert, the best alternate cognitive system?) Even though we d achieve 100% accuracy, we still need to measure the accuracy of our s that accuracy is maintained or improved as we continue development. describe how we verify accuracy of the components. This post describ the accuracy of the whole.

ars TECHNICA BIZ & IT TECH SCIENCE POLICY CARS GAMING

CREATING LIFE —

MIT, IBM team up on $240 million effort to rule the AI world

The open-ended research will explore consumer tech, health, and security applications.

ANNALEE NEWITZ - 9/7/2017, 2:15 PM

Maybe not, but a company or group that is so **incurious** about, or simply **not confident in**, their technology that they **do not want to see if and how it works** should be approached with **major caution**…

3. N-of-1, Aggregated N-of-1, Personal Threshold-Based, etc. Trials

Trials on Single Subjects: Motivation and Designs

COMMENT

STATISTICS A call to police the whole data–analysis pipeline, not just *P* values p.612 | SPRING BOOKS Does Nicholas Stern's global vision admit ground truth? p.614 | SPRING BOOKS Metaphor pile-up obscures the meaning of junk DNA p.615 | SPRING BOOKS Grind, politics and dirty tricks in life of polio-vaccine pioneer p.620

ILLUSTRATION BY GREG CLARKE

Time for one-person trials

Precision medicine requires a different type of clinical trial that focuses on individual, not average, responses to therapy, says **Nicholas J. Schork**.

Every day, millions of people are taking medications that will not help them. The top ten highest-grossing drugs in the United States help between 1 in 25 and 1 in 4 of the people who take them (see 'Imprecision medicine'). For some drugs, such as statins — routinely used to lower cholesterol — as few as 1 in 50 may benefit[1]. There are even drugs that are harmful to certain ethnic groups because of the bias towards white Western participants in classical clinical trials[2].

Recognition that physicians need to take individual variability into account is driving huge interest in 'precision' medicine. In January, US President Barack Obama announced a US$215-million national Precision Medicine Initiative. This includes, among other things, the establishment of a national database of the genetic and other data of one million people in the United States.

Classical clinical trials harvest a handful of measurements from thousands of people. Precision medicine requires different ways of testing interventions. Researchers need to probe the myriad factors — genetic and environmental, among others — that shape a person's response to a particular treatment.

Studies that focus on a single person — known as *N*-of-1 trials — will be a crucial part of the mix. Physicians have long done these in an ad hoc way. For instance, a doctor may prescribe one drug for hypertension and monitor its effect on a person's blood pressure before trying a different one. But few clinicians or researchers have formalized this approach into well-designed trials — usually just a handful of measurements are taken, and only during treatment.

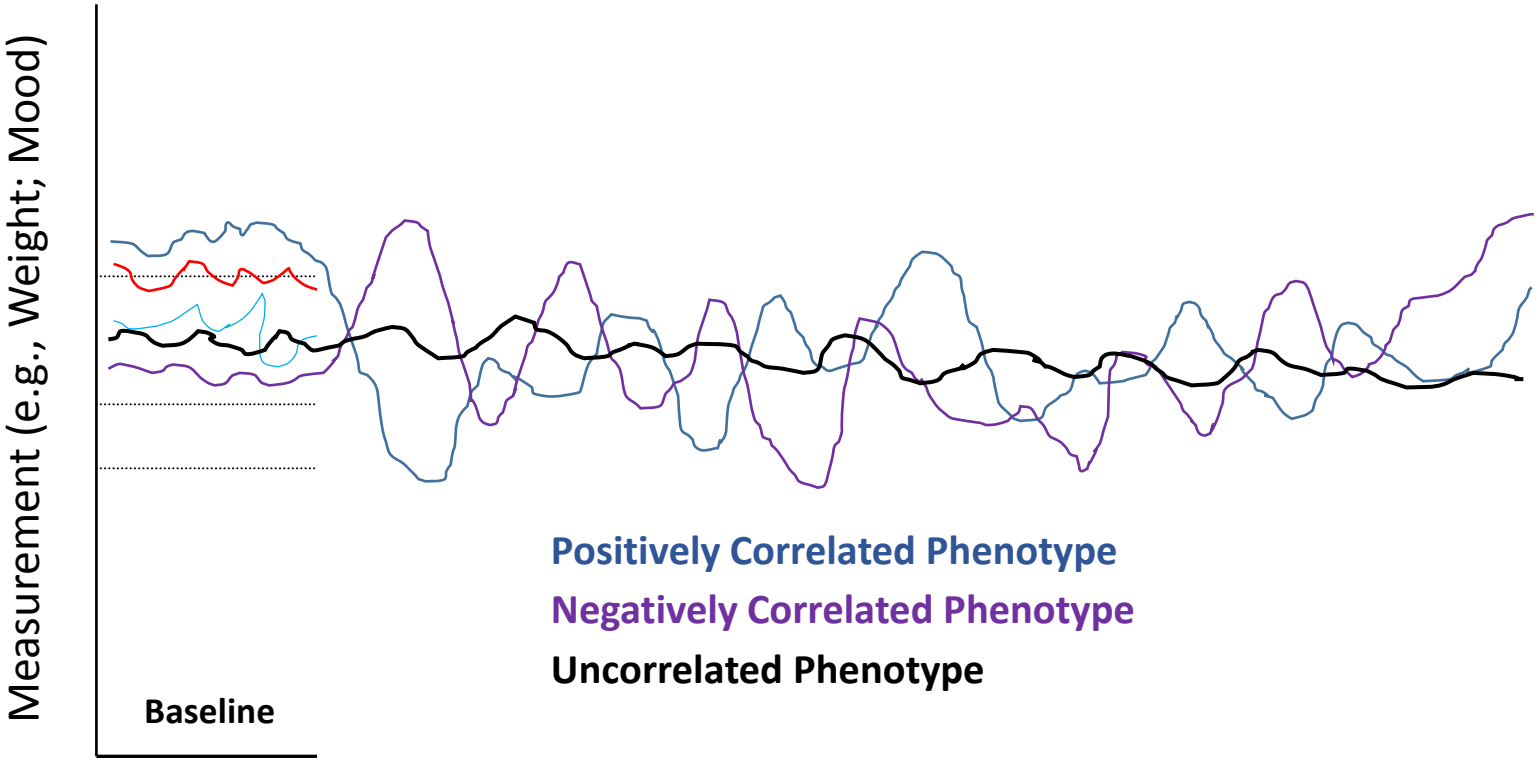
If enough data are collected over a sufficiently long time, and appropriate control interventions are used, the trial participant can be confidently identified as a responder or non-responder to a treatment. Aggregated results of many *N*-of-1 trials (all carried out in the same way) will offer information about how to better treat subsets of the population or even the population at large.

USA FDA Organized Meeting, ASCPT 2012

- A greater focus on the ***science of response*** should emerge from and **guide** clinical trials
- Most large phase III trials don't generate enough data on any one person to determine if they are **unequivocal responders/non-responders** to an intervention
- Focus: objectively assess ***patient's condition/well being,*** not necessarily the intervention…

Equipoise and Single Subject or 'N-of-1' Clinical Trials

Basic Goal: Make *objective* claims about the utility of an intervention for an *individual*
(Most trials focus on population effects; do not have data to identify *unequivocal* responders)



Standard design and statistical methods can be leveraged: randomization, blinding, washout periods, sequential and adaptive designs, multivariate outcomes, etc. **Causality** can be inferred via temporal data

(Lillie EO, …, Schork NJ. Per Med. 2011 Mar;8(2):161-173. PMID:21695041; **Magnuson V, Wang Y, Schork NJ.** F1000 2016 Feb. 3. PMID:28781744)

Table 1. Examples of individual and combined n-of-1 studies investigating the utility of an intervention in pain and discomfort related to a disease.

Disease	Trials (n)	Intervention (Dx)	Results	Ref.
Chronic neuropathic pain	73	Gabapentin	N-of-1 trials impacted Tx use of gabapentin	[40]
Childhood arthritic pain	6	Amitriptyline	No benefit of amitriptyline	[37]
Refractory neuralgia	1	Spinal cord stimulation	Study led to effective use of stimulation	[61]
Osteoarthitis				
Nausea from chemothera				
Skeletal cramping				
Chronic pain				
Osteoarthritis pain				
Chronic pain				
Migraine				
Osteoarthritis				
Depression				
Chronic pain				
Osteoarthritis pain				

Dx: Diagnosis; NSAID: Nonster

Table 2. Examples of individual and combined n-of-1 studies investigating the utility of an intervention in the treatment of a disease.

Disease	Trials (n)	Intervention (Dx)	Results	Ref.
COPD	26	Ambulatory oxygen	Reported use of oxygen is biased	[71]
OCTD	1	L-arginine diet	L-arginine improved health	[72]
Brain injury	NR	Methylphenidate	No benefit of methylphenidate	[73]
Oral mucositis	16	Topical vitamin E	No benefit of topical vitamin E	[74]
Chronic fatigue	4	Spirulina	No effect of spirulina	[75]
ADHD	86	Stimulants	28 out of 64 trials led to change of Tx	[56]
Anticoagulation	7	Generic/brand warfarin	No difference between generic/brand	[76]
Sleep disturbances	15	Temazepam	Temazepam is beneficial	[67]
Sleep disturbances	42	Valerian	Valerian did not improve sleep	[77]
COPD	27	Eformoteral	No effect of eformoterol	[78]
Cystic fibrosis	48	Recombinant DNase	Marginal improvements with Dx	[79]
Severe CM poisoning	1	Donepezil	No effect of donepezil on memory	[80]
Reflux disease	32	Omeprazole/ranitidine	Utility of n-of-1 trials was observed	[81]
Depression	5	Methylphenidate	Two patients improvement with Dx	[68]
Cystic fibrosis	52	Recombinant DNase	Marked Improvements after Dx	[82]
ADHD	43	Methylphenidate	Improvement with methylphenidate	[83]
Chronic airflow limits	68	Theophylline	N-of-1 studies no better than standard Tx	[84]

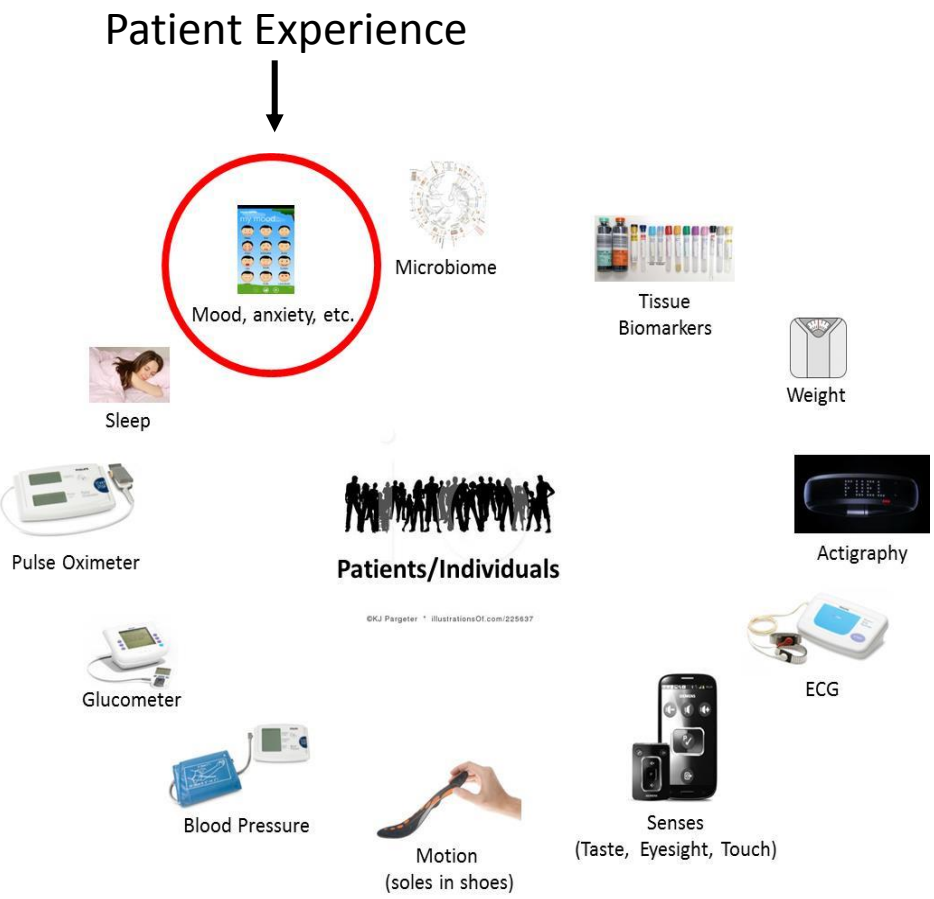
ADHD: Attention deficit hyperactivity disorder; CM: Carbon monoxide; COPD: Chronic obstructive pulmonary disease; Dx: Diagnosis; NR: Not reported; OCTS: Overlap connective tissue disease; Tx: Treatment.

Although many studies leverage, e.g., blinding, multiple crossovers, etc. they are not very sophisticated in terms of measurements or data analysis (Med Care 2011; 49:761-768): **Design Optimization is Possible!**

Lillie EO, Patay B, Diamant J, Issell B, Topol EJ, Schork NJ. The n-of-1 clinical trial: the ultimate strategy for individualizing medicine? Per Med. 2011 Mar;8(2):161-173. PMID:21695041

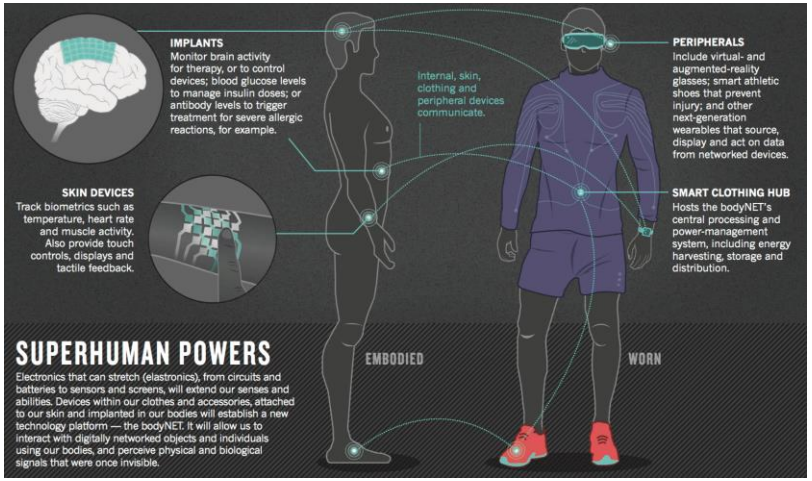
Wireless Medical Data Collection Devices:

Primary or Surrogate Endpoint Monitoring



"You can't list your iPhone as your primary-care physician."

***The New Yorker*, 5/25/15**



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Annu. Rev. Nutr. 2017. 37:395–422

Single-Subject Studies in Translational Nutrition Research

Nicholas J. Schork[1,2,3] and Laura H. Goetz[2,4,5]

Patrick J. Stover

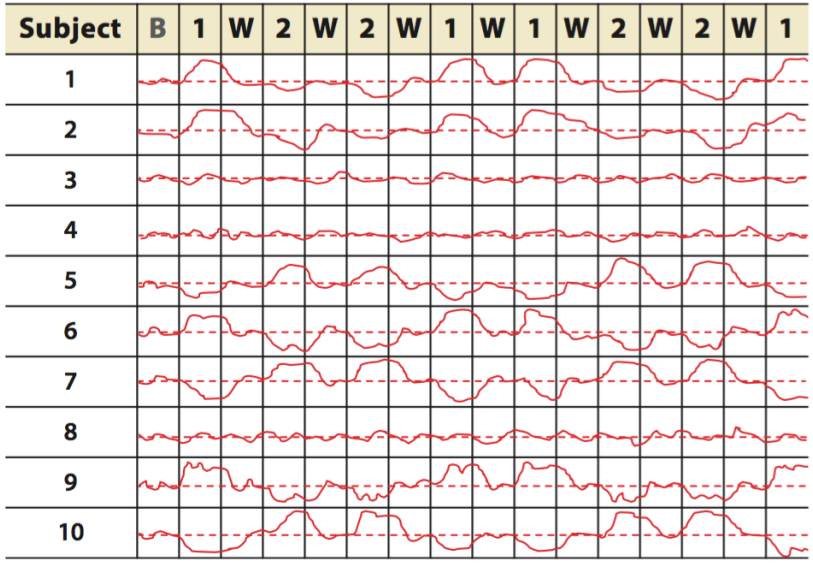
Editor

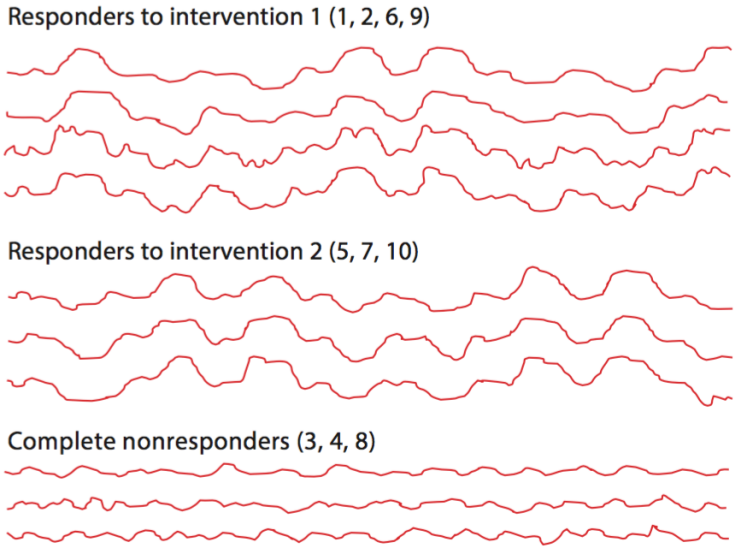
Annual Review of Nutrition

Different Designs (e.g., Sequential)

#	Design period	B	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1	2 Blocks	B	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	2
2	4 Blocks	B	1	1	1	1	2	2	2	2	1	1	1	1	2	2	2	2
3	Alternate	B	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2
4	Washout	B	1	W	2	W	1	W	2	W	1	W	2	W	1	W	2	X
5	Random	B	1	2	1	W	2	W	2	1	2	W	1	1	2	1	W	2
6	Random in periods	B	1	2	W	2	1	W	1	2	W	1	2	W	2	1	X	
7	Single arm	B	1	1	W	1	1	W	1	1	W	1	W	1	W	1	W	1
8	Sequential	B	1	2	1	2	1	2	1	2	X							
9	Adaptive	B	1	2	W	2	1	W	1	1	1	W	2	1	1	W	1	1
10	Threshold crossover	B	2	2	2	1	1	1	1	1	W	1	1	1	1	X		

Response Profile Similarity Analysis: Use N-of-1 Studies to 'Bring Out a Phenotype*'





*Consider Monitoring Post Nutritional Challenge (e.g., OGTT) to Bring Out a Phenotype

Single Subject Microbiome Studies: Impact of Diet

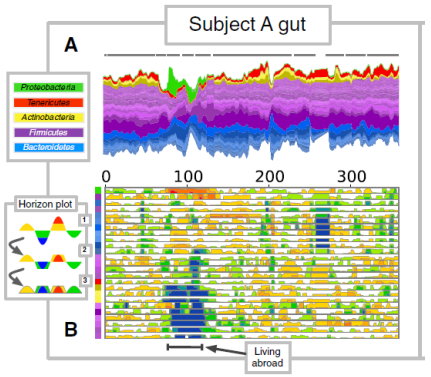
Genome Biology 2014, **15**:R89

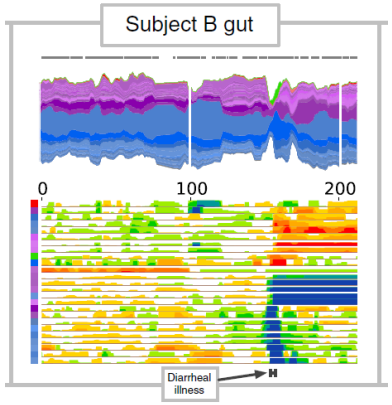
Host lifestyle affects human microbiota on daily timescales

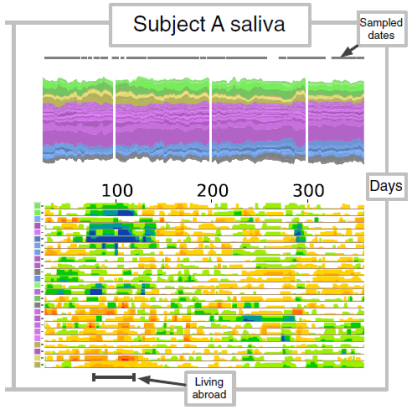
Lawrence A David[1,2,11], Arne C Materna[3], Jonathan Friedman[4], Maria I Campos-Baptista[5], Matthew C Blackburn[6], Allison Perrotta[7], Susan E Erdman[8] and Eric J Alm[4,7,9,10*]

Table 1 Significant correlations between Subject A's metadata and microbiota

Body site	Lag (days)	Host factor	Representative OTUs (n)	ρ	*P* value	Abun. (%)	Cluster ID	Total OTUs
Subject A Gut	0	Stool: Hardness	*Eggerthella/Clostridium* (11)	-0.30	1.0E-06	0.2144	10	23
	0	Stool: Time Of Day	*Eggerthella/Clostridium* (11)	0.27	7.4E-06	0.2144	10	23
	1	Nutrition: Fiber	*Clostridium* (6)	-0.38	7.4E-06	0.0442	6	9
	1	Nutrition: Fiber	Ruminococcaceae/*F. prausnitzii* (4)	-0.44	1.1E-07	0.3745	8	8
	1	Nutrition: Fiber	*Eggerthella/Clostridium* (11)	-0.39	3.3E-06	0.2144	10	23
	1	Nutrition: Fiber	*Ruminococcus/R. gnavus/Clostridium* (4)	-0.51	2.9E-10	0.5479	51	12
	1	Nutrition: Fiber	*Ruminococcus/R. gnavus/Clostridium* (5)	-0.51	3.8E-10	0.3495	52	7
	1	Nutrition: Fiber	*Blautia* (3)	-0.38	7.6E-06	0.0346	53	3
	1	Nutrition: Fiber	Bifidobacteriales (13)	0.36	1.6E-05	6.0786	86	13
	1	Nutrition: Fiber	*Coprococcus* (8)	0.44	7.2E-08	4.2192	89	12
	1	Nutrition: Fiber	*Clostridium* (1)	-0.42	4.6E-07	0.0716	111	1
	1	Nutrition: Fiber	*Ruminococcus/R. gnavus/Clostridium* (6)	-0.44	1.2E-07	2.0690	118	14
	1	Nutrition: Fiber	*Roseburia/E. rectale* (30)	0.37	8.4E-06	5.0446	127	40
	1	Food: OrangeJuice	*Clostridium* (1)	0.28	4.7E-06	0.0457	106	2
	1	Food: BreakfastBar	*Ruminococcus/R. gnavus/Clostridium* (4)	-0.27	6.6E-06	0.5479	51	12
	1	Food: BreakfastBar	*Ruminococcus/R. gnavus/Clostridium* (5)	-0.40	2.9E-11	0.3495	52	7
	1	Food: BreakfastBar	Bifidobacteriales (13)	0.27	9.5E-06	6.0786	86	13
	1	Food: BreakfastBar	*Clostridium* (1)	-0.43	5.3E-13	0.0716	111	1
	1	Food: Yogurt	Bifidobacteriales (2)	0.45	2.7E-14	0.0069	85	2
	1	Food: Fruits: Fresh	Clostridiales (4)	-0.27	1.1E-05	0.1866	120	9
	1	Food: Fruits: Citrus	Ruminococcaceae/*F. prausnitzii* (4)	0.36	1.7E-09	1.7152	107	4
	1	Food: Soup	Clostridiales (1)	-0.25	3.3E-05	0.0014	62	2
	1	Food: Soup	*Blautia* (21)	-0.26	2.4E-05	3.8126	68	31
	1	Food: Soup: Other	Clostridiales (1)	-0.27	1.3E-05	0.0014	62	2
	1	Food: Soup: Other	*Blautia* (21)	-0.28	4.2E-06	3.8126	68	31
Subject A Saliva	-7	Exercise: TookPlace	*S. mutans/S. sanguinis* (2)	-0.28	1.6E-05	0.0142	21	2
	1	OralCare: Flossing	*S. mutans/S. sanguinis* (2)	-0.30	2.5E-06	0.0142	21	2
	1	Fitness: BodyFat	*Prevotella* (4)	-0.36	1.4E-06	1.5761	35	14



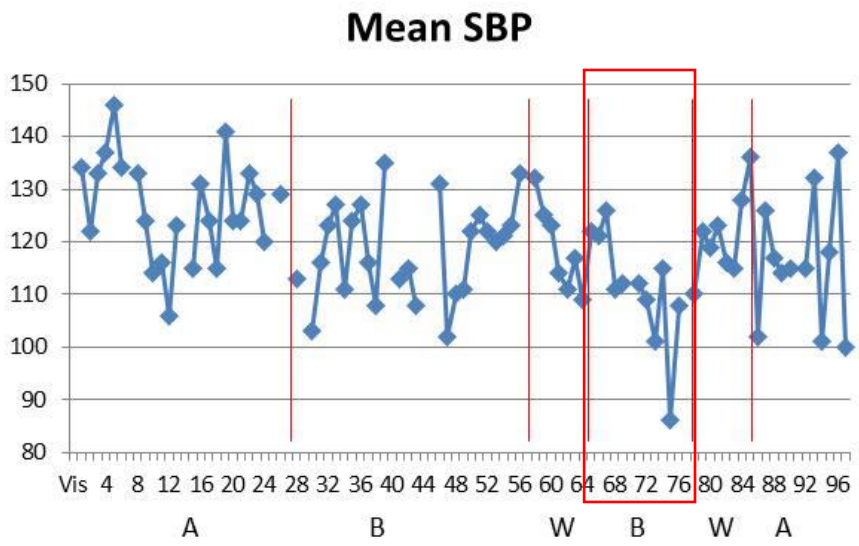


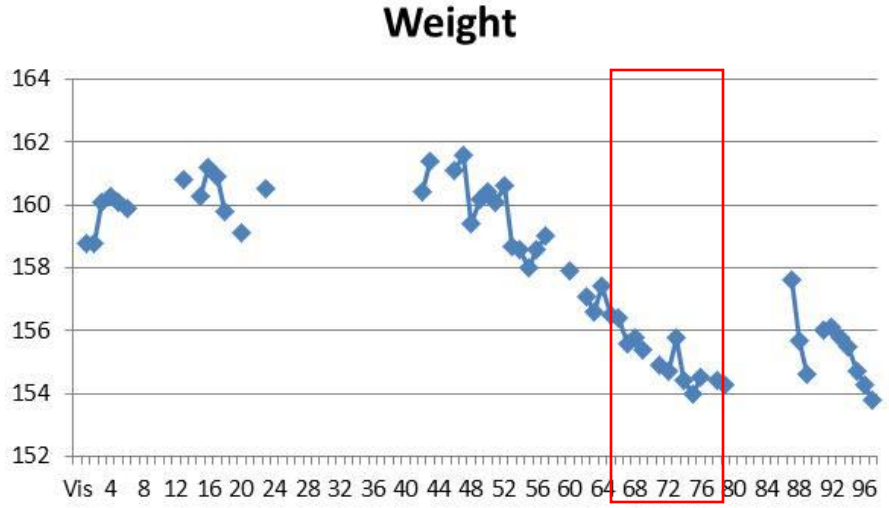


Example N-of-1 Trial: The '1HAT' Antihypertensive Trial

(https://clinicaltrials.gov/ct2/show/NCT012587)

- N-of-1, double blind, crossover trial with washout periods
- Lisinopril (10 mg oral/d; ACE inhibitor) vs. Hydrochlorothiazide (25 mg oral/d; Diuretic)
- Pharmacy provided pills with same presentation/packaging
- BP measurements daily (at least 4 times) with covariates collected (e.g., weight)
- One of the patient's experience detailed below:





- Could not attribute BP drop to the drug; patient became much more health conscious

Example N-of-1 Trial: Genetically-Mediated Sleep Disorder

Patient Background

- 60 year-old female, treated for anxiety, depression and genetic sleep phase disorder (Seasonal Affective Disorder)
- *Polypharmacy* an issue: antidepressants impact sleep; sleep aids impact mood…
- Different drugs tested in combination:
  - ✓ Cymbalta (CYM): treat depression, anxiety
  - ✓ Temazepam (TEM): treat insomnia, anxiety
  - ✓ Melatonin (MEL): treat sleep-phase disorder
- Measurements and outcomes:
  - ✓ Zeo: sleep time, sleep phases
  - ✓ PAM-RL: restless legs
  - ✓ Fitbit: activity, sleep
  - ✓ Equivital belt: vital signs (e.g., HR)
  - ✓ Sleep image device: sleep apnea
- No blinding; washouts = no medications

Vicki Magnuson, Ph.D.
Study Coordinator

Results

- Cymbalta exacerbated sleep disturbances
- Drug removal unmasked sleep apnea condition (data not shown)
- Personalized trials for complicated, multi-faceted conditions are necessary

The Dangers of 'Polypharmacy,' the Ever-Mounting Pile of Pills

Paula Span
THE NEW OLD AGE APRIL 22, 2016

The New York Times

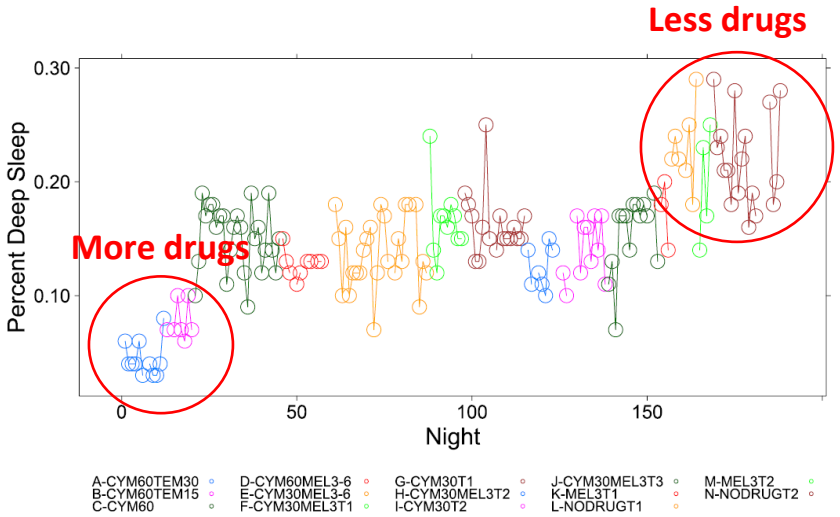


Table 5. Predicted sleep architecture responses at intermediate Cymbalta doses.

Cymbalta dose	Time to REM hours	Percent wake	Percent light	Percent deep	Percent REM
0 mg	1.27	10.5	35.4	22.3	34.2
10 mg	2.09	13.9	36.9	20.0	31.1
20 mg	2.91	17.4	38.5	17.7	27.9
30 mg	3.73	20.8	40.0	15.4	24.8

Magnuson et al. F1000 (in review)

Population vs. Personal Thresholds

J Clin Oncol 31:387-392.

Longitudinal Screening Algorithm That Incorporates Change Over Time in CA125 Levels Identifies Ovarian Cancer Earlier Than a Single-Threshold Rule

Charles W. Drescher, Chirag Shah, Jason Thorpe, Kathy O'Briant, Garnet L. Anderson, Christine D. Berg, Nicole Urban, and Martin W. McIntosh

Biomarker (e.g., Cholesterol or DNA Damage Level, etc.)

1	2	3	4	5	6	7	8	9	10
1	4	3	1	2	3	4	5	3	3
2	2	5	3	1	1	1	1	4	5
3	3	2	4	4	2	2	3	2	2
4	1	1	2	3	5	3	2	1	1
5	5	4	5	5	4	8	7	7	6
6	8	8	6	7	10	5	4	8	8
7	7	7	11	6	11	11	11	5	4
8	6	10	7	11	8	10	6	10	9
9	9	6	8	8	6	6	8	6	7
10	11	14	14	9	14	14	12	11	11
11	14	11	10	10	7	7	10	9	**20**
12	12	9	9	12	9	9	9	**20**	10
13	13	13	16	16	16	12	16	13	13
14	10	16	12	13	15	15	13	12	15
15	15	15	15	15	15	17	**20**	15	12
16	16	12	13	14	12	16	14	22	22
17	17	17	18	18	13	13	15	14	18
18	18	18	17	21	18	25	21	18	14
19	**20**	25	25	19	**20**	**20**	19	25	25
20	25	16	21	**20**	22	22	18	16	16
21	21	**20**	**20**	17	17	24	17	17	17
22	19	21	22	22	21	21	22	21	21
23	25	19	24	25	24	18	24	23	25
24	24	24	19	23	19	19	23	25	24
25	23	23	23	24	23	23	25	24	23

Population Threshold

Early Disease

Signal!

Personal Threshold

Personal Average

Time

But do the historical values for an individual reflect "health?"

Ex Vivo Assessment of Nutrient-Mediated DNA Damage

Am J Clin Nutr 2010;91(suppl):1438S–54S.

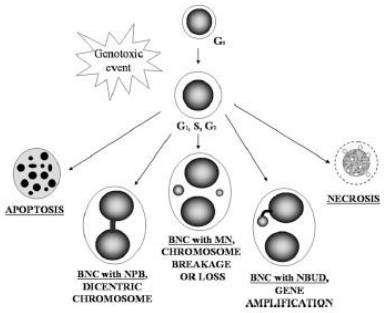
Dietary reference values of individual micronutrients and nutriomes for genome damage prevention: current status and a road map to the future[1–4]

Michael F Fenech

TABLE 1
Strengths and weaknesses of best-validated DNA damage assays for nutritional studies in humans[1]

	DNA damage assays							
	CBMN-Cyt	Red blood cell micronucleus	Buccal micronucleus cytome	Comet	DNA oxidation	DNA methylation	Telomere length	mtDNA deletion
DNA damage events measured								
DNA breaks	Yes	Yes	Yes	Yes	No	No	No	Yes
Misrepair of DNA breaks	Yes	Yes	Yes	No	No	No	No	No
Oxidized DNA bases	No	No	No	Yes[2]	Yes	No	No	No
Chromosome malsegregation	Yes[3]	Yes[3]	Yes[3]	No	No	No	No	No
Chromosomal deletions	Yes[3]	Yes[3]	Yes[3]	No	No	No	No	No
Dicentric chromosome or telomere end fusion	Yes[4]	No	No	No	No	No	No	No
Telomere length	No	No	No	No	No	No	Yes	No
Hypo/hypermethylation of DNA	No	No	No	No	No	Yes	No	No
Abasic sites in DNA	No	No	No	Yes[5]	No	No	No	No
mtDNA damage	No	No	No	No	No	No	No	Yes
Other features								
Distinguishes DNA damage in viable cells from cell death[6]	Yes	Yes	Yes	No	No	No	No	No
Suitable for in vitro studies	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Cell type in which assay is performed	PBLs	RBCs	Oral mucosa	Any cell type	Any cell type	Any cell type	Any cell type	Any cell type

[1] CBMN-Cyt, cytokinesis-block micronucleus cytome; mtDNA, mitochondrial DNA; PBLs, peripheral blood lymphocytes; RBCs, red blood cells.
[2] If used in combination with glycosylase enzymes that remove oxidized bases.
[3] By measuring micronuclei with/without centromere staining.
[4] By measuring nucleoplasmic bridges with/without telomere staining.
[5] If alkaline version of the assay is used.
[6] The inability to distinguish between DNA damage from dead or from viable cells may confound DNA damage results.



Mutagenesis vol. 23 no. 3 pp. 191–205, 2008
Advance Access Publication 7 March 2008

REVIEW

The comet assay in human biomonitoring: gene–environment interactions

Maria Dusinska[1,2,*] and Andrew R. Collins[3]

Uses of the comet assay at different stages of biomonitoring

External exposure	**Internal exposure**	**Individual susceptibility**	**Intermediate effects**	**Endpoint**
Monitoring of environment	*Bioavailability* *Metabolism* *Excretion* *Antioxidant status*	*Genotypic/phenotypic variation:* *Phase I/II metabolism* *DNA repair* *Immune function* *Antioxidant enzymes*	*Mutations* *Chromosome aberrations* *Apoptosis*	*Disease* *Death*

Increasing relevance to risk estimation

Comet assay measures:

Environmental contamination (ecogenotoxicology)	DNA breaks Base damage	DNA repair capacity (phenotypic variation): Strand break rejoining Base excision repair Nucleotide excision repair	Oxidative DNA damage is marker of oxidative stress and may therefore be a predictive marker of diseases associated with oxidative stress	Elevated DNA damage is associated with various disease states (as cause or effect)

Resistance to oxidation by H_2O_2

Consider *in vitro/ex vivo* cellular challenge-induced phenotypes as indicators of *in vivo* changes

The Schork Group

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JCVI Funded Faculty and Scientists: Kuan Ding, Agnes Chan, Yongwook Choi
TGen Funded Research Faculty: Gil Speyer and Rebecca Halperin

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