CLINICAL INNOVATION: Fair & Effective Incentives for New Uses of Established Drugs

The impact of technology and large databases on the development of new medicines from existing drugs

Moderator: Dr Felix Frueh *OpusThree*

Panellists:

- **Dr Iris Grossman** *VP, Head of Early Stage Development, CMO organization, R&D, Teva Pharmaceuticals*
- **Dr Tony Altar** *Chief Scientific Officer and Senior Vice-president, Verge Genomics, Inc*

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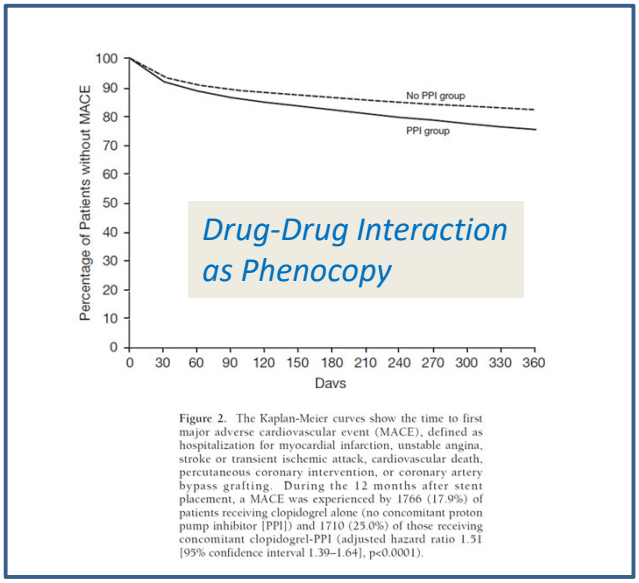
The Impact of Technology and Large Databases on the Development of New Medicines from Existing Drugs

CLINICAL INNOVATION
Fair and Effective Incentives for New Uses of Established Drugs

February 9, 2018 – Washington, DC

Felix Frueh, PhD
Opus Three LLC on behalf of TEVA

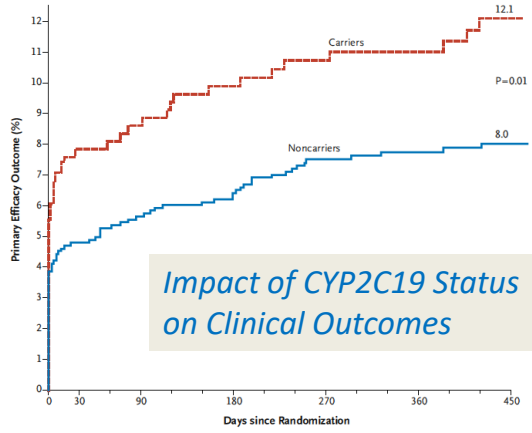
Use of **Large Databases** to Optimize Existing Drugs



Drug-Drug Interaction as Phenocopy

Figure 2. The Kaplan-Meier curves show the time to first major adverse cardiovascular event (MACE), defined as hospitalization for myocardial infarction, unstable angina, stroke or transient ischemic attack, cardiovascular death, percutaneous coronary intervention, or coronary artery bypass grafting. During the 12 months after stent placement, a MACE was experienced by 1766 (17.9%) of patients receiving clopidogrel alone (no concomitant proton pump inhibitor [PPI]) and 1710 (25.0%) of those receiving concomitant clopidogrel-PPI (adjusted hazard ratio 1.51 [95% confidence interval 1.39–1.64], p<0.0001).

Source: Kreutz et al. *Pharmacotherapy* 2010;30(8):787–796



Impact of CYP2C19 Status on Clinical Outcomes

Source: NEJM (2009);360:354-62

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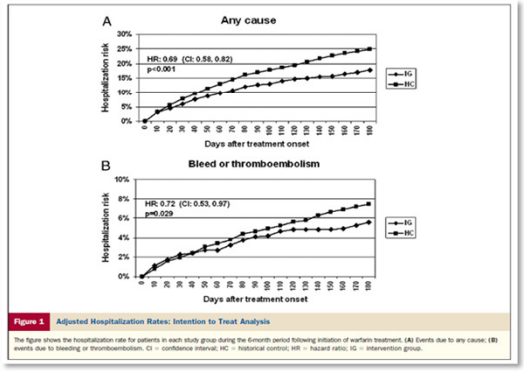
Use of **Real-World Evidence** to Optimize Existing Drugs

Table 1. Range of expected therapeutic warfarin doses based on select *CYP2C9* and *VKORC1* genotypes[a]

VKORC1 rs9923231 variants	*CYP2C9* genotype					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5–7 mg	5–7 mg	3–4 mg	3–4 mg	3–4 mg	0.5–2 mg
AG	5–7 mg	3–4 mg	3–4 mg	3–4 mg	0.5–2 mg	0.5–2 mg
AA	3–4 mg	3–4 mg	0.5–2 mg	0.5–2 mg	0.5–2 mg	0.5–2 mg

[a]Reproduced from http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/009218s108lbl.pdf



J. Am. Coll. Cardiol. 2010;55;2804-2812

Opinion

Cell Press

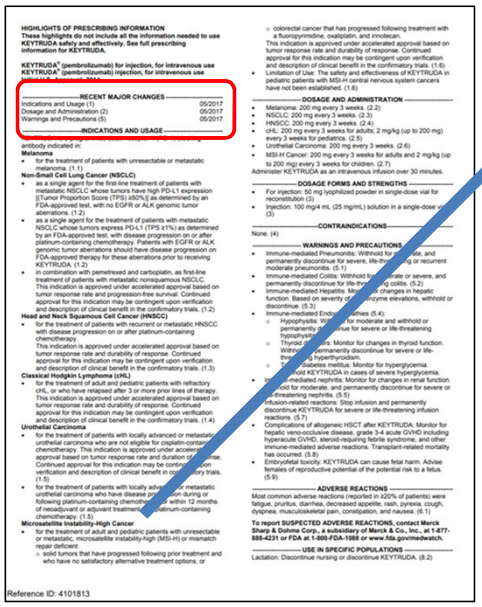
On rat poison and human medicines: personalizing warfarin therapy

Felix W. Frueh

Medco Research Institute, LLC, 7315 Wisconsin Avenue, Bethesda, MD 20814, United States

Teaching old dogs new tricks is difficult, but lessons learned from such efforts can be invaluable. Warfarin is an old drug, difficult to administer and a leading cause of drug-related mortality and hospitalizations. **New genetic tests for optimizing warfarin therapy have not been adopted.** The debate over precise clinical utility and cost effectiveness of these tests misses more important points of building a better, cheaper, and more efficient infrastructure to measure the true real-world impact of personalized medicine. However, this same debate about how, when, and where such testing is appropriate has been invaluable to the field of personalized medicine: progress beyond science, in policy, regulations, and logistics can be highlighted along the path to safer and more efficacious warfarin therapy.

Use of **New Technology** to Optimize Existing Drugs
From Organ-specific to Biomarker-defined Disease


HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KEYTRUDA safely and effectively. See full prescribing information for KEYTRUDA.

KEYTRUDA® (pembrolizumab) for injection, for intravenous use
KEYTRUDA® (pembrolizumab) injection, for intravenous use

RECENT MAJOR CHANGES

Indications and Usage (1)	05/2017
Dosage and Administration (2)	05/2017
Warnings and Precautions (5)	05/2017

INDICATIONS AND USAGE

Reference ID: 4101813

Keytruda (pembrolizumab) Label

Microsatellite Instability-High Cancer

- for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient
  - **solid tumors that have progressed following prior treatment** and who have no satisfactory alternative treatment options, or
  - colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

WINTHER Trial: Therapies Chosen by AI

106 (100%) eligible patients

83 (78%) qualified for targeted therapy,

23 (22%) had no therapeutic options.

69 (65%) got a targeted therapy,

37 (35%) received therapy based on OncoKEM® recommendation

Source: ASCO 2017 Annual Meeting
http://abstracts.asco.org/199/AbstView_199_185752.html

More Choices for More Patients

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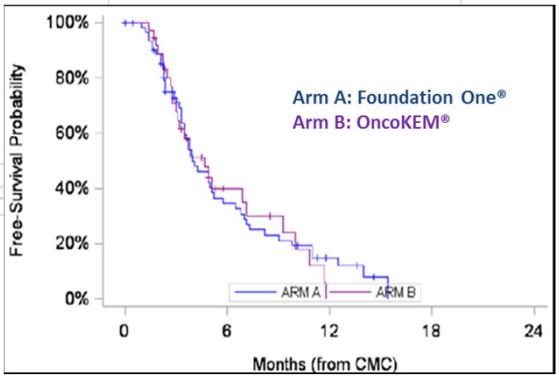

Source: ASCO 2017 Annual Meeting
http://abstracts.asco.org/199/AbstView_199_185752.html

Outlook

- Diseases will be increasingly defined at the molecular level
- Disease mechanisms/ pathophysiology will be better understood
- Decision networks including pathophysiology, mechanism of drug action, patient characteristics and other clinical/non-clinical factor will be created
- Potential of non-indicated (i.e. off-label) uses of drugs will be identified using those networks
- Artificial intelligence-based clinical decision support will surpass human ability to identify and make the best decisions
- One drug – one (initially identified) indication will become a thing of the past

→ What will the consequences be for IP protection (of drugs)?
→ Which elements within these networks can be protected?

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Speakers

- Dr. Iris Grossman
  - VP, Global Head of Early Stage Clinical Development, TEVA
- Dr. Tony Altar
  - Chief Scientific Officer, Verge Genomics

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A multi-pronged approach for drug repurposing

Iris Grossman, PhD

VP, Head, Early Stage Clinical Development, Global R&D, Teva

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Drug Repurposing: Different approaches; Different Data Sources/Types; Different paths to benefit patients

- **Life Cycle Management – R&D integral component**
- **NTEs:** New Therapeutic Entities
- **Literature-based label expansion to unmet medical needs**
- **Molecular-based repurposing approach**
- **Real World Data (RWD)-based repurposing approach**
- **BioMarker (BM)-supported repurposing paths**
- **Nutrepurposing?**
- **FDA 2017+:** harnessing small and big data, sometimes even as alternative to clinical trials

The IDEA Index 2016 – celebrating innovation

The most exciting innovators in the biopharma industry

Alexion
BioMarin
Celgene
Gilead
Incyte
Johnson & Johnson
Novo Nordisk
Otsuka
Regeneron
Teva

"For a truly patient-centred approach in novel therapeutic entities (NTEs), challenging the gap between unmet need and solution, putting known molecules into novel approaches"

Literature-based label expansion to unmet medical needs

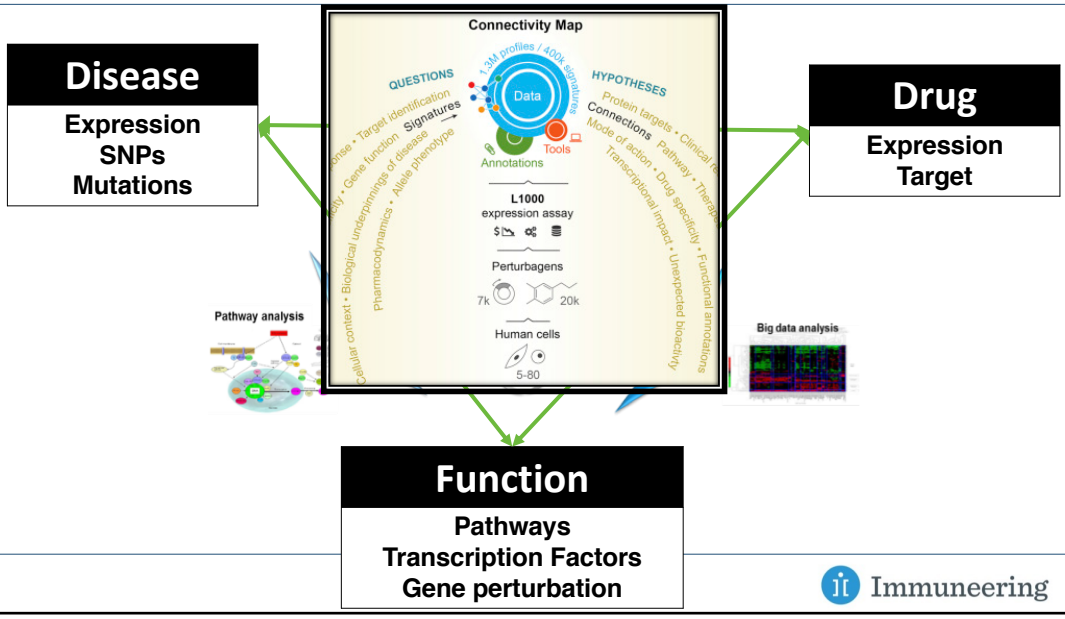
Teva Secures European Approval of Trisenox® for First Line Treatment of Low to Intermediate Risk Acute Promyelocytic Leukemia (APL) Nov. 21, 2016

Decision solely based on published academic data endorsing the benefit of Trisenox® as first chemotherapy-free treatment for APL and marks important advancement for patients in Europe

Teva Announces U.S. FDA Approval of TRISENOX® (arsenic trioxide) Injection for First Line Treatment of Acute Promyelocytic Leukemia

JERUSALEM--(BUSINESS WIRE)--Jan. 15, 2018-- Teva Pharmaceutical Industries Ltd. (NYSE and TASE: TEVA) announced that the U.S. Food and Drug Administration (FDA) has approved the use of TRISENOX® (arsenic trioxide) injection in combination with tretinoin for the treatment of adults with newly-diagnosed low-risk acute promyelocytic leukemia (APL) whose APL is characterized by the presence of the t(15;17) translocation or PML/RAR-alpha gene expression. The approval was based on a Priority Review by the FDA on

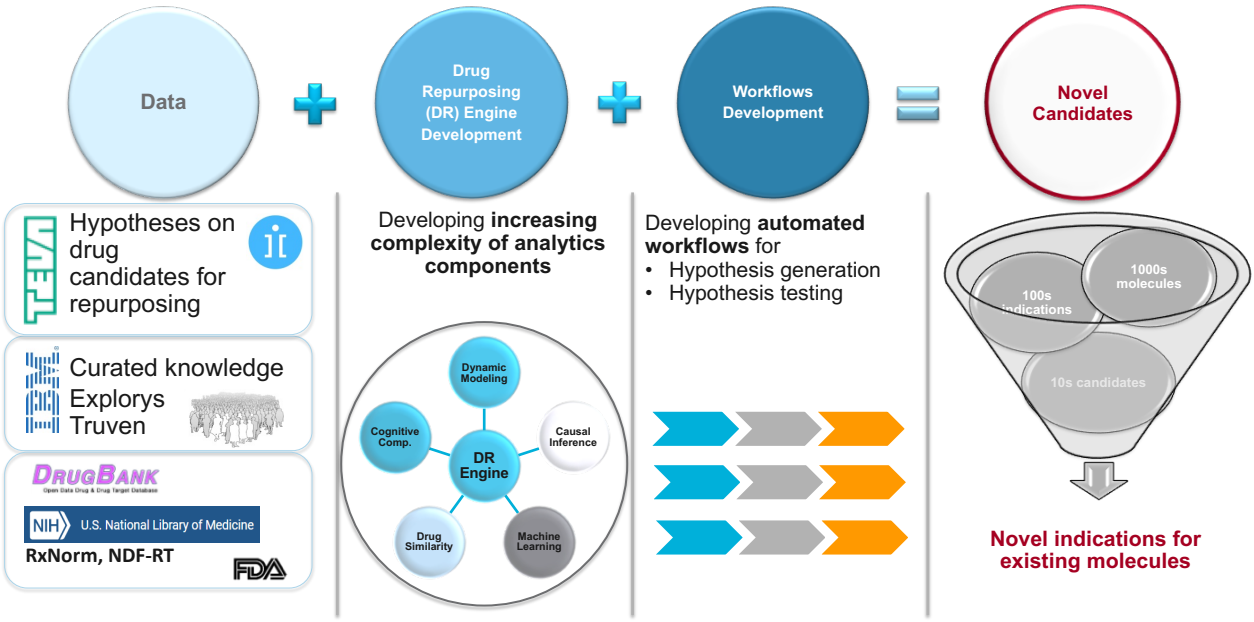
Molecular-based repurposing approach



Immuneering

IBM Research

RWD-based repurposing approach



IBM Research

RWE Data

explorys
An IBM Company

TRUVEN
HEALTH ANALYTICS
IBM Watson Health

Explorys SuperMart

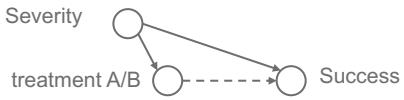
- Clinical, claims, accounting, device, community, and patient derived data
- Over **50M** patients (~15% of USA)
- 26 leading healthcare networks with **>317,000 providers**
- Includes: demographics, diagnoses, procedures, admissions, prescribed drugs, vitals and laboratory values.

Truven MarketScan®

- Healthcare claims information
- Over **100M** patients
- Three sub-databases: **Commercial, Medicare, Medicaid**
- Includes: demographics, diagnoses, procedures, admissions, prescription drug claims, enrollment data

IBM Research

Main Biases in RWE



- **Confounding bias:** The treatment and the outcome share a cause
  - *E.g. Clinical decisions depend on the severity of patient's conditions*
- **Selection biases:** The procedure for selecting individuals selected into the analysis biases results
  - *E.g. Differential loss to follow-up: patients with high severity tend to drop from a study earlier than others*
- **Measurement biases:** when the association between treatment and outcome is weakened or strengthened as a result of the process by which the study data are measured
  - *E.g. Adherence to treatment*

[Hernan and Robins 2016]

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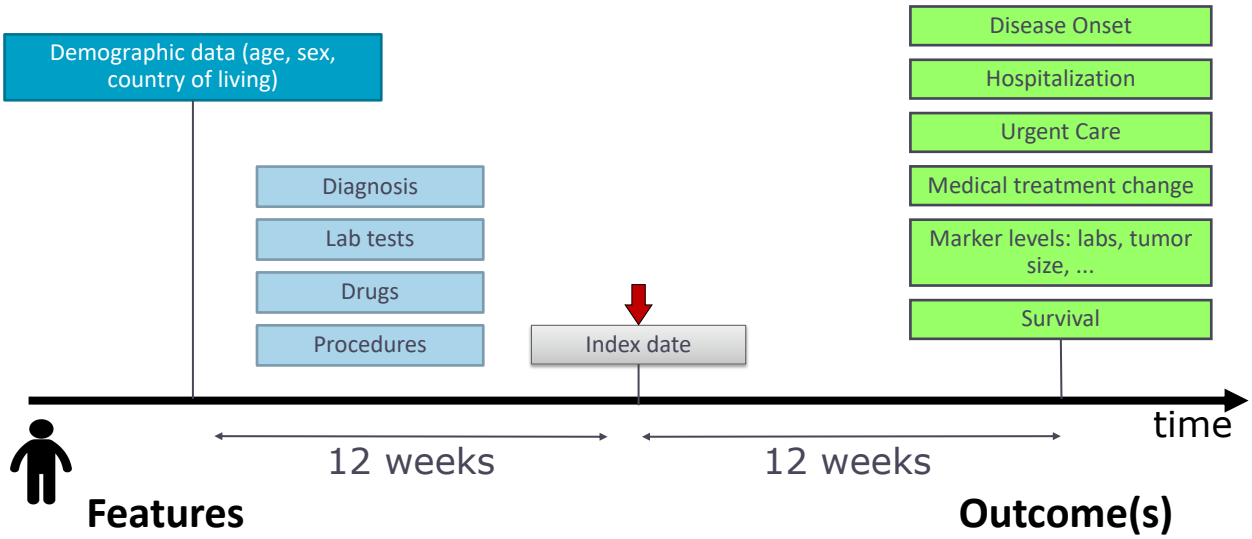
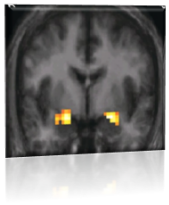
From raw data to Features to Outcome Prediction

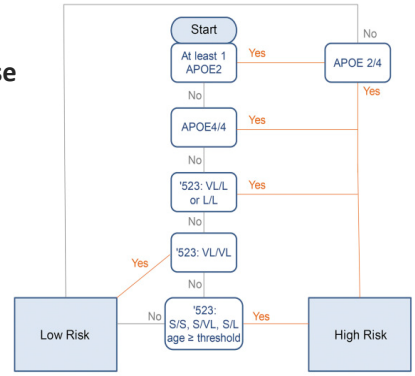


BM-supported repurposing: a clinically tested example

- Deep understanding of the **cognitive impairment continuum**
- **Mechanistic understanding** of PPAR-gamma agonist class
- 2-week healthy volunteer BOLD imaging study to demonstrate **dose utility at a fraction of T2D lowest approved dose**



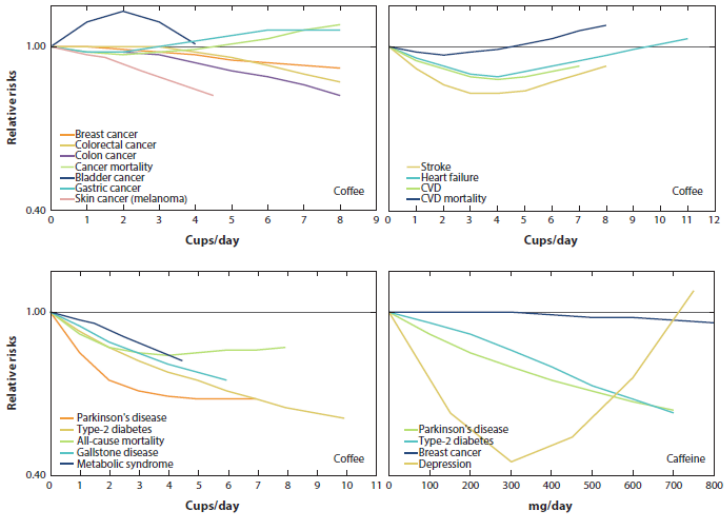
- **Biomarker-targeted study**, enriching for fast progressers
- FDA agreement to conduct a **single registration clinical trial** for delay of onset of MCI
- Jan 2018: **futility analysis** declared treatment arms stopped



Lutz et al. 2016. Alz Dement Trans Res Clin Interv

21

Nutrepurposing - Repurposing Coffee?



[Grosso et al 2017]

22

Figure 4
Findings from dose-response meta-analyses of observational studies on coffee or caffeine using relative risk as the metric.

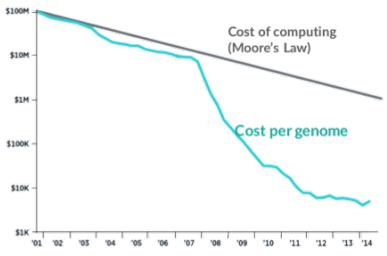
FDA is integrating Small and Big Data into indication expansion and repurposing (2017+)

- **Cures Act**
- Associated multiple FDA guidances:
  - Targeted therapeutics for low-frequency subsets of disease via ***in-vitro* determination of efficacy** for indication expansion (e.g. Vertex's Kalydeco)
  - Use of **Real-World Evidence** to Support Regulatory Decision-Making for Medical Devices
  - **Repurposing** via RWE is being investigated (workshops ongoing)
- **Software** as Medical Device

THE TIME IS RIGHT

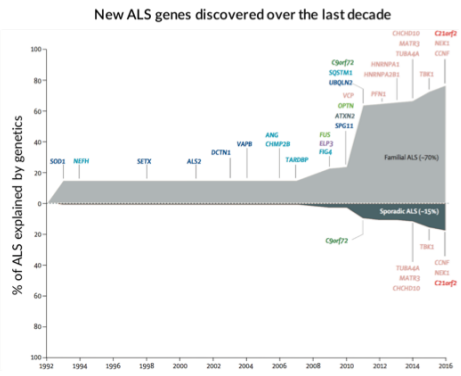
Advances in sequencing are breaking open new CNS biology

The cost of sequencing is plummeting faster than the cost of computing



Human genetics is revealing new pathways at an unprecedented pace

New ALS genes discovered over the last decade



THE TIME IS RIGHT

A patient-centric, systems approach to drug discovery

Poor targets
Targets with poor links to human disease biology

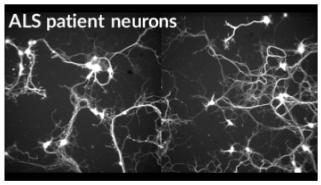
Poor models
Preclinical models that are not predictive of human disease

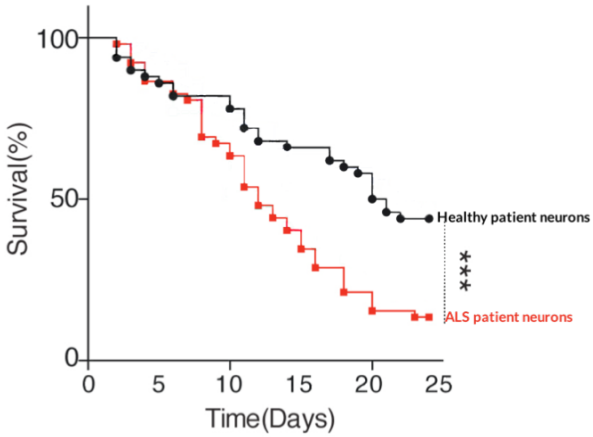
Poor trials
Heterogeneous patient populations

Research	Preclinical	Clinical
Human genetic targets		
We begin from day one using patient data to map out patient disease signatures.		
validated in		
	Patient-relevant models	
	We use patient disease signatures to select pre-clinical models most predictive of human disease biology	
	translated to	
		Targeted trials
		Patient disease signatures enable identification of new biomarkers and patient enrichment strategies

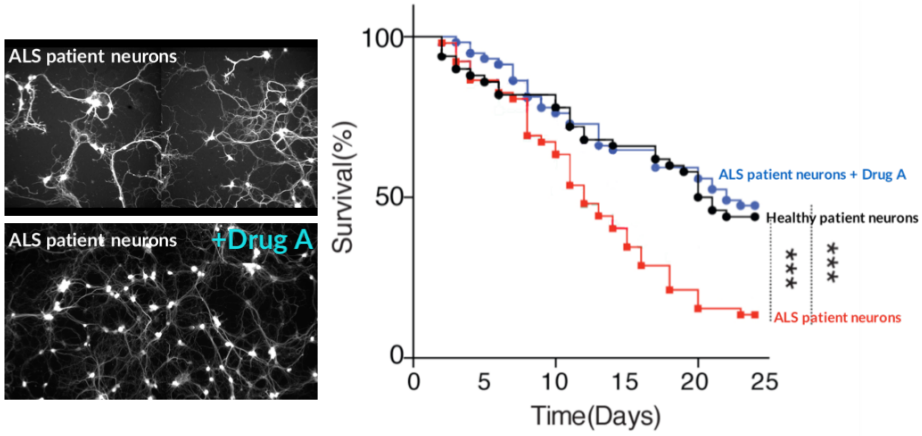
VRG-101

A small molecule inhibitor of a novel Verge target





VRG-101 A small molecule inhibitor of a novel Verge target *fully rescues degeneration* of ALS patient neurons



Persistence in Drug Discovery Enhances Repurposing for new Therapies

Dapoxetine HCl (Prilogy). Short acting SSRI candidate for depression. Lilly → PPD Pharmaco → Approval by EMA for premature ejaculation (writstwatch test). Thus, it elevates mood after all.

Aripiprazole (Abilify). Partial dopamine receptor agonist intended for schizophrenia. Our discovery of serotonin 1A receptor partial agonism expanded description of Abilify as a dopamine-serotonin stabilizer (Arvid Carlsson), adding bipolar illness and depression indications. Otsuka → Otsuka + Bristol-Myers Squibb → NDA approval 2002.

Muscarinic receptor agonists. Gene expression profiling of schizophrenics' brain post-mortem and human neurons in an *in vitro* screen found a novel M1 receptor target (Altar et al 2005, 2008), also a top gene whose mutation increases risk for schizophrenia (Ripke et al 2016). Three companies now developing M1 agonist drugs.

STA-5326 (Apilimod). Structure patented in 2011, tested for Crohn's disease and now cancer. Its target, a kinase, found independently by Verge Genomics' analysis of mRNA changes in ALS spinal cord (Nature Medicine), when blocked protects motor neurons. Use patent filed for ALS in 2016.

Advances in sequencing are breaking open new CNS biology

Human genetics is revealing new pathways at an unprecedented pace

New ALS genes discovered over the last decade