



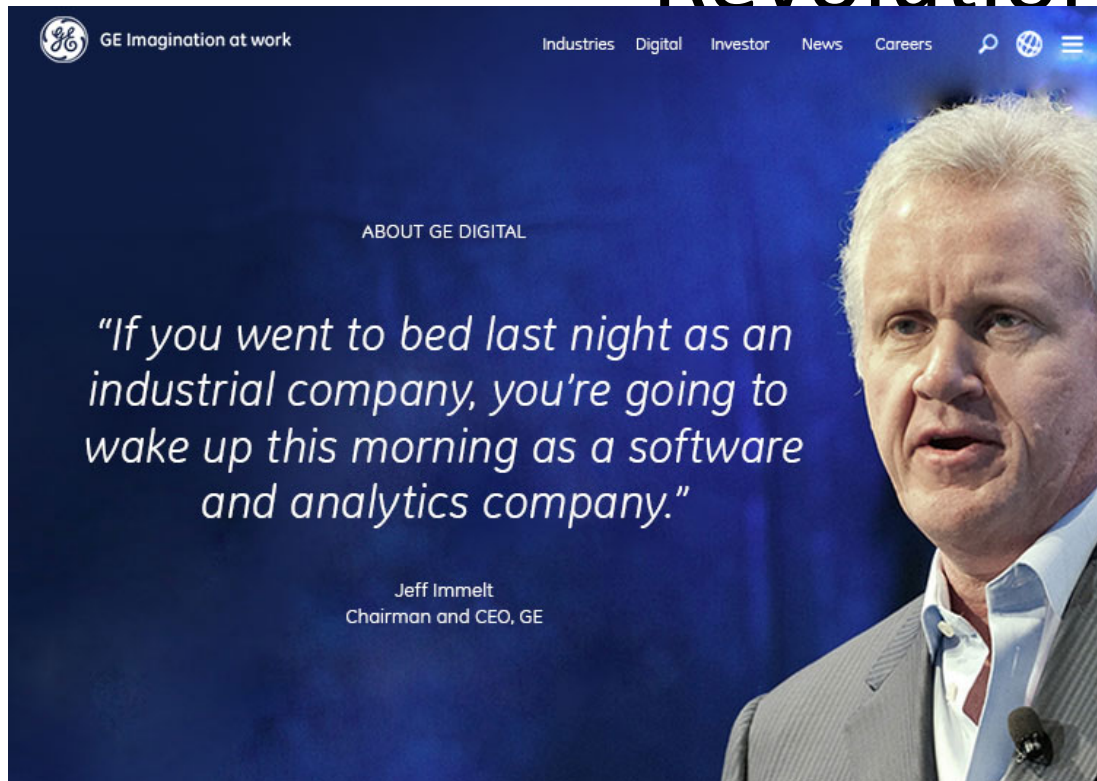
Shaping the Future of
Drug Development

The New Drug Development Paradigm February 2019

Agenda

- A new digital world
- Why now for Pharma
- Healthcare is changing
- Clinical Development is Changing
- Regulatory Viewpoints
- A thought on a New Drug Development Paradigm
- Advanced Analytics

Healthcare is in the Midst of a Digital Revolution



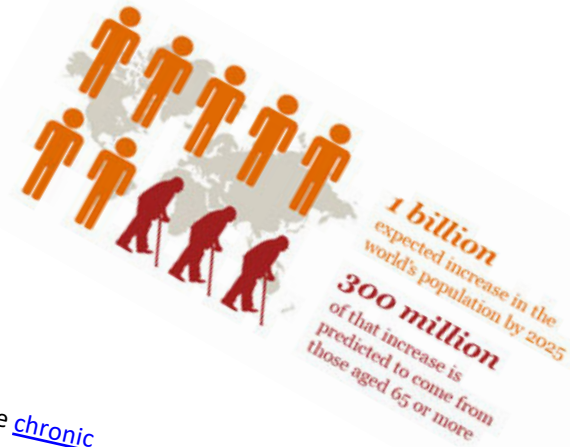
How has digital changed your daily life?

Industries disrupted by Digital:

- Camera (Kodak)
- Movie/Videos (Blockbuster)
- Communications (US Mail)
- Music (Virgin Records)
- Books
- Retail
- Banking
- Investment
- Advertising
- Libraries
- Taxi
- Automotive
- Television
- Hotel

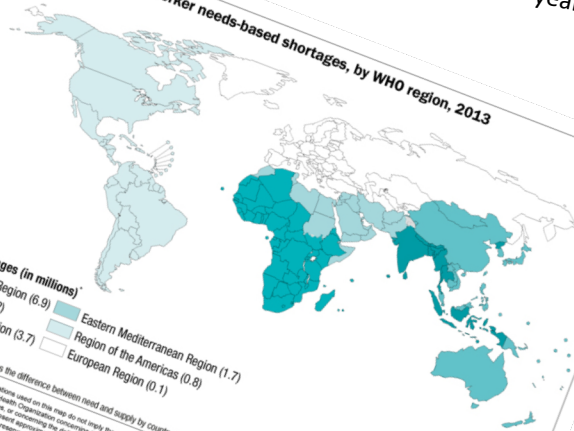
Why Now Population Dynamics

According to the [United Nations](#), the world's population is expected to increase by one billion people by 2025. Of that billion, 300 million will be people aged 65 or older, as life expectancy around the globe continues to rise. Additional healthcare resources and service innovation is needed globally to deliver the long-term care and chronic disease management services required by a rapidly increasing senior population



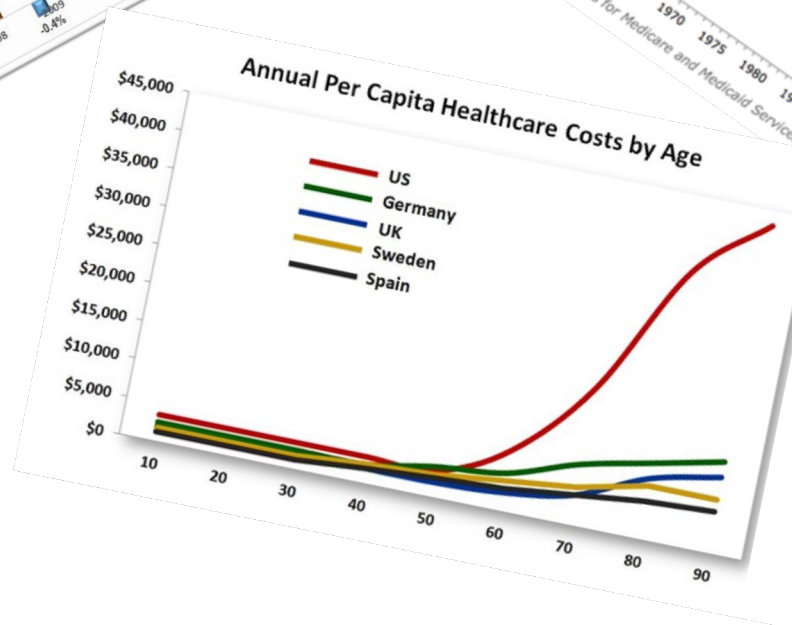
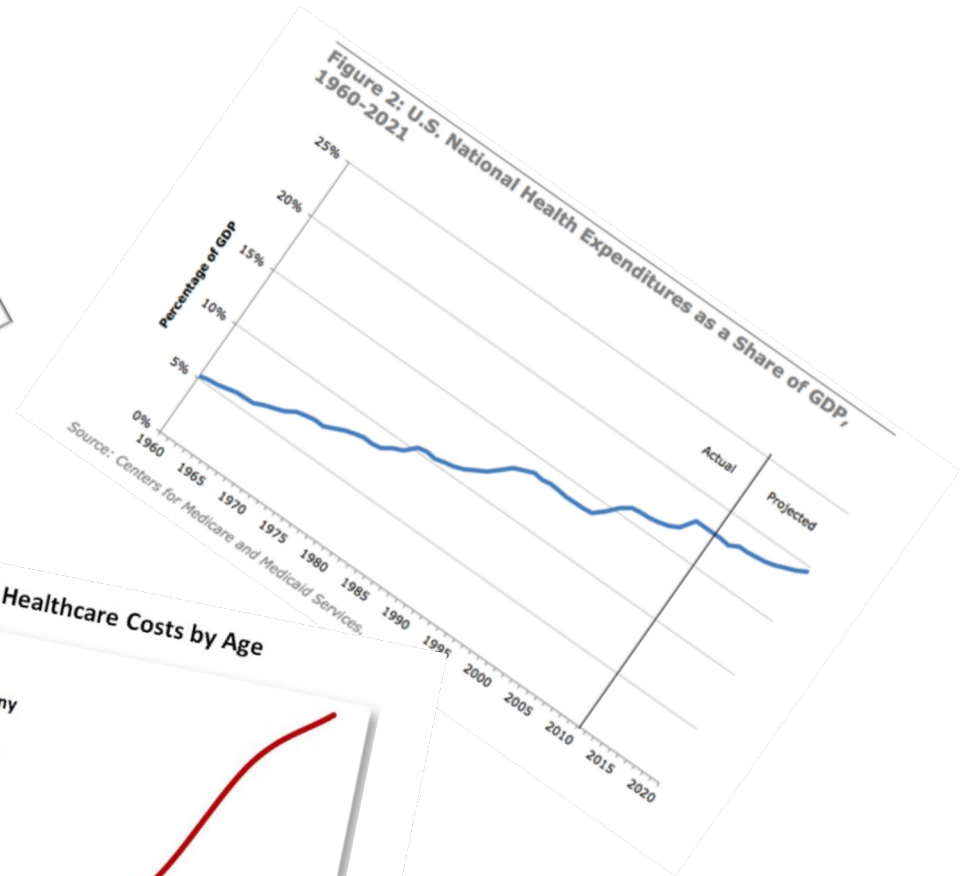
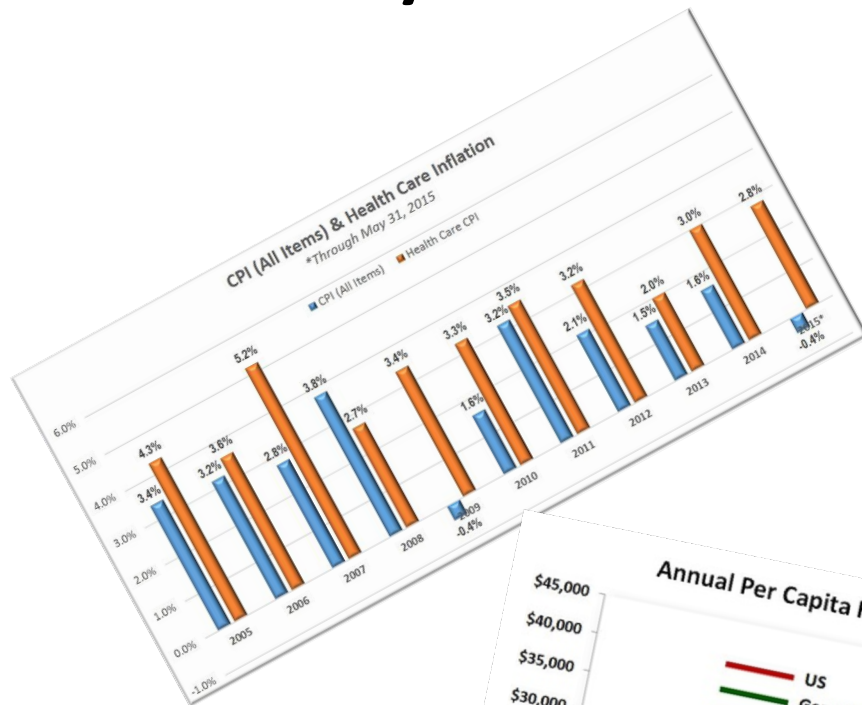
- Approximately 80% of older adults have at least one [chronic disease](#), and 77% have at least two. Four chronic diseases—heart disease, cancer, stroke, and diabetes—cause almost two-thirds of all deaths each year.

Estimates of health worker needs-based shortages, by WHO region, 2013



U.S. faces 90,000 doctor shortage by 2025,
medical school association warns

Why Now Healthcare costs



Why Now AI

Johnson & Johnson a collaborative effort with IBM's



Novartis collaboration with IBM Watson for the purpose of improving health outcomes and for breast cancer patients

The need for AI in Healthcare



Bringing a new pharmaceutical drug to market takes about 12 years and can reach upwards of \$1 billion in R&D expenditures, industry leaders are now seeking more efficient methods of approaching this process and machine learning is emerging as a potential solution.

How AI Is Transforming Drug Creation
Pharmaceutical companies hope computers can help them find new medications that are faster, cheaper—and more likely to be effective

Why now Data

IBM Explorys Platform

 **Project Baseline**

ClinicalStudy
DataRequest.com



The future of
health begins with
All_{of}Us

 **TransCelerate**
BIOPHARMA INC.
ACCELERATING THE DEVELOPMENT OF NEW MEDICINES



 **the HUMAN project**

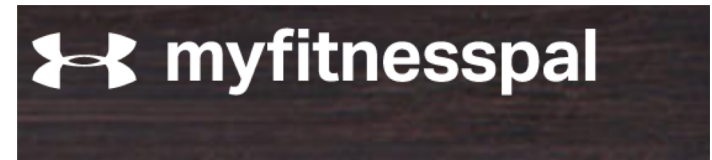
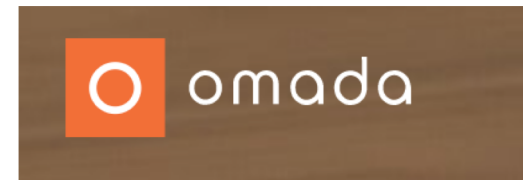
TRUVEN
HEALTH ANALYTICS®
IBM Watson Health™



Healthcare is changing....



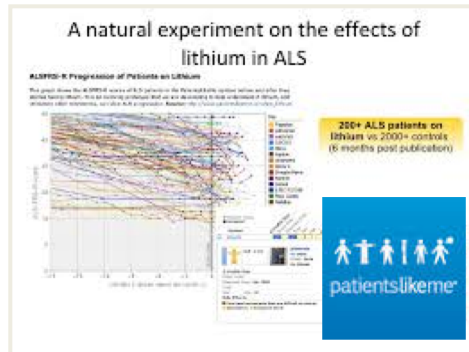
**Yale researchers tapping into emerging
secure cloud platform for sharing patient
data - HUGO**



New Entrants in the Drug Development Field



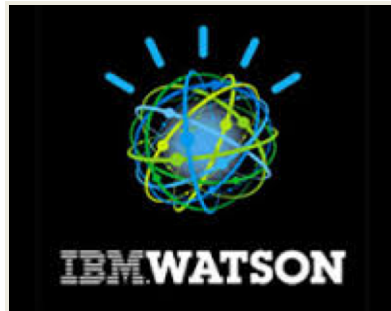
AKILI
A different type of medical product



Cystic Fibrosis Foundation made \$3.3 billion from a single pill



Screenshot via kalydeco.com
By John Tassi, Bloomberg News



New Healthcare Paradigms

- Growing trend for strong evidence on Pharmaceuticals from outside of Pharma

TheScientist
EXPLORING LIFE. INSPIRING INNOVATION

News - Magazine - Multimedia - Subjects - Surveys - Careers -

The Scientist • January 2017 Issue • Features

Repurposing Existing Drugs for New Indications

An entire industry has sprung up around resurrecting failed drugs and recycling existing compounds for novel indications.

- Clinical Decision Support Tools start to gain traction

Mayo unveils EHR-integrated clinical decision support tool for ordering lab tests

- Patient becoming more involved....

patientslikeme®

- Questions on Data Ownership

**THE HENRIETTA LACKS
FOUNDATION™**

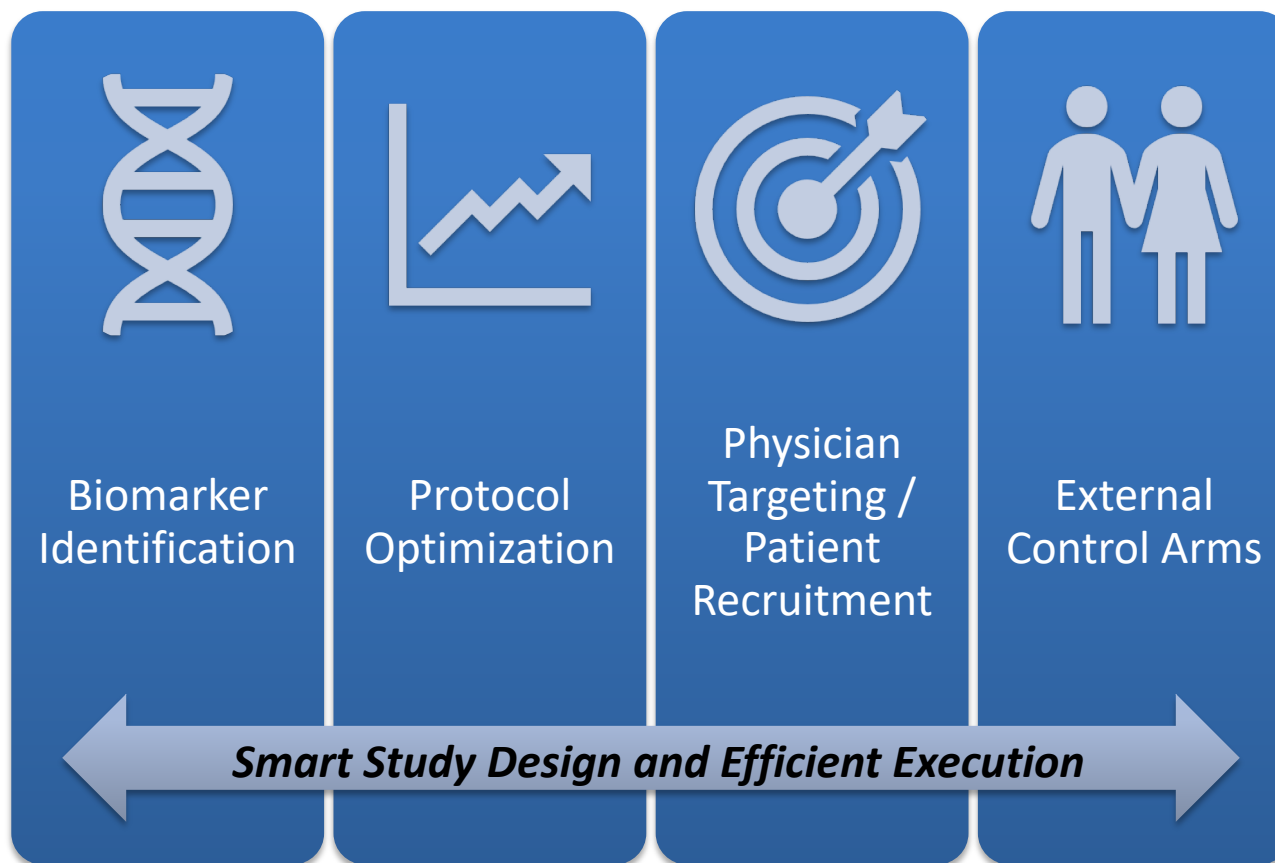
— EST. 2010 —

Accelerated
Cure
project
for multiple sclerosis

Where will Drug Development now fit within this digitally driven evolving ecosystem?

Changing Face of Clinical Development

Clinical Development / Trial Support

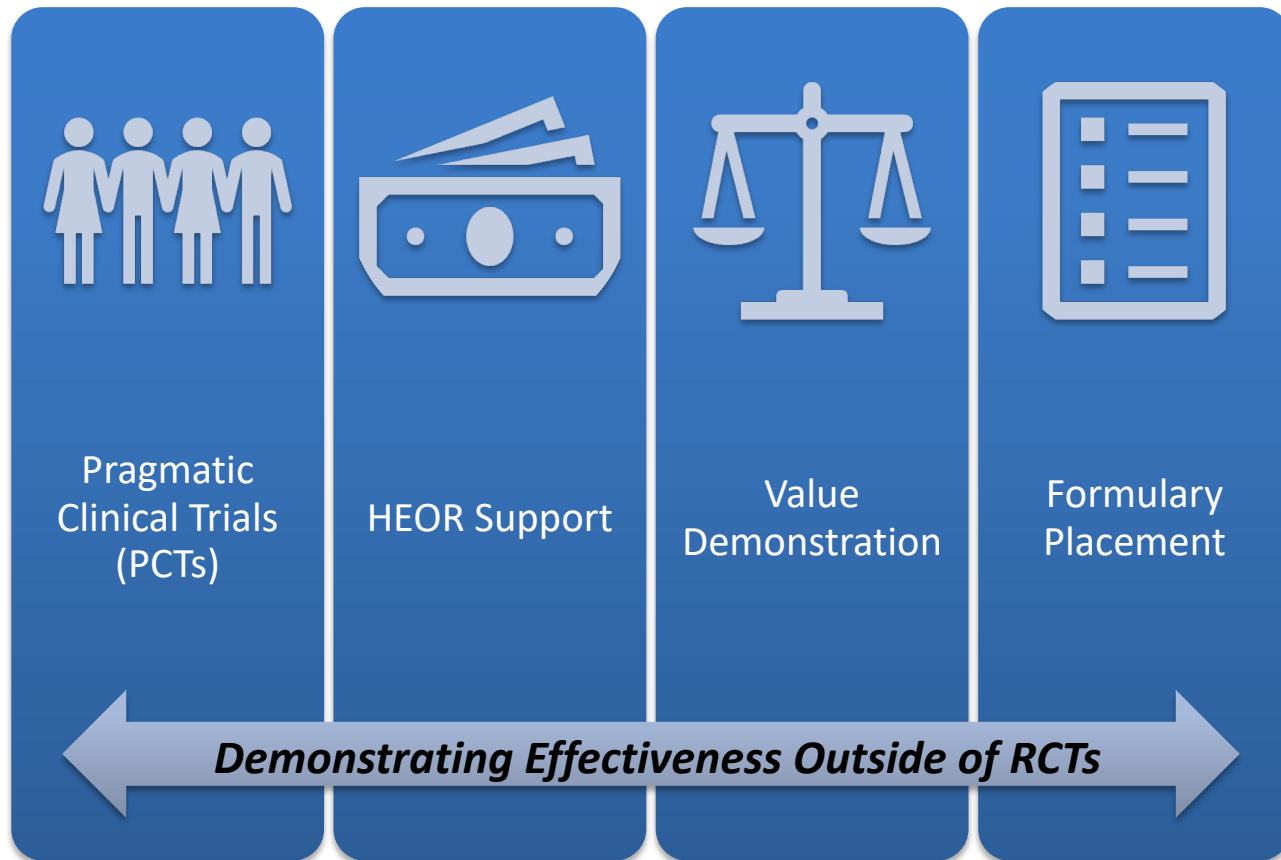


**Roche's External Control Arms Show
What Real-World Evidence Can Look Like
In Practice**

J Comp Eff Res. 2014 May;3(3):259-70. doi: 10.2217/ce.14.16.

Pre-study feasibility and identifying sensitivity analyses for protocol pre-specification in comparative effectiveness research.

Medical Affairs / Launch Support



[J Innov Health Inform.](#) 2015 Nov 4;22(3):368-73. doi: 10.14236/jhi.v22i3.177.

Rectangular Snip

Creating and using real-world evidence to answer questions about clinical effectiveness.

[Clin Drug Investig.](#) 2018 Jun;38(6):481-490. doi: 10.1007/s40261-018-0637-1.

Rectangular Snip

Epoetin Biosimilars in the Treatment of Renal Anemia: What Have We Learned from a Decade of European Experience?

EHRs have the potential to resolve bottlenecks in clinical research

- EHRs routinely used in clinical care
- In many European countries almost 90% of health records are digital with longitudinal axis of over 10 years
- Need of trustworthy partnerships with hospital networks and Pharma
- Focus on data privacy and legal/ethical concerns
- Data standardization and harmonization work needed



Leveraging Healthcare Data to Optimize Drug Development

Data Types

Insights:

Real-World Data

- Claims
- EMR
- Mobile
- Questionnaires

- Efficacy to effectiveness
- Event prediction
- Disease progression
- Medication initiation and switching
- Personal care pathways
- Value-based therapies

Clinical Trials

- Clinical Data
- 'Omics

- Biomarker discoveries
- Patient stratification/
subpopulations
- Adverse events
- Drug repurposing

Pre-Clinical Development

- 'Omics
- Phenotypes

- Novel targets
- Drug combinations
- Diagnostics

January 31, 2019 - Real-world data gathered directly from EHRs and other data sources, paired with advances in machine learning, will be crucial for architecting the next generation of successful clinical trials, says FDA Commissioner Dr. Scott Gottlieb.

Regulatory Viewpoint

Regulators opening up to RWE and creating new legislation

– **FDA**

- 21st Century Cures Act
- Promoting the Use of Complex Innovative Designs in Clinical Trials
- Guidance on Use of Electronic Health Record Data in Clinical Investigations

– **EU**

- IMI initiatives like EHR4CR
- Topic at the European Commission/EMA–FDA bilateral meeting 18-19 June 2018

Extract from FDA Commissioner Scott Gottlieb statement in January 2019

- Digital technologies create new opportunities to transform health care and empower patients to make better informed decisions about their health. Digital tools are rapidly evolving, and to keep pace with this promising innovation, the FDA must modernize its approach to regulation.
- I announced in the [Digital Health Innovation Action Plan](#) that the FDA would pilot a Digital Health Precertification (Pre-Cert) Program to make sure that patients continue to have access to new treatments that meet our gold standard for safety and effectiveness. Since that announcement, we've been advancing policies that reimagine our oversight of digital health tools to be more efficient and promote patient safety throughout the product lifecycle.
- We've seen the promise of innovation in products like [artificial intelligence software](#) that can help alert physicians to a potential stroke and [smart watches](#) that can help identify atrial fibrillation.
- Today, we're announcing that, based on the Pre-Cert pilot, we've drafted a regulatory framework to test new approaches for the review of digital health device applications.

Real-World Outcomes of Patients with Metastatic Non-Small Cell Lung Cancer Treated with Programmed Cell Death Protein 1 Inhibitors in the Year Following U.S. Regulatory Approval

SEAN KHOZIN,^a KENNETH R. CARSON,^{b,c} JIZU ZHI,^a MELISA TUCKER,^b SHANNON E. LEE,^b DAVID E. LIGHT,^b MELISSA D. CURTIS,^b MARTA BRALIC,^b IRENE KAGANMAN,^b ANALA GOSSAI,^b PHILIP HOFMEISTER,^b ARACELIS Z. TORRES,^b REBECCA A. MIKSAD,^b GIDEON MICHAEL BLUMENTHAL,^a RICHARD PAZDUR,^a AMY P. ABERNETHY^{id}^b

^aU.S. Food and Drug Administration, Silver Spring, Maryland, USA; ^bFlatiron Health, New York, New York, USA; ^cDepartment of Medicine, Washington University in St. Louis, St. Louis, Missouri, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Non-small cell lung cancer • Real-world evidence • Electronic health records • Overall survival • Nivolumab • Pembrolizumab

Current regulatory experience with FDA for ML

- ML algorithms initially will be evaluated on a case-by-case basis, both within CDER and CDRH.
- FDA has not moved toward creating a universal policy on ML.
- OCE is leading the way in terms of building its capacity around ML algorithms
- If the Oncology group's efforts are successful, they could provide a model for other Review Divisions to follow in ML.
- The emergence of public-private partnerships (PPPs) focused on ML is a promising development. These types of consortia could be a key part of the solution to the data sharing/data availability problem.
- CDRH has an internal group looking at machine learning; it is also participating (via a PPP) in a recently launched Artificial intelligence (AI) Initiative aimed at developing AI approaches in the areas of quality, regulatory affairs and supply chain operations.
- One of the challenges for CDRH is how to approach ML software that is updated frequently

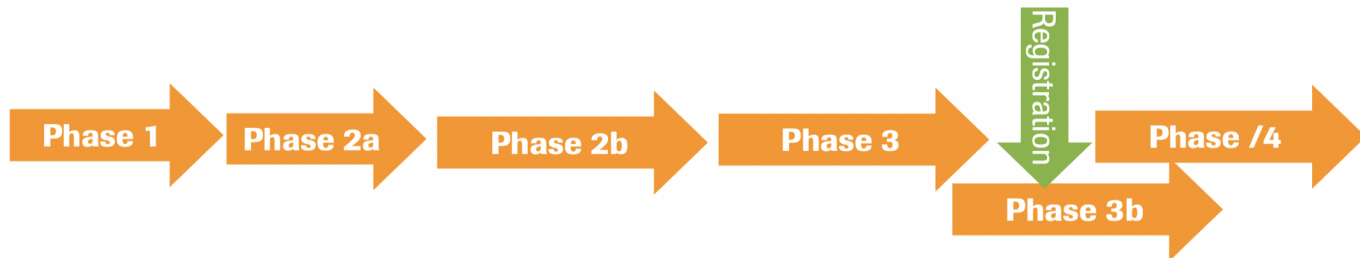
New Drug Development Paradigm

Developing a New Paradigm for Drug Development – Meeting October 7th 2016

- A group of Life sciences professionals held a 1-day meeting with MIT Media Lab to discuss the potential to develop a new paradigm for drug development. This was prompted by a changing healthcare environment resulting from the adoption of new technologies and the evolution of systems biology.
- A model proposed taking a molecule into patients via examining extensively the action of the molecule on a small cohort using a systems biology approach.
- For this to be successful the group felt that :
 - Pharmaceutical Industry, Providers and Payers would have to develop a robust, consistent and dynamic data sharing environment
 - Clarity would be needed on who owns data and how broad access is achieved to accelerate research
 - New incentive models would need to be developed across multiple stakeholders in the clinical trial ecosystem to ensure strong participation and data sharing
 - A new paradigm on potential liability will need to be introduced requiring new models of indemnification (e.g. joint liabilities)
 - Regulators would have to be open to the new model and build the associated needed capabilities and resources

The Challenge

Traditional approach to drug development requires sequential drug testing through phase



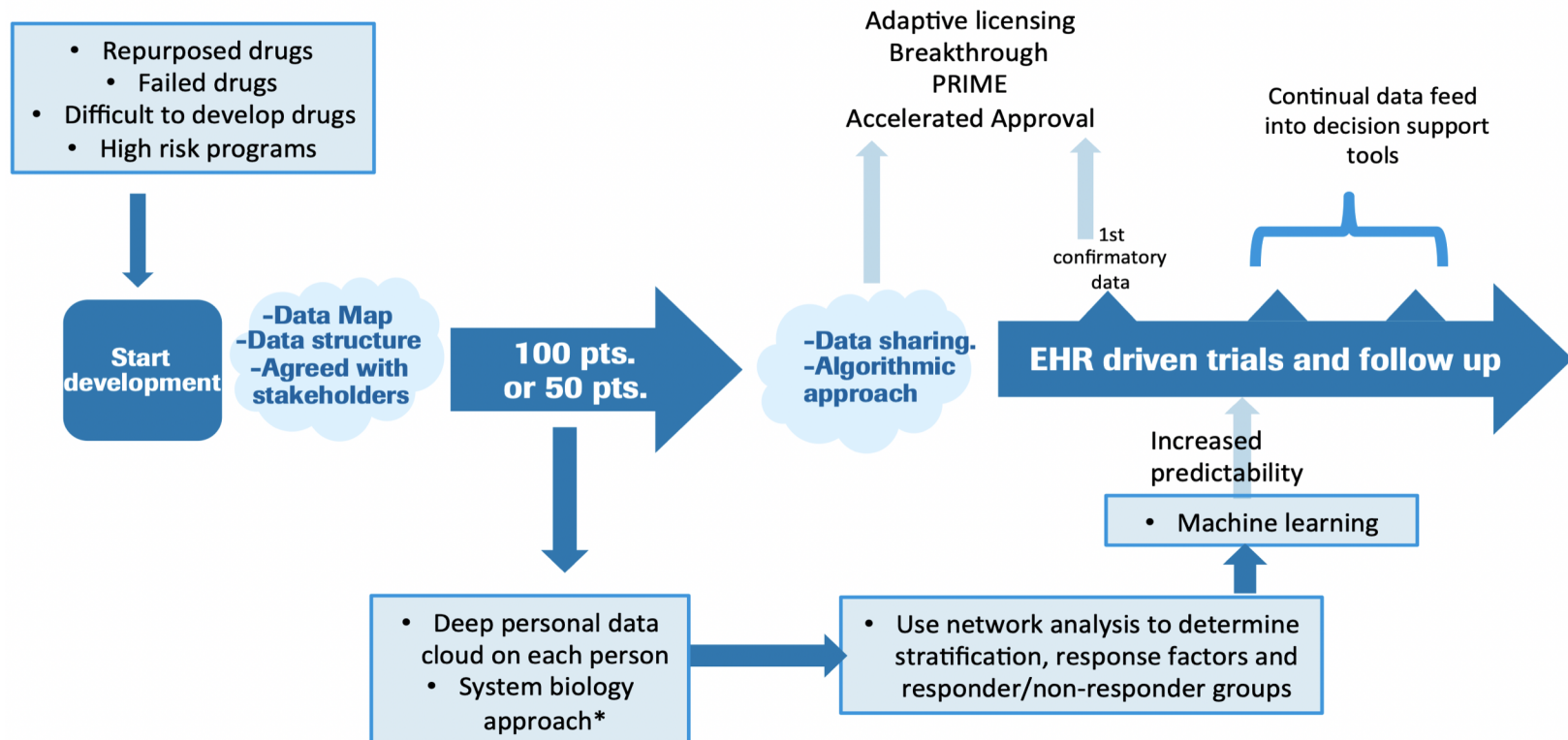
In some indications this has been successfully adapted e.g. with breakthrough designation but for many indications (Asthma, MS, Lupus, wet AMD, Neuroscience), the model is essentially unchanged

What if..

A radical new approach to drug development could be adopted which deploys new technology such as **systems biology**, **machine learning**, **cloud technology** with *increased predictability* of the outcome?

What would this be?

New Process – Parallel in-silico development



Dynamic Digital Tool vs. the Label

Current
Label

AVASTIN®
prescribed to treat:
 contains the active ingredient bevacizumab(s/s)

Consumer Medicine Information

What is in this leaflet
 This leaflet answers common questions about AVASTIN infusion. It does not contain all the available information. It does not take the place of talking to your doctor or pharmacist. All medicines have risks and benefits. Your doctor has weighed the risks of giving AVASTIN against the benefits they expect it will have for you. **You have any concerns about taking this medicine, ask your doctor or pharmacist. Keep this leaflet with the medicine. You may need to read it again.**

What AVASTIN is used for
 AVASTIN is used to treat:
 • breast tumours
 • metastatic (spreading) cancer of the large bowel (colorectal cancer), breast and lung in combination with chemotherapy agents
 • kidney cancer (renal cell cancer) in combination with interferon therapy (INTERFERON-α)
 AVASTIN contains the active ingredient bevacizumab. AVASTIN belongs to a group of medicines known as anti-angiogenic (or anti-cancer) agents. These are more effective when AVASTIN is used with anti-cancer agents. AVASTIN belongs to a class known as anti-angiogenic agents. Anti-angiogenic agents inhibit angiogenesis (the process of forming new blood vessels in your body). AVASTIN selectively binds to vascular endothelial growth factor (VEGF), a protein found on the walls that line blood vessels. Tumours produce high levels of VEGF, which stimulates blood vessels to grow, thereby providing the tumour with nutrients and oxygen. When AVASTIN blocks VEGF it slows the blood supply to the tumour, stopping or slowing down its growth. There are many different types of medicines used to treat breast tumours and metastatic cancer of the large bowel, breast, lung and kidney. Your doctor may have prescribed AVASTIN for another purpose. **Ask your doctor if you have any questions about why AVASTIN has been prescribed for you.** AVASTIN is not suitable for you. This medicine is available only with a doctor's prescription.

Before you are given AVASTIN
 AVASTIN contains the active ingredient bevacizumab. **When you must not be given it**
 Do not use AVASTIN if:
 1. you have had an allergic reaction to AVASTIN or any ingredients listed at the end of this leaflet

is a class known as anti-angiogenic agents. Anti-angiogenic agents inhibit angiogenesis (the process of forming new blood vessels in your body). AVASTIN selectively binds to vascular endothelial growth factor (VEGF), a protein found on the walls that line blood vessels. Tumours produce high levels of VEGF, which stimulates blood vessels to grow, thereby providing the tumour with nutrients and oxygen. When AVASTIN blocks VEGF it slows the blood supply to the tumour, stopping or slowing down its growth. There are many different types of medicines used to treat breast tumours and metastatic cancer of the large bowel, breast, lung and kidney. Your doctor may have prescribed AVASTIN for another purpose. **Ask your doctor if you have any questions about why AVASTIN has been prescribed for you.** AVASTIN is not suitable for you. This medicine is available only with a doctor's prescription.

Before you are given it
 Tell your doctor if:
 1. you are pregnant or plan to become pregnant. Do not use AVASTIN if you are pregnant. AVASTIN may cause damage to your unborn baby. Your doctor will advise you about using AVASTIN during pregnancy.
 2. you have had an allergic reaction to any medicine or any of the ingredients listed at the end of this leaflet.
 3. you have had an allergic reaction to any of the ingredients listed at the end of this leaflet.

Table 1
 Administration Every 4 Weeks
 Xolair Doses (milligrams) Administered by Subcutaneous Injection Every 4 Weeks for Adults and Adolescents 12 Years of Age and Older

Pre-treatment Serum IgE (IU/mL)	Body Weight (kg)			
	30-60	> 60-70	> 70-90	> 90-150
≤ 30	100	150	300	300
> 30	100	150	300	300

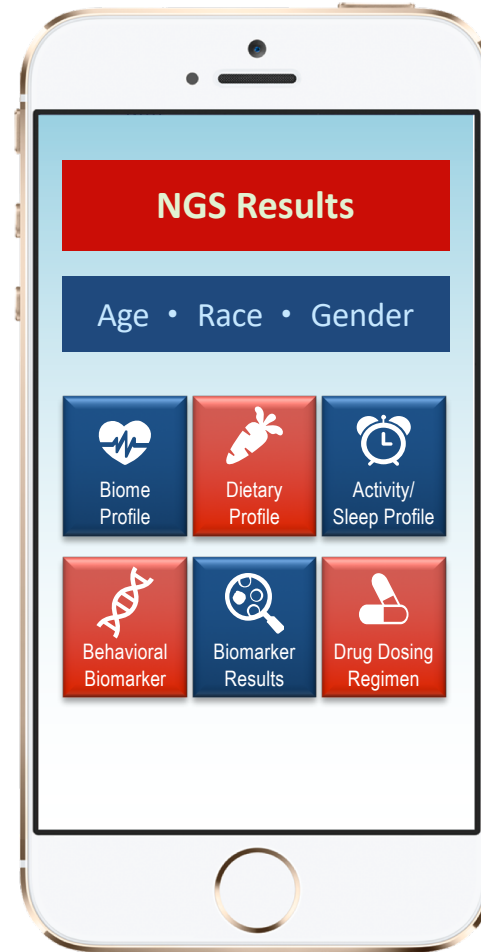
SEE TABLE 2

Table 2
 Administration Every 2 Weeks
 Administered by Subcutaneous Injection Adolescents 12 Years of Age and Older

Body Weight (kg)	Dose (mg)		
	60-70	> 70-90	> 90-150
60-70	225	225	300
70-90	225	300	300
90-150	300	375	375

DO NOT DOSE

AVASTIN® (bevacizumab) For Intravenous Use
 Genentech



Personalized
Digital
Label

Advanced Analytics

Potential Opportunities for Artificial Intelligence and Machine Learning in Clinical Development

Clinical Trial Development Process opportunities to use with how AI/ML

Research Hypothesis

Protocol Development

Site Set Up

Subject Recruitment

Data Collection

Patient Engagement & Education

Chatbot Help Line

Trial Analysis & Reporting

Submission

Safety Evaluation

Opportunities

Clinical Trial Matching

Chatbots

Deep Neural Networks

Open Data

Open Science

Data Analytics

Artificial Intelligence applications beyond Clinical Trials

EHRs

Precision Medicine

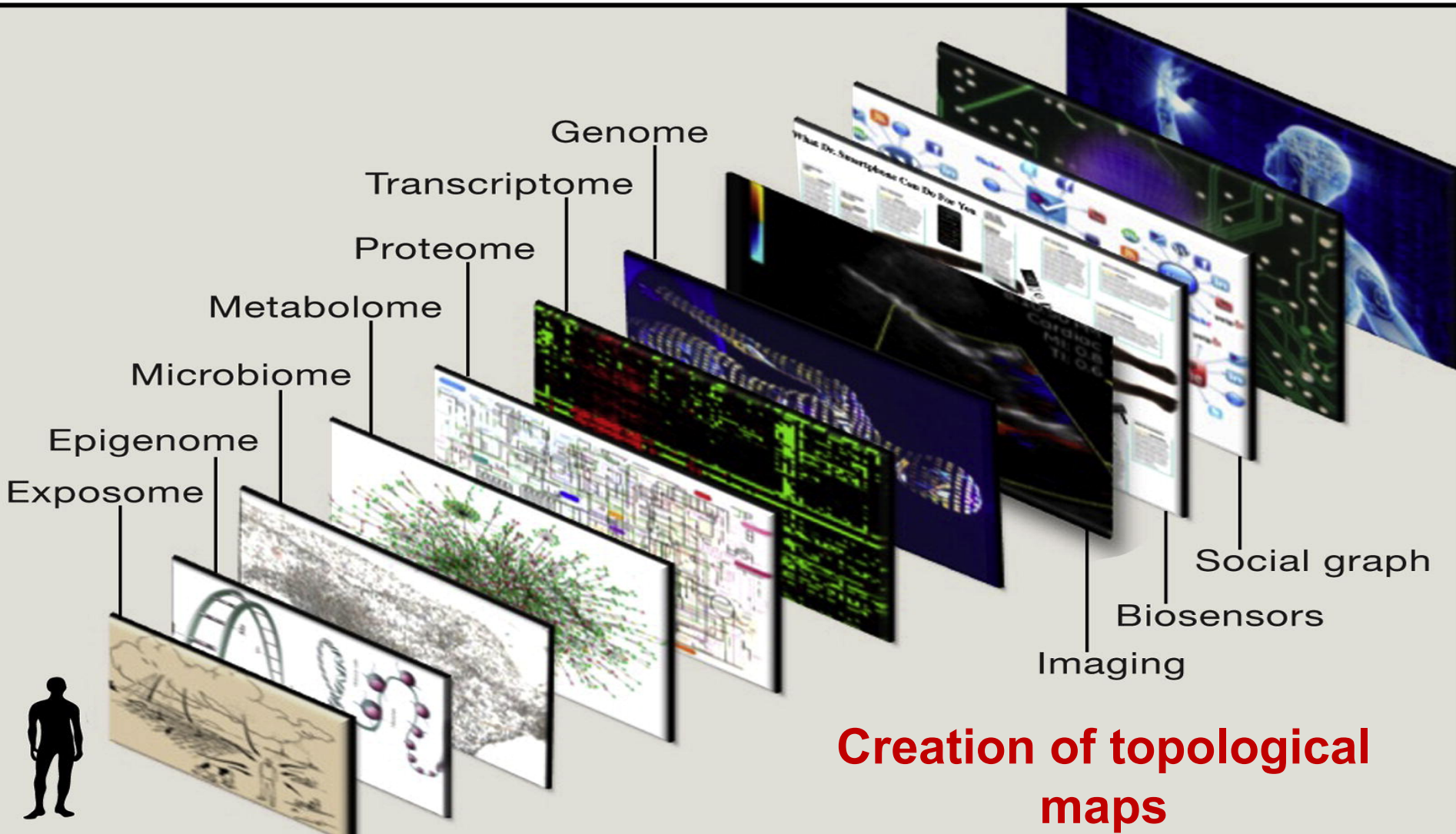
Sensors

Systems Biology

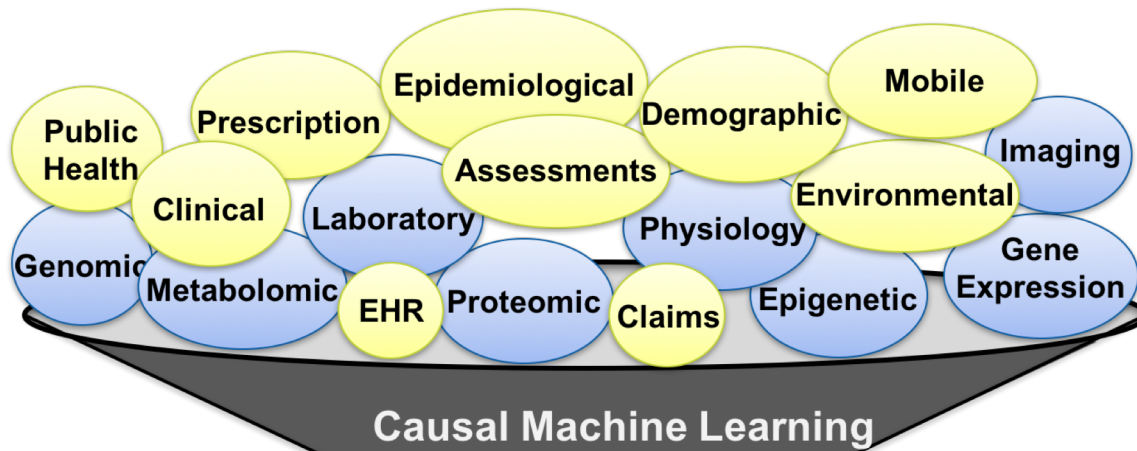
Voice Recognition

PRECISION MEDICINE:

Integrating multi-omics, clinical and real world data

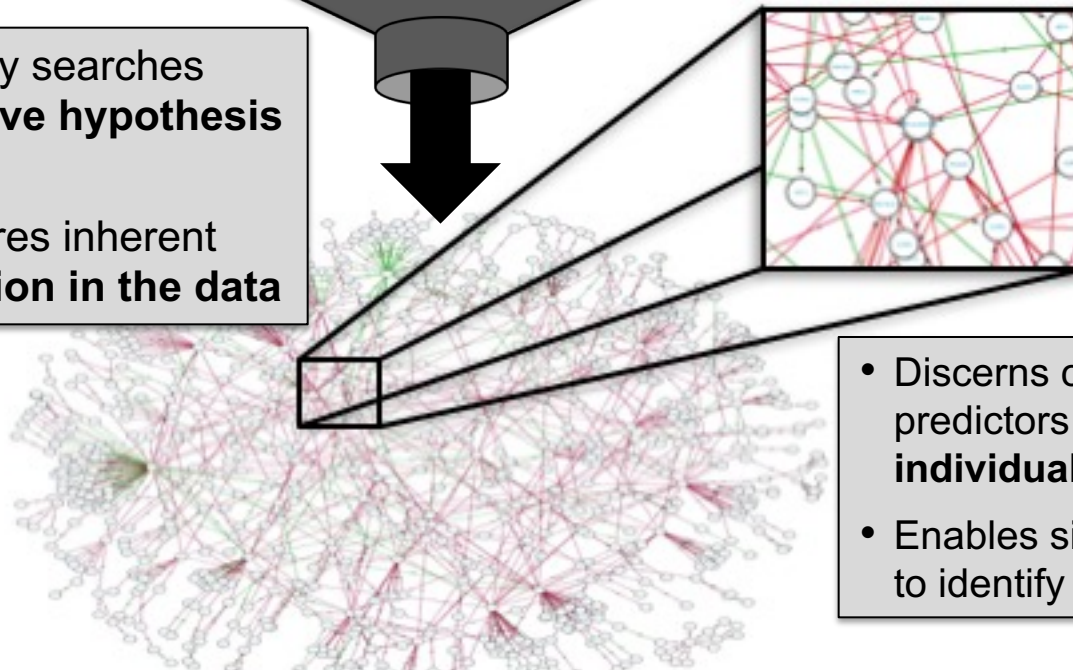


Causal Machine Learning for Healthcare Data



- Incorporates **all raw data**
- **Unlimited data** types at once
- **Millions of variables, billions of data points**, and their interactions

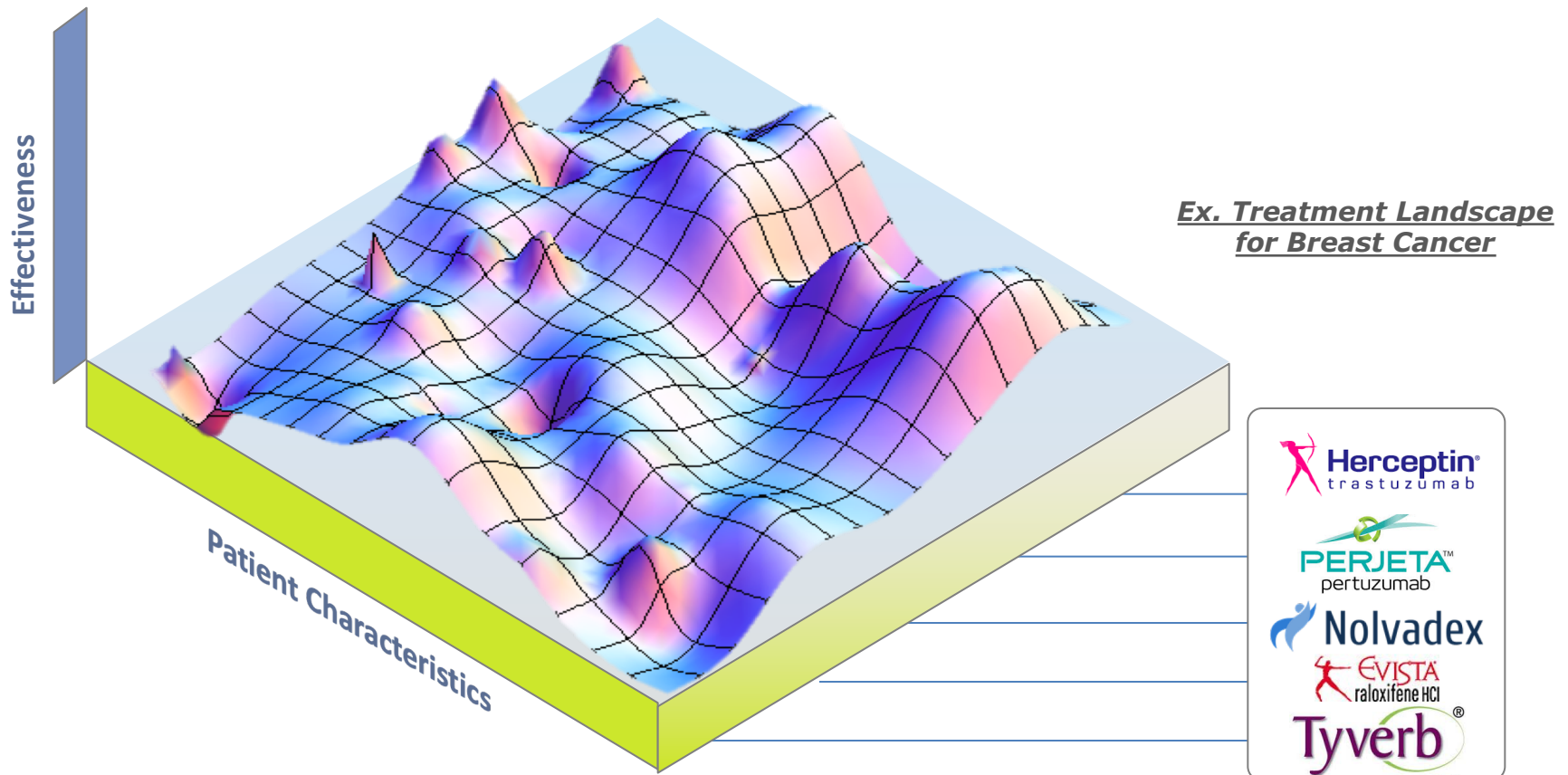
- Rapidly searches **massive hypothesis space**
- Captures inherent **variation in the data**



- Discerns complex **causal mechanisms** & predictors across populations & on an **individual level**
- Enables simulations of '**what-if**' scenarios to identify **effects on outcomes**

Comparative Effectiveness Treatment Algorithms

***Improving Outcomes and Reducing Costs Means Being Patient-Centric:
There is a “Right Treatment” for the Right Patient at the Right Time***



A confluence of macro-level factors is leading to a burning platform - to harness data and adopt analytics that disrupt pharma business as usual

The Explosion of Healthcare Information...



...and New Capabilities in Advanced Analytics...



...Are Redefining the Nature of Work in Healthcare



- **Explosion of data** (e.g., by 2020 healthcare data doubles every 3 months versus 3 years)
- **Nature of data is changing** (e.g. traditional R&D data now linked to EHR, etc.) such that the static is becoming dynamic
- **Expansion of data availability** (e.g. patient group data in social media, mobile apps, multi-omics, sensors, imaging, etc.)
- **Cognitive computing and machine learning** (e.g. information clustering and deep learning driving decisions making previously intractable problems solvable)
- **Integrated-Interactive dashboards** (e.g. Integrated cross functional real time data views constructed on agile data lakes)
- New **technology-focused entrants** (e.g., IBM Watson, Google/Alphabet, AWS, SFDC, Moderna, Illumina) are challenging the traditional models within healthcare and bio pharma
- Integration of clinical trial, omic/imaging data, real world evidence and social media is creating **new sources of safety and value signals for Pharma and Regulators**
- Focus on **developing personalized treatment pathways** for patients
- **New methods to engage patients and providers** and including them more in the process of diagnosis, treatment and monitoring
- Increasing **reliance on building ecosystems** to address the needs for evolving information capabilities

The Burning Platform: As technology, data, expertise, and investment in this area continues to unfold, future financial sustainability in pharma is dependent on the ability to utilize data as a critical asset to deliver augmented intelligence in decision-making across the value chain and to leverage advanced analytics/cognitive approaches to do so

Final Thoughts

- A major step to move forward is to address data aggregation and availability
- Next generation is not just for evidence generation but also can improve efficiencies
- Confidentiality concerns will be and have to be addressed e.g. Blockchain
- Digital Health and RWD are all about Advanced Analytics and programming
- Academia and Pharma need to co operate more to realize the value of the new Data Science era
- Pharma Data Science in Clinical Development is a lot broader than the Clinical Trial

Questions